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Negative emotionality, depressive symptoms and cortisol diurnal rhythms: **O4** 1 Analysis of a community sample of middle-aged males

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ABSTRACT

Prior research suggests that individuals with particular personality traits, like negative emotionality, are at 31 greater risk for adverse health outcomes. Despite bivariate associations between negative emotionality, 32 depressive symptoms and the hypothalamic pituitary adrenal axis (HPA axis), few studies have sought to 33 understand the biological pathways through which negative emotionality, depressive symptomatology and 34 03 cortisol-one of the primary hormonal products of the HPA axis-are associated. The present study explored 35 whether negative emotionality influenced cortisol dysregulation through current depressive symptomatol- 36 ogy and whether negative emotionality served as a moderator of the relationship between depressive 37 symptoms and cortisol. In the community-based Vietnam Era Twin Study of Aging, 783 male twins completed 38 two days of cortisol saliva sampling in their natural environments. Three measures of cortisol were analyzed: 39 waking levels, the cortisol awakening response, and the peak to bed slope. Depressive symptoms significantly 40 mediated the associations between negative emotionality and the peak to bed slope. A 2-way interaction 41 between depressive symptoms and negative emotionality was significant for the peak to bed slope and for 42 waking levels of cortisol. Exploration of the interactions illustrated that depressive symptoms only affected 43 cortisol slopes at average or high levels of negative emotionality and only affected waking levels at low levels 44 of negative emotionality. Negative emotionality and depressive symptoms were not related to the cortisol 45 awakening response. This is the first study to find indirect associations between negative emotionality and 46 peak to bed cortisol slopes through depressive symptoms. These findings illustrate the complex interplay 47 between personality characteristics, depressive symptoms and different indices of the cortisol diurnal 48 rhythm.

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Negative emotionality, depressive symptoms and cortisol diurnal 55 rhythms: mediating and moderating pathways 56

Prior research suggests that individuals with particular personality 57traits, like negative emotionality, are at greater risk for adverse health 58outcomes (for reviews see Friedman, 2000; Kern and Friedman, 2011; 5960 Smith and Gallo, 2001). Studies have found that higher levels of

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negative emotionality were associated with risky health behaviors 61 (e.g. Caspi et al., 1997), inflammatory markers and subsequent disease 62 (Black, 2003; Sutin et al., 2010), and subjective well-being (e.g. 63 Friedman et al., 2010). Negative emotionality has been shown to be 64 stable over adulthood and consistent across situations; thus it has 65 been conceptualized as "trait" marker of vulnerability toward general 66 distress.

An indicator of health that has not been closely examined in 68 relation to negative emotionality is the hypothalamic pituitary 69 adrenal axis (HPA axis). The HPA axis is one of the body's major 70 stress responding systems. This association is particularly important 71

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as negative emotionality may influence how an individual perceives 7273 the stressors in their environment. The HPA axis reacts to stressors in 74 the environment by activating a complex cascading of events, 75eventually resulting in the release of cortisol. Under normal circumstances (i.e., in the absence of specific stressors), cortisol 76 follows a daily rhythm. Specifically, cortisol follows a diurnal pattern 77 by which cortisol levels are high upon awakening in the morning, 78 79peak about thirty minutes after waking (commonly called the cortisol 80 awakening response; CAR), and decline across the waking day 81 (Kirschbaum and Hellhammer, 1989; Pruessner et al., 1997). Prior 82 research has found elevations of cortisol in relation to negative or depressed mood in non-clinical populations (Knight et al., 2010; 83 Pruessner et al., 2003; Sjögren et al., 2006) and more persistent, 84 Q6 85 chronic life stressors (Miller et al., 2007), but its associations with the personality trait negative emotionality has yet to be examined. 86

Negative emotionality and cortisol 87

To our knowledge, there are no studies of adults that have 88 investigated associations between negative emotionality and cortisol. 89 However, negative emotionality is closely associated with neuroti-90 cism (Tellegen, 1985), and is linked with broad negative affectivity 91 92(Patrick et al., 2002), which both have been linked with HPA axis activity. Although not all studies have found differences in diurnal 93 cortisol rhythms in subjects high in neuroticism as compared to those 94 with low neuroticism (Kirschbaum et al., 1992a, 1992b; Schommer et **O7** 95 al., 1999; van Santen et al., 2010), neuroticism has been associated 96 97 with differences in HPA axis regulation in everyday life (e.g. diurnal measures; Hauner et al., 2008; Schlotz et al., 2006). Some studies have 98 found increased levels of cortisol at waking in individuals high in 99 neuroticism (Portella et al., 2005; Wetherell et al., 2006), while others 100 101 reported positive associations between neuroticism and higher 102evening levels of cortisol (Gerritsen et al., 2009). A recent study 103 found higher average level of cortisol across the whole day in subjects high in neuroticism (Nater et al., 2010). 104

105 Relationships among depression, negative emotionality and cortisol

There is evidence that personality traits are associated with 106 depression (Fanous et al., 2007; Kahn et al., 2005, Kendler et al., 107 1993). Because negative emotionality is a propensity to experience 108 109 psychological distress that has been shown to be stable over adulthood and consistent across situations, it has been conceptualized 110 as a "trait" marker of vulnerability toward general distress and may 111 predispose an individual to experiencing higher levels of depressive 112 symptoms. Therefore, negative emotionality may impact HPA axis 113 114 regulation through higher levels of depressive symptomatology. In addition, there is both cross-sectional and prospective evidence that 115cortisol is associated with depressive symptoms, although relation-116 ships with salivary cortisol may be weaker (for review see Stetler and 117 Miller, 2011). van den Bergh et al. (2008) argued that by looking at 118 119 symptom levels rather than simply the presence of a disorder we may 120 be able to identify pre-disease pathways in all parts of the depressive symptoms continuum by using biological markers as "vulnerability 121markers." Indeed, Pruessner et al. (2003) found that higher levels of 122depressive symptoms were associated with greater cortisol awaken-123124 ing responses, and others report associations between depressed mood and flatter diurnal cortisol rhythms (Knight et al., 2010; Sjögren 125et al., 2006). A recent meta-analysis investigating chronic stress and 126alterations in HPA-axis regulation argued that even when a person 127does not develop a psychiatric condition, greater emotional distress is 128associated with flatter diurnal cortisol (Miller et al., 2007). 129

Despite bivariate associations between negative emotionality, 130depressive symptoms and cortisol, no studies have examined these 131 three constructs simultaneously. In the present study we examine 132133 whether a stable personality characteristic, negative emotionality, influences cortisol dysregulation through current depressive symp- 134 tomatology. In addition, previous studies have not specifically 135 examined whether the relationship between depressive symptoms 136 and HPA axis dysregulation is modified by personality characteristics 137 such as negative emotionality. To the extent that negative emotion- 138 ality can be considered a marker of a liability to general distress, it 139 may exacerbate the effects of depressive symptomatology on cortisol. 140 Thus, experiences of depressive symptomatology may be more 141 strongly associated with HPA axis dysregulation among individuals 142 with high levels of negative emotionality. 143

The present study

In this study we examined the potential pathways among negative 145 emotionality, depressive symptoms and indices of the cortisol diurnal 146 rhythm. The present study extends previous work by considering the 147 joint pathways through which negative emotionality and depressive 148 symptoms are associated with diurnal rhythms of cortisol and by 149 testing whether negative emotionality moderates the association 150 between depressive symptoms and diurnal rhythms of cortisol in a 151 large sample of community-dwelling men. We focused on three 152 measures of the diurnal pattern of cortisol - waking levels, slope of 153 the diurnal rhythm across the day and the CAR because of the findings 154 between these parameters and major depression or depressive 155 symptoms in prior research (as outlined above). We hypothesized 156 the following: 1) negative emotionality and depressive symptoms 157 would be independently associated with indicators of the cortisol 158 diurnal rhythm; 2) depressive symptoms would partially mediate the 159 associations between negative emotionality and cortisol; and 3) levels 160 of negative emotionality would moderate the associations between 161 depressive symptoms and cortisol such that the relationship between 162 depressive symptoms and cortisol dysregulation is higher among 163 people with higher levels of negative emotionality. 164

Method

Participants

The sample for this study included a subset of male monozygotic 167 and dizygotic twins who took part in the Vietnam Era Twin Study of 168 Aging (VETSA). The VETSA has been described in detail elsewhere 169 (Kremen et al., 2006). VETSA twins were randomly selected for 170 recruitment from a pool of 3322 twin pairs in the Vietnam Era Twin 171 Registry who served in the US military at some time during the 172 Vietnam era (1965–1975), were aged 51–60 during the VETSA data 173 collection, and who took part in a prior study of psychological health 174 in 1992 (Tsuang et al., 2001). These individuals were not selected as 175 Veteran Affairs patients and most were never in combat or in Vietnam 176 (Kremen et al., 2006). There were 1237 participants in the VETSA 177 (mean age = 55.9, SD = 2.58). Eighty-eight percent of the sample was 178 Caucasian, 4.3% African-American, 2.9% Hispanic, .9% Native American, 179 and .4% Pacific Islander. Compared to national data for men in their 180 50s (National Health and Nutrition Examination Survey, NHANES III, 181 **Q8** 2007; National Center for Disease Statistics. Health and United States, 182 Q9 2003), the VETSA participants are similar to the larger US population 183 of men in this age range based on demographic (age, education, 184 income, marital status, employment) and health data (prevalence of 185 chronic health problems, diabetes, and hypertension). Two years after 186 the VETSA study began, an additional study was initiated to 187 understand the role of cortisol and other hormonal dysregulation as 188 a risk factor for cognitive aging. Approximately one-third (N = 442) of 189 VETSA participants had already been studied and were ineligible for 190 the additional cortisol study. Of the remaining 795 subjects, 786 191 (98.9%) participated in the hormone data collection study between 192 2005 and 2007. The analyses reported herein were non-twin analyses. 193

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194 Procedures

Participants completed salivary collection in their naturalistic 195 196 settings on two non-consecutive "typical" working days (for full description of saliva collection procedures see Franz et al., 2010). 197Cortisol kits were mailed via courier and participants received a 198reminder call the day before they were to begin sampling to ensure 199that materials were received, to go over procedures and to answer any 200201 questions. Materials included: 4.5 mL Cryotube vials, original Trident sugarless gum, straws, tissues, detailed instructions, a daily log, pen, a 202203reminder watch set for all of the sampling times, and a storage container with a MEMS 6[™] (Aardax) track cap for detecting 204compliance with protocol. The materials were tested to ensure that 205206 they did not alter the assays. On each day participants were asked to provide samples at waking, 30 min post waking, 10:00 am, 3:00 pm, 207 and 9:00 pm or bedtime for a total of 10 samples per participant. 208 Participants with non-standard schedules (i.e., night shift workers) 209 provided samples at equivalent time periods based on their wake 210 time. At each sampling point, participants provided a saliva sample, 211 placed it in the storage container (with the track cap so the entry was 212 logged) and filled out a written log reporting on their mood, food and 213 drink consumption, medication use, alcohol use and whether or not 214 215they smoked or exercised in the last hour. Lastly, participants also 216 filled out an extensive psychosocial questionnaire at home and brought the questionnaire to their study site. 217

218 Measures

219 Cortisol

Participants provided five samples a day for two days. Cortisol was 220 collected by passive drool until the participant had provided at least 2212222.25 mL of saliva. If necessary, they chewed Trident gum to stimulate 223saliva and removed the gum prior to providing the sample. Participants stored and refrigerated their saliva samples in an 224225insulated lunch bag included with the cortisol kits. At the end of the two days, they sent the saliva samples via overnight mail to the 226University of California, Davis to be assayed. Salivary assays were 227228 estimated in duplicate using commercial radioimmunoassay kits (Siemens Medical Solutions Diagnostics, Los Angeles, CA). The 229sensitivity of the cortisol assay is 1.39 nmol/L and the intra- and 230inter-assay coefficients of variation are 3.96 and 5.66 respectively. All 231232saliva samples from each individual participant were assayed together in batches containing one to three individuals. Three individuals were 233excluded due to lost (N=1) or contaminated (N=2) samples, 234 resulting in a final sample of N = 783. There was very little missing 235236data due to participant lapses or technical problems (~1.0%) although 2370.1% of samples were re-coded as missing because they had values greater than 50 nanomoles per liter (nmol/L; Hellhammer et al., 2009; 238 Nicolson, 2008; see Franz et al., 2010 for more details). Individual 239cortisol values were positively skewed (skewness range = 1.7 to 20.1) 240and were log transformed to approximate normality. Analyses 241242focused on three indices of cortisol patterns throughout the day, as 243described in detail below.

244 Negative emotionality

Negative emotionality was assessed using Tellegen's Multidimen-245sional Personality Questionnaire (MPQ) factor-form NZ; the NZ 246 version is considered to be very similar to the Brief Form (Caspi, 247 2000; Caspi et al., 1997; Krueger et al., 2000; Patrick et al., 2002). 248 Validity of the psychometric properties of the MPQ is well documen-249 ted (Krueger et al., 2000; Patrick et al., 2002; Tellegen, 1985). The 250251MPQ is a self-report questionnaire and consists of 11 scales. The three subscales of interest in this study are Stress Reaction, Alienation, and 252Aggression, which when summed together make up the broad trait of 253Negative Emotionality (NEM). This trait was our primary interest for 254255 these analyses because of overlap with measures of trait neuroticism (Tellegen, 1985). The stress reaction scale has 14 items and assesses 256 whether someone is prone to negative emotions or is easily worried 257 or anxious (α =.86). The alienation scale has 17 items and detects 258 whether someone often feels victimized, mistreated or pushed around 259 (α =.83). Lastly, the aggression scale has 18 items and assesses 260 whether someone enjoys aggression, is physically aggressive, or is 261 vindictive (α =.75). These three subscales were summed to create a 262 total NEM score with a possible range of 0 to 49. 263

Depressive symptoms

Depressive symptoms were assessed using the Center for 265 Epidemiologic Studies Depression Scale (CES-D: Radloff, 1977). The 266 scale is made up of 20 items designed to measure levels of depressive 267 symptoms experienced in the past week. Participants circled re- 268 sponses ranging from 0 to 3, with 0 indicating that they had 269 experienced that symptom rarely or <1 day of the week and 3 270 indicating that they had experienced that symptoms most of that 271 week or 5-7 days. The CES-D has been checked for reliability across 272 several age groups, has good internal consistency within the VETSA 273 sample (α =.90), and has been found to be highly correlated with 274 indicators of major depression based on accepted cut-off scores (Rush 275 Q10 et al., 2000; Shafer, 2006). Items were summed to create a composite 276 Q11 scale with a possible range of 0 to 60. This measure was positively 277 skewed (skewness = 1.72) and therefore was log transformed prior to 278 analysis. 279

Cova	riator
COVU	rutes

As part of the cortisol collection procedure, participants were 281 asked to record whether they had smoked, eaten, drunk alcohol, taken 282 medication, or exercised before each sample. Responses at each time 283 were coded as 0 (no) or 1 (yes). In accordance with prior research 284 (Kirschbaum et al., 1992a, 1992b), smoking prior to the sample 285 collection was the only variable consistently related to cortisol level. 286 In addition, data were collected on several other variables known to 287 be associated with cortisol including wake time and number of hours 288 slept prior to the days of sampling (see Doane et al., 2010 for details). 289

Data preparation and manipulation

Cortisol follows a predictable diurnal rhythm with relatively high 291 levels at wake time, followed by an increase of 50-60% in the 20- 292 40 min after waking (known as the cortisol awakening response), a 293 rapid decline in the subsequent few hours, and a slower decrease 294 throughout the remainder of the day to reach the lowest point near 295 midnight (Pruessner et al., 1997). We simulated this growth curve 296 pattern using the statistical program WinBUGS (Spiegelhalter et al., 297 2004). WinBUGS uses Markov Chain Monte Carlo (MCMC) which 298 allowed us to control for the non-independence of samples intro- 299 duced when individuals were assayed in batches, and further allowed 300 us to include nicotine use as a time-varying covariate in the analysis. 301 To account for the batch effects, we set the *i*th assayed value of the *j*th 302 twin by Y_{iik} , where the subscript k further indicates the batch in which 303 the value was assayed such that assays in the same batch have the 304 same value of *k*. We used each participant's log-transformed cortisol 305 values at each time point to model the waking value of cortisol 306 (WAKE), the cortisol slope from wake up to the peak (cortisol 307 awakening response, CAR), and the exponential decay after the peak 308 until bedtime or peak-to-bed slope for each day, while also accounting 309 for batch and nicotine use. A larger CAR indicates a greater difference 310 between waking and peak levels of cortisol at the wake and wake $+30_{311}$ samples, while a lower PTB slope indicates "flatter" cortisol slopes 312 across the day. Parameter estimates for WAKE, CAR, and PTB for each 313 participant were then exported for use as the main dependent 314 variables in all analyses. 315

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Fig. 1. Latent factor path model testing the direct and indirect effects of negative emotionality and depressive symptoms on cortisol. Dotted lines represent nonsignificant paths and full lines represent significant paths (p < .05). Panels represent: a) generalized model and b) latent factor path model for peak to bed cortisol diurnal slope estimates. There is also a significant indirect effect of negative emotionality through depressed model to the peak to bed slope.

316 Analytic strategy

Analyses were conducted on 735 (94% of the original 783) participants who had complete data for all cortisol parameters, predictors and covariates. The sample consisted of 340 "complete" twin pairs (N=680 individuals) and 55 men whose twin did not participate in the study. Analyses were performed in three stages: 1) mediational models; 2) moderation analyses; and 3) post hoc exploration of moderation effect.

324 Mediation

The first stage of analysis used a latent factor path model to test 325models of WAKE, CAR and PTB as predicted by depressive symptoms 326 327 and NEM. These models were run to determine if negative emotionality affected cortisol through its effect on depressive 328 symptoms. To accomplish this we fit a full model specifying direct 329 and indirect effects of NEM on the cortisol parameters as well as direct 330 effects of depressive symptoms on the cortisol parameters (see 331 332 Fig. 1a). Cortisol parameters were defined as latent variables with corresponding indicators measured over the two days. Hours of sleep 333 and wake time (averaged across the two days) were also included as 334 covariates of the cortisol latent factors. Paths were estimated from 335 NEM to depressive symptoms and cortisol. A path was also specified 336 337 from depressive symptoms to cortisol. For ease of interpretation, all 338 variables were standardized in the analysis. The cluster command was

t1.1 Table 1

Descriptive	statistics f	or dependent	and independent	variables	(N = 735).

t1.2t1.3 Variable SD Minimum Maximum Mean Average wake time cortisol (nmol/L)^{a,b} t14 9698 5 4 3 7 1 385 38 066 t1.5 Average wake + 30 min cortisol (nmol/L)^{a,b} 13.591 6.952 1.611 46.729 Average 10:00 am cortisol (nmol/L)^{a,b} 5.835 3.323 1.392 24.720 t1.6 Average 3:00 pm cortisol (nmol/L)^{a,b} 4.123 1.390 23.582 2.307 t1.7 Average bedtime cortisol (nmol/L)^{a,b} t1.8 2.707 2.239 1.390 25.160 Negative emotionality 10.168 7.755 0.000 45.000 t1.9 Depressive symptoms from the CES-D^b 8.104 7.943 0.000 52.000 t1.10

^a Day 1 and Day 2 values have been averaged.

^b Raw values are presented for descriptive purposes but log transformed values are used in all analyses.

used to account for the correlated observations of participants from 339 the same family (i.e., twins within pairs). 340

Mediation models were fit using MPlus 3.0 (Muthén and Muthén, 341 Q13 1998–2004). Maximum likelihood estimation was used and absolute 342 model fit was assessed with the chi-squared statistic, the comparative 343 fit index (CFI) and the root mean square error of approximation 344 (RMSEA). The criterion of acceptable fit was >.95 for the CFI and <.06 345 RMSEA (Hu and Bentler, 1999). 346

Moderation

The role of NEM as a significant moderator of the depressive 348 symptoms-cortisol associations was tested using three-level hierar- 349 chical linear models to account for the nesting of days within persons, 350 and persons nested within family (Raudenbush and Bryk, 2002; 351 Singer and Willett, 2003). In these models the cortisol parameters 352 (WAKE, CAR, PTB) for each person at each day were the outcome 353 variables, and were predicted by day-varying covariates of hours of 354 sleep and wake time (Level 1), and the person level predictors of 355 depressive symptoms, NEM, and the interaction between NEM and 356 depressive symptoms (Level 2). Clustering for individuals nested 357 within families occurred at Level 3. Predictors were grand mean 358 centered prior to creating interaction terms and were then standard- 359 ized for ease of interpretation and for comparison of estimates with 360 other studies. 361

Testing interaction betwee	en negative emotionality and	
lepressive symptoms		

Significant two-way interactions between depressive symptoms 364 and NEM were further explored using the simple slopes technique for 365 hierarchical linear modeling as outlined in Preacher et al. (2006) for 366 interactions between two Level 2 predictors. This method expands on 367 typical simple slopes techniques (e.g., Aiken and West, 1991), as it 368 accounts for the nesting of the data and possible covariation both 369 within and between levels of the nested data. Briefly, we utilized the 370 online calculator developed by Preacher et al. (http://people.ku.edu/ 371 ~preacher/interact/hlm2.htm) to produce simple slopes estimates, 372 standard errors and *p*-values for associations of depressive symptoms 373 and cortisol at low, average, and high levels of NEM. The online 374 calculator also produced an estimate of the range of NEM where the 375 relationship between depressive symptoms and cortisol was statistically significant. 377

Results

Preliminary and descriptive analyses

Descriptive statistics for our primary independent and dependent ³⁸⁰ variables and covariates are presented in Table 1. For simplicity, ³⁸¹ cortisol values are shown averaged across Day 1 and Day 2. Note that ³⁸² the mean raw cortisol values follow the expected diurnal rhythm with ³⁸³ levels high in the morning, peaking 30 min after waking and slowly ³⁸⁴ declining across the day. Simple correlations among the predictors, ³⁸⁵ the various cortisol parameters and covariates are shown in Table 2. ³⁸⁶

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t2.1 Table 2

Intercorrelation table of main predictors, covariates and cortisol parameters (N=735).

t2.2 t2.3		2	3	4	5	6	7
t2.4 1. V t2.5 2. C t2.6 3. F t2.7 4. N t2.8 5. E t2.9 6. F	Wake time cortisol (nmol/L) Cortisol awakening response Peak to bed cortisol slope Negative emotionality Depressive symptoms Hours of sleep the night before Walte time	-0.314**	600** -0.212**	.047 .009 077*	.070* 007 104** .578**	018 204** .164 .037 .009	069* 046 044 .011 026 .273**

t2.11 ** *p*<.01.

As expected, NEM was significantly associated with depressive symptoms (r=.58, p=.000). WAKE was associated with depressive symptoms (r=.070, p=.05) and PTB was associated with NEM and depressive symptoms (r=-.077, p=.05; r=.104, p=.005). This indicated that higher levels of depressive symptomatology were associated with higher levels of cortisol at waking and with flatter cortisol slopes from peak to bedtime, and NEM was associated with

cortisol slopes from peak to bedtime, and NEM was associated with flatter cortisol slopes from peak to bedtime. CAR was not significantly associated with either of the primary predictors of interest (NEM: r = .009, p = .80; depressive symptoms; r = -.007, p = .85).

397 Mediation analyses

Structural equation models predicting WAKE and CAR from NEM and depressive symptoms did not reveal significant meditation pathways. Neither depressive symptoms nor NEM were associated with WAKE (NEM: $\beta = .025$, SE = .045, p = .58; depressive symptoms: $\beta = .067$, SE = .045, p = .13) or with CAR (NEM: $\beta = .052$, SE = .050, p = .30; depressive symptoms $\beta = -.034$, SE = .049, p = .49).

404 In contrast, there was significant mediation for PTB. Results from 405the mediation models are shown in Fig. 1b. All estimates presented in Fig. 1b are standardized estimates. There was good absolute fit of the 406 model to the data for PTB ($X^2(5) = 5.014$, p = .41; RMSEA = .002, 407 CFI = 1.000). There were significant direct effects of NEM on 408 depressive symptoms ($\beta = .59$, SE = .027, p = .00) indicating positive 409associations. There was a significant direct path from depressive 410 symptoms to PTB ($\beta = -.13$, SE = .061, p = .021) indicating that 411 higher levels of depressive symptoms were associated with flatter PTB 412 slopes (see Fig. 1b). There were no significant direct effects of NEM on 413 PTB; however there was a significant indirect effect of NEM through 414 depressive symptoms on PTB ($\beta = -.072$, SE = .036, p = .023), 415 indicating that depressive symptomatology was a significant media-416 tor of the effects of NEM on PTB. Additionally, hours of sleep was 417 418 associated with PTB slopes ($\beta = .20$, SE = .059, p = .001).

419 Moderation analyses

420 Standardized estimates from the HLM moderation analyses are 421 presented in Table 3. There were no main effects of depressive symptoms ($\beta_{01} = .066$, SE = .041, p = .11) or NEM ($\beta_{02} = .010$, 422SE = .041, p = .74) with waking levels of cortisol. However, the 2- 423 way interaction between depressive symptoms and NEM was 424 significantly associated with WAKE ($\beta_{03} = -.062$, SE = .031, p = .04) 425 indicating that NEM was a significant moderator of the depressive 426 symptoms–WAKE associations. For CAR, there were no main effects of 427 depressive symptoms ($\beta_{01} = -.019$, SE = .034, p = .58) or NEM 428 ($\beta_{02} = .031$, SE = .034, p = .42), and the 2-way interaction between 429 NEM and depressive symptoms was not significant ($\beta_{03} = -.014$, 430 SE = .024, p = .59). Depressive symptoms were significantly associat- 431 ed with PTB ($\beta_{01} = -.076$, SE = .037, p = .04) while NEM as a main 432 effect was not associated with PTB ($\beta_{02} = -.021$, SE = .038, p = .06). 433 The 2-way interaction between depressive symptoms and NEM was 434 significant ($\beta_{03} = -.021$, SE = .010, p = .05) indicating that NEM was 435 a significant moderator of the depressive symptoms.

Interactions between negative emotionality and depressive symptoms 43

In order to explore the significant interactions between depressive 438 symptoms and NEM for WAKE and PTB, we calculated simple slopes 439 using the online calculator developed by Preacher et al. (2006). Slopes 440 Q14 were calculated at low (1 SD below the sample mean), average 441 (sample mean), and high (1 SD above the sample mean) values of 442 NEM. These calculations revealed that there was a significant 443 association between depressive symptoms and WAKE at low levels 444 of NEM (β =.128, *SE*=.05, *t*=2.53, *p*=.01) but not at average 445 (β =.066, *SE*=.04, *t*=1.62, *p*=.11) or high levels (β =.003, *SE*=.05, 446 *t*=.07, *p*=.94). The online calculator indicated that the relationship 447 between depressive symptoms and WAKE was statistically significant 448 at values of NEM less than -.239 (51.7% of the sample). 449

In contrast, the simple slopes calculations for PTB indicated that 450 there was a significant association between depressive symptoms and 451 PTB slope at average ($\beta = -.076$, SE = .04, t = 2.04, p = .04) and high 452 ($\beta = -.097$, SE = .04, t = 2.56, p = .01) levels of NEM, but not at low 453 levels of NEM ($\beta = -.055$, SE = .04, t = 1.41, p = .16). This was 454 confirmed via the region of significance values: the relationship 455 between depressive symptoms and PTB was significant at values of 456 NEM values greater than -0.13 which corresponds to 43.2% of the 457 sample. An illustration of the simple slopes for relationships between 458

t3.1 Table 3

Moderator models for waking level and peak to bed slopes (N = 735).

t3.3		Waking levels of	cortisol	Cortisol awakeni response	ng	Peak to bed slop	es
t3.4		Coefficient	SE	Coefficient	SE	Coefficient	SE
t3.5	Level 1 intercept, ITO						
t3.6	Average level, β_{00}	.037	.036	.009	.034	013	.036
Q1 t3.7	Depressive symptoms, β_{01}	.066	.041	019	.034	076 ^{*,**}	.037
t3.8	Negative emotionality, β_{02}	.010	.041	.031	.034	021	.038
t3.9	Depressive symptoms negative emotionality, β_{03}	062^{*}	.031	014	.024	021*	.010

Note: Analyses covaried for the effects of hours of sleep and wake time at Level 1.

t3.10 * p<.05.

t3.12 ** p<.01.

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t2.12 * p<.05.

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Fig. 2. Simple slope plots for a) wake values of cortisol estimates by levels of depressive symptoms at low, average and high levels of negative emotionality and b) peak to bed cortisol diurnal slope estimates by levels of depressive symptoms at low, average and high levels of negative emotionality. All slope estimates have been adjusted for batch, nicotine, hours of sleep and wake time.

depressive symptoms with WAKE and PTB at low, average, and highlevels of NEM can be seen in Figs. 2a and b, respectively.

461 Discussion

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To our knowledge this is the first epidemiological study to 462 463 examine relationships between NEM, depressive symptoms and measures of diurnal cortisol in a sample of men studied in their 464 naturalistic settings. In this large community-dwelling sample of 465 middle-aged men, significant correlations were found between both 466 NEM and depressive symptoms with PTB cortisol slopes and between 467 468 depressive symptoms and wake values of cortisol. The CAR was not associated with any of the predictors. Mediation analyses revealed 469 that the relationship between NEM and PTB slope was mediated 470 through depressive symptoms. Thus, depressive symptoms had a 471 direct effect on cortisol, while the effects of NEM on cortisol were 472473 indirect. Furthermore, NEM significantly moderated the associations 474 between depressive symptoms and PTB slopes and waking values. Specifically, individuals with high levels of depressive symptoms and 475average or above average levels of NEM had the flattest PTB slopes, 476while individuals with high levels of depressive symptoms and low 477478 levels of NEM had the highest waking values.

To our knowledge no studies have looked specifically at the 479associations between NEM, depressive symptoms and diurnal 480 measures of cortisol concurrently. In some studies investigating the 481 role of neuroticism, HPA axis activity has been primarily based on 482laboratory pharmacological or psychological stress-response para-483digms (McCleery and Goodwin, 2001; Oswald et al., 2006; Zobel et al., 484 2004) or single day cortisol measures (Gerritsen et al., 2009; Portella 485et al., 2005). No prior study has sought to test whether depressive 486 487 symptoms played a significant meditational role. Previous findings looking at the direct effects between neuroticism or NEM and diurnal 488 cortisol rhythms from naturalistic settings have found *direct* associ-489 ations between neuroticism and greater cortisol in adults (Nater et al., 490 2010; Polk et al., 2005;) and flatter cortisol slopes and neuroticism in 491 adolescents (Hauner et al., 2008). Our findings differ in that we found 492 an *indirect* association between NEM and flatter cortisol slopes 493 through depressive symptoms suggesting that depressive symptoms 494 is a significant mediator of the relationship between NEM and cortisol. 495

In addition, we found two significant moderator effects of NEM on 496 the depressive symptom-cortisol associations. First, as hypothesized, 497 our findings indicated that the association between PTB slopes and 498 depressive symptoms was stronger in subjects scoring average or high 499 on NEM. Moreover, while there were no differences between subjects 500 in PTB slopes based on their scores of NEM at low levels of depressive 501 symptoms when depressive symptoms were high, men with higher 502 NEM scores had significantly flatter PTB slopes than men with lower 503 NEM scores. These results may suggest that NEM and depressive 504 symptomatology both contribute to high levels of allostatic load 505 within individuals (McEwen, 2003). That is, the repeated stressors 506 associated with having high levels of NEM and high levels of 507 depressive symptoms interact over time resulting in a continuous 508 daily activation of the HPA-axis that can become "biologically 509 embedded" (e.g., Bhagwagar and Cowen, 2008). Thus, there is a 510 "flattening" of the diurnal cortisol curve in those who experience high 511 levels of both NEM and depressive symptoms. The flattening of the 512 diurnal cortisol curve over the course of the day has implications for 513 both physical and mental health over the life course. Prior research 514 has shown that flatter diurnal curves are risk factors for cardiovas- 515 cular disease and diabetes (Rosmond and Bjorntorp, 2000), cognitive 516 decline (Beluche et al., 2010) and decreased life expectancy among 517 cancer patients (Sephton et al., 2000). 518

An unexpected finding was that depressive symptoms were only 519 associated with waking values of cortisol at low levels of NEM. An 520 intriguing interpretation of this result is that disruptions in waking 521 levels of cortisol are "normative" adaptations to stress among 522 individuals without an underlying liability to distress (i.e. individuals 523 with low levels of NEM), as these individuals show predictable 524 physiological changes associated with high depressive symptoms. In 525 contrast, individuals who have an underlying liability to distress (i.e. 526 individuals with high levels of NEM) may not show the short term 527 physiological changes because of chronic activation of the HPA axis or 528 allostatic load (McEwen, 2003). However, given that this is an 529 unexpected finding, coupled with the fact that there were no main 530 effects of NEM or depressive symptoms on waking levels of cortisol, 531 the interaction between NEM and depressive symptoms for wake 532 values of cortisol should be replicated in other samples. 533

Limitations and future directions

There are several limitations to the current research. First, the 535 magnitude of the effects found in this study between our primary 536 predictors and cortisol were small. It is not uncommon to find effect 537 sizes of this magnitude when studying biomarkers like cortisol within 538 large community samples. For example, a recent publication from the 539 Whitehall Study (N=2968 men; Kumari et al., 2010) reported a 540 difference in diurnal cortisol slopes based on level of depressive 541 symptoms, such that men who scored higher than 16 on the CES-D 542 had flatter slopes than men who had lower scores on the CES-D, 543 similar to patterns in the present study. However, the absolute 544 difference between groups in diurnal cortisol slopes for the Whitehall 545 Study was quite small (>16 on CES-D = -.129; <16 on CES-D = 546-.127). Indeed, a recent meta-analysis found that the associations 547 among depression and cortisol were smallest in studies that used 548 salivary measures of cortisol which was the methodology used in both 549 the Whitehall Study and the present study (Stetler and Miller, 2011). 550

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L.D. Doane et al. / Hormones and Behavior xxx (2011) xxx-xxx Conclusions

It is worth noting that cortisol dysregulation is only a small part of 551 552a complex, biological system whereby stress and depression "get under the skin" to impact health and well-being. While any individual 553554effect on biomarkers is likely to be small in absolute terms, together small perturbations in the system can lead to clinically relevant 555dysfunction over time. Another explanation for the relatively small 556effect sizes is that short-term indicators such as depressive symptoms 557over the past week may be insufficient to fully capture the complete 558559range of environmental and psychosocial factors that could account for individual differences in HPA axis activity. Significant variations in 560 561HPA axis activity are likely best explained by multiplicative indicators of stress and depression over time that may, in fact, contribute to 562563clinically meaningful dysregulation. Nevertheless, the fact that 564significant differences in diurnal patterns of cortisol across the day can be detected in a community sample of men is important. In 565 particular, our finding that personality characteristics moderate the 566 effects of depressive symptoms on cortisol regulation provides insight 567 into potential sources of individual differences in the dynamic 568relationship between depression and cortisol, and may help us to 569understand why stress and depression have more severe conse-570quences for some individuals than others. 571

A second limitation is that our study population consists solely of 572573men. Given that women have a higher likelihood of experiencing 574 depression and depressive symptoms (Kessler, 2006; for review see Hyde et al., 2008) our results regarding the mediating and moderating 575pathways relating to cortisol dysregulation may not generalize to 576women. Nevertheless, depression is less well-studied in men, and our 577578study is based on a large national community dwelling sample of men, rather than relying on small clinical or selected samples. 579

Finally, we are limited by the cross-sectional nature of the data used 580in this study. This may have particular implications for our mediation 581582analyses, as our underlying assumption was that depressive symptoms 583mediated the effects of NEM on cortisol; however, it is possible that the 584direction of causality could be reversed. Our assumption regarding the causal relationship between NEM and depression was grounded 585primarily by the fact that our measure of NEM was based on questions 586 regarding how the individual usually feels, whereas our measure of 587 588 depression was based symptoms during the previous week. In addition, there is evidence from other samples that negative emotionality and 589related characteristics such as neuroticism have substantial stability 590over time (e.g. Costa et al., 2000; Johnson et al., 2005), supporting our 591592assumption that NEM is an enduring personality characteristic. Thus, we assumed that NEM reflects a more trait-like measure, while depressive 593symptoms scores are likely to capture variations in the shorter term. Of 594course, the true nature and direction of effects within the biological 595596 pathways underlying these associations can only be understood 597through the analysis of prospective data.

We also note that there was substantial phenotypic overlap 598(r=0.58) between NEM and depressive symptoms in the present 599study. Consistent with the literature on genetic overlap between 600 neuroticism and depression, previous results from our sample (Franz 601 602 et al., in press) indicate almost complete genetic overlap between the 603 subscales of NEM and depressive symptoms, although the phenotypic correlations were also due, in part, to common nonshared environ-604 mental factors. As such, the observed moderation and mediation 605 606 effects in the present study may, in part, be a function of perturbations 607 in depressive symptomatology due to relatively short-term (e.g., week-to-week) fluctuations in environmental factors, or they may be 608 due to disruptions in underlying systems that are partially controlled 609 by genetic factors. If genetic factors do, in fact, contribute to the 610 comorbidities between NEM and depressive symptoms, future 611 612 research using genetically informative analyses should strive to understand how the stability of negative emotionality relates to 613 changes in both depressed mood and diurnal cortisol rhythms, as well 614 as understand further the interplay of both genetic and environmental 615 616 contributions to these associations.

To our knowledge this is the first epidemiological study to 618 demonstrate the dynamic associations between negative emotional- 619 ity, depressive symptoms and diurnal cortisol rhythms collected from 620 men in their naturalistic settings. We believe that our findings not 621 only extend prior work by beginning to deconstruct the pathways 622 through which NEM and cortisol are associated, but that they also may 623 explain some of the inconsistencies of past literature. If past research 624 has not accounted for levels of depressive symptoms and only looked 625 for the direct associations between personality traits and cortisol, they 626 may have missed significant pathways through depressive symptom- 627 atology. Results of this study should encourage future research in 628 population based samples of both men and women to understand if 629 there are varying gendered pathways through which both personality 630 characteristics and short term depressive symptomatology influence 631 alterations in HPA-axis regulation. 632

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References

Aiken, L.S., West, S.G., 1991. Multiple Regression: Testing and Interpreting Interactions. 670 Sage, Newbury Park, CA. 671

- Beluche, I., Carrière, I., Ritchie, K., Ancelin, M.L., 2010. A prospective study of diurnal 672 cortisol and cognitive function in community-dwelling elderly people. Psychol. 673 Med. 40. 1039-1049 674
- Bhagwagar, Z., Cowen, P.J., 2008. 'It's not over when it's over': persistent neurobiolog-675 ical abnormalities in recovered depressed patients. Psychol. Med. 38, 307-313. 676

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- 684 685
- 686
- 687
- 688 689

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after domestic travel. Health Psychol. 29, 117-123. 690 Fanous, A.H., Neale, M.C., Aggen, S.H., Kendler, K.S., 2007. A longitudinal study of 691 692 personality and major depression in a population-based sample of male twins. 693 Psychol. Med. 37, 1163-1172.

syndrome X, Brain Behay, Immun, 17, 350-364.

to adulthood, I. Pers, Soc. Psychol. 78, 158–172.

694 Franz, C.E., York, T.P., Eaves, L.J., Mendoza, S.P., Hauger, R., Hellhammer, D., Jacobson, 695 K.C., Levine, S., Lupien, S., Lyons, M.J., Prom-Wormley, E., Xian, H., Kremen, W.S., 696 2010. Genetic and environmental influences on cortisol regulation across days and 697 contexts in middle-aged men. Behav. Genet. 40, 467-479.

Black, P.H., 2003. The inflammatory response is an integral part of the stress response:

Caspi, A., 2000. The child is father of the man: personality continuities from childhood

Caspi, A., Begg, D., Dickson, N., Harrington, H., Langley, J., Moffitt, T.E., Silva, P.A., 1997.

from a longitudinal study. J. Pers. Soc. Psychol. 73, 1052-1063.

Personality differences predict health-risk behaviors in young adulthood: evidence

implications for atherosclerosis, insulin resistance, type II diabetes and metabolic

- 698 Franz, C. E., York, T. P., Eaves, L. J., Prom-Wormley, E., Jacobson, K.C., Lyons, M. J., Xian, H., 699 Panizzon, M.S., Jimenez, E., & Kremen, W.S. in press. Adult romantic attachment, 700 negative emotionality, and depressive symptoms in middle aged men: a multivariate genetic analysis. Behav. Genet. e-pub available December 30, 2010.
- 702 Friedman, H.S., 2000. Long-term relations of personality and health: dynamisms, 703 mechanisms, tropisms. J. Pers. 68, 1089-1107.
- 704 Friedman, H.S., Kern, M.L., Reynolds, C.A., 2010. Personality and health, subjective well-705being and longevity in adults age. J. Pers. 78, 179-216.
- Gerritsen, L., Geerlings, M., Bremmer, M., Beekman, A., Deeg, D., Penninx, B., Comijs, H., 707 2009. Personality characteristics and hypothalamic-pituitary-adrenal axis regula-708 tion in older persons. Am. J. Geriatr. Psychiatry 17, 1077-1084.
- 709 Hauner, K., Adam, E.K., Mineka, S., Doane, L.D., DeSantis, A., Zinbarg, R., Craske, M., 710Griffith, J., 2008. Neuroticism and introversion are associated with salivary cortisol 711 patterns in adolescents. Psychoneuroendocrinology 33, 1344-1356.
- 712 Hellhammer, D.H., Wüst, S., Kudielka, B.M., 2009. Salivary cortisol as a biomarker in 713stress research. Psychoneuroendocrinology 34, 163-171
- 714 Hu, L., Bentler, P.M., 1999. Cutoff criteria for fit indexes in covariance structure analysis: 715conventional criteria versus new alternatives. Struct. Equ. Modeling 6, 1-55.
- 716Hyde, J.S., Mezulis, A.H., Abramson, L.R., 2008. The ABCs of depression: integrating 717affective, biological, and cognitive models to explain the emergence of the gender 718 difference in depression. Psychol. Rev. 115, 291-313.
- 719 Johnson, W., McGue, M., Krueger, R.F., 2005. Personality stability in late adulthood: a behavioral genetic analysis. J. Pers. 73, 523-551. 720
- Kahn, A.A., Jacobson, K.C., Gardner, C.O., Prescott, C.A., Kendler, K.S., 2005. Personality 721 722 and comorbidity of common psychiatric disorders. Br. J. Psychiatry 186, 190-196. 723 Kendler, K.S., Gatz, M., Gardner, C.O., Pederse, N.L., 2006. Personality and major 724 depression. Arch. Gen. Psychiatry 63, 1113-1120.
- Kendler, K.S., Neale, M.C., Kessler, R.C., Heath, A.C., Eaves, L.J., 1993. A longitudinal twin 725 726 study of personality and major depression in women. Arch. Gen. Psychiatry 50, 727 853-862
- Kessler, R.C., 2006. The epidemiology of depression among women. In: Keyes, C.L.M., 728729 Goodman, S.H. (Eds.), Women and Depression. Cambridge University Press, New 730 York, pp. 22-37.
- Kirschbaum, C., Bartussek, D., Strasburger, C.J., 1992a. Cortisol responses to psychological 731 732 stress and correlations with personality traits. Pers. Individ. Differ. 13, 1353-1357. 733 Kirschbaum, C., Hellhammer, D., 1989. Salivary cortisol in psychobiological research: an
- 734 overview. Neuropsychobiology 22, 150-169.
- 735Kirschbaum, C., Wust, S., Strasburger, C., 1992b. "Normal" cigarette smoking increases 736 free cortisol in habitual smokers. Life Sci. 50, 435-442.
- 737 Kern, M.L., Friedman, H.S., 2011. Personality and pathways of influence on physical 738 health. Soc. Pers. Compass 5, 76-87.
- Knight, J.M., Avery, E.F., Janssen, I., Powell, L.H., 2010. Cortisol and depressive symptoms 739740 in a population-based cohort of midlife women. Psychosom. Med. 72, 855-861.
- 741 Kremen, W., Thomspon-Brenner, H., Leung, Y., Grant, M., Franz, C., Eisen, S., Jacobson, K., 742 Boake, C., Lyons, M., 2006. Genes, environment and time: the Vietnam Era Twin 743 Study of Aging (VETSA). Twin Res. Hum. Genet. 9, 1009-1022.
- 744 Krueger, R.F., Caspi, A., Moffitt, T.E., 2000. Epidemiological personology: the unifying 745 role of personality in population-based research on problem behaviors. J. Pers. 68. 746 967-998
- 747 Kumari, M., Badrick, E., Chandola, T., Adler, N.E., Epel, E., Seeman, T., Kirschbaum, C., Marmot, M., 2010. Measures of social position and cortisol secretion in an aging 748 749 population: findings from the Whitehall II study. Psychosom. Med. 72, 27-34.
- McCleery, J.M., Goodwin, G.M., 2001. High and low neuroticism predict different 750751 cortisol responses to the combined Dexamethasone-CRH test. Biol. Psychiatry 49, 410-415. 752
- McEwen, B.S., 2003. Mood disorders and allostatic load. Biol. Psychiatry 54, 200-207. 753 754Miller, G.E., Chen, E., Zhou, E., 2007. If it goes up, must it come down? Chronic stress and the
- 755 hypothalamic-pituitary-adrenocortical axis in humans. Psychol. Bull. 133, 25-45. Muthén, L.K., Muthén, B.O., 1998-2004. Mplus. Statistical Analyses with Latent 756 757 Variables, User's Guide, Muthén & Muthén, Los Angeles, CA.
- Nater, U.M., Hoppmann, C., Klumb, P.L., 2010, Neuroticism and conscientiousness are 758759associated with cortisol diurnal profiles in adults-role of positive and negative Q17/60 affect. Psychoneuroendocrinology. 845

- National Center for Disease Statistics, Health, United States, 2003, Hvattsville, MD: U.S. 761 Department of Health and Human Services. Centers for Disease Control and 762 Prevention. 763764
- National Health and Nutrition Examination Survey (NHANES III), 2007. Trends in Health and Aging. Accessed April 20. Nicolson, N.A., 2008, Measurement of cortisol. In: Luecken, L.I., Gallo, L.C. (Eds.). 765
- 766 Handbook of Physiological Research Methods in Health Psychology. Sage 767 Publications, pp. 37-74. 768
- Oswald, L.M., Zandi, P., Nestadt, G., Potash, J.B., Kalaydjan, A.E., Wand, G.S., 2006. 769 Relationship between cortisol responses to stress and personality. Neuropsycho-770 pharmacology 31, 1583-1591. 771
- Patrick, C.J., Curtin, J.J., Tellegen, A., 2002. Development and validation of a brief 772 form of the multidimensional personality questionnaire. Psychol. Assess. 14, 773 50 - 163774
- Polk, D.E., Cohen, S., Dovle, W.I., Skoner, D.P., Kirschbaum, C., 2005. State and trait affect 775 as predictors of salivary cortisol in healthy adults. Psychoneuroendocrinology 30, 776 261-272
- Portella, M.J., Harmer, C.J., Flint, J., Cowen, P., Goodwin, G.M., 2005. Enhanced early 778 morning salivary cortisol in neuroticism. Am. J. Psychiatry 162, 807-809. 779
- Preacher, K.J., Curran, P.J., Bauer, D.J., 2006. Computational tools for probing interaction 780 effects in multiple linear regression, multilevel modeling, and latent curve analysis. 781 J. Educ. Behav. Stat. 31, 437-448. 782
- Pruessner, J.C., Wolf, O.T., Hellhammer, D.H., Buske-Kirschbaum, A., von Auer, K., Jobst, 783 S., Kaspers, F., Kirschbaum, C., 1997. Free cortisol levels after awakening: a reliable 784 biological marker for the assessment of adrenocortical activity. Life Sci. 61, 785 2539-2549. 786
- Pruessner, M., Hellhammer, D.H., Pruessner, J.C., Lupien, S.J., 2003. Self-reported 787 depressive symptoms and stress levels in healthy young men: associations with the 788 cortisol response to awakening. Psychosom. Med. 65, 92-99. 789
- Radloff, L.S., 1977. The CES-D scale: a self-report depression scale for research in the 790general population. Appl. Psychol. Meas. 3, 385-401. 701
- Raudenbush, S.W., Bryk, A.S., 2002. Hierarchical Linear Models: Application and Data 792Analysis Methods. Sage Publications, Thousand Oaks, CA. 793
- Raudenbush, S.W., Bryk, A.S., Congdon, R., 2004. Computer Software. Scientific Software 794 International, Inc, Lincolnwood, IL. 795
- Rosmond, R., Bjorntorp, P., 2000. The hypothalamic-pituitary-adrenal axis activity as a 796 predictor of cardiovascular disease, type 2 diabetes, and stroke. J. Intern. Med. 247, 797 188 - 197798
- Schlotz, W., Schulz, P., Hellhammer, J., Stone, A.A., Hellhammer, D.H., 2006. Trait anxiety 799 moderates the impact of performance pressure on salivary cortisol in everyday life. 800 Psychoneuroendocrinology 31, 459-472. 801
- Schommer, N.C., Kudielka, B.M., Hellhammer, D.H., Kirschbaum, C., 1999. No evidence 802 for a close relationship between personality traits and circadian cortisol rhythm or 803 a single cortisol stress response. Psychol. Rep. 84, 840-842. 804
- Sephton, S., Sapolsky, R., Kraemer, H., Spiegel, D., 2000. Diurnal cortisol rhythm as a 805 predictor of breast cancer survival. J. Natl. Cancer Inst. 92, 994-1000. 806
- Singer, J.D., Willett, J.B., 2003. Applied Longitudinal Data Analysis: Modeling Change 807 and Event Occurrence. Oxford University Press, Oxford. 808
- Sjögren, E., Leanderson, P., Kristenson, M., 2006. Diurnal saliva cortisol levels and 809 relations to psychosocial factors in a population sample of middle-aged Swedish 810 men and women. Int. J. Behav. Med. 13, 193-200. 811
- Spiegelhalter, D., Thomas, A., Best, N., Lunn, D., 2004. WinBUGS User Manual Version 812 2.0. Imperial College and Medical Research Council, London. 813
- Smith, T.W., Gallo, L.C., 2001. Personality traits as risk factors for mental illness. In: 814 Baum, A., Revenson, T.A., Singer, J. (Eds.), Handbook of Health Psychology, pp. 815 139-172. 816

Stetler, C., Miller, G.E., 2011. Depression and hypothalamic-pituitary-adrenal activa- 817 tion: a quantitative summary of four decades of research. Psychosom. Med. 73, 818 114-126. 819

- Sutin, A.R., Terracciano, A., Deiana, B., Naitza, S., Ferrucci, L., Uda, M., Schlessinger, D., 820 Costa, P.T., 2010. High neuroticism and low conscientiousness are associated with 821 interleukin-6. Psych. Med. 40, 1485-1493. 822
- Tellegen, A., 1985. Structures of mood and personality and their relevance to assessing 823 anxiety, with an emphasis on self-report. In: Tuma, A.H., Maser, J.D. (Eds.), Anxiety 824 and the Anxiety Disorders. Erlbaum, Hillsdale, NJ, pp. 681-706. 825
- Tsuang, M.T., Bar, J.L., Harley, R.M., Lyons, M.J., 2001. The Harvard twin study of 826 substance abuse: what we have learned. Harv. Rev. Psychiatry 9, 267-279. 827
- Van den Bergh, B.R., Van Calster, B., Pinna Puissant, S., Van Huffel, S., 2008. Self-reported 828 symptoms of depressed mood, trait anxiety and aggressive behavior in post- 829 pubertal adolescents: associations with diurnal cortisol profiles. Hormones Behav. 830 54. 253–257. 831
- van Santen, A., Vreeburg, S., Willem Vander Does, A.J., Spinhoven, P., Zitman, F.G., 832 Penninx, B.W.J.H., 2010. Psychological traits and the cortisol awakening 833 response: results from the Netherlands Study of Depression and Anxiety. 834 Psychoneuroendocrinology.
- 835 Wetherell, M.A., Crown, A.L., Lightman, S.L., Miles, J.N., Kaye, J., Vedhara, K., 2006. The 836 four-dimensional stress test: psychological, sympathetic-adrenal-medullary, para- 837 sympathetic, and hypothalamic-pituitary-adrenal responses following inhalation 838 of 35% CO2. Psychoneuroendocrinology 31, 736-747. 839
- Zobel, A., Barkow, K., Schulze-Rauschenbach, S., Von Widdern, O., Metter, M., Pfeiffer, U., 840 Schnell, S., Wagner, M., Maier, W., 2004. High neuroticism and depressive 841 temperament are associated with dysfunctional regulation of the hypothalamic- 842 pituitary-adrenocortical system in healthy volunteers. Acta Psychiatr. Scand. 109, 843 392-399. 844

Costa, P.T., Herbst, J.H., McCrae, R.R., Siegler, I.C., 2000. Personality at midlife: stability, intrinsic maturation, and response to life events. Assessment 7, 365-378. Doane, L.D., Kremen, W.S., Eaves, L.J., Eisen, S.A., Hauger, R., Hellhammer, D., Levine, S., Lupien, S., Lvons, M.I., Mendoza, S., Prom-Wormley, E., Xian, H., York, T.P., Franz, C.E., Jacobson, K.C., 2010. Associations between jet lag and cortisol diurnal rhythms

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