The longitudinal association of actigraphy-estimated sleep with grief in middle-aged and elderly persons

Maud de Feijter [a], Mary-Frances O'Connor [b], Brian J. Arizmendi [b,c], M. Arfan Ikram [a], Annemarie I. Luik [a,d,*]

[a] Department of Epidemiology, Erasmus MC, University Medical Center Rotterdam, the Netherlands
[b] Department of Psychology, University of Arizona, USA
[c] Department of Psychology, Phoenix VA Health Care System, USA
[d] Department of Child and Adolescent Psychiatry/Psychology, Erasmus MC, University Medical Center Rotterdam, the Netherlands

ARTICLE INFO

ABSTRACT

Most people experience grief after a loss, about 10% develop complicated grief, often accompanied by sleep complaints. Yet, the role of objectively estimated poor sleep remains unclear. Therefore, we assessed the cross-sectional and longitudinal association of actigraphy-estimated sleep with grief. We included 1,776 participants (mean age: 61.8 ± 8.9 years, 55% women) of a prospective population-based cohort. Of 1,471 participants (83%) repeated measures of grief were available (median follow-up 6 years, inter quartile range 5.6–6.3). At baseline, sleep was objectively estimated using actigraphy (mean duration 6.0 ± 0.8 days). At baseline and follow-up, participants were asked about significant losses and completed the Dutch Inventory of Complicated Grief (17 items, cut-off $\geq$22). At baseline 1,521 (86%) participants experienced no grief, 44 (2%) acute grief ($<$6 months, any grief score), 158 (9%) non-complicated grief ($\geq$6 months, grief score$<$22), and 53 (3%) complicated grief ($\geq$6 months, grief score$\geq$22). In those indicating any grief (n = 255), low sleep efficiency (B = -0.16, 95%CI = -0.30;-0.02), long sleep onset latency (B = 0.07, 95%CI = 0.01; 0.14), and long wake after sleep onset (B = 0.06, 95%CI = 0.01; 0.10) were cross-sectionally associated with more grief symptoms. Over time, those with a short total sleep time (OR = 0.59, 95%CI = 0.39; 0.91), low sleep efficiency (OR = 0.95, 95%CI = 0.91; 0.99), long sleep onset latency (OR = 1.02, 95%CI = 1.00; 1.04), and long wake after sleep onset (OR = 1.02, 95%CI = 1.00; 1.03) at baseline more often experienced complicated grief than non-complicated grief at follow-up. This study suggests that objectively estimated poor sleep is associated with grief over time. Poor sleep might not only accompany grief, but also be a risk factor for developing complicated grief after a loss.

1. Introduction

Losing of a loved one is an ubiquitous life event, particularly with increasing age (Boelen and Hoijtink, 2009), with grief as the most common response (Rosenzweig et al., 1997). Over time, most people recover from grief, but for about 10%, grief remains unresolved and causes significant impairment in daily life, also known as complicated grief (Lundorff et al., 2017; Nakajima, 2018). People suffering from complicated grief experience symptoms such as disbelief, avoidance, emotional numbness, and an adverse impact on social, work or school life (Boelen and Hoijtink, 2009; Kristensen et al., 2017). When unresolved or complicated grief reaches the level of a clinical disorder, the term prolonged grief disorder is used in the International classification of diseases, 11th edition (World Health, 2018) and persistent complex bereavement disorder is used in the Diagnostic and statistical manual of mental disorders, 5th edition (Association, 2013). Of note, even though these disorders are sometimes comorbid with depressive disorders, they are distinct (Kristensen et al., 2017; Prigerson et al., 1995a; Prigerson and MaCiejewski, 2006).

One construct commonly associated with grief is poor sleep (Boelen and Lancee, 2013; Lancel et al., 2020; Milic et al., 2019; Stahl and Schulz, 2014). On one hand poor sleep during grief might be caused by worry and hyperarousal (Eisma et al., 2020), which makes it more difficult to fall asleep and more likely to awaken during the night (Bao et al., 2017). On the other hand, poor sleep is also associated with less effective emotion regulation which may maintain or worsen symptoms

of psychological disorders, such as complicated grief. A recent population-based study in middle-aged and elderly persons reported shorter self-rated sleep duration and lower self-rated sleep quality in those experiencing complicated and non-complicated grief when compared to those without grief (Milic et al., 2019). A recent review additionally suggested that poor sleep is associated with the number of grief symptoms, and may be more severe and longer-lasting in those with complicated grief as opposed to other types of grief (Lancel et al., 2020). So far most studies have relied on self-rated indicators of sleep (Boelen and Lancee, 2013; Milic et al., 2019; Monk et al., 2008; Stahl and Schulz, 2014), rather than objective estimates (Monk et al., 2009; Prigerson et al., 1995a; Reynolds et al., 1992), yet this could introduce bias due to shared variance in self-rating both grief and sleep (Buysse et al., 2008). The few studies that use a longitudinal design to assess temporality often focus on the effect of grief on self-rated sleep disturbance (Buckley et al., 2009; Erlangsen et al., 2017; Lancel et al., 2020; Milic et al., 2019; Richardson et al., 2003). There is, however, growing evidence that sleep may be not only a symptom, but also a risk factor for developing complicated grief after a significant loss (Lancel et al., 2020; Richardson et al., 2003). Yet, in many studies using self-rated measures of sleep, the association between grief and sleep has been explained by comorbid depressive symptoms (Boelen and Lancee, 2013; Milic et al., 2019; Tanimukai et al., 2015).Although the association could indeed be dependent on comorbidity with depressive symptoms, it could also be that a shared method bias explains these results (Conway, 2002). Therefore using objective estimates of sleep, which are thought to measure physiological sleep, can provide new insights (Buysse et al., 2008).

In order to improve our understanding of development of complicated grief, we studied the cross-sectional and longitudinal association of actigraphy-estimated and self-rated sleep with type of grief and the number of grief symptoms in a population-based cohort of middle-aged and elderly persons.

2. Methods

2.1. Participants & design

This study was conducted within the Rotterdam Study, a prospective population-based cohort of middle-aged and elderly inhabitants of Rotterdam, the Netherlands. Details of the study design have been described previously (Ikram et al., 2020). The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

From December 2004 until April 2007, we invited 2,614 participants to wear an actigraph to estimate their sleep, of whom 2,071 participants (79%) agreed. Of those that agreed, 196 participants were excluded due to incomplete sleep data (including participants with <4 complete nights of actigraphy and sleep diary). Another 57 participants were excluded due to incomplete information about grief at baseline, 11 due to grieving over a pet or a sick person, and 31 due to a possible impaired cognition (Mini Mental State Examination <23 or missing) (Tombaugh and McIntyre, 1992). Therefore, a total number of 1,776 participants were included at baseline.

For 1,501 participants of the baseline sample, information on grief was obtained for a second time between February 2011 and July 2014. This second grief assessment was performed independent of grief status at baseline. Loss to follow-up occurred because participants died (n = 105) or withdrew from the study (n = 163). Of those who participated, we excluded repeated measurements for 30 participants because of incomplete or invalid data at follow-up and 7 participants because they indicated grief over a pet or sick person at follow-up. Therefore, repeated data were available for a total of 1,471 persons (83% of baseline sample).

2.2. Sleep

At baseline all participants were invited to wear an actigraph (ActiWatch, model AW4, Cambridge Technology Ltd, Cambridge, United Kingdom) for 7 consecutive days and nights on their non-dominant wrist. Additionally, participants were asked to fill out a sleep diary every day and press a marker button on the actigraph to obtain the clock times for when they initiated sleep (time to bed) and when they got out of bed (get-up time). This information was used to determine the analysis window for the actigraphy.

Actigraphy recordings were sampled at 32 Hz in 30-second epochs. To estimate sleep, an averaged score was calculated for each 30-s epoch, taking into account weighted values of previous and following epochs. A threshold of 20 was used to distinguish sleep from wake (Kosmadopoulos et al., 2014; Kushida et al., 2001). Total sleep time was defined as nightly sleep duration and calculated as the sum in time difference of epochs scored as asleep, between sleep start and sleep end. Sleep efficiency was defined as the time sleeping whilst in bed (100*total sleep time/time in bed), where time in bed was defined as the time difference between time to bed and get-up time (based on the sleep diary or marker button). Sleep onset latency was defined as the time it took participants to fall asleep, calculated as the time difference between time to bed and sleep start. Wake after sleep onset was defined as the total time scored as awake between sleep start and sleep end.

To assess 24-hour activity rhythms we estimated interdaily stability, intradaily variability, and L5 onset time. The nparACT R package was used to calculate interdaily stability, indicating the rhythm stability over days, intradaily variability, indicating fragmentation of the rhythm relative to its 24-hour amplitude, and L5 onset, indicating the average clock time the 5 consecutive hours with least activity of the day started (Blume et al., 2016; Van Someren, 1997).

The Pittsburgh Sleep Quality Index (PSQI) was used to obtain self-rated overall sleep quality (Buysse et al., 1991). A global score, ranging from 0 to 21, was calculated as the sum of 7 component scores, with a higher score indicating poorer sleep quality. If less than 6 component scores were available, PSQI was considered missing. For participants with 6 out of 7 valid PSQI component scores, a weighted global score was calculated by multiplying with 7/6.

2.3. Grief

During the home interview, at baseline and at follow-up, all participants were asked whether they were still grieving over someone who had died in recent months or years. In case of a positive answer two follow-up questions were asked: "*When did this person die?*" and "*Who was this person?*". Additionally, grief symptoms were assessed using the Dutch version of the Inventory of Complicated Grief (ICG) (Prigerson et al., 1995b). The Dutch version of the ICG is a 17-item self-report scale on symptoms of complicated grief (Boelen et al., 2003), questions were asked on a 5-point scale (0-never, 4-always), providing a potential score range of 0–68. The cut-off score for complicated grief of the Dutch version was set to 22, accounting for the smaller number of items than the original version (Boelen et al., 2003; Prigerson et al., 1995b).

Based on the ICG score and time since the loss, participants were divided into four groups: (1) no grief, encompassing participants that indicated no grief at the time of the interview; (2) acute grief, encompassing participants with <6 months since loss irrespective of their ICG score; (3) non-complicated grief, encompassing participants with ≥6 months since loss and an ICG-score <22; and (4) complicated grief,

encompassing participants with ≥6 months since loss and an ICG-score ≥22. Participants were divided into these four groups at baseline and at follow-up, and the division at follow-up was independent from the division at baseline. Thus, a person at follow up might be in the "no grief" group, even though they were in one of the grief groups at baseline, because the self-report question was whether they were still grieving over someone who had died, and not just the fact of whether someone had died.

2.4. Other variables

Based on previous literature, the following variables were assessed as possible confounders: age, sex, depressive symptoms, education, smoking, cognitive status, and body mass index (BMI)(Milic et al., 2019). Age, sex, depressive symptoms, education and smoking behavior were assessed during the home interview. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression scale (CES-D)(Beekman et al., 1994). Education was assessed at baseline as primary education (primary), lower/intermediate general education or lower vocational education (low), intermediate vocational education or higher general education (middle), or higher vocational education or university (high). Smoking was classified as never, former, or current smoker. Cognitive status and BMI were assessed at the research center. To obtain cognitive status, participants were screened with the Mini Mental State Examination (Tombaugh and McIntyre, 1992). To calculate BMI (kg/m^2), height and weight were assessed on calibrated scales at the research center without heavy clothing and shoes.

2.5. Statistical analyses

Missing values for covariates were less than 5% and handled by multiple imputation using the MICE R package (Buuren and Groothuis-Oudshoorn, 2010). Statistical analyses were performed using imputed data sets, and pooled statistics were presented (Rubin, 2004). Sleep variables were checked with regard to outliers, which were set to 4 standard deviations (SD) from the mean. To overcome model difficulties with small value range, we multiplied interdaily stability and intradaily variability with a factor 10. To correct for multiple testing, we used the false discovery rate (FDR) to calculate the adjusted p-values, based on 5 determinants (Benjamini and Hochberg, 1995). Analyses are performed in R version R 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria, www.R-project.org).

First, to estimate the association between sleep and grief at baseline, multi-nominal testing was used. These analyses provided the odds ratio (OR) of being in a certain type of grief, with each unit increase in the sleep variable under study. We selected non-complicated grief, rather than no grief, as a reference category in order to assess the effect of sleep on grief type. We did not draw comparison to the no grief group as this would have included the effect of sleep on the possibility of experiencing a loss, as this group contained both those not having experienced any loss and therefore not grieving as well as those having experienced a loss but not grieving. Second, in participants indicating any grief, we used cross-sectional linear regression models to estimate the association of sleep with the continuous number of grief symptoms at baseline. To estimate whether the association between sleep and grief differed between people suffering from acute grief (<6 months) and people who had been grieving for longer (≥6 months), we repeated the cross-sectional linear regression models, stratified for duration of grief.

To estimate the longitudinal association of baseline sleep and grief at follow-up, we used multi-nominal analyses. To overcome possible presence of grief at baseline biasing our associations, we performed a sensitivity analysis in which we repeated the longitudinal analyses in a sample excluding participants who indicated any grief at baseline and participants who indicated grief about a loss occurring before baseline at the second grief assessment.

All associations were analyzed for total sleep time, sleep efficiency,

sleep onset latency, wake after sleep onset, and self-rated sleep quality, using three models. Model 1 was adjusted for sex and age only. In model 2 we adjusted for sex, age, education, smoking, and BMI, this selection was based on previous literature. In model 3 we adjusted for all model 2 confounders and additionally depressive symptoms, to assess whether associations were independent of depressive symptomatology. In the longitudinal analyses, all models were additionally adjusted for follow-up time. As exploratory analyses, we assessed the, cross-sectional and longitudinal multi-nominal models for relations of 24-hour activity rhythms, interdaily stability, intradaily variability and L5 onset time, with grief.

3. Results

At baseline 1,776 participants were included with a mean age of 61.8 ± 8.9 years and 55% women (see Table 1). At baseline 1,521 (85.6%) participants reported no grief, 44 (2.5%) acute grief, 158 (8.9%) non-complicated grief, and 54 (3.0%) complicated grief. Participants experiencing grief for a longer period of time reported grief over a partner or a child most often (Table 1). Valid repeated measurements were available for 1,471 participants with a median follow-up time of 6 years (IQR = 5.6–6.3). At follow-up 1,270 (86.3%) participants reported no grief, 38 (2.6%) acute grief, 122 (8.3%) non-complicated grief, and 41 (2.8%) complicated grief.

3.1. Sleep and grief at baseline

At baseline, no significant cross-sectional associations of sleep and 24-hour activity rhythms with type of grief at baseline were found when correcting for multiple testing (Table 2, Supplementary Tables 1–2). In the sample of participants who indicated any grief at baseline (n = 255), indicators of poor sleep were associated with the continuous number of grief symptoms (Table 3). A low sleep efficiency (B = −0.16, 95%CI = −0.30;-0.02), long sleep onset latency (B = 0.07, 95%CI = 0.01; 0.14), long wake after sleep onset (B = 0.06, 95%CI = 0.01; 0.10), and low self-rated sleep quality (B = 0.59, 95%CI = 0.30; 0.89, a high PSQI score reflects poor sleep quality) were associated with more grief symptoms. After correcting for depressive symptoms, none of the associations remained significant (Supplementary Table 3).

After stratification, in participants with <6 months since loss short total sleep time (B = −4.11, 95%CI = −7.41;-1.07), long sleep onset latency (B = 0.18, 95%CI = 0.03; 0.33), and poor self-rated sleep quality (B = 1.00, 95%CI = 0.20; 1.79) were associated with more grief symptoms (Supplementary Table 4). In participants with >6 months since loss only self-rated sleep quality was significantly associated with more grief symptoms (B = 0.51, 95%CI = 0.18; 0.83, Supplementary Table 4).

3.2. Sleep at baseline and grief at follow-up

Over time, poor sleep at baseline was associated with increased odds on complicated grief (Table 4, Supplementary Table 5). Those with short total sleep time (OR = 0.59, 95%CI = 0.39; 0.91), low sleep efficiency (OR = 0.95, 95%CI = 0.91; 0.99), long sleep onset latency (OR = 1.02, 95%CI = 1.00; 1.04), long wake after sleep onset (OR = 1.02, 95%CI = 1.00; 1.03), and poor self-rated sleep quality (OR = 1.13, 95%CI = 1.03; 1.23) at baseline were more likely to report complicated grief than non-complicated grief at follow-up (Table 4). For 24-hour activity rhythms, interdaily stability and intradaily variability were not associated with the odds of experiencing complicated grief compared to non-complicated grief at follow-up (Supplementary Table 5) Those with a later L5 onset time at baseline were more likely to report complicated grief than non-complicated grief at follow-up (OR = 1.51, 95%CI = 1.09; 2.07). After additional correction for depressive symptoms, none of the associations remained significant (Supplementary Table 6).

We repeated the longitudinal analyses in a subsample (n = 1,285),

Table 1
Baseline characteristics of the study population at baseline, separated for type of grief.

	No grief (n = 1,521)	Acute grief (n = 44)	Non-complicated grief (n = 158)	Complicated grief (n = 53)
	Mean ± SD N (%) Median (IQR)	Mean ± SD N (%) Median (IQR)	Mean ± SD N (%) Median (IQR)	Mean ± SD N (%) Median (IQR)
Demographics				
Age (years)	61.5 ± 8.9	63.0 ± 10.7	63.0 ± 8.6	64.5 ± 9.7
Women	798 (52.5%)	27 (61.4%)	108 (68.3%)	39 (73.6%)
Education				
Primary	117 (7.7%)	4 (9.1%)	13 (8.3%)	6 (11.6%)
Low	614 (40.7%)	15 (34.1%)	58 (36.7%)	29 55.8%)
Intermediate	452 (30.0%)	14 (31.8%)	53 (33.5	15 (28.8%)
High	326 (21.6%)	11 (25.0%)	34 (21.5%)	2 (3.8%)
Cognitive status (score)[a]	28.1 ± 1.6	27.9 ± 1.8	28.1 ± 1.5	27.7 (1.7)
Depressive symptoms (score)[b]	3 (1–6)	7 (0–13)	5 (2–9)	8 (4–19)
Body mass index (kg/m²)	27.7 ± 4.2	27.2 ± 3.9	28.2 ± 4.0	29.6 ± 5.4
Smoking				
Never	484 (31.8%)	15 (34.1%)	37 (23.4%)	13 (24.5%)
Former	762 (50.1%)	20 (45.5%)	91 (57.6%)	31 (58.5%)
Current	275 (18.1%)	9 (20.4%)	30 (19.0%)	9 (17.0%)
Actigraphy-estimated sleep				
Total sleep time (hour:min)	6:06 ± 0:55	6:16 ± 0:49	6:04 ± 0:50	6:03 ± 0:53
Sleep efficiency (%)	74.6 ± 8.5	75.6 ± 9.5	73.8 ± 8.4	72.5 ± 8.5
Sleep onset latency (min)	21 ± 16	21 ± 15	22 ± 18	28 ± 21
Wake after sleep onset (min)	63 ± 26	61 ± 30	61 ± 24	67 ± 27
Interdaily stability (score)[c]	0.78 ± 0.11	0.79 ± 0.08	0.78 ± 0.11	0.76 ± 0.12
Intradaily variability (score)[c]	0.42 ± 0.14	0.44 ± 0.15	0.44 ± 0.13	0.42 ± 0.12
L5 onset (hour:min)[c]	1:15 ± 2:06	1:34 ± 2:00	1:27 ± 2:15	1:36 ± 2:06
Self-rated sleep				
Self-rated sleep quality (score)	3.8 ± 3.5	4.0 ± 3.2	4.9 ± 3.7	6.1 ± 4.8
Grief				
Duration since loss (months)	–	2 (0–3)	39 (18–75)	32 (16–67)
ICG score	-	11.0 ± 7.6	11.6 ± 5.3	30 ± 6.3
Loss				
Partner	–	2 (4.5%)	45 (28.7%)	16 (30.2%)
Child	–	1 (2.3%)	9 (5.7%)	10 (18.7%)
Other	–	35 (79.6%)	85 (53.8%)	119 (36.0%)
>1 person	–	6 (13.6%)	18 (11.8%)	8 (15.1%)

Variables are stated as number (percentage), mean ± standard deviation, or median (inter quartile range). Missing values at baseline: Self-rated sleep quality is missing for 30 participants (1.7%), education for 13 (0.7%), depressive symptoms for 2 (0.1%) and body mass index for 16 (0.9%). For other variables there are no missing values.
[a] Assessed using the Center for Epidemiological Studies Depression scale.
[b] Assessed using the Mini-Mental State Examination.

[c] Assessed for 1,448 (95.3%) participants with no grief, 44 (100%) participants with acute grief, 149 (94.3%) participants with non-complicated grief, and 52 (98.1) participants with complicated grief.

excluding participants who indicated any grief at baseline or who indicated at the second grief assessment any grief from a loss occurring before baseline, in order to overcome potential grief at baseline affecting our observations. The effect sizes remained similar, but only total sleep time (OR = 0.39, 95%CI = 0.21; 0.72) and self-rated sleep quality (OR = 1.26, 95%CI = 1.10; 1.43) reached significance in participants reporting complicated grief, opposed to non-complicated grief, at follow-up (data not shown).

Analyses adjusted for sex and age only, model 1, showed similar results to model 2 (data not shown).

4. Discussion

Three findings stand out from this population-based sample study of middle-aged and elderly adults. First, we found no cross-sectional association of actigraphy-estimated sleep with type of grief (i.e., none, acute, non-complicated, complicated), but self-rated poor sleep was related to type of grief. Second, in contrast, multiple indicators of poor actigraphy-estimated sleep, such as a low sleep efficiency, long sleep onset latency, long wake after sleep onset, and a poor self-rated sleep quality were cross-sectionally associated with the continuous number of grief symptoms in those that indicated any grief after the loss of a loved one. Third, baseline short total sleep time, low sleep efficiency, long sleep onset latency, long wake after sleep onset latency, poor self-rated sleep quality, and a delayed rhythm were associated with a higher chance of having complicated grief after a mean follow-up of 6 years compared to non-complicated grief. These longitudinal results remained significant for sleep duration and self-rated sleep quality after excluding participants with any grief at baseline.

We observed no cross-sectional associations between objective sleep estimates and type of grief, except for a better self-rated sleep quality in non-grieving individuals, compared to non-complicated grievers. The absence of a difference between those with non-complicated grief and those with acute grief or complicated grief in any sleep estimate seems to suggest that levels of self-rated sleep quality and objectively estimated sleep are similar in participants with grief, independent of type of grief. Overall, this is in line with previous studies assessing subjective measures of sleep (Lancel et al., 2020; Milic et al., 2019; Szuhany et al., 2020), but was not yet known for objective sleep measures such as actigraphy (Lancel et al., 2020). This is important as subjective sleep measures reflect psychological aspects of sleep, i.e. the experience of sleep, while objective sleep measures reflect physiological sleep abnormalities. Thus, whereas the first is important to get insight into psychological mechanisms, the latter is providing insights in the potential biological mechanisms. Yet, our work also suggests that this lack of association might be due to the categorization of grief status, as multiple indicators of objective and self-rated poor sleep were related to the number of grief symptoms in those indicating any grief. Although our study is the first to show this for actigraphy-estimated sleep, previous work has demonstrated the association of self-rated sleep, polysomnography-assessed sleep and insomnia with number of grief symptoms (Boelen and Lancee, 2013; Buysse et al., 2008; Hardison et al., 2005; Reynolds et al., 1992; Szuhany et al., 2020), suggesting that the categorization of grief can have large impact on the results. The discrepancy between the results of type of grief and number of grief symptoms could be explained by the duration criteria of type of grief. For example, sleep disturbances might be partly resolved in participants with complicated grief and non-complicated grief, due to habituation to the grief and normalization of the associated hyperarousal (Eisma et al., 2020), and only subjective feelings of poor sleep remain over time (Pyrke et al., 2017). This notion is further supported by differential results between those with a less than 6 months since the loss and those

Table 2

Cross-sectional associations of sleep with type of grief at baseline, compared to non-complicated grief (n = 158).

	No grief (n = 1,521)			Acute grief (n = 44)			Complicated grief (n = 53)		
	Adjusted Odds Ratio (95% CI)	P-value	Corrected P-value	Adjusted Odds Ratio (95% CI)	P-value	Corrected P-value	Adjusted Odds Ratio (95% CI)	P-value	Corrected P-value
Total sleep time (hour)	1.09 (0.90; 1.33)	0.38	0.48	1.39 (0.93; 2.10)	0.11	0.33	0.98 (0.68; 1.43)	0.93	0.93
Sleep efficiency (%)	1.01 (0.99; 1.03)	0.33	0.48	1.03 (0.99; 1.07)	0.20	0.33	0.99 (0.95; 1.02)	0.52	0.65
Sleep onset latency (min)	1.00 (0.99; 1.01)	0.70	0.70	1.00 (0.98; 1.02)	0.73	0.73	1.01 (1.00; 1.03)	0.08	0.20
Wake after sleep onset (min)	1.00 (1.00; 1.01)	0.31	0.48	1.00 (0.98; 1.01)	0.72	0.73	1.01 (1.00; 1.02)	0.12	0.20
Self-rated sleep quality (score)	0.95 (0.90; 0.99)	0.015	0.08	0.94 (0.85; 1.04)	0.20	0.33	1.07 (0.99; 1.12)	0.09	0.20

Total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset were estimated using actigraphy, self-rated sleep quality was assessed using the Pittsburgh Sleep Quality Index. Effect estimates were adjusted for age, sex, education, smoking, and body mass index (model 2). None of the associations remained significant (<0.05) after correcting for multiple testing using FDR.

Table 3

Cross-sectional associations of sleep with number of grief symptoms in those participants that indicated any grief at baseline (n = 255).

	Grief symptoms		Corrected p-value
	Adjusted coefficient (95% CI)	P-value	
Total sleep time (hour)	−1.403 (−2.828; 0.022)	0.05	0.05
Sleep efficiency (%)	−0.158 (−0.295;-0.021)	0.024	0.039*
Sleep onset latency (min)	0.072 (0.007; 0.137)	0.031	0.039*
Wake after sleep onset (min)	0.057 (0.010; 0.103)	0.017	0.039*
Self-rated sleep quality (score)	0.592 (0.296; 0.888)	<0.001	<0.001*

Total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset were estimated using actigraphy, self-rated sleep quality was assessed using the Pittsburgh Sleep Quality Index. Effect estimates were adjusted for age, sex, education, smoking, and body mass index (model 2). * P-value remained significant (<0.05) after correcting for multiple testing, using FDR.

with 6 months or longer since the loss.

Our work also showed that actigraphy-estimated short sleep duration, low sleep efficiency, long sleep onset latency, long wake after sleep onset, poor self-rated sleep and a more delayed 24-hr rhythm at baseline were associated with increased odds of experiencing complicated grief 6 years later. This suggests that poor sleep prior to a loss event, both self-rated and objectively measured, could potentially create a vulnerability for developing complicated grief. Although we lack power to sufficiently investigate whether this vulnerability solely depends on grief-related poor sleep (e.g., from a different loss experience), excluding those with baseline grief and those with grief at follow-up that started before baseline from our analyses, did not substantially impact our effect sizes. This may suggest that it is the poor sleep per se, and not the baseline

grief, that accounts for the association between poor sleep and grief at follow-up. Mechanistically, this might be explained by the association of poor sleep with an exaggerated stress response and better memory of negative experiences (Devine et al., 2019; Kim et al., 2019). Additionally, poor sleep has been associated with less effective emotion regulation and more time spent in negative mood states (Watling et al., 2017), which in turn could impair the individual's ability to cope with this stressful event and make one more vulnerable to develop complicated grief after a loss. These findings support the idea that people with poor sleep are more vulnerable to a range of mental health problems, (Wulff et al., 2010), and the importance of an increased awareness about sleep by general practitioners, psychologists, psychiatrists and other medical specialists. Preventing or targeting poor sleep early on, could potentially help reduce psychopathology, including complicated grief, although causal pathways remain to be investigated.

The longitudinal associations of sleep with grief did not remain significant after correction for baseline depressive symptoms when taking into account multiple testing correction. Yet, the effect sizes of the actigraphy-estimated sleep parameters remained largely the same. Complicated grief shares many symptoms with depression, including sleep disturbance (Kristensen et al., 2017), and could be a confounder as well as a mediator. Although associations did not remain significant, we speculate that the relation between objectively estimated sleep and complicated grief cannot solely be attributed to their shared association with depressive symptomatology based on the stability of the effect sizes in the longitudinal associations. However, cross-sectionally effect sizes were attenuated, suggesting overlap of symptoms plays a larger role when measured grief and depressive symptoms are measured concurrently.

Several limitations should be considered when interpreting our findings. First, grief symptoms were only assessed when participants self-reported they were experiencing grief due to the death of a loved

Table 4

Longitudinal associations of baseline sleep with type of grief at follow-up, compared to non-complicated grief (n = 122).

	No grief (n = 1,521)			Acute grief (n = 44)			Complicated grief (n = 53)		
	Adjusted Odds Ratio (95% CI)	P-value	Corrected P-value	Adjusted Odds Ratio (95% CI)	P-value	Corrected P-value	Adjusted Odds Ratio (95% CI)	P-value	Corrected P-value
Total sleep time (hour)	1.00 (0.79; 1.26)	0.99	0.99	0.92 (0.59; 1.43)	0.71	0.99	0.59 (0.39; 0.91)	0.017	0.028*
Sleep efficiency (%)	1.00 (0.98; 1.03)	0.92	0.99	1.00 (0.96; 1.05)	0.99	0.99	0.95 (0.91; 0.99)	0.007	0.023*
Sleep onset latency (min)	1.00 (0.99; 1.01)	0.97	0.99	1.00 (0.97; 1.02)	0.73	0.99	1.02 (1.00; 1.04)	0.032	0.032*
Wake after sleep onset (min)	1.00 (1.00; 1.01)	0.44	0.99	1.00 (0.99; 1.02)	0.92	0.99	1.02 (1.00; 1.03)	0.026	0.032*
Self-rated sleep quality (score)	1.01 (0.96; 1.07)	0.72	0.99	1.01 (0.91; 1.13)	0.83	0.99	1.13 (1.03; 1.23)	0.009	0.023*

Total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset were estimated using actigraphy, self-rated sleep quality was assessed using the Pittsburgh Sleep Quality Index. Effect estimates were adjusted for age, sex, education, smoking, and body mass index (model 2). * P-value remained significant (<0.05) after correcting for multiple testing, using FDR.

one. Thus, those who experienced a death, but not grief, were included in the non-grieving group. Second, we determined complicated grief with a questionnaire and not a clinical interview, the method required for a clinical diagnosis. Third, although having repeated measurements is a strength, we were only able to include two time points between five and nine years apart. We could therefore not take into account fluctuations in sleep or grief symptoms that occurred between these two time points. Nevertheless, having objective measures of sleep and repeated grief assessments in a population-based sample over this period of time is unique in our field of research, allowing us to assess temporal associations with actigraphy-estimated sleep for the first time.

To summarize, in our study of middle-aged and elderly persons, poor sleep was associated with more grief symptoms at baseline in those participants that indicated any grief, associations could not be fully explained by depressive symptomatology. Over time, those with poor baseline sleep were more likely to develop complicated grief after a loss, implying sleep may be a potential risk factor for developing psychopathology such as complicated grief after a loss. This study highlights that preventing or targeting sleep problems early on could help to prevent onset of psychopathology in the general population, although causality remains to be determined with regards to complicated grief.

Previous presentation

Part of this work has been presented orally at the European Sleep Research Society 2020 congress, the abstract of less than 400 words was published in the Journal of Sleep Research 2020; 29 (S1):24.

Location of work

Annemarie I. Luik, Department of Epidemiology, Erasmus MC University Medical Center, Rotterdam, the Netherlands.

Author statement

Maud de Feijter, Data Curation, Formal analysis, Investigation, Methodology, Project Administration, Validation, Visualization, Writing – Original Draft, Writing – Review & Editing.

Mary-Frances O'Connor, Conceptualization, Methodology, Writing – Review & Editing, Supervision.

Brian J. Arizmendi, Methodology, Writing – Review & Editing.

M. Arfan Ikram, Data Curation, Investigation, Project Administration, Resources , Supervision, Writing – Review & Editing.

Annemarie I. Luik, Conceptualization, Data Curation, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Writing – Original Draft, Writing – Review & Editing.

Declaration of competing interest

The authors report no conflict of interest.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.02.042.

References

Association, A.P., 2013. Diagnostic and Statistical Manual of Mental Disorders, Edition, Fifth, vol. 21.

Bao, Y.P., Han, Y., Ma, J., Wang, R.J., Shi, L., Wang, T.Y., He, J., Yue, J.L., Shi, J., Tang, X.D., 2017. Cooccurrence and bidirectional prediction of sleep disturbances and depression in older adults: meta-analysis and systematic review. Neurosci. Biobehav. Rev. 75, 257–273.

Beekman, A.T.F., Van Limbeek, J., Deeg, D.J.H., Wouters, L., Van Tilburg, W., 1994. Een screeningsinstrument voor depressie bij ouderen in de algemene bevolking: de bruikbaarheid van de Center for Epidemiologic Studies Depression Scale (CES-D). Tijdschr Gerontol. Geriatr. 25, 95–103.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. Roy. Stat. Soc. B 57 (1), 289–300.

Blume, C., Santhi, N., Schabus, M., 2016. 'nparACT' package for R: a free software tool for the non-parametric analysis of actigraphy data. MethodsX 3, 430–435.

Boelen, P.A., Den Bout, J.V., De Keijser, J.O.S., Hoijtink, H., 2003. Reliability and validity of the Dutch version of the inventory of traumatic grief (ITG). Death Stud. 27 (3), 227–247.

Boelen, P.A., Hoijtink, H., 2009. An item response theory analysis of a measure of complicated grief. Death Stud. 33 (2), 101–129.

Boelen, P.A., Lancee, J., 2013. Sleep difficulties are correlated with emotional problems following loss and residual symptoms of effective prolonged grief disorder treatment. Depression Res. Treat. 2013.

Buckley, T., Bartrop, R., McKinley, S., Ward, C., Bramwell, M., Roche, D., Mihailidou, A. S., Morel-Kopp, M.C., Spinaze, M., Hocking, B., 2009. Prospective study of early bereavement on psychological and behavioural cardiac risk factors. Intern. Med. J. 39 (6), 370–378.

Buuren, S.v., Groothuis-Oudshoorn, K., 2010. mice: multivariate imputation by chained equations in R. J. Stat. Software 1–68.

Buysse, D.J., Hall, M.L., Strollo, P.J., Kamarck, T.W., Owens, J., Lee, L., Reis, S.E., Matthews, K.A., 2008. Relationships between the Pittsburgh sleep quality index (PSQI), epworth sleepiness scale (ESS), and clinical/polysomnographic measures in a community sample. J. Clin. Sleep Med. 4, 563–571, 06.

Buysse, D.J., Reynolds Iii, C.F., Monk, T.H., Hoch, C.C., Yeager, A.L., Kupfer, D.J., 1991. Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). Sleep 14 (4), 331–338.

Conway, J.M., 2002. Method Variance and Method Bias in Industrial and Organizational Psychology.

Devine, J.K., Bertisch, S.M., Yang, H., Scott-Sutherland, J., Wilkins, A., Molina, V., Henrikson, K., Haack, M., 2019. Glucocorticoid and inflammatory reactivity to a repeated physiological stressor in insomnia disorder. Neurobiol. Sleep Circadian Rhythms 6, 77–84.

Eisma, M.C., de Lang, T.A., Boelen, P.A., 2020. How thinking hurts: rumination, worry, and avoidance processes in adjustment to bereavement. Clin. Psychol. Psychother.

Erlangsen, A., Runeson, B., Bolton, J.M., Wilcox, H.C., Forman, J.L., Krogh, J., Shear, M. K., Nordentoft, M., Conwell, Y., 2017. Association between spousal suicide and mental, physical, and social health outcomes: a longitudinal and nationwide register-based study. JAMA Psychiatr. 74 (5), 456–464.

Hardison, H.G., Neimeyer, R.A., Lichstein, K.L., 2005. Insomnia and complicated grief symptoms in bereaved college students. Behav. Sleep Med. 3 (2), 99–111.

Ikram, M.A., Brusselle, G., Ghanbari, M., Goedegebure, A., Ikram, M.K., Kavousi, M., Kieboom, B.C.T., Klaver, C.C.W., de Knegt, R.J., Luik, A.I., Nijsten, T.E.C., Peeters, R. P., Van Rooij, F.J.A., Stricker, B.H., Uitterlinden, A.G., Vernooij, M.W., Voortman, T., 2020. Objectives, design and main findings until 2020 from the Rotterdam Study. Eur. J. Epidemiol. 35 (5), 483–517.

Kim, S.Y., Kark, S.M., Daley, R.T., Alger, S.E., Rebouças, D., Kensinger, E.A., Payne, J.D., 2019. Interactive effects of stress reactivity and rapid eye movement sleep theta activity on emotional memory formation. Hippocampus.

Kosmadopoulos, A., Sargent, C., Darwent, D., Zhou, X., Roach, G.D., 2014. Alternatives to polysomnography (PSG): a validation of wrist actigraphy and a partial-PSG system. Behav. Res. Methods 46 (4), 1032–1041.

Kristensen, P., Dyregrov, K., Dyregrov, A., 2017. What distinguishes prolonged grief disorder from depression? Tidsskrift for den Norske laegeforening: tidsskrift for praktisk medicin, ny raekke 137 (7), 538–539.

Kushida, C.A., Chang, A., Gadkary, C., Guilleminault, C., Carrillo, O., Dement, W.C., 2001. Comparison of actigraphic, polysomnographic, and subjective assessment of sleep parameters in sleep-disordered patients. Sleep Med. 2 (5), 389–396.

Lancel, M., Stroebe, M., Eisma, M.C., 2020. Sleep disturbances in bereavement: a systematic review. Sleep Med. Rev. 101331.

Lundorff, M., Holmgren, H., Zachariae, R., Farver-Vestergaard, I., O'Connor, M., 2017. Prevalence of prolonged grief disorder in adult bereavement: a systematic review and meta-analysis. J. Affect. Disord. 212, 138–149.

Milic, J., Saavedra Perez, H., Zuurbier, L.A., Boelen, P.A., Rietjens, J.A., Hofman, A., Tiemeier, H., 2019. The longitudinal and cross-sectional associations of grief and complicated grief with sleep quality in older adults. Behav. Sleep Med. 17 (1), 31–40.

Monk, T.H., Begley, A.E., Billy, B.D., Fletcher, M.E., Germain, A., Mazumdar, S., Moul, D.
    E., Katherine Shear, M., Thompson, W.K., Zarotney, J.R., 2008. Sleep and circadian
    rhythms in spousally bereaved seniors. Chronobiol. Int. 25 (1), 83–98.

Monk, T.H., Germain, A., Buysse, D.J., 2009. The sleep of the bereaved. Sleep Hypn.: Int.
    J. Sleep Dream Hypn. 11 (1).

Nakajima, S., 2018. Complicated grief: recent developments in diagnostic criteria and
    treatment. Phil. Trans. Biol. Sci. 373 (1754), 20170273.

Prigerson, H.G., Frank, E., Kasl, S.V., Reynolds, C.F., Anderson, B., Zubenko, G.S.,
    Houck, P.R., George, C.J., Kupfer, D.J., 1995a. Complicated grief and bereavement-
    related depression as distinct disorders: preliminary empirical validation in elderly
    bereaved spouses. Am. J. Psychiatr. 152 (1), 22–30.

Prigerson, H.G., MaCiejewski, P.K., 2006. A call for sound empirical testing and
    evaluation of criteria for complicated grief proposed for DSM-V. Omega J. Death
    Dying 52 (1), 9–19.

Prigerson, H.G., Maciejewski, P.K., Reynolds Iii, C.F., Bierhals, A.J., Newsom, J.T.,
    Fasiczka, A., Frank, E., Doman, J., Miller, M., 1995b. Inventory of Complicated Grief:
    a scale to measure maladaptive symptoms of loss. Psychiatr. Res. 59 (1–2), 65–79.

Pyrke, R.J.L., McKinnon, M.C., McNeely, H.E., Ahern, C., Langstaff, K.L., Bieling, P.J.,
    2017. Evidence-based design features improve sleep quality among psychiatric
    inpatients. HERD: Health Environ. Res. Des. J. 10 (5), 52–63.

Reynolds, C.F., Hoch, C.C., Buysse, D.J., Houck, P.R., Schlernitzauer, M., Frank, E.,
    Mazumdar, S., Kupfer, D.J., 1992. Electroencephalographic sleep in spousal
    bereavement and bereavement-related depression of late life. Biol. Psychiatr. 31 (1),
    69–82.

Richardson, S.J., Lund, D.A., Caserta, M.S., Dudley, W.N., Obray, S.J., 2003. Sleep
    patterns in older bereaved spouses. Omega J. Death Dying 47 (4), 361–383.

Rosenzweig, A., Prigerson, H., Miller, M.D., Raynolds Iii, C.F., 1997. Bereavement and
    late-life depression: grief and its complications in the elderly. Annual Review of
    Medicine.

Rubin, D.B., 2004. Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons.

Stahl, S.T., Schulz, R., 2014. Changes in routine health behaviors following late-life
    bereavement: a systematic review. J. Behav. Med. 37 (4), 736–755.

Szuhany, K.L., Young, A., Mauro, C., García de la Garza, A., Spandorfer, J., Lubin, R.,
    Skritskaya, N.A., Hoeppner, S.S., Li, M., Pace-Schott, E., 2020. Impact of sleep on
    complicated grief severity and outcomes. Depress. Anxiety 37 (1), 73–80.

Tanimukai, H., Adachi, H., Hirai, K., Matsui, T., Shimizu, M., Miyashita, M., Tsuneto, S.,
    Shima, Y., 2015. Association between depressive symptoms and changes in sleep
    condition in the grieving process. Support. Care Canc. 23 (7), 1925–1931.

Tombaugh, T.N., McIntyre, N.J., 1992. The mini-mental state examination: a
    comprehensive review. J. Am. Geriatr. Soc. 40 (9), 922–935.

Van Someren, E.J.W., 1997. Actigraphic monitoring of movement and rest-activity
    rhythms in aging, Alzheimer's disease, and Parkinson's disease. IEEE Trans. Rehabil.
    Eng. 5 (4), 394–398.

Watling, J., Pawlik, B., Scott, K., Booth, S., Short, M.A., 2017. Sleep loss and affective
    functioning: more than just mood. Behav. Sleep Med. 15 (5), 394–409.

World Health, O., 2018. International Classification of Diseases for Mortality and
    Morbidity Statistics (11th Revision).

Wulff, K., Gatti, S., Wettstein, J.G., Foster, R.G., 2010. Sleep and circadian rhythm
    disruption in psychiatric and neurodegenerative disease. Nat. Rev. Neurosci. 11 (8),
    589.