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Religion, spirituality and diurnal rhythms of salivary cortisol and dehydroepiandrosterone in postmenopausal women

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ABSTRACT

Background: Religion and spirituality (R/S) are important resources for coping with stress and are hypothesized to influence health outcomes via modulation of the hypothalamic-pituitary-adrenal (HPA) axis, though this has not been evaluated extensively. In this study, we examined associations between several measures of religiosity or spirituality (R/S) and three HPA axis biomarkers: cortisol, dehydroepiandrosterone (DHEA), and cortisol: DHEA ratio.
Methods: Sample included 216 female postmenopausal Nurses' Health Study II participants who provided up to five timed saliva samples: immediately upon awakening, 45 min, 4 h, and 10 h after waking, and prior to going to sleep during a single day in 2013. Multivariable-adjusted linear mixed models with piecewise cubic spline functions and adjustment for potential covariates were used to estimate the cross-sectional associations of eight R/S measures with diurnal rhythms of cortisol, DHEA, and the cortisol/DHEA ratio.
Results: There was little evidence of association between the eight R/S measures analyzed and diurnal rhythms of cortisol, DHEA, and the cortisol/DHEA ratio. Women who reported that R/S was very involved in understanding or dealing with stressful situations had slower night rise in cortisol than those who did not. Greater levels of religious struggles were associated with higher cortisol levels throughout the day. Higher non-theistic daily spiritual experiences scores were associated with slower DHEA night rise, and a higher cortisol/DHEA ratio upon waking and at night. However, these associations were significantly attenuated when we excluded women reporting bedtimes at least 30 min later than usual.
Conclusion: Observed associations were driven by those with late sleep schedules, and given the number of comparisons made, could be due to chance. Future research using larger, more diverse samples of individuals is needed to better understand the relationship between R/S and HPA axis biomarkers.

1. Introduction

A growing body of evidence has documented important influences of religion and spirituality (R/S) on health [1]. Greater use of religion to deal with stressful situations and other positive religious coping strategies (e.g. looking to God for strength, seeking help from God to let go of anger) has also been associated with positive mental and physical health outcomes, including lower rates of depression [2] and hypertension [3].Whereas, negative religious coping strategies or religious struggles (e.g., responding to a stressful situation by feeling abandoned

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or punished by God or questioning one's beliefs) have been linked to worse physical and mental health, including poorer psychological well-being and mortality [4,5]. While evidence regarding the relationship between R/S and health continues to grow, the potential biological mechanisms through which R/S affects health remain underexplored and poorly understood.

The hypothalamic-pituitary-adrenal (HPA) axis has been suggested as one potential biological pathway through which R/S influences health and affects survival [6]. Through its two main secretory products (i.e., cortisol and dehydroepiandrosterone (DHEA)), the HPA-axis plays a critical role in maintaining homeostasis and allostasis [7,8]. These hormones have a diurnal rhythm, with high cortisol levels upon awakening that continue to rise and reach a peak 30–45 min after waking (awakening response), and then decline over the course of the day, at first rapidly, and then more slowly until the nadir point is reached around bedtime [9,10]. Altered diurnal rhythms in cortisol, including elevated and/or blunted awakening response and flatter diurnal cortisol slope, have been associated with stress and have been shown to increase risk of several chronic conditions, including cardiovascular disease [11], depression [12], and cancer [13].

DHEA, an androgen secreted in parallel to cortisol, has been observed to antagonize the effects of cortisol because of its anti-glucocorticoid properties [8]. For example, while cortisol has been found to have neurotoxic effects on the hippocampus, DHEA has been shown to be neuroprotective [14]. Unlike cortisol, DHEA levels have been shown to exhibit a sharp decrease at awakening with subsequent progressive decline throughout the day before an increase around bedtime [9,10]. Although research is still emerging, low or high levels of DHEA or dehydroepiandrosterone-sulfate (DHEAS) have been linked to certain diseases including atrial fibrillation [15], type-2 diabetes [16], certain types of cancers [17,18], and mortality [19].

The cortisol to DHEA ratio has also been used to assess HPA-axis functioning, given the antagonistic effects of DHEA on cortisol [8]. In comparison to cortisol, cortisol:DHEA levels are marked by a sharp rise at awakening that is followed by a declining trend over the course of the day, and then an increase around bedtime [20]. Elevated cortisol/DHEA ratio has been linked to depression [21] and hypertension [22]. Further, a 2010 prospective cohort study of US army veterans found higher cortisol:DHEA ratio was associated with an increased risk of all-cause, cancer-related or other cause of mortality after 15 years of follow-up [23].

R/S may influence HPA-axis functioning by facilitating positive coping strategies in dealing with stressful life situations. However, studies published to date on the association between R/S and cortisol have been mixed [24–28]. Koenig and colleagues (2012), in their review of studies published between 2000 and 2010, found that only 4 of 11 high-quality studies reported an inverse association between R/S (including the extent of religiosity and spirituality) and cortisol levels. Previous studies have not explored multiple aspects of R/S. Additionally, studies have primarily included clinical subjects that may not be representative of community-dwelling populations. The role of R/S on DHEA or cortisol/DHEA has been even less studied, with no significant associations observed in these studies [29–31].

This current study addresses these gaps in the literature by expanding the range of R/S measures analyzed, along with a rigorous assessment of HPA-axis functioning using cortisol, DHEA, and cortisol to DHEA ratio diurnal rhythms. Using data on 216 postmenopausal female Nurses' Health Study II participants enrolled in the Mind-Body Study (MBS), we assessed cross-sectional associations between these HPA-axis outcomes and multiple dimensions of R/S, including the self-reported extent to which one is areligious or spiritual person, religious service attendance, positive religious coping, religious and spiritual struggles, non-theistic daily spiritual experiences, and theistic daily spiritual experiences.

2. Methods

2.1. Study population

The Mind Body Study (MBS) includes female participants of the NHSII, an ongoing longitudinal study of 116,429 female registered nurses, aged 25–42 years at baseline (1989), who completed and returned an initial questionnaire regarding their health and lifestyle [32]. NHSII participants receive biennial follow-up questionnaires to update their lifestyle practices, other exposures, and disease diagnoses. In 2013, 688 postmenopausal NHSII participants who had previously provided blood/urine samples in 2008–2011 were invited to participate in the MBS, designed to examine psychosocial stressors in relation to biomarkers [20]. Women who reported having experienced sexual abuse in childhood on a 2001 questionnaire were oversampled to increase the representation of those experiencing chronic stress [20,33].

Of the 688 women invited to participate in the MBS, 293 (33.9%) expressed interest and were mailed a consent form that provided details of the study. Of these 293 women, 269 signed the consent form, and 233 completed an online questionnaire and returned sample kits that included timed saliva collection over one day. The study protocol was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

2.2. Timed saliva samples collection and biomarker assays

MBS participants were mailed sample collection kits and asked to provide timed saliva samples to be collected at five times within one day: immediately upon waking (before getting out of bed), 45 min after waking, 4 h after waking, 10 h after waking, and just prior to bed. Participants were asked to fill out a log documenting the time saliva was collected, and record whether they drank, ate, exercised, and brushed their teeth, and whether they felt excited or worried around the time of saliva collection [20]. Samples were placed in the refrigerator prior to overnight shipping the next day with a cold pack to the laboratory. Aliquots of the saliva samples were stored in the vapor phase of liquid nitrogen freezers until analysis. Assays were performed using a competitive chemiluminescence immunoassay (CLIA-approved) in the Laboratory for Biological Health Psychology (Dr. Nicholas Rohleder) at Brandeis University (Waltham, MA). Samples were assayed in duplicate, and samples with duplicate CVs >10% were rerun. CVs for blinded QC pools were <6%. Cortisol and DHEA are stable in saliva up to 4 days with delayed freezing [34].

2.3. Measures

2.3.1. Religion and spirituality (R/S)

Religious Service Attendance. Religious service attendance was assessed on the 2013 MBS baseline questionnaire, which was completed approximately 1 month after saliva collection, by asking: "How often do you go to religious meetings or services?" Response options included: 1) more than once a week, 2) once a week, 3) one to three times a month, 4) less than once per month, and 5) never or almost never. Attendance was categorized as frequent (at least once a week), moderate (one to three times a month), and minimal (less than once a month or never).

Extent of religiosity or spirituality. Extent of religiosity or spirituality—and all other R/S measures assessed in this analysis—were assessed in a follow-up questionnaire fielded in 2014, about 11–12 months after saliva collection [20]. Two questions using the same stem, "To what extent do you consider yourself …" were asked. One was "a religious person?"; the other was "a spiritual person?" Response options included: 1) not at all, 2) slightly, 3) moderately, and 4) very. "Slightly" and "not at all" were combined to create three-level variables.

Religious coping. Overall religious coping behavior was assessed using a question from the Brief Multidimensional Measure of Religion and Spirituality (BMMRS) [35]: "To what extent is your religion or spirituality involved in understanding or dealing with stressful situations in any way?" Response options included: 1) not involved at all, 2) not very involved, 3) somewhat involved, and 4) very involved. Religious coping was categorized as high (very involved), moderate (somewhat involved), and low/never (not very involved or not involved at all). Positive religious coping was assessed using five items from the Brief RCOPE [36], which asked: "In facing recent stressful life events, I …: 1) "looked for a stronger connection with God; " 2) "sought God's love and care; " 3) "tried to put my plans into action together with God; " 4) "tried to see how God might be trying to strengthen me in this situation; " and 5) "sought help from God in letting go of my anger." A mean score was calculated among persons answering at least four of the five items, accounting for the number of the items answered. Higher scores indicated greater use of positive religious coping.

Religious and spiritual struggles were assessed using four items from the Religious and Spiritual Struggles Scale [37], which asked: "In facing recent stressful life events, I: 1) "felt abandoned by God; " 2) "felt as though God were punishing me; " 3) "questioned God's love for me; " and 4) "felt guilty for not living up to my (highest) moral standards." Participants responded to these items on a 4-point scale from 4 (a great deal) to 1 (not at all). Respondents that selected 'not applicable' were treated as missing. An average score was derived from persons answering at least three of the four items accounting for number of items answered. Higher scores indicated greater religious or spiritual struggles. The single item religious coping question was asked of all participants, while the positive religious coping items and religious struggles scale were not asked of participants who reported that they did not believe in God (N = 16).

Daily spiritual experiences. Non-theistic and theistic daily spiritual experiences (DSES) were assessed with the Daily Spiritual Experience Scale [38,39], a measure assessing "a person's perception of the transcendent in daily life and her perception of her interaction with or involvement of the transcendent in life [39]. The non-theistic subscale evaluated spiritual experiences outside a theistic frame and included four items: 1) "I am spiritually touched by the beauty of creation; " 2) "I feel deep inner harmony or peace; " 3) "I feel a selfless caring for others; " and 4) "I feel thankful for the blessings in my life." Theistic DSES items included: 1) "I feel God's love for me, directly; " 2) "I feel God's love for me through others; " 3) "I ask for God's help in the midst of daily spiritual activities; " and 4) "I desire to be closer to God or in union with God." Participants indicated how often they had each spiritual experience on a 4-point scale from 4 (most days) to 1 (hardly ever). An average score was derived from persons that answered at least three of the four items (non-theistic DSES and theistic DSES) accounting for the number of items answered. Higher scores reflected a greater frequency of non-theistic and theistic daily spiritual experiences.

2.3.2. Covariates

The covariates considered in this study included those found to be associated with HPA diurnal rhythms of cortisol and DHEA [33,40], or those that were significant in a univariate regression model at $p \leq 0.20$. These include age, body mass index (kg/m^2), current smoking status, alcohol intake (g/day), caffeine intake (mg/day), child and adolescent abuse, duration of lifetime shiftwork, poor sleep, type 2 diabetes, hypertension, anxiety, depressive symptoms, physician-diagnosed depression, and medication use (including antidepressant, minor-tranquilizer, beta-blocker, DHEA medication, testosterone, and oral steroid use. Child and adolescent abuse were assessed using questions from the Revised Conflict Tactics Scale [41]. Poor sleep, depressive symptoms, and anxiety were assessed using Pittsburgh Sleep Quality Index (PSQI) scale [42], short-form Center for Epidemiological Study-Depression (CES-D) scale [43], and Generalized Anxiety Disorder-7 (GAD-7) scale [44] respectively. Covariates were assessed either at the time of saliva sample collection or on the nearest main questionnaire prior to the MBS study (primarily from the 2011 and 2013 questionnaires). Birthdate and height were collected at baseline in 1989.

2.4. Statistical analysis

Analyses excluded participants with missing information on all the five main R/S measures (N = 2), missing two or more timed saliva collections (N = 8), premenopausal (N = 1), or those who were extreme outliers (>3 IQR above the 75th percentile value and <3 IQR below the 25th percentile) for more than two of the five-timed saliva collections (N = 6). The final sample size consisted of 216 participants. Cortisol, DHEA, and cortisol:DHEA ratio trajectories were examined as a function of time since waking. Cortisol, DHEA, and cortisol:DHEA values were natural log-transformed to improve the normality of their distribution.

To examine differences in diurnal cortisol and DHEA rhythms according to level of each R/S measure, we used linear mixed regression models with piecewise linear spline functions. Within-individual and within-day variation was accounted for using a random effect and assuming an unstructured covariance matrix. Three knots were fitted at 45 min, 4 h, and 16 h after awakening to evaluate three cortisol and DHEA parameters: (1) awakening response (change from waking level to 45 min after awakening); (2) early decline (change from 45 min to 4 h after awakening); (3) late decline (change from 4 h to 16 h after awakening); (4) night rise (change from 16 h after awakening to bedtime); and (5) area under the curve (AUC) (from awakening to 16 h after awakening). To evaluate whether these parameters differed by R/S status, cross-product interaction terms between each R/S variable and the linear spline terms were also included in the model, as follows:

$$\log(\text{biomarkers}) = \beta_0 + \beta_1 T + \beta_2 S_1 + \beta_3 S_2 + \beta_4 S_3 + \beta_5(R/S) + \beta_6 (R/S)^*T + \beta_7 (R/S)^*S_1 + \beta_8 (R/S)^*S_2 + \beta_9 (R/S)^*S_3 + \beta\text{covariates} + \text{random effect} + \varepsilon$$

where T is the time of saliva collection, R/S is the R/S variable, and S_1, S_2, and S_3 are linear spline terms defined as.

S_1 = T-0.75 (45min) if T > 0.75, otherwise $S_1 = 0$;
S_2 = T-4 if T > 4, otherwise $S_2 = 0$;
S_3 = T-16 if T > 16, otherwise $S_3 = 0$;

Linear combinations of the β coefficients were used to estimate differences in the parameters (as described above) by R/S status. For example, the difference in the slope of awakening rise by R/S status was estimated by β_6, the difference in the slope of early decline was estimated by $\beta_6 + \beta_7$, and the difference in the slope of late decline was estimated by $\beta_6 + \beta_7 + \beta_8$. We exponentiated these estimates and subtracted one to calculate percent differences in these parameters. Estimates for the overall diurnal slope (change from awakening to bedtime) were also derived by fitting linear mixed regression models with a single linear term. Models were run separately for cortisol, DHEA, and cortisol:DHEA ratio to provide estimates for each of the diurnal rhythm parameters.

Multivariable models adjusted for time-dependent characteristics or behaviors at the time of each saliva collection (whether participants ate, drank, brushed, exercised, happy, or were worried), as well as all time-invariant covariates, described previously. Missing indicators were used to handle missing data on R/S measures and covariates. Two sets of sensitivity analyses were conducted. First, because these medications may affect cortisol and DHEA levels, we excluded 14 women who reported current use of oral steroids or DHEA medications. Second, because a late sleep schedule has been shown to affect bedtime cortisol and DHEA rise in previous studies [33,40,45], we conducted sensitivity analyses excluding 18 women who went to bed at least 30 min past their usual bedtime on the day saliva was collected. All analyses were performed using SAS 9.4 for UNIX (SAS Institute, Cary, NC).

3. Results

Table 1 shows age and age-adjusted characteristics of study participants, women predominantly of white race (>93%), and a few women of

Table 1
Age and age-adjusted sample characteristics of participants in the MBS by religious coping and religious struggle, as assessed in 2013.

	To what extent is your religion or spirituality involved in dealing with stressful situations			Religious struggle[b]	
	Not involved or not very involved (n = 42)	Somewhat involved (n = 54)	Very involved (n = 93)	No religious struggle (n = 85)	Some religious struggle (n = 65)
Age, years[a]	62.0 (3.2)	59.9 (4.6)	60.3 (3.9)	60.6 (4.1)	60.5 (4.1)
White race, %	95	95	94	95	91
Hispanic ethnicity, %	6	2	0	1	0
Body mass index	25.4 (4.1)	26.7 (7.4)	26.9 (6.0)	26.3 (6.1)	27.8 (6.5)
Current smokers, %	1	5	2	2	3
Alcohol drinking, g/day	3.4 (0.0, 12.5)	3.6 (0.0, 10.3)	2.2 (0.0, 11.1)	3.6 (0.0, 10.8)	1.3 (0.0, 8.1)
Caffeine intake, mg/day	190.9 (182.5)	156.7 (130.4)	176.1 (134.3)	180.6 (134.8)	159.3 (144.5)
Physical activity, METs/wk	25.7 (11.2, 53.4)	28.0 (8.2, 45.4)	17.8 (6.3, 41.1)	19.3 (7.7, 38.2)	18.4 (6.4, 41.0)
Childhood/adolescent abuse, %	40	32	33	34	26
Duration of lifetime shiftwork, yrs	3.6 (5.3)	3.2 (4.2)	4.0 (4.7)	3.2 (3.9)	5.0(5.5)
Poor sleep (PSQI score > 5), %	57	62	61	61	69
Type 2 diabetes, %	8	4	8	7	8
Hypertension, %	35	25	35	28	41
10-item CES-D	7.1 (5.7)	5.5 (4.4)	5.9 (4.9)	5.0 (4.4)	7.5 (5.2)
Anxiety symptoms (GAD score ≥5), %	36	21	19	19	25
Antidepressant use, %	43	29	20	20	29
Minor tranquilizer use, %	14	7	7	7	7
Beta-blocker use, %	10	8	12	11	16
DHEA medication, %	1	2	3	5	3
Testosterone therapy, %	0	2	1	2	0
Oral steroid, %	1	5	4	2	5
Extent of religiosity (Very), %	0	12	61	32	48
Extent of spirituality (Very), %	0	23	85	47	61
Service attendance (≥1/week), %	2	22	66	41	53
Nontheistic daily spiritual experiences	3.1 (0.6)	3.4 (0.5)	3.7 (0.4)	3.6 (0.5)	3.5 (0.5)
Theistic daily spiritual experiences	1.7 (0.7)	2.9 (0.9)	3.6 (0.5)	3.3 (0.9)	3.3 (0.8)

Values are means (SD) or medians (Q25, Q75) for continuous variables, percentages or ns or both for categorical variables, and are standardized to the age distribution of the study population.
Abbreviations: R/S: Religion or spirituality; PSQI= Pittsburgh sleep quality index; CES-D = Center for Epidemiologic Studies Depression Scale; GAD-7 = Generalized Anxiety Disorder 7-item scale.
[a] Value is not age adjusted.

[b] Excludes those who do not believe in God; no religious struggle (where religious struggle score = 1.00), some religious struggle (where religious struggle score > 1.00).

Hispanic ethnicity (<5%) according to religious coping and religious struggle. Women who reported high use of R/S in coping with stressful life situations were slightly younger compared those who rarely or never used their religion or spirituality to cope with stressful situations (60.3 yrs vs. 62.0 yrs) (Table 1). Women who reported that their religion or spirituality was very important in coping with stressful situations (49.2%) had somewhat higher mean BMI (26.9 kg/m^2 vs. 25.4 kg/m^2) and lower levels of physical activity (17.8 MET-hrs/wk vs. 25.7 MET-hrs/wk), compared to those who reported little or no positive R/S coping, while women experiencing religious struggles had higher mean BMI (27.8 kg/m^2 vs. 26.3 kg/m^2) and lower physical activity levels (18.4 MET-hrs/wk vs. 19.3 MET-hrs/wk) compared to those with no struggle. History of childhood/adolescent abuse was highest among women who reported that their R/S was not involved in coping with stressful life situations, compared to those whose R/S was "very" involved in their coping with stressful life situations (40% vs. 33%), but lower among women with some religious struggles relative to those with no religious struggle (26% vs. 34%). Elevated anxiety symptoms were more prevalent among women with little or no involvement of R/S coping relative to high involvement (36% vs.19%), and among those with some religious struggles relative to those without struggle (25% vs.19%). Similarly, on average, the presence of depressive symptoms was higher among women who reported little or no use of R/S coping vs. those reporting high levels of positive religious coping (7.1% vs. 5.9%) and among those with some religious/spiritual struggles vs. those with no religious/spiritual struggles (7.5% vs. 5.0%). Meanwhile, compared to women who reported attending religious services never or less than once per month, women that attended services greater than once per week were less likely to be current smokers, have a history of childhood/adolescent abuse, have elevated anxiety symptoms, and to have depressive symptoms (Supplementary Table 1).

Religious coping was associated with diurnal rhythms of cortisol, DHEA, and the cortisol to DHEA ratio only for nighttime cortisol rise (Table 2; Fig. 1). Compared to those who reported low involvement of R/S in coping with life situations, women who reported that their religion or spirituality was 'very important' in coping with stressful situations had a slower nighttime cortisol rise relative to those with lesser levels of R/S coping (PD: 18.9, 95% CI: 31.7-, −3.7; p = 0.02). This association remained significant in sensitivity analyses that excluded women who reported the use of oral steroids or DHEA medication (Supplementary Table 2), but was not significant after exclusion of women who reported going to bed later than usual on the night that their saliva samples were collected (Supplementary Table 3). We did not observe any significant associations between the extent to which a woman identified as religious/spiritual person, or attended religious services and diurnal rhythms of cortisol, DHEA, or their ratio (Table 2;

Table 2
Percent differences (95% CIs) in diurnal rhythms (waking level, awakening response, early decline, late decline, night rise, cortisol slope, and AUC) of cortisol, DHEA, and their ratio according to the extent of religiosity, the extent of spirituality, religious service attendance, and religious coping (N = 216)[a].

	Religious coping	Extent of Religiosity	Extent of Spirituality	Service attendance
	% D (95% CI)	% D (95% CI)	% D (95% CI)	% D (95% CI)
Cortisol				
Waking level[b]	−0.5 (−10.4, 10.4)	1.4 (−8.0, 11.7)	1.5 (−8.4, 12.5)	−0.9 (−9.4, 8.3)
Awakening response[c]	10.2 (−6.8, 30.2)	8.8 (−6.6, 26.7)	3.8 (−12.1, 22.5)	−2.4 (−15.2, 12.4)
Early decline[d]	−0.2 (−4.0, 3.6)	−2.0 (−5.4, 1.5)	0.0 (−3.7, 3.9)	0.3 (−2.9, 3.6)
Late decline[e]	−0.3 (−1.7, 1.1)	0.7 (−0.6, 2.0)	0.3 (−1.1, 1.7)	0.4 (−0.8, 1.6)
Night rise[f]	−18.9 (−31.7, −3.7)	−10.4 (−23.5, 5.0)	−9.9 (−23.7, 6.4)	−10.5 (−23.6, 4.9)
Cortisol slope[g]	−0.4 (−1.4, 0.6)	0.2 (−0.7, 1.1)	0.1 (−0.9, 1.1)	0.1 (−0.7, 0.9)
AUC[h]	0.7 (−0.5, 2.0)	0.8 (−0.3, 1.9)	0.9 (−0.3, 2.1)	0.0 (−1.1, 1.0)
Dehydroepiandrosterone (DHEA)				
Waking level[b]	0.2 (−15.8, 19.2)	−3.7 (−18.1, 13.1)	1.0 (−14.7, 19.6)	−1.1 (−14.8, 14.7)
Awakening response[c]	−2.8 (−17.3, 14.3)	−3.6 (−16.8, 11.8)	−4.2 (−18.3, 12.5)	−8.6 (−20.3, 4.7)
Early decline[d]	1.9 (−1.8, 5.8)	1.1 (−2.3, 4.6)	1.1 (−2.6, 4.9)	1.9 (−1.2, 5.2)
Late decline[e]	0.1 (−1.2, 1.5)	0.3 (−0.9, 1.6)	0.4 (−0.9, 1.8)	−0.2 (−1.4, 0.9)
Night rise[f]	−14.4 (−27.6, 1.1)	−7.7 (−20.9, 7.6)	−5.4 (−19.5, 11.3)	−2.9 (−16.7, 13.2)
Cortisol slope[g]	0.2 (−0.8, 1.1)	0.3 (−0.6, 1.1)	0.4 (−0.6, 1.3)	0.0 (−0.8, 0.8)
AUC[h]	0.6 (−2.0, 3.2)	−0.3 (−2.7, 2.1)	0.4 (−2.1, 3.0)	−0.6 (−2.8, 1.6)
Cortisol to DHEA ratio				
Waking level[b]	−1.0 (−16.2, 16.9)	5.1 (−9.9, 22.6)	−0.1 (−15.0, 17.5)	−0.2 (−13.4, 15.0)
Awakening response[c]	13.0 (−3.7, 32.6)	12.6 (−2.7, 30.3)	8.1 (−7.7, 26.6)	6.7 (−6.8, 22.0)
Early decline[d]	−2.1 (−5.6, 1.6)	−3.1 (−6.3, 0.2)	−0.9 (−4.5, 2.7)	−1.6 (−4.5, 1.5)
Late decline[e]	−0.4 (−1.7, 0.9)	0.3 (−0.8, 1.5)	−0.2 (−1.4, 1.1)	0.7 (−0.4, 1.8)
Night rise[f]	−6.1 (−19.7, 9.9)	−0.7 (−14.1, 14.8)	−3.3 (−17.0, 12.6)	−7.9 (−20.3, 6.4)
Cortisol Slope[g]	−0.6 (−1.4, 0.2)	−0.1 (−0.8, 0.7)	−0.3 (−1.1, 0.6)	0.1 (−0.6, 0.8)
AUC[h]	0.1 (−2.6, 2.7)	1.0 (−1.4, 3.5)	0.4 (−2.2, 2.9)	0.5 (−1.7, 2.7)

Adjusted for age, saliva collection characteristics (ate, drank, brushed, exercised, happy, or worried), history of shiftwork, BMI, physical activity, alcohol intake, caffeine intake, smoking, poor sleep, history of childhood/adolescent child abuse, hypertension, diabetes, depression, anxiety, beta-blocker use, minor tranquilizer use, oral steroid use, DHEA medication, and testosterone therapy.

[a] Percent change for one unit increase in the R/S measure (Religious coping (very involved versus not very involved); extent of religiosity, (very versus not at all/slightly); extent of spirituality (very versus not at all/slightly); service attendance (≥1/month versus <1/month or never)).

[b] Biomarker level at awakening.

[c] Change in biomarker from awakening to 45 min after awakening.

[d] Change in biomarker from 45 min after awakening to 4 h after awakening.

[e] Change in biomarker from 4 h after awakening to 16 h after awakening.

[f] Change in biomarker from 16 h after awakening to bedtime.

[g] Change in biomarker from awakening to bedtime.

[h] Area under the curve, total biomarker levels from wake time to 16 h after awakening.

Fig. 2).

On average, a one-unit increase in the R/S struggle score was associated with a 4.9% greater AUC for cortisol (95% CI: 0.4, 9.3; p = 0.03; Table 3; Supplemental Figure 1). Although this association was similar when we excluded women who reported the use of oral steroids or DHEA medication (Supplementary Table 4), it was not significant when we excluded women reporting later than usual bedtimes (Supplementary Table 5). Further, for each one unit increase in non-theistic DSES, we observed a 40.8% (CI: 61.0, −10.2; p = 0.01) slower nighttime DHEA rise, a 43.5% (PD: 43.5, 95% CI: 9.8, 87.6; p = 0.008) increase in cortisol:DHEA ratio at waking, and a 53.7% (PD: 53.7, 95% CI: 3.9, 127.3; p = 0.03) higher nighttime rise in cortisol:DHEA ratio (Table 3; Supplementary Figure 2). These associations persisted when we excluded women who reported the use of oral steroids or DHEA medication (Supplementary Table 4). However, when we excluded women with late bedtimes, only the associations with waking levels of the cortisol:DHEA ratio remained significant (Supplementary Table 5). We did not observe any significant associations between positive religious coping or theistic DSES and diurnal rhythms of cortisol, DHEA, or their ratio (Table 3; Supplementary Figure 1 and Supplementary Figure 2).

4. Discussion

This study examined the association between various dimensions of R/S—including beliefs, activities, experiences, and coping behaviors—and HPA-axis diurnal rhythms of cortisol, DHEA, and their ratio, among a sample of 216 postmenopausal women in the NHSII prospective cohort study. Modest alterations in HPA axis rhythms for three R/S measures were observed: overall religious coping, religious struggles, and non-theistic daily spiritual experiences. As hypothesized, higher levels of religious struggles were associated with higher total cortisol concentration over the day (i.e AUC), while women who reported that their religion or spirituality was very important in coping with a stressful situation were less likely to have an elevated nighttime cortisol level. However, our results appeared to be driven by women with late sleep schedules, and our results largely became non-significant when these participants were excluded.

With respect to prior literature, our study replicates some findings, while other results are disparate. For example, a study involving 1460 adults ages 25–74, of whom 92.6% were White and 56% were females observed that negative religious struggles were significantly associated

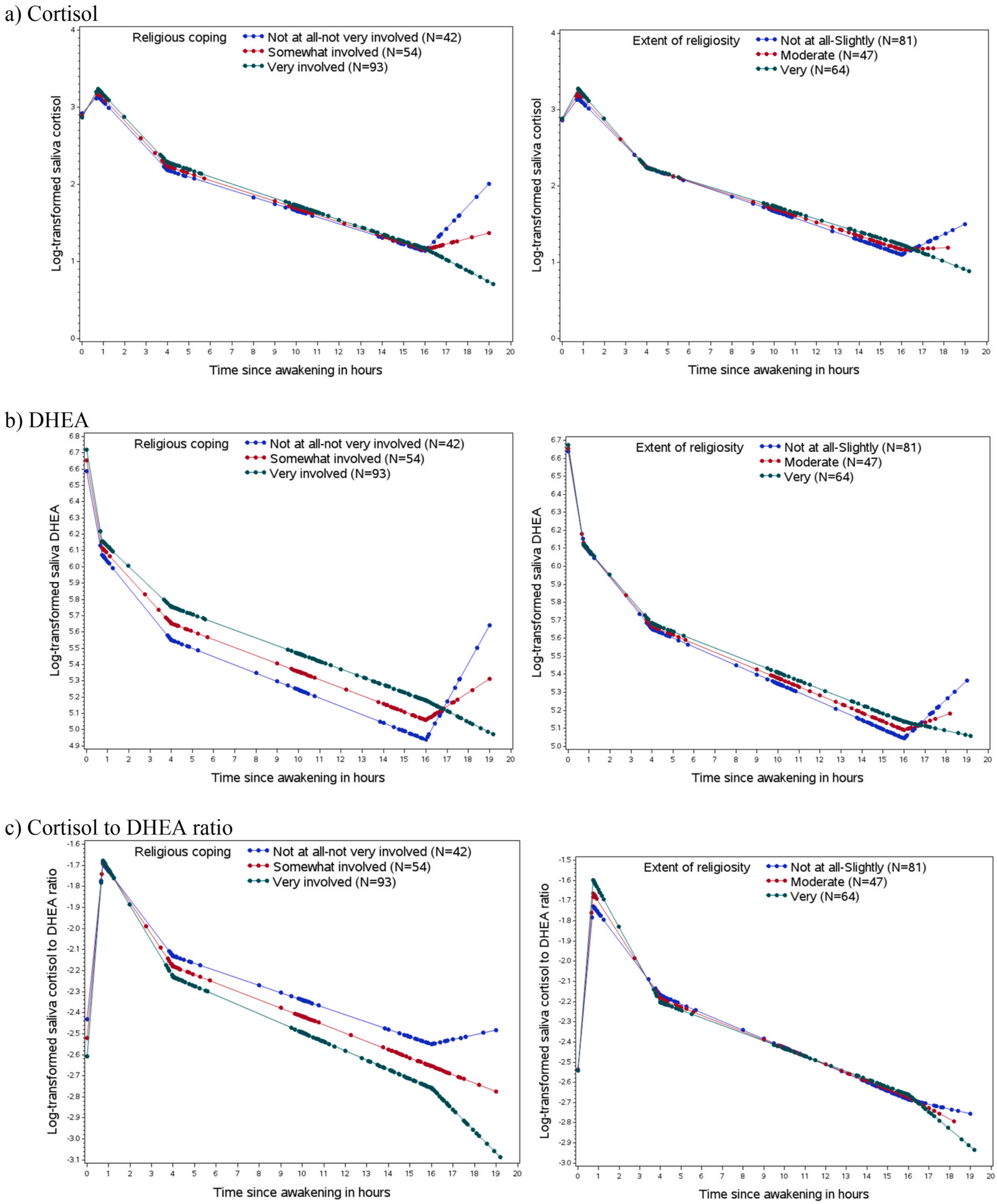

Fig. 1. Diurnal rhythms by religious coping and the extent of religiosity. Dots represent predicted values from mixed models at the actual time of the saliva collection. Legends are provided within each figure.

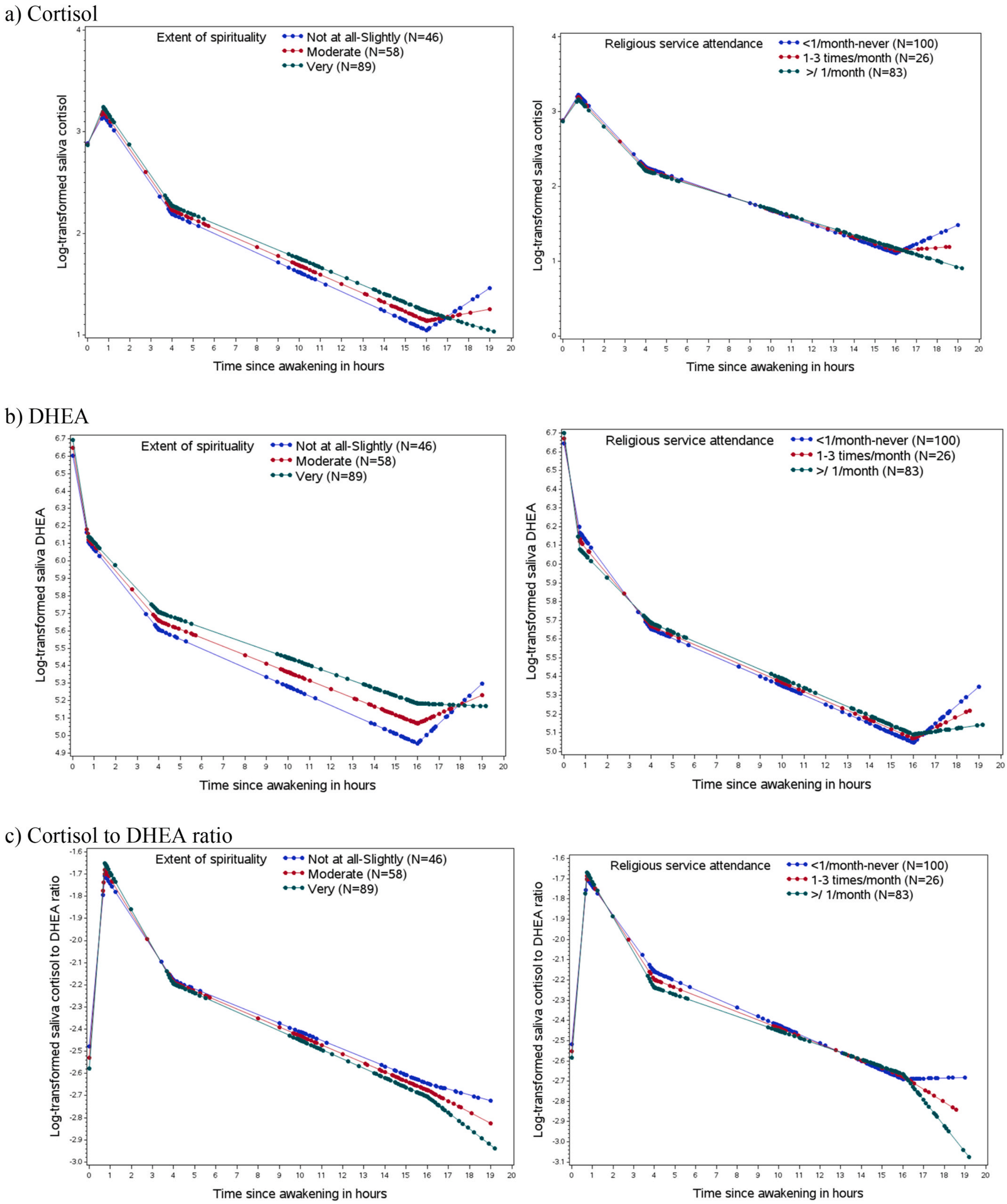

Fig. 2. Diurnal rhythms by the extent of religiosity and religious service attendance. Dots represent predicted values from mixed models at the actual time of the saliva collection. Legends are provided within each figure.

Table 3
Percent differences (95% CIs) in diurnal rhythms (waking level, awakening response, early decline, late decline, night rise, cortisol slope, and AUC) of cortisol, DHEA, and their ratio according to religious struggle, positive religious coping, non-theistic DSES, and theistic DSES (N = 178)[a].

	Religious struggle	Positive religious coping	Non-theistic DSES	Theistic DSES
	% D (95% CI)	% D (95% CI)	% D (95% CI)	% D (95% CI)
Cortisol				
Waking level[b]	4.2 (−27.7, 50.1)	8.8 (−0.9, 19.5)	10.4 (−7.1, 31.1)	2.8 (−7.7, 14.6)
Awakening response[c]	26.2 (−30.6, 129.7)	−2.0 (−16.3, 14.8)	−10.5 (−32.0, 17.8)	−2.7 (−18.5, 16.2)
Early decline[d]	4.0 (−9.5, 19.5)	−2.7 (−6.2, 0.9)	−3.8 (−9.6, 2.4)	−3.5 (−7.4, 0.5)
Late decline[e]	−0.3 (−5.5, 5.1)	0.2 (−1.1, 1.5)	2.1 (−0.1, 4.4)	1.4 (−0.1, 2.9)
Night rise[f]	1.4 (−36.0, 60.7)	−9.6 (−23.3, 6.5)	−17.8 (−46.6, 26.6)	5.2 (−16.0, 31.7)
Cortisol slope[g]	1.1 (−2.3, 4.6)	−0.6 (−1.5, 0.3)	0.6 (−1.0, 2.2)	0.3 (−0.7, 1.4)
AUC[h]	4.9 (0.4, 9.3)	0.0 (−1.1, 1.2)	0.1 (−1.9, 2.1)	−0.5 (−1.8, 0.8)
Dehydroepiandrosterone (DHEA)				
Waking level[b]	27.3 (−28.7, 127.4)	4.3 (−9.8, 20.5)	−23.1 (−41.9, 1.8)	−10.9 (−24.7, 5.6)
Awakening response[c]	5.0 (−39.7, 82.8)	−2.3 (−15.6, 13.1)	−1.0 (−24.3, 29.3)	−0.4 (−15.6, 17.5)
Early decline[d]	2.2 (−10.1, 16.3)	0.2 (−3.2, 3.6)	−1.0 (−6.8, 5.1)	−0.2 (−3.9, 3.7)
Late decline[e]	0.7 (−4.2, 5.8)	−0.4 (−1.7, 0.8)	1.9 (−0.2, 4.0)	0.8 (−0.6, 2.2)
Night rise[f]	26.7 (−18.1, 96.1)	−7.6 (−20.9, 7.9)	−40.8 (−61.0, −10.2)	−3.3 (−21.9, 19.7)
Cortisol slope[g]	1.5 (−1.8, 4.8)	−0.4 (−1.3, 0.4)	0.9 (−0.7, 2.4)	0.6 (−0.4, 1.6)
AUC[h]	5.9 (−3.0, 14.8)	0.2 (−2.0, 2.4)	−3.4 (−7.6, 0.7)	−1.4 (−4.0, 1.2)
Cortisol to DHEA ratio				
Waking level[b]	−16.1 (−53.1, 50.1)	3.9 (−10.2, 20.1)	43.5 (9.8, 87.6)	14.9 (−3.1, 36.2)
Awakening response[c]	20.1 (−31.3, 109.8)	0.4 (−13.3, 16.4)	−10.4 (−31.2, 16.6)	−1.9 (−16.9, 15.8)
Early decline[d]	1.2 (−11.0, 15.2)	−2.8 (−6.0, 0.6)	−2.7 (−8.3, 3.3)	−3.3 (−6.9, 0.4)
Late decline[e]	−0.7 (−5.4, 4.3)	0.6 (−0.6, 1.8)	0.1 (−1.9, 2.1)	0.5 (−0.8, 1.9)
Night rise[f]	−22.1 (−49.4, 19.8)	−3.8 (−17.5, 12.0)	53.7 (3.9, 127.3)	9.7 (−11.1, 35.3)
Cortisol Slope[g]	−0.5 (−3.4, 2.6)	−0.2 (−1.0, 0.6)	−0.3 (−1.6, 1.1)	−0.2 (−1.1, 0.7)
AUC[h]	−0.6 (−9.7, 8.5)	−0.2 (−2.4, 2.1)	3.4 (−0.8, 7.6)	0.9 (−1.8, 3.5)

Adjusted for age, saliva collection characteristics (ate, drank, brushed, exercised, happy, or worried), history of shiftwork, BMI, physical activity, alcohol intake, caffeine intake, smoking, poor sleep, history of childhood/adolescent child abuse, hypertension, diabetes, depression, anxiety, beta-blocker use, minor tranquilizer use, oral steroid use, DHEA medication, and testosterone therapy.

[a] Percent difference in the corresponding slope for 1 unit increase of R/S score, (i.e. positive coping, religious struggle, non-theistic daily spiritual experiences (non-theistic DSES) and theistic daily spiritual experiences theistic DSES). Corresponding sample size (n = 178), except for non-theistic daily spiritual experiences (n = 216).

[b] Biomarker level at awakening.

[c] Change in biomarker from awakening to 45 min after awakening.

[d] Change in biomarker from 45 min after awakening to 4 h after awakening.

[e] Change in biomarker from 4 h after awakening to 16 h after awakening.

[f] Change in biomarker from 16 h after awakening to bedtime.

[g] Change in biomarker from awakening to bedtime.

[h] Area under the curve, total biomarker levels from wake time to 16 h after awakening.

with flatter diurnal cortisol slope (not observed in the present study), though not with awakening levels or awakening response (as seen in the present study) [28]. With respect to positive religious coping, Tobin and colleague found, as we did, no association with cortisol levels at awakening, cortisol awakening response, and diurnal cortisol slope [28], but this differs from two other prior studies [26,46]. Merritt et al. [46] in a study involving 30 African American (AA) female caregivers and 48 AA non-caregivers found that higher combined religious coping scores and higher positive religious coping scores were associated with flatter cortisol slopes among caregivers but not non-caregivers, controlling for age and education only. Hulett et al. [26] in a pilot study involving 41 breast cancer survivors, observed a positive significant correlation between positive religious coping and cortisol awakening response, although authors did not adjust for potential confounders. The differences in findings may be due to differences in study population, unmeasured confounding, and/or variability due to small sample sizes. For example, in contrast to studies by Hulett et al. and Merritt & McCallum, our study rigorously controlled for multiple potential confounding variables and had a reasonably large sample size.

For other R/S measures examined in relation to diurnal cortisol rhythms, no significant differences between the extent of religiosity, extent of spirituality, religious service attendance, non-theistic daily spiritual experiences, or theistic daily spiritual experiences, and diurnal cortisol rhythms were found. Our results with respect to religious service attendance and diurnal cortisol rhythms are similar to findings from two previous studies that found no evidence of an association between religious service attendance and cortisol levels measured during the day [47,48], but different from another recent study that observed an inverse association between frequent religious service attendance and mean cortisol level among a sample of 227 Black young adults, with six years of follow up [25]. In addition, our null findings with respect to assessing the association between the extent of religiosity or spirituality and diurnal cortisol rhythms are in contrast to four other studies that have documented a significant association between identifying as someone who is “very” religious or spiritual and lower cortisol levels [24,27,47,48].

Some possible reasons to explain why our results contrast with findings from other previous studies include the number and timing of the saliva collections, as well as study population characteristics (such as age, sex, chronic disease status, and postmenopausal status). Young adults tend to have more robust diurnal rhythms than older adults; and it could be harder to observe R/S - diurnal rhythms associations in older people due to high variability from other factors [49]. Other possible reasons include small sample size, the lack of consistency in definition of R/S measures across studies, and overall, the measures of R/S may capture different facets of this exposure and thus results in different findings.

We also assessed non-theistic daily spiritual exercises, which capture some sense of transcendence for many, but do not rely on believing in God or some other Divine being. Higher non-theistic daily spiritual experiences, such as feeling deep inner harmony or peace, communion with nature, or a selfless caring for others, were associated with the slower nighttime rise of DHEA levels, higher wakeup levels of cortisol: DHEA ratio, and higher nighttime rise of cortisol:DHEA ratio. However, in sensitivity analyses that excluded women with late sleep schedules, our results became mostly null except for the relationship between non-theistic daily spiritual experiences and waking levels of cortisol:DHEA ratio. Only two known studies have assessed the DHEA or cortisol:DHEA ratio by self-reported R/S measures [30,31]. Hill and colleagues observed no association between the frequency of religious service attendance and DHEA in a sample of U.S adults aged 57–85 years [30]. Maselko et al., in a study involving 853 adults aged 70–80 years examined the relationship between frequency of religious service attendance and ten-item cumulative allostatic index including serum dehydroepiandrosterone sulfate [31]. They found that frequent religious service attendance of at least once a week was associated with lower allostatic levels among women, although it was not driven by one or two specific components of allostatic load index examined including DHEAS [31].

In this study, most observed associations were eliminated once we excluded women who went to bed later than their usual on the day of the saliva collection, suggesting that most of the observed association was driven by this small subgroup. Studies have reported an increase in night time cortisol levels following one night of sleep disturbances, independent of other sleep disorders or problems [50]. It is possible that going to bed as little as 30 min beyond normal bedtime schedule can reflect physical or emotional experiences that affect diurnal rhythms of cortisol, DHEA, and cortisol-DHEA ratio. Research has shown changes or alterations in cortisol levels across the day following same-day social and emotional experiences or feelings, such as anger or feeling fatigued [51]. It is also possible that nighttime values and AUC are more sensitive to acute stressors or prior day experiences compared to awakening responses or waking values. There is also the possibility of an outcome measurement error. Because of a rise in HPA hormone levels around bedtime, people who went to bed later would have had higher levels than would have otherwise been observed had they gone to bed at their usual time. Future studies that tease out the effects of acute change in sleep schedules or sleep timing, as well as the effect of acute stressors or emotional or physical experiences in the assessment of R/S and HPA-axis biomarkers, would be helpful.

This study has several strengths, including the use of a well-characterized cohort, assessment of several dimensions of R/S, adjustment for important potential confounders, and examination of five timed saliva samples in our assessment of associations between R/S and diurnal rhythms of cortisol and DHEA.

However, several limitations should be noted. First, saliva samples were collected at home by the participants and the time of collection was self-documented. To ensure participants collected the samples at the appointed times, participants were asked to write down scheduled collection times following our protocol instructions for the remaining 4 collections after they woke up and completed the first collection. These scheduled times served as a reminder for the participants. At each collection, participants also recorded the actual collection time, which was used in the analysis. The data points of actual collection time were clustered at our planned time [20,33], suggesting that the majority of our participants closely followed our protocol. However, saliva sampling collection took place during a single day and may have led to misclassification of cortisol, DHEA, or the cortisol to DHEA ratio due to day-to-day variations. A previous study documented higher short-term stability (days) (ICCs:0.17–0.74), but lower long-term stability (ICCs: 0.05–0.42) in salivary cortisol over 6 years [52]. Second, our study was cross-sectional, and except for religious service attendance, all R/S measures were assessed one year after saliva collection. It is unlikely that participants' coping style and other R/S measures changed dramatically over one year, but future studies in which the R/S measures are collected before or at the same time as biospecimens would be valuable. Third, our sample size was relatively small and included predominantly white female nurses, limiting our statistical power and generalizability of our results to other populations, particularly racial/ethnic minorities [33]. Fourth, we assessed several exposures and outcomes, with a relatively small sample size; some findings may be spurious. Finally, although adjustments were made for important potential confounders, the residual confounding by unmeasured factors always remains possible.

In conclusion, this study examined the associations of eight different measures of religiosity or spirituality R/S measures with three HPA-axis biomarkers, diurnal rhythms of cortisol, DHEA, and the cortisol/DHEA ratio. Some dimensions of R/S were associated with diurnal rhythms of HPA axis biomarkers in this sample of white women, although these were driven largely by those with late sleep schedules. Understanding the ways in which religious and spiritual beliefs and experiences influence biomarkers in the stress pathway – as a resource for resilience or in deleterious ways - could help inform more efficacious interventions aimed at improving the health of patients and communities. Examining how multiple dimensions of R/S may directly influence HPA axis biomarkers or modify the relationship between a particular psychosocial stressor exposure and risk of disease may help inform novel psychosocial interventions to community dwelling adults or hospital patients to promote better health and well-being. Future research should explore the mechanisms through which R/S influence HPA-axis biomarkers in larger and more diverse racial/ethnic groups.

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Human participant protection

The study protocol was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health.

Authorship contribution

Conceptualization- OOI, ETW, AES.
Data Curation-OOI, ETW, DS, TH, ST.
Formal analysis- OOI, ETW, DS, TH.
Funding acquisition- AES, TH, ST.
Investigation, Methodology, Software; Supervision- OOI, ETW, AES.
Writing-original draft- OOI, ETW, TH, ST, BVK, AES.
Review & Editing –OOI, ETW, TH, ST, BVK, AES.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Note: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpnec.2021.100064.

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