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ORIGINAL PAPER

Religiosity/Spirituality and Physiological Markers of Health

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Abstract
The long-standing interest in the effects of religiosity and spirituality (R/S) on health outcomes has given rise to a large and diverse literature. We conducted a meta-analysis on research involving R/S and physiological markers of health to elucidate both the scope and mechanism(s) of this phenomenon. A combined analysis found a significant, but small, beneficial effect. Subgroup analyses found that some measures of both extrinsic and intrinsic religiosity were significantly associated with health. Several outcome measures, including blood pressure, C-reactive protein, and cardiovascular health markers, were significantly associated with R/S. Our findings suggest that R/S benefits health, perhaps through minimizing the disruptive effects of stress/depression on inflammation. We hope that researchers can use these results to guide efforts aimed at elucidating the true mechanism(s) linking religious/spiritual beliefs and physical health.

Keywords Religiosity · Spirituality · Prayer · Health · Meta-analysis · Immune function · Stress

Introduction

Modern, evidenced-based scientific research has begun lately to explore the objective health benefits of religiosity and spirituality (R/S). Between 1993 and 2002, there was a 600% increase in scientific publications focusing on "spirituality and health" and a 27% increase in "religion and health" publications (Stefanek et al. 2005). Large-scale epidemiological studies have frequently found that religious involvement is associated with decreased morbidity and mortality, longer life expectancy, and improved outcomes following illness and medical procedures, among many mental and physical benefits (Lee and Newberg 2005). In an almost 30-year study of over 5000 participants, frequent church attendance was associated with a 23% lower mortality risk (Strawbridge et al. 1997). A follow-up study with similar methodology identified a 28% reduction in mortality risk (Koenig et al. 1999a, b). In a recent meta-analysis, R/S was associated with significant reductions in mortality in healthy, but not diseased populations (Chida et al. 2009). Several

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different, and not mutually exclusive, explanations for these results have been proposed, including the benefits of R/S-derived coping mechanisms, fostering of hope and optimism, social support from a congregation, and higher rates of positive health behaviors (e.g., lower rates of alcohol and drug use, tobacco consumption, risky sexual behavior) (reviewed in Koenig 2002). Explanations that focus on positive mood and social support share a grounding in recent research on the biological connections between mind and body in fields such as psychoneuroimmunology and psychosomatic medicine. By promoting overall mental well-being, religious and spiritual practices may directly influence several biological systems, including the sympathetic nervous, endocrine, and immune systems (Hill et al. 2017).

One of the earliest studies exploring connections between R/S and physiological functioning found that watching a religious-themed film was associated with higher levels of secretory immunoglobulin A (sIgA) (McClelland 1988). More recent studies have found inverse relationships between religious attendance and interleukin-6 (IL-6) (Koenig et al. 1997; Lutgendorf et al. 2004), a potent inflammatory cytokine and potential contributing factor in several chronic illnesses, including arthritis and coronary heart disease (Hunter and Jones 2015). Other studies have identified positive associations among multiple religious measures (e.g., attendance, prayer, importance of R/S) and CD4+ T cell counts in HIV-positive men (Woods et al. 1999a), as well as effects on HIV disease progression (Ironson et al. 2011; Kremer et al. 2015). Religiosity has also been associated with natural killer cell activity and lymphocyte counts and subsets in women with metastatic breast cancer (Sephton et al. 2001). Several other objective measures of health have been explored as well, including body mass index (BMI), blood pressure, hypertension, and glycosylated hemoglobin (HbA1c), a marker of glucose control and diabetes. In general, R/S measures appear protective against high blood pressure and hypertension (e.g., Larson et al. 1989; Edmondson et al. 2005; Hill et al. 2014). However, results for BMI and HbA1c are not as clear. Schlundt et al. (2008) found that religious involvement was positively, but weakly, associated with BMI. Higher religiosity was also associated with higher BMI and greater odds of overweight/obesity among Asian Indian immigrants to the USA (Bharmal et al. 2013). Conversely, Kortt and Dollery (2014) report that religious importance was negatively associated with BMI in Australia, though only in women. In a separate study, religious well-being was positively related to HbA1c (Newlin et al. 2008). Because religion and spirituality have also been linked with reduced mortality risk, as outlined above, we have an indication that all or some of these specific changes in physiological measures have concrete health benefits (at least as indicated by reduced mortality), thereby avoiding the problem of "statistical significance without clinical significance."

Despite the general finding that R/S is positively associated with health (Seeman et al. 2003), some studies (in addition to those listed above) suggest that these relationships are more nuanced. While some studies have found no association between health benefits and R/S measures (Fitchett and Powell 2009; Murray-Swank et al. 2007; Newlin et al. 2003), others find associations only in some groups. Neither religious coping nor behavior was associated with CD4+ cell counts in HIV + African-American women (Woods et al. 1999b), in direct contrast to results from HIV + men. While multiple measures of R/S were associated with lower blood pressure in men, the same measures were associated with higher blood pressure in women (Tartaro et al. 2005). Other research has found variability depending on specific R/S and outcome measures. For instance, prayer was associated with a higher likelihood of hypertension and spirituality with increased diastolic blood pressure, while measures of meaning and forgiveness dimensions were associated with decreased diastolic blood pressure and hypertension (Buck et al. 2009).

Given the broadly defined nature of "health" and R/S, it is unsurprising that diverse methods and analytical strategies have been used, resulting in a somewhat heterogenous literature (although there are notable broad trends Seeman et al. 2003). We performed a meta-analysis to characterize better this large body of work and determine which aspects of R/S are linked with specific health outcomes. While there are several existing meta-analyses on R/S and health, ours differs in meaningful ways. Masters and Spielmans' (2007) meta-analysis was focused only on distant intercessory prayer. Jim et al. (2015) restricted their analyses to only cancer patients and included measures of subjective well-being. An early meta-analysis by McCullough et al. (2000) explored religious involvement and mortality, as did Chida et al. (2009). In contrast, our analysis includes both healthy individuals and patients with any illness and is limited to objective measures of health, as it is possible to report higher subjective health while burdened with disease. Our analysis focuses on physiological markers of health, excluding mortality which has been covered in previous analyses, so that we might uncover possible biological pathways linking R/S and health outcomes.

Methods

Articles of interest were found by searching PubMed, Web of Science, and Google Scholar for the following terms: "religion and health," "spirituality and health," "religion and immune function," "religion and immunity," "spirituality and immune function," and "spirituality and immunity." We excluded studies not in English, review papers, and papers not reporting results of an objective measure of health (e.g., subjective health, well-being). Of the 184 papers initially identified, 137 were included in our database. We dropped from analysis any papers that did not report odds ratios, risk ratios, correlations, or group mean differences. Several papers reported results for multiple markers of health. Our final dataset is comprised of 618 results from 87 studies (Fig. 1).

A random effects meta-analysis was conducted using the *metafor* package for R (http://www.R-project.org). Random effects analysis allows for inconsistent effect sizes among studies and is generally preferred when high inter-study heterogeneity is expected (Borenstein et al. 2009). To maximize the number of studies available for analysis, all effect sizes were converted to standardized mean difference (d). Correlations (r) and their variances (as calculated by the *metafor* package) were converted using the equations found in Borenstein et al. (2009). Odds and risk ratios were log-transformed and variances calculated from the reported 95% confidence intervals using R code found at metafor-project.org. Log odds ratios and variances were then converted following Borenstein et al. (2009).

R/S measures were categorized broadly, including attendance/activity, importance to self, coping, global religiosity, global spirituality, extrinsic religiosity, and intrinsic religiosity. Health outcomes were similarly categorized, including body composition/weight, blood pressure, T cell (e.g., CD4+, CD8+) types/counts/percentages, and pro-inflammatory cytokines (IL-6 and similar cytokines). Categories and the measures therein are presented in Table 1. Finally, studies were categorized based on whether participants were healthy or the category of illness they had (e.g., cancer, chronic heart disease, HIV). This distinction is important in light of Chida et al's (2009) findings of greater R/S effects on mortality in healthy, but not ill, individuals. It may be that the salubrious effects of religion are weakened by a positive diagnosis or an advanced disease stage (Chida et al. 2009).

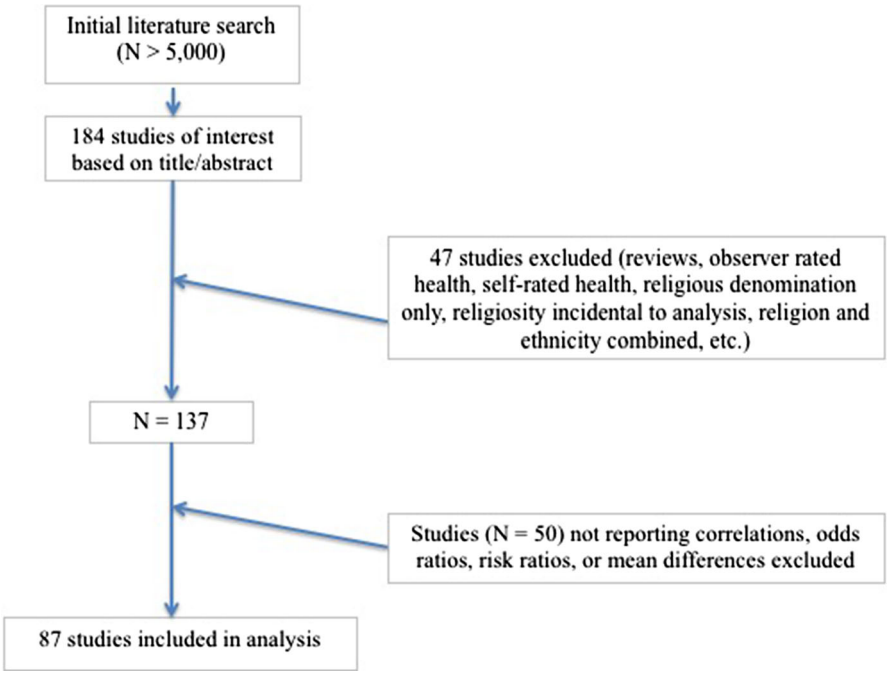

Fig. 1 Study selection flowchart

We assessed inter-study heterogeneity with the I^2 statistic, where low values indicate that observed variances in effect sizes are likely artefactual, whereas larger values indicate the presence of other variables (Borenstein et al. 2009). Funnel plots with tests of asymmetry, Rosenthal's fail-safe *N*, and trim and fill methods were used to determine any publication bias. Rosenthal's *N* calculated the number of studies finding no association between the variables required to make the *p* value of the meta-analysis nonsignificant. The trim and fill method imputes the number of missing studies required to produce a truly symmetrical funnel plot and produces an estimated effect size based on these "missing" studies (Duvall and Tweedie 2000).

Results

Overall

Religiosity and spirituality, broadly construed, are associated with improved objective measures of health (e.g., decreased cholesterol or inflammatory markers). The full analysis found significant associations between all measures of R/S and all physiological health markers ($N = 618$, $d = -0.05$, $p < 0.0001$, $I^2 = 98.30\%$). However, this result is tempered by the extremely high inter-study heterogeneity.

Table 1 Variable categories and outcomes

Religiosity/spirituality categories and measures	
Attendance/activity	Attendance; attendance and importance of religion (index measure); religious activity; daily devotional activities; frequency of religious practice; observance frequency; participation; religious practices; religious activity; worship frequency; synagogue activities; religious behavior; donations; involvement; organized religion/religious activities
Beliefs	Beliefs; orthodoxy; strength of childhood beliefs; strength of beliefs relative to parents; strength of beliefs; divine health deferral; religious fatalism; index measure of faith; gain in faith; forgiveness
Coping	Coping; religious coping; spiritual coping; comfort; spiritual support intervention; benefits of spirituality; religious well-being; spiritual well-being; solving problems using religion; God-mediated locus of control
Extrinsic	Extrinsic religion
Global religiosity	Religiosity; self-rated religiosity; observer rated religiosity; subjective religion; pro-religious beliefs
Global religiosity/spirituality	Religion/spirituality, religion/spirituality index measures
Global spirituality	Spirituality; self-rated spirituality; observer rated spirituality
Importance to self	Importance of religion; commitment; salience; identity; importance of parental religious beliefs; sense of purpose; meaning; moral guidelines derived from religion; application of religion in life; religious knowledge
Intrinsic	Intrinsic religion
Media	Use of religious media (television, radio, etc.)
Meditation	Mindfulness meditation; Buddhist walking meditation; meditation duration; Buddhist compassion meditation; mantras
Negative experiences	Negative religious coping; negative congregational support; negative spiritual experience; negative view of God; negative spiritual coping; congregational problems
Positive experiences	Positive religious coping; positive congregational support; positive spiritual experience; positive view of God
Prayer	Pray to decide; private prayer; prayer and bible reading (index measure); prayer duration; prayer, study, and meditation (index measure); colloquial prayer; petitionary prayer
Private	Private religion affiliation/practices; private religiosity; non-organized religious activity
Public	Public religion affiliation/practices
Religiosity/spirituality experiences	Daily spiritual experiences; frequency of spiritual feelings; religious experiences; spiritual experiences; religious conversion; religious reverence
Social measures	Contact with religious leader; social support; percent of social network in church; percent of social network in same religion; active in congregation; has clergy confidant; anticipated social support from congregation; emotional support received; congregational benefits; religious support

Table 1 continued

Religiosity/spirituality categories and measures	
Spiritual exercise	Qigong; Tai Chi
Spiritual struggle	Religious struggle; spiritual struggle; loss of faith
Health Outcome Categories and Measures	
Antibodies	Influenza vaccine antibody titer
Basophils	Basophil count; eosinophil count
Blood pressure	Total blood pressure; systolic blood pressure; diastolic blood pressure; mean arterial pressure; systolic/diastolic blood pressure reactivity
Body composition/weight	Body mass index; obesity; overweight/obese
Burden of illness	Illness burden; illness severity; "miscellaneous disease"
Cancer diagnosis	Colon cancer
Cancer measures	Karnofsky score; Symptom Distress score; cancer duration; cancer comorbidity
Chronic illness	Chronic illness diagnosis, number of chronic illnesses; chronic illness index measures
Cholesterol	Triglycerides; low-density lipoprotein; total cholesterol; hypercholesterolemia; high-density lipoprotein; very low-density lipoprotein; dyslipidemia; high cholesterol diagnosis
Clotting factors	D-dimer; fibrinogen
Cognitive/brain health	Alzheimer's psychopathology; cognitive decline; Parkinson's severity; schizophrenia; neurological disease; neurocognitive functioning; "clock" test; dementia; global deterioration scale score
Diabetes	Diabetes; insulin resistance; fasting insulin levels
Diagnosed disease	Gastrointestinal disease; genitourinary disease; respiratory disease
Functional health	Grip strength
Globulins	α-1 globulin; α-2 globulin; β globulin; γ globulin
Glucose measures	Hemoglobin A1c; fasting blood glucose
Heart attack risk factors	Acute coronary syndrome; myocardial infarction risk factors; ejection fraction; atrial fibrillation
Heart disease	Heart attack; cardiovascular disease; coronary heart disease
Heart rate	Heart rate; pulse rate; high resting pulse; heart rate variability/reactivity; cardiac autonomic regulation; sympathetic and para-sympathetic cardiac activity

Table 1 continued

Religiosity/spirituality categories and measures	
HIV	HIV symptoms; HIV viral load; long-term survival with HIV
Hospitalization	Length of hospitalization; physical illness severity and length of hospitalization index measure
Innate immune function measures	Epstein-Barr virus antibodies; delayed-type hypersensitivity reaction
Kidney health	Kidney disease severity; dialysis duration
Lymphocytes	Lymphocyte count; lymphocyte percentage; lymphocyte proliferation
Monocytes/neutrophil measures	Monocyte count; neutrophil count; white blood cell count; neutrophil apoptosis; ratio of neutrophils to lymphocytes; neutrophil percentage; monocyte percentage; polymorphonuclear cell bactericidal ability
Natural killer cell measures	Natural killer cell count; Natural killer cell activity
Non-specific inflammation	C-reactive peptide
Operation outcomes	Post-operation complications; positive surgery outcomes
Other cytokines	IL-7; IL-8
Pro-inflammatory cytokines	IL-6; IFN-γ; IL-6 secreting cells, TNF-α secreting cells; IL-1
Skin health	Psoriasis skin lesion clearance
Stress markers	Hypertension; allostatic load; cortisol
Stroke	Stroke severity; stroke recurrence
T cells	CD4 cell count; CD4 cell percentage; T cell count; T helper cell count; T cytotoxic cell count; T cytotoxic cell percentage; ratio of T helper cells to T cytotoxic cells
Th2 cytokines/anti-inflammatory markers	IL-9; IL-10; adiponectin (high molecular weight)
Vascular disease indicators	Ankle-brachial index; basal brachial diameter; brachial ankle pulse wave velocity; carotid intima-media thickness; coronary artery calcium; flow mediated dilation; peak brachial diameter; left ventricle mass; soluble vascular cell adhesion molecules
Viral infection	Herpes simplex virus 2; hepatitis C virus; hepatitis B virus; human herpesvirus 8

Measures of Religiosity and Spirituality

To avoid spurious findings based on only a few results, subgroups with fewer than 10 observations were not analyzed. Subgroup analysis found that measures of religious participation and attendance at services ($N = 232$, $d = -0.07$, $p < 0.0001$, $I^2 = 97.84\%$), overall religiosity ($N = 29$, $d = 0.09$, $p < 0.03$, $I^2 = 96.46\%$), intrinsic religiosity ($N = 17$, $d = -0.06$, $p = 0.0004$, $I^2 = 0.29\%$), prayer ($N = 42$, $d = -0.16$, $p = 0.0001$, $I^2 = 76\%$), and religious/spiritual meditation ($N = 39$, $d = -0.48$, $p < 0.0001$, $I^2 = 76.92\%$) were significantly associated with health outcomes in our sample, although inter-study heterogeneity was generally high. With the notable exception of overall religiosity, associations are inverse, indicating that R/S measures were linked with positive health outcomes (e.g., lower BMI, lower inflammatory markers). Religiosity appears to be associated with increased BMI, cholesterol, and kidney disease markers, among others.

Health Outcomes

Cardiovascular

Blood pressure ($N = 82$, $d = -0.23$, $p < 0.0001$, $I^2 = 92.77\%$), cholesterol ($N = 61$, $d = -0.1$, $p = 0.0005$, $I^2 = 75.27\%$), markers of vascular health ($N = 22$, $d = -0.22$, $p = 0.04$, $I^2 = 96.43\%$), markers of myocardial infarction ($N = 13$, $d = -0.31$, $p < 0.0001$, $I^2 = 91.52\%$), and hypertension/stress ($N = 34$, $d = -0.06$, $p < 0.0001$, $I^2 = 25.17\%$) were all significantly associated with R/S.

Inflammation and Immunity

T cells ($N = 14$, $d = 0.34$, $p < 0.0001$, $I^2 = 0\%$) showed a positive relationship with R/S. These observations are largely derived from patients with HIV; elevated T cell counts are indicative of reduced HIV disease progression. Neutrophils/monocytes ($N = 23$, $d = -0.26$, $p < 0.0001$, $I^2 = 41.99\%$), viral infections ($N = 12$, $d = -0.3$, $p < 0.0001$,

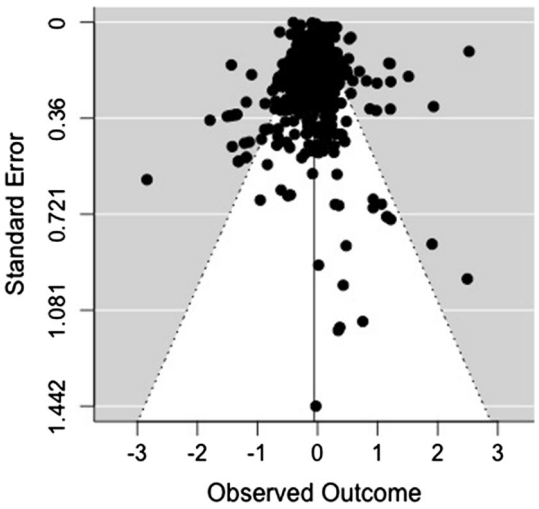

Fig. 2 Funnel plot of all studies

Table 2 Publication bias statistics, measures of religiosity and spirituality

Subgroup	Estimated missing studies	Estimated *p* value	Estimated effect size	Fail-safe *N*
Full analysis	72	0.54	0.009	106,778
Attendance/ importance	20	< 0.0001	− 0.1	88,751
Overall religiosity	6	0.0005	0.16	2222
Intrinsic religiosity	3	0.3	− 0.03	51
Prayer	0	0.0001	− 0.16	1074
Meditation	2	0.001	− 0.4	955

Table 3 Publication bias statistics, outcome measures

Subgroup	Estimated Missing Studies	Estimated *p* value	Estimated effect size	Fail-safe *N*
BMI	0	0.05	0.04	98
Blood pressure	22	0.16	− 0.07	1167
Cholesterol	3	0.004	− 0.08	45
Vascular health	0	0.04	− 0.22	327
T cells	0	< 0.0001	0.34	117
Neutrophil/monocytes	0	< 0.0001	− 0.26	403
Viral infections	0	< 0.0001	− 0.3	86
MI risk markers	6	< 0.0001	− 0.42	45,211
Diabetes risk markers	2	0.0004	0.17	277
Stress	1	< 0.0001	− 0.06	469
CRP	0	0.0001	− 0.22	121

Table 4 Publication bias statistics, participant condition categories

Subgroup	Estimated Missing Studies	Estimated *p* value	Estimated effect size	Fail-safe *N*
Generally healthy	100	0.03	0.04	13,276
Diabetics	0	0.003	− 0.4	215
Cancer treatment	2	< 0.0001	− 0.24	325

Table 5 Publication bias statistics, study sample

Subgroup	Estimated Missing Studies	Estimated *p* value	Estimated effect size	Fail-safe *N*
Population	67	0.002	0.06	9184
Clinical/convenience	0	0.001	− 0.06	52,852

I^2 = 10.93%), and C-reactive protein (N = 12, d = − 0.21, p = 0.0001, I^s = 55.45%) were also significant.

Metabolic

Like T cells, diabetes risk markers (N = 15, d = 0.15, p = 0.003, I^2 = 68.40%) and BMI (N = 70, d = 0.04, p = 0.05, I^2 = 83.8%) also showed a positive association with R/S measures.

Healthy Versus Sick Participants

In generally healthy individuals, R/S was significantly associated with health outcomes (N = 365, d = − 0.08, $p < 0.0001$, I^2 = 97.35%). Diabetics (N = 29, d = − 0.4, p = 0.003, I^2 = 62.01%) and participants undergoing cancer treatment (N = 22, d = − 0.3, $p < 0.0001$, I^2 = 45.73%) also showed significant associations. The data for diabetic individuals are derived from three studies only, and cancer treatment data are from a single source. Given this, both associations may be spurious.

Sampling Strategy

We divided our database between those studies that sought to measure a wider population (e.g., NHANES) and those studies that used a clinical or convenience sample. In both cases, the relationships between R/S and biological measures of health were statistically significant (N = 215, d = − 0.05, p = 0.03, I^2 = 97.98% and N = 403, d = − 0.06, p = 0.001, I^2 = 95.43%, respectively). Sampling strategy and study design do not appear to greatly affect results in our database.

Publication Bias

Figure 2 shows the funnel plot for all observations. The trim and fill method imputes 72 "missing" observations, the addition of which negates the significance of the findings (p = 0.54). Trim and fill results and fail-safe Ns for significant findings are given in Tables 2, 3, and 4. Estimated missing study numbers are generally small and with two exceptions (prayer and neutrophils/monocytes); addition of these missing data renders associations nonsignificant. At the same time, fail-safe Ns are fairly large, lending confidence to our results (Table 5).

Discussion

We demonstrate significant associations between several measures of R/S and multiple objective measures of health. However, effect sizes were generally small and inter-study heterogeneity was generally high, suggesting the presence of some moderating or confounding variables among studies. Nevertheless, this is the first meta-analysis of the large and growing literature on links between R/S and physical markers of health, and our analysis offers key insights into which measures of R/S are most closely associated with health, and which health outcomes are most affected by R/S.

Notably, measures of both extrinsic and intrinsic religiosity were associated with health in our study. Intrinsic, or subjective religiosity, contrasts with extrinsic religiosity, which

can be thought of as the social aspects of religious affiliation (Koenig and Büssing 2010). The distinction between personal and social religiosity is a critical one, as the health effects of each may be different. Indeed, Maltby and Day (2003) found that an extrinsic orientation was associated with anxiety in the face of stressful events, as well as feelings of loss or sadness. The opposite was true for intrinsic religiosity, indicating that intrinsic orientations may be associated with positive psychological outcomes (with plausible connections to physical health), whereas extrinsic orientations are linked with poorer outcomes (ibid). There is also evidence that intrinsic religiosity is related to an internal locus of control (Coursey et al. 2013). Several positive health behaviors and outcomes, such as exercise, lower fat consumption, and reduced cortisol reactivity to experimental psychosocial stressors, have been linked with an internal health-related locus of control (i.e., the belief that one is responsible for their own health) (Steptoe and Wardle 2001; Kirschbaum et al. 1995; Pruessner et al. 2005). In their meta-analysis of cancer patients, Jim et al. (2015) found that measures of "cognitive" and "affective" religiosity, which overlap with intrinsic religiosity to an extent, were associated with better physical well-being and other aspects of health. While measures of religious attendance and participation were significantly associated with objective health markers in our analysis, both prayer and meditation (aspects of intrinsic religiosity) showed stronger effect sizes, suggesting that intrinsic religiosity may be more strongly linked with health outcomes.

While R/S was largely associated with positive health outcomes in a number of domains, elevated diabetes markers and BMI were associated with religious or spiritual beliefs and behaviors. However, in the first case 40% of the effect sizes were derived from diabetic participants, and this result may therefore simply reflect a sampling bias. One should also be cautious regarding the interpretation of the positive association of BMI with R/S. A larger BMI does not necessarily equate with obesity or poor health, as BMI is problematic (although widely used) measure of obesity. For instance, BMI does not measure body fat distribution which may play a greater role in disease and mortality risk than BMI alone (Nuttall 2015; Sahakyan et al. 2015), nor does BMI distinguish from body fat mass and body lean mass (Nuttall 2015). Nonetheless, these findings echo other results that show associations between religion and increased BMI (Hill et al. 2017). Cline and Ferraro (2006) suggest that this somewhat counterintuitive result may be related to the use of food and sodas at religious functions rather than alcohol, or that religious organizations may be a welcoming space for overweight/obese individuals, among other possible explanations. In our study, the strongest associations between R/S and health markers were found with C-reactive protein, myocardial infarction risk factors, vascular health markers, monocytes/neutrophils, and T cells. It is worth noting that these measures require laboratory testing, which may reduce statistical "noise" in the results (with the caveat that many of these results come from relatively few studies).

As noted above, T cell data are frequently derived from HIV patients in our dataset. Spiritual and religious well-being were negatively associated with depressive symptoms and positively associated with CD4+ cell counts and percentages (Dalmida et al. 2009). Although there were no significant relationships between immune markers and religious coping or religious behavior, depression was inversely related to religious coping in another sample of HIV-positive participants (Woods et al. 1999a). Depression has significant effects on HIV treatment and disease progression, including immune dysfunction and reduced adherence to treatment (Leserman et al. 1999; Schuster et al. 2011). Furthermore, both greater social support and positive states of mind have been linked with better treatment adherence (Gonzalez et al. 2004). Both extrinsic and intrinsic aspects of religiosity could therefore be slowing HIV progression by reducing depression through

increased social support and positive coping mechanisms. Considering the strong, bidirectional links between depression and physical health (Kiecolt-Glaser et al. 2002; Moussavi et al. 2007), the anti-depressive effects of R/S may be a major mechanism to explain observed health benefits (but see Koenig 2009 and VanderWeele 2016).

In parallel with the results of Chida et al. (2009) meta-analysis that found reduced associations with cardiovascular disease mortality, we found significant reductions in markers of myocardial infarction and vascular disease. These may in turn be related to the observed reductions in C-reactive protein, monocytes, and neutrophils. Inflammation plays an important role in vascular injury, atherogenesis, and thrombosis (Brown et al. 2001), and the ratio of neutrophils to lymphocyte is a marker of increased risk of mortality from myocardial infarction (Núñez et al. 2008). C-reactive protein is a strong predictor of cardiovascular events, including stroke, in both women (Ridker et al. 2000) and men (Koenig et al. 1999a, b). Mechanistically, C-reactive protein appears to interact with both low-density lipoproteins and macrophages to contribute to atherosclerotic lesions (Singh et al. 2009) and can also induce apoptosis in vascular smooth muscle cells (Blaschke 2004). Considering the relationships among inflammation (including C-reactive protein), depression (Valkanova et al. 2013) and stress (Steptoe et al. 2007), it may be that R/S operates through these pathways to reduce systemic inflammation with subsequent effects on cardiovascular health.

As further support, we find a strongly significant negative effect (albeit small) on R/S and measures of stress and hypertension. Over half of observational studies reviewed by Koenig (2002) found that levels of anxiety and fear were significantly reduced in more religious individuals. Kaplan et al. (2005) find compelling evidence for the same, reporting that highly religious Jewish participants in the Gaza Strip had few symptoms of stress-related complaints and the lowest sense of personal threat, relative to other groups in the area and despite consistent exposure to violent attacks. Baseline religiosity negatively predicted salivary cortisol levels in a longitudinal study of African-American youths (Assari et al. 2015), and female fibromyalgia patients with higher intrinsic religiosity exhibited more rhythmic diurnal cortisol patterns, which are contraindicative of chronically elevated cortisol levels (Dedert et al. 2004). Beyond these connections between R/S and cortisol, a considerable body of research highlights connections between the stress response and the immune system (Webster-Marketon and Glaser 2008). Because stress tends to result in decreased immune function, we might expect more religious participants to have normal or even higher levels of immune markers, contrary to the negative associations found here. However, stress is also known to affect movement of neutrophils, monocytes, and other immune cells from the body's core to the periphery where they are more likely to encounter a pathogen (Dhabhar 2014). Changes in these cell counts may not represent changes in immune function, but rather in the distribution of cells throughout the body. Our findings of inverse relationships between R/S and blood pressure and monocytes/neutrophils may lend some support to the anxiolytic effects of religion and downstream effects on health. This awaits further confirmation.

Meta-analyses are useful tools to assess the statistical relationships among a set of variables and explore reasons for observed heterogeneity, including hidden confounders and moderators. But these analyses are of course limited by the quality and quantity of published research. In addition to the challenges of studying such broad topics as R/S and health, several salient methodological critiques have been aimed at this body of the literature. These include adequate controls, the use of cross-sectional versus longitudinal studies, and a better consideration of religious context (VanderWeele 2016). For instance, Young et al. (2011) found that attempted suicide rates in adolescents were two to four

times higher in cases of religious "mismatch," where students had a different religion than their school. In cases like this, religion could be detrimental to health, rather than protective. The costs of religiosity are also highlighted by spiritual struggles. These attempts to maintain a threatened belief system can be interpersonal, related to doubts about beliefs, or arise from perceived conflicts with the divine (McConnell et al. 2006). In addition to psychological health (Ellison and Lee 2010) and mortality (Pargament et al. 2001), spiritual struggles can have effects on other physiological outcomes, including increased IL-6 levels (Ai et al. 2009a, b).

Our results are also influenced by study selection criteria. Inclusion of additional publications could affect our findings, as could adjustments to our categorization of R/S measures and health outcomes. Our aim was to provide some direction for future research into the effects of religion and spirituality on objective health outcomes. Based on our findings and the attributes of existing studies, we propose investigations into immunological, inflammatory, and hormonal correlates of R/S, as these are known to be affected by psychosocial stress. While this is speculative to a degree, understanding the precise mechanism(s) that connect R/S with biological health outcomes will not only advance the field considerably but also provide further insight into the connections between mood, personality, and health, a burgeoning research topic in fields such as psychoneuroimmunology and psychosomatic medicine. We additionally suggest the use of study designs that experimentally affect feelings of intrinsic R/S to distinguish the effects of intrinsic orientations from extrinsic. Recent research has found that some measures of R/S (e.g., belief in supernatural agents, overall religiosity) can be experimentally manipulated (e.g., Gervais and Norenzayan 2012; Shariff et al. 2008), and religious primes have also been used to explore the connections between R/S and outcomes such as pro-sociality (reviewed in Shariff et al. 2015). Additionally, administration of vaccines has previously been used to determine how immune responses are shaped by psychological parameters (e.g., Rosenkranz et al. 2003). We believe that study designs along these lines are an excellent step in further elucidating the exact mechanisms underlying the apparent health benefits of religiosity and spirituality.

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Compliance with Ethical Standards

Conflict of interest All authors declares that they have no conflict of interest.

Human and Animal Rights This article does not contain any studies with human participants or animals performed by any of the authors.

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