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Association of diurnal cortisol rhythm with chronic pain: Evidence from a prospective cohort study in community-dwelling adults

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ABSTRACT

Despite clinical evidence linking hypothalamic-pituitary-adrenal (HPA) axis dysfunction to chronic pain, epidemiological findings remained mixed. Data from 1246 respondents aged 34–84 at baseline, obtained from the Midlife in the United States (MIDUS) study and its subproject, the National Study of Daily Experiences (NSDE), were used to examine associations between salivary diurnal cortisol rhythms and chronic pain outcomes over a seven-year follow-up period, using mixed-effects logistic regression models adjusted for sociodemographics, lifestyle, and health-related factors. Furthermore, to examine the role of diurnal cortisol rhythms in the development or persistence of chronic pain, the associations were stratified by chronic pain status at baseline. Over a median follow-up of 7.6 years (IQR 6.3–8.3), blunter declines in early post-wake (0.5–4.5 h after waking, OR = 2.16, 95 % CI = 1.41–3.32, P < 0.001) and mid post-wake (4.5–15 h after waking, OR = 1.93, 95 % CI = 1.28–2.90, P < 0.01) cortisol levels were associated with higher odds of developing chronic multisite pain compared to those who remained pain-free at follow-up. In the same subgroup, a blunted early post-wake cortisol decline was associated with higher odds of developing chronic multisite pain, compared to developing chronic non-multisite pain (OR = 2.73, 95 % CI = 1.49–4.99, P < 0.01). No other robust associations were found. Our results suggest that blunted diurnal cortisol declines may play an important role in chronic multisite pain development.

Perspective: This prospective study found that blunting in diurnal cortisol decline was associated with higher odds of developing chronic multisite pain. The rate of diurnal cortisol decline may provide information for identifying at-risk populations.

Introduction

Chronic pain, defined as pain persisting or recurring for over three months,[1] is highly prevalent and associated with significant socioeconomic impacts, poor prognosis, and limited options for monitoring and prevention.[2] Its widespread bodily distribution and interference contribute to poor health,[3–5] reduced quality of life,[6,7] negative effects on employment status,[8,9] and increased medical costs,[10,11] necessitating mechanistic investigations.

The hypothalamic-pituitary-adrenal (HPA) axis, a neurohormonal system regulating glucocorticoid levels, is central to stress responses, circadian rhythms, and metabolic and immunological balance.[12] HPA axis dysfunction is a potential relevant biological contributor to chronic pain due to its involvement in neuroinflammatory processes,[13] heightened pain sensitivity,[14] genetic susceptibility,[15] brain structural alterations[16]–which are known correlates of chronic pain–and its potential to mediate the effects of psychosocial influences on pain outcomes.[17]

Diurnal cortisol rhythm provides key insights into HPA axis functioning,[18–20] and is typically characterized into two phases: cortisol awakening response (CAR) and diurnal cortisol slope (DCS). CAR, the rapid increase in cortisol levels within 30–45 min after waking, is activated by a central control network originating in the hypothalamus.[21] Reduced CAR disrupts circadian alignment, energy metabolism, immune regulation, and neurocognitive and emotional processes,[21] mechanisms implicated in chronic pain pathology.[22–27]

The rapid rise in cortisol levels then triggers negative feedback via glucocorticoid and mineralocorticoid receptors (GRs and MRs), in the

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hypothalamus, hippocampus, and pituitary, regulated by the suprachiasmatic nucleus (SCN).[12,28] GRs become active when cortisol exceeds basal levels, while MRs provide inhibitory control during diurnal nadir.[20,29] This regulation may be captured by the DCS; its blunting, often indicative of GR down-regulation and potentially accompanied by increased MR affinity,[30,31] correlates with chronic pain.[31]

Area under curve (AUC) reflects total daily cortisol secretion, while cortisol dynamic range (CDR) measures the peak-to-nadir difference. Both parameters are influenced by mechanisms regulating CAR and DCS, while AUC may additionally reflect epigenetic GR modulation and direct neural input,[32] and CDR may be affected by age-related SCN neuronal degeneration,[20,33] potentially linking decreases in both to chronic pain mechanisms.[34,35]

Cross-sectional studies have observed lower saliva cortisol levels[36,37] in individuals with fibromyalgia and chronic multisite musculoskeletal pain, including reduced waking cortisol levels,[38] lower AUC relative to ground,[38] and flatter diurnal slopes.[38] However, cohort studies have yielded mixed results.[39–42] Cohort studies have reported associations between high post-dexamethasone serum cortisol levels, low morning salivary cortisol levels, high evening salivary cortisol levels,[39] and blunted diurnal rhythms[40] with chronic widespread pain and multisite musculoskeletal pain. Other cohort studies found no associations.[41,42] Inadequate sample sizes,[39] blood measurements being sensitive to acute stressors,[39,40] a high proportion of participants with depression/anxiety,[41,42] and short-duration salivary assessments,[39,41,42] may contribute to the mixed findings. Additionally, the uniform slope approach may overlook temporal-specific regulatory mechanisms of cortisol decline.

These inconsistencies underscore the need for population-based studies with robust cortisol protocols to clarify the prospective relationship between HPA axis dysfunction and chronic pain. Using the Midlife in the United States (MIDUS) study and its subproject, we examined prospective associations between diurnal cortisol parameters and chronic pain outcomes over a seven-year follow-up. Additionally, we explored these associations separately in those with and without chronic pain at baseline, as the relationship may depend on pain chronicity.[43] Based on reviews of HPA functionality and chronic pain, and existing literature, we hypothesized that diurnal cortisol rhythm indicative of HPA axis dysfunction, reflected in blunted CAR, blunted DCS, lower AUC, and narrower CDR, would be prospectively associated with chronic pain onset and persistence.

Method

Ethics

This study did not necessitate obtaining informed consent from participants, as the data were collected by other organizations and subsequently made publicly accessible. Given that the dataset is anonymized and in the public domain, there are no ethical concerns or privacy issues related to its use in this research.

Data

MIDUS is a longitudinal study, focusing on the impact of social, psychological, and physiological factors on health as people age from early adulthood to later life. The baseline survey (MIDUS 1) recruited non-institutionalized, English-speaking adults aged 25 to 74 from various locations across the United States in 1995–1996. The study included a national probability sample, with over-sampling from selected metropolitan areas, a sample of siblings of the main respondents, and a national sample of twin pairs. MIDUS 2 was conducted in 2004–2006 as a follow-up to MIDUS 1 and MIDUS 3 is a follow-up to MIDUS 2 conducted in 2013–2014. The study gathered comprehensive data via telephone interviews and self-administered questionnaires.[44] To examine day-to-day life, information on daily experiences over a span of consecutive eight days was collected through the National Study of Daily Experiences (NSDE) between 2004 and 2009 as a part of MIDUS 2. In the NSDE, participants completed brief daily phone interviews and answered questions about their past week on the last interview day. Participants were also asked to provide four saliva samples each day from days two to five.

Our study examined diurnal cortisol rhythm measured during NSDE at MIDUS 2, in association with chronic pain outcomes measured at MIDUS 3. We excluded participants who failed to provide at least one valid cortisol sample within the sampling time, exhibited anomalous sleep patterns (such as waking before 4 a.m., after 11 a.m., or being awake for more than 20 h in a day), experienced cortisol measurement errors, or dropped out at MIDUS 3.[45,46] A flow diagram for the study cohort is illustrated in Fig. 1.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, or in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results.

Measures

Salivary cortisol sample collection information and calculation of diurnal cortisol rhythm parameters at NSDE

Saliva samples were collected immediately upon awakening, 30 min after awakening, prior to lunch, and at bedtime.[47] Participants were advised to gather samples prior to consuming food or beverages or brushing their teeth. Furthermore, they were requested to avoid any caffeinated items such as coffee, tea, soda, or chocolate before sample collection.[47]

Data on the precise timing of each saliva sample collection provided by respondents were collected through nightly phone interviews and a paper log included with the collection kit, which included an instruction sheet and sixteen numbered, color-coded salivettes. Additionally, a subset of respondents were given a "Smart Box" to store their salivettes. These boxes were equipped with a computer chip that tracked when the box was opened and closed.[45,47] The correlations between self-reported times (from both paper-pencil logs and nightly phone interviews) exceeded 0.9 at each of the four sampling points. The correlations between self-reported times and those recorded by the "smart box" ranged between 0.75 and 0.95.[45] Participants sent all 16 salivettes using a pre-addressed, prepaid courier package. The salivettes were shipped to the MIDUS Biological Core at the University of Wisconsin and stored at − 60 °C. Cortisol concentrations were measured using a luminescence immunoassay (IBL, Hamburg, Germany), with intra- and inter-assay variation below 5 %.[47]

The parameters of diurnal cortisol rhythm were operationalized as CAR, DCSs, the AUC with respect to ground, and CDR. Specifically, a multilevel model with piecewise linear segments was utilized with fixed knots to model the diurnal cortisol trajectory with natural log-transformation, setting the fixed knots at 0.5 h, 4.5 h, and 15 h after awakening, consistent with prior practices.[32,45,48] Detailed information on the model and its sample is provided in Supplementary Tables 1–2 and Supplementary Figs. 1–3, with model specifications outlined in Supplementary materials, Section A.

Fixed-effects estimates were combined with corresponding random effects at both familial and individual levels to obtain individual-specific estimates of growth curve parameters.[48] The slope in each segment was used to represent the cortisol slope. The slope in the first segment (from awakening to 0.5 h) captures the CAR, the slope in the second segment captures the early post-wake DCS occurring from 0.5 to 4.5 h post-awakening, and the slope in the third segment captures the mid post-wake DCS spanning 4.5–15 h post-awakening. The slope in the fourth segment captures the late post-wake DCS, extending beyond 15 h post-awakening, with a maximum duration of 20 h; 95 % of observed

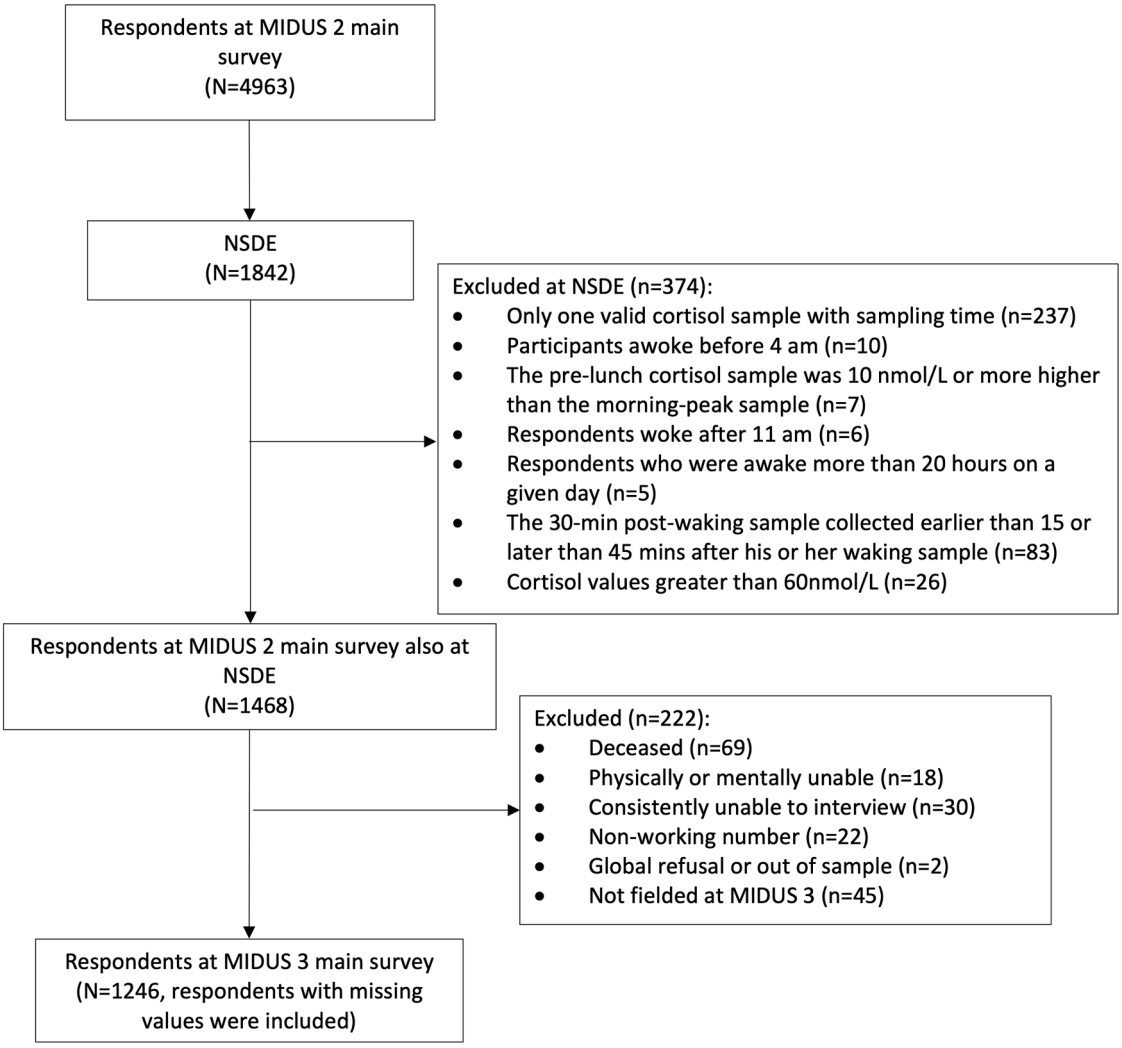

Fig. 1. Flowchart for the analytic sample.

days concluded by 18 h post-awakening.

Cortisol estimates at specific individual timings (relative to awakening) were computed, and the logarithmic AUC was calculated using the trapezoidal formula,[49] by first adding the areas of each trapezoid from awakening time to 30 min post-awakening, from 30 min post-awakening to 4.5 h post-awakening, and from 4.5 h post-awakening to bedtime. For individuals whose bedtime occurred less than 15 h after awakening, the area from 4.5 h post-awakening to bedtime was directly added. For individuals whose bedtime occurred more than 15 h after awakening, the areas from 4.5 to 15 h post-awakening and from 15 h post-awakening to bedtime were calculated separately and then summed. The CDR was calculated as the logarithmic peak cortisol minus the logarithmic nadir cortisol.[45,48] We then conducted exploratory factor analysis (EFA) to explore whether these parameters capture overlapping or distinct aspects of diurnal cortisol rhythms (see Supplementary Table 3). Cortisol parameters were standardized at the between-individual level to facilitate comparison of the predictive utility of the different parameters in the regressions.[48,50]

Chronic pain outcomes at follow-up (MIDUS 3)

The presence of chronic pain, as well as pain-related interference and the number of chronic pain sites were measured in both MIDUS 2 and MIDUS 3. Chronic pain outcomes in MIDUS 3 were used as the dependent variables in this study. Respondents were asked "Do you have chronic pain, that is do you have pain that persists beyond the time of normal healing and has lasted from anywhere from a few months to many years?", if they answered positively, they would be then asked about chronic pain interference. A pain interference index was generated by calculating a mean score of how much pain interfered with respondents' activity, mood, relations, sleep, and enjoyment, ranging from 0 to 10.[51,52] The pain interference index was further categorized into no pain, low-interference pain (≤ 4), and high-interference pain (> 4) as categorical variable, based on the recommended threshold for the Pain Interference Subscale.[51] In addition, if respondents reported having chronic pain, they were asked about the location of the pain, including head, neck, back, arms, legs, shoulders, hips, knees, and other sites. The pain sites were summed up into an index and then categorized it into no pain, non-multisite pain (1–2 pain regions), or multisite pain (3 or more pain regions) as a categorical variable.[53,54]

Covariates

MIDUS 2 individual level covariates were chosen based on their known associations with both cortisol patterns and chronic pain outcomes. These variables included income-to-needs ratio, education, age, sex assigned at birth, race, marital status, physical activity, smoking and drinking status, parental abuse, body mass index (BMI), multimorbidity, and chronic pain at MIDUS 2.[45,55–57] Furthermore, the present study controlled for the use of steroid inhalers, oral steroids,[58,59] antidepressants or anti-anxiety medications,[60,61] birth control pills,[62,63] and other hormonal medications.

The income-to-needs ratio and education levels were coded on a scale from 0 to 2.[64] Using the Poverty Thresholds by Size of Family and Number of Children from the United States Census Bureau (https://www.census.gov/data/tables/time-series/demo/income-poverty/historical-poverty-thresholds.html), we calculated the ratio between household income and poverty thresholds. A ratio below 1 indicates poverty, 1–2 indicates low income, and above 2 indicates adequate or affluent income, following previous classification practices.[65] These categories were then scaled from 2 to 0, where 2 represents high socioeconomic disadvantage and 0 represents low socioeconomic disadvantage. Similarly, educational attainment was scaled into three levels: possessing a bachelor's degree or higher, completion of high school/GED or some college, and less than a high school education. Age and BMI were coded as continuous variables. Race and ethnicity were based on self-report and categorized into White and Black, Indigenous and People of Color (BIPOC).

The summary score for physical activity was calculated using three questions that inquired about the frequency of engagement in light, moderate, and vigorous activities, rated on a 6-point scale (1-never to 6-several times a week). To emphasize the importance of more vigorous activities, weights of 1, 3, and 5 were assigned to light, moderate, and vigorous activities respectively. The summary score was determined by taking the weighted average of the responses.[64] Smoking status was categorized into three groups, people who currently smoke, previously smoked, or have never smoked. Besides, alcohol consumption patterns were defined in terms of people who drink moderately/heavily, people who drink lightly, and people who rarely drink/do not drink.

Parental abuse was categorized into two ordinal variables: emotional and physical abuse.[54] These were derived from averaging the reported abuse from both parents. The scale ranges from 1 to 3, with 1 indicating no abuse and 3 indicating severe abuse. The scale increases in increments of 0.5.

Chronic condition index[66] was coded as a binary variable, with < 2 indicating fewer than two chronic conditions, and ≥ 2 indicating two or more chronic conditions to represent multimorbidity.[67] Medication uses were coded as yes vs no.

Statistical analyses

Descriptive statistics

We compared characteristics between participants without chronic pain at baseline and those with chronic pain at baseline. For continuous variables that followed a normal distribution, analysis of variance (ANOVA) was applied. The Kruskal-Wallis tests were used for continuous variables that did not meet normality assumptions. Categorical variables were compared using the Chi-Square tests. The comparisons were further examined with effect size measures (Cohen's d/Phi/Cramér's V) and their confidence intervals.

Main prospective analyses

Mixed-effects logistic regressions were used to examine the prospective associations between each specific cortisol parameter measured at baseline and chronic pain outcomes at follow-up, with each cortisol parameter analyzed in separate models. Family-level random intercepts were included to account for correlations between individuals from the same family.[33] Pooled analyses (including those with and without chronic pain at baseline) were performed to estimate the overall effect while adjusting for baseline chronic pain status and other covariates.

To evaluate whether diurnal cortisol rhythm differentially contributes to the development versus persistence of chronic pain, we conducted subgroup analyses stratified by baseline chronic pain status. Specifically, in participants without chronic pain at baseline, we examined associations between cortisol parameters and three chronic pain outcomes at follow-up: the presence of chronic pain, pain interference, and pain widespreadness; in those with baseline chronic pain, we assessed cortisol associations with these chronic pain outcomes at follow-up. The subgroup analyses adjusted for all covariates except baseline chronic pain status in both subgroups. This stratification may allow us to disentangle distinct biological mechanisms underlying pain chronicity.

Exploratory factor analysis

To examine whether the selected diurnal cortisol indicators represent overlapping or distinct underlying biological processes, we conducted an EFA (see Supplementary Table 3). We selected EFA rather than principal component analysis (PCA), as our goal was to uncover potential latent constructs underlying diurnal cortisol dynamics, rather than simply reducing dimensionality. An oblique (promax) rotation was applied to allow for potential correlations among factors. Factor loadings exceeding .40 were presented.[68(p151)] The number of factors to retain was based on the Kaiser criterion, eigenvalues > 1.[68(p168)]

Robustness checks

The present study conducted a set of robustness checks, including multiple imputation, inverse probability of attrition weighting, exclusion of respondents with depression or anxiety, exclusion of respondents who used steroid inhalers, oral steroids, other hormonal treatments, antidepressants, anti-anxiety medications, and birth control, additional adjustment for daily stressor severity, using Bonferroni correction to account for multiple testing, formal moderation analyses, and an approximate positive outcome control (Supplementary Tables 4–10).

Results

Sample description

Table 1 compares the characteristics of participants without chronic pain (n = 762) to those reporting chronic pain (n = 429) at baseline. The median follow-up period was 7.6 years (IQR 6.3–8.3). Compared to those without chronic pain at baseline, participants with chronic pain at baseline reported higher degrees of pain interference and pain widespreadness at follow-up. Additionally, participants with higher pain interference at follow-up were more likely to overlap with those experiencing more pain regions, regardless of baseline pain status (participants with baseline chronic pain: $\chi^2 = 761$, $P < 0.001$; participants without baseline chronic pain: $\chi^2 = 400$, $P < 0.001$).

As shown in Table 1, participants with chronic pain at baseline exhibited a flatter CAR and late post-wake DCS, and a narrower CDR, compared to those without chronic pain. However, the effect sizes of these differences were small. Compared to participants without chronic pain, those reporting chronic pain at baseline were more likely to be taking birth control pills, to have more socioeconomic disadvantages in terms of their income-to-needs ratio and education, to be older, more likely to be assigned female at birth, to report multimorbidity, and to have a higher BMI. Although statistically significant, the effect size for differences in pain outcomes at follow-up, as well as in education, multimorbidity, and BMI, were small.

Associations between diurnal cortisol rhythm and chronic pain outcomes

Table 2 shows results from the mixed-effects logistic regressions for the prospective associations between baseline diurnal cortisol rhythm and chronic pain outcomes at follow-up, based on both the stratified subgroup analyses and analyses in the full sample. Fig. 2A–F display the estimated baseline diurnal cortisol trajectories by chronic pain outcomes at follow-up, stratified by baseline chronic pain status. This helps illustrate potential differences in the rate of cortisol change across distinct segments of the day between pain outcome subgroups.

Association of diurnal cortisol rhythm at baseline with presence of chronic pain at follow-up

In those without chronic pain at baseline, a blunter late post-wake

Table 1
Characteristics of study participants with cortisol parameters stratified by the presence of baseline chronic pain.

Pain status at baseline (MIDUS 2)		No chronic pain (N = 762)	Reporting chronic pain (N = 429)		
Variables	N	Mean (SD)/N (%)	Mean (SD)/N (%)	P-value	Cohen's d/phi/Cramér's V (95 % CI)[1]
Pain outcomes at follow-up (MIDUS 3)[2]					
Presence of chronic pain	1124			< 0.001	0.36 (0.31, 1.00)**
No		525 (72.8 %)	147 (36.5 %)		
Yes		196 (27.2 %)	256 (63.5 %)		
Pain interference	1092			< 0.001	0.36 (0.31, 1.00)**
No pain		525 (73.7 %)	147 (38.7 %)		
Low-interference chronic pain		137 (19.2 %)	133 (35.0 %)		
High-interference chronic pain		50 (7.02 %)	100 (26.3 %)		
Pain widespreadness	1116			< 0.001	0.39 (0.34, 1.00)**
No pain		525 (73.0 %)	147 (37.0 %)		
Chronic non-multisite pain		144 (20.0 %)	123 (31.0 %)		
Chronic multisite pain		50 (6.95 %)	127 (32.0 %)		
Cortisol parameters at baseline (MIDUS 2)[3]					
CAR (0–30 min)	1185	0.53 (0.29)	0.47 (0.38)	0.011	0.16 (0.04, 0.28)
Early post-wake DCS (30 min to 4.5 h)	1185	− 0.14 (0.05)	− 0.13 (0.05)	0.211	− 0.08 (− 0.20, 0.04)
Mid post-wake DCS (4.5–15 h)	1185	− 0.16 (0.04)	− 0.15 (0.04)	0.066	− 0.11 (− 0.23, 0.01)
Late post-wake DCS (after 15 h)	1185	− 0.14 (0.04)	− 0.13 (0.04)	0.019	− 0.14 (− 0.26, − 0.02)
CDR	1183	2.49 (0.48)	2.38 (0.57)	0.001	0.21 (0.08, 0.33)*
AUC	1183	4.84 (0.32)	4.81 (0.40)	0.110	0.10 (− 0.02, 0.22)
Covariates at baseline (MIDUS 2)					
Pain outcomes					
Pain interference	422	/			
Low-interference chronic pain			311 (73.7 %)		
High-interference chronic pain			111 (26.3 %)		
Pain widespreadness	429	/			
Chronic non-multisite pain			259 (60.4 %)		
Chronic multisite pain			170 (39.6 %)		
Medication uses					
Steroid inhaler	1191			0.622	0.02 (0.00, 1.00)
No		739 (97.0 %)	413 (96.3 %)		
Yes		23 (3.02 %)	16 (3.73 %)		
Oral steroid meds	1191			1.000	0.00 (0.00, 1.00)
No		741 (97.2 %)	417 (97.2 %)		
Yes		21 (2.76 %)	12 (2.80 %)		
Other hormonal meds	1191			0.122	0.05 (0.00, 1.00)
No		739 (97.0 %)	423 (98.6 %)		
Yes		23 (3.02 %)	6 (1.40 %)		
Anti-depressant or anti-anxiety meds	1191			0.146	0.04 (0.00, 1.00)
No		685 (89.9 %)	373 (86.9 %)		
Yes		77 (10.1 %)	56 (13.1 %)		
Birth control pills	1191			0.001	0.09 (0.05, 1.00)
No		674 (88.5 %)	350 (81.6 %)		
Yes		88 (11.5 %)	79 (18.4 %)		
Sociodemographics					
Income-to-needs scale	1169	0.21 (0.54)	0.32 (0.65)	0.004	− 0.18 (− 0.30, − 0.05)
Education	1189	0.55 (0.54)	0.66 (0.58)	0.001	− 0.20 (− 0.32, − 0.08)*
Age	1191	54.7 (11.3)	56.9 (11.3)	0.001	− 0.19 (− 0.31, − 0.07)
Ethnicity	1170			0.702	0.02 (0.00, 1.00)
White		721 (95.9 %)	398 (95.2 %)		
Black, Indigenous and People of Color (BIPOC)		31 (4.12 %)	20 (4.78 %)		
Sex assigned at birth	1191			0.024	0.07 (0.02, 1.00)
Male		355 (46.6 %)	170 (39.6 %)		
Female		407 (53.4 %)	259 (60.4 %)		
Marital status	1190			0.107	0.05 (0.00, 1.00)
Divorced/separated/widowed/never married		180 (23.6 %)	120 (28.0 %)		
Married		582 (76.4 %)	308 (72.0 %)		
Health behavior					
Physical activity	1109	29.6 (10.4)	29.5 (10.9)	0.873	0.01 (− 0.11, 0.13)
Smoking status	1191			0.054	0.07 (0.00, 1.00)
People who currently smoke		76 (9.97 %)	52 (12.1 %)		
People who previously smoked		455 (59.7 %)	274 (63.9 %)		
People who have never smoked		231 (30.3 %)	103 (24.0 %)		
Drinking status	1191			0.260	0.05 (0.00, 1.00)
People who drink moderately/heavily		240 (31.5 %)	136 (31.7 %)		
People who drink lightly		234 (30.7 %)	114 (26.6 %)		

(continued on next page)

Table 1 (*continued*)

Pain status at baseline (MIDUS 2) Variables	N	No chronic pain (N = 762) Mean (SD)/N (%)	Reporting chronic pain (N = 429) Mean (SD)/N (%)	P-value	Cohen's d/ phi/ Cramér's V (95 % CI)[1]
People who rarely drink/do not drink		288 (37.8 %)	179 (41.7 %)		
Health conditions					
Multimorbidity	1191			< 0.001	0.25 (0.20, 1.00)*
No		401 (52.6 %)	115 (26.8 %)		
Yes		361 (47.4 %)	314 (73.2 %)		
BMI	1146	27.2 (5.01)	28.6 (6.11)	< 0.001	− 0.25 (− 0.38, − 0.13)*
Parental abuse at MIDUS 1					
Childhood emotional abuse	1100			0.975	0.02 (0.00, 1.00)
1 (Never)		246 (34.6 %)	128 (32.9 %)		
1.5		103 (14.5 %)	57 (14.7 %)		
2		189 (26.6 %)	103 (26.5 %)		
2.5		89 (12.5 %)	52 (13.4 %)		
3 (Most frequent)		84 (11.8 %)	49 (12.6 %)		
Childhood physical abuse	1108			0.587	0.05 (0.00, 1.00)
1 (Never)		318 (44.6 %)	161 (40.8 %)		
1.5		112 (15.7 %)	59 (14.9 %)		
2		174 (24.4 %)	102 (25.8 %)		
2.5		59 (8.27 %)	41 (10.4 %)		
3 (Most frequent)		50 (7.01 %)	32 (8.10 %)		

[1] Tests for effect size: Cohen's d: *small effect (≥ 0.20 & < 0.50); **medium effect (≥ 0.50 & < 0.80); *** large effect (≥ 0.80); Phi: *small effect (≥ 0.10 & < 0.30); **medium effect (≥ 0.30 & < 0.50); *** large effect (≥ 0.50); Cramer's V: *small effect (≥ 0.10 & < 0.30); **medium effect (≥ 0.30 & < 0.50); *** large effect (≥ 0.50).

[2] At follow-up, low interference pain includes 196 with chronic non-multisite pain and 80 with chronic multisite pain, while high interference pain includes 66 and 86, respectively. Similarly, chronic non-multisite pain includes 196 with low interference pain and 66 with high interference pain, while chronic multisite pain includes 80 and 86, respectively. Among participants with no baseline pain, 80.0 % with non-multisite pain reported low-interference pain, while 20.0 % reported high-interference pain. For those with multisite pain, 53.2 % had low-interference pain, and 46.8 % had high-interference pain ($\chi^2 = 761$, $P < 0.001$). Among participants with baseline pain, 68.7 % of those with non-multisite pain had low-interference pain, while 31.3 % reported high-interference pain. For multisite pain, 45.8 % had low-interference pain, and 54.2 % had high-interference pain ($\chi^2 = 400$, $P < 0.001$).

[3] Note that cortisol parameters were non-standardized. An increase of CAR indicates a steeper CAR, whereas an increase of in DCSs indicates flatter DCSs. A higher value in CDR indicates a wider CDR, while a higher value in AUC indicates a larger AUC.

DCS at baseline was associated with higher odds of developing chronic pain (OR = 1.26, 95 % CI = 1.03–1.55, $P < 0.05$) (Table 2), though this was not visually apparent in Fig. 2A, likely due to greater variability at the late post-wake segment.

No significant associations were observed (Table 2) for those with

Table 2
Results from the mixed-effects logistic regressions for the prospective associations between baseline diurnal cortisol rhythm and presence of chronic pain, chronic pain interference and chronic non-multisite/multisite pain at follow-up[†].

	Subgroups				Full sample	
	No baseline chronic pain		Reporting chronic pain at baseline		Adjusting for chronic pain at baseline	
	N	OR (95 % CI)	N	OR (95 % CI)	N	OR (95 % CI)
Presence of chronic pain at MIDUS 3 (Ref: no pain)						
CAR (0–30 min)	610	0.93 (0.77, 1.13)	310	1.08 (0.81, 1.42)	920	0.96 (0.83, 1.12)
Early post-wake DCS (30 min to 4.5 h)	610	1.02 (0.84, 1.24)	310	1.07 (0.80, 1.43)	920	1.03 (0.89, 1.20)
Mid post-wake DCS (4.5–15 h)	610	1.08 (0.89, 1.32)	310	1.05 (0.79, 1.40)	920	1.07 (0.92, 1.25)
Late post-wake DCS (after 15 h)	610	**1.26 (1.03, 1.55)***	310	0.94 (0.71, 1.26)	920	1.15 (0.99, 1.35)
CDR	610	0.90 (0.74, 1.09)	310	0.89 (0.66, 1.20)	920	0.89 (0.77, 1.04)
AUC	610	1.09 (0.89, 1.33)	310	0.97 (0.73, 1.30)	920	1.03 (0.88, 1.20)
Low-interference pain at MIDUS 3 (Ref: no pain)						
CAR (0–30 mins)	568	1.11 (0.90, 1.37)	224	0.95 (0.69, 1.29)	792	1.05 (0.89, 1.24)
Early post-wake DCS (30 min to 4.5 h)	568	1.16 (0.93, 1.45)	224	0.96 (0.69, 1.33)	792	1.08 (0.91, 1.29)
Mid post-wake DCS (4.5–15 h)	568	1.08 (0.86, 1.35)	224	0.97 (0.70, 1.34)	792	1.03 (0.86, 1.22)
Late post-wake DCS (after 15 h)	568	0.83 (0.66, 1.04)	224	1.03 (0.76, 1.40)	792	0.89 (0.75, 1.05)
CDR	568	1.06 (0.86, 1.30)	224	1.15 (0.83, 1.58)	792	1.08 (0.92, 1.28)
AUC	568	0.90 (0.72, 1.13)	224	1.04 (0.75, 1.43)	792	0.95 (0.80, 1.13)
High-interference pain at MIDUS 3 (Ref: no pain)						
CAR (0–30 min)	490	1.01 (0.67, 1.53)	190	1.09 (0.71, 1.67)	680	0.97 (0.75, 1.25)
Early post-wake DCS (30 min to 4.5 h)	490	**1.85 (1.09, 3.16)***	190	0.89 (0.59, 1.33)	680	1.28 (0.98, 1.66).
Mid post-wake DCS (4.5–15 h)	490	**1.82 (1.09, 3.02)***	190	0.83 (0.55, 1.24)	680	1.26 (0.68, 2.33)
Late post-wake DCS (after 15 h)	490	1.52 (0.95, 2.45).	190	0.70 (0.46, 1.06)	680	1.09 (0.83, 1.43)
CDR	490	0.79 (0.53, 1.19)	190	0.87 (0.56, 1.37)	680	0.81 (0.63, 1.04)
AUC	490	1.08 (0.71, 1.64)	190	0.92 (0.59, 1.42)	680	0.94 (0.73, 1.23)
High-interference pain at MIDUS 3						

(*continued on next page*)

Table 2 (*continued*)

	Subgroups				Full sample	
	No baseline chronic pain		Reporting chronic pain at baseline		Adjusting for chronic pain at baseline	
	N	OR (95 % CI)	N	OR (95 % CI)	N	OR (95 % CI)
(Ref: low-interference pain)						
CAR (0–30 min)	154	1.10 (0.68, 1.77)	174	0.91 (0.64, 1.28)	328	0.94 (0.73, 1.20)
Early post-wake DCS (30 min to 4.5 h)	154	**2.60 (1.44, 4.70)****	174	1.10 (0.74, 1.62)	328	**1.37 (1.04, 1.81)***
Mid post-wake DCS (4.5–15 h)	154	2.48 (0.94, 6.55)	174	1.01 (0.70, 1.47)	328	1.26 (0.96, 1.64)
Late post-wake DCS (after 15 h)	154	1.25 (0.75, 2.08)	174	0.86 (0.59, 1.26)	328	0.97 (0.75, 1.26)
CDR	154	0.77 (0.37, 1.59)	174	0.92 (0.65, 1.29)	328	0.88 (0.69, 1.14)
AUC	154	0.89 (0.49, 1.62)	174	0.86 (0.60, 1.22)	328	0.86 (0.66, 1.11)
Chronic non-multisite pain at MIDUS 3 (Ref: no pain)						
CAR (0–30 min)	570	1.08 (0.88, 1.34)	214	0.82 (0.56, 1.19)	784	1.01 (0.84, 1.21)
Early post-wake DCS (30 min to 4.5 h)	570	1.15 (0.93, 1.43)	214	0.96 (0.68, 1.34)	784	1.09 (0.91, 1.29)
Mid post-wake DCS (4.5–15 h)	570	1.06 (0.85, 1.31)	214	0.99 (0.7, 1.39)	784	1.02 (0.86, 1.21)
Late post-wake DCS (after 15 h)	570	0.83 (0.66, 1.04)	214	1.06 (0.78, 1.45)	784	0.87 (0.74, 1.04)
CDR	570	1.09 (0.88, 1.34)	214	1.02 (0.70, 1.48)	784	1.06 (0.89, 1.26)
AUC	570	0.87 (0.69, 1.09)	214	0.91 (0.63, 1.32)	784	0.88 (0.73, 1.06)
Chronic multisite pain at MIDUS 3 (Ref: no pain)						
CAR (0–30 min)	491	0.83 (0.56, 1.21)	227	0.88 (0.62, 1.26)	703	0.89 (0.71, 1.10)
Early post-wake DCS (30 min to 4.5 h)	491	**2.16 (1.41, 3.32)*****	227	0.93 (0.64, 1.34)	703	1.26 (0.99, 1.60).
Mid post-wake DCS (4.5–15 h)	491	**1.93 (1.28, 2.90)****	227	0.92 (0.64, 1.34)	703	1.22 (0.96, 1.55)
Late post-wake DCS (after 15 h)	491	**1.58 (1.03, 2.43)***	227	0.87 (0.59, 1.29)	703	1.11 (0.87, 1.44)
CDR	491	0.74 (0.51, 1.06)	212	0.77 (0.53, 1.12)	703	0.81 (0.65, 1.01)
AUC	491	0.81 (0.54, 1.21)	212	0.76 (0.51, 1.12)	703	0.83 (0.66, 1.04)
Chronic multisite pain at MIDUS 3 (Ref: chronic non-multisite pain)						
CAR (0–30 min)	157	1.14 (0.71, 1.84)	186	0.80 (0.56, 1.14)	343	0.87 (0.68, 1.12)
Early post-wake DCS (30 min to 4.5 h)	157	**2.73 (1.49, 4.99)****	186	0.95 (0.65, 1.39)	343	**1.33 (1.01, 1.75)***
Mid post-wake DCS (4.5–15 h)	157	**2.21 (1.24, 3.91)****	186	0.98 (0.68, 1.41)	343	1.21 (0.93, 1.57)
Late post-wake DCS (after 15 h)	157	1.17 (0.71, 1.93)	186	0.96 (0.67, 1.37)	343	0.98 (0.76, 1.27)
CDR	157	1.00 (0.62, 1.62)	186	0.80 (0.57, 1.12)	343	0.85 (0.67, 1.09)
AUC	157	0.86 (0.54, 1.38)	186	0.69 (0.48, 1.00)	343	**0.76 (0.58, 0.98)***

Statistical significance markers: * $P < 0.05$; ** $P < 0.01$; *** $p < 0.001$

† Adjusted for age, race, sex assigned at birth, income-to-needs ratio, education, marital status, physical activity index, smoking and drinking status, multimorbidity, BMI, childhood experiences of parental emotional and physical abuse, and medication intakes (e.g., steroid inhalers, oral steroids, antidepressants, anti-anxiety medications, birth control pills, and other hormonal medications). A random intercept at the family level was included, to allow for correlations between individuals from the same family.

Note that cortisol parameters were standardized. An increase of one standard deviation in CAR indicates a steeper CAR, whereas an increase of one standard deviation in DCSs indicates flatter DCSs. One standard deviation increase in CDR indicates a wider CDR, while one standard deviation increase in AUC indicates a larger AUC.

chronic pain at baseline (Fig. 2B) or for the full sample.

Association of diurnal cortisol rhythm at baseline with chronic high-interference pain at follow-up

Among individuals without chronic pain at baseline, blunter early post-wake and mid post-wake DCSs at baseline were associated with higher odds of developing high-interference pain, relative to no pain at follow-up, as shown in Table 2. Each one standard deviation increase in the early post-wake DCS and the mid post-wake DCS, the odds of developing high-interference pain were 85 % (OR = 1.85, 95 % CI = 1.09–3.16, $P < 0.05$) and 82 % (OR = 1.82, 95 % CI = 1.09–3.02, $P < 0.05$) higher. Within this same subgroup, a blunter early post-wake DCS at baseline was significantly associated with higher odds of developing high-interference pain, relative to low-interference pain at follow-up (OR = 2.60, 95 % CI = 1.44–4.70, $P < 0.01$), as shown in Table 2. Fig. 2C illustrates a marginally flatter diurnal cortisol profile during the early and mid post-wake segments among individuals who developed high-interference pain, compared to those who remained pain-free and, for the early post-wake segment, also flatter than among those who developed low-interference pain.

Among individuals with chronic pain at baseline, no significant associations were observed between cortisol parameters and pain interference (Table 2 and Fig. 2D).

In the full sample, a blunter early post-wake DCS at baseline was significantly associated with higher odds of developing high-interference pain (OR = 1.37, 95 % CI = 1.04–1.81, $P < 0.05$), with low-interference pain as the reference group (Table 2).

Lastly, no significant associations were observed between diurnal cortisol parameters at baseline and low-interference pain at follow-up, either within subgroups (Table 2 and Figs. 2C, 2D) or in the full

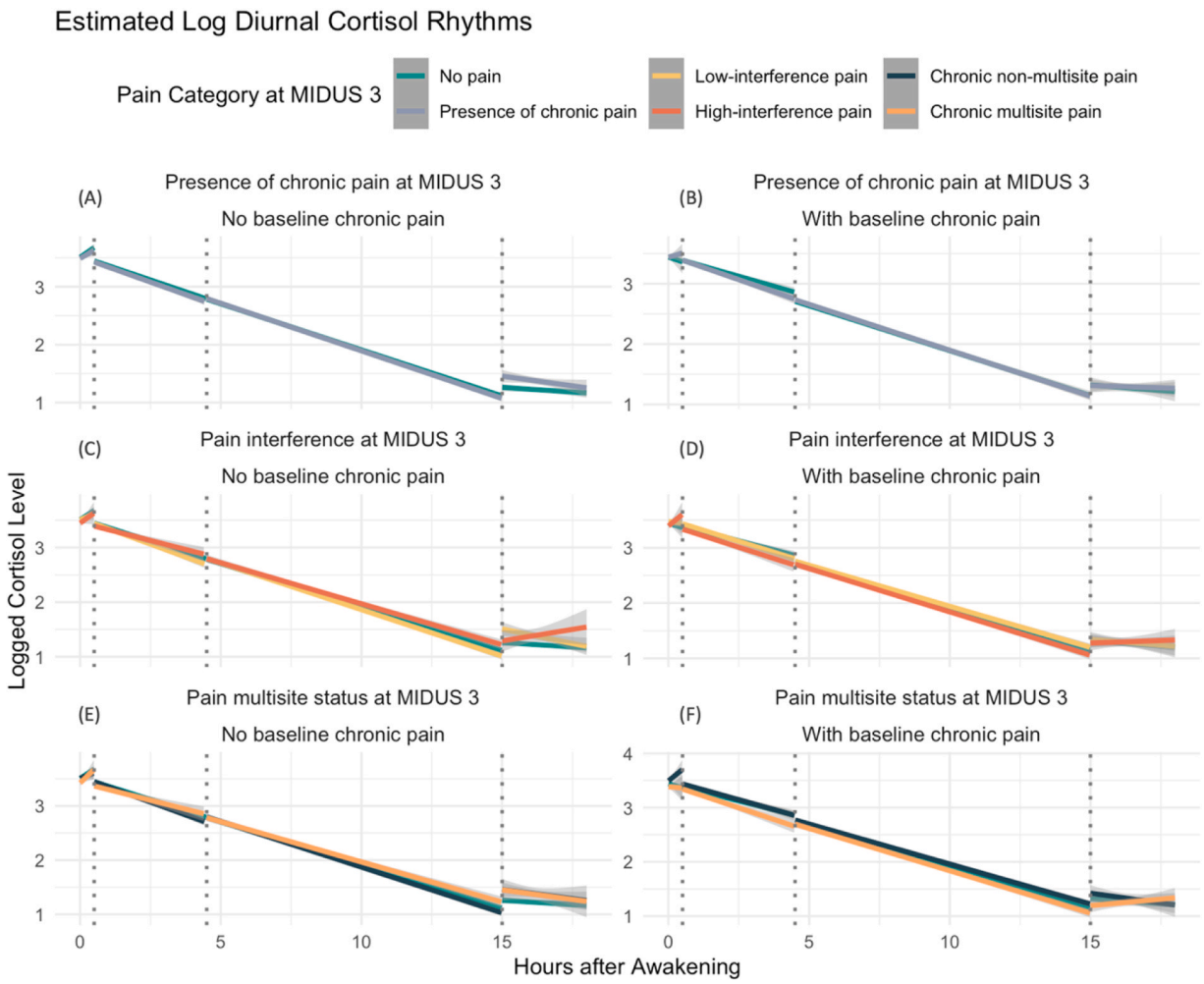

Fig. 2. Diurnal cortisol trajectories of participants by chronic pain conditions at follow-up, stratified by baseline chronic pain status. Predicted values of logged cortisol levels were derived from the multilevel model of time since awakening, with covariates held at their reference values and random effects included. Vertical dashed lines at 0.5, 4.5, and 15 h post-awakening indicate model knot points.

sample (Table 2).

Association of diurnal cortisol rhythm at baseline with chronic multisite pain at follow-up

Among individuals without chronic pain at baseline, a blunter early post-wake DCS (OR = 2.16, 95 % CI = 1.41–3.32, P < 0.001), mid post-wake DCS (OR = 1.93, 95 % CI = 1.28–2.90, P < 0.01), and late post-wake DCS (OR = 1.58, 95 % CI = 1.03–2.43, P < 0.05) at baseline were associated with higher odds of developing chronic multisite pain, relative to no pain at follow-up, as shown in Table 2. Within this subgroup, blunted early post-wake (OR = 2.73, 95 % CI = 1.49–4.99, P < 0.01) and mid post-wake (OR = 2.21, 95 % CI = 1.24–3.91, P < 0.01) DCSs at baseline was significantly associated with higher odds of developing chronic multisite pain at follow-up, relative to chronic non-multisite pain, as shown in Table 2. In Fig. 2E, individuals without chronic pain at baseline who later developed chronic multisite pain exhibited a marginally flatter diurnal cortisol profile in the early and mid post-wake segments, relative to both those who remained pain-free and those who developed chronic non-multisite pain; the pattern was less clear in the late post-wake segment.

Among individuals with pre-existing chronic pain at baseline, no significant associations were observed between any baseline cortisol measure and multisite pain at follow-up (Table 2 and Fig. 2F).

In the full sample, blunted early post-wake DCS at baseline was significantly associated with higher odds of chronic multisite pain at follow-up, with chronic non-multisite pain as the reference group (OR = 1.33, 95 % CI = 1.01–1.75, P < 0.05), as shown in Table 2. A higher AUC at baseline was significantly associated with lower odds of chronic multisite pain at follow-up, with chronic non-multisite pain as the reference group, but only in the full sample (OR = 0.76, 95 % CI = 0.58–0.98, P < 0.05), as shown in Table 2.

Lastly, no significant associations were observed between diurnal cortisol parameters at baseline and non-multisite pain at follow-up, either within subgroups (Table 2 and Figs. 2E, 2F) or in the full sample (Table 2).

Exploratory factor analysis results

According to EFA, two factors were retained based on Kaiser's criterion (eigenvalues > 1), together explaining 84 % of the total variance (46 % and 38 %, respectively) (Supplementary Table 3). The first factor showed high loadings for early post-wake DCS, mid post-wake DCS, late post-wake DCS. The second factor was primarily defined by strong loadings for CAR, CDR and AUC.

Robustness checks

The robustness checks revealed that, among participants who did not report chronic pain at baseline, the associations between baseline early and mid post-wake DCSs and chronic multisite pain at MIDUS 3 (relative

to no pain) (See Supplementary Table 7), as well as between the early post-wake DCS and chronic multisite pain at MIDUS 3 (relative to chronic non-multisite pain) (See Supplementary Table 8), remained robust across model specifications. These findings were further supported by formal moderation analyses testing the interaction between baseline cortisol parameters and baseline chronic pain status, which confirmed that the observed associations were specific to individuals without chronic pain at baseline (See Supplementary Table 9).

Associations between the baseline late post-wake DCS and the presence of chronic pain at MIDUS 3 (See Supplementary Table 5); early and mid post-wake DCSs and high-interference pain (vs. no pain) (See Supplementary Table 6); the late post-wake DCS and chronic multisite pain (vs. no pain) (See Supplementary Table 7); and the early or mid post-wake DCS and high-interference pain (vs. low-interference pain) were not robust (See Supplementary Table 8). In the full sample, no associations remained robust (See Supplementary Table 8).

Results from the positive outcome control, conducted to assess whether our analytic approach could replicate the known association, supported the validity of the modeling strategy. We observed a significant cross-sectional association between AUC and chronic multisite pain (See Supplementary Table 10), consistent with prior findings.[37,38]

Discussion

In this U.S. cohort of community-dwelling adults with multi-day cortisol collection, blunter early and mid post-wake DCSs predicted higher odds of developing chronic multisite pain about seven years later among pain-free individuals at baseline. Also, the early post-wake DCS was associated with chronic multisite pain compared to chronic non-multisite pain, among individuals without baseline chronic pain. Sensitivity analyses did not substantially change these associations. No other robust associations were found in the same subgroup. Among those with pre-existing chronic pain, no clear associations were found between diurnal cortisol rhythm and chronic pain outcomes. Moreover, in the full sample, no robust associations were found between diurnal cortisol rhythm and chronic pain outcomes.

A previous study found that a blunted diurnal cortisol rhythm predicted an increased risk of new-onset chronic widespread pain 15 months later.[39] However, it had a smaller cohort size (n = 269). Additionally, the previous study used actual clock time, and cortisol samples might have been taken at different points in each individual's diurnal cycle, potentially leading to measurement bias.[18] Using waking time as a reference in our study provided a consistent basis for capturing the natural rhythms of the participants. However, a study from the Netherlands Study of Depression and Anxiety (NESDA) reported no association between diurnal cortisol rhythm and the development of chronic widespread pain.[41] The inclusion of cohorts with a high proportion of depression and anxiety[41] may obscure the relationship,[38] as HPA-axis alterations in these conditions may confound cortisol patterns independently of pain.[69] By overcoming these limitations, our study further corroborated earlier evidence, enriching and extending the current epidemiological literature on the DCS and health outcomes.[55]

Our use of multilevel growth curve approach with knots may capture the temporal regulatory processes that may underlie DCSs. The EFA shows all DCSs loaded variably onto Factor 1, plausibly relating to a GR-MR continuum[20]—from GR-dominant activity following the morning peak to MR-driven control by evening. A recent study using multi-day salivary sampling suggested that the decline after the morning peak may serve as a biomarker of GR sensitivity as a steeper decline was associated with greater dexamethasone suppression.[32] The dexamethasone suppression test is a commonly used functional assay to infer GR sensitivity.[70] The post-CAR DCS might be more sensitive to GR-related feedback, as it was associated with more feedback inhibition indicators compared to later DCSs.[32] Therefore, if GR sensitivity underlies associations between DCSs and chronic multisite pain, the attenuated effect sizes observed for our later DCSs may reflect their reduced modulation by GR-mediated feedback inhibition.

Moreover, emerging evidence suggests that both awakening and the subsequent cortisol peak are significantly associated with adrenal sensitivity,[32] potentially modulated via extrapituitary mechanisms including sympathetic innervation of the adrenal gland through the splanchnic nerve.[21] Given the fact that both levels at awakening and peak define CAR—and, by extension, directly inform the computation of CDR and AUC—these interrelated parameters might reflect a shared underlying mechanism related to adrenal sensitivity,[71] as captured by Factor 2. However, these interpretations remain speculative and require further validation.

Notably, the early post-wake DCS shows a larger effect size in predicting chronic multisite pain when contrasted with chronic non-multisite pain, than when contrasted with remaining pain-free. This pattern may reflect the important role of GR downregulation in driving the widespreadness of pain. GR downregulation reduces cortisol inhibition of catecholamine release,[31,72] which exacerbates systematic inflammation and induces nociception. Additionally, the inflammation heightens the excitability of sensory transmission pathways across multiple anatomical regions, leading to both peripheral and central sensitization.[73] Moreover, impaired GR function fails to inhibit nuclear factor-κB,[74] promoting widespread algogen transcription and further sensitization and hyperalgesia.[75,76] These processes may help explain why early post-wake DCS is associated with the onset of chronic multisite pain but not with the onset of non-multisite pain, although this interpretation remains speculative and warrants further investigation.

Furthermore, our results may highlight the potential relevance of DCS flattening as a potential indicator of chronic multisite pain progression.[39] Recent studies suggest that individuals experiencing acute pain or non-chronic regional pain, representing the early to mid-stages of chronic widespread pain development, often exhibit higher cortisol levels.[43,77,78] However, as pain progresses toward chronicity, the DCS may become progressively blunted according to previous research.[39] As pain transitions to a chronic state, cortisol levels tend to decline. For example, the latest meta-analysis and cross-sectional epidemiological studies have consistently indicated that individuals with fibromyalgia and chronic multisite musculoskeletal pain have lower cortisol levels.[36–38] While some studies have still observed increased cortisol levels following the onset of chronic pain,[78] recent evidence suggests this may reflect transient rise due to pain episodes within chronic pain, but in the long term, the HPA axis function becomes downregulated, leading to decreased cortisol levels.[43] Taken with our prospective findings, DCS flattening may emerge as a mid-to-late stage marker of chronic multisite pain development, offering a temporal framework for understanding the transition from early hypercortisolism to long-term hypocortisolism.

Among respondents with baseline chronic pain, we found no associations between diurnal cortisol rhythm and chronic pain outcomes at follow-up, echoing the null association found in a previous study.[42] This may attenuate associations in our analyses in the full sample. Chronic pain may become self-sustaining through central sensitization, in which neurons become hypersensitive, responding excessively to normal stimuli or producing amplified responses to noxious stimuli.[79] Therefore, pain persistence may be less dependent on the HPA axis. Due to limited sample sizes within groups defined by baseline chronic pain subtypes and follow-up pain outcomes, formal analyses were not feasible. These subgroups may represent clinically relevant phenotypes, and future adequately powered studies should examine whether diurnal cortisol patterns predict subsequent pain trajectories.

We did not find a robust association between diurnal cortisol rhythms and pain interference. One possibility is that reports of pain interference may reflect modulation by the anterior cingulate cortex,[80] shaping the pain experience through mechanisms such as attentional focus, emotional distress, and cognitive appraisal.[81,82] In our sample, about 47 % of individuals with multisite pain overlapped with those reporting high-interference pain. The observed differences in the association between the HPA axis and pain outcomes suggest that the reports

of pain interference by those with multisite pain may be further affected by the complex interplay of biopsychosocial factors rather than by the pain condition alone.[83] Given the significant clinical implications of pain interference, further studies on its underlying mechanisms are needed.

Our study has several key advantages, including repeated measurements of salivary cortisol over multiple days in naturalistic settings and a community-based cohort study design. The study has following limitations. We could not obtain clinically validated pain measures from the MIDUS, such as chronic widespread pain or fibromyalgia, possibly including individuals with milder symptoms.[38] Additionally, the measurement of chronic pain lacks a minimum duration of three months and implicitly assumes preexisting tissue damage, making it less reflective of the broader biopsychosocial dimensions of pain. Moreover, the study could not detect changes in chronic pain status between MIDUS 2 NSDE and MIDUS 3, potentially misclassifying those who recovered by MIDUS 3 as not experiencing chronic pain during the seven-year follow-up. Another limitation of the study is the strict criteria for selecting participants with viable cortisol data, which may introduce selection bias and limit the generalizability to the wider U.S. population. Meanwhile, BIPOC participants are underrepresented, indicating the need to increase the inclusion of ethnic minorities in future studies. Despite our cautious adjustment for confounders, the possibility of residual confounding due to imprecise measurements or unknown factors cannot be excluded in our study. Despite the advantages of cortisol collection via NSDE, factors like differences in collection times between groups, discrepancies between actual and intended collection times, and knot selection may affect the accuracy of diurnal cortisol rhythm modeling. Furthermore, sensitivity analyses and adjustments for confounding factors led to the disappearance of certain associations. Studies with larger sample sizes may provide more robust results.

Based on this prospective cohort study, flattening of diurnal cortisol slopes—particularly in the early post-wake period—may indicate elevated risk for chronic multisite pain development. These associations remained robust after adjustment for confounders and sensitivity checks. Outcome-specific contrasts further highlight the distinct relevance of the early post-wake DCS in differentiating pain phenotypes. Therefore, the rate of diurnal cortisol decline may provide information for identifying at-risk populations. Future studies are needed to elucidate the biological significance of these cortisol-based indicators and clarify the validity of the early post-wake DCS as a proxy for GR sensitivity. Future research may benefit from examining the potential restorative role of the diurnal cortisol rhythm in recovery from chronic multisite pain.

CRediT authorship contribution statement

YL: Conceptualization, data acquisition, analysis, visualization, writing, review and editing. **RL, LF:** Analysis, review and editing. **CB:** Conceptualization, analysis, review and editing.

Disclosures (funding & COI)

L.F. acknowledges funding from the ESRC Research Centre on Micro-Social Change (ES/S012486/1). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The authors declare no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jpain.2025.105458.

Data Availability

The data backing the conclusions of this study can be found openly at the Inter-university Consortium for Political and Social Research. Information about data access is available at https://www.icpsr.umich.edu/web/ICPSR/series/203. The analysis code used in this study can be made available upon request.

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