Social Science & Medicine 209 (2018) 174–181

Contents lists available at ScienceDirect

Social Science & Medicine

journal homepage: www.elsevier.com/locate/socscimed

Loneliness in middle age and biomarkers of systemic inflammation: Findings from Midlife in the United States

Paula V. Nersesian[a,*], Hae-Ra Han[a], Gayane Yenokyan[b], Roger S. Blumenthal[c], Marie T. Nolan[a], Melissa D. Hladek[a], Sarah L. Szanton[a,b]

[a] Johns Hopkins School of Nursing, 525 N. Wolfe St., Baltimore, MD 21205, USA
[b] Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St., Baltimore, MD 21205, USA
[c] Johns Hopkins School of Medicine, 733 N. Broadway, Baltimore, MD 21205, USA

ARTICLE INFO

Keywords:
Loneliness
Middle age
Systemic inflammation
Interleukin-6
Fibrinogen
C-reactive protein

ABSTRACT

Objective: Middle-aged adults who are lonely have an elevated likelihood of death. Systemic inflammation may contribute to these increased odds. Using population-level data, this study tested if systemic inflammation is associated with loneliness in a broad age range of middle-aged adults in the United States.
Methods: This study used data from the Midlife in the US (MIDUS) survey Biomarker Project, which collected data on psychological, social, and physiological measures from a sample of middle-aged adults. This sample included the 927 participants who were 35–64 years at Biomarker Project data collection. MIDUS collected baseline data from 1995-1996 and a follow-up survey was conducted from 2004-2006. The baseline Milwaukee sample of African Americans was collected in 2005–2006 and the biomarker database was collected in 2004–2009. Biomarkers were obtained from a fasting blood sample. Self-reported loneliness was categorized as feeling lonely or not feeling lonely. Hierarchical regressions examined the association between biomarkers of systemic inflammation (interleukin-6, fibrinogen, C-reactive protein) and feeling lonely, adjusted for covariates.
Results: Twenty-nine percent of the sample reported feeling lonely most or some of the time. There was a positive significant relationship between loneliness and the three systemic inflammation biomarkers after controlling for covariates: interleukin-6 ($n = 873$) (b [se] = 0.07 [0.03], $p = .014$); fibrinogen ($n = 867$) (b [se] = 18.24 [7.12], $p = .011$); and C-reactive protein ($n = 867$) (b [se] = 0.08 [0.04], $p = .035$).
Conclusions: Feeling lonely is associated with systemic inflammation in middle-aged community-dwelling US adults.

1. Introduction

Loneliness is a complex emotional state linked to individual perceptions of one's social relationships; prevalence estimates range from 7% to 39% among community-dwelling adults from the United States (US) and Europe (Savikko et al., 2005; Shiovitz-Ezra and Leitsch, 2010; Theeke, 2010; Victor et al., 2005). The feeling of loneliness is subjective and quite distinct from social isolation, which is an objective measure (Holt-Lunstad et al., 2010). Substantial research reflects the importance of loneliness as a psychosocial factor that influences individual human experience and societies (Cohen-Mansfield et al., 2015; Ong et al., 2016). At an individual level, loneliness in older adults is linked with functional decline (Luo et al., 2012; Theeke et al., 2016a), and adverse physical and emotional conditions such as elevated blood pressure (Hawkley et al., 2006; Sorkin et al., 2002; Yang et al., 2014), depression (Cacioppo et al., 2010; Jaremka et al., 2014), and even death (Holt-Lunstad et al., 2015, 2010; Holt-Lunstad and Smith, 2016). The health risks of loneliness are comparable to smoking about 15 cigarettes per day (Cacioppo and Hawkley, 2003; Hawkley et al., 2003; House et al., 1988; Shavelle et al., 2008). At a societal level, health systems are strained by excess health services utilization by people who feel lonely (Gerst-Emerson and Jayawardhana, 2015), costing the public sector an additional $15,000 (£12,000) per person over 15 years (Fulton and Jupp, 2015).

While people can feel lonely at any age (Shankar et al., 2011), middle age is a period of life when people face numerous challenges in

Abbreviations: BMI, body mass index; CES-D, Center for Epidemiological Studies Depression Scale; CRP, C-reactive protein; CVD, cardiovascular disease; IL-6, Interleukin-6; MIDUS, Midlife in the United States; US, United States

* Corresponding author. 525 N. Wolfe St., Baltimore, MD 21205, USA.
E-mail addresses: pnersesian@jhu.edu (P.V. Nersesian), hhan2@jhu.edu (H.-R. Han), gyenoky1@jhu.edu (G. Yenokyan), rblument@jhmi.edu (R.S. Blumenthal), mnolan3@jhu.edu (M.T. Nolan), mhladek1@jhu.edu (M.D. Hladek), sszanto1@jhu.edu (S.L. Szanton).

https://doi.org/10.1016/j.socscimed.2018.04.007
Received 20 June 2017; Received in revised form 15 March 2018; Accepted 5 April 2018
Available online 30 April 2018
0277-9536/

their social relationships due to shifts in family structure, progression or changes in one's occupation, and changes in health status. These challenges expose middle-aged adults to multiple stressors over many decades (Antonucci et al., 2001) and can have serious consequences. For example, a recent meta-analysis found higher odds of all-cause mortality among lonely middle-aged adults than lonely older adults (Holt-Lunstad et al., 2015). Middle age is also a time of life when the risk of developing cardiovascular disease (CVD) is high (Mozaffarian et al., 2015). Indeed, loneliness has been linked to poor cardiovascular outcomes in studies of young adults and older middle-aged people. For example, associations were found between higher total peripheral resistance, lower cardiac output, and elevated blood pressure in these groups (Hawkley et al., 2006, 2003). Studies that included middle-aged adults have also found poor social relationships (loneliness and social isolation) to be risk factors for coronary heart disease and stroke (Thurston and Kubzansky, 2009; Valtorta et al., 2016). Nevertheless, younger middle-aged adults (35–50 years old) are less often included in such studies, and therefore these findings cannot be generalized to the middle age group as a whole.

One mechanism linking loneliness and negative cardiovascular outcomes is dysregulation of the inflammatory response (Cacioppo et al., 2011; Cole et al., 2015). Interleukin-6 (IL-6), fibrinogen, and C-reactive protein (CRP) are recognized as key biomarkers of systemic inflammation associated with cardiovascular events (Danesh and Fibrinogen Studies Collaboration, 2005; Kannel et al., 2012; McManus et al., 2013). Although gene expression studies have established a connection between loneliness and a dysregulated inflammatory response (Cole et al., 2007), investigations of the relationship between loneliness and circulating markers of systemic inflammation implicated in CVD have yielded inconsistent findings. For example, analyses from the United States and Great Britain showed no relationship between loneliness and CRP or loneliness and fibrinogen (McDade et al., 2006; Mezuk et al., 2016; Shankar et al., 2011). However, Cole's examination of circulating CRP among 14 study participants in his gene expression study showed CRP levels to be twice as high in high lonely participants compared to low lonely participants (Cole et al., 2007). In studies that applied an acute stressor to participants in a laboratory setting, a significant relationship was found between loneliness and elevated fibrinogen and loneliness and IL-6 levels (Hackett et al., 2012; Jaremka et al., 2013; Steptoe et al., 2004). The multiple roles assumed by middle age adults can generate stress as the opportunities and demands of this life stage build. Some people may embrace the demands from a positive standpoint, while others may become stressed and overwhelmed (Antonucci et al., 2001). Using a biopsychosocial model allows biological, psychological, and social factors to be considered in an integrated manner when analyzing health outcomes (Johnson and Acabchuk, 2018). Examining loneliness and inflammation in middle age through this lens offers a unique opportunity to consider stressors and health indicators in an understudied group.

Given the prevalence of loneliness, the ongoing challenges, demands and stress in middle age, and negative cardiovascular outcomes associated with systemic inflammation, the aim of this study was to examine the association between loneliness and biomarkers of systemic inflammation among a nationwide sample of 35 to 64-year-old participants in MIDUS. It was hypothesized that loneliness would be associated with elevated biomarker values for IL-6, fibrinogen, and CRP.

2. Methods

2.1. Sample

The data for this analysis were drawn from a nationwide sample of participants from the Biomarker Project, a special study of the MIDUS survey. The baseline MIDUS sample enrolled non-institutionalized middle-aged and older adults in the coterminous United States through random digit dialing from 1995 to 1996 ($N = 7108$) (Dienberg Love et al., 2010). A follow-up survey was conducted 10 years later from 2004-2009 ($N = 4963$). A sample of African Americans from Milwaukee was enrolled in 2005 and 2006 ($N = 592$). These surveys collected information through telephone interviews and self-administered questionnaires (Radler, 2014). The Biomarker Project sample ($n = 1255$) was drawn from the baseline MIDUS and Milwaukee samples. Data were collected in 2004–2009 during a two-day visit at three clinical research sites: University of Wisconsin, Madison; University of California, Los Angeles; and Georgetown University, Washington, D.C. (Brim et al., 2011; Radler, 2014; Ryff et al., 2012, 2013).

For this study, data from 927 participants age 35–64 years at the time of Biomarker Project data collection was used. MIDUS recruited siblings and twins as part of the survey design, and this sample includes 115 family clusters. Data on demographic, psychosocial, and physical health factors, and systemic inflammation biomarker values required for this analysis were drawn from: MIDUS baseline, MIDUS follow-up, the Milwaukee sample, and the Biomarker Project. Biological samples (blood) and clinical measures were collected during the Biomarker Project. An analysis of missing data showed that 92% of the records were complete.

Most of the MIDUS data are publicly available through the ICPSR data repository (https://www.icpsr.umich.edu/) (Radler, 2014). However, a data use agreement is required for the Milwaukee data, given the geographically circumscribed area of sampling and given that, an agreement was executed. Details regarding the Biomarker Project biological specimens and the self-administered questionnaires, which include psychometric scales, are reported elsewhere (Ryff et al., 2012, 2011, 2010). The institutional review board at the University of Wisconsin, Madison approved MIDUS data collection procedures. Institutional review boards at clinical data collection sites approved the substudy, and each participant provided written informed consent.

2.2. Measures

Loneliness. Loneliness was measured using a single item included in the Center for Epidemiological Studies Depression Scale (CES-D): “During the past week, I felt lonely …” The respondent then chose among four ordinal responses: rarely or none of the time, some or a little of the time, occasionally, and most or all of the time (Radloff, 1977). As in prior studies (O'Luanaigh et al., 2012; Routasalo et al., 2006), answers of “rarely or none of the time” were classified as not feeling lonely and responses in any of the other three categories were classified as feeling lonely. To explain why, the distribution across the four responses was skewed toward lower levels of loneliness, and those who indicated that they were rarely lonely were seen as qualitatively different from those who reported higher levels of loneliness. A small number of respondents ($n = 32$) reported feeling lonely “most or all of the time,” so this variable was dichotomized into rarely or none of the time versus some, a little, and most or all of the time. The one-item measure of loneliness from the CES-D is an adequate measure for this study. AARP's recent study on loneliness in adults 45 years and older used both the UCLA Loneliness Scale and a single item measure, which the AARP Research Analyst reported to be highly correlated in their study ($r = .735$, $p < .001$) (AARP, 2010). Furthermore, an analysis comparing the CES-D single item and the three-item scale based on the UCLA Loneliness scale demonstrated that the CES-D single-item was a sensitive measure (Shiovitz-Ezra and Ayalon, 2012). No difference was found in self-identified loneliness by gender, which has been reported elsewhere (Borys and Perlman, 1985; Hawkley et al., 2008).

Systemic Inflammation. Three pro-inflammatory cytokines—IL-6, fibrinogen, and CRP—served as the measures of systemic inflammation. Among them, CRP is the only marker widely used in clinical practice when evaluating cardiovascular and inflammatory diseases (Varadhan et al., 2014). Fibrinogen is also used as a clinical marker for cardiovascular-related conditions (Goto, 2008). Although IL-6 has both pro- and anti-inflammatory characteristics, most research identifies

Table 1
Assay ranges for biomarkers of systemic inflammation.

Assay	Assay Range[a]	Cut-point of clinical significance[b]
IL-6	0.156–10 pg/mL12 minimum value 0.156 pg/mL	> 5 pg/mL
Fibrinogen	60-1200 mg/dL	Males: 200–375 mg/dL Females: 200–430 mg/dL
CRP	0.0175–110 mg/dL minimum value 0.015 mg/dL	≥ 2 mg/dL

Note. pg = picograms. mL = milliliters. dL = deciliters.
[a] Biomarker Project, 2004–2009 Blood, Urine, and Saliva Data (Ryff et al., 2011).
[b] Mayo Medical Laboratories (2017).

significant rises in anti-inflammatory IL-6 during and immediately after exercise (Woods et al., 2012). Thus, for this study, high values of these biomarkers were interpreted as a reflection of an increased pro-inflammatory state (Coe et al., 2011). Blood samples were drawn after fasting on day 2 according to protocol at all sites. Ten participants (5.8%) were missing IL-6 data, and 17 participants (6.5%) were missing data for fibrinogen and CRP. IL-6 was assayed using blood serum at the MIDUS Biocore Lab at the University of Wisconsin, Madison, and fibrinogen and CRP were assayed using blood plasma at the Laboratory for Clinical Biochemistry Research at the University of Vermont, Burlington. CRP values of < 0.15 μg/dL or < 0.16 μg/dL were adjusted to 0.14 μg/dL by the MIDUS investigators to account for extremely low values. Table 1 summarizes assay ranges for the systemic inflammation biomarkers and cut-points of clinical significance (Ryff et al., 2011).

Covariates. Covariates were obtained from MIDUS baseline, MIDUS follow-up, the Milwaukee sample, and the Biomarker Project and included those that have been shown in prior research to influence loneliness and inflammation. The demographic variables included in the model were: age, sex, race (white, black, multi-racial/other), and education (up to high school completion and greater than high school) (Abbasi, 2011; Cohen-Mansfield et al., 2016; Valtorta et al., 2016). The psychosocial variables were included in the model due to their associations with loneliness and stress, which influences systemic inflammation (Abbasi, 2011; Hackett et al., 2012; Hensley et al., 2012; Jaremka et al., 2013; Martin et al., 1997). The specific variables included were: a) perceived stress score from Cohen's Perceived Stress Scale (Cohen et al., 1983), b) positive relations with others, a component of Ryff's scale of psychosocial well-being (Ryff, 1989), c) social integration, a component of Keyes' Social well-being scale (Keyes, 1998), d) a social support measure of self-reliance that assesses aversion to asking for help, developed by Lachman for MIDUS (Lachman and Weaver, 1995), and e) married/cohabitating (married or living with someone as if married or not). History of ever having smoked regularly was included due to its inflammatory properties and association with loneliness (Dyal and Valente, 2015).

Physical health measures were included, including number of symptoms or chronic conditions, blood pressure, and body mass index (BMI) due to their established relationships with loneliness and inflammation (Cohen-Mansfield et al., 2015; Hawkley et al., 2010; Martin et al., 1997; Theeke et al., 2016a). Depression and regular exercise were not included as covariates since they were conceptualized as mediators of the relationship between feeling lonely and systemic inflammation. Household income was not included as a covariate because when it was tested as an interaction term with feeling lonely, the result was not significant.

2.3. Statistical analyses

Statistical analyses included descriptive statistics and hierarchical linear regression. The characteristics of the study sample were examined by loneliness status using bivariate analyses. Missing data were assessed. To avoid multicollinearity, one variable was selected when two variables measuring a single construct were highly correlated ($r > 0.60$) (e.g., BMI and waist circumference). The distributions of the three systemic inflammation variables were assessed for normality; IL-6 and CRP were not normally distributed, and they were transformed using natural log, whereas the fibrinogen residuals were nearly normally distributed so transformation was not performed. Hypothesis testing using hierarchical linear regression was conducted to examine the loneliness-inflammation relationship. All tests were evaluated at 0.05 level of statistical significance.

Regression models were run for each of the three systemic inflammation biomarkers. Variable groupings were added in the following order: Model 1—demographic covariates (age, sex, race, and education); Model 2—psychosocial variables (perceived stress, social integration, social support, and positive relations with others); Model 3—health behaviors and physical health measures (history of ever having smoked regularly, regular physical exercise, blood pressure, and BMI). Results are presented as unstandardized beta coefficients.

Mediation analyses were run for depression and regular exercise to examine the conceptual assumption that they serve as mediators of the relationship between feeling lonely and biomarker values of systemic inflammation.

Scatter plots of residuals against fitted values with lowess smoothing lines were constructed to check goodness of fit. The assumptions for hierarchical linear regression were tested: linearity, normal distribution of residuals, and equal variance. Where heteroscedasticity was identified, robust standard errors were estimated using the Huber/White sandwich estimator (Huber, 1967; White, 1980). Because this sample includes siblings, which created potential correlation of outcomes, sandwich estimation was clustered to test for violation of independence of error terms. Sensitivity analyses were conducted to examine outcomes when CRP values were truncated at values ≥ 10 mg/dL to eliminate observations that may represent acute injury or infection and using a narrower definition of middle age (40–64 years). The data were analyzed using Stata 14 (StataCorp, LP, College Station, Texas).

3. Results

Descriptive statistics of the sample appear in Table 2. The mean age for this middle-aged sample was 52 years ($SD = 7.47$) and the prevalence of loneliness was 29%. The lonely versus not lonely groups were significantly different in bivariate analysis on all measures except sex and blood pressure. Correlations among variables can be viewed in the online supplemental materials. A report of feeling lonely was significantly positively correlated with higher stress scores ($r = 0.45$, $p < .001$). There were weaker, yet significant, correlations with number of symptoms and chronic conditions ($r = 0.13$, $p < .001$) and body mass index ($r = 0.12$, $p < .01$). A report of feeling lonely was significantly negatively correlated with positive relations with others ($r = -0.33$, $p < .001$). There were weaker, yet significant, correlations with social integration ($r = -0.26$, $p < .001$) and age ($r = -0.10$, $p < .001$). The three biomarkers of systemic inflammation were all significantly correlated with feeling lonely, and they were also significantly correlated with one another: Log IL-6 and fibrinogen ($r = 0.44$, $p < .001$), Log IL-6 and Log CRP ($r = 0.55$, $p < .001$), and fibrinogen and Log CRP ($r = 0.56$, $p < .001$).

Regression analyses showed that feeling lonely was significantly positively associated with all three biomarkers of systemic inflammation in the unadjusted models: Log IL-6 ($n = 915$) (b [se] = 0.11 [0.02], $p < .001$), fibrinogen ($n = 908$) (b [se] = 23.52 [6.09], $p < .001$), and Log CRP ($n = 908$) (b [se] = 0.14 [0.04], $p < .001$)). It was also true for the fully adjusted models: Log IL-6 ($n = 873$) (b [se] = 0.07 [0.03], $p = .014$) Table 3, fibrinogen ($n = 867$) (b [se] = 18.24 [7.12], $p = .011$) Table 4, and Log CRP ($n = 867$) (b [se] = 0.08 [0.04], $p = .035$) Table 5).

Table 2
Sample characteristics by loneliness status.

Characteristics	Study Sample (n = 927)		Lonely (n = 272)		Not Lonely (n = 652)		p
	M (*SD*)	*N* (%)	*M* (*SD*)	*N* (%)	*M* (*SD*)	*N* (%)	
Demographics							
Age (years)	51.90 (7.47)		50.86 (7.30)		52.35 (7.50)		.006
Sex							
Male		394 (42.50)		116 (42.65)		278 (42.64)	> .99
Female		533 (57.50)		156 (57.35)		374 (57.36)	
Race							
White		674 (75.14)		172 (65.90)		502 (79.30)	< .001†
Black		195 (21.74)		83 (31.80)		110 (17.38)	
Multiracial/Other		28 (3.12)		6 (2.30)		21 (3.32)	
Education							
≤High school		245 (26.46)		90 (33.09)		153 (23.50)	.003
≥Some college		681 (73.54)		182 (66.19)		498 (76.50)	
Psychosocial							
Perceived stress scale score	22.77 (6.52)		27.27 (6.41)		20.91 (5.59)		< .001
Social well-being: Social integration	14.44 (4.22)		12.74 (4.34)		15.16 (3.94)		< .001
Social support:							
Do not ask for help unless have to	1.93 (0.93)		1.76 (0.92)		1.99 (0.92)		< .001
Marital status							
Married or Living with Someone		601 (64.90)		117 (43.01)		484 (74.35)	< .001
Not married or Living with Someone		325 (35.10)		155 (56.99)		167 (25.65)	
Psychological well-being:							
Positive relations with others	16.30 (4.06)		14.33 (2.30)		17.14 (3.63)		< .001
Smoking History							
Ever smoked cigarettes regularly		429 (46.33)		144 (52.94)		282 (43.32)	.008
Never smoked cigarettes regularly		497 (53.67)		128 (47.06)		369 (56.68)	
Physical Health							
Symptoms or chronic conditions							
Any		844 (91.14)		261 (95.96)		580 (89.09)	.001
None		82 (8.86)		11 (4.04)		71 (10.91)	
Number	3.60 (2.76) IQR: 3		4.15 (2.91)		3.36 (2.64)		< .001
Blood pressure							
Systolic	129.13 (17.67)		128.58 (16.68)		129.39 (18.07)		.52
Diastolic	76.65 (10.72)		76.97 (10.52)		76.53 (10.83)		.57
Body mass index	30.05 (7.03)		31.30 (7.82)		29.51 (6.61)		< .001
Overweight: 25.0–29.9		307 (33.19)		64 (23.62)		243 (37.33)	< .001†
Obese: ≥30		398 (43.03)		143 (52.77)		252 (38.71)	
Blood biomarkers							
L-6	2.83 (2.79)		3.49 (3.46)		2.54 (2.39)		< .001
Fibrinogen	344.22 (84.93)		360.35 (90.41)		336.83 (80.91)		< .001
CRP	3.01 (4.48)		3.68 (4.76)		2.63 (3.71)		< .001

Note. p-values obtained from Student's t-test for continuous variables and Pearson's χ^2 for categorical variables. †Fisher's exact for race and body mass index. IQR = Interquartile range, IL-6 = Interleukin-6, CRP = C-reactive protein.

Table 3
Loneliness in simple and multivariable regression for log-transformed IL-6 (n = 873).

Variable	Model 1			Model 2			Model 3		
	b	*p*	95% *CI*	*b*	*p*	95% *CI*	*b*	*p*	95% *CI*
Lonely vs not lonely	.10	< .001	.05, .14	.09	.002	.03, .14	.07	.014	.01, .12
Age (years)	.01	< .001	.00, .01	.01	< .001	.00, .01	.00	.015	.00, .01
Female vs male	.06	.005	.02, .10	.06	.010	.01, .10	.05	.015	.01, .09
Black vs White	.19	< .001	.13, .24	.17	< .001	.12, .23	.11	< .001	.05, .16
Multi-racial/Other vs White	.04	.568	-.10, .19	.04	.591	-.11, .19	.02	.798	-.12, .16
High school graduate or less vs greater than high school	.05	.062	.00, .10	.05	.051	.00, .10	.03	.198	-.02, .08
Perceived stress score				.00	.533	.00, .01	.00	.871	.00, .00
Social integration score				.00	.814	.00, .01	.00	.312	.00, .01
Social support: Self-reliance (not asking for help score)				.01	.549	-.02, .03	.01	.581	-.02, .03
Not married or cohabitating vs married or cohabitating				.03	.218	-.02, .08	.03	.164	-.01, .08
Psychological well-being: Positive relations with others score				.00	.677	-.01, .01	.00	.903	-.01, .01
Ever smoked regularly vs never smoked regularly							.05	.013	.01, .09
Number of symptoms or chronic conditions							.01	.064	.00, .02
Systolic blood pressure (mmHg)							.00	.336	.00, .00
Body mass index (kg/m^2)							.02	< .001	.01, .02

Note. b = unstandardized regression coefficient.

Table 4
Loneliness in simple and multivariable regression for fibrinogen (n = 867).

Variable	Model 1			Model 2			Model 3		
	b	*p*	*95% CI*	*b*	*p*	*95% CI*	*b*	*p*	*95% CI*
Lonely vs not lonely	19.69	.002	7.10, 32.29	22.76	.002	8.26, 37.26	18.24	.011	4.26, 32.21
Age (years)	1.59	< .001	0.89, 2.28	1.49	< .001	0.79, 2.18	1.08	.003	0.37, 1.80
Female vs male	28.34	< .001	18.13, 39.33	28.62	< .001	17.84, 39.41	28.09	< .001	17.36, 38.83
Black vs White	41.89	< .001	27.37, 56.41	42.05	< .001	26.22, 57.87	29.34	< .001	14.25, 44.43
Multi-racial/Other vs White	38.42	.048	0.29, 76.55	38.38	.048	0.25, 76.51	34.04	.074	−3.33, 71.40
High school graduate or less vs greater than high school	10.04	.126	−2.82, 22.90	11.67	.079	−1.34, 24.68	8.01	.214	−4.64, 20.67
Perceived stress score				−0.14	.769	−1.11, 0.82	−0.28	.549	−1.20, 0.64
Social integration score				0.39	.607	−1.09, 1.86	0.75	.303	−0.67, 2.16
Social support: Self- reliance (not asking for help score)				5.92	.039	0.30, 11.55	5.21	.048	0.04, 10.39
Not married or cohabitating vs married or cohabitating				2.78	.683	−10.57, 16.13	3.06	.637	−9.64, 15.75
Psychological well-being: Positive relations with others score				0.39	.625	−1.18, 1.96	0.23	.770	−1.31, 1.77
Ever smoked regularly vs never smoked regularly							4.82	.375	−5.84, 15.48
Number of symptoms or chronic conditions							1.34	.217	−0.79, 3.46
Systolic blood pressure (mmHg)							−0.02	.873	−0.32, 0.27
Body mass index (kg/m^2)							3.37	< .001	2.50, 4.25

Note. b = unstandardized regression coefficient.

Using clustered robust errors to account for potential dependence of outcomes due to familial correlation did not substantially change these results. Sensitivity analyses conducted to examine the association between reporting feeling lonely and CRP values < 10 (values ≥ 10 excluded) showed a non-significant relationship in the fully adjusted model. Sensitivity analysis conducted using a narrower definition of middle age (40–64 years) showed little change in the beta coefficients for IL-6 and fibrinogen, and the relationships remained significant. For CRP, although the beta coefficients changed very little, the fully adjusted model became non-significant; the p-value increased to .055. Neither depression nor regular exercise were shown to be mediators of the relationship between feeling lonely and biomarker values of systemic inflammation.

4. Discussion

A significant positive association emerged between self-report of loneliness and biomarker values of IL-6, fibrinogen, and CRP in a community sample of middle-aged adults in the United States. To our knowledge, this study is the first to examine the association between loneliness in a broad age range of middle-aged community-dwelling US adults and systemic inflammation. Prior studies that included a younger sample (mean age ~50 years) showed significant associations with fibrinogen and IL-6 (Hackett et al., 2012; Jaremka et al., 2013; Steptoe et al., 2004). However, prior studies that included participants on average 10 years older did not show significant relationships between loneliness and systemic inflammation (McDade et al., 2006; Mezuk et al., 2016; Shankar et al., 2011). There are several possible explanations for these findings. Systemic inflammation may be more prevalent among younger middle-aged adults than previously understood, and this may be particularly true in the United States. Independent analyses by Shiels and Case, which demonstrated rising morbidity and mortality among middle-aged Americans due to “diseases of despair” in the time period that coincides with MIDUS data collection for this study (1995–2009), may help explain these findings (Case and Deaton, 2015; Shiels et al., 2017).

Increased systemic inflammation may be an early warning of impending poor health outcomes in middle-age. The concept of “inflammaging” describes chronic systemic inflammation that signals risk for morbidity and mortality (Franceschi and Campisi, 2014; Acabchuk et al., 2017). Given the association between chronic exposure to inflammatory proteins (such as CRP) and clotting factors (such as fibrinogen) and negative cardiovascular outcomes, middle-aged adults with high levels of these circulating biomarkers may be at greater risk for coronary disease, myocardial insufficiency, myocardial infarction (Goto, 2008), and metabolic conditions (Whisman, 2010). The finding of an association between loneliness and increased IL-6, CRP, and fibrinogen values may reflect initiation of inflammaging in

Table 5
Loneliness in simple and multivariable regression for log-transformed CRP (n = 867).

Variable	Model 1			Model 2			Model 3		
	b	*p*	*95% CI*	*b*	*p*	*95% CI*	*b*	*p*	*95% CI*
Lonely vs not lonely	.10	.009	.03, .18	.13	.004	.04, .22	.08	.035	.01, .16
Age (years)	.00	.736	-.00, .01	.00	.958	-.00, .00	-.00	.034	-.01, .00
Female vs male	.16	< .001	.10, .23	.17	< .001	.10, .23	.17	< .001	.11, .23
Black vs White	.20	< .001	.11, .28	.20	< .001	.11, .29	.07	.110	-.02, .15
Multi-racial/Other vs White	.01	.939	-.19, .20	.01	.936	-.19, .20	-.03	.716	-.21, .14
High school graduate or less vs greater than high school	.07	.054	-.00, .15	.08	.040	.00, .16	.04	.305	-.03, .11
Perceived stress score				.00	.258	-.01, .00	-.01	.081	-.01, .00
Social integration score				.00	.880	-.01, .01	.00	.483	-.01, .01
Social support: Self-reliance (not asking for help score)				.02	.247	-.02, .06	.02	.338	-.02, .05
Not married or cohabitating vs married or cohabitating				.01	.851	-.08, .09	.01	.778	-.06, .08
Psychological well-being: Positive relations with others score				.00	.781	-.01, .01	-.00	.870	-.01, .01
Ever smoked regularly vs never smoked regularly							.07	.035	.00, .13
Number of symptoms or chronic conditions							.01	.048	.00, .03
Systolic blood pressure (mmHg)							.00	.131	-.00, .00
Body mass index (kg/m^2)							.03	< .001	.03, .04

Note: b = unstandardized regression coefficient.

this sample. Environmental factors, including slow US economic growth from 2000, which resulted in increased unemployment and underemployment among middle-aged workers, particularly those in the middle earnings group (Hipple, 2015; Ilg, 2001), may have a role in the relationship between loneliness and systemic inflammation.

Exercise is also relevant. Whether participants did or did not exercise regularly (defined in MIDUS as ≥20 min 3 times per week) was eliminated as a potential confounder since loneliness predicts reduced physical activity, and therefore it should not confound the association of loneliness with inflammation (Hawkley and Capitanio, 2015). Instead, physical exercise might act as a mediator, where some of the effect of loneliness on inflammatory markers can be explained by lack of physical exercise. Demands of family and work in middle age may be an obstacle to regular exercise in middle age. In this sample, 30% of lonely participants reported not exercising regularly. For IL-6, higher levels may be the result of its anti-inflammatory properties, not its pro-inflammatory properties. However, participants fasted for this study, and blood was collected in the morning after an overnight stay in a clinical facility. Participants were asked to avoid strenuous activity before the blood draw, so it is unlikely that their IL-6 and CRP levels were influenced by exercise (Ryff et al., 2011). Additionally, the other two biomarkers, which lack anti-inflammatory characteristics, were also significant in a positive direction. These results were significant even when body mass was controlled for. Obesity is known to have an influence on CRP, IL-6, and fibrinogen (Blaha et al., 2011; Ditschuneit et al., 1995). A genetic contribution may also explain some of the variation in IL-6 and CRP levels (Amaral et al., 2015; Kathiresan, 2006).

Feeling lonely was linked with higher fibrinogen and IL-6 values, consistent with prior findings (Hackett et al., 2012; Jaremka et al., 2013; Steptoe et al., 2004). Prior analyses included application of a laboratory-controlled stressor, but this study did not. It may be that multiple stressors of middle age and the changes that occur during middle age supply a continuous dose of stress. In middle age, children grow into adolescence and leave home; aging parents require assistance and support; work demands increase as experience and status advances; and physical changes occur including decreased visual acuity, menopause, wear and tear on the skeletal system, and a decline in muscle mass. The changes of middle age can also be positive as families evolve, careers mature, and involvement in the community activities expands. Either way, changes and challenges in middle age can be viewed as sources of stress. The question remains why this study's positive findings were different from studies which failed to show a significant relationship between loneliness and CRP and fibrinogen (McDade et al., 2006; Mezuk et al., 2016; Shankar et al., 2011). A possible explanation is that their models included outcomes of loneliness, including depression and sleep disturbance, which might have acted as mediators. Some of the effect of loneliness on the biomarkers of inflammation may be explained by including these conditions in the model (Hawkley and Capitanio, 2015). These and other studies also used survey samples; however, the mean age of their participants was about ten years older than our participants, and in one study (Mezuk et al., 2016), the participants were free of cardiovascular disease at enrollment.

4.1. Limitations

The absence of an inflammatory index that can be applied to this dataset is a limitation. An inflammatory index that weights IL-6, CRP and fibrinogen according to their role in the overall pro-inflammatory response, such as the one developed by Varadhan, would add more precision to this analysis (Varadhan et al., 2014). His team developed an index evaluating 15 markers of inflammation, including CRP and IL-6, as potential predictors of all-cause mortality on a sample of 6755 older adults. They found the additive combination of IL-6 and Tumor necrosis factor-alpha receptor 1 (TNF-αR1) was the best predictor, and IL-6 was the best single predictor of all-cause mortality. Morrisette-Thomas used principal component analysis on a sample of 1010 older adults to develop two comprehensive axes of variation in the inflammatory system using 19 inflammatory biomarkers, which allowed for a more nuanced evaluation of pro- and anti-inflammatory activity, co-morbidities, and aging (Morrisette-Thomas et al., 2014). Simons created an index of inflammatory to antiviral cell types using monocytes, natural killer cells, β-cells and T-cells (Simons et al., 2017). Unfortunately, the MIDUS sample did not include TNF-αR1 or other measures of pro- or anti-inflammation that would allow the use of a validated index.

An association in the opposite direction is also a possibility where systemic inflammation affects loneliness, perhaps through advancement of coronary artery disease and the resulting decreased activity, which could limit socialization. This will need to be explored in future studies. Given the cross-sectional nature of this study, causal inferences cannot be made. This study has other limitations. Compared to 2010 US Census Bureau data (the census closest to the conclusion of the Biomarker Project data collection), this sample included more white and black participants and fewer multi-racial participants and those representing other racial groups than reported by the Census (Humes et al., 2011). This sample also contains disproportionately more females than males than the national averages in 2010 (Howden and Meyer, 2011). The single item measure of loneliness in this study could also be considered a limitation, even though single item measures have been used in many studies (Holmén and Furukawa, 2002; Holwerda et al., 2014; Savikko et al., 2005), including the item from the CES-D (O'Luanaigh et al., 2012; Thurston and Kubzansky, 2009). Nevertheless, this simple measure might have underestimated loneliness (Holt-Lunstad et al., 2010). Considering the rapid expansion of social networking (which typically involves self-disclosure) during the period when these data were collected, reluctance to self-identify as lonely may have been declining in the mid-2000s. Further research is required on the measures of loneliness in light of these changes in the US.

5. Conclusions

This study contributes to the body of research on loneliness among an understudied group: middle-aged adults, particularly those in the earlier part of middle age. These results also contribute to knowledge of the relationship between loneliness and a precursor of cardiovascular disease: systemic inflammation. A causal direction could not be ascertained in this cross-sectional study, and more evidence is needed before these findings can be translated into practice. Expanding understanding of the loneliness-inflammation relationship in middle age may inform policy on community-level loneliness interventions and enhance individual care for lonely people in clinical settings. Reducing loneliness has the potential to improve quality of life and physical and mental health outcomes in middle-aged adults. Tests of loneliness interventions have demonstrated some success (Masi et al., 2011; Theeke et al., 2016b). Further research might explore whether existing interventions influence loneliness' relationship with systemic inflammation.

Acknowledgements

This research was supported by the Pre-doctoral Clinical Research Training Program, Grant Number TR001078, awarded by Johns Hopkins Institute for Clinical and Translational Research. Data management was supported through Grant Number 1UL1TR001079 from the National Center for Research Resources and NCATS, NIH; the Interdisciplinary Training in Cardiovascular Health Research grants, 5T32NR012704-04 and 5T32NR012704-03, awarded by Johns Hopkins University School of Nursing under a grant from the National Institute of Nursing Research, NIH; the Jonas Nurse Scholars Program; and the NEF Liesel M. Hiemenz scholarship. The MIDUS 1 study was supported by the John D. and Catherine T. MacArthur Foundation Research

Network on Successful Midlife Development, the MIDUS 2 research was supported by a grant from the National Institute on Aging (P01-AG020166) to conduct a longitudinal follow-up of the MIDUS 1 investigation, and MIDUS biomarker research was further supported by the following grants M01-RR023942 (Georgetown), M01-RR00865 (UCLA) from the General Clinical Research Centers Program and UL1TR000427 (UW) from the NCATS, NIH. Support provided by Chakra Budhathoki, PhD in project development and Gwendolyn Clemens in data management is appreciated.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.socscimed.2018.04.007.

References

AARP, 2010. Loneliness Among Older Adults: a National Survey of Adults 45+. Washington, DC.

Abbasi, I.S., 2011. The Influence of Neuroticism on Stress Perception and its Resultant Negative Affect. Perception. San José State University.

Acabchuk, R.L., Kamath, J., Salamone, J.D., Johnson, B.T., 2017. Stress and chronic illness: the inflammatory pathway. Soc. Sci. Med. 185, 166–170. http://dx.doi.org/10.1016/j.socscimed.2017.04.039.

Amaral, W.Z., Krueger, R.F., Ryff, C.D., Coe, C.L., 2015. Genetic and environmental determinants of population variation in interleukin-6, its soluble receptor and C-reactive protein: insights from identical and fraternal twins. Brain Behav. Immun. 49, 171–181. http://dx.doi.org/10.1016/j.bbi.2015.05.010.

Antonucci, T.C., Akiyama, H., Merline, A., 2001. Dynamics of social relationships in midlife. In: Lachman, M.E. (Ed.), Handbook of Midlife Development. John Wiley & Sons, Inc., New York, pp. 571–598.

Blaha, M.J., Rivera, J.J., Budoff, M.J., Blankstein, R., Agatston, A., O'Leary, D.H., Cushman, M., Lakoski, S., Criqui, M.H., Szklo, M., Blumenthal, R.S., Nasir, K., 2011. Association between obesity, high-sensitivity C-reactive protein ≥2 mg/L, and subclinical atherosclerosis: implications of JUPITER from the Multi-Ethnic Study of Atherosclerosis. Arterioscler. Thromb. Vasc. Biol. 31, 1430–1438. http://dx.doi.org/10.1161/ATVBAHA.111.223768.

Borys, S., Perlman, D., 1985. Gender differences in loneliness. Pers. Soc. Psychol. Bull. 11, 63–74. http://dx.doi.org/10.1177/0146167285111006.

Brim, O.G., Baltes, P.B., Bumpass, L.L., Cleary, P.D., Featherman, D.L., Hazzard, W.R., Kessler, R.C., Lachman, M.E., Markus, H.R., Marmot, M.G., Rossi, A.S., Ryff, C.D., Shweder, R.A., 2011. National Survey of Midlife Development in the United States (MIDUS), 1995-1996. http://dx.doi.org/10.3886/ICPSR02760.v8. [WWW Document].

Cacioppo, J.T., Hawkley, L.C., 2003. Social isolation and health, with an emphasis on underlying mechanisms. Perspect. Biol. Med. 46, S39–S52. http://dx.doi.org/10.1353/pbm.2003.0063.

Cacioppo, J.T., Hawkley, L.C., Norman, G.J., Berntson, G.G., 2011. Social isolation. Ann. N. Y. Acad. Sci. 1231, 17–22. http://dx.doi.org/10.1111/j.1749-6632.2011.06028.x.

Cacioppo, J.T., Hawkley, L.C., Thisted, R.A., 2010. Perceived social isolation makes me sad: 5-year cross-lagged analyses of loneliness and depressive symptomatology in the Chicago Health, Aging, and Social Relations Study. Psychol. Aging 25, 453–463. http://dx.doi.org/10.1037/a0017216.

Case, A., Deaton, A., 2015. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. Proc. Natl. Acad. Sci. Unit. States Am. 112, 201518393. http://dx.doi.org/10.1073/pnas.1518393112.

Coe, C.L., Love, G.D., Karasawa, M., Kawakami, N., Kitayama, S., Markus, H.R., Tracy, R.P., Ryff, C.D., 2011. Population differences in proinflammatory biology: Japanese have healthier profiles than Americans. Brain Behav. Immun. 25, 494–502. http://dx.doi.org/10.1016/j.bbi.2010.11.013.

Cohen-Mansfield, J., Hazan, H., Lerman, Y., Shalom, V., 2016. Correlates and predictors of loneliness in older-adults: a review of quantitative results informed by qualitative insights. Int. Psychogeriatr. 28, 557–576. http://dx.doi.org/10.1017/S1041610215001532.

Cohen-Mansfield, J., Hazan, H., Lerman, Y., Shalom, V., 2015. Correlates and predictors of loneliness in older-adults: a review of quantitative results informed by qualitative insights. Int. Psychogeriatr. 1–20. http://dx.doi.org/10.1017/S1041610215001532.

Cohen, S., Kamarck, T., Mermelstein, R., 1983. A global measure of perceived stress. J. Health Soc. Behav. 24, 385–396.

Cole, S.W., Capitanio, J.P., Chun, K., Arevalo, J.M.G., Ma, J., Cacioppo, J.T., 2015. Myeloid differentiation architecture of leukocyte transcriptome dynamics in perceived social isolation. Proc. Natl. Acad. Sci. Unit. States Am. 112, 201514249. http://dx.doi.org/10.1073/pnas.1514249112.

Cole, S.W., Hawkley, L.C., Arevalo, J.M., Sung, C.Y., Rose, R.M., Cacioppo, J.T., 2007. Social regulation of gene expression in human leukocytes. Genome Biol. 8, R189. http://dx.doi.org/10.1186/gb-2007-8-9-r189.

Danesh, J., Fibrinogen Studies Collaboration, 2005. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality. J. Am. Med. Assoc. 294, 1799–1810. http://dx.doi.org/10.1001/jama.294.14.1799.

Dienberg Love, G., Seeman, T.E., Weinstein, M., Ryff, C.D., 2010. Bioindicators in the MIDUS national study: protocol, measures, sample, and comparative context. J. Aging Health 22, 1059–1080. http://dx.doi.org/10.1177/0898264310374355.

Ditschuneit, H.H., Flechtner-Mors, M., Adler, G., 1995. Lipoprotein(a) in obesity before and after weight reduction. Nutr. Metabol. Cardiovasc. Dis. 6, 32–38. http://dx.doi.org/10.1002/j.1550-8528.1995.tb00119.x.

Dyal, S.R., Valente, T.W., 2015. A systematic review of loneliness and smoking: small effects, big implications. Subst. Use Misuse 50, 1697–1716. http://dx.doi.org/10.3109/10826084.2015.1027933.

Franceschi, C., Campisi, J., 2014. Chronic inflammation (Inflammaging) and ts potential contribution to age-associated diseases. J. Gerontol. Biol. Sci. 69, S4–S9. http://dx.doi.org/10.1093/gerona/glu057.

Fulton, L., Jupp, B., 2015. Investing to Tackle Loneliness. A Discussion Paper, London.

Gerst-Emerson, K., Jayawardhana, J., 2015. Loneliness as a public health issue: the impact of loneliness on health care utilization among older adults. Am. J. Publ. Health 105, 1013–1018. http://dx.doi.org/10.2105/AJPH.2014.302427.

Goto, M., 2008. Inflammating (inflamation + aging): a driving force for human aging based on an evolutionarily antagonistic pleiotropy theory? Biosci. Trends 2, 218–230.

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, 1801–1809. http://dx.doi.org/10.1016/j.psyneuen.2012.03.016.

Hawkley, L.C., Burleson, M.H., Berntson, G.G., Cacioppo, J.T., 2003. Loneliness in everyday life: cardiovascular activity, psychosocial context, and health behaviors. J. Pers. Soc. Psychol. 85, 105–120. http://dx.doi.org/10.1037/0022-3514.85.1.105.

Hawkley, L.C., Capitanio, J.P., 2015. Perceived social isolation, evolutionary fitness and health outcomes: a lifespan approach. Philos. Trans. R. Soc. B 370, 20140114. http://dx.doi.org/10.1098/rstb.2014.0114.

Hawkley, L.C., Hughes, M.E., Waite, L.J., Masi, C.M., Thisted, R.A., Cacioppo, J.T., 2008. From social structural factors to perceptions of relationship quality and loneliness: the Chicago health, aging, and social relations study. J. Gerontol. B Psychol. Sci. Soc. Sci. 63, S375–S384 doi:63/6/S375 [pii].

Hawkley, L.C., Masi, C.M., Berry, J.D., Cacioppo, J.T., 2006. Loneliness is a unique predictor of age-related differences in systolic blood pressure. Psychol. Aging 21, 152–164. http://dx.doi.org/10.1037/0882-7974.21.1.152.

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. Psychol. Aging 25, 132–141. http://dx.doi.org/10.1037/a0017805.

Hensley, B., Martin, P., Margrett, J.A., MacDonald, M., Siegler, I.C., Poon, L.W., 2012. Life events and personality predicting loneliness among centenarians: findings from the Georgia centenarian study. J. Psychol. 146, 173–188. http://dx.doi.org/10.1080/00223980.2011.613874.

Hipple, S.F., 2015. People who are not in the labor force: why aren't they working? Beyond the Numbers 4, 1–14.

Holmén, K., Furukawa, H., 2002. Loneliness, health and social network among elderly people—a follow-up study. Arch. Gerontol. Geriatr. Arch. Gerontol. Geriatr 35, 261–274. http://dx.doi.org/10.1016/S0167-4943(02)00049-3.

Holt-Lunstad, J., Smith, T.B., 2016. Loneliness and social isolation as risk factors for CVD : implications for evidence-based patient care and scientific inquiry. Heart 102, 987–989. http://dx.doi.org/10.1136/heartjnl-2015-309242.

Holt-Lunstad, J., Smith, T.B., Baker, M., Harris, T., Stephenson, D., 2015. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. Perspect. Psychol. Sci. 10, 227–237. http://dx.doi.org/10.1177/1745691614568352.

Holt-Lunstad, J., Smith, T.B., Layton, J.B., 2010. Social relationships and mortality risk: a meta-analytic review. PLoS Med. 7. http://dx.doi.org/10.1371/journal.pmed.1000316.

Holwerda, T.J., Deeg, D.J.H., Beekman, A.T.F., van Tilburg, T.G., Stek, M.L., Jonker, C., Schoevers, R. a, 2014. Feelings of loneliness, but not social isolation, predict dementia onset: results from the Amsterdam Study of the Elderly (AMSTEL). J. Neurol. Neurosurg. Psychiatry 85, 135–142. http://dx.doi.org/10.1136/jnnp-2012-302755.

House, J.S., Landis, K.R., Umberson, D., 1988. Social relationships and health. Science 241, 540–545. http://dx.doi.org/10.1126/science.3399889.

Howden, L.M., Meyer, J.A., 2011. Age and Sex Composition, vol. 2010 2010 Census Briefs, Washington, DC.

Huber, P., 1967. The behavior of maximum likelihood estimates under nonstandard conditions. In: Proc. Fifth Berkeley Symp. …, pp. 221–233 doi:citeulike-article-id:2607115.

Humes, K., Jones, N., Ramirez, R., 2011. Overview of Race and Hispanic Origin, vol. 2010 2010 Census Briefs, Washington, DC.

Ilg, R.E., 2001. Who was affected as teh economy started to slow? Issues Labor Stat 01–05, 16–17.

Jaremka, L.M., Andridge, R.R., Fagundes, C.P., Alfano, C.M., Povoski, S.P., Lipari, A.M., Agnese, D.M., Arnold, M.W., Farrar, W.B., Yee, L.D., Carson 3rd, W.E., Bekaii-Saab, T., Martin, E.W.J., Schmidt, C.R., Kiecolt-Glaser, J.K., 2014. Pain, depression, and fatigue: loneliness as a longitudinal risk factor. Health Psychol. 33, 948–957. http://dx.doi.org/10.1037/a0034012.

Jaremka, L.M., Fagundes, C.P., Peng, J., Bennett, J.M., Glaser, R., Malarkey, W.B., Kiecolt-Glaser, J.K., 2013. Loneliness promotes inflammation during acute stress. Psychol. Sci. 24, 1089–1097. http://dx.doi.org/10.1177/0956797612464059.

Johnson, B.T., Acabchuk, R.L., 2018. What are the keys to a longer, happier life? Answers from five decades of health psychology research. Soc. Sci. Med. 196, 218–226. http://dx.doi.org/10.1016/j.socscimed.2017.11.001.

Kannel, W.B., Wolf, P.A., Castelli, W.P., Agostino, R.B., 2012. Fibrinogen and risk of cardiovascular disease: the framingham study. JAMA 9, 1183–1186.

Kathiresan, S., 2006. Contribution of clinical correlates and 13 C-Reactive protein gene polymorphisms to interindividual variability in serum C-Reactive protein level. Circulation 113, 1415–1423. http://dx.doi.org/10.1161/CIRCULATIONAHA.105.

591271.
Keyes, C.L.M., 1998. Social well-being. Soc. Psychol. Q. 61, 121–140.
Lachman, M.E., Weaver, S.L., 1995. Seeking Social Support: Scale Developed for the MIDUS Survey.
Luo, Y., Hawkley, L., Waite, L., Cacioppo, J., 2012. Loneliness, health, and morality in old age: a national longitudinal study. Soc. Sci. Med. 74, 907–914. http://dx.doi.org/10.1016/j.socscimed.2011.11.028.Loneliness.
Martin, P., Hagberg, B., Poon, L.W., 1997. Predictors of loneliness in centenarians: a parallel study. J. Cross Cult. Gerontol. 12, 203–224. http://dx.doi.org/10.1023/A:1006587502257.
Masi, C.M., Chen, H.-Y., Hawkley, L.C., Cacioppo, J.T., 2011. A meta-analysis of interventions to reduce loneliness. Pers. Soc. Psychol. Rev. 15, 219–266. http://dx.doi.org/10.1177/1088868310377394.
Mayo Medical Laboratories, 2017. Rochester Test Catalog. [WWW Document].
McDade, T.W., Hawkley, L.C., Cacioppo, J.T., 2006. Psychosocial and behavioral predictors of inflammation in middle-aged and older adults: the chicago health, aging, and social relations study. Psychosom. Med. 68, 376–381. http://dx.doi.org/10.1097/01.psy.0000221371.43607.64.
McManus, D.D., Beaulieu, L.M., Mick, E., Tanriverdi, K., Larson, M.G., Keaney, J.F., Benjamin, E.J., Freedman, J.E., 2013. Relationship among circulating inflammatory proteins, platelet gene expression, and cardiovascular risk. Arterioscler. Thromb. Vasc. Biol. 33, 2666–2673. http://dx.doi.org/10.1161/ATVBAHA.112.301112.
Mezuk, B., Choi, M., DeSantis, A.S., Rapp, S.R., Diez Roux, A.V., Seeman, T., 2016. Loneliness, depression, and inflammation: evidence from the multi-ethnic study of atherosclerosis. PLoS One 11, e0158056. http://dx.doi.org/10.1371/journal.pone.0158056.
Morrisette-Thomas, V., Cohen, A.A., Fülöp, T., Riesco, É., Legault, V., Li, Q., Milot, E., Dusseault-Bélanger, F., Ferrucci, L., 2014. Inflamm-aging does not simply reflect increases in pro-inflammatory markers. Mech. Ageing Dev. 139, 49–57. http://dx.doi.org/10.1016/j.mad.2014.06.005.
Mozaffarian, D., Benjamin, E.J., Go, A.S., Arnett, D.K., Blaha, M.J., Cushman, M., de Ferranti, S., Despres, J.-P., Fullerton, H.J., Howard, V.J., Huffman, M.D., Judd, S.E., Kissela, B.M., Lackland, D.T., Lichtman, J.H., Lisabeth, L.D., Liu, S., Mackey, R.H., Matchar, D.B., McGuire, D.K., Mohler, E.R., Moy, C.S., Muntner, P., Mussolino, M.E., Nasir, K., Neumar, R.W., Nichol, G., Palaniappan, L., Pandey, D.K., Reeves, M.J., Rodriguez, C.J., Sorlie, P.D., Stein, J., Towfighi, A., Turan, T.N., Virani, S.S., Willey, J.Z., Woo, D., Yeh, R.W., Turner, M.B., 2015. Heart disease and stroke Statistics–2015 update: a report from the American heart association. Circulation 131, e29–e322. http://dx.doi.org/10.1161/CIR.0000000000000152.
O'Luanaigh, C., O'Connell, H., Chin, A.V., Hamilton, F., Coen, R., Walsh, C., Walsh, J.B., Coakley, D., Molloy, A., Scott, J., Cunningham, C.J., Lawlor, B.A., 2012. Loneliness and vascular biomarkers: the dublin healthy ageing study. Int. J. Geriatr. Psychiatr. 27, 83–88. http://dx.doi.org/10.1002/gps.2695.
Ong, A.D., Uchino, B.N., Wethington, E., 2016. Loneliness and health in older adults: a mini-review and synthesis. Gerontology 62, 443–449. http://dx.doi.org/10.1159/000441651.
Radler, B.T., 2014. The midlife in the United States (MIDUS) series: a national longitudinal study of health and well-being. Open Health Data 2, 2–5. https://doi.org/10.5334/ohd.ai.
Radloff, L.S., 1977. A self-report depression scale for research in the general population. Appl. Psychol. Meas. 1, 385–401. http://dx.doi.org/10.1177/014662167700100306.
Routasalo, P.E., Savikko, N., Tilvis, R.S., Strandberg, T.E., Pitkälä, K.H., 2006. Social contacts and their relationship to loneliness among aged people - a population-based study. Gerontology 52, 181–187. http://dx.doi.org/10.1159/000091828.
Ryff, C., Almeida, D.M., Ayanian, J.S., Carr, D.S., Cleary, P.D., Coe, C., Davidson, R., Krueger, R.F., Lachman, M.E., Marks, N.F., Mroczek, D.K., Seeman, T., Seltzer, M.M., Singer, B.H., Sloan, R.P., Tun, P.A., Weinstein, M., Williams, D., 2012. National Survey of Midlife Development in the United States (MIDUS II), 2004-2006. http://dx.doi.org/10.3886/ICPSR04652.v6. [WWW Document].
Ryff, C.D., 1989. Happiness is everything, or is it? Explorations on the meaning of psychological well-being. J. Pers. Soc. Psychol. 57, 1069–1081. http://dx.doi.org/10.1037/0022-3514.57.6.1069.
Ryff, C.D., Seeman, T., Weinstein, M., 2013. National Survey of Midlife Development in the United States (MIDUS II): Biomarker Project, 2004-2009. http://dx.doi.org/10.3886/ICPSR29282.v6. [WWW Document].
Ryff, C.D., Seeman, T.E., Weinstein, M., 2011. National Survey of Midlife Development in the United States (MIDUS II): Biomarker Project, 2004-2009 Blood, Urine, and Saliva Data. http://dx.doi.org/10.3886/ICPSR29282.v4.
Ryff, C.D., Seeman, T.E., Weinstein, M., 2010. National Survey of Midlife Development in the United States (MIDUS II): Biomarker Project, 2004-2009, Self Administered Questionnaire. http://dx.doi.org/10.3886/ICPSR29282.v4.
Savikko, N., Routasalo, P., Tilvis, R.S., Strandberg, T.E., Pitkälä, K.H., 2005. Predictors and subjective causes of loneliness in an aged population. Arch. Gerontol. Geriatr. 41, 223–233. http://dx.doi.org/10.1016/j.archger.2005.03.002.
Shankar, A., McMunn, A., Banks, J., Steptoe, A., 2011. Loneliness, social isolation, and behavioral and biological health indicators in older adults. Health Psychol. 30, 377–385. http://dx.doi.org/10.1037/a0022826.
Shavelle, R.M., Paculdo, D.R., Strauss, D.J., Kush, S.J., 2008. Smoking habit and mortality: a meta-analysis. J. Insur. Med. 40, 170–178.
Shiels, M.S., Chernyavskiy, P., Anderson, W.F., Best, A.F., Haozous, E.A., Hartge, P., Rosenberg, P.S., Thomas, D., Freedman, N.D., de Gonzalez, A.B., 2017. Trends in premature mortality in the USA by sex, race, and ethnicity from 1999 to 2014: an analysis of death certificate data. Lancet 6736, 1–12. http://dx.doi.org/10.1016/S0140-6736(17)30187-3.
Shiovitz-Ezra, S., Ayalon, L., 2012. Use of direct versus indirect approaches to measure loneliness in later life. Res. Aging 34, 572–591. http://dx.doi.org/10.1177/0164027511423258.
Shiovitz-Ezra, S., Leitsch, S.A., 2010. The role of social relationships in predicting loneliness: the national social life, health, and aging project. Soc. Work. Res. 34, 157–167. http://dx.doi.org/10.1093/swr/34.3.157.
Simons, R.L., Lei, M.K., Beach, S.R.H., Barr, A.B., Cutrona, C.E., Gibbons, F.X., Philibert, R.A., 2017. An index of the ratio of inflammatory to antiviral cell types mediates the effects of social adversity and age on chronic illness. Soc. Sci. Med. 185, 158–165. http://dx.doi.org/10.1016/j.socscimed.2017.03.005.
Sorkin, D., Rook, K.S., Lu, J.L., 2002. Loneliness, lack of emotional support, lack of companionship, and the likelihood of having a heart condition in an elderly sample. Ann. Behav. Med. 24, 290–298 doi:ISSN 0883–6612.
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, 593–611. http://dx.doi.org/10.1016/S0306-4530(03)00086-6.
Theeke, L.A., 2010. Sociodemographic and health-related risks for loneliness and outcome differences by loneliness status in a sample of U.S. older adults. Res. Gerontol. Nurs. 3, 113–125. http://dx.doi.org/10.3928/19404921-20091103-99.
Theeke, L.A., Mallow, J.A., Moore, J., Mc Burney, A., Vangilder, R., Barr, T., Theeke, E., Rellick, S., Petrone, A., 2016a. Using gene expression analysis to examine changes in loneliness, depression and systemic inflammation in lonely chronically ill older adults. Open J. Nurs. 6, 620–631. http://dx.doi.org/10.4236/ojn.2016.68066.
Theeke, L.A., Mallow, J.A., Moore, J., McBurney, A., Rellick, S., VanGilder, R., 2016b. Effectiveness of LISTEN on loneliness, neuroimmunological stress response, psychosocial functioning, quality of life, and physical health measures of chronic illness. Int. J. Nurs. Sci. 3, 242–251. http://dx.doi.org/10.1016/j.ijnss.2016.08.004.
Thurston, R.C., Kubzansky, L.D., 2009. Women, loneliness, and incident coronary heart disease. Psychosom. Med. 71, 836–842. http://dx.doi.org/10.1097/PSY.0b013e3181b40efc.
Valtorta, N.K., Kanaan, M., Gilbody, S., Ronzi, S., Hanratty, B., 2016. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. Heart 1009–1016. http://dx.doi.org/10.1136/heartjnl-2015-308790.
Varadhan, R., Yao, W., Matteini, A., Beamer, B.A., Xue, Q.L., Yang, H., Manwani, B., Reiner, A., Jenny, N., Parekh, N., Daniele Fallin, M., Newman, A., Bandeen-Roche, K., Tracy, R., Ferrucci, L., Walston, J., 2014. Simple biologically informed inflammatory index of two serum cytokines predicts 10 year all-cause mortality in older adults. Journals Gerontol. - Ser. A Biol. Sci. Med. Sci. 69 A, 165–173. http://dx.doi.org/10.1093/gerona/glt023.
Victor, C.R., Scambler, S.J., Bowling, A., Bond, J., 2005. The prevalence of, and risk factors for, loneliness in later life: a survey of older people in Great Britain. Ageing Soc. 25, 357–375. http://dx.doi.org/10.1017/S0144686X04003332.
Whisman, M. a, 2010. Loneliness and the metabolic syndrome in a population-based sample of middle-aged and older adults. Health Psychol. 29, 550–554. http://dx.doi.org/10.1037/a0020760.
White, H., 1980. A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. Econometrica 48, 817–838.
Woods, J.A., Wilund, K.R., Martin, S.A., Kistler, B.M., 2012. Exercise, inflammation and aging. Aging Dis 3, 130–140.
Yang, Y.C., Boen, C., Harris, K.M., 2014. Social relationships and hypertension in late life: evidence from a nationally representative longitudinal study of older adults. J. Aging Health 27, 403–431. http://dx.doi.org/10.1177/0898264314551172.