

Multidimensional Religiousness and Spirituality Are Associated With Lower Interleukin-6 and C-Reactive Protein at Midlife: Findings From the Midlife in the United States Study

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Abstract

Background Religiousness and spirituality (R/S) are associated with lower morbidity and mortality, yet the physiological mechanisms underlying these associations are under-studied. Chronic inflammation is a plausible biological mechanism linking R/S to downstream health given the sensitivity of the immune system to the social environment and the role of inflammation in many chronic diseases.

Purpose The purpose of the present study was to examine associations between multiple R/S dimensions and two markers of chronic inflammation, interleukin-6 (IL-6) and C-reactive protein (CRP).

Methods In this cross-sectional study, data came from biological subsamples of two cohorts from the Midlife in the United States (MIDUS) Study (combined $N = 2,118$). Predictors include six R/S measures (service attendance, spirituality, private religious practices, daily spiritual experiences, religious coping, and R/S-based mindfulness). Outcomes include log-transformed IL-6 and CRP. Covariates include age, gender, cohort, race, educational attainment, body mass index (BMI), smoking status, and physical activity.

Results Older adults, women (vs. men), non-White (vs. White) adults, those with higher BMIs, current smokers, and those not meeting physical activity guidelines had significantly higher IL-6 and CRP. In fully adjusted models, greater spirituality, daily spiritual experiences, religious coping, and R/S-based mindfulness were associated with lower IL-6. Higher spirituality was also associated with lower CRP.

Conclusions Many dimensions of R/S may be health protective for adults given their associations with lower levels of chronic inflammation. Findings underscore the importance of examining multiple dimensions of R/S to understand mechanistic pathways.

Lay summary

People who are religious and spiritual are often healthier and live longer than people who are less religious and spiritual. Researchers are trying to understand why. We know that religiousness and spirituality can help people manage stress and make healthy choices, which might contribute to less chronic inflammation. Chronic inflammation can lead to cardiovascular diseases, diabetes, and other chronic conditions. This study examined data from over 2,000 participants of the Midlife in the United States (MIDUS) Study to determine whether midlife and older adults who are more religious and spiritual have less chronic inflammation. People who reported greater spirituality, more frequent spiritual experiences, use their religious/spiritual beliefs to cope with stressors, and use their religion/spirituality to practice mindfulness had lower inflammation than individuals who had less of these religious/spiritual characteristics. These findings are important because they provide knowledge about which dimensions of religiousness and spirituality are connected to health and present a biological pathway (bodily inflammation) that connects religiousness and spirituality to chronic diseases.

Keywords Spirituality · Religion · Mindfulness · Inflammation · IL-6 · C-reactive protein

Introduction

Religion and spirituality are central components of life for many people, and general population studies indicate a high prevalence of religiousness and spirituality (R/S) in the USA and globally. Eighty-eight percent of U.S. adults believe in God, a higher power, or a spiritual force [1]. Seventy percent of U.S. adults are spiritual and 58% are religious [1].

Globally, more than 80 countries favor a specific religion, and 8 in 10 people identify with a religious group. Among those who do not, most hold some form of transcendent or spiritual belief [2, 3].

Despite the consensus that religiousness and spirituality are distinct constructs, they are considered multidimensional with overlapping features. Dimensions of R/S may

include behaviors such as attending religious services or engaging in prayer, using religious or spiritual beliefs to cope with stressors, having spiritual experiences, among others [4]. Researchers agree that significant challenges exist in distinguishing between religiousness and spirituality in empirical study [5]. To better understand their similarities and differences, Harris et al. [6] conducted a definitional content analysis of religious concepts used in peer-reviewed journals. Their results indicated that the terms “religiousness” and “spirituality” are multidimensional, overlapping, and often poorly defined. Nevertheless, they proposed working definitions of “religiousness” as “ritual, institutional, or codified spirituality which is culturally sanctioned,” and “spirituality” as “a search for or relationship with the sacred” (p. 1). According to findings from the Pew Research Center, U.S. adults themselves also view these constructs as multidimensional and overlapping [1].

Given the role of R/S in shaping belief systems, social networks, and behavior [7], it is unsurprising that R/S influences health and mortality [8, 9]. To date, religious service attendance has been the focus of most research in this area. This is, in large part, because service attendance was the only R/S dimension included in most population-wide epidemiological surveys until more recently. Findings from these studies reveal that R/S is associated with reduced risk of all-cause mortality [8, 10–12], cause-specific mortality [13, 14], and morbidity [9]. Although these data provide a foundational understanding of the connections between R/S and health, service attendance is insufficient as a standalone measure of R/S for many reasons. Most importantly, it fails to capture the many ways that R/S can be experienced and expressed (e.g., in the privacy of one’s home). Moreover, outside factors may impact an individual’s ability to attend services. This becomes particularly problematic in cross-sectional studies of R/S and health because illness may affect an individual’s ability to attend services.

The mechanistic pathways underlying associations between R/S, morbidity, and mortality remain an area of intrigue for investigators, and a surge in the empirical study of R/S in recent years has contributed to new understandings of how R/S may relate to physical health. Masters et al. [15] suggest there are three plausible and empirically supported pathways linking R/S with physical health. The first pathway is the behavioral pathway, in which R/S enhances behavioral self-regulation (e.g., engaging in healthy behaviors and limiting unhealthy behaviors), contributing to improvements in physical health. A recent review of the literature indicates that individuals who report greater R/S are more physically active, have a healthier diet, and are more likely to receive cancer screenings [16]. They are also less likely to smoke cigarettes, abuse substances, and engage in high-risk sexual behavior [16]. This may be for many reasons, including religious prescriptions and proscriptives for health behavior, or motives more internal to the individual such as the desire to align behavior with religious/spiritual goals and values [17]. A second pathway links R/S to health via social support. There is a well-established relationship between social support and health outcomes [18], and if R/S nourishes high-quality social support, it could plausibly influence health via this pathway. In a prospective study investigating associations between R/S and mortality, Kim et al. [19] found a mediating effect of social support. Interestingly, there is evidence that receiving social support in the context of one’s religious or spiritual community provides

health benefits above and beyond general social support [20]. A third pathway examines influences on physiology via psychological or emotional processes that are independent of social support, such as emotional self-regulation [21]. Research has found stress-buffering effects of prayer on cardiovascular reactivity [22] and meta-analytic findings suggest associations between prayer and meditation with various physical health indicators, including immune function biomarkers [9].

Chronic inflammation is a plausible biological mechanism linking R/S to downstream health given the sensitivity of the immune system to the social environment [23] and the role of inflammation in the pathophysiology of several major chronic diseases [24]. Chronic inflammation can contribute to poor health outcomes over the lifespan [24]. It is implicated in the pathogenesis of several major chronic diseases and conditions, such as autoimmune diseases [25], type 2 diabetes [26], cardiovascular disease [27], cancer [28], and depression [29], among others [30]. In behavioral science research, chronic inflammation is often indexed by circulating levels of biomarkers such as interleukin-6 (IL-6) and C-reactive protein (CRP). Prospective studies indicate that higher circulating levels of these biomarkers predict a variety of health outcomes, such as increased risk for type 2 diabetes [31], depression [32], and hypertension [33]. In older adults, elevated levels of these markers predict a greater risk of cardiovascular disease, frailty, physical and cognitive decline, and multimorbidity [34]. The purpose of the present study was to investigate the relationships between multiple dimensions of R/S and two inflammatory biomarkers among a large and diverse sample of midlife and older adults from the Midlife in the United States (MIDUS) national survey. We investigate whether spirituality, service attendance, private religious/spiritual practices, religious/spiritual coping, daily spiritual experiences, and R/S-based mindfulness independently predict IL-6 and CRP.

There is emerging evidence that R/S is associated with inflammatory biomarkers. Recent meta-analytic data suggest that R/S (including service attendance, intrinsic religiosity, and religious/spiritual meditation) predicts lower levels of CRP, lower white blood cell count, and fewer viral infections [9]. There is also a growing evidence base suggesting that mindfulness-based interventions may improve immunity-related biomarkers [35]. As is the case for the R/S-health literature at large, most individual studies of R/S and inflammatory biomarkers use religious service attendance as a proxy for R/S. This limits our understanding of which dimensions of R/S are beneficial to health, and this may have important implications for translational research. Some researchers have begun to study the relationships between multiple dimensions of R/S and inflammation, but results are generalizable to specific populations. For example, Tavares et al. [36] investigated multiple dimensions of R/S as possible moderators of the association between perceived stress and CRP among older adults in the Health and Retirement Study. Findings revealed that intrinsic religiousness (i.e., internalized religiousness; religiousness as an end in itself) moderated the stress–CRP association such that perceived stress was not associated with CRP among those who had higher intrinsic religiousness. This same moderating effect was not present for service attendance and prayer, indicating that some dimensions of R/S may be more effective at buffering stress than others. Relatedly, using data from the Landmark Study of Spirituality and Health, Ironson et al. [37] studied a subsample of 643

middle-aged and older adults experiencing an average or higher-than-average number of life stressors. Their study included measures of multiple dimensions of R/S such as prayer, religious meaning, religious hope, general meaning, general hope, and sense of peace, as well as several covariates (age, gender, education, body mass index [BMI], smoking, alcohol use, social support). After controlling for covariates, service attendance was the only dimension of R/S found to predict CRP, underscoring the importance of investigating multiple dimensions of R/S to determine which may have the strongest associations with inflammation.

To summarize, researchers have begun to investigate the relationships between R/S and inflammatory biomarkers, but most published studies to date test only one specific dimension of R/S or include unique samples (e.g., highly stressed individuals [37]; individuals with comorbid conditions [38]; highly religious individuals [39]). The present study contributes to the literature by investigating multiple dimensions of R/S as individual predictors of two inflammatory biomarkers within a large national sample of adults, offering a more comprehensive understanding of how specific dimensions of R/S may relate to chronic inflammation among the U.S. population at large.

Methods

Participants

In this cross-sectional study, data came from biomarker subsamples from the second wave of the core cohort (M2) and refresher cohort (MR) of the MIDUS Study. MIDUS is a national, longitudinal survey of health and aging among U.S. adults that began in 1995–1996. A second wave of the study (M2; $N = 4,963$) was conducted in 2004–2009 and included a new sample of Black adults from Milwaukee, Wisconsin ($n = 592$). A subset of M2 respondents ($n = 1,255$, including $n = 201$ Milwaukee respondents) provided biological data. In 2011–2014, a new cohort of adults was recruited into the study that matched the age and gender distribution of the baseline sample (MIDUS Refresher [MR]; $N = 3,577$), and a new sample of Black adults from Milwaukee ($N = 508$). A subsample of these MR participants ($n = 863$, including $n = 117$ Milwaukee respondents) provided biological data, thus resulting in a combined sample of 2,118 biomarker participants from the M2 and MR cohorts.

To be eligible for biological data collection, respondents must have completed the prior waves of survey collection and agreed to travel to one of three General Clinic Research Centers (GCRC) for an overnight stay. In a prior report assessing differences in demographic and health characteristics between the M2 and MR participants, Love et al. [40] found the M2 biomarker subsample participants were comparable to the M2 survey sample on most demographic variables (i.e., age, gender, race, income, marital status, BMI, self-rated health, chronic conditions, and physician visits), but they reported more education and were less likely to smoke than the M2 survey sample. The MR biomarker subsample was comparable to the broader MR survey sample on gender, race, marital status, BMI, and several chronic conditions. However, the MR biomarker subsample participants were older, had more education and higher income, more physician visits, better self-rated health, and were less likely to smoke than the MR survey sample [41]. Data collection procedures were approved by the Institutional Review Boards at the University

of Wisconsin-Madison, Georgetown University, and the University of California, Los Angeles. Written informed consent was obtained from all participants.

Measures

Multidimensional religiousness/spirituality

Several dimensions of participants' religious/spiritual lives were assessed: (i) spirituality, (ii) religious/spiritual service attendance, (iii) private religious practices, (iv) religious coping, (v) daily spiritual experiences, and (vi) R/S-based mindfulness. Scales were all coded such that higher scores reflected higher R/S. Spirituality was assessed with two items "How spiritual are you?" and "How important is spirituality in your life?" on a scale from 1 ("a lot") to 4 ("not at all"). Internal consistency was 0.92 in the analytic sample [42, 43]. Service attendance was measured as the frequency with which respondents attended religious or spiritual services with five response options ranging from "never" to "once a day or more." These responses were coded to reflect attendance at least weekly (reference group), less than weekly, or never. Private religious practice was captured as the sum of "How often do you meditate or chant"; "How often do you pray in private"; and "How often do you read the Bible or other religious literature?" Responses were rated on a scale from 1 ("once a day or more") to 6 ("never"), and internal consistency was 0.70 in the analytic sample [42, 43]. Religious coping was measured as the sum of six items assessing the extent to which participants use their R/S for comfort (e.g., "I look to God for strength, support, and guidance"). Responses were rated on a scale from 1 ("a great deal") to 4 ("none"), and internal consistency was 0.73 in the analytic sample [42, 43]. Daily spiritual experiences were assessed by asking respondents to complete an abbreviated version of the Daily Spiritual Experience Scale [44]. The measure includes five items assessing the frequency with which participants experience various everyday spiritual experiences (e.g., "On a daily basis, how often do you experience a feeling of deep inner peace or harmony?"). Responses were rated on a scale from 1 ("often") to 4 ("never"), and the internal consistency was 0.89 in the analytic sample [42, 43]. Finally, R/S-based mindfulness was measured with a 9-item scale asking participants to report the degree to which they try to be more mindful because of their religion or spirituality (e.g., "Because of your religion or spirituality, do you try to be more engaged in the present moment?"). Responses were rated on a scale from 1 ("strongly agree") to 5 ("strongly disagree"), and internal consistency was 0.95 in the analytic sample [42, 43].

Inflammation

Inflammatory markers (serum IL-6 and plasma CRP) were assessed using a fasting blood sample taken on the morning of the participants' second day of the GCRC clinic visit. Assays were conducted using the same laboratories and procedures for M2 and MR biomarker participants. Serum IL-6 levels were measured with the Quantikine High-sensitivity ELISA kit #HS600B (R&D Systems, Minneapolis, MN). The inter-assay coefficient of variance (CV) was 12.3% for M2 and 15.7% for MR and the intra-assay CV was 3.3% for M2 and 3.7% for MR. Plasma CRP levels were measured with the BNII nephelometer (Dade Behring, Inc., Deerfield, IL). Samples with undetectable CRP were re-assayed by immunoelectrochemiluminescence using a high-sensitivity

assay kit (Meso Scale Diagnostics #K151STG). Given the technical difficulties associated with the use of plasma in MSD kits, the CRP assays beginning in 2016 were conducted on serum using the MSD technology, and corrections were applied at the MIDUS BioCore. The M2 inter- and intra-assay CVs ranged from 2.1% to 5.7%, and the MR inter- and intra-assay CVs ranged from 1.1% to 4.4%. Distributions for IL-6 and CRP were positively skewed and were naturally log-transformed for analyses.

Covariates

Covariates included age, gender, race (White [reference category], Black, and other race), cohort (M2 vs. MR), educational attainment, BMI, smoking status (current regular smoker vs. not), and physical activity (150 min per week of moderate/vigorous activity vs. not). Educational attainment was assessed with 12 categories ranging from no school/some grade school to doctoral or other professional degree. Education was treated as a continuous variable in analyses. Height and weight were measured by GCRC staff at the biomarker clinic visit and were used to calculate BMI (weight in kilograms divided by height in meters squared), which is a predictor of inflammation [45]. Smoking status, which is inversely associated with both religiousness [46] and inflammation [47] was assessed by asking participants “Do you smoke cigarettes regularly now?” (Yes/No). Physical activity, which is also inversely associated with inflammation [48] and possibly with religiousness [49,50] was assessed by asking respondents to self-report the amount of moderate/physical activity they obtain per week. The degree of physical activity was coded as either meeting recommended Centers for Disease Control and Prevention (CDC) guidelines or not (i.e., 150 min per week of moderate/vigorous activity [51]). Covariate selection followed the recommendations of O’Connor et al. [45].

Supplemental analyses additionally included perceived stress and positive social relationships as covariates. Perceived stress was assessed via the 10-item Perceived Stress Scale (PSS [52]) at the M2 and MR biomarker visits. The PSS asks participants to indicate the extent to which they experienced stress over the last month on a 5-point scale ranging from 1 (Never) to 5 (Very often) and internal consistency was 0.86. Positive social relationships were assessed with the 7-item Positive Relations with Others scale from Ryff’s model of psychological well-being during the M2 and MR survey [43,53]. An example item is, “People would describe me as a giving person, willing to share my time with others.” Seven response options ranged from “strongly agree” to “strongly disagree,” and internal consistency was 0.78.

Statistical Analyses

Ordinary least squares regression models were used to examine each R/S measure as a predictor of IL-6 and CRP, respectively. Covariates were entered in two blocks. Model 1 covariates included age, gender, cohort, race, and education, and Model 2 added BMI, smoking, and physical activity. [Supplementary Tables S1 and S2](#) show results for Models 3 and 4, which consecutively added perceived stress and positive social relationships as covariates. [Supplementary Tables S3–S10](#) show associations between R/S and inflammatory markers in gender- and race-stratified models.

All continuous variables were standardized as *z*-scores with a mean of zero and an *SD* of one. We used results from regression analyses to compute adjusted effect sizes (squared semi-partial

correlations) of the unique association of each interactive effect with inflammation across models. The squared semi-partial correlation is equivalent to the unique change in R^2 estimated for that predictor, over and above the other covariates in a given model, thus providing a clear estimate of the percent of unique variance accounted for by predictors in each model. Assumptions of the ordinary least squares model were verified, including assessments for outliers, normality of residuals, homoscedasticity, and independence of errors.

Results

Descriptive statistics on the analytic sample are provided in [Table 1](#). Bivariate correlations among all study variables and partial correlations among study variables, holding age constant, are provided in [Table 2](#). Older adults, women, non-White adults, those with lower educational attainment, those with higher BMIs, current smokers, and those not meeting physical activity guidelines had significantly higher IL-6 and CRP. IL-6 and CRP were moderately correlated with each other ($r = .56$), and all R/S variables were significantly associated with each other, with bivariate correlations ranging from 0.20 to 0.71. Partial correlations holding age constant revealed similar patterns among study variables ([Table 2](#), values below diagonal). Given the similarity between unadjusted and partial correlations, it is unlikely that age is a major confound in the associations of interest between R/S measures and inflammatory markers.

[Tables 3 and 4](#) display results from regression models predicting IL-6 and CRP, respectively. Collectively, the full

Table 1 Descriptive Statistics for the Combined MIDUS 2 and MIDUS Refresher Biomarker Samples ($N = 2,118$)

	<i>M</i> (<i>SD</i>) or %	Range
Age (in years)	54.7 (12.7)	25–86
Gender (% women)	54.9%	
Race		
% White	74.5%	
% Black or African American	18.9%	
% Other race	6.6%	
MIDUS cohort (% M2 core)	59.3%	
Education (% high school or less)	23.6%	
Interleukin-6 (pg/mL)	2.9 (2.8)	0.12–23.0
C-reactive protein (μg/mL)	3.3 (5.3)	0.05–79.3
Religious service attendance		
% At least weekly	43.4%	
% Less than weekly	31.3%	
% Never	24.6%	
Spirituality	6.5 (1.7)	2–8
Private religious practices	9.8 (4.5)	3–18
Daily spiritual experiences	15.8 (3.2)	5–20
Religious coping	18.3 (3.9)	6–24
Mindfulness	34.2 (6.8)	9–45
Body mass index	30.0 (7.1)	15–78
% Current smokers	13.4%	
% Meets CDC physical activity guidelines	58.3%	

MIDUS Midlife in the United States.

Table 2 Bivariate Correlations and Partial Correlations, Holding Age Constant, Among Study Variables

Measure	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
1. Weekly attendance		.44***	.60***	.30***	.54***	.30***	.04*	-.004	.10***	-.09***	-.02	.03	.01	-.16***	-.02
2. Spirituality	.24***		.65***	.45***	.66***	.57***	.01	.01	.06*	-.19***	.14***	-.07**	.03	-.03	-.05*
3. Private religious practices	.60***	.65***		.43***	.71***	.49***	.09**	.05*	.10***	-.17***	.22***	-.09***	.07**	-.02	-.07**
4. Daily spiritual experiences	.28***	.45***	.42***		.51***	.47***	.03	.03	.19***	-.20***	.05*	.001	-.01	-.10***	.004
5. Religious coping	.53***	.66***	.70***	.51***		.50***	.02	.02	.08***	-.19***	.14***	-.07**	.03	-.08***	-.01
6. Mindfulness	.30***	.57***	.49***	.46***	.50***		.02	.04	.02	-.20***	.17***	-.09***	.02	.03	-.01
7. IL-6	.02	-.01	.06**	-.03	-.01	.01		.56***	.27***	-.04	.16***	-.16***	.38***	.09***	-.20***
8. CRP	-.01	.003	.04*	.02	.01	.04	.57***		.05*	-.16***	.14***	-.17***	.47***	.05*	-.19***
9. Age										.06**	-.20***	-.03	-.05*	-.11***	-.04*
10. Gender (women = ref.)	-.11***	-.20***	-.18***	-.21***	-.20***	-.20***	-.05**	-.16***			-.11***	.08***	-.03	-.001	.07**
11. Race (White = ref.)	.04*	.15***	.24***	.09***	.16***	.17***	.22***	.16***	-.10***			-.22***	.18***	.17***	-.13***
12. Educational attainment	.03	-.08**	-.10***	.01	-.07**	-.09***	-.16***	-.18***	.07**	-.23***			-.16***	-.24***	.13***
13. BMI	.02	.02	.07**	-.01	.02	.02	.41***	.47***	-.01	.17***	-.15***			-.03	-.16***
14. Current smoking	-.14***	-.02	-.003	-.08***	-.06**	.03	.12***	.07**	.02	.15***	-.24***	-.04			-.08***
15. Physical activity	-.02	-.04	-.07**	.01	-.01	-.01	-.19***	-.19***	.08***	-.14***	.12***	-.15***	-.08***		

Note: Interleukin (IL)-6 and C-reactive protein (CRP) are naturally log-transformed. The race variable compares White adults to all non-White adults. Bivariate correlations are provided above the diagonal in non-shaded cells and partial correlations holding age constant are provided below the diagonal in shaded cells. BMI body mass index.

* $p < .05$.
 ** $p < .01$.
 *** $p < .001$.

Table 3 Religiousness and Spirituality Measures Predict Interleukin-6.

	Model 1			Model 2		
	B (SE)	p	ΔR^2	B (SE)	p	ΔR^2
Service attendance (\geq weekly = ref.) ^a						
Less than weekly	-0.04 (0.04)	.31	<.001	-0.05 (0.03)	.15	.001
Never attend	0.01 (0.04)	.72	<.001	-0.01 (0.04)	.90	<.001
Spirituality ^a	-0.04 (0.02)	.016	.002	-0.04 (0.02)	.020	.002
Private religious practices ^a	0.004 (0.02)	.81	<.001	0.002 (0.02)	.92	<.001
Daily spiritual experiences ^a	-0.04 (0.02)	.012	.003	-0.03 (0.02)	.058	.001
Religious coping ^a	-0.04 (0.02)	.019	.002	-0.03 (0.02)	.073	.001
Mindfulness ^a	-0.03 (0.02)	.036	.002	-0.03 (0.02)	.092	.001
Age ^b	0.24 (0.02)	<.001	.086	0.25 (0.02)	<.001	.091
Gender ^b (women = ref.)	-0.03 (0.03)	.28	<.001	-0.04 (0.03)	.17	.001
Race ^b (Black vs. White)	0.42 (0.04)	<.001	.039	0.24 (0.04)	<.001	.012
Race ^b (Other race vs. White)	0.14 (0.07)	.038	.042	0.12 (0.06)	.043	.001
Cohort ^b (M2 = ref.)	0.04 (0.03)	.26	.002	0.03 (0.03)	.40	<.001
Educational attainment ^b	-0.08 (0.02)	<.001	.009	-0.02 (0.02)	.13	.001
Current smoking ^b				0.22 (0.05)	<.001	.009
Physical activity ^b				-0.15 (0.03)	<.001	.008
BMI ^b				0.28 (0.02)	<.001	.118

Note: All continuous predictors are z-scored. ΔR^2 = squared semi-partial correlation indicating the unique change attributable to that predictor variable. BMI body mass index.

^aEach religiousness/spirituality measure is entered in a separate regression model.

^bCoefficients for the covariates come from a model containing no religiousness/spirituality variables.

Table 4 Religiousness and Spirituality Measures Predict C-Reactive Protein

	Model 1			Model 2		
	B (SE)	p	ΔR^2	B (SE)	p	ΔR^2
Service attendance (\geq weekly = ref.) ^a						
Less than weekly	0.05 (0.06)	.40	<.001	0.06 (0.05)	.29	<.001
Never attend	0.04 (0.07)	.51	<.001	0.03 (0.06)	.56	<.001
Spirituality ^a	-0.06 (0.03)	.026	.002	-0.05 (0.02)	.025	.002
Private religious practices ^a	-0.02 (0.03)	.42	<.001	-0.03 (0.02)	.19	.001
Daily spiritual experiences ^a	-0.03 (0.03)	.30	<.001	-0.01 (0.02)	.75	<.001
Religious coping ^a	-0.05 (0.03)	.063	.002	-0.04 (0.03)	.15	.001
Mindfulness ^a	-0.03 (0.03)	.33	<.001	-0.01 (0.02)	.63	<.001
Age ^b	0.11 (0.03)	<.001	.008	0.12 (0.02)	<.001	.009
Gender ^b (women = ref.)	-0.34 (0.05)	<.001	.019	-0.35 (0.05)	<.001	.020
Race ^b (Black vs. White.)	0.40 (0.07)	<.001	.014	0.09 (0.06)	.18	.001
Race ^b (Other race vs. White)	0.05 (0.11)	.62	<.001	0.03 (0.09)	.79	<.001
Cohort ^b (M2 = ref.)	0.20 (0.06)	<.001	.006	0.16 (0.05)	.001	.004
Educational attainment ^b	-0.17 (0.03)	<.001	.018	-0.09 (0.03)	<.001	.004
Current smoking ^b				0.20 (0.07)	.005	.003
Physical activity ^b				-0.23 (0.05)	<.001	.008
BMI ^b				0.54 (0.02)	<.001	.177

Note: All continuous predictors are z-scored. ΔR^2 = squared semi-partial correlation indicating the unique change attributable to that predictor variable. BMI body mass index.

^aEach religiousness/spirituality measure is entered in a separate regression model.

^bCoefficients for the covariates come from a model containing no religiousness/spirituality variables.

models accounted for approximately 28% of the variance in IL-6 and CRP. **Table 3**, Model 1 showed that spirituality, daily spiritual experiences, religious coping, and R/S-based mindfulness were significantly, inversely associated with IL-6 in models that included age, gender, race, cohort, and education. Because IL-6 is log-transformed, exponentiated coefficients are interpreted as a multiplicative factor for a one-unit change in the independent variable. Specifically, a 1-SD increase in spirituality, daily spiritual experiences, religious coping, and R/S-based mindfulness were each associated with a 4% decrease in IL-6 in Model 1 (i.e., $\exp(-0.04) = 0.96$). These associations were attenuated in Model 2, which added BMI, smoking status, and physical activity as covariates. Only spirituality remained significantly associated with IL-6 in Model 2, and a 1-SD increase in spirituality was associated with a 4% decrease in IL-6. Spirituality was inversely associated with CRP in both Models of **Table 4**. A 1-SD increase in spirituality was associated with a 6% decrease in CRP in Model 1 and a 5% decrease in CRP in Model 2. R/S variables accounted for 0.2%–0.3% unique variance in inflammatory markers, which is less than the variance accounted for by age, smoking, and physical activity, respectively.

Supplemental Analyses

Supplementary Tables S1 and S2 show associations between R/S and IL-6 and CRP with perceived stress and positive social relationships included as covariates. Perceived stress was not associated with IL-6 or CRP, and associations between R/S and inflammatory markers were unchanged with the inclusion of perceived stress as a covariate (Model 3). The positive social relationships scale was associated with lower IL-6, but not CRP. A 1-SD increase in positive social relationships was associated with a 5% decrease in IL-6. With

positive social relationships included in the model, spirituality was no longer significantly associated with IL-6. Associations between spirituality and CRP were unchanged with positive social relationships included in Model 4.

Supplementary Tables S3–S6 show associations between R/S and IL-6 and CRP in gender-stratified models. Among women, spirituality and daily spiritual experiences were associated with lower IL-6 in models that controlled for age, race, sample, educational attainment, current smoking, physical activity, and BMI. A 1-SD increase in spirituality and daily spiritual experiences was associated with a 5% decrease in IL-6 among women (**Supplementary Table S3**, Model 2). The associations between spirituality and daily spiritual experiences and IL-6 were not significantly different from zero among men. None of the R/S measures were associated with CRP in gender-stratified models. **Supplementary Tables S7–S10** show associations between IL-6 and CRP in race-stratified models. Among White adults, spirituality was associated with lower IL-6 such that a 1-SD increase in spirituality was associated with a 4% decrease in IL-6 in models that adjusted for age, gender, sample, education, current smoking, physical activity, and BMI. Spirituality and religious coping were associated with lower CRP among White adults. A 1-SD increase in spirituality and religious coping was associated with a 7% and 6% decrease in CRP, respectively, in models that adjusted for age, gender, sample, education, current smoking, physical activity, and BMI. None of the R/S measures were significantly associated with IL-6 or CRP among non-White adults.

An additional three sets of models were run as sensitivity analyses. First, we excluded 121 individuals with CRP values greater than 10 $\mu\text{g/mL}$, as this may indicate the presence of an acute infection [54]. Associations between R/S measures and CRP, and between covariates and CRP, were identical to those presented in the full sample. Second, because the

MIDUS core sample included siblings and twins (18.6% of the analytic sample), supplemental analyses were conducted using generalized estimating equations with an exchangeable within-cluster covariance structure to adjust for biological dependencies in the data. Conclusions regarding the results were identical to those presented previously. Finally, supplemental analyses tested an interaction between cohort (M2 vs. MR) and each R/S variable. Results showed that associations between R/S measures and IL-6 and CRP did not differ by study cohort (data not shown).

Discussion

Given the growing interest in examining the biological mechanisms that connect R/S to downstream morbidity and mortality, the goal of this study was to examine cross-sectional associations between multiple dimensions of R/S and two markers of chronic inflammation. Consistent with prior evidence suggesting that some dimensions of R/S may predict lower levels of inflammation, we demonstrated significant associations between multiple dimensions of R/S and lower IL-6 and CRP in a large and diverse sample of midlife and older adults. Our findings thus complement and extend prior research in this area, which largely consists of studies with smaller sample sizes, those that test only one or two dimensions of R/S [55], and those with unique samples, such as highly religious participants [39], participants with comorbid conditions [38], participants experiencing higher-than-average stress [37], and older adults [36].

Six R/S dimensions were measured: (i) spirituality, (ii) service attendance, (iii) private religious practices, (iv) religious coping, (v) daily spiritual experiences, and (vi) R/S-based mindfulness. Findings revealed associations between four of these dimensions of R/S and either IL-6 or CRP after controlling for age, gender, cohort, race, and educational attainment. Spirituality, daily spiritual experiences, religious coping, and R/S-based mindfulness were significantly, inversely associated with IL-6. Spirituality was also inversely associated with CRP. Engagement in private religious practices (prayer, meditation/chanting, reading religious text) and service attendance were not associated with IL-6 nor with CRP. It is unclear why engagement in private religious practice and service attendance did not demonstrate the same protective benefits against inflammation as the other dimensions of R/S, though it is possible that some people may turn to religious practices and service attendance when encountering health challenges. Skipper et al. [56], for example, found that men with hypertension engaged in more prayer and meditation than men without hypertension. As such, there are likely multiple and potentially opposing factors to consider when understanding the health effects associated with these aspects of R/S.

There are other moderating factors to consider to understand how religious behaviors and practices affect health, including mindfulness. For example, Rudaz et al. [57] found that private religious practices were associated with personal growth only when mindfulness was also high. Prior research indicates that the degree of religiousness varies by gender and race [58], and that the impact of religious involvement may differ across groups [59]. In our gender-stratified models, associations were generally similar between women and men, with the exception that spirituality and daily spiritual experiences were associated with lower IL-6 among women, and not men, in models that controlled for age, race, sample,

educational attainment, current smoking, physical activity, and BMI. Race-stratified analyses indicated that spirituality and religious coping were associated with inflammatory biomarkers among White adults only. The literature would benefit from further exploration of interactions between multiple dimensions of R/S and inflammatory markers by gender and race, perhaps also investigating whether differences exist by gender identity versus biological sex.

Collectively, our findings indicate that fostering R/S may be protective against chronic inflammation. Taken together, R/S variables accounted for 0.2%–0.3% unique variance in inflammatory markers. Effect sizes for R/S variables were small but comparable to other psychosocial factors, such as conscientiousness, purpose in life, and optimism [41, 60]. Furthermore, whereas effects appear small at the individual level, they may still represent important effects within the population that can accumulate over the life course [61, 62].

Physical health outcomes, including inflammatory markers, are determined by many factors, such as genetics, environmental factors, and behaviors. Masters et al. [15] suggest there exist three plausible and empirically supported pathways linking R/S with physical health. The first pathway, behavioral self-regulation, involves engagement in healthy behaviors, which may reduce the risk of developing chronic inflammation. Our findings provide support for this pathway as spirituality remained the only R/S variable significantly associated with IL-6 and CRP after including smoking, physical activity, and BMI as covariates in the models. It is well known that religious prescriptions and proscriptions for health behavior within certain religious communities contribute to beneficial physical health outcomes [63]. Motives more internal to the individual, such as the desire to align behavior with religious/spiritual goals and values may also contribute to associations between R/S and physical health via behavioral regulation [17]. Finally, religious or spiritual identity that aligns with healthy behavioral practices may reduce the burden on executive function and lead to greater automaticity in sustaining healthy behavioral patterns [64].

The second pathway by which R/S may influence physical health is via social support. Spirituality, which was significantly associated with IL-6 and CRP after accounting for behavioral factors, was no longer significantly associated with IL-6 when social support was added to the model. This provides support for social support as a mechanism linking spirituality with inflammation, though associations between spirituality and CRP remained unchanged with social support included in the model. Social support was operationalized as positive relations with others, which captures the extent of warm and trusting social relationships and is distinct from the number of social connections or the degree to which one can count on others in times of need [65]. Future research should interrogate these additional instrumental and emotional aspects of social support in order to fully understand how social support may mediate R/S and health associations. The third pathway by which R/S may influence physical health is via psychological and emotional self-regulation (e.g., altering mood, refocusing awareness). Prior research indicates this form of self-regulation may affect inflammatory processes via stress buffering [60]. Supplemental analyses showed that controlling for perceived stress over the prior month did not change associations between R/S and inflammation, failing to support the stress-buffering hypothesis and suggesting that behavioral or social support pathways may be more relevant.

Why most R/S measures were associated with IL-6 and not with CRP remains unclear. The “spirituality” scale, which measures how important spirituality is to an individual’s identity and life, was the only dimension of R/S associated with both IL-6 and CRP and also the only dimension of R/S not accounted for by the behavioral pathway. In a recent national survey assessing spirituality in the USA, the Pew Research Center found that respondents viewed connectedness as an essential component of spirituality. Further investigation could assess whether spiritual social support (connectedness with a spiritual community or with a higher power) would predict beneficial health outcomes above and beyond general social support, as Debnam et al. investigated in a religious context [20].

Of note, the observed associations between R/S dimensions and inflammation in this study do not appear to be the result of unobserved genetic predispositions. This is important as psycho-social-environmental influences may be more amenable to modification via intervention. Although some dimensions of R/S would not be appropriate targets of psychological or behavioral intervention (e.g., attempts to change someone’s religious affiliation), understanding the protective role of certain R/S dimensions can provide insight into effective intervention development. For example, results from this study may suggest a role for leveraging an individual’s religious values in a behavioral intervention aimed at supporting immune health. What this may look like in practice could be assisting individuals with aligning their health or self-care goals with their already existing religious/spiritual values. Results also suggest that social connectedness may be a valuable target of intervention for spiritual individuals.

Conclusions drawn from this study should be interpreted considering several limitations. Despite broad efforts in the field to differentiate between “religiousness” and “spirituality,” and some evidence that they may operate via somewhat different pathways [21], many of the R/S dimensions used in this study cannot be categorized as a “religiousness” versus a “spirituality” variable. Many items asked participants questions such as “Because of your religion or spirituality, do you...” This prevents investigators from being able to dissociate whether results were influenced by dimensions typically associated with “religiousness,” “spirituality,” or both. Findings from the Pew Research Center indicate that more individuals identify as both religious and spiritual than either religious alone or spiritual alone [1]. Future research is warranted to investigate what differences may exist between these subgroups with respect to health outcomes. It is also important to consider that these data are cross-sectional in nature and caution should be used regarding interpretations of the directionality of these associations. Another limitation of our study is a limited exploration of gender and race interactions between R/S variables and biomarker outcomes. Prior studies indicate that the impact of R/S on health can vary by gender and race [59, 66]. Further investigation into these interactions may provide a more nuanced understanding of how R/S affects different subsets of individuals. Moreover, our study investigated U.S. adults in midlife and beyond. Results are thus generalizable to that population and future research would benefit from further investigation into how R/S affects chronic inflammation in different age groups (e.g., in children and adolescents). The field would also benefit from future studies testing associations between R/S and inflammatory biomarkers at multiple time points to elucidate

the ways in which R/S and inflammation function across time to contribute to health outcomes across the life course. Our study is limited by its focus on predominantly individual-level indicators and future research should investigate interactions between R/S and health by community- and system-level influences and other important social determinants of health that impact individuals. Future investigators should also consider replicating these results with additional inflammatory biomarkers, such as tumor necrosis factor (TNF)- α and other cytokines. A final limitation is that we were unable to investigate dimensions of R/S that may contribute to *increased* levels of circulating inflammatory biomarkers. Prior research indicates that some dimensions of R/S may contribute to adverse health outcomes [67]. For example, among a sample of 236 patients undergoing cardiac surgery, those who reported greater spiritual struggle 2 days prior to surgery had greater IL-6 levels the day of surgery [68]. Future research may benefit from investigating potential immune-compromising dimensions of R/S.

To summarize, religious coping, spirituality, daily spiritual experiences, and R/S-based mindfulness were associated with lower levels of circulating inflammatory biomarkers in a national sample of U.S. adults. Service attendance and engagement in private religious practice (e.g., prayer, meditation, reading religious text) were not associated with inflammatory biomarkers in this sample. Collectively, findings indicate that some dimensions of R/S may be health-protective for adults and underscore the importance of examining multiple dimensions of R/S to understand mechanistic pathways underlying the relationships between R/S and health.

Supplementary Material

Supplementary material is available at *Annals of Behavioral Medicine* online.

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Compliance with Ethical Standards

Authors’ Statement of Conflict of Interest and Adherence to Ethical Standards Kaitlyn M. Vagnini, Jennifer Morozink

Boylan, Monica Adams, and Kevin S. Masters declare that they have no conflict of interest.

Authors' Contributions Kaitlyn M. Vagnini (Conceptualization [equal], Data curation [equal], Writing – original draft [lead]), Jennifer Morozink Boylan (Conceptualization [equal], Formal analysis [lead], Funding acquisition [equal], Methodology [equal], Writing – original draft [supporting]), Monica Adams (Data curation [equal], Writing – review & editing [equal]), and Kevin S. Masters (Conceptualization [equal], Funding acquisition [equal], Writing – review & editing [equal])

Transparency Statement The study was pre-registered at the Open Science Framework <https://doi.org/10.17605/OSF.IO/JQ7BG>. The analysis plan was registered prior to beginning data collection at the Open Science Framework <https://doi.org/10.17605/OSF.IO/JQ7BG>. The analytic code used to conduct the analyses presented in this study is not available in a public archive. They may be available by emailing the corresponding author. All materials used to conduct the study are available in a public archive: <https://www.icpsr.umich.edu/web/ICPSR/series/203> and <https://midus.colectica.org/>.

Data Availability

De-identified data from this study are available in a protected archive: <https://www.icpsr.umich.edu/web/ICPSR/series/203> and <https://midus.colectica.org/>.

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