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SUMMARY

Insomnia symptoms are highly prevalent in depressed older adults. This study investigates the association between hypothalamic–pituitary–adrenal (HPA) axis activity and symptoms of insomnia, respectively, sleep duration among 294 depressed and 123 non-depressed older adults of the Netherlands Study of Depression in Older people (NESDO) study. Insomnia symptoms were defined as clinically relevant when having a score ≥ 10 points on the Women's Health Initiative Insomnia Rating Scale (WHIIRS). Sleep duration was categorized in short (≤ 6 h per night), normal (7–8 h per night) and long (≥ 9 h per night) duration. Salivary cortisol levels were used to assess the following cortisol parameters for HPA axis activity: area under the curve with respect to the increase (AUCi) and to the ground (AUCg), diurnal slope, evening cortisol level and dexamethasone suppression ratio. Clinically relevant insomnia symptoms were present in 46% of the participants. Thirty-two per cent of the participants were short sleepers, whereas 16% were long sleepers. However, univariate analyses showed no differences in any of the HPA axis parameters between people with and without insomnia symptoms or between the three groups with different sleep duration. In addition, no significant interaction was found between a diagnosis of depression or the severity of depressive symptoms and any of the cortisol parameters in relation to insomnia symptoms or sleep duration.

INTRODUCTION

Symptoms of insomnia are common in late life, with prevalences in non-institutionalized older adults ranging from 20 to almost 50% (Ohayon, 2002; Ohayon and Reynolds, 2009). Disturbances in sleep have a major impact on quality of life and increase the risk of falls (Stone *et al.*, 2014), substance use and physical and mental health problems, such as depression (Foley *et al.*, 2004). It has been suggested that sleep disturbances might be associated with dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis (Buckley and Schatzberg, 2005). A cascade of processes in the HPA axis results in the excretion of cortisol in a diurnal rhythm, with a post-awakening increase (Elder *et al.*, 2014; Pruessner *et al.*, 1997) followed by a decline throughout the day, reaching the lowest point during the first half of the nightly sleep period and rising again until the morning (Weitzman *et al.*, 1971). To measure the negative feedback loop of the HPA axis, the dexamethasone suppression test (DST) was developed (APA, 1987) initially to diagnose Cushing's disease. The DST has also been proposed as a biomarker of psychiatric diseases such as depression (American Psychiatric Association, 1987). Dexamethasone suppresses the nocturnal production of adrenocorticotrophic hormone (ACTH), resulting in low cortisol levels the next morning (Buckley and Schatzberg, 2005). However, research

outcomes on the association between cortisol levels and sleep duration and insomnia symptoms are not consistent. In a population-based study (mean age 61 ± 6 years), self-reported short sleep duration and symptoms of insomnia were associated with a flatter diurnal slope in cortisol secretion due to raised evening cortisol (Kumari *et al.*, 2009), and short sleep duration was associated with an increased cortisol awakening response. Another study found no association between awakening cortisol and sleep duration or quality in middle-aged adults (Zhang *et al.*, 2011). A recent population-based study in middle-aged adults found an association between poor subjective sleep quality and enhanced negative feedback of the HPA axis after the intake of 0.25 mg dexamethasone the night before (Luik *et al.*, 2015).

Insomnia symptoms are reported in 40–90% of patients with depression (Tsuno *et al.*, 2005). Previous studies in depressed older adults showed that depression is associated with both increased and decreased basal cortisol levels (Bremmer *et al.*, 2007; Penninx *et al.*, 2007), higher evening cortisol in a normal circadian cortisol pattern (Balardin *et al.*, 2011) and a higher awakening response, and a flatter morning curve (Rhebergen *et al.*, 2015). It has been suggested that depression results in hyperactivity of the HPA axis, which inhibits sleep and increases awakenings (Arborelius *et al.*, 1999). Conversely, fragmented sleep might exacerbate HPA axis dysfunction which, in turn, may worsen sleep (Buckley and Schatzberg, 2005).

Previous studies have shown that changes in some cortisol parameters were related to age (Veldhuis *et al.*, 2013), as well as the occurrence of symptoms of insomnia (Ohayon, 2002; Ohayon and Reynolds, 2009). However, it is not known whether the influence of HPA axis activity on sleep also changes with age. Therefore, the present study measured the association between HPA axis activity and insomnia symptoms in a large cohort of both depressed and non-depressed participants of the Netherlands Study of Depression in Older persons (NESDO). We hypothesized that insomnia symptoms and shorter sleep duration are associated with an increased cortisol awakening response and evening cortisol levels, and that these relationships are stronger in depressed older than in non-depressed older adults.

METHODS

NESDO is a prospective cohort study including 378 older adults (≥ 60 years) with a diagnosis of depression according to the DSM-IV criteria in the past 6 months, and 132 non-depressed older adults without a lifetime diagnosis of depression. All were recruited between 2007 and 2010 from university medical centres, mental health-care institutes and general practitioners (Comijs *et al.*, 2011). Exclusion criteria were a primary clinical diagnosis of dementia, psychotic or bipolar disorder, a Mini-Mental State Examination (MMSE) score < 18 points and insufficient command of the Dutch language (Comijs *et al.*, 2011). The study protocol of NESDO was approved by the Ethical Review Board of the VU University Medical Centre and by the local ethical review board of each participating centre. As data on sleep disturbances covered a period of 4 weeks, we included individuals with a diagnosis of major depression, minor depression or dysthymia in the past 4 weeks, resulting in 307 with depression and 132 non-depressed people. Twenty-two individuals were excluded because of missing Women's Health Initiative Insomnia Rating Scale (WHIIRS) data and another 77 were excluded because of missing cortisol data [diurnal slope could be computed for 340 (82%) individuals]. Compared with excluded participants, those included had more years of education [11.2 years standard deviation (SD) ± 3.7 versus 10.0 years (SD ± 3.2); $P = 0.003$; F-value 8.9; df = 1], were more physically active [median 1872 interquartile range (IQR): 794–3903 versus 930 (240–3708); $P = 0.01$], had fewer symptoms of anxiety [13.4 (SD ± 11.0) versus 17.7 (SD ± 14.8); $P = 0.004$; F-value 8.51; df = 1], less pain [47.0 (SD ± 20.4) versus 53.0 (SD ± 23.1); $P = 0.018$; F-value 5.62; df = 1] and fewer depressive symptoms [modified Inventory of Depressive Symptoms (IDS): median 20 (IQR: 7–31) versus median 24.0 (IQR: 9–36); $P = 0.032$]. No significant differences were found in age, smoking, use of alcohol or psychotrophic medication, exposure to daylight, body mass index (BMI), WHIIRS scores, MMSE scores and number of chronic diseases.

Assessment of sleep characteristics

Sleep disturbances were assessed with the self-report WHIIRS. This scale has a test–retest reliability of 0.96 and an alpha coefficient for internal consistency of 0.78 (Levine *et al.*, 2003a, 2005). The WHIIRS assesses sleep-related complaints during the past 4 weeks and consists of five items: trouble falling asleep, waking up several times a night, waking up earlier than planned to, trouble getting back to sleep after waking up too early and sleep quality, with higher scores (max. 20 points) indicating more severe disturbances (Levine *et al.*, 2003a). Presence of clinically relevant insomnia symptoms was defined by WHIIRS ≥ 10 points, which is considered indicative for clinically relevant sleep disturbances (Levine *et al.*, 2003b). We also asked about mean sleep duration per night in the past 4 weeks: answers were categorized in short (≤ 6 h), normal (> 6 and < 9 h) or long duration (≥ 9 h).

Assessment of cortisol levels

HPA axis activity was assessed by cortisol levels in saliva using Salivettes (Sarstedt Co., Nümbrecht, Germany), which were collected by the participants on two consecutive days. Participants were not allowed to eat, drink tea/coffee or to brush their teeth within 15 min before sampling, and no dental work in the 24 h prior to sampling was allowed. Six saliva samples were taken: at the time of awakening (T1),

30 min post-awakening (T2), 45 min post-awakening (T3), 60 min post-awakening (T4) and at 22:00 hours (T5). Dexamethasone suppression was measured the next morning at awakening (T6) after 0.5 mg dexamethasone ingestion the night before (directly after T5). Participants were asked to return the samples by post. Details on the laboratory analysis have been reported previously (Rhebergen *et al.*, 2015). Five cortisol parameters were used: (1) the area under the curve with respect to the increase (AUCi), which is a measure of the dynamics of the cortisol awakening response (CAR) (calculated from T1 to T4); (2) the area under the curve with respect to the ground (AUCg), reflecting the total cortisol secretion in the first hour after awakening (calculated from T1 to T4). Both AUCi and AUCg were calculated by using Pruessner's formulae (Pruessner *et al.*, 2003); (3) the diurnal slope, which is the decline of cortisol during the day (T1 minus T5); (4) the evening cortisol level (T5); and (5) the cortisol suppression ratio, which is calculated by dividing the cortisol level at awakening (T1) by the cortisol level at awakening the day after ingestion of 0.5 mg dexamethasone at 22:00 hours on the day before (T6). Cortisol assessments that exceeded the time protocol by more than 5 min (all samples) or when cortisol levels were more than two SD above the mean (samples T1–T4), the cortisol parameters were excluded.

Assessment of sociodemographic, lifestyle and clinical characteristics

Based on previous research, various possible confounders of the relation between cortisol parameters and sleep were examined and grouped into sociodemographic (Belvederi Murri *et al.*, 2014; Ohayon, 2002), lifestyle (Gardner *et al.*, 2013; Ohayon, 2002), clinical (Belvederi Murri *et al.*, 2014; Ohayon, 2002) and sampling factors (Vreeburg *et al.*, 2009). A standard interview assessed sociodemographic characteristics. The Composite International Diagnostic Interview (CIDI) was used to assess the diagnosis of depression according to DSM-IV criteria (Wittchen, 1994). The IDS self-report (IDS-SR) was used to measure the severity of depressive symptoms (range: 0–84 points) (Rush *et al.*, 1996) during the past week. Four questions of the IDS that refer to sleeping problems were excluded, resulting in a 'modified IDS' with scores ranging from 0 to 72 points. The Beck Anxiety Inventory (BAI) was used to measure the severity of anxiety in the past week (range: 0–63 points) (Beck *et al.*, 1988). The presence and number of chronic diseases were assessed using a self-report questionnaire. The Graded Chronic Pain Scale (GCPS) was used to measure the intensity of pain during the past 6 months (Von Korff *et al.*, 1992). Currently used medications were classified according to the Anatomical Therapeutic Chemical classification system (ATC/DDD index). Physical activity was measured using the International Physical Activity Questionnaire (IPAQ) in metabolic equivalent (MET)-min per week (Craig *et al.*, 2003). The use of alcohol was assessed with the Alcohol Use Disorders Identification Test (AUDIT) (Babor *et al.*, 2001), categorized into abstainers (0 points), moderate (1–4 points) or at-risk drinkers ($\geq$ 5 points). Current smoking behaviour was assessed with standardized questions (none, or current smoker).

As more daylight and early awakenings are associated with different cortisol parameters (Vreeburg *et al.*, 2009), sampling factors such as time of awakening and the season on the first sampling day, categorized by months with less daylight (October–February) and more daylight (March–September), were examined.

Statistical analysis

Data were analysed using SPSS version 22.0 and are presented as numbers (%), means ($\pm$ SD) and medians (IQR]) where appropriate. Total WHIIRS scores were dichotomized [WHIIRS $<$ 10 points and WHIIRS $\geq$ 10 points, indicating the presence of clinically relevant insomnia symptoms (no/yes)]. Cortisol parameters and the sociodemographic, lifestyle, clinical and sampling characteristics of older adults with and without clinically relevant insomnia symptoms and of older adults with different sleep duration were compared, using the one-way analysis of variance (ANOVA), Mann–Whitney or Kruskal–Wallis tests (in cases of non-normal distribution) for continuous data, and chi-square tests for categorical data (when count $<$ 5 Fisher's exact tests). Sensitivity analyses with tertiles of WHIIRS scores (0–6, 7–12 and $\geq$ 13 points) and with hours of sleep per night ($\leq$ 5 h, 6–8 h and $\geq$ 9 h) were also performed.

To assess possible multicollinearity, correlation coefficients were calculated between the covariates. As all correlation coefficients were below 0.80, all variables were used for further analysis. We performed logistic regression analysis with insomnia symptoms as outcome and multinominal regression analyses with sleep duration as the outcome. Independent variables were the cortisol parameters that showed a *P*-value below 0.20 in the descriptive analyses. Multivariate analyses were adjusted for all relevant covariates that showed a *P*-value below 0.10 in the univariate analyses. For all significant covariates, Cohen's *d* and Phi coefficients, and when necessary Cramer's V, were calculated in order to assess the effect size. Effect sizes of 0.3 were considered moderate (0.21 for Cramer's V) and values greater than 0.5 a large effect size (0.35 for Cramer's V). For sleep duration, individuals with normal sleep duration (7–8 h per night) were used as a reference group. To study whether the associations between cortisol parameters and sleep disturbances and sleep duration are different for depressed and non-depressed older adults, interaction terms between cortisol parameters and depression diagnosis (cortisol $\times$ depression) and between cortisol parameters and depression severity (cortisol $\times$ modified IDS) were tested in fully adjusted regression models. In addition, analyses were repeated in stratified analyses.

RESULTS

Table 1 summarizes the characteristics of the total study sample (mean age 70.1 years; SD ± 7.2, 59% women). None of the included individuals used corticosteroids. The characteristics of the subgroups (with/without insomnia symptoms and the three groups of different sleep duration) are shown in the Supporting information, Tables S1 and S2.

Table 2 shows that there were no significant differences in any of the cortisol parameters between individuals with (WHIIRS ≥ 10) and without (WHIIRS < 10) clinically relevant insomnia symptoms. Sensitivity analyses comparing groups according to tertiles of WHIIRS scores showed similar results (data not shown). Logistic regression analyses to study the association between cortisol parameters and clinically relevant insomnia symptoms were not performed, as none of the cortisol parameters in the univariate analyses reached a *P*-value < 0.20.

Table 1 Sociodemographic, lifestyle and clinical characteristics of the study population (*n* = 340)

Characteristics	*Mean, median or* n
Sociodemographic	
Age, years, mean (± SD)	70.1 (7.2)
Gender, female, *n* (%)	202 (59.4)
Education years, mean (± SD)	11.2 (3.7)
Having a partner, *n* (%)	214 (62.9)
Lifestyle characteristics	
Physical activity, METS per week, median (IQR)	1872 (794–3903)
Use of alcohol	
Abstainers of alcohol, *n* (%)	106 (31.2)
Moderate use of alcohol, *n* (%)	155 (45.6)
At-risk drinkers, *n* (%)	27 (7.9)
Smoking, current, *n* (%)	67 (19.7)
Body mass index, mean (± SD)	26.4 (4.2)
Clinical characteristics	
WHIIRS score, median (IQR)	9.0 (4–14)
Number of chronic diseases, mean (± SD)	2.3 (1.6)
Pain intensity, mean (± SD)	47.0 (20.4)
Psychotrophic medication use*, *n* (%)	233 (68.5)
CIDI depression, *n* (%)	237 (69.7)
Modified IDS score, median (IQR)	20.0 (7–31)
MMSE score, median (IQR)	28.0 (27–29)
BAI score, mean (± SD)	13.4 (11.0)
Sampling characteristics	
Time of awakening, median (IQR)	7:27 (7:00–8:00)
More daylight, *n* (%)	220 (64.7)

METS: metabolic equivalents; WHIIRS: Women's Health Initiative Insomnia Rating Scale; CIDI: Composite International Diagnostic Interview; IDS: Inventory of Depressive Symptoms; MMSE: Mini Mental State Examination; BAI: Beck Anxiety Inventory; SD: standard deviation; IQR: interquartile range.
*Psychotrophic medication includes anaesthetic, analgesic, antiepileptic, anti-Parkinson, psycholeptic, psychoanaleptic and nervous system drugs.

No significant differences were found for any of the cortisol parameters between individuals with a short, normal or long sleep duration. Because the *P*-value of the AUCg and AUCi was < 0.20, their associations with sleep duration were studied further in multinominal logistic regression analyses using participants with a sleep duration of 7–8 h as the reference group, but this did not show any significant association between the AUCg and AUCi, on one hand, and sleep duration on the other hand (Table 3); nor did sensitivity analyses of sleep duration (i.e. ≤ 5, 6–8, ≥ 9 h per night) show any significant association with cortisol parameters (all $P > 0.05$; data not shown). Multinominal regression using diurnal slope ($P = 0.089$), AUCg ($P = 0.094$) and AUCi ($P = 0.122$) showed no significant association between cortisol and tertiles of sleep duration (data not shown). Testing the interaction terms cortisol × depression diagnosis and cortisol × depression severity in relation to sleep duration in multivariable regression models revealed no significant interaction terms (data not shown). Also, stratified analysis of the association between cortisol, sleep duration and insomnia symptoms in depressed and non-depressed older adults did not show any significant results (Supporting information, Tables S3–S5).

DISCUSSION

In contrast to our hypothesis, we found no associations between any of the cortisol parameters and insomnia symptoms or sleep duration. It has been thought that the HPA axis plays an important role in modulating sleep (Buckley and Schatzberg, 2005), but associations between sleep parameters and cortisol are not found consistently (Elder *et al.*, 2014). Our results are in line with those of another cross-sectional study that found no association between the cortisol awakening response and sleep duration or sleep quality in healthy middle-aged adults (Zhang *et al.*, 2011). However, our results are in contrast with a cross-sectional study among community-dwelling individuals (mean age 61 years) that found that short sleep (≤ 5 h per night) was associated with a steeper morning rise in cortisol (Kumari *et al.*, 2009). In the latter study, insomnia symptoms were also associated with a flatter diurnal slope, and evening cortisol was raised in individuals reporting more serious sleep disturbances (Kumari *et al.*, 2009). However, this study differed from ours in the assessment of sleep duration using five categories the night before saliva sampling, whereas we assessed mean sleep duration during the past month and categorized this into three categories. Our study also differed in the definition of short sleep (≤ 6 h instead of ≤ 5 h per night), although sensitivity analyses did not change our results. Studies also differ in the assessment tool for insomnia symptoms. We used the WHIIRS in which participants were asked how many times a week during the past 4 weeks their sleep was disturbed, whereas others, e.g. the above-mentioned study, used the Jenkins questionnaire, with an additional question for disturbed or restless

Table 2 Cortisol parameters in older people without/with clinically relevant insomnia symptoms and different sleep duration

	WHIIRS < 10 (n = *183, 53.8%)*	*WHIIRS ≥ 10* (n = *157, 46.2%)*		P-*value**
AUCg, median (IQR)	17.59 (13.62 to 22.75)	18.30 (14.23 to 25.68)		0.34
AUCi, median (IQR)	1.22 (−2.47 to 5.74)	0.24 (−3.08 to 4.80)		0.36
Evening level, median (IQR)	4.04 (2.63 to 5.57)	3.50 (2.50 to 5.82)		0.49
Diurnal slope, median (IQR)	12.10 (7.12 to 17.19)	12.11 (7.26 to 19.73)		0.60
Cortisol suppression ratio, median (IQR)	2.71 (1.74 to 3.72)	2.67 (1.56 to 4.39)		0.96
	≤ 6 h/night (*n* = 108, 31.8%)	> 6 and < 9 h/night (*n* = 179, 52.6%)	≥ 9 h/night (*n* = 58, 15.6%)	*P*-value*
AUCg, median (IQR)	18.44 (13.21 to 25.23)	18.13 (14.73 to 24.09)	16.49 (11.89 to 21.23)	0.14
AUCi, median (IQR)	0.73 (−2.06 to 5.07)	1.17 (−2.32 to 6.52)	−1.07 (−3.91 to 3.44)	0.12
Evening level, median (IQR)	3.44 (2.50 to 5.44)	4.02 (2.52 to 5.74)	3.86 (2.68 to 5.71)	0.68
Diurnal slope, median (IQR)	10.58 (6.30 to 18.46)	12.54 (8.14 to 18.66)	11.97 (6.69 to 17.91)	0.31
Cortisol suppression ratio, median (IQR)	2.68 (1.47 to 4.41)	2.66 (1.77 to 3.87)	3.03 (1.66 to 4.03)	0.98

WHIIRS: Women's Health Initiative Insomnia Rating Scale; AUCg: area under the curve with respect to the ground; AUCi: area under the curve with respect to the increase; IQR: interquartile range.
**P*-values by Mann–Whitney *U*-test or Kruskal–Wallis test when appropriate.

Table 3 Associations of sleep duration with cortisol parameters with $P < 0.20$ in the univariate analyses, using 7–8 h of sleep per night as reference group

	Sleep duration ≤ 6 h/night n = *78 (36.4%)*			*Sleep duration ≥ 9 h/night* n = *31 (14.5%)*		
	Wald	*OR (95% CI)*	P-*value*	*Wald*	*OR (95% CI)*	P-*value*
AUCg	1.46	0.98 (0.94–1.02)	0.23	1.48	0.97 (0.91–1.02)	0.22
AUCi	0.48	0.99 (0.95–1.03)	0.49	2.20	0.96 (0.91–1.01)	0.14

Multivariate regression analyses adjusted for age, gender, partner status, years of education, alcohol consumption, use of psychotrophic medication, number of chronic diseases, a diagnosis of depression, severity of anxiety, pain intensity and time of awakening.
AUCg: area under the curve with respect to the ground; AUCi: area under the curve with respect to the increase; OR: odds ratio; CI: confidence interval.

sleep considering the number of days during the past 4 weeks (Kumari *et al*., 2009). Furthermore, the mean age in our sample was higher and we included a substantial number of depressed individuals (although we found no significant difference between depressed and non-depressed participants).

A study among middle-aged adults using a low-dose dexamethasone suppression test found an association between poor subjective sleep quality and shorter sleep duration and enhanced feedback of the HPA axis (Luik *et al*., 2015). We could not replicate this finding, which may be explained (partly) by the older age of our population and use of a higher dose of dexamethasone (0.5 versus 0.25 mg), resulting in a stronger suppression with a decrease in the range of serum levels. Our results are not in accordance with a study in a sleep laboratory that reported an association between elevated plasma cortisol levels and total wake time (sum of sleep latency and wake time after sleep onset) in non-depressed older adults (mean age 71 years) (Vgontzas *et al*., 2003). Important strengths of the latter study are the measurements of cortisol levels during a 3-day period and the use of objective measures for sleep disturbances. Conversely, sleeping in a sleep laboratory can be stressful, and thereby influence HPA-activity (Kudielka *et al*., 2012).

As cortisol has a diurnal rhythm, the time of measurement is critical. There could have been measurement errors due to non-compliance with the sampling instructions or dexamethasone ingestion. However, a recent study that assessed the association between HPA axis activity and depression showed higher morning cortisol levels and a less dynamic awakening response in depressed older adults compared with non-depressed older adults (Rhebergen *et al*., 2015). These latter results are in accordance with a recent meta-analysis by Belvederi Murri *et al.* (2014). Therefore, it seems unlikely that our findings are a result of measurement errors.

Contrary to our hypothesis, no interaction was found between depression or depressive symptoms and cortisol levels with respect to insomnia symptoms or duration of sleep. This is in line with a study showing that the relation between salivary cortisol levels and sleep duration is not influenced by mental health status (Kumari *et al*., 2009). It has been suggested that frailty in older adults is associated

with a blunted cortisol response, due possibly to exhaustion of the HPA axis (Johar *et al*., 2014). In the latter study, frailty was determined according to the Fried criteria, including weight loss, exhaustion or fatigue, physical inactivity, low walking speed and low grip strength (Fried *et al*., 2001). The older adults in our study with clinically relevant insomnia symptoms were less physically active, had more chronic diseases, more pain and used more medication, making them more vulnerable to frailty. This may (partly) explain the non-significant results in our study.

This study is one of the largest studies describing HPA axis activity among older adults with and without clinically relevant insomnia symptoms. Some limitations of our study need to be addressed. First, both over- and under-estimation of insomnia symptoms may have occurred due to the subjective nature of our sleep measures, especially in depressed individuals, as they tend to report a lower total sleep time more often than actigraphically assessed individuals (Van den Berg *et al*., 2008). Ideally, polysomnography would have been used; unfortunately, this is not possible in this large study. Secondly, the WHIIRS was validated originally for women only. However, it has also been tested widely for reliability and validity, and norms are presented by age and ethnicity (Levine, 2003b). Also, face-value the items are not sex-specific. Thirdly, we measured cortisol parameters during one day and the DST on the following day, whereas it is reported that multiple days of sampling may be more reliable (Hellhamer *et al*., 2007). Fourthly, because the most severely depressed individuals may have been unwilling/unable to participate, our conclusions cannot be generalized to severely depressed older adults.

In conclusion, in our sample of older adults' HPA axis activity was not related to clinically relevant insomnia symptoms and sleep duration, and the presence of depression did not alter this. Further research is required to gain more insight into the biology of insomnia symptoms in depressed older adults.

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AUTHOR CONTRIBUTIONS

Data collection was conducted by NESDO and data analyses by RP and HC. All authors were involved in study design and preparation of the manuscript.

CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Sociodemographic, lifestyle, and clinical characteristics in older persons without (WHIIRS $<$ 10) and with (WHIIRS $\geq$ 10) clinically relevant insomnia symptoms

Table S2. Sociodemographic, lifestyle and clinical characteristics in groups with different sleep durations

Table S3. Cortisol parameters in depressed older adults with and with clinically relevant insomnia symptoms (WHIIRS $<$ 10/WHIIRS $\geq$ 10) and different sleep durations

Table S4. cortisol parameters in non-depressed older adults without/with clinically relevant insomnia symptoms (WHIIRS $<$10 / WHIIRS $\geq$ 10) and different sleep duration

Table S5. Associations of sleep durations, using 7-8 hours per night as reference group, respectively clinically relevant insomnia symptoms with cortisol parameters with $p<0.20$ in the univariate analyses (depressed respectively non-depressed older adults)