LONELINESS IN MIDDLE AGE: BIOMARKERS OF CARDIOMETABOLIC
HEALTH AND THE INFLUENCE OF PERCEIVED NEIGHBORHOOD QUALITY

by
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Abstract

Problem Statement

Loneliness is an emotional state of perceived lack of positive relationships that increases odds of death, particularly among middle-aged adults. Inflammation contributing to cardiovascular disease may drive poor outcomes. Molecular level studies show loneliness influences the inflammatory response, but clinical studies of inflammatory biomarkers and loneliness are inconsistent. Loneliness is linked to cardiometabolic function through higher blood pressure, lack of regular exercise, and poor sleep quality. However, studies examining loneliness and metabolic syndrome drew different conclusions. Therefore, we examined relationships between loneliness and systemic inflammation and metabolic syndrome. Also, research among European older adults demonstrated that living conditions and social integration influence loneliness, but it is not clear if these factors influence loneliness in middle-aged US adults.

Methods

This is a secondary analysis of the Biomarker Project, a special study of Midlife in the US (MIDUS). Baseline MIDUS data was collected from 1995-1996 (N=7,108) and a follow-up survey was conducted from 2004-2006 (N=4,963). A sample of African Americans from Milwaukee was surveyed in 2005-2006 (N=592). The Biomarker Project enrolled participants from the MIDUS baseline and Milwaukee samples. Data were collected from 2004-2009 (N=1,255). Our sample includes Biomarker Project participants age 35-64 years (n=927). Controlling for potential confounders, we conducted multivariable linear regression to test whether feeling lonely is associated with higher levels of inflammatory biomarkers, and we conducted multivariable logistic
regression to test whether feeling lonely is associated with metabolic syndrome and its individual criteria. With loneliness as the dependent variable, we also tested its association with perceived neighborhood quality and if social integration mediates the relationship.

**Results**

After adjustment, feeling lonely was: positively associated with higher interleukin-6, fibrinogen, and C-reactive protein values; and not associated with metabolic syndrome or its criteria. Perceived neighborhood quality was associated with loneliness after adjustment, and social integration partially mediated the relationship.

**Conclusions**

The results provide evidence for an association between feeling lonely and systemic inflammation implicated in development of cardiovascular disease among middle-aged US adults. And neighborhood factors and social integration influence the development of loneliness. Loneliness interventions at individual and community levels may improve psychosocial well-being, health outcomes, and survival.

**Advisor:** Sarah L. Szanton, PhD, ANP, FAAN
Dedication

I dedicate this educational milestone to my mother Kathleen and my late father Andrew who missed seeing me meet this milestone by just a year. Their support of my passion for learning and adventure never failed me.

I dedicate this accomplishment to my husband Richard McAlee who was encouraging, patient, and supportive through the entire process.

And importantly, I dedicate this dissertation to my dear daughter Kira.
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My colleagues at John Snow, Inc. helped ease my transition from a 20-year international public health career to student life with a lovely send-off. My new colleagues, especially my dear cohort-mates, Christina, Damali, Laura, Melissa, Mia, and Scott provided a warm welcome, and they have been a source of support and encouragement throughout this journey.

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It is an honor to be counted as one among nurses and public health professionals who make a difference in the lives of others every day. Thank you to everyone who helped me gain the skills and knowledge that allows me to respond positively and confidently to what Martin Luther King Jr. posed as “Life’s most persistent and urgent question”

“What are you doing for others?”
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Chapter 1: Introduction

Background

In this study, we seek a clearer understanding of the relationships between loneliness and systemic inflammation, and loneliness and metabolic syndrome. To expand understanding of the development of loneliness and the social determinants that influence its genesis, we also examine the relationship between perceptions of neighborhood quality, social integration, and loneliness. This study is a secondary analysis of data from the Midlife in the United States (MIDUS) survey. The sample includes 927 participants who are middle-aged US adults age 35-64 years. Descriptions of the key constructs follow.

Loneliness

Loneliness is a prevalent and complex emotional state of perceived lack of positive relationships with others. It is distressing for many people and has significant individual consequences, including an increased odds of death, particularly among middle-aged adults. Despite a demonstrated association between loneliness and poor health outcomes, physiological mechanisms driving this association are not completely clear.

Middle Age

Understanding loneliness in middle age and its relationship with health outcomes is important both because middle-aged adults have higher odds of mortality related to loneliness and because loneliness in old age is associated with patterns of social engagement established 20 years earlier. This finding suggests that loneliness
interventions in middle age may have long-lasting effects on health and well-being into older adulthood.

**Inflammation**

Inflammation, a contributor to cardiovascular disease (CVD),\(^\text{15–18}\) is a potential pathway for loneliness to influence health. At the molecular level, loneliness has been found to influence the inflammatory response through conserved transcriptional response to adversity.\(^\text{19}\) However, studies with human subjects in a laboratory environment and epidemiological studies have produced inconsistent results.\(^\text{20–25}\) Clarifying the relationship between loneliness and inflammation is crucial given inflammation’s contribution to adverse health outcomes through development and perpetuation of cardiovascular disease.\(^\text{15,16,26}\)

**Metabolic Syndrome**

Loneliness may also be associated with cardiometabolic function. Studies show that people who are lonely have higher blood pressure,\(^\text{27–29}\) a lack of regular exercise,\(^\text{30–32}\) and poor sleep quality.\(^\text{30,33,34}\) Hypertension is a component of the metabolic syndrome and lack of regular exercise and poor sleep quality are associated with metabolic syndrome.\(^\text{35–38}\) A particularly important observation is that two studies that specifically examined associations between loneliness and the metabolic syndrome in European samples drew opposite conclusions.\(^\text{39,40}\)

**Neighborhood Quality and Social Integration**

In addition to uncertainty regarding the relationships between loneliness and biological markers of cardiometabolic health, much remains to be understood about the
development of loneliness and the factors that influence its emergence. Genetic research has demonstrated that loneliness is polygenic and that a portion of loneliness is heritable.\textsuperscript{41} Environmental factors, particularly social factors, also play a role in the development of loneliness. Aside from family members and friends, neighbors are possibly the next closest people available for interaction and development of relationships. Prior research with older adults has demonstrated that quality of living conditions influences loneliness. Specifically, people with lower income levels and those living in deprived neighborhoods compared to those living in more affluent neighborhoods are lonelier.\textsuperscript{42} The degree to which someone is integrated into their neighborhood and their broader community also has a role in the development of loneliness.\textsuperscript{43} It is not clear, however, how neighborhood quality influences loneliness and how social integration mediates that relationship in middle-aged adults.

**Purpose and Specific Aims**

The purpose of this study is to test whether there is a significant relationship between loneliness among middle-aged US adults and biomarkers of cardiometabolic health. A secondary objective is to address the gap in knowledge of the influence of neighborhood quality and social integration on the development of loneliness in middle-aged adults. This investigation is urgent given: the high prevalence of loneliness in the US;\textsuperscript{44} limited understanding of factors that contribute to the feeling of loneliness;\textsuperscript{45} the challenges, demands and stress in middle age;\textsuperscript{46,47} the negative cardiovascular outcomes associated with systemic inflammation\textsuperscript{15,16,26} and metabolic syndrome;\textsuperscript{48} and the lack of US-based research on the influence of perceived neighborhood quality and social integration on loneliness.
Specific Aims

**Aim 1:** Examine the association between loneliness and biomarkers of systemic inflammation among a nationwide sample of 35 to 64 year-old participants in MIDUS.

Hypothesis 1: Loneliness will be associated with elevated biomarker values for interleukin-6, fibrinogen, and C-reactive protein after controlling for covariates.

**Aim 2:** Examine the associations between loneliness and metabolic syndrome, and loneliness and the individual criteria that comprise the syndrome among a nationwide sample of 35 to 64 year-old participants in MIDUS.

Hypothesis 2a: Loneliness will be associated with meeting a sufficient number of criteria to be classified as having metabolic syndrome after controlling for covariates.

Hypothesis 2b: Loneliness will be associated with meeting the individual criteria that comprise the metabolic syndrome after controlling for covariates.

**Aim 3:** Examine the relationship between perceived neighborhood quality and loneliness and the mediating influence of social integration on that relationship among a nationwide sample of 35 to 64 year-old participants in MIDUS.

Hypothesis 3a: Perceived neighborhood quality will have a significant relationship with loneliness after controlling for covariates.

Hypothesis 3b: Social integration will mediate the relationship between perceived neighborhood quality and loneliness after controlling for covariates.
Conceptual Framework

Two frameworks guided the development of this study: The World Health Organization (WHO) Social Determinants Conceptual Framework,\(^49\) and the “Individual and societal factors in loneliness”.\(^42\) The WHO Social Determinants Conceptual Framework (Figure 1) guided the overall design of this study on social relationships and health. The framework developed by the WHO Commission on Social Determinants of Health points to intermediary determinants of social determinants of health, which includes material circumstances and psychosocial factors, as factors which influence health and well-being. In this analysis, loneliness is a psychosocial factor proposed to be associated with health through cardiometabolic function. Perceived neighborhood quality represents material circumstances of living that influence health and we propose that loneliness will be influenced by perceived neighborhood quality.

Figure 1

*WHO framework on the social determinants of health*
The “Individual and societal factors in the emergence of loneliness” is a theoretical framework developed by de Jong Gierveld (page 292)\(^{42}\) which maps factors that influence the development of loneliness. This framework specifically informed the development and analysis of aim 3. The constructs from the individual level of the framework were addressed in our analysis (social level constructs were not included). Specifically, this framework places quality of living conditions and level of social integration on the pathway to development of loneliness. This pathway was tested in this study.

**Dissertation Organization**

This dissertation is organized into five chapters. Chapter 1 includes introductory and background material, the purpose and specific aims, and the theoretical frameworks used to guide this research. Chapters 2-4 are submission-ready data-based manuscripts resulting from this dissertation research using Biomarker Project data from the MIDUS survey. The topic of chapter two is associations between loneliness and biomarkers of systemic inflammation. Chapter 3 focuses on associations between loneliness and metabolic syndrome, and loneliness and the individual components of metabolic syndrome. Chapter 4 examines the influences of neighborhood quality and social integration on loneliness. And Chapter 5 provides a summary of findings, places this study in the context of psychosocial research, and discusses limitations of the study and implications for research, practice, and policy.
Chapter 2: Manuscript 1

Cover page

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Loneliness in Middle Age and Biomarkers of Systemic Inflammation: Findings from MIDUS

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, we tested if systemic inflammation is associated with loneliness in a broad age range of middle-aged adults in the United States.

Methods:
We 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. Our sample included the 927 participants who were 35-64 years at Biomarker Project data collection. MIDUS collected baseline data from 1995-1996; a follow-up survey was conducted from 2004-2006; the baseline Milwaukee sample of African Americans was collected in 2005-06; and biomarker data 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. Multivariable regression was used to examine 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) (β
LONELINESS AND SYSTEMIC INFLAMMATION

(standard error \{SE\}=0.07[0.03], \textit{p}=.014), fibrinogen (n=867) (\beta [SE]= 18.24[7.12], \textit{p}=.011), and C-reactive protein (n=867) (\beta [SE]= 0.08[0.04], \textit{p}=.035).

Conclusions:

Feeling lonely is associated with systemic inflammation in middle-aged community-dwelling US adults.

Key Words:

loneliness, middle age, systemic inflammation, interleukin-6, fibrinogen, C-reactive protein

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
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 (1–4). The feeling of loneliness is subjective and quite distinct from social isolation, which is an objective measure (5). Substantial research reflects the importance of loneliness as a psychosocial factor that influences individual human experience and societies (6,7). At an individual level, loneliness in older adults is linked with adverse physical and emotional conditions such as elevated blood pressure (8–10) depression (11,12) and even death (5,13,14). The health risks of loneliness are comparable to smoking about 15 cigarettes per day (15–18). At a societal level, health systems are strained by excess health services utilization by the lonely (19), costing the public sector an additional $15,000 (£12,000) per person over 15 years (20).

While people can feel lonely at any age (21), middle age is a period of life when people face numerous challenges in their social relationships due to shifts in family structure, progression in one’s occupation, and changes in health status. These challenges expose middle-aged adults to multiple stressors over many decades (22) 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 (13). Middle age is also a time of life when the risk of developing cardiovascular disease (CVD) is high (23). 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 (9,16). 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 (24,25). Nevertheless, younger middle-aged adults (35 to 50 year olds) are less often included in such studies and therefore we cannot generalize these findings to the middle age group as a whole.

One mechanism linking loneliness and these negative cardiovascular outcomes is dysregulation of the inflammatory response (26,27). Interleukin-6 (IL-6), fibrinogen, and C-reactive protein (CRP) are recognized as key biomarkers of systemic inflammation associated with cardiovascular events (28–30). Although gene expression studies have established a connection between loneliness and a dysregulated inflammatory response (31), investigations of the relationship between loneliness and circulating markers of systemic inflammation implicated in CVD have yielded inconsistent findings. For example, analyses from the US and Great Britain showed no relationship between loneliness and CRP or loneliness and fibrinogen (21,32,33). However, a significant relationship was found between loneliness and elevated fibrinogen and loneliness and IL-6 levels when participants were exposed to an acute stressor in a laboratory setting (34–36). 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 (22). Examining loneliness and inflammation in middle age offers us a unique opportunity to consider these stressors 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
LONELINESS AND SYSTEMIC INFLAMMATION

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. We hypothesized that loneliness would be associated with elevated biomarker values for IL-6, fibrinogen, and CRP.

**Methods**

**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 original MIDUS sample enrolled non-institutionalized middle-aged and older adults in the coterminous United States through random digit dialing from 1995 to 1996 (N=7,108) (37). A follow-up survey (MIDUS 2) was conducted 10 years later from 2004-2009 (N=4,963). 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 (38). The Biomarker Project sample (n=1,255) was drawn from the original MIDUS and Milwaukee samples. Data were collected over two days at three clinical research sites: University of Wisconsin, Madison; University of California, Los Angeles; and Georgetown University, Washington, DC. (38–41).

For this study, we used data from 927 participants age 35-64 years at the time of Biomarker Project data collection. MIDUS recruited siblings and twins as part of the survey design and our sample includes 115 family clusters. Data on demographic, psychosocial, and physical health factors, and systemic inflammation biomarkers values required for our 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/) (38). However, a data use agreement is required for the Milwaukee data given the geographically circumscribed area of sampling and an agreement was executed. Details regarding the Biomarker Project biological specimens data, and the self-administered questionnaires, which include psychometric scales are reported elsewhere (40,42,43). 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 sub-study and each participant provided written informed consent.

**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 (44). As in prior studies (45,46), we classified the answers of “rarely or none of the time” as not feeling lonely and responses in any of the other three categories were classified as feeling lonely.
Systemic Inflammation

Three inflammatory cytokines—IL-6, fibrinogen, and CRP—served as the measures of systemic inflammation. High values of these biomarkers reflect increased inflammation (47). 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 ug/dL or <0.16 ug/dL were adjusted to 0.14 ug/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 (43).

Table 1

Assay ranges for biomarkers of systemic inflammation

<table>
<thead>
<tr>
<th>Assay</th>
<th>Assay Range*</th>
<th>Cut-point of clinical significance**</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6</td>
<td>0.156-10 pg/mL</td>
<td>&gt; 5 pg/mL</td>
</tr>
<tr>
<td></td>
<td>min 0.156 pg/mL</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>60-1200 mg/dL</td>
<td>Males: 200-375 mg/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Females: 200-430 mg/dL</td>
</tr>
<tr>
<td>CRP</td>
<td>0.0175-110 mg/dL</td>
<td>≥2mg/dL</td>
</tr>
<tr>
<td></td>
<td>min 0.015 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

* Biomarker Project, 2004-2009 Blood, Urine, and Saliva Data (43)
**Mayo Medical Laboratories (48)

Covariates

Covariates were obtained from MIDUS baseline, MIDUS follow-up, the Milwaukee sample, and the Biomarker Project. We selected covariates 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 a high school) (6,24,49). The psychosocial variables were included in the model due to their associations with loneliness and stress, which influences systemic inflammation (35,36,50–52). The specific variables included were: a) perceived stress score from Cohen’s Perceived Stress Scale (53), b) positive relations with others, a component of Ryff’s scale of psychosocial well-being (54), c) social integration, a component of Keyes’ Social well-being scale (55), d) a social support measure of self-reliance that assesses aversion to asking for help, developed by Lachman for MIDUS (56), and e) married/cohabitating (married or living with someone as if married or not). We also included history of ever having smoked regularly due to its inflammatory properties and association with loneliness (57). We also included physical health measures including number of symptoms or chronic conditions, blood pressure, and body mass index (BMI) due to their established relationships with loneliness and inflammation (6,52,58,59).

Statistical Analyses

Statistical analyses included descriptive statistics and multiple linear regression. The characteristics of the study sample were examined by loneliness status using bivariate analyses. Missing data was assessed. To avoid multicollinearity, we selected one variable 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. Hypothesis testing using
multiple linear regression was conducted to examine the loneliness-inflammation relationship. All tests were run 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).

Scatter plots of residuals against fitted values with lowess smoothing lines were constructed to check goodness of fit. We tested the assumptions for multiple linear regression: linearity, normal distribution of residuals, and equal variance. Where heteroscedasticity was identified, robust standard errors were estimated using the Huber/White sandwich estimator (60,61). Because this sample includes siblings, which created potential correlation of outcomes, we used clustered sandwich estimation 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 more narrow definition of middle age (40-64 years). The data were analyzed using Stata Special Edition 14 for Windows (StataCorp, LP, College Station, Texas).
Results

Descriptive statistics of the sample are presented in Table 2.

Table 2

Sample characteristics by loneliness

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Study Sample n=927</th>
<th>Lonely n=272 29%</th>
<th>Not Lonely n=652 71%</th>
<th>p value</th>
</tr>
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<td>Age (years)</td>
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<td>M (SD)</td>
<td>M (SD)</td>
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<td>50.86 (7.30)</td>
<td>52.35 (7.50)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>533 (57.50)</td>
<td>116 (42.65)</td>
<td>278 (42.64)</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>674 (75.14)</td>
<td>172 (65.90)</td>
<td>502 (79.30)</td>
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<td>Black</td>
<td>195 (21.74)</td>
<td>83 (31.80)</td>
<td>110 (17.38)</td>
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<tr>
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<td>Multiracial/Other</td>
<td>28 (3.12)</td>
<td>6 (2.30)</td>
<td>21 (3.32)</td>
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<td>Education</td>
<td>≤High school</td>
<td>245 (26.46)</td>
<td>90 (33.09)</td>
<td>153 (23.50)</td>
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<td>≥Some college</td>
<td>681 (73.54)</td>
<td>182 (66.19)</td>
<td>498 (76.50)</td>
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<td>Marital status</td>
<td>Married or Living with Someone</td>
<td>601 (64.90)</td>
<td>117 (43.01)</td>
<td>484 (74.35)</td>
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<td>Not married or Living with Someone</td>
<td>325 (35.10)</td>
<td>155 (56.99)</td>
<td>167 (25.65)</td>
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<td>Smoking History</td>
<td>Ever smoked cigarettes regularly</td>
<td>429 (46.33)</td>
<td>144 (52.94)</td>
<td>282 (43.32)</td>
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<td>Never smoked cigarettes regularly</td>
<td>497 (53.67)</td>
<td>128 (47.06)</td>
<td>369 (56.68)</td>
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<td>261 (95.96)</td>
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<td>None</td>
<td>82 (8.86)</td>
<td>11 (4.04)</td>
<td>71 (10.91)</td>
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<tr>
<td></td>
<td>Number</td>
<td>3.60 (2.76) IQR: 3</td>
<td>4.15 (2.91)</td>
<td>3.36 (2.64)</td>
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<tr>
<td>Blood pressure</td>
<td>Systolic</td>
<td>129.13 (17.67)</td>
<td>128.58 (16.68)</td>
<td>129.39 (18.07)</td>
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<td>Diastolic</td>
<td>76.65 (10.72)</td>
<td>76.97 (10.52)</td>
<td>76.53 (10.83)</td>
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<td>Body mass index</td>
<td>Overweight: 25.0-29.9</td>
<td>30.05 (7.03)</td>
<td>31.30 (7.82)</td>
<td>29.51 (6.61)</td>
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<td>Obese: ≥30</td>
<td>307 (33.19)</td>
<td>64 (23.62)</td>
<td>243 (37.33)</td>
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<td>396 (43.03)</td>
<td>143 (52.77)</td>
<td>252 (38.71)</td>
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<td>Blood biomarkers</td>
<td>IL-6</td>
<td>2.83 (2.79)</td>
<td>3.49 (3.46)</td>
<td>2.54 (2.39)</td>
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<td>Fibrinogen</td>
<td>344.22 (84.93)</td>
<td>360.35 (90.41)</td>
<td>336.83 (80.91)</td>
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<tr>
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<td>CRP</td>
<td>3.01 (4.48)</td>
<td>3.68 (4.76)</td>
<td>2.63 (3.71)</td>
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<td>CRP ≥2mg/L</td>
<td>336 (36.92)</td>
<td>113 (42.01)</td>
<td>222 (34.74)</td>
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</table>

Note. Left justified values are mean and standard deviation: M (SD); Right justified values are number and percent: N (%); p-values obtained from Student’s t test for continuous variables and Pearson’s Chi-square for categorical variables. *Fisher’s exact for race and body mass index; IL-6=Interleukin 6; CRP=C-reactive protein

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. Variables...
positively correlated with loneliness were: black race, not married or cohabitating, and higher stress scores. Positive relations with others and social integration were negatively correlated with loneliness. The three biomarkers of systemic inflammation were all significantly correlated with feeling lonely and they were also significantly correlated with one another: IL-6 and fibrinogen (r=0.34, p<.001), IL-6 and CRP (r=0.38, p<.001), and fibrinogen and CRP (r=0.50, 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) (β [SE]= 0.11[0.02], p<.001), fibrinogen (n=908) (β [SE]= 23.52[6.09], p<.001), and log CRP (n=908) (β [SE]= 0.14[0.04], p<.001)), and the fully adjusted models (log IL-6 (n=873) (β [SE]= 0.07[0.03], p=.014) Table 3, fibrinogen (n=867) (β [SE]= 18.24[7.12], p=.011) Table 4, and log CRP (n=867) (β [SE]= 0.08[0.04], p=.035) Table 5).
Table 3

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
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<th></th>
<th>Model 2</th>
<th></th>
<th></th>
<th>Model 3</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>p</td>
<td>95% CI</td>
<td>β</td>
<td>p</td>
<td>95% CI</td>
<td>β</td>
<td>p</td>
<td>95% CI</td>
</tr>
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<td>Lonely vs not lonely</td>
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<td>&lt;.001</td>
<td>.05, 14</td>
<td>.09</td>
<td>.002</td>
<td>.03, 14</td>
<td>.07</td>
<td>.014</td>
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<td>.00, 01</td>
<td>.06</td>
<td>.010</td>
<td>.01, 01</td>
<td>.06</td>
<td>.050</td>
<td>.01, 01</td>
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<td>Female vs male</td>
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<td>.005</td>
<td>.02, 10</td>
<td>.06</td>
<td>.010</td>
<td>.01, 10</td>
<td>.05</td>
<td>.015</td>
<td>.01, 09</td>
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<td>Black vs White</td>
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<td>.13, 24</td>
<td>.17</td>
<td>&lt;.001</td>
<td>.12, 23</td>
<td>.11</td>
<td>&lt;.001</td>
<td>.05, 09</td>
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<tr>
<td>Multi-racial/Other vs White</td>
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<td>.568</td>
<td>-.10, 19</td>
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<td>.591</td>
<td>-.11, 19</td>
<td>.02</td>
<td>.798</td>
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<td>.062</td>
<td>-.00, 10</td>
<td>.05</td>
<td>.051</td>
<td>-.00, 10</td>
<td>.03</td>
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<td>.00</td>
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<td>.01</td>
<td>.581</td>
<td>-.02, 03</td>
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<td>.677</td>
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<td>.00</td>
<td>.903</td>
<td>-.01, 01</td>
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<tr>
<td>Ever smoked regularly vs never smoked regularly</td>
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<td></td>
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<td>.05</td>
<td>.013</td>
<td>.01, 09</td>
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<tr>
<td>Number of symptoms or chronic conditions</td>
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<td>.064</td>
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<td>Systolic blood pressure (mmHg)</td>
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<td>.336</td>
<td>-.00, 00</td>
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<td>Body mass index (kg/m²)</td>
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<td>.01, 02</td>
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Note: β=regression coefficient, p=p-value, CI=confidence interval, vs=versus
Table 4

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

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<tr>
<th>Variable</th>
<th>Model 1</th>
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<th>Model 2</th>
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<th>Model 3</th>
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<td>95% CI</td>
<td>B</td>
<td>P</td>
<td>95% CI</td>
<td>β</td>
<td>p</td>
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<tr>
<td>Lonely vs not lonely</td>
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<td>7.10, 32.29</td>
<td>22.76</td>
<td>.002</td>
<td>8.26, 37.26</td>
<td>18.24</td>
<td>.011</td>
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<td>Age (years)</td>
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<td>0.89, 2.28</td>
<td>1.49</td>
<td>&lt;.001</td>
<td>0.79, 2.18</td>
<td>1.08</td>
<td>.003</td>
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<tr>
<td>Female vs male</td>
<td>28.34</td>
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<td>18.13, 39.33</td>
<td>28.62</td>
<td>&lt;.001</td>
<td>17.84, 39.41</td>
<td>28.09</td>
<td>&lt;.001</td>
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<tr>
<td>Black vs White</td>
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<td>&lt;.001</td>
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<td>42.05</td>
<td>&lt;.001</td>
<td>26.22, 57.87</td>
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<td>0.25, 76.51</td>
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<td>-2.82, 22.90</td>
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<td>-1.11, 0.82</td>
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<td>.549</td>
<td>-1.20, 0.64</td>
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<td>.303</td>
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<td>.770</td>
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Note: β=regression coefficient, p=p-value, CI=confidence interval, vs=versus
Table 5

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
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<th></th>
<th>Model 2</th>
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<th>Model 3</th>
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<tr>
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<td>p</td>
<td>95% CI</td>
<td>β</td>
<td>p</td>
<td>95% CI</td>
<td>β</td>
<td>p</td>
<td>95% CI</td>
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<td>Lonely vs not lonely</td>
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<td>.009</td>
<td>.03,.18</td>
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<td>.004</td>
<td>.04,.22</td>
<td>.08</td>
<td>.035</td>
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<td>.17</td>
<td>&lt;.001</td>
<td>.10,.23</td>
<td>.17</td>
<td>&lt;.001</td>
<td>.11,.23</td>
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<td>.00,.03</td>
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<td>.00,.04</td>
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</table>

*Note: β=regression coefficient, p=p-value, CI=confidence interval, vs=versus*

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 more narrow 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.

Discussion

We found a significant positive association between self-report of loneliness and biomarker values of IL-6, fibrinogen, and CRP in a community sample of middle-aged adults in the US. 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 (34–36). However, prior studies that included participants on average 10 years older did not show significant relationships between loneliness and systemic inflammation (21,32,33). 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 US. The independent analyses by Shiels and Case demonstrating 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 our findings (62,63). Increased systemic inflammation may be a “canary in the coal mine”-type warning of impending poor health outcomes in this age group. Environmental factors, such as slow economic growth in the US since 2000 which resulted in increased unemployment and underemployment among middle-aged workers, particularly those in the middle earnings group (64,65) may have a role in the relationship between loneliness and systemic inflammation.
Exercise among the middle-aged participants should also be considered. 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 (66). 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. Exercise can reduce IL-6 and CRP levels (67). However, demands of family and work in middle age may be an obstacle to regular exercise for people in middle age. In our 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. Even if this were the case, the other two biomarkers, which lack pro-inflammatory characteristics, were also significant in a positive direction. Our results were significant even when we controlled for body mass as a potential confounder. Obesity is known to have an influence on CRP, IL-6, and fibrinogen (68,69). A genetic contribution may also explain some of the variation in IL-6 and CRP levels (70,71).

We observed a positive relationship between feeling lonely and higher fibrinogen and IL-6 values, consistent with prior findings (34–36). However, prior analyses included application of a laboratory controlled stressor and ours 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 exciting 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 our positive findings were different from studies which failed to show a significant relationship between loneliness and CRP and fibrinogen (21,32,33). 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 these conditions being included in the model (66). 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 (33) the participants were free of cardiovascular disease at enrollment.

However, an association in the opposite direction is also a possibility where systemic inflammation affects loneliness. Given the cross-sectional nature of this study, we cannot make causal inferences. This study has other limitations. Compared to US Census Bureau data from 2010 (the census closest to the conclusion of the Biomarker Project data collection) our sample included more white and black participants, and fewer multi-racial participants and those representing other racial groups reported by the Census (72). Our sample also contains disproportionately more females than males than the national averages in 2010 (73). The single item measure of loneliness in this study could also be considered a limitation. Although single item measures of loneliness have been used in many studies (3,74,75), including the one-item measure from the CES-D (25,46), a simple measure might have underestimated loneliness (5). 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 \((r=.735, p<.001)\) (76). 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 (77). We also found no difference in self-identified loneliness by gender, which has been reported elsewhere (78,79). Considering the rapid expansion of social networking (which typically involves self-disclosure) during the period when this data was collected, reluctance to self-identify as lonely may have been declining in the mid-2000s. New social media is opening ways of looking at socializing and socialization (80). Further research is required on the measures of loneliness in light of these changes in the US.

The strengths of this analysis are that it adds to a limited body of literature examining loneliness in a sample of middle-aged adults residing in the US. The rich objective and subjective data collected directly from participants enabled analysis of personal perceptions and biological measures from a large survey sample.

**Conclusion**

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. Our results also contribute to knowledge of the relationship between loneliness and a precursor of cardiovascular disease: systemic inflammation. We are unable to ascertain a causal direction 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
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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. Further research on the factors that modify loneliness’ relationship with systemic inflammation may allow development of interventions that are precisely targeted.

Acknowledgements

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Chapter 3: Manuscript 2

Loneliness in Middle Age and Metabolic Syndrome: Findings from Midlife in the US

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Abstract

Objectives: Loneliness is an established health risk in middle age, but there is inconclusive evidence of a relationship between loneliness in middle age and metabolic syndrome. The objective of this study was to determine if loneliness is associated with metabolic syndrome among a sample of middle-aged adults. Methods: Socioeconomic, psychosocial, and physiological measures were collected from adults (35-64 years) residing in the US (n=927) who participated in the Midlife in the US (MIDUS) Biomarker Project. Using multivariable logistic regression, we sought to isolate the association between loneliness and metabolic syndrome. Self-reported loneliness was categorized as a binary variable, biological measures were obtained during an overnight stay at a clinical research center, and metabolic syndrome was classified by NCEP ATP-III criteria. Adjustments were made for demographics, social integration, social support, depression, smoking history, physical activity, and sleep quality. Results: Twenty-nine percent of the sample reported feeling lonely most or some of the time. There was not a significant increased odds of metabolic syndrome if lonely in simple logistic regression (OR=1.34, \( p = .059 \), 95% CI=0.99, 1.80) or in the multivariable model (OR=1.08, \( p = .649 \), 95% CI: 0.77, 1.51). In regressions of individual metabolic syndrome criteria, loneliness was significantly associated with obesity in simple logistic regression models, but was non-significant in complex models. Conclusions: Significant increased odds of obesity among lonely community-dwelling middle-aged US adults and findings which suggest depression, lack of regular exercise, and poor sleep quality influence the relationship between loneliness and metabolic syndrome provides evidence of a multifactorial relationship. Key words: loneliness, metabolic syndrome, middle aged
Introduction

Loneliness is defined as unfulfilled expectations of the quality or quantity of one’s relationships (Perlman & Peplau, 1998). Prevalence estimates of loneliness range from 7% to 39% among community-dwelling American and European middle-aged and older adults (Savikko, Routasalo, Tilvis, Strandberg, & Pitkälä, 2005; Shiovitz-Ezra & Leitsch, 2010; Theeke, 2010; Victor, Scambler, Bowling, & Bond, 2005). Loneliness has significant health implications. It is associated with elevated blood pressure (Hawkley, Masi, Berry, & Cacioppo, 2006; Sorkin, Rook, & Lu, 2002; Yang, Boen, & Harris, 2014), depression (Cacioppo, Hawkley, & Thisted, 2010; Jaremka et al., 2014), and death (Holt-Lunstad, Smith, & Layton, 2010). Loneliness also strains health systems as a result of excess health care utilization by people who feel lonely (Gerst-Emerson & Jayawardhana, 2015). Estimates from an analysis in the United Kingdom are that caring for lonely older adults costs the public sector an additional $15,000 (£12,000) per person over 15 years (Fulton & Jupp, 2015).

Loneliness in middle age appears to have special significance. Although people of any age can feel lonely (Shankar, McMunn, Banks, & Steptoe, 2011), the unique challenges and demands of middle age (Antonucci, Akiyama, & Merline, 2001) may influence feeling of loneliness in this age group. In middle age, relationships shift due to changes in family structure: children move out and sometimes parents move in. A majority of people in middle age continue to work outside the home (Sterns & Huyck, 2001), which provides opportunities for engaging with others. But as work responsibilities change, relationships do too. The demands of multiple roles in middle age can generate conflict or build tolerance within family and work relationships, resulting in
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stress or enhanced well-being (Coverman, 1989). Reduced mobility beginning in the 40s for some people results from age-related changes in muscles, bones, and joints (Whitbourne, 2001). Hormonal changes accompanying menopause can result in weight gain for women (Davis et al., 2012). These changes become challenges for some middle-aged adults and expose them to stress over several decades (Antonucci et al., 2001).

Indeed, a recent meta-analysis revealed that lonely middle-aged adults had higher odds of all-cause mortality (excluding suicide and accidents) than lonely older adults (Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015).

Risk of developing cardiovascular disease (CVD) is also high in middle age (D. Mozaffarian et al., 2015). Substantial evidence points to psychological distress, psychosocial factors, and socioeconomic status as predictors of cardiovascular risk (Winning, 2015; Karas, 2016; Gallo, 2012; Manuck, 2010; Pyykkonen, 2010; Goldbacher, 2007; Raikkonen, 2007; Prescott, 2007; Whittaker, 2012). Loneliness has established associations with poor cardiovascular functioning through higher peripheral resistance, lower cardiac output, and elevated blood pressure (Hawkley, Burleson, Berntson, & Cacioppo, 2003; Hawkley et al., 2006), and loneliness is a risk factor for coronary heart disease and stroke (Thurston & Kubzansky, 2009; Valtorta, Kanaan, Gilbody, Ronzi, & Hanratty, 2016). Metabolic dysfunction may contribute to these risks (Steptoe, Shankar, Demakakos, & Wardle, 2013a; Yang et al., 2016). There is abundant evidence which has confirmed associations between psychosocial factors such as acute and chronic stress, social support, being treated unfairly, psychological distress, and socioeconomic status and metabolic disease (Boylan & Ryff, 2015; De Vogli, Brunner, & Marmot, 2007; L C Gallo et al., 2012; Manuck, Phillips, Gianaros, Flory, & Muldoon,
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2010; Ortiz, Myers, Schetter, Rodriguez, & Seeman, 2015). However, there are only two published studies that specifically examine the relationship between loneliness and the metabolic syndrome. Both samples included English-speaking Europeans; one identified an association with metabolic syndrome and the other did not (O’Luanaigh et al., 2012; Whisman, 2010).

In the US, according to 2003-2012 National Health and Nutrition Examination Survey data, the prevalence of metabolic syndrome in adults was 33% (Aguilar, Bhuket, Torres, Liu, & Wong, 2016). Despite the substantial prevalence of loneliness and metabolic syndrome in the US, and evidence of an association between loneliness and cardiometabolic risk, there are no studies of loneliness and the clinical classification of metabolic syndrome among US adults. Thus, the aim of this study was to examine the relationship between loneliness and the metabolic syndrome and its components in a nationwide sample of middle-aged US adults age 35 to 64 years. Clearer understanding was sought on whether people who self-report as lonely have higher odds of being classified with metabolic syndrome or its criteria using metabolic data collected at a clinical research site. We hypothesized that people who feel lonely would meet the individual criteria for metabolic syndrome and that they would meet a sufficient number of criteria to classify them as having metabolic syndrome.

Methods

Sample

Data for this study was drawn from MIDUS, a multi-study a national survey of adult US adults. The baseline sample was recruited in 1995-1996 (N=7,108). Non-institutionalized middle-aged and older adults (25-74 years) residing in the contiguous
United States were primarily recruited through random digit dialing (siblings and twins of original enrollees were also recruited). A follow-up survey was conducted in 2004-2006 (N=4,963). A sample of African Americans, the Milwaukee sample, was recruited in 2005-2006 (N=592). The sample for this study (n=927 adults age 35-64 years) was drawn from a MIDUS sub-study, the Biomarker Project, which was conducted in 2004-2009 (N=1,255) and included participants from the baseline sample and the Milwaukee sample of African Americans (Dienberg Love, Seeman, Weinstein, & Ryff, 2010).

Biomarker Project data were collected during an overnight stay at three clinical research sites: University of Wisconsin, Madison; the University of California, Los Angeles; and Georgetown University, Washington, D.C. (Brim et al., 2011; Radler, 2014; C. Ryff et al., 2012; C. D. Ryff, Seeman, & Weinstein, 2013). Siblings and twins also recruited at baseline resulted in 115 family clusters in the study sample. Data used in this analysis were collected in the MIDUS baseline, MIDUS follow-up, Milwaukee sample, and Biomarker Project through telephone interviews, self-administered questionnaires that included psychometric instruments, fasting blood samples, and clinical measures. Information is available for analysis on demographic characteristics, psychosocial well-being, health behaviors, and physical health. The Biomarker Project biological specimens data, the self-administered questionnaires, and the psychometric scales have been previously reported (C. Ryff et al., 2012; C. D. Ryff, Seeman, & Weinstein, 2010, 2011). Institutional review boards of The University of Wisconsin-Madison and the two other clinical sites approved MIDUS data collection procedures. Each participant in the Biomarker Project provided written informed consent. Most of the MIDUS data are publicly available through the ICPSR data repository (https://www.icpsr.umich.edu/).
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(Radler, 2014). However, a data use agreement was required for Milwaukee sample data due to the circumscribed area of recruitment.

Measures

*Loneliness*

Loneliness was measured using a single item from the Center for Epidemiological Studies Depression Scale (CES-D): “During the past week, I felt lonely…” Possible responses were: rarely or none of the time, some or a little of the time, occasionally, and most or all of the time (Radloff, 1977). Responses were dichotomized, as in prior studies (O’Luanaigh et al., 2012; Savikko et al., 2005), as “rarely or none of the time” (not lonely), and any of the other three categories (lonely).

*Metabolic syndrome*

The metabolic syndrome criteria established by the National Cholesterol Education Program (NCEP) Adult Treatment Panel-III (ATP-III) were used in this analysis. Participants were classified as having metabolic syndrome if they meet three of the following five criteria: 1) obesity: waist circumference >40 inches/101.6 cm for males or >35 inches/88.9cm for females; 2) hyperglycemia: fasting glucose ≥100 mg/dl or taking medication for hyperglycemia; 3) dyslipidemia: triglycerides ≥ 150 mg/dl or taking medication for elevated triglycerides; 4) dyslipidemia: HDL cholesterol <40 mg/dl for males or <50 mg/dl for females or taking medication for elevated HDL; 5) hypertension: blood pressure > 130 mmHg systolic or > 85 mmHg diastolic or taking

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1 For our analysis, study participants met the criteria for taking a medication for hypertriglyceridemia if they were taking fibrates. We did not include other pharmacological treatments for hypertriglyceridemia because other treatments, such as niacin, could be taken for other purposes, which could provide an overestimate. We opted for a more conservative approach.
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medication for hypertension (Huang, 2009). Seventeen participants (2% of the total sample) could not be classified due to missing data in at least one of the criteria.

Blood pressure and waist circumference measures were obtained through a physical examination according to standard procedures at all sites. Medication history was obtained through completion of a detailed medication chart (Dienberg Love et al., 2010). For HDL cholesterol, triglycerides, and blood glucose analyses, a fasting blood sample was obtained on day 2 according to a standardized study collection protocol at all sites. The samples were processed according to protocol and frozen in 1mL aliquots. HDL cholesterol and triglyceride level assays were performed at Meriter Labs using a Cobas Integra® analyzer, and blood glucose was assayed at the ARUP laboratories using an automated analyzer made by Roche Modular Analytics (C. D. Ryff et al., 2011). The MIDUS investigators accounted for extremely high HDL levels by adjusting values >120 mg/dL to 121 mg/dL. Table 1 summarizes the assay ranges for the metabolic syndrome criteria analyzed with blood samples and the metabolic syndrome criteria cut-points.

Table 1

<table>
<thead>
<tr>
<th>Assay</th>
<th>Assay Range</th>
<th>Cut-point for metabolic syndrome criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-cholesterol</td>
<td>0-155 mg/dL</td>
<td>&lt;40 mg/dL for males</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;50 mg/dL for females</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0-875 mg/dL</td>
<td>≥ 150 mg/dL</td>
</tr>
<tr>
<td>Glucose</td>
<td>2-750 mg/dL</td>
<td>≥100 mg/dl</td>
</tr>
</tbody>
</table>

Covariates

Demographic variables that have been shown to influence metabolic syndrome or the individual elements of the syndrome and loneliness were included in the final model. They were: age, sex, race (categorized into two groups to avoid small cell size: a)
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black/African American and b) white, multiracial, and other races), education (two categories: up to high school completion and education beyond a high school diploma), and household income (three categories with cutpoints at $30,000 and $60,000) (Backholer et al., 2016; Cohen-Mansfield, Hazan, Lerman, & Shalom, 2015; Linda C. Gallo, De Los Monteras, Ferent, Urbina, & Talavera, 2007; Hall et al., 2012; Hwang & Lee, 2014; Lidfeltdt et al., 2003; Morozink, Friedman, Coe, & Ryff, 2010; Saylor & Friedmann, 2015; Wildman et al., 2011; Yamamoto, Okazaki, & Ohmori, 2011). Two social factors were included in the model due to their established association with loneliness, their high correlation with loneliness in this sample, and their association with metabolic syndrome (Cohen-Mansfield, Hazan, Lerman, & Shalom, 2016; Feldman & Steptoe, 2003; Martin, Hagberg, & Poon, 1997; Pakalska-Korcala et al., 2008; Steptoe, Shankar, Demakakos, & Wardle, 2013b; Yang et al., 2016): a) social integration from Keyes’ Social well-being scale (Keyes, 1998), and b) social support, a self-reliance measure of aversion to asking for help (M. E. Lachman & Weaver, 1995). A mental health variable was included: binary measure of being depressed or not based on DSM-III criteria. Marital status was not included since it has been shown to influence metabolic syndrome only through depression (Henry et al., 2015). Health behavior characteristics included in the model were dichotomized for presence or absence of the following a) history of ever having smoked regularly, b) regular exercise (≥ 20 min 3 times per week), and c) poor sleep quality over the past month based on the global score of the Pittsburgh Sleep Quality Index defined as 5 or more. These three variables are established consequences of loneliness (Cacioppo et al., 2010; Cacioppo, Hughes, Waite, Hawkley, & Thisted, 2006; Hawkley & Capitanio, 2015; Jaremka et al., 2014; Kurina et al., 2011;
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Newall, Chipperfield, Bailis, & Stewart, 2012; Pels & Kleinert, 2016) and are associated with metabolic syndrome (Hall et al., 2012; Jennings, Muldoon, Hall, Buysse, & Manuck, 2007; Loponen, Hublin, Kalimo, Manttari, & Tenkanen, 2010; Saylor & Friedmann, 2015).

**Statistical Analyses**

Statistical analyses included descriptive statistics, simple logistic regression, and multiple logistic regression. Sample characteristics were examined by loneliness status using descriptive bivariate analyses. The regression models added covariates in three groups. The objective was to create a parsimonious model that avoided multicollinearity and controlled for important potential confounding variables to isolate the unbiased relationship between loneliness and the outcomes while providing a robust statistical result that can be generalized. The assumptions for logistic regression were tested for violations. The relationship between continuous variables included in the models and log odds of the metabolic syndrome were examined using visual displays. This sample includes siblings, creating potential correlation of outcomes among study participants. Clustered-correlated robust variance estimation was used to account for non-independence of error terms (Rogers, 1993). The results were similar to the ones without accounting for these dependencies, so the data reported is logistic regression without cluster-correlated variance estimates in the Results. Because three of the covariates may function like mediators in the analysis given that they are consequences of loneliness and associated with metabolic syndrome, all three are included in the final model. The variables are depression, regular exercise, and sleep quality. Fourteen percent of
participant were missing at least one piece of data for analysis. The sleep variable had the largest number of missing data items so data were imputed for that variable.

Hypothesis testing of the loneliness-metabolic syndrome relationship was conducted by running simple and multivariable logistic regression for meeting the criteria for metabolic syndrome and for each of the five individual metabolic syndrome criteria. The probability level was set a priori at 5% \( p \leq 0.05 \) to identify statistically significant associations with dependent variables. Covariates were added in this order: demographic characteristics (model 1), social factors (model 2), and mental health and health behaviors (model 3). Multicollinearity was assessed by examining pairwise correlations of variables and standard errors of beta coefficients. The data were analyzed using Stata Special Edition 14 for Windows (StataCorp, LP, College Station, Texas).

**Results**

Descriptive statistics of the sample are shown in Table 2. Forty percent of the study participants (n=363) met the criteria for metabolic syndrome. Among those with metabolic syndrome, 34% (n=125) felt lonely. Bivariate analyses to compare lonely versus not lonely participants demonstrated no difference between the two groups by sex \( p=0.998 \), blood pressure (systolic blood pressure mmHg \( p=0.524 \); diastolic blood pressure mmHG \( p=0.571 \)), hyperglycemia \( p=0.433 \), and dyslipidemia based on elevated triglyceride values \( p=0.472 \). All other characteristics showed statistically significant differences between lonely and not lonely participants.
Table 2

Sample characteristics by loneliness

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Study Sample n=927 M (SD)</th>
<th>Lonely n=272 29% N (%)</th>
<th>Not Lonely n=652 71% M (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.90 (7.47)</td>
<td>50.86 (7.30)</td>
<td>52.35 (7.50)</td>
<td>0.006</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>394 (42.50)</td>
<td>116 (42.65)</td>
<td>278 (42.64)</td>
<td>0.998</td>
</tr>
<tr>
<td>Female</td>
<td>533 (57.50)</td>
<td>156 (57.35)</td>
<td>374 (57.36)</td>
<td></td>
</tr>
<tr>
<td>Race:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, Multi</td>
<td>702 (78.26)</td>
<td>178 (68.20)</td>
<td>523 (82.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>195 (21.74)</td>
<td>83 (31.80)</td>
<td>110 (17.38)</td>
<td></td>
</tr>
<tr>
<td>Education:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;High school</td>
<td>245 (26.46)</td>
<td>90 (33.09)</td>
<td>153 (23.50)</td>
<td>0.003</td>
</tr>
<tr>
<td>&gt;Some college</td>
<td>681 (73.54)</td>
<td>182 (66.19)</td>
<td>498 (76.50)</td>
<td></td>
</tr>
<tr>
<td>Total household income:</td>
<td>$0-29,999</td>
<td>197 (21.58)</td>
<td>84 (31.70)</td>
<td>110 (17.05)</td>
</tr>
<tr>
<td>$30,000-59,999</td>
<td>228 (24.97)</td>
<td>76 (28.68)</td>
<td>152 (23.57)</td>
<td></td>
</tr>
<tr>
<td>$60,000+</td>
<td>488 (53.45)</td>
<td>105 (39.62)</td>
<td>383 (59.38)</td>
<td></td>
</tr>
<tr>
<td>Social</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social well-being: Social integration</td>
<td>14.44 (4.22)</td>
<td>12.74 (4.34)</td>
<td>15.16 (3.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Social support: Do not ask for help unless have to</td>
<td>1.93 (0.93)</td>
<td>1.76 (0.92)</td>
<td>1.99 (0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mental Health</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression diagnosis: Yes</td>
<td>134 (14.46)</td>
<td>69 (25.37)</td>
<td>63 (9.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>793 (85.54)</td>
<td>203 (74.63)</td>
<td>589 (90.34)</td>
<td></td>
</tr>
<tr>
<td>Health Behaviors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smoked cigarettes regularly</td>
<td>429 (46.33)</td>
<td>144 (52.94)</td>
<td>282 (43.32)</td>
<td>0.008</td>
</tr>
<tr>
<td>Never smoked cigarettes regularly</td>
<td>497 (53.67)</td>
<td>128 (47.06)</td>
<td>369 (56.68)</td>
<td></td>
</tr>
<tr>
<td>Regular exercise</td>
<td>716 (77.32)</td>
<td>192 (68.20)</td>
<td>523 (80.34)</td>
<td>0.001</td>
</tr>
<tr>
<td>No regular exercise</td>
<td>210 (22.68)</td>
<td>80 (29.41)</td>
<td>128 (19.66)</td>
<td></td>
</tr>
<tr>
<td>Sleep score (PSQI) &lt;5</td>
<td>314 (36.43)</td>
<td>46 (16.04)</td>
<td>267 (44.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sleep score (PSQI) ≥5</td>
<td>548 (63.57)</td>
<td>209 (81.96)</td>
<td>338 (55.87)</td>
<td></td>
</tr>
<tr>
<td>Metabolic Syndrome &amp; Components</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>363 (39.98)</td>
<td>125 (34.44)</td>
<td>238 (65.56)</td>
<td>0.008</td>
</tr>
<tr>
<td>Obesity measured by waist circumference</td>
<td>&gt;102cm (M) &gt;88cm (F)</td>
<td>97.42 (17.66)</td>
<td>100.16 (17.17)</td>
<td>96.23 (17.75)</td>
</tr>
<tr>
<td></td>
<td>≤102cm (M) ≤88cm (F)</td>
<td>492 (53.19)</td>
<td>164 (60.52)</td>
<td>325 (49.92)</td>
</tr>
<tr>
<td>Hyperglycemia measured by fasting blood glucose</td>
<td>FBS &lt;100mg/dL</td>
<td>102.19 (30.53)</td>
<td>103.37 (33.42)</td>
<td>101.63 (29.24)</td>
</tr>
<tr>
<td></td>
<td>FBS ≥100mg/dL</td>
<td>345 (37.83)</td>
<td>106 (39.41)</td>
<td>238 (37.13)</td>
</tr>
<tr>
<td>Dyslipidemia measured by triglycerides</td>
<td>Triglycerides &lt;150mg/dL</td>
<td>135.92 (147.41)</td>
<td>141.07 (141.89)</td>
<td>133.40 (149.46)</td>
</tr>
<tr>
<td></td>
<td>Triglycerides ≥150mg/dL</td>
<td>651 (70.92)</td>
<td>193 (71.22)</td>
<td>457 (70.50)</td>
</tr>
<tr>
<td>Dyslipidemia measured by HDL cholesterol</td>
<td>mg/dL</td>
<td>55.15 (18.23)</td>
<td>53.21 (17.73)</td>
<td>55.99 (18.40)</td>
</tr>
<tr>
<td></td>
<td>&lt;40 (M) &lt;50 (F)</td>
<td>289 (31.55)</td>
<td>98 (36.30)</td>
<td>190 (29.50)</td>
</tr>
<tr>
<td></td>
<td>≥40 (M) ≤50 (F)</td>
<td>627 (68.45)</td>
<td>172 (63.70)</td>
<td>454 (70.50)</td>
</tr>
<tr>
<td>Hypertension measured by blood pressure</td>
<td>Systolic Blood pressure</td>
<td>&gt;130 mmHg</td>
<td>129.13 (17.67)</td>
<td>128.58 (16.68)</td>
</tr>
<tr>
<td></td>
<td>≤130 mmHg</td>
<td>410 (44.32)</td>
<td>122 (45.02)</td>
<td>287 (44.09)</td>
</tr>
<tr>
<td></td>
<td>Diastolic Blood pressure</td>
<td>&gt;85 mmHg</td>
<td>515 (55.68)</td>
<td>149 (54.98)</td>
</tr>
<tr>
<td></td>
<td>≤85 mmHg</td>
<td>76.65 (10.72)</td>
<td>76.97 (10.52)</td>
<td>76.53 (10.83)</td>
</tr>
</tbody>
</table>

Note. Left justified values are mean and standard deviation: M (SD); Right justified values are number and percent: N (%); p-values obtained from Student’s t test for continuous variables and Pearson’s Chi-square for categorical variables. PSQI=Pittsburgh sleep quality index, M=male, F=female, FBS=fasting blood sugar, HDL=high density lipoprotein
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The relationship between loneliness and metabolic syndrome was not significant in the unadjusted model (OR=1.34, p=.059, 95% CI=0.99, 1.80) or in the models adjusting for potential confounders (Table 3). Depression diagnosis, regular physical exercise, and history of smoking are established consequences of loneliness. After these three variables were added in model 3, there was a substantial decrease in the beta coefficient for loneliness (model 2: b=0.23, model 3: b=0.08). A classical test of mediation was not performed, but the change in beta coefficients suggests that these three constructs have complicated relationships that may be in the causal pathway.

Table 3

*Loneliness in simple and multivariable regression with metabolic syndrome (n=854)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>p</td>
<td>CI</td>
</tr>
<tr>
<td>Lonely vs not lonely</td>
<td>1.31</td>
<td>.092</td>
<td>0.96, 1.79</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.02</td>
<td>.048</td>
<td>1.00, 1.04</td>
</tr>
<tr>
<td>Female vs male</td>
<td>0.61</td>
<td>.001</td>
<td>0.46, 0.81</td>
</tr>
<tr>
<td>Black vs Other races</td>
<td>1.09</td>
<td>.631</td>
<td>0.76, 1.58</td>
</tr>
<tr>
<td>High school graduate or less vs greater than high school</td>
<td>1.30</td>
<td>.117</td>
<td>0.94, 1.81</td>
</tr>
<tr>
<td>Annual household income $30,000-59,000 vs &lt;$30,000</td>
<td>0.85</td>
<td>.433</td>
<td>0.56, 1.29</td>
</tr>
<tr>
<td>$60,000 + vs &lt;$30,000</td>
<td>0.90</td>
<td>.613</td>
<td>0.61, 1.34</td>
</tr>
<tr>
<td>Social integration score</td>
<td>0.97</td>
<td>.146</td>
<td>0.94, 1.01</td>
</tr>
<tr>
<td>Social support: Self-reliance (not asking for help score)</td>
<td>1.14</td>
<td>.105</td>
<td>0.97, 1.33</td>
</tr>
<tr>
<td>Depression diagnosis vs not</td>
<td>1.20</td>
<td>.396</td>
<td>0.78, 1.85</td>
</tr>
<tr>
<td>Ever smoked regularly vs never smoked regularly</td>
<td>0.88</td>
<td>.387</td>
<td>0.65, 1.18</td>
</tr>
<tr>
<td>No regular exercise vs exercises regularly</td>
<td>1.67</td>
<td>.003</td>
<td>1.19, 2.35</td>
</tr>
<tr>
<td>Poor sleep quality vs good quality sleep</td>
<td>1.30</td>
<td>.001</td>
<td>1.11, 1.52</td>
</tr>
</tbody>
</table>

*Note.* vs=versus
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Table 4 summarizes associations between loneliness and individual metabolic syndrome criteria: obesity, hyperglycemia, dyslipidemia based on triglycerides, dyslipidemia based on HDL-cholesterol, and hypertension. The relationship between loneliness and obesity was significant in the logistic regression models including demographic and social variables, but became non-significant after adjustment for depression and health behaviors.

Table 4

<table>
<thead>
<tr>
<th></th>
<th>Obesity</th>
<th>Hyperglycemia</th>
<th>Dyslipidemia (Triglycerides)</th>
<th>Dyslipidemia (HDL-Cholesterol)</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (CI)</td>
<td>OR (CI)</td>
<td>OR (CI)</td>
<td>OR (CI)</td>
<td>OR (CI)</td>
</tr>
<tr>
<td>Lonely vs not lonely</td>
<td>1.58**</td>
<td>1.15</td>
<td>0.98</td>
<td>1.28</td>
<td>1.27</td>
</tr>
<tr>
<td></td>
<td>(1.17, 2.13)</td>
<td>(0.85, 1.55)</td>
<td>(0.71, 1.37)</td>
<td>(0.93, 1.75)</td>
<td>(0.94, 1.73)</td>
</tr>
<tr>
<td>Lonely vs not lonely after demographic variables included</td>
<td>1.50*</td>
<td>1.08</td>
<td>0.99</td>
<td>1.32</td>
<td>1.20</td>
</tr>
<tr>
<td></td>
<td>(1.10, 2.06)</td>
<td>(0.79, 1.49)</td>
<td>(0.70, 1.41)</td>
<td>(0.95, 1.83)</td>
<td>(0.87, 1.67)</td>
</tr>
<tr>
<td>Lonely vs not lonely after demographic and social variables included</td>
<td>1.40*</td>
<td>1.12</td>
<td>0.89</td>
<td>1.23</td>
<td>1.24</td>
</tr>
<tr>
<td></td>
<td>(1.01, 1.93)</td>
<td>(0.81, 1.56)</td>
<td>(0.62, 1.27)</td>
<td>(0.88, 1.73)</td>
<td>(0.89, 1.72)</td>
</tr>
<tr>
<td>Lonely vs not lonely after demographic, social, mental health, and health behavior variables included</td>
<td>1.26</td>
<td>1.05</td>
<td>0.74</td>
<td>1.12</td>
<td>1.13</td>
</tr>
<tr>
<td></td>
<td>(0.90, 1.77)</td>
<td>(0.75, 1.48)</td>
<td>(0.51, 1.08)</td>
<td>(0.79, 1.59)</td>
<td>(0.80, 1.60)</td>
</tr>
</tbody>
</table>

Note. HDL=high density lipoprotein, OR=odds ratio, CI=95% confidence interval, vs=versus
*p<.05 **p<.01

Discussion

In this analysis, loneliness was not significantly associated with metabolic syndrome. In addition, the estimated odds ratio decreased towards the null (from 1.31 in the model adjusted for demographics to 1.08 in the model including covariates that may be potential mediators). The results were as hypothesized where reporting loneliness would increase odds of metabolic syndrome, but the associations were weaker possibly.
due to inclusion of variables that may be in the causal pathway. This may be the first study to examine the association between loneliness and metabolic syndrome in middle-aged community-dwelling US adults. Because participants as young as 35 years were included, our findings contribute to a better understanding of loneliness and metabolic syndrome in middle-aged adults. The mean age of our sample (52 years) was more than a decade younger than the two studies that identified associations between loneliness and metabolic syndrome or its elements (75 and 64 years, respectively) (O’Luanaigh et al., 2012; Whisman, 2010). Because similar associations were not observed in our middle-aged sample with a younger mean age, prevention efforts addressing loneliness may preserve cardiometabolic dysfunction in this age group. However, more evidence is needed to translate any findings into practice.

For comparison, regressions were run on this study sample using the same covariates used in the study conducted by Whisman (2010) (age, married/cohabitating, race, sex, income, smoking history) and a significant relationship was found between loneliness and metabolic syndrome in this study sample, which is the same outcome reported in the published paper. These variables, except for marriage/cohabitation status, were included in our analysis. Marriage/cohabitation status was not included in our analysis because prior findings demonstrated that the effect of marriage on metabolic syndrome is mediated by depression (Henry et al., 2015). Depression was included in our analysis. A comparison was also made between the design and findings of this study to the other published analysis of loneliness and metabolic syndrome. The results from the study by O’Luanaigh et al. (2012), which sought to clarify the pathway between loneliness and metabolic dysfunction, were similar to our findings which were largely
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but not completely non-significant. An important difference is that their mean age was 23 years higher than ours, and an important similarity is that both studies used the same measure of loneliness and similar adjustments for socio-demographics, depression, physical exercise, smoking, and social engagement. That study also controlled for alcohol consumption and dietary intake and this study did not. These comparative analyses suggest that the relationship between loneliness and metabolic syndrome is complex and multifactorial.

An important finding from this study is the high prevalence of metabolic syndrome in this sample of middle-age US adults (40%). This finding alone points to the need for further examination of the factors that may be contributing to such a significant burden of cardiometabolic ill-health in middle-age adults. It is possible that the multiple stressors of middle age and the many changes that occur during middle age supply a continuous dose of stress, whether positive or negative. Whether seen positively or negatively, the numerous demands and resulting stress reduce leisure time and the ability to engage in healthy behaviors, such as regular physical exercise. There is a trend in sedentary behavior in the US which increases the risk of developing metabolic syndrome (Dariush Mozaffarian et al., 2016). When loneliness is also present unhealthy behaviors may be further exacerbated. In fact, in this sample 30% of the lonely participants said they did not exercise regularly. And a large proportion (61%) of lonely study participants were classified as obese in this sample. Obesity is an established physiologic determinant of cardiometabolic disease (Hotamisligil, 2006; Wildman et al., 2011). Cumulative exposure over the lifespan to unhealthful behaviors increases the risk of metabolic syndrome (Dariush Mozaffarian et al., 2016).
The representativeness of our sample is a limitation of our study. Data from the 2010 US Census, the closest to the conclusion of the Biomarker Project data collection, shows that our sample had fewer multi-racial participants and participants of races other than white or black, compared to the census findings (Humes, Jones, & Ramirez, 2011). This sample is also disproportionately female (58%) compared to national averages in 2010 (Howden & Meyer, 2011). Although single item measures of loneliness are not unusual (Holmén & Furukawa, 2002; Holwerda et al., 2014; Savikko et al., 2005; Thurston & Kubzansky, 2009), the measure we used could have underestimated loneliness, and therefore this measure might be considered a limitation (Holt-Lunstad et al., 2010). However, a recent study by AARP on loneliness in adults 45 years and older used a multi-item measure (the UCLA Loneliness Scale) and a single item measure for loneliness and they found the measures to be highly correlated in their study ($r=.735$, $p<.001$) (AARP, 2010; G. Oscar Anderson (AARP Senior Research Advisor), 2016).

Moreover, an analysis comparing the single item measure of loneliness from the CES-D, which was used in this study, and a commonly used three-item scale demonstrated that the CES-D single-item was a sensitive measure (Shiovitz-Ezra & Ayalon, 2012). In prior studies, gender bias was identified when using a single measure, but that finding was not apparent in this sample (Borys & Perlman, 1985; Hawkley et al., 2008). A difference in willingness to self-disclose loneliness may reflect changes in contemporary American society. Given the rapid expansion of social networking in the mid-2000s when this data were collected, participants may not have been reluctant to self-identify as lonely. The pervasiveness of new social media is expanding views of socializing and socialization.
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(Parigi & Henson, 2014). Given this new social reality, future research on the measures of loneliness in the US is warranted.

This study makes an important contribution to research about adults in middle age. It adds to a limited body of literature examining loneliness in middle-aged US adults and it provides information to inform social science research, clinical care, and social care. The MIDUS data also provide a large sample and rich subjective data collected directly from participants. This enables researchers to include both felt emotions and biological data from a large sample to explore contemporary questions which may help shape clinical and social care. As evidence increases on the utility of incorporating new, more sensitive biomarkers of cardiometabolic risk into syndromic classifications of metabolic risk, associations with psychosocial factors such as loneliness may become even more important to examine (Eckel & Cornier, 2014).

Conclusion

In this study, the relationship between loneliness and the metabolic syndrome was examined along with the individual metabolic syndrome criteria in a sample of middle-aged adults residing in the US. Unlike other studies examining loneliness, ours included study participants in the earlier part of middle age beginning at 35 years. We demonstrated significant increased odds of obesity among lonely participants, but the significance of the association disappeared when depression and health behaviors were included in the regression. Likewise, the strength of the relationship between metabolic syndrome and loneliness weakened when covariates that are known to be consequences of loneliness were added to the model. These findings suggest that some of the relationship might be mediated by consequences of loneliness such as depression, no
regular exercise, and poor sleep quality. Efforts to improve cardiometabolic health has the potential to improve quality of life and physical and mental health outcomes in middle-aged adults. Further research on the loneliness-metabolic syndrome relationship is needed in US-based populations.

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Chapter 4: Manuscript 3

The Relationship Between Loneliness and Perceived Neighborhood Quality is Mediated by Social Integration in a Sample of Middle-Aged US Adults

Target journal: Social Science and Medicine

Title: The relationship between loneliness and perceived neighborhood quality is mediated by social integration in a sample of middle-aged US adults

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Keywords:
USA; Loneliness; Neighborhood; Social integration; Middle age, MIDUS

Research highlights:
- Perceived neighborhood quality and social integration influence loneliness.
- Loneliness is prevalent among community-dwelling middle-aged US adults.
- Longstanding adults and new arrivals may both be susceptible to loneliness.

Suggested reviewers: Teresa Seeman
Abstract

Loneliness is prevalent, associated with poor health outcomes, and confers increased odds of death. Middle-aged adults face even higher odds of death from loneliness than older lonely adults, but the factors that make middle-age adults vulnerable are unclear. Neighborhood quality and social integration are associated with self-reported health. The model of “Individual and societal factors in the emergence of loneliness” (de Jong Gierveld, 2012, p.292) places quality of living conditions and social integration on the pathway to loneliness. In this study, we examine the relationship between perceived neighborhood quality and loneliness in a sample of middle-aged US adults, and we further investigate the influence of social integration on that relationship. Data were drawn from the Midlife in the US (MIDUS) survey Biomarker Project. Middle-aged participants (35-64 years) were included in our sample (n=927). Baseline MIDUS data were collected in 1995 and 1996 and a follow-up survey was conducted from 2004 to 2006. A sample of African American participants in Milwaukee was surveyed in 2005 and 2006. The Biomarker Project, which enrolled participants from the baseline MIDUS survey and the Milwaukee sample, collected data from 2004 to 2009. Simple and multiple logistic regression were used to examine the relationship between perceived neighborhood quality and loneliness and we found the relationship to be significant in simple regression and in models controlling for demographics, social support, and physical health. We also found that social integration partially mediated the relationship between perceived neighborhood quality and loneliness. These significant results point to municipalities, charitable organizations, and neighborhood associations as possible targets for interventions that address neighborhood quality. Strategies that promote a
sense of safety, foster a feeling of belonging, and create opportunities for connections among neighbors may prevent loneliness, improve health and well-being, and reduce the odds of mortality attributable to loneliness.

**Introduction**

People who are lonely have poor health outcomes and increased odds of death (Cacioppo, Hawkley, and Thisted 2010; Hawkley et al. 2006; Holt-Lunstad et al. 2015; Holt-Lunstad, Smith, and Layton 2010; Holt-lunstad and Smith 2016; Jaremka et al. 2014; Sorkin, Rook, and Lu 2002; Yang, Schorpp, and Harris 2014). A wide range of sociodemographic, psychological, social, and environmental factors have been identified as predictors of loneliness (Cohen-Mansfield et al. 2016). Because loneliness, a psychosocial condition, concerns individual perception of whether one’s relationships are of sufficient quality and quantity (Perlman and Peplau 1998), examination of social contributors to loneliness is essential.

Social factors including social fragmentation, social cohesion, social engagement, and social isolation are associated with mental health, chronic disease risk behaviors, and mortality (Erdem et al. 2015; Holt-Lunstad et al. 2010; Ivory et al. 2011; Samuel et al. 2015). Social integration is a measure of social well-being which is specifically posited to influence loneliness. Indeed, the theoretical framework proposed by de Jong Gierveld describes “Individual and societal factors in the emergence of loneliness” and places social integration on a pathway from quality of living conditions to loneliness (de Jong Gierveld and Tesch-Römer 2012a). They argue that social integration can protect against loneliness. This is important to consider since lack of positive social relationships carries...
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health risks comparable to smoking about 15 cigarettes per day (House, 1988; Hawkley 2003; Cacioppo, 2003; Shavelle, 2008).

The quality of living conditions includes neighborhood factors. Studies conducted in the United Kingdom and The Netherlands demonstrated that neighborhood quality is associated with loneliness among adults over age 60 (Scharf and de Jong Gierveld 2008). Social capital is a composite measure of social engagement, participation in activities, a feeling of trust, and a sense of belonging to the neighborhood that is also associated with loneliness (Nyqvist et al. 2016). Low social capital, and specifically low levels of trust, have been identified as risk factors for loneliness in a sample of adults spanning a wide age range (15-80 years) in Finland (Nyqvist et al. 2016). Environmental barriers, including unsafe neighborhoods and inadequate resources for socializing, were mentioned in focus groups of adults over 60 years in Israel as factors contributing to loneliness (Cohen-Mansfield et al. 2016). We were unable to identify United States (US)-based studies that specifically examined loneliness in the context of neighborhood quality.

The relationships between neighborhood characteristics, social integration, and health are complex. For example, among adults of all ages in the US, low social integration was found in high-poverty neighborhoods, but neighbors had more contact with each other in high-poverty compared to low-poverty neighborhoods (Marcus et al. 2015). Also, among US adults, neighborhood characteristics and perceived neighborhood quality have been found to influence self-rated health (Weden, Carpiano, and Robert 2008). However, it is not known if perceptions of neighborhood quality are related to loneliness among US adults.
For our analysis, we focus on 35-64 year-old middle-aged adults. People in this age group tend to be highly engaged in work and family life. But that does not mean that they are protected from feeling lonely. A recent meta-analysis found that lonely middle-aged adults have higher odds of death than lonely older adults (Holt-Lunstad, 2015). We also know from recent analyses that white middle-aged US adults have experienced an uptick in death rates compared to prior decades (Shiels, 2017; Case, 2015). Unintentional poisoning and other proximal effects of “diseases of despair,” which include depression, alcoholism, and substance abuse, appear to account for the increase in mortality from unintentional poisoning, liver disease, and suicide. Loneliness and how people relate to their neighborhood may be part of a complex web of factors contributing to the rising death rates. Economic decline, job loss, and substance abuse may result in more middle-aged adults remaining at home, as opposed to working outside of their neighborhood. If people perceive their neighborhood as unsafe or unfriendly they may be reluctant to leave their home and interact with others. However, if they integrate into their community, loneliness may be abated.

Thus, our study examines the influence of perceived neighborhood quality on loneliness among middle-aged US adults and how their self-reported degree of social integration mediates that relationship. We hypothesize that participants who perceive their neighborhood quality as low will have higher odds of feeling lonely compared with those who perceive neighborhood quality as high. We also hypothesize that more socially integrated participants will have lower odds of feeling lonely, even if they perceive their neighborhood quality as low.
Methods

Sample

Our sample of 927 middle-aged adults was drawn from the Biomarker Project of the Midlife in the US (MIDUS) survey. MIDUS enrolled 7,108 non-institutionalized middle-aged and older adults residing in the contiguous US in 1995 and 1996 through random digit dialing (Dienberg Love et al. 2010). Ten years later, a follow-up survey was conducted and an additional sample of African Americans was recruited in Milwaukee (the Milwaukee sample). The Biomarker Project recruited 1,255 participants from the MIDUS baseline survey and the Milwaukee sample. From this group, we limited our sample to records of participants age 35-64 years. Biomarker Project participants provided biological, clinical, and psychometric data during a two-day stay at one of three clinical research sites in the US. Demographic, socioeconomic, psychosocial, and physical health data for our analysis was also collected through telephone interviews, self-administered questionnaires, and psychometric instruments. Data for this analysis are from the Biomarker Project, MIDUS baseline and follow-up surveys, and the Milwaukee Sample. The MIDUS sampling design includes siblings and twins and our sample had 115 family clusters (Brim et al. 2011; Radler 2014; Ryff, Seeman, and Weinstein 2011, 2013). Analysis of missing data showed that 94% of the records were complete.

The ICPSR data repository at the University of Michigan houses the MIDUS data (https://www.icpsr.umich.edu) which are mostly publicly available (Radler 2014). However, to access the Milwaukee Sample data, which was collected from a limited geographic area, a data use agreement was executed. Detailed information on MIDUS has been previously reported (Ryff et al. 2012; Ryff, Seeman, and Weinstein 2010). The
institutional review board at the University of Wisconsin, Madison approved the MIDUS study and written informed consent was obtained from all participants.

**Measures**

*Loneliness*

The primary outcome for this analysis is self-reported loneliness. We used a single item measure from the Center for Epidemiological Studies Depression Scale (CES-D) (Radloff 1977) which has been used in prior nationwide surveys examining loneliness (Thurston and Kubzansky 2009). The question about loneliness was structured with four ordinal responses following the prompting question “During the past week, I felt lonely…” Response options were: rarely or none of the time, some or a little of the time, occasionally, and most or all of the time. We classified the answers into two groups representing not lonely (“rarely or none of the time”) and lonely (all other responses) as has been done in prior studies (O’Luanaigh et al. 2012; Routasalo et al. 2006). The loneliness measure was collected during the Biomarker Project visit to a clinical research site.

*Perceived Neighborhood Quality*

Perceived neighborhood quality is the independent variable for this analysis. It is a measure of personal beliefs about neighborhood safety and people’s neighbors. The four-item scale has a Cronbach’s $\alpha$ of .68 in the MIDUS sample. Scores ranged from 1-4 where high scores reflect positive perception of neighborhood quality (Brim, Bumpass, and Cleary 2009). We dichotomized this continuous variable based on the distribution of the data because it did not have a linear relationship with the log odds of the outcome.
variable, loneliness. The new variable reflects whether participants perceive their neighborhood as low quality (score of ≤3) or high quality (>3). The perceived neighborhood quality measure was collected during the MIDUS follow-up survey and Milwaukee sample data collection which preceded the Biomarker Project by 2.25 years on average.

Social Integration

Social integration is a measure of social well-being which includes three items and has a Cronbach’s $\alpha$ of .73 in the MIDUS data. A greater feeling of social integration is reflected by higher scores. Indicators measured in this scale are a sense of belonging, a feeling of closeness to members of the community, and a perception of the community as a comforting resource (Brim et al. 2009). The social integration measure used in this study was collected during the MIDUS follow-up survey and the Milwaukee sample data collection which preceded the Biomarker Project and measurement of the loneliness variable by 2.25 years on average.

Covariates

Demographic, psychosocial, and physical health covariates were selected based on prior research that demonstrated their associations with perceived neighborhood quality and loneliness. Demographic variables included age, self-reported race, education dichotomized as less than or equal to completion of high school and more than high school, and income in three categories (cutpoints at $30,000 and $60,000) (Cohen-Mansfield et al. 2016; Morozink et al. 2010). The social support variables measure the degree to which the participant seeks social support, and whether they are married or
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cohabitating (Cohen-Mansfield et al. 2016; Hawkley et al. 2010; Martin, Hagberg, and Poon 1997). We control for poor physical health through two continuous variables (Cohen-Mansfield et al. 2016; Hawkley et al. 2010; Nummela, Seppänen, and Uutela 2011). The first includes participants with up to three symptoms or chronic conditions and the second includes participants with four or more. Variables associated with perceived neighborhood quality that are also established consequences of loneliness should not confound the relationship and therefore they are not included. These variables are depression, regular exercise, and sleep quality (Hawkley, 2015; Jaremka, 2014; Newall, 2013; Pels, 2016).

Statistical Analysis

First, we examined the characteristics of the study sample by loneliness status using bivariate analyses. We specified the multivariable regression model a priori based on prior research related to our study aim. We examined continuous variables for a linear relationship with the log odds of loneliness, and those which violated the assumption were converted to categorical variables or linear splines were used to create multiple continuous variables. We also tested for independence of error terms using clustered sandwich estimation because our sample includes siblings and may have correlated outcomes.

We ran simple logistic regression of perceived neighborhood quality and loneliness, and multivariable logistic regression models, adjusting first for demographic variables (model 1: age, race, education, and household income), followed by variables of social support (model 2: married or cohabitating, and whether one asks for help when needed), and finally adjusting for number of symptoms and chronic conditions (model 3).
We noted the covariates associated with substantial odds of feeling lonely. We then ran a test of mediation using the approach described by Barron and Kenny (1986) to determine if social integration mediated the relationship between perceived neighborhood quality and loneliness. The probability level was set a priori at 5% ($p \leq .05$) to identify a statistically significant association between perceived neighborhood quality and loneliness. Sensitivity analyses compared the results when a more narrow age range of 40-64 years was used. Stata Special Edition 14 for Windows (StataCorp, LP, College Station, Texas) was used to analyze the data.

**Theoretical Framework**

The theoretical framework developed by loneliness researcher de Jong Gierveld (de Jong Gierveld and Tesch-Römer 2012b, p.292) (Figure 1) places the variables of interest in this analysis on a pathway whereby quality of living conditions is mediated by social integration, which interacts with social expectations and leads to loneliness.

Figure 1

*Theoretical framework of “Individual and societal factors in the emergence of loneliness”*


**Results**

A summary of the sample characteristics overall and by loneliness status is provided in Table 1. Tests of the assumptions required for logistic regression revealed no violations. We confirmed that error terms were independent despite the inclusion of siblings in the sample. We only used cases with complete data for simple and
multivariable logistic regression. This resulted in a small amount of missing data in this sample (6%).

Table 1

*Sample characteristics by loneliness*

<table>
<thead>
<tr>
<th></th>
<th>Study Sample</th>
<th>Lonely n=272 (29%)</th>
<th>Not Lonely n=652 (71%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>N (%)</td>
<td>M (SD)</td>
<td>N (%)</td>
</tr>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.90 (7.47)</td>
<td></td>
<td>50.86 (7.30)</td>
<td>52.35 (7.50)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, Multiracial, and other</td>
<td>702 (78.26)</td>
<td>178 (68.20)</td>
<td>523 (82.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>195 (21.74)</td>
<td>83 (31.80)</td>
<td>110 (17.38)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤High school</td>
<td>245 (26.46)</td>
<td>90 (33.09)</td>
<td>153 (23.50)</td>
<td>0.003</td>
</tr>
<tr>
<td>≥Some college</td>
<td>681 (73.54)</td>
<td>182 (66.19)</td>
<td>498 (76.50)</td>
<td></td>
</tr>
<tr>
<td>Total household income: $0-29,999</td>
<td>197 (21.58)</td>
<td>84 (31.70)</td>
<td>110 (17.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$30,000-59,999</td>
<td>228 (24.97)</td>
<td>76 (28.68)</td>
<td>152 (23.57)</td>
<td></td>
</tr>
<tr>
<td>$60,000 +</td>
<td>488 (53.45)</td>
<td>105 (39.62)</td>
<td>383 (59.38)</td>
<td></td>
</tr>
<tr>
<td><strong>Social</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married or Living with</td>
<td>601 (64.90)</td>
<td>117 (43.01)</td>
<td>484 (74.35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Someone</td>
<td>325 (35.10)</td>
<td>155 (56.99)</td>
<td>167 (25.65)</td>
<td></td>
</tr>
<tr>
<td>Social support:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doesn’t ask for help</td>
<td>369 (39.81)</td>
<td>139 (51.29)</td>
<td>229 (35.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asks for help</td>
<td>553 (59.19)</td>
<td>132 (48.71)</td>
<td>419 (64.66)</td>
<td></td>
</tr>
<tr>
<td>Social well-being:</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Social integration score</td>
<td>14.44 (4.22)</td>
<td>12.74 (4.34)</td>
<td>15.16 (3.94)</td>
<td></td>
</tr>
<tr>
<td>Perceived neighborhood quality:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived as low</td>
<td>225 (24.32)</td>
<td>104 (38.38)</td>
<td>119 (18.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perceived as high</td>
<td>700 (75.68)</td>
<td>167 (61.62)</td>
<td>532 (81.72)</td>
<td></td>
</tr>
<tr>
<td><strong>Physical Health</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms or chronic conditions:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>525 (56.88)</td>
<td>139 (51.10)</td>
<td>386 (59.29)</td>
<td>0.022</td>
</tr>
<tr>
<td>≥ 4</td>
<td>398 (43.12)</td>
<td>133 (48.90)</td>
<td>265 (40.71)</td>
<td></td>
</tr>
</tbody>
</table>

*Note. Left justified values are mean and standard deviation: M (SD); Right justified values are number and percent: N (%)*

Those who perceived their neighborhood quality as low had higher odds of feeling lonely than those who perceived their neighborhood quality as high. In simple regression, those who perceived their neighborhood quality to be low compared to those who perceived it as high were twice as likely to report feeling lonely (OR=2.05, p <.001, 95% CI=1.44, 2.90), and the relationship remained significant even after adjusting for potential confounders (Table 2).
Table 2

*Perceived neighborhood quality in simple and multivariable regression for loneliness (n=868)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>p</td>
<td>95% CI</td>
</tr>
<tr>
<td>Low vs high perceived neighborhood quality</td>
<td>2.05</td>
<td>&lt;.001</td>
<td>1.44, 2.90</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.98</td>
<td>.024</td>
<td>0.96, 1.00</td>
</tr>
<tr>
<td>Black vs other races</td>
<td>1.26</td>
<td>.238</td>
<td>0.86, 1.87</td>
</tr>
<tr>
<td>High school graduate or less vs at least some college</td>
<td>1.24</td>
<td>.238</td>
<td>0.87, 1.76</td>
</tr>
<tr>
<td>Annual household income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$30,000-59,000 vs &lt;$30,000</td>
<td>0.74</td>
<td>.163</td>
<td>0.48, 1.13</td>
</tr>
<tr>
<td>$60,000 + vs &lt;$30,000</td>
<td>0.47</td>
<td>&lt;.001</td>
<td>0.31, 0.71</td>
</tr>
<tr>
<td>Not married or cohabitating vs married or cohabitating</td>
<td>3.04</td>
<td>&lt;.001</td>
<td>2.12, 4.36</td>
</tr>
<tr>
<td>Doesn’t ask for help when needed vs asks for help</td>
<td>1.53</td>
<td>.009</td>
<td>1.11, 2.10</td>
</tr>
<tr>
<td>0-3 Symptoms or chronic conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-20 Symptoms or chronic conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note:* vs=versus, OR=odds ratio, p=p-value, CI=confidence interval

In the model that adjusted for all covariates, participants who perceived their neighborhood as low quality had 81% increased odds of feeling lonely than participants who perceived their neighborhood quality as high. The odds of feeling lonely increased 42% for each added symptom or chronic condition. Participants who were not married or cohabitating had three times the odds of feeling lonely compared with people who were married or cohabitating. The social support variable, which represented whether people do not ask for help when needed showed 56% increased odds of feeling lonely if the measure was ranked high compared to when it was ranked low.

Social integration partially mediated the effect of perceived neighborhood quality on loneliness. (Figure 2). The indirect effect was 0.26.
Figure 2

Social integration partially mediates the relationship between perceived neighborhood quality and loneliness

![Diagram showing the relationship between perceived neighborhood quality, social integration, and loneliness with statistical coefficients and p-values]

Note.

a = Results of linear regression after controlling for age, race, education, household income, married or cohabitating, whether one asks for help when needed, and number of symptoms and chronic conditions

b & c = Results of logistic regression after controlling for age, race, education, household income, married or cohabitating, whether one asks for help when needed, and number of symptoms and chronic conditions

c' = Results of logistic regression after controlling for age, race, education, household income, married or cohabitating, whether one asks for help when needed, and number of symptoms and chronic conditions and including social integration

Sensitivity analysis using 40-64 years demonstrated no change in the significance, direction, or strength of the relationships between perceived neighborhood quality and feeling lonely or the mediating effect of social integration.

Discussion

In this study of community-dwelling middle-aged US adults, we found that perceived neighborhood quality had a large impact on self-reported feelings of loneliness, even in conservative models. We also found that social integration partially mediated this
relationship. These findings confirmed our hypotheses and validated individual level factors in the de Jong Gierveld theoretical model. To our knowledge, this is the first study of a sample of US adults to demonstrate the interrelations between perceptions of neighborhood quality, social integration, and loneliness. Although many studies have examined objective characteristics of neighborhoods, fewer have considered how perceptions of one’s living conditions influence feelings of loneliness. This study also validates the importance of social integration in the relationship between perceived neighborhood quality and loneliness.

In our sample, being integrated into one’s community partially protected participants from loneliness when they perceived their neighborhood quality as low. This finding suggests that feeling lonely is directly affected by how neighborhood quality is perceived, and that other factors are also involved. Further investigation of factors not included in our model would improve the ability to translate this finding to practice. For example, socioeconomic factors not included in this analysis may provide additional insight into the complex interlinkages between neighborhood characteristics, measures of sociality, and health. US-based studies have demonstrated that favorable socioeconomic status is associated with better self-rated health and outcomes for depression, hostility, and stress. (Everson-Rose et al. 2011; Wen, Hawkley, and Cacioppo 2006). Other studies found lower levels of physical activity in neighborhoods perceived as unsafe, with high incivility, and with low social cohesion (Rachele et al. 2016; Samuel et al. 2015; Tucker-Seeley et al. 2009). These findings are relevant because people who feel lonely have lower levels of physical activity (Hawkley and Capitanio 2015; Pels and Kleinert 2016).
Changes in physical characteristics of communities may also play a role in perceptions of neighborhood and how middle-aged adults do or do not interact with members of their communities. As smaller commercial areas within communities are being supplanted by larger commercial areas accessible primarily by car, there are fewer opportunities for neighbors to spontaneously engage. Changes in neighborhood composition may also influence perceptions of quality. Focus group participants in Israel pointed to an influx of migrants and an outflow of family and friends from their community resulting in feeling unsafe (Cohen-Mansfield, 2015). The health and well-being of people moving into communities is also important. Populations, such as migrants, refugees, and veterans may be susceptible to loneliness as they face the challenges of integrating (migrants and refugees) or reintegrating (veterans) into neighborhoods after leaving highly cohesive communities. If potentially vulnerable groups fail to successfully integrate, loneliness and its increased morbidity and mortality risks may result. Future research should examine loneliness within these groups and their ability to integrate into their community, perceptions of neighborhood quality, and health outcomes.

Policymakers would benefit from research examining structural neighborhood characteristics that promote interaction and integration, such as development of libraries, parks, and walkable commercial areas. Perceived neighborhood quality, social integration, and loneliness could be measured at baseline and after structural alterations designed to improve neighborhood safety, build cohesion, and enhance integration. Translation of our findings would be improved with such study results.
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Limitations of this study include lack of representation of ethnic and racial groups such as people of Hispanic heritage. For example, perceptions of neighborhood quality and social integration among Hispanic populations may differ from the primarily white and African American participants in our study. We also do not know how long participants lived in their neighborhood nor how much time they spent there. It takes time to integrate after moving to a new neighborhood, town, or region, and this could affect social integration scores and its influence on the neighborhood-loneliness relationship. Also, a single-item measure was used to assess self-reported loneliness. This direct measure, taken from the CES-D, may not have captured people who feel lonely but are reluctant to report it (Holt-Lunstad et al. 2010).

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References


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Chapter 5: Discussion

Summary of the Findings

This study revealed a prevalence of loneliness of 29%, an association between loneliness and systemic inflammation, and influences of perceived neighborhood quality and social integration on loneliness among middle-aged US adults age 35-64 years. Multivariable linear regression results provided evidence of lonely participants having elevated biomarker values for systemic inflammation, specifically IL-6, fibrinogen, and CRP, all which are implicated in the development and progression of cardiovascular disease. Results of multivariable logistic regression did not provide support for an association between loneliness and metabolic syndrome or its individual criteria. The results of multivariable logistic regression did provide evidence of a relationship between perceived neighborhood quality and self-reported loneliness. The data also showed that the relationship is partially mediated by social integration.

The sample for this study was 927 US adults age 35-64 years who participated in the Biomarker Project of the Midlife in the US (MIDUS) survey. Data for this study were collected at MIDUS baseline (1995-1996), follow-up (2004-2006), Milwaukee Sample baseline (2005-2006), and Biomarker Project (2004-2009).\textsuperscript{50-56}

Multivariable linear regression was used to test hypothesis 1, which examined the relationship between three biomarkers of systemic inflammation implicated in the development and progression of cardiovascular disease (interleukin-6, fibrinogen, and C-reactive protein)\textsuperscript{16,57,58} and loneliness. The results, after adjusting for confounding, are shown in Table 1.
Table 1

*Loneliness in multivariable regression for biomarkers of systemic inflammation*

<table>
<thead>
<tr>
<th>Biomarker of Inflammation</th>
<th>n</th>
<th>β</th>
<th>p-value</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin-6*</td>
<td>873</td>
<td>.07</td>
<td>.014</td>
<td>.01, .12</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>867</td>
<td>18.24</td>
<td>.011</td>
<td>4.26, 32.21</td>
</tr>
<tr>
<td>C-reactive protein*</td>
<td>867</td>
<td>.08</td>
<td>.035</td>
<td>.01, .16</td>
</tr>
</tbody>
</table>

*Note.* n=sample size, β=beta coefficient

Results control for age, sex, race, education, perceived stress, social integration, social support, positive relations with others, smoking history, regular exercise, blood pressure and body mass index.

*Interleukin-6 and C-reactive protein were transformed using natural log.*

Multivariable logistic regression was used to test hypotheses 2a and 2b which examined the relationship between metabolic syndrome and its individual components and loneliness. The results, after adjusting for confounding, are shown in Table 2.

Table 2

*Loneliness in multivariable regression for metabolic syndrome and its components (n=854)*

<table>
<thead>
<tr>
<th>Metabolic Syndrome and its components</th>
<th>Odds Ratio</th>
<th>p-value</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome</td>
<td>1.08</td>
<td>.649</td>
<td>0.77, 1.51</td>
</tr>
<tr>
<td>Obesity</td>
<td>1.26</td>
<td>.172</td>
<td>0.90, 1.77</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1.05</td>
<td>.759</td>
<td>0.75, 1.48</td>
</tr>
<tr>
<td>Dyslipidemia based on triglycerides</td>
<td>0.74</td>
<td>.117</td>
<td>0.51, 1.08</td>
</tr>
<tr>
<td>Dyslipidemia based on HDL cholesterol</td>
<td>1.12</td>
<td>.529</td>
<td>0.79, 1.59</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.13</td>
<td>.485</td>
<td>0.80, 1.60</td>
</tr>
</tbody>
</table>

*Note.* Results control for age, sex, race, education, household income, social integration, social support, depression, smoking history, regular exercise, and poor sleep quality.

Simple and multivariable logistic regression were used to test hypothesis 3a, which examined the relationship between perceived neighborhood quality and loneliness.

The odds ratio was significant in simple logistic regression and all three multivariable models. Table 3 provides a summary of the results.
Table 3

Perceived neighborhood quality in simple and multivariable regression for loneliness (n=868)

<table>
<thead>
<tr>
<th>Regression Model</th>
<th>Odds Ratio</th>
<th>p-value</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple logistic regression</td>
<td>2.64</td>
<td>&lt;.001</td>
<td>1.90, 3.65</td>
</tr>
<tr>
<td>Socio-demographic variables added</td>
<td>2.05</td>
<td>&lt;.001</td>
<td>1.44, 2.90</td>
</tr>
<tr>
<td>Social support variables added</td>
<td>1.92</td>
<td>&lt;.001</td>
<td>1.34, 2.75</td>
</tr>
<tr>
<td>Physical health variable added</td>
<td>1.81</td>
<td>.001</td>
<td>1.26, 2.61</td>
</tr>
</tbody>
</table>

Note. Results control for the following:
- Socio-demographic variables: age, race, education, and household income
- Social support variables: married or cohabitating, and self-reliance
- Physical health variable: number of symptoms and chronic conditions

To test whether social integration mediated the relationship between perceived neighborhood quality and loneliness (hypothesis 3b), we used Baron and Kenny’s test of mediation. Figure 1 provides a summary of the results of mediation analysis demonstrating that social integration partially mediates the relationship between perceived neighborhood quality and loneliness after adjusting for potential confounders.
Figure 1

*Social integration partially mediates the relationship between perceived neighborhood quality and loneliness*

Note.  
\[ a = \text{Results of linear regression after controlling for age, race, education, household income, married or cohabitating, whether one asks for help when needed, and number of symptoms and chronic conditions} \]
\[ b \& c = \text{Results of logistic regression after controlling for age, race, education, household income, married or cohabitating, whether one asks for help when needed, and number of symptoms and chronic conditions} \]
\[ c' = \text{Results of logistic regression after controlling for age, race, education, household income, married or cohabitating, whether one asks for help when needed, and number of symptoms and chronic conditions and including social integration} \]

**Contribution to Psychosocial Research**

This study makes important contributions to the psychosocial literature on loneliness in middle-aged adults. The sample investigated in this study includes a wider age range than most studies examining loneliness among middle-aged adults by including participants from 35 years up to the traditional age of retirement, 65 years. There are few studies examining associations between loneliness and biomarkers of systemic inflammation among a sample of community-dwelling middle-aged adults in the US and this study has the lowest mean age of those that have been conducted. Similar studies of
systemic inflammation among lonely people included adults in middle-age, but four of the six studies had a mean age of at least ten years older than the sample included in this study. And although two studies had similar mean age as this study, one age range was much wider and one was much narrower. Also, based on an extensive literature search, it appears that this is the only study which examines associations between loneliness and the metabolic syndrome in a US-based sample. It also appears to be the youngest sample examined for these associations. Of the two studies examining metabolic syndrome and loneliness, both draw their samples from European samples and both include older participants (>51 and >65 years, respectively) than this study.

Increasing our understanding of the health challenges faced by middle-aged US adults is particularly important given recent reports of rising morbidity and mortality rates among white, American Indian, and Alaska native middle-aged US adults. The distal causes are not specific, but “diseases of despair” including chronic pain, depression, alcoholism, and substance abuse may be the drivers of death caused by unintentional poisonings, suicides, and chronic liver disease. Considering the high prevalence of loneliness found in this study among middle-aged US adults, loneliness may also play a role.

The findings from this study are highly relevant to the loneliness literature. The analysis showed an association between loneliness and systemic inflammation biomarkers implicated in cardiovascular disease among a community-dwelling sample of middle-aged US adults. Molecular research has demonstrated the influence of loneliness on inflammation, making it a plausible pathway through which loneliness influences health. However, the inconclusive findings from prior clinical studies of
inflammatory biomarkers have left the inflammation question unresolved.\textsuperscript{20–23,25,60} The results presented here provide additional evidence that inflammation is associated with loneliness. And although the direction of the relationship cannot be discerned from this cross-sectional study, it provides additional evidence for the importance of considering loneliness a factor associated with cardiovascular disease.

The validation of individual level factors in de Jong Gierveld’s model of “Individual and societal factors in the emergence of loneliness” (p. 292)\textsuperscript{42} is an important contribution made by this research to the loneliness literature specifically, and the psychosocial literature more broadly. This is particularly salient since there do not appear to be other studies validating the role of perceived neighborhood quality on the emergence of loneliness among middle-aged or US-based samples. This study also makes a unique contribution by validating the important role of social integration as a factor in the development of loneliness. This finding is key since offering opportunities for social integration is a less daunting task than transforming neighborhoods. Importantly, social integration appeared to only partially mediate the relationship between perceived neighborhood quality and loneliness suggesting that other factors may also influence the relationship. Alternatively, neighborhood may have a more central role in feelings of loneliness.

\textbf{Limitations}

The single-item measure of loneliness may be seen as a limitation of this study based on older studies that suggest a bias against self-identifying as lonely.\textsuperscript{64} However, many studies have used a single-item measure,\textsuperscript{65–67} including the single item used in this study.\textsuperscript{40,68} And analyses of various measures of loneliness have confirmed that the single
item question regarding loneliness in the Center for Epidemiological Studies Depression scale (CES-D) \(^{69}\) is a sensitive measure.\(^{70-72}\) Furthermore, in this sample, there was no difference in self-identified loneliness by gender. This finding contrasts with previous studies where males had lower rates of loneliness than women when a single item measure included the word “lonely.”\(^{73,74}\)

The time from the MIDUS follow-up survey and Milwaukee sample data collection to biomarker data collection ranged from 0-63 months with a mean of 2.25 years. Contemporaneous data collection of the variables used in this study would have been advantageous. However, the time lag between data collection of perceived neighborhood quality and loneliness enabled us to perform mediation analysis.

The lack of representativeness of the Biomarker Project sample compared to the US population at the time of data collection is also a limitation.\(^{75}\) In particular, the sample used in this study had disproportionately more females than males compared to the national average. The sample also included more white and black participants and fewer multi-racial participants and participants of other races than national averages in 2010. Finally, MIDUS data collection did not include information on Hispanic ethnicity, and as a result, the data used in this analysis omits information on Hispanic ethnic origin.

**Implications**

**Research**

These findings provide direction for future research in several areas. First, replication of the systemic inflammation analysis in a different sample of middle-aged US adults may further elucidate psychosocial factors and sub-clinical processes that
increase risk of cardiovascular disease. Second, although the one item loneliness measure from the CES-D has been used in other samples,

40,68 it would be useful to have a conclusive study comparing this measure with a multi-item measure in a sample of middle-aged US adults. Results from such a study may provide evidence of the validity of a simple measure which would be available whenever the CES-D is completed. Third, qualitative research on the lived experience of lonely middle-aged adults may provide insight into felt causes of loneliness and relationship challenges faced by lonely middle-aged adults. Fourth, to enhance our cross-sectional findings, obtaining loneliness measures at regular intervals in longitudinal population-based surveys would enable causal inference and an understanding of the changes in loneliness over time. And finally, given the recent reports of rising mortality rates among middle-aged Americans, a closer examination of loneliness as a potential driver of the conditions implicated in the increased death rate is warranted.

Practice

The results of this study provide support for primary care providers and preventive services providers to assess the psychosocial status of their clients. If the single item measure of loneliness is a truly valid measure, lonely clients could be easily identified in primary care and referred for social or psychological services, and counseled regarding the physical health benefits of establishing and maintaining satisfying relationships. Likewise, clinical providers serving clients from communities that may be perceived as low quality, such as areas facing urban blight or neglected communities in rural areas, should be made aware of the risk of developing loneliness and the health risks
associated with it. A better understanding of loneliness by health care providers more generally may allow the identification of clients who are lonely.

Community strategies, such as The Village model,\textsuperscript{76,77} which are designed to support older adults and enable them to age in place, may serve a dual role if lonely middle-aged adults can become involved as home visitors.

\textit{Policy}

Social services agencies and departments linked to municipal or local governments could include in-service training for their staff on the signs of loneliness, health risks associated with it, and resources that may be available for lonely adults. Raising awareness about loneliness in middle-age may help social services workers identify people at risk. Providing charitable organizations and neighborhood associations with information about loneliness may sensitize them to clients and people in their local areas who are at risk. Likewise, their bylaws might address outreach to middle-aged neighbors at risk of loneliness, such as empty-nesters, recently divorced, widows, and widowers. Finally, public and private employers may find it economically beneficial to develop policies addressing loneliness through workplace interventions. A recent report estimates the cost of loneliness to employers in the United Kingdom at more than $3 billion (£2.5 billion).\textsuperscript{78} These findings suggest that workplace interventions may present a win-win opportunity if the findings can be translated to the US-context.

\textbf{Conclusion}

This dissertation research contributes to science and serves as a building block for future inquiry about loneliness in middle-age. The findings reported here offer multiple
opportunities for further research using both quantitative and qualitative methods.

Furthermore, the conduct of the study has served as an important springboard for the principal investigator’s career as a scientist.
References for Chapters 1 and 5


43. Thomese F, Tilburg T Van, Knipscheer KCPM. Continuation of exchange with


70. AARP. *Loneliness among Older Adults: A National Survey of Adults 45+.* Washington, DC; 2010.


72. Shiovitz-Ezra S, Ayalon L. Use of Direct Versus Indirect Approaches to Measure


Appendix 1: Support

This research was supported by: the Pre-doctoral Clinical Research Training Program, TR001078, awarded by Johns Hopkins Institute for Clinical and Translational Research under a grant from the National Center for Advancing Translational Sciences (NCATS) a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical 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.
Appendix 2: Curriculum Vitae

CURRICULUM VITAE
PART I

PERSONAL DATA

University Address: Paula V. Nersesian
Johns Hopkins University School of Nursing
525 N. Wolfe Street
Baltimore, MD 21205
pnersesian@jhu.edu

EDUCATION

<table>
<thead>
<tr>
<th>Year</th>
<th>Degree</th>
<th>Institution</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-2017</td>
<td>PhD (Conferral May 25, 2017)</td>
<td>Johns Hopkins University School of Nursing</td>
<td>Baltimore, MD</td>
</tr>
<tr>
<td>1992</td>
<td>Master of Public Health (MPH)</td>
<td>Johns Hopkins University School of Hygiene and Public Health</td>
<td>Baltimore, MD</td>
</tr>
<tr>
<td>1987</td>
<td>Bachelor of Science in Nursing (BSN)</td>
<td>University of Michigan</td>
<td>Ann Arbor, MI</td>
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LICENSURE & CERTIFICATION

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<th>Year</th>
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<tbody>
<tr>
<td>1989-present</td>
<td>Maryland Board of Nursing, Maryland Department Health and Mental Hygiene</td>
<td>RN</td>
<td>License Number: R102417</td>
</tr>
<tr>
<td>2015</td>
<td>Johns Hopkins University School of Nursing</td>
<td>Post-Graduate Certificate</td>
<td>Nursing Education</td>
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</tbody>
</table>

PROFESSIONAL EXPERIENCE

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<tr>
<th>Years</th>
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<tr>
<td>2015-present</td>
<td>Lecturer</td>
<td>Johns Hopkins University School of Nursing</td>
<td>Baltimore, MD</td>
</tr>
<tr>
<td>2014-2015</td>
<td>Special Volunteer</td>
<td>National Institutes of Health, National Institute of Nursing Research</td>
<td>Bethesda, MD</td>
</tr>
<tr>
<td>2013-2017</td>
<td>PhD Student &amp; Candidate</td>
<td>Johns Hopkins University School of Nursing</td>
<td>Baltimore, MD</td>
</tr>
<tr>
<td>Year</td>
<td>Role Description</td>
<td>Organization</td>
<td>Location</td>
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<tr>
<td>------------</td>
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<td>----------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>2005-present</td>
<td>Senior Public Health Specialist</td>
<td>John Snow, Inc.</td>
<td>Arlington, VA</td>
</tr>
<tr>
<td>1992-1993</td>
<td>Primary Health Care Advisor: Landour Community Health Project</td>
<td>University of California</td>
<td>Uttar Pradesh, India</td>
</tr>
<tr>
<td>1992</td>
<td>Community Health Nurse: Migrant Health Program</td>
<td>Colorado Department of Health</td>
<td>Fort Morgan, CO</td>
</tr>
<tr>
<td>1990-1991</td>
<td>Community Health Nurse: Tuberculosis and Refugee Clinic</td>
<td>Prince George’s County Health Department</td>
<td>Cheverly, MD</td>
</tr>
<tr>
<td>1989-1991</td>
<td>Staff Nurse: Operating Rooms (cardio-thoracic specialization)</td>
<td>Washington Adventist Hospital</td>
<td>Takoma Park, MD</td>
</tr>
<tr>
<td>1989 (October)</td>
<td>Nurse Volunteer: Kenyatta National Hospital</td>
<td>Operation Smile</td>
<td>Nairobi, Kenya</td>
</tr>
<tr>
<td>1987-1988</td>
<td>Cancer/HIV-AIDS Nurse Trainee</td>
<td>Cancer Nurse Training Program, National Cancer Institute, National Institutes of Health</td>
<td>Bethesda, MD</td>
</tr>
</tbody>
</table>
HONORS AND AWARDS

1987  Graduated Cum Laude, University of Michigan, Ann Arbor, Michigan
1987  Admitted to Sigma Theta Tau, International Honor Society of Nursing, Rho chapter

RESEARCH

Research and Education Grants

2016  Jonas V Veterans Healthcare Scholarship awarded by the Jonas Center for Nursing and Veterans Healthcare in support of PhD studies at Johns Hopkins University School of Nursing

2016  Liesel M. Hiemenz Scholarship awarded by Nurses Educational Funds, Inc. in support of PhD studies emphasizing public health at Johns Hopkins University School of Nursing

2016-2017  NIH TL1 Fellowship: Pre-doctoral Clinical Research Training Program, TR001078, awarded by Johns Hopkins Institute for Clinical and Translational Research under a grant from the National Center for Advancing Translational Sciences (NCATS) a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research, in support of PhD studies at Johns Hopkins University School of Nursing

2015-2016  Graduate Teaching Assistantship in genetics, Johns Hopkins University School of Nursing in support of PhD studies at Johns Hopkins University School of Nursing

2014  NIH/NINR: Summer Genetics Institute in support of preparatory work for PhD dissertation research

2013-2015  NIH T32 Fellowship awarded by Johns Hopkins University School of Nursing: Interdisciplinary Training in Cardiovascular Health Research, 5T32NR012704-04 and 5T32NR012704-03, under a grant from the National Institute of Nursing Research, National Institutes of Health, in support of PhD studies at Johns Hopkins University School of Nursing

2013-2015  Johns Hopkins University School of Nursing Institutional Scholarship in support of PhD studies

1992  University of California, Berkeley, Professional Studies Program in India, postgraduate research fellowship

1992  Lazarian Graduate Scholarship/Armenian Relief Society in support of postgraduate research in India
1991 Lillian Hiss/Ethel Crosby Scholarship in support of MPH studies at Johns Hopkins University School of Hygiene and Public Health

1991 Lazarian Graduate Scholarship/Armenian Relief Society in support of MPH studies at Johns Hopkins University School of Hygiene and Public Health

1991 Maryland District 20 Senatorial Scholarship in support of MPH studies at Johns Hopkins University School of Hygiene and Public Health

1991 Professional Nurse Traineeship Grant in support of MPH studies at Johns Hopkins University School of Hygiene and Public Health


PRACTICE

Volunteer activities

1987–1990 Volunteer, HIV and AIDS Services, Whitman Walker Clinic, Washington, DC

1989 Nurse Volunteer, Operation Smile, Kenyatta National Hospital, Nairobi, Kenya

SCHOLARSHIP

(*Data-based)

Peer Reviewed Publications


Manuscripts

1. *Nersesian, P.V., Han, H., Yenokyan, G., Blumenthal, R., Nolan, M., and Szanton, S. Loneliness in Middle Age and Biomarkers of Systemic Inflammation: Findings from MIDUS (Formatting for submission)

2. *Nersesian, P.V., Han, H., Yenokyan, G., Blumenthal, R., Nolan, M., and Szanton, S. Loneliness in Middle Age and the Metabolic Syndrome: Findings from MIDUS (Formatting for submission)

3. *Nersesian, P.V., Samuel, L.J., Yenokyan, G., Han, H., and Szanton, S. The relationship between loneliness and perceived neighborhood quality is mediated by social integration in a sample of middle-aged US adults (Formatting for submission)
Invited Publications


Invited Book Chapters


Invited Presentations


Presentations

International


National


Other

Program assessments and evaluation reports


Blogs


Guidance documents


PROFESSIONAL ACTIVITIES

Membership

2015-present American Heart Association
2014-present Data Managers Interest Group, Johns Hopkins University Institute for Clinical and Translational Research
2013-present Preventive Cardiovascular Nurses Association
1995-2012 American Public Health Association
1987-present Sigma Theta Tau International Honor Society of Nursing

Consultations

International

2003 World Health Organization, Meeting Chairperson and Invited International Technical Advisor, Consultation on Procurement Policy for Injection Devices, sponsored by WHO/Essential Drugs and Medicines Policy

National

1995 US Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau, Consultant, External review of Healthy Start Program in Cleveland, OH
1996 US Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau, Consultant, External review of Healthy Start Program in Chicago, IL

Proposal Review Activities

1997 US Department of Health and Human Services, Maternal and Child Health Bureau, External reviewer of continuing grant applications, Healthy Start Program, Rockville, MD

Short Courses

2015 Clinical Nursing Leadership, Johns Hopkins University School of Nursing, Baltimore, MD
2015  Principles and Practice of Clinical Research, National Institutes of Health Clinical Center, Bethesda, MD

2014  Summer Genetics Institute, National Institutes of Health/National Institute of Nursing Research, Bethesda, MD

2004  World Health Organization, Technical Briefing: Essential Drugs and Medicines Policy, Geneva, Switzerland

2001  Decentralization of Health Systems, Harvard University, School of Public Health, Stowe, VT

2001  Drug Policy Issues, Boston University and World Health Organization/Essential Drugs and Medicines Policy, Geneva, Switzerland


1999  Logistics Management, FPLM Project/John Snow, Inc., Arlington, VA

1997  World Health Organization, Technical Briefings: Child Health Division and Global Programme on Vaccines, Geneva, Switzerland

1996  Integrated Management of Childhood Illness, Zambian Ministry of Health, Kitwe, Zambia

In-Country Work Experience

North America  USA
Africa  Botswana, Kenya, Mozambique, Namibia, Rwanda, Sierra Leone, South Africa, Uganda, and Zambia
Asia  India, Nepal, Thailand, and Vietnam
# Curriculum Vitae
## Part II

### EDUCATIONAL ACTIVITIES

#### Classroom Instruction

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<tr>
<td>Summer 2016</td>
<td>Clinical Instructor, graduate-level 13-student traditional course</td>
<td>NR.500.602 SU Public Health Theory and Practice</td>
<td>Taught assessment and proposal development to graduate students with concentration in public health. Responsible for supporting and evaluating 6 students.</td>
<td>Johns Hopkins School of Nursing</td>
</tr>
<tr>
<td>Fall 2015</td>
<td>Lecturer, graduate-level 72-student traditional course</td>
<td>NR.110.502.0101.FA15/Physiological/Pathophysiological Basis for Advanced Nursing Practice I</td>
<td>Developed and delivered lecture on genetics and its application to nursing practice</td>
<td>Johns Hopkins School of Nursing</td>
</tr>
<tr>
<td>Winter 2015</td>
<td>Teaching Assistant, pre-licensure-level 80-student traditional course</td>
<td>NR.110.312.0201.SP15/Psychiatric Mental Health Nursing</td>
<td>Prepared PTSD research lecture, delivered it live, and recorded it in studio for use in subsequent classes</td>
<td>Johns Hopkins School of Nursing</td>
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#### Online Instruction

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<tr>
<td>Spring 2016</td>
<td>Lecturer, graduate-level 48-student online course</td>
<td>NR.110.502.8101.SP16/Physiological/Pathophysiological Basis for Advanced Nursing Practice I</td>
<td>Developed series of lectures on genetics and its application to nursing practice; recorded lecture series in multi-media studio</td>
<td>Johns Hopkins School of Nursing</td>
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#### Clinical Instruction

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<tr>
<td>Spring 2016</td>
<td>Clinical Instructor, pre-licensure-level 8-student clinical course</td>
<td>NR.110.405.0201.FA15 Public Health Nursing/NR.110.405P.0205.FA15 PHN Practicum-Community Dwelling Older Adults</td>
<td>Taught public health nursing to second degree students in a community setting, developing and facilitating policy and community enrichment.</td>
<td>Johns Hopkins School of Nursing</td>
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</table>
Fall 2015: Clinical Instructor, pre-licensure-level 8-student clinical course NR.110.405.0201.FA15 Public Health Nursing/NR.110.405P.0205.FA15 PHN Practicum-Community Dwelling Older Adults 

Taught public health nursing to second degree students in a community setting, developed and facilitated policy and community enrichment experiences for students.

New Course Development

Spring 2015: Teaching Assistant, graduate-level 48-student online course NR.110.502.8101.SP15/Physiological/Pathophysiological Basis for Advanced Nursing Practice I 

Developed components of the revised genetics module focused on family influence on the genome and epigenome. Contributions included recorded lectures and interactive online exercises.

ACADEMIC SERVICE

Committee member

1992: Johns Hopkins University, School of Hygiene and Public Health, MPH Academic Committee, Student Representative

Johns Hopkins University East Baltimore Campus

2014 & 2016: School of Nursing & School of Medicine, Volunteer facilitator/mentor for Inter-professional Education Orientation

2016: School of Nursing, Volunteer technical resource for development of F31 job aids for PhD students and management tools for the PhD program

2016: School of Nursing, Volunteer staff for Summer Research Institute on Developing Behavioral Interventions

MENTORING AND ADVISEMENT

Professional Mentor

2014-2015: Johns Hopkins, Bloomberg School of Public Health, Alumni Mentor Program Anna Chung, RN (MSN/MPH Program) and Kayla Thielk Nyakinye, RN, NP (MPH Program)

2011–2012: University of Michigan School of Nursing, Alumni Mentor Program Megan Thomas, Accelerated second career BSN program
Mentored approximately ten undergraduate, graduate, and post-graduate students, and one post-doctoral trainee completing an internship at John Snow, Inc.