Journal of Aging and Health
2022, Vol. 34(6-8) 883–892

DOI: 10.1177/08982643221074857
journals.sagepub.com/home/jah

Loneliness, Social Isolation, and All-Cause Mortality in a Large Sample of Older Adults

Timothy L. Barnes, PhD, MPH, MHI[1], Manik Ahuja, PhD, MA[1], Stephanie MacLeod, MS[1], Rifky Tkatch, PhD[1], Laurie Albright, MSW, MA[2], James A. Schaeffer, RPh[1], and Charlotte S. Yeh, MD[3]

Abstract

Objectives: Using data from a large random sample of U.S. older adults (*N* = 7982), the effect of loneliness and social isolation on all-cause mortality was examined considering their separate and combined effects. **Methods:** The UCLA-3 Loneliness Scale and the Social Network Index (SNI) were used to define loneliness and social isolation. Cox proportional hazards regression models were performed. **Results:** Among study participants, there were 548 deaths. In separate, adjusted models, loneliness (severe and moderate) and social isolation (limited and moderate social network) were both associated with all-cause mortality. When modeled together, social isolation (limited and moderate social network) along with severe loneliness remained significantly associated with mortality. **Discussion:** Results demonstrate that both loneliness and social isolation contribute to greater risk of mortality within our population of older adults. As the COVID-19 pandemic continues, loneliness and social isolation should be targeted safely in efforts to reduce mortality risk among older adults.

Keywords

loneliness, social isolation, all-cause mortality, older adults, health outcomes

Background

The recent global COVID-19 pandemic has altered the landscape of social and in-person interactions in the U.S. In early 2020, the rapid spread of COVID-19 almost immediately altered daily life, professional work environments, home situations, schooling and childcare, as well as social activities due to stay-at-home orders and other restrictions implemented to control the virus. Across both urban and rural areas, these new protocols impacted all aspects of life, with devastating effects touching not only physical and mental health but also important social and personal health indicators. Personal determinants of health (PDOH) are considered the individual-level resources that can help to support positive health outcomes; the key PDOH include resilience, optimism, purpose in life, and social connectedness (MacLeod et al., 2021). Even prior to the pandemic, these PDOH—including social connectedness—were already critical to positive health outcomes later in life. However, with the onset of the pandemic, the sudden restriction of social connection has made loneliness and social isolation more urgent.

Loneliness and social isolation are two distinct constructs that help define a larger concept known as *social connection*. Social connection refers to the various structural, functional, and quality aspects of social relationships (National Academies of Sciences Engineering, and medicine (NASEM (2020); Holt-Lunstad et al., 2017), and includes specific constructs such as loneliness, social isolation, and social support. Loneliness is typically defined as the subjective state of a person's sense of belonging and the quality of social relationships (Cacioppo et al. 2002; Cornwell & Waite, 2009; Ong et al., 2016). Meanwhile, social isolation focuses on an objective count of relationships, social interactions, and social contacts, determined by their quantity and/or quality (Cudjoe et al., 2020; MacLeod et al., 2018). Research efforts in the field of social connection primarily focus on one or two of these aspects separately or in combination (Barnes et al., 2021).

[1]UnitedHealth Group, Eden Prairie, MN, USA
[2]UnitedHealthcare, Minneapolis, MO, USA
[3]AARP Services, Inc, Washington, DC, USA

Corresponding Author:
Timothy L. Barnes, PhD, MPH, MHI, Optum Labs, United Health Group Inc, 11000 Optum Circle, Eden Prairie, MN 55344, USA.
Email: timothy.barnes@optum.com

Reports from various studies indicate up to 55% of older adults age 65 years or older in the U.S. report some degree of loneliness (Musich et al., 2015; Perissinotto et al. 2012). Similarly, 20% to 40% of older adult populations age 60 years and older in the U.S. and elsewhere are socially isolated (Cudjoe et al., 2020; MacLeod et al., 2018). Many healthcare experts acknowledge that older adults comprise a segment of the population that is especially vulnerable to social isolation during the COVID-19 pandemic, potentially due to pre-existing health conditions that could be exacerbated as a result of increased loneliness and limited social activities (Berg-Weger & Morley, 2020; Holt-Lunstad, 2020; Wu, 2020).

Evidence for the impact of loneliness, social isolation, and other aspects of social connection on health outcomes has been well documented in the literature over the years (NASEM 2020; Musich et al., 2015; MacLeod et al., 2018; Barnes et al., 2021). For instance, both have been independently associated with negative physical and mental health outcomes later in life including higher rates of depression and cognitive decline (Beutel et al., 2017; Drageset et al., 2013; Holt-Lunstad et al., 2010; Holt-Lunstad et al. 2015; Holt-Lunstad et al. 2017; IOM, 2014; Kelly et al., 2017; Kuiper et al., 2015; Luo & Waite., 2014; Musich et al., 2015; Ong et al., 2016; Penninkilampi et al., 2018; Perissinotto et al. 2012; Rico-Uribe et al., 2018). In addition, loneliness has shown independent associations with depression, poor sleep, hypertension, and many other poor health outcomes (Hackett et al., 2012; Hawkley et al., 2010; MacLeod et al., 2018; Musich et al., 2015; Perissinotto et al. 2012; Steptoe et al., 2004). Meanwhile, social isolation has been associated with increased cardiovascular disease risk, inflammatory processes, increased dementia risk, disability, cognitive decline, and reduced quality of life (QOL) in independent analyses (Barth et al., 2010; Bassuk et al., 1999; Grant et al., 2009; Heffner et al., 2011; Shankar et al., 2011; Steptoe et al., 2013). Finally, both have shown significant associations with mortality, with social isolation typically regarded as the strongest indicator of the two constructs (Steptoe et al., 2013). However, limited research has explored the effects on mortality of loneliness and social isolation in combination.

Studies examining the potential relationship between social connection and mortality began decades ago, with researchers focused on measures such as presence, extent, and types of social ties and relationships (NASEM 2020). These measures, individually and in combination, were shown to be significantly predictive of mortality, even after controlling for many other factors (NASEM 2020). One such study (1979) showed four factors in combination predicted mortality (e.g., marital status, frequency of contacts with other friends and relatives, membership and frequency of participation in voluntary organizations, and frequency of attendance at religious services) (Berkman & Syme, 1979). In fact, by combining the four factors into a *social network index*, a calculated relative risk for all-cause mortality was approximately two-fold for the socially isolated participants versus the more socially integrated group. Thus, socially isolated participants were twice as likely to die as those who were more socially integrated (Berkman & Syme, 1979; NASEM 2020).

Further evidence to support this finding includes a comprehensive meta-analysis by Holt-Lunstad et al. (2010) encompassing 148 studies that evaluated many measures of social connection. In this analysis, overall results demonstrated that participants with stronger social connections had greater odds of survival (Holt-Lunstad et al., 2010). In addition, other studies have shown similar findings indicating that the odds of mortality decrease with stronger indicators of social connection (Holt-Lunstad et al., 2015; Luo et al., 2012; Rico-Uribe et al., 2018; Shor & Roelfs, 2015; Tanskanen & Anttila, 2016). However, although evidence between loneliness and increased risk of mortality exist (Drageset et al., 2013; Holt-Lunstad et al., 2015; Luo & Waite, 2014; Perissinotto et al. 2012; Rico-Uribe et al., 2018), the predictive effect of loneliness on mortality (independent of depression) appears to be weaker, if not to a lesser extent than that of social isolation (NASEM 2020).

Although various research studies have examined the risk of mortality in relation to loneliness, social isolation, and other social connection constructs, most have examined these relationships separately. Only a limited number of studies have examined both loneliness and social isolation within the same sample; similarly, current research lacks evidence on the combined impact of these two constructs in the same analysis. The most well-known study by Steptoe et al. (2013) in a large national sample ($n = 6500$) in the United Kingdom found that both social isolation and loneliness were associated with mortality when considered independently and with limited covariates. However, loneliness was not independent of demographic factors such as age or health status and did not increase the risk associated with social isolation. Only social isolation remained significantly associated with mortality after controlling for multiple factors (Steptoe et al., 2013). Elsewhere, other research supports this finding, demonstrating that social isolation has more influence on the risk for mortality even when adjusting for loneliness and other risk factors, although the same is not true for loneliness (Beller & Wagner, 2018; Hakulinen et al., 2018; Ong et al., 2016). These studies have been primarily conducted in countries such as the United Kingdom and Germany; however, no large study has been performed in a large sample of adults in the U.S. examining the combined impact of loneliness and social isolation on mortality. Therefore, the current study adds unique knowledge to the literature by examining the impacts of loneliness and social isolation in a large sample of U.S. older adults, as well as by describing deaths associated with COVID-19 during the study period.

Statement of Purpose

The primary purpose of this study was to examine and describe the separate and combined effects of loneliness and social isolation on all-cause mortality in a large sample of U.S. older adults. Based on the previous literature, we hypothesize that loneliness and social isolation in combination will be associated with an increased risk for mortality due to various causes, with social isolation potentially the strongest indicator of all-cause mortality as compared to loneliness. This analysis is unique because there are currently no major studies examining both loneliness and social isolation and their combined impact on mortality in a large sample of U.S. older adults. Furthermore, considering growing concerns about the social connections of older individuals especially in the context of COVID-19 restrictions, and how those connections impact health outcomes, renewed focus on the combined effects of loneliness and social isolation is warranted. The current study may help to identify potential risk factors and points of intervention to better serve older adults and reduce loneliness, social isolation, and related risk of mortality in this vulnerable population.

Methods

Study Participants

Approximately 5 million individuals are covered by an AARP® Medicare Supplement Plan from UnitedHealthcare Insurance Company or an affiliate (collectively "UnitedHealthcare"), herein referred to as AARP Medicare Supplement insureds. These plans are offered in all 50 states, Washington DC, and various US territories.

In 2018 and 2019, random samples of AARP Medicare Supplement insureds, 65 years or older, with 12 months of continuous coverage, were surveyed as a larger research effort to improve customer experience. Surveys were administered from June through August of each year in which 16,000 AARP Medicare Supplement insureds (per year) were mailed surveys using a nationally randomized methodology. In total, 8672 participants completed surveys (4696 respondents in 2018 and 3976 respondents in 2019), an overall 27% response rate. After accounting for missed eligibility ($n = 19$), missing/incomplete survey responses ($n = 649$), and deaths prior to follow-up periods ($n = 22$), 7982 participants were included in this study. This study was approved by the New England Institutional Review Board.

Survey and Data Collection

Surveys were developed by UnitedHealthcare to assess customer experience and aspects of health including psychosocial and wellness constructs on a yearly basis. For this study, measures of loneliness and social networks (an indicator of social isolation) were examined in relation to several other survey components (e.g., quality of life), and administrative and medical claims data.

Demographics and Socioeconomic Factors

Demographic factors included age and gender; socioeconomic indicators were based on zip codes. Age groups were defined as 64–69, 70–74, 75–79, 80–84, and ≥ 85 years. Geographic regions (Northeast, South, Midwest, and West), Rural Urban Commuting Area (e.g., urban, suburban, and rural), and low, medium, and high minority areas were geocoded from respondents' zip codes. Survey respondents' medium household income designation (low, medium, or high) was also assessed.

Health Status

Medical claims data were used to describe health status using the Charlson Comorbidity Index (CCI) (Charlson et al., 1987; Klabunde et al., 2007; Sundararajan et al., 2004) and Hierarchical Condition Category (HCC) scores (McCall & Cromwell, 2011; Pope et al., 2011). The CCI focuses on the presence of specific comorbid conditions, which are used to calculate a health index. Higher CCI scores indicate a greater number of comorbidities and poorer overall health status. Similarly, the HCC score is used by Centers for Medicare & Medicaid Services (CMS) to risk-adjust medical payments across various medical plans according to the health status of the different insured populations. Hierarchical Condition Category scores can be used as a surrogate measure of the health status of selected subgroups in Medicare populations. Hierarchical Condition Category subgroups were defined as follows: HCC scores < 0.5; HCC scores 0.5 to < 1.2; HCC scores 1.2 to < 2.8, and HCC scores ≥ 2.8, with higher scores indicating poorer health status.

Loneliness

Loneliness was captured using the 3-item Revised University of California, Los Angeles

(UCLA-3) Loneliness Scale (Hughes et al., 2004). The UCLA-3 asks how often respondents feel: 1) left out, 2) lack of companionship, and 3) isolated from others. For each item, possible responses were: "never or hardly ever" (3 points), "some of the time" (2 points), and "often" (1 point). Responses were then reverse-coded and summed to a score ranging from 3 to 9, with higher scores indicating greater loneliness. Cronbach's α for this measure was 0.73. For the purpose of this study, we classified participants into three categories based on their score: 3 = no loneliness; 4–5=moderate loneliness; 6–9=severe loneliness. Categories have been used in other studies to examine mortality and other health outcomes (Steptoe et al., 2013; NASEM 2020).

Social Isolation

Social isolation was based on questions from an adapted Social Network Index (SNI) (Musich et al., 2019), which counts the number of social connections. Specifically, five questions were used to assess SNI: 1) In a typical week, how many times do you talk on the telephone with family, friends, or neighbors? 2) In a typical week, how often do you get together with friends or relatives, such as going out together or visiting in each other's homes? 3) How often do you attend church or religious services or activities of your religious organization (per month)? 4) How often do you attend meetings of the club or organizations you belong to (per month)? and 5) Are you married or living together with someone in a partnership? Responses to questions 1–4 were scored 0 times=0, 1–2 times=1, 3–4 times=2, and 5 or more times=3. Responses to married or living together were scored yes=1 and no=0. All responses were summed for a score ranging from 0–13, with higher scores indicating greater social diversity, and lower scores indicating greater social isolation. Categories of social networks were based on the SNI score: 0–4 represented a "limited" social network, 5–7 a "medium" social network, and ≥ 8 a "diverse" social network (Aung et al., 2016; Musich et al., 2019).

Mortality Data

The primary outcome of interest in this study was all-cause mortality, which was determined from mortality data from the UnitedHealthcare membership repository. The study assessed all-cause mortality between June 2018 and May 2021, and COVID-19 related mortality in 2020–2021. The date of death was extracted for each participant from the repository. Survival time was calculated as the number of days from study index date of June 1, 2018 and the date of death. In addition to all-cause mortality, we further assessed COVID-19 related deaths that occurred between January 1, 2020 and May 31, 2021. COVID-19 deaths were based on ICD-10 diagnosis codes from medical claims data, which included the following: U.071, B.9721, B.342, B.9729, Z.03818, Z.20828, Z.1159, .9721, .1152,Z.20822,Z.8616,J.1282 (Centers for Disease Control and Prevention (CDC), 2021; Gundlapalli et al., 2021). Overall, the mortality rate was 6.9% (n = 548), which consisted of those who had died between the time of the index date and study end date.

Statistical Analyses

This analysis involved comparisons between survey participants who died versus those who survived after participating in the survey. Prior to initiating primary analyses, survey respondents and non-respondents were assessed to account for any potential selection bias; however, no significant differences in characteristics emerged. Basic summary statistics and bivariate comparison between groups were performed (Table 1). Descriptive statistics included values and distributions for sociodemographic variables, health status, and loneliness and social isolation designations. Next, Cox Proportional Hazards regression models were performed to estimate the hazard ratios (HRs) of all-cause mortality and 95% CIs associated with loneliness and social isolation, respectively. No loneliness and least isolated categories were used as the reference groups. Survival time was measured in months from the end of survey period (July 31 of each survey year) to the date of death or end of study period, which was May 31, 2021. Multiple models were assessed adjusting for various socio-demographic characteristics and health status. Potential confounders addressed included age, education, household income, gender, census geographic region, and rural/urban location of residence. Potential confounders of health status/health burden included CCI and HCC scores.

Final results presented two types of models (Table 2). In Model A, we separately examined the association between loneliness with all-cause mortality, as well as social isolation with all-cause mortality. In the loneliness model, severe loneliness and moderate loneliness were included, with no loneliness used as the referent group. For social isolation, we included limited social network, moderate social network, and diverse social network as the reference group. In Model B, we jointly assessed both loneliness and social isolation. We included loneliness (severe, moderate) and social isolation (diverse, moderate), along with controls to assess their association with all-cause mortality. Violations of the proportional hazard assumption that remained constant over time were tested with the Gramsch and Therneau test of the Schoenfield residuals (Grambsch & Therneau, 1994). Such violations were resolved by re-parameterization of variables and splitting the period of risk appropriately. All analyses were completed using SAS Enterprise Guide Version 7.1 (SAS Institute Inc, Cary, NC, USA).

Results

Our study population included 7982 older adults over 65 who were randomly sampled from eligible AARP Medicare Supplement insureds. Descriptive statistics assessing differences between the participants who died (n = 548) and those who survived (n = 7434) are presented in Table 1. Generally, participants who died were older, male, and less healthy as compared to those participants who survived. Specifically, 48.8% of participants who died were 85 years or older as compared to the group who survived (15.4% ≥ 85 years). Additionally, 52.6% were male among those who died as compared to 43.8% who survived. Twenty-four percent of participants who died had HCC scores of 2.80 or greater and 34% had CCI scores of 5 or greater.

Severe loneliness (30.3%; n = 166 vs. 18.7%; n = 1389) and limited social network (44.9%; n = 246 vs. 28.6%; n = 2123) was higher in participants who died as compared to those who survived. Moderate loneliness (29.0%; n = 159 vs.

Table 1. Socio-Demographics, Health Characteristics, and Mortality in a Large Sample of Older Adults (*N*=7982).

	Total (*N* = 7982)		Died (*n* = 548)		Survived (*n* = 7434)		
	N	%	*n*	%	*n*	%	p-value[a]
Age (in years)							
65–69	1431	17.9	30	5.5	1401	18.8	<0.001
70–74	2118	26.5	71	13.0	2047	27.5	
75–79	1763	22.1	92	16.8	1671	22.5	
80–84	1334	16.7	97	17.7	1237	16.6	
≥85	1336	16.7	258	47.1	1078	14.5	
Gender							
Male	3533	45.0	272	49.6	3261	43.9	0.002
Female	4449	55.0	276	50.4	4173	56.1	
Minority (proxy by zip code)							
Low	4292	53.8	310	56.6	3982	53.6	0.370
Medium	3435	43.0	223	40.7	3213	43.2	
High	255	3.2	15	2.7	240	3.2	
Median household income (proxy by zip code)							
Low	1183	14.8	100	18.2	1083	14.6	0.05
Medium	2965	37.1	204	37.2	2761	37.1	
High	3834	48.0	244	44.5	3590	48.3	
Region							
Northeast	1953	24.5	160	29.2	1793	24.1	0.00
Midwest	1572	19.7	110	20.1	1462	19.7	
South	2776	34.8	189	34.5	2587	34.8	
West	1681	21.1	89	16.2	1592	21.4	
Rural urban commuting area							
Urban	5615	70.3	371	67.7	5244	70.5	0.37
Suburban	1290	16.2	97	17.7	1193	16.0	
Rural	1077	13.5	90	16.4	997	13.4	
HCC score							
<0.50	1865	23.4	22	4.0	1844	24.8	<0.001
0.50 to < 1.20	3523	44.1	146	26.6	3378	45.4	
1.20 to < 2.80	2082	26.1	247	45.1	1833	24.7	
≥2.80	512	6.4	133	24.3	379	5.1	
Charlson Comorbidity Score							
No comorbidity	2885	36.1	62	11.3	2823	38.0	<0.001
CCI score (1–2)	2789	34.9	157	28.6	2632	35.4	
CCI score (3–4)	1326	16.6	141	25.7	1185	15.9	
CCI score (≥5)	982	12.3	188	34.3	794	10.7	
Loneliness (UCLA-3)							
No loneliness	4448	55.7	223	40.7	4224	56.8	<0.001
Moderate loneliness	1977	24.8	159	29.0	1818	24.5	
Severe loneliness	1557	19.5	166	30.3	1389	18.7	
Social isolation (SNI)							
Limited social network	2371	29.7	246	44.9	2123	28.6	<0.001
Moderate social network	3458	43.3	222	40.5	3235	43.5	
Diverse social network	2153	27.0	80	14.6	2076	27.9	

Abbreviations: HCC; Hierarchical Condition Category, CCI; Charlson Comorbidity Index, SNI; Social Network Index.
[a]Chi-square test for categorical variables, significance at *p*-value <0.05.

24.5%; $n = 1818$) was also higher in the participants who died as compared to survivors, while the number of participants with a diverse social network was much higher in those who survived (27.9%; $n = 2076$ vs. 14.6%; $n = 80$).

Multiple Cox Proportional Hazard models were conducted to predict mortality using each construct independently and then in combination (Table 2). Model A shows the constructs independently, while Model B shows them modeled together.

Table 2. Association Between Loneliness, Social Isolation, and Mortality in a Large Sample of Older Adults (*N* = 7982).

	Model A (Separately)				Model B (Together)			
	Hazard Ratio	95% CI		*p*-value	Hazard Ratio	95% CI		*p*-value
		Lower	Upper			Lower	Upper	
Moderate loneliness	1.33	1.09	1.63	0.006	1.22	0.99	1.50	0.061
Severe loneliness	1.57	1.28	2.93	<0.001	1.31	1.06	1.62	0.011
Moderate social network	1.70	1.32	2.20	<.0001	1.64	1.27	2.12	0.000
Limited social network	2.47	1.91	3.18	<0.001	2.28	1.76	2.96	<0.001

Note. Cox Proportional Hazard Regression Models.
Model A: Each construct modeled separately adjusted for socio-demographics and health status.
Model B: Constructs modeled together adjusted for socio-demographics and health status.
Reference groups: No Loneliness and Diverse Social Network.

Table 3. COVID-19 Related Diagnoses and Deaths in a Large Sample of Older Adults (*N*=548).

ICD-10 Code	Diagnosis and Description	*N* out of Total Deaths[a]	% out of Total Deaths
U071	**COVID-19**	50	9.1
B9721	SARS-associated coronavirus as the cause of diseases classified elsewhere	1	0.2
B342	Coronavirus infection, unspecified	4	0.7
B9729	Other coronavirus as the cause of diseases classified elsewhere	3	0.5
Z03818	Encounter for observation for suspected exposure to other biological agents ruled out; note: If the patient is asymptomatic and there is possible exposure to COVID-19	17	3.1
Z20828	Contact w and exposure to viral communicable diseases; contact with and (suspected) exposure to COVID-19 (per CDC)	66	12.0
Z1159	Encounter for screening for other viral diseases	31	5.7
B9721	SARS-associated coronavirus causing disease	1	0.2
Z1152	Encounter for screening for COVID-19	1	0.2
Z20822	Contact with and (suspected) exposure to COVID-19	11	2.0
Z8616	Personal history of COVID-19	0	0.0
J1282	Pneumonia due to coronavirus disease	11	2.0

[a]Multiple ICD-codes could be associated with a single death. Thus, counts are not mutually exclusive.

In Model A, both severe loneliness (HR = 1.57, CI: 1.28–2.93; $p < 0.001$) and moderate loneliness (HR = 1.33, CI: 1.09–1.63; $p = 0.006$) were significantly associated with mortality. In addition, Model A also shows both limited (HR = 2.47, CI: 1.91–3.18; $p < 0.001$) and moderate social isolation (HR = 1.70, CI: 1.32–2.20; $p < 0.001$) as independent predictors of mortality.

In Model B, in which both constructs are modeled together, limited social network (HR = 2.28, CI: 1.76–2.96; $p < 0.001$), moderate social network (HR = 1.64, CI: 1.27–2.12; $p < 0.001$), and severe loneliness (HR = 1.31, CI: 1.06–1.62; $p = 0.011$) were all significantly associated with an increased risk of all-cause mortality. Moderate loneliness (HR = 1.22, CI: 0.99–1.50; $p = 0.061$) was marginally associated with an increased risk of all-cause mortality.

Finally, based on the events of the COVID-19 pandemic, COVID-19 related diagnoses and deaths are reported in Table 3. Specifically, there were 50 COVID-19 deaths based on ICD-10 code U071, which were potentially associated with 9.1% of all deaths in our study population. However, the number could be higher when considering any suspicion of a coronavirus infection, and/or contact or exposure to COVID-19 as reported in Table 3. Based on the limited number of diagnoses of COVID-19, further analyses specific to COVID-19 were not attainable.

Discussion

The purpose of this study was to examine and describe the separate and combined effects of loneliness and social isolation on all-cause mortality in a large sample of U.S. older adults. Greater all-cause mortality risks were observed among participants experiencing either loneliness or social isolation. Specifically, moderate, and severe loneliness and moderate and limited social networks were both associated with all-cause mortality in separate, adjusted Cox regression models. When modeled together, severe loneliness and limited and moderate social networks remained significantly associated

with mortality, with limited social networks demonstrating twice the risk of all-cause mortality as compared to those with a diverse social network. These findings are consistent with previous research including a 2013 study demonstrating that social isolation was the stronger predictor of all-cause mortality risk in older adults as compared to loneliness (Steptoe et al., 2013). However, in this study, severe loneliness remained significant after controlling for both constructs in the same model along with other covariates. This result signals that it is important for interventions targeting social connection to consider both the loneliness and social isolation components in order to prevent mortality in older adults.

The findings of this study contribute to the limited number of studies that have identified social isolation as a strong contributor to increased risk of mortality when adjusting for loneliness; however, the full impact of loneliness is still not clear. In a large sample of middle-aged and older adults in Germany, Beller and Wagner found an interaction between loneliness and social isolation. The higher the social isolation, the larger the effect of loneliness on mortality; this in turn led to higher levels of loneliness, which had a larger effect of social isolation (Beller & Wagner, 2018). Hakulinen and colleagues in the UK Biobank study found a significant association between social isolation and mortality (Hakulinen et al., 2018). However, their study did not find this association for loneliness and did not focus on older adults including ages 40 to 69. Therefore, it may not be reflective of the general older adult population, and not individuals living in the U.S.

The findings in this study demonstrate that social isolation and loneliness predict mortality over a three-year period. The three-year period included the COVID-19 pandemic as a catastrophic event that caused several negative physical and psychological health outcomes. However, we were unable to identify a significant prevalence of mortality rates due to COVID-19 to include in this analysis. We are aware that loneliness rates increased for many older adults (Ungar et al., 2021). Therefore, studies such as these, that emphasize the importance of social relationships, are vital during uncertain times.

This study contributes to literature in this area suggesting that having poor social relationships or a lack of relationships is as strong a risk factor for poor health outcomes as smoking, heart disease, obesity, and lack of physical activity (House et al., 1988; NASEM 2020). Further, the introduction of another stressor and risk factor, such as a global pandemic, only compounds the immediate need to address loneliness and social isolation among those who are most vulnerable.

Recommendations to address loneliness and social isolation include programs to improve social skills, enhance social support, increase opportunities for social interactions, and treatment to address maladaptive social cognition (Cacioppo et al. 2015; Dilip et al., 2020; Perissinotto et al. 2019). For instance, efforts to address loneliness and social isolation through mindfulness strategies have been attempted, demonstrating in some cases that individuals who receive mindfulness training subsequently report reduced loneliness (Gilmartin et al., 2017; Lindsay et al., 2019; Tkatch et al., 2017). That said, the most effective interventions for social isolation have involved those rooted in some theory, group and activity-based, utilizes existing community resources, and targets specific populations (NASEM 2020; Dickens et al., 2011). As for loneliness, interventions that address maladaptive thinking appear to be the most effective (Masi et al., 2011; NASEM 2020). However, all strategies that address loneliness and social isolation still warrant further investigation. One focal point for researchers could be examining how technology could be leveraged to better connect older adults (Barbosa et al., 2019). For instance, a recent study found that online mindfulness sessions were beneficial in reducing perceived stress, anxiety, and loneliness in a sample of older adults (Tkatch et al., 2017). Future interventions that counterbalance physical restrictions to interact with others could be important in addressing loneliness and social isolation for years to come. Lastly, the impact cultural backgrounds have on the effects of social connection constructs such as loneliness should also be considered. Studies have shown stronger effects of loneliness on health observed in collectivistic countries as compared to individualistic countries such as in the U.S. (Beller & Wagner, 2020).

Limitations of this study include the population of AARP Medicare Supplement insureds, which may not generalize to all older adults or other Medicare Supplement members in the U.S. Although this study utilized a randomized sampling methodology including assessment of respondents and non-respondents, unaccounted bias may still exist. In addition, survey data was based on a low response rate, and potential vulnerability to unaccounted selection bias. That said, our response rate of 27% is comparable and not uncommon in mailed surveys conducted among older adults (Edelman et al., 2013). Yet another limitation is a full assessment of depression, which has been found to be highly associated with both constructs, was not used for this study. In this study, self-reported depression was assessed using the PHQ-2 (Kroenke et al., 2003). However, it was not included as a cofounder in our analysis due to the high correlation ($r = 0.7–0.8$) with loneliness scores. Additionally, the use of zip-code-based median household income, may not be the best proxy of socioeconomic status, and have the potential risk of measurement error. For instance, people with high income could live in a low-income zip-code. Other limitations include the metrics capturing loneliness and social isolation. Although, the ULCA-3 Loneliness Scale and the SNI have been validated and successfully used in many studies, there is potential for misclassification bias due to the nature of the survey questions and recall bias by study participants. Further, classification of participants into specific groups and altering those classifications of loneliness or social isolation could impact the magnitude of associations. Future analyses could explore different cut points and continuous metrics.

Finally, while all-cause mortality provides the most compelling evidence of the impact of social isolation and potentially loneliness, these two factors are also associated with the elevation of certain specific major causes of death (NASEM 2020). Despite significant evidence that supports an association between social isolation, loneliness, and other social connection measures and risk of mortality, there is not necessarily a causal association without the absence of randomized control trials or experiments.

Despite these limitations, the numerous strengths of this study include the use of a large random sample of older adults in the U.S., as compared to similar studies performed in other countries (NASEM 2020). In addition, this research provides assessment of both loneliness and social isolation in one analysis, utilizing robust data encompassing both psychosocial and claims-based measures. As such, this study adds to the growing evidence on the importance of maintaining strong social connections to support better health outcomes within older age groups. Finally, this study was conducted during the COVID-19 pandemic and highlights the impact reported loneliness and social isolation can potentially have on death risk.

Conclusions

Since early 2020, the COVID-19 pandemic has highlighted the importance and value of social connections, especially among older adults (Holt-Lunstad, 2020). As well-established factors in quality of life and health outcomes later in life, both loneliness and social isolation have shown to be major health risks in the research literature over time. However, with restricted interactions and social distancing regulations during the pandemic, increased loneliness and social isolation among at-risk older adults have become more urgent (Wu, 2020). This study sought to examine both the separate and combined effects of loneliness and social isolation on all-cause mortality in a large sample of U.S. older adults. Previous research had not explored the impacts of loneliness and social isolation in combination directly on outcomes related to all-cause mortality in a broad older population specific to the U.S. Thus, these results are a significant contribution to what is known about these factors and their impacts on mortality among older adults. It was expected that the combination of loneliness and social isolation would increase the risk for mortality and that social isolation likely would be the strongest indicator of all-cause mortality. Our findings confirmed these expectations. That said, efforts that address both should be explored in future interventions. These results contribute to the loneliness and social isolation research landscape and emphasize the importance to develop and support efforts to improve social connections among older adults.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Timothy L. Barnes https://orcid.org/0000-0003-1428-4609
Stephanie MacLeod https://orcid.org/0000-0003-2490-8948

References

Aung, M. N., Moolphate, S., Aung, T. N., Katonyoo, C., Khamchai, S., & Wannakrairot, P. (2016). The social network index and its relation to later-life depression among the elderly aged 80 years in Northern Thailand. *Clinical Interventions in Aging*, *2016*(11), 1067–1074. https://doi.org/10.2147/CIA.S108974

Barbosa Neves, B., Franz, R., Judges, R., Beermann, C., & Baecker, R. (2019). Can digital technology enhance social connectedness among older adults? A feasibility study. *Journal of Applied Gerontology*, *38*(1), 49–72. https://doi.org/10.1177/0733464817741369

Barnes, T. L., MacLeod, S., Tkatch, R., Ahuja, M., Albright, L., Schaeffer, J. A., & Yeh, C. S. (2021). Cumulative effect of loneliness and social isolation on health outcomes among older adults. *Aging & Mental Health*, 1–8. https://doi.org/10.1080/13607863.2021.1940096

Barth, J., Schneider, S., & von Känel, R. (2010). Lack of social support in the etiology and the prognosis of coronary heart disease: A systematic review and meta-analysis. *Psychosomatic Medicine*, *72*(3), 229–238. https://doi.org/10.1097/PSY.0b013e3181d01611

Bassuk, S. S., Glass, T. A., & Berkman, L. F. (1999). Social disengagement and incident cognitive decline in community-dwelling elderly persons. *Annals of Internal Medicine*, *131*(3), 165–173. htttps://doi.org/10.7326/0003-4819-131-3-199908030-00002

Beller, J., & Wagner, A. (2018). Loneliness, social isolation, their synergistic interaction, and mortality. *Health Psychology*, *37*(9), 808–813. https://doi.org/10.1037/hea0000605

Beller, J., & Wagner, A. (2020). Loneliness and Health: The moderating effect of cross-cultural individualism/collectivism. *Journal of Aging and Health*, *32*(10), 1516–1527. https://doi.org/10.1177/0898264320943336

Berg-Weger, M., & Morley, J. E. (2020). Loneliness and social isolation in older adults during the COVID-19 Pandemic: Implications for gerontological social work. *The Journal of Nutrition, Health & Aging*, *24*(5), 456–458. https://doi.org/10.1007/s12603-020-1366-8

Berkman, L. F., & Syme, S. L. (1979). Social networks, host resistance, and mortality: A nine-year follow-up study of Alameda county residents. *American Journal of Epidemiology*, *109*(2), 186–204. https://doi.org/10.1093/oxfordjournals.aje.a112674

Beutel, M. E., Klein, E. M., Brähler, E., Reiner, I., Jünger, C., Michal, M., Wiltink, J., Wild, P. S., Münzel, T., Lackner, K. J., & Tibubos, A. N. (2017). Loneliness in the general population: Prevalence, determinants and relations to mental health. *BMC Psychiatry*, *17*(1), 97. https://doi.org/10.1186/s12888-017-1262-x

Cacioppo, J. T., Hawkley, L. C., Crawford, L. E., Ernst, J. M., Burleson, M. H., Kowalewski, R. B., Malarkey, W. B., Van

Cauter, E., & Berntson, G. G. (2002 May-Jun). Loneliness and health: Potential mechanisms. *Psychosomatic Medicine*, *64*(3), 407–417. https://doi.org/10.1097/00006842-200205000-00005

Cacioppo, S., Grippo, A. J., London, S., Goossens, L., & Cacioppo, J. T. (2015). Loneliness: Clinical import and interventions. *Perspect Psychol Sci*, *10*(2), 238–249. https://doi.org/10.1177/1745691615570616

Centers for Disease Control and Prevention (CDC). (2021). *ICD-10-CM official guidelines for coding and reporting FY 2021–UPDATED January 1, 2021*." October 1, 2020 – September 30, 2021. https://www.cdc.gov/nchs/data/icd/ICD-10cmguidelines-FY2021-COVID-update-January-2021-508.pdf

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Disease*, *40*(5), 373–383. https://doi.org/10.1016/0021-9681(87)90171-8

Cornwell, E. Y., & Waite, L. J. (2009). Social disconnectedness, perceived isolation, and health among older adults. *Journal of Health and Social Behavior*, *50*(1), 31–48. https://doi.org/10.1177/002214650905000103

Cudjoe, T. K. M., Roth, D. L., Szanton, S. L., Wolff, J. L., Boyd, C. M., & Thorpe, R. J. Jr. (2020). The epidemiology of social isolation: National health and aging trends study. *Journals of Gerontology. Series B: Psychological Sciences and Social Sciences*, *75*(1), 107–113. https://doi.org/10.1093/geronb/gby037

Dickens, A. P., Richards, S. H., Greaves, C. J., & Campbell, J. L. (2011). Interventions targeting social isolation in older people: A systematic review. *BMC Public Health*, *11*, 647. https://doi.org/10.1186/1471-2458-11-647

Dilip, J.V., Ellen, L.E., & Cacioppo, S. (2020). Battling the modern behavioral epidemic of loneliness: Suggestions for research and interventions. *JAMA Psychiatry*, *77*(6), 553–554. https://doi.org/10.1001/jamapsychiatry.2020.0027

Drageset, J., Eide, G. E., Kirkevold, M., & Ranhoff, A. H. (2013). Emotional loneliness is associated with mortality among mentally intact nursing home residents with and without cancer: A five-year follow-up study. *Journal of Clinical Nursing*, *22*(1–2), 106–114. https://doi.org/10.1111/j.1365-2702.2012.04209.x

Edelman, L. S., Yang, R., Guymon, M., & Olson, L. M. (2013 Jul-Aug). Survey methods and response rates among rural community dwelling older adults. *Nursing Research*, *62*(4), 286–291. https://doi.org/10.1097/NNR.0b013e3182987b32

Gilmartin, H., Goyal, A., Hamati, M. C., Mann, J., Saint, S., & Chopra, V. (2017). Brief mindfulness practices for healthcare providers—A systematic literature review. *The American Journal of Medicine*, *130*(10), 1219.e1–1219.e17. https//doi.org/10.1016/j.amjmed.2017.05.041

Grambsch, P. M., & Therneau, T. M. (1994). Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*, *81*(3), 515–526. https://doi.org/10.1093/biomet/81.3.515

Grant, N., Hamer, M., & Steptoe, A. (2009). Social isolation and stress-related cardiovascular, lipid, and cortisol responses. *Annals of Behavioral Medicine*, *37*(1), 29–37. https://doi.org/10.1007/s12160-009-9081-z

Gundlapalli, A. V., Lavery, A. M., Boehmer, T. K., Beach, M. J., Walke, H. T., Sutton, P. D., & Anderson, R. N. (2021). Death certificate-based ICD-10 diagnosis codes for COVID-19 mortality surveillance-United States, January-December 2020. *MMWR. Morbidity and mortality Weekly Report*, *70*(14), 523–527. https://doi.org/10.15585/mmwr.mm7014e2

Hackett, R. A., Hamer, M., Endrighi, R., Brydon, L., & Steptoe, A. (2012). Loneliness and stress-related inflammatory and neuroendocrine responses in older men and women. *Psychoneuroendocrinology*, *37*(11), 1801–1809. https://doi.org/10.1016/j.psyneuen.2012.03.016

Hakulinen, C., Pulkki-Råback, L., Virtanen, M., Jokela, M., Kivimäki, M., & Elovainio, M. (2018). Social isolation and loneliness as risk factors for myocardial infarction, stroke and mortality: UK Biobank cohort study of 479,054 men and women. *Heart*, *104*(18), 1536–1542. https://doi.org/10.1136/heartjnl-2017-312663

Hawkley, L. C., Thisted, R. A., Masi, C. M., & Cacioppo, J. T. (2010). Loneliness predicts increased blood pressure: 5-year cross-lagged analyses in middle-aged and older adults. *Psychology and Aging*, *25*(1), 132–141. https://doi.org/10.1037/a0017805

Heffner, K. L., Waring, M. E., Roberts, M. B., Eaton, C. B., & Gramling, R. (2011). Social isolation, c-reactive protein, and coronary heart disease mortality among community-dwelling adults. *Social Science & Medicine*, *72*(9), 1482–1488. https://doi.org/10.1016/j.socscimed.2011.03.016

Holt-Lunstad, J. (2020 June 22). *The double pandemic of social isolation and COVID-19: Cross-sector policy must address both, health affairs blog*. https://www.healthaffairs.org/do/10.1377/hblog20200609.53823/full/

Holt-Lunstad, J., Robles, T. F., & Sbarra, D. A. (2017). Advancing social connection as a public health priority in the United States. *American Psychologist*, *72*(6), 517–530. https://doi.org/10.1037/amp0000103

Holt-Lunstad, J., Smith, T. B., Baker, M., Harris, T., & Stephenson, D. D. (2015). Loneliness and social isolation as risk factors for mortality: A meta-analytic review. *Perspectives on Psychological Science*, *10*(2), 227–237. https://doi.org/10.1177/1745691614568352

Holt-Lunstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: A metanalytic review. *PLOS Medicine*, *7*(7), Article e1000316. https://doi.org/10.1371/journal.pmed.1000316

House, J. S., Landis, K. R., & Umberson, D. (1988). Social relationships and health. *Science*, *241*(4865), 540–545. https://doi.org/10.1126/science.3399889

Hughes, M. E., Waite, L. J., Hawkley, L. C., & Cacioppo, J. T. (2004). A short scale for measuring loneliness in large surveys: Results form two population-based studies. *Research for Aging*, *26*(6), 655–672. https://doi.org/10.1177/0164027504268574

IOM. (2014). *Capturing social and behavioral domains and measures in electronic health records: Phase 2*. The National Academies Press.

Kelly, M. E., Duff, H., Kelly, S., McHugh Power, J. E., Brennan, S., Lawlor, B. A., & Loughrey, D. G. (2017). The impact of social activities, social networks, social support and social relationships on the cognitive functioning of healthy older adults: A systematic review. *Systematic Reviews*, *6*(1), 259. https://doi.org/10.1186/s13643-017-0632-2

Klabunde, C. N., Legler, J. M., Warren, J. L., Baldwin, L. M., & Schrag, D. (2007). A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. *Annals of Epidemiology*, *17*(8), 584–590. https://doi.org/10.1016/j.annepidem.2007.03.011

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2003). The patient health questionnaire-2: Validity of a two-item depression screener. *Medical Care*, *41*(11), 1284–1292. https://doi.org/10.1097/01.MLR.0000093487.78664.3C

Kuiper, J. S., Zuidersma, M., Oude Voshaar, R. C., Zuidema, S. U., van den Heuvel, E. R., Stolk, R. P., & Smidt, N. (2015). Social relationships and risk of dementia: A systematic review and meta-analysis of longitudinal cohort studies. *Ageing Research Reviews*, *22*, 39–57. https://doi.org/10.1016/j.arr.2015.04.006

Lindsay, E. K., Young, S., Brown, K. W., Smyth, J. M., & Creswell, J. D. (2019). Mindfulness training reduces loneliness and increases social contact in a randomized controlled trial. *Proceedings of the National Academy of Sciences*, *116*(9), 3488–3493. https://doi.org/10.1073/pnas.1813588116

Luo, Y., & Waite, L. J. (2014). Loneliness and mortality among older adults in China. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *69*(4), 633–645. https://doi.org/10.1093/geronb/gbu007.

Luo, Y., Hawkley, L. C., Waite, L. J., & Cacioppo, J. T. (2012). Loneliness, health, and mortality in old age: A national longitudinal study. *Social Science & Medicine 74*(6):907–914.

MacLeod, S., Kraemer, S., Tkatch, R., Fellows, A., Albright, L., McGinn, M., Schaeffer, J., & Yeh, C.S. (2021). Defining the personal determinants of health for older adults. *Journal of Behavioral Health*, *10*(1), 1–6.

MacLeod, S., Musich, S., Parikh, R.B., Hawkins, K., Keown, K., & Yeh, C.S. (2018). Examining approaches to address loneliness and social isolation among older adults. *J Aging Geriatr Med*, *2*(1), 1–8. https://doi.org/10.4172/2576-3946.1000115

Masi, C. M., Chen, H. Y., Hawkley, L. C., & Cacioppo, J. T. (2011). A metaanalysis of interventions to reduce loneliness. *Personality and Social Psychology Review*, *15*(3), 219–266. https://doi.org/10.1177/1088868310377394

McCall, N., & Cromwell, J. (2011). Results of the medicare health support disease-management pilot program. *The New England Journal of Medicine*, *365*(18), 1704–1712. https://doi.org/10.1056/NEJMsa1011785

Musich, S., Wang, S. S., Hawkins, K., & Yeh, C. S. (2015 Jan-Dec). The impact of loneliness on quality of life and patient satisfaction among older, sicker adults. *Gerontology and Geriatric Medicine*, *6*(1), 2333721415582119. https://doi.org/10.1177/2333721415582119

Musich, S., Wang, S.S., Slindee, L., Krawemer, S., & Yeh, C.S. (2019). Association of resilience and social networks with pain outcomes among older adults. *Population Health Management*, *22*(6), 511–521. https://doi.org/10.1089/pop.2018.0199

National Academies of Sciences Engineering, and medicine, NASEM. (2020). *Social isolation and loneliness in older adults: Opportunities for the health care system*. The National Academies Press. https://doi.org/10.17226/25663

Ong, A. D., Uchino, B. N., & Wethington, E. (2016). Loneliness and health in older adults: A mini-review and synthesis. *Gerontology*, *62*(4), 443–449. https://doi.org/10.1159/000441651

Penninkilampi, R., Casey, A. N., Singh, M. F., & Brodaty, H. H. (2018). The association between social engagement, loneliness, and risk of dementia: A systematic review and meta-analysis. *Journal of Alzheimer's Disease*, *66*(4), 1619–1633. https://doi.org/10.3233/JAD-180439

Perissinotto, C., Holt-Lunstad, J., Periyakoil, V. S., & Covinsky, K. (2019). A practical approach to assessing and mitigating loneliness and isolation in older adults. *Journal of the American Geriatrics Society*, *67*(4), 657–662. https://doi.org/10.1111/jgs.15746

Perissinotto, C. M., Stijacic Cenzer, I., & Covinsky, K. E. (2012). Loneliness in older persons: A predictor of functional decline and death. *Archives Internal Medicine*, *172*(14), 1078–1083. https://doi.org/10.1001/archinternmed.2012.1993

Pope, G.C., Kautter, J., Ingber, M.J., Freeman, S., Sekar, R., & Newhart, C. (2011). *Evaluation of the CMS-HCC risk adjustment model: Final report*. March 2011 www.cms.gov/Medicare/Health-Plans/MedicareAdvtgSpecRateStats/downloads/evaluation_risk_adj_model_2011.pdf

Rico-Uribe, L. A., Caballero, F. F., Martín-María, N., Cabello, M., Ayuso-Mateos, J. L., & Miret, M. (2018). Association of loneliness with all-cause mortality: A meta-analysis. *Plos One*, *13*(1), Article e0190033. https://doi.org/10.1371/journal.pone.0190033

Shankar, A., McMunn, A., Banks, J., & Steptoe, A. (2011). Loneliness, social isolation, and behavioral and biological health indicators in older adults. *Health Psychology*, *30*(4), 377–385. https://doi.org/10.1037/a0022826

Shor, E., & Roelfs, D. J. (2015). Social contact frequency and all-cause mortality: A meta-analysis and meta-regression. *Social Science & Medicine*, *128*, 76–86. https://doi.org/10.1016/j.socscimed.2015.01.010

Steptoe, A., Owen, N., Kunz-Ebrecht, S. R., & Brydon, L. (2004). Loneliness and neuroendocrine, cardiovascular, and inflammatory stress responses in middle-aged men and women. *Psychoneuroendocrinology*, *29*(5), 593–611. https://doi.org/10.1016/S0306-4530(03)00086-6

Steptoe, A., Shankar, A., Demakakos, P., & Wardle, J. (2013). Social isolation, loneliness, and all-cause mortality in older men and women. *Proceedings of the National Academy of Sciences*, *110*(15), 5797–5801. https://doi.org/10.1073/pnas.1219686110

Sundararajan, V., Henderson, T., Perry, C., Muggivan, A., Quan, H., & Ghali, W. A. (2004). New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *Journal of Clinical Epidemiology*, *57*(12), 1288–1294. https://doi.org/10.1016/j.jclinepi.2004.03.012

Tanskanen, J., & Anttila, T. (2016). A prospective study of social isolation, loneliness, and mortality in Finland. *American Journal of Public Health*, *106*(11), 2042–2048. https://doi.org/10.2105/AJPH.2016.303431

Tkatch, R., Bazarko, D., Musich, S., Wu, L., MacLeod, S., Keown, K., Hawkins, K., & Wicker, E. (2017). A pilot online mindfulness intervention to decrease caregiver burden and improve psychological well-being. *Journal of Evidence-Based Complementary & Alternative Medicine*, *22*(4), 736–743. https://doi.org/10.1177/2156587217737204

Ungar, R., Wu, L., MacLeod, S., Tkatch, R., Kraemer, S., Huang, J., Schaeffer, J., & Yeh, C. (2021). The impact of COVID-19 on older adults: Results from an annual survey. *Geriatr Nurs*, *31*(44), 131–136.

World Health Organization (WHO). (2021). *Social determinants of health*. https://www.who.int/social_determinants/en

Wu, B. (2020). Social isolation and loneliness among older adults in the context of COVID-19: A global challenge. *Global Health Research and Policy*, *5*(1), 27. https://doi.org/10.1186/s41256-020-00154-3