# Perioperative brain functioning

*Effects of anesthesia on neurometabolism, cognition and sleep-wake timing*

van Zuylen, M.L.

**Publication date**
2022

**Citation for published version (APA):**
van Zuylen, M. L. (2022). *Perioperative brain functioning: Effects of anesthesia on neurometabolism, cognition and sleep-wake timing*. [Thesis, fully internal, Universiteit van Amsterdam].

# CHAPTER 6

## The effects of surgery and general anaesthesia on sleep-wake timing: CLOCKS observational study

Mark L. van Zuylen, Arjen J.G. Meewisse, Werner ten Hoope, Wietse J. Eshuis,
Markus W. Hollmann, Sarah E. Siegelaar, Dirk Jan Stenvers, Jeroen Hermanides

*Adapted from:*
*Anaesthesia; January 2022, 77(1):73-81.*

# SUMMARY

Surgery and general anesthesia have the potential to disturb the body's circadian timing system, which may affect postoperative outcomes. Animal studies suggest that anesthesia could induce diurnal phase shifts, but clinical research is scarce. We hypothesized that surgery and general anesthesia would result in perioperative changes in diurnal sleep-wake patterns in patients. In this single center prospective cohort study, we recruited patients ≥ 18 years scheduled for elective surgery receiving ≥30 minutes of general anesthesia. The Munich Chronotype Questionnaire and Pittsburgh Sleep Quality Index were administered to determine baseline chronotype, sleep characteristics and sleep quality. Perioperative sleeping patterns were logged. Ninety-four patients with a mean (SD) age of 52 (17) years were included; 56 (60%) were female. The midpoint of sleep (SD) three nights before surgery was 03:33 (55 min) and showed a phase advance of 40 minutes to 02:53 (67 min) the night after surgery ($P < 0.001$). This correlated with the midpoint of sleep three nights before surgery and was not associated with age, sex, duration of general anesthesia or intra-operative dexamethasone use. Perioperatively, patients had lower subjective sleep quality and worse sleep efficiency. Disruption started from one night before surgery and did not normalize up until six days after surgery. We conclude that there is a perioperative phase advance in midpoint of sleep, confirming our hypothesis that surgery and general anesthesia disturb the circadian timing system. Patients had decreased subjective sleep quality, worse sleep efficiency and increased daytime fatigue.

# INTRODUCTION

All mammals possess a circadian timing system that generates 24-h rhythms in many physiological processes. The central clock is situated in the hypothalamic suprachiasmatic nucleus, and this nucleus forwards its timing signal to peripheral 'clocks' throughout the body via hormonal and neuronal signals [60]. The suprachiasmatic nucleus co-ordinates 24-h rhythms in sleep-wake activity, hormone secretion, metabolism, cognitive functioning and autonomous nervous system activity [61]. Individuals differ in chronotype, reflected by their preferred sleep-wake timing, expressed as the midpoint of sleep (i.e. time at which a person is in mid-sleep on work-free days), thus resulting in 'larks' (people with an early midpoint of sleep who generally go to bed early and wake up early) and 'owls' (people with a later midpoint). Further definitions of these and other terms used in this field are given in Supplementary Table 1.

Several aspects of anesthetics have the potential to disturb the circadian timing system. The suprachiasmatic nucleus neurons contain NMDA and GABA receptors, and activation of these receptors affects clock gene expression and entrainment of the internal clock [64]. Most drugs used for general anesthesia are either NMDA-receptor-antagonists or GABA-agonists [64]. In animal studies, general anesthesia induced strong diurnal (i.e. daily) phase shifts, depending on the internal time at which hypnotics are given [65]. A phase shift means that the peak and trough of a diurnal rhythm will shift to earlier or later in the day (phase advance vs. phase delay). In the case of sleep-wake rhythms, a phase advance means that the midpoint of sleep shifts to earlier in the night, and a phase delay means that the midpoint of sleep shifts to later in the night. Human observational postoperative studies showed a delay in the endogenous rhythm of plasma melatonin levels and melatonin metabolite excretion. Moreover, disturbances in the core body temperature and in the daily rhythm of serum cortisol secretion were also found [66-68]. Glucocorticoids, which are frequently administered during surgery, mimic endogenous cortisol and have strong effects on the molecular clock [69].

The potential disruption of the circadian timing system by anesthesia is relevant, as circadian disturbances and sleep irregularity can worsen human health [62] and disturbance of the circadian timing system might negatively affect an individual's ability to recover from surgery [63]. Knowledge about the impact of anesthesia on the internal clock could enable 'chronotherapy', where the timing of medical interventions such as surgery and administration of medication are timed to match an individual patient's endogenous rhythm. This principle is already applied in administration of some chemotherapies [172] and statins [173].

Therefore, we examined the perioperative changes in sleep-wake rhythm in patients undergoing elective surgery with general anesthesia by measuring pre- and post-surgery sleep timing and subjective sleep quality. We hypothesized that surgery and general anesthesia have a phase-shifting effect on an individual's rhythm, whereby the effect depends on medication types used and their timing relative to the individual's normal midpoint of sleep, resulting in a worsened subjective sleep quality after surgery.

## METHODS

The CLOCKS study was a single center prospective cohort study. The study was approved by the local medical ethics committee. Informed consent was obtained from all patients before start of the study, which was performed according to the Declaration of Helsinki [174] and registered [175]. Performance, recording, analysis and reporting was done according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for reporting observational studies [176].

Adult patients (≥18 years old) scheduled for elective surgery under general anesthesia lasting ≥30 min were recruited in the pre operative assessment at the outpatient clinic of the Department of Anesthesiology, Amsterdam UMC. Patients were screened for eligibility and included during July and August 2020.

To minimize bias from known contributors of disturbed perioperative circadian rhythm, patients with an increased risk of postoperative delirium were not eligible to participate in the study (i.e. patients undergoing cardiac surgery; those of ASA physical status grade 3 or 4; and patients scheduled for postoperative ICU admission). Further exclusion criteria were night-shift work the week before or after surgery, or general anesthesia in the month before inclusion. We determined that patients experiencing postoperative delirium, diagnosed using the Delirium Observation Screening scale, would be excluded *post hoc*.

In order to determine a shift in sleep-wake rhythm, a day-to-day sleeping log was used for tracking sleep-wake patterns during the study period. The Munich-ChronoType-Questionnaire (MCTQ) [177] was used to calculate baseline midpoint sleep on work-free days and to determine chronotype, which is determined by correcting midpoint sleep on work-free days for sleep deficit on workdays (abbreviated to MSFsc). The MCTQ contains questions about sleep duration; sleep on- and offset time; sleep latency; sleep inertia;, alarm clock use; and percentage of patients taking naps. It is a validated questionnaire to determine chronotype and correlates with diurnal patterns in the plasma levels of melatonin and cortisol [178].

To assess subjective sleep quality, the Pittsburgh Sleep Quality Index (PSQI) [179] was used, a useful tool for studying subjective sleep quality in clinical groups [180]. The PSQI has 19 questions measuring seven domains important in impaired sleep quality: subjective sleep quality; sleep duration; sleep disturbances; sleep latency; habitual sleep efficiency; use of sleep medication; and daytime fatigue, making up a total score between 0 and 21, with higher scores indicating a lower sleep quality. The PSQI was filled in twice: three days before surgery, and again seven days after surgery. The first questionnaire was used to determine baseline subjective sleep quality in the month prior to surgery, so patients could act as their own control. The second questionnaire measured subjective sleep quality in the week after surgery. Relevant patient characteristics and perioperative data were also obtained.

The primary outcome was the diurnal phase shift the night after surgery, measured by comparing the midpoint of sleep three nights before surgery (as measured by the sleeping log) to midpoint of sleep the night after surgery.

As secondary outcomes we analysed the night-to-night changes from the three nights before to seven nights after surgery in midpoint of sleep and other sleep variables (i.e. sleep duration; sleep on- and offset times; sleep latency and inertia; alarm clock use; and percentage of patients taking naps). To account for possible confounding because of hospitalisation, sleep variables for day surgery were compared to data for inpatient surgery. To determine which factors might affect a possible phase shift the night after surgery, baseline and perioperative patient characteristics were correlated with possible change in the midpoint of sleep the night after surgery, Δ-NAS denoting the deduction of the midpoint of sleep the night after surgery from the midpoint of sleep three nights before surgery. Pre operative and one week postoperative subjective sleep quality, as measured by the PSQI questionnaire, were compared to assess how surgery and general anesthesia affect the quality of sleep.

One study, observing changes in circadian rhythm in 35 stroke patients, showed a mean (SD) MSFsc (midpoint sleep on work-free days corrected for sleep deficit on workdays) of

03:00 (48 min) before and 03:18 (48 min) after stroke [181]. To be able to detect a shift of 18 min with the reported SD of 48 min, we needed a sample size of at least 58 patients to obtain this effect-size (Cohen's *d*) at a significance level of 0.05 (ß = 0.8).

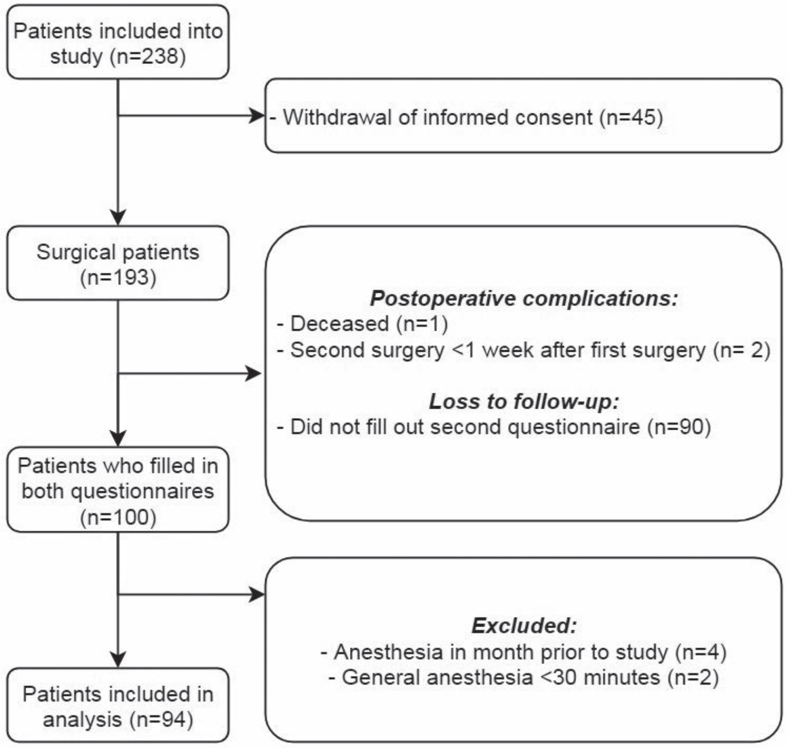
Baseline characteristics such as age, ASA physical status classification [79], surgical risk stratification [182] and perioperative complications were assessed and compared for all included patients, including those lost to follow-up. Normality was assessed using the Shapiro-Wilk test. When data were normally distributed, a paired t-test was performed, when data were non-normally distributed a Mann-Whitney U test was used for comparison.

Phase shift on the first night after surgery versus midpoint of sleep three nights before surgery was analysed using a paired t-test. Linear regression was used to analyse the effects of midpoint of sleep three nights before surgery on the diurnal phase shift the first night after surgery. Multivariable regression was used to determine whether any of the potential predictors were significant. Sleeping log data (sleep duration; sleep on- and offset times; sleep latency and inertia; alarm clock use; and percentage of patients taking naps) were compared and visualized using repeated measures ANOVA for continuous dependent variables and Wilcoxon signed-rank tests for categorical dependent variables. Spearman's correlation was used to correlate patient characteristics, perioperative data and circadian variables with Δ-NAS. Pre- and postsurgical total PSQI scores and PSQI subscales were compared using paired t-tests to evaluate if subjective sleep quality deteriorated after surgery and general anesthesia. Lastly, Spearman's correlation was used to examine if increased Δ-NAS resulted in a lower subjective sleep quality after surgery.

## RESULTS

We included patients over a period of two months (July and August 2020). A total of 319 patients were eligible for inclusion, of whom 238 provided informed consent. A total of 100 patients filled in both sets of questionnaires. After exclusion, 94 patients were included in the analysis (Fig. 1). Patient characteristics of all excluded patients are presented and compared to the included patients in Supplementary Table 2. Mean age (SD) of included patients was 52 (17) years and 56 (60%) were female. Type of surgery, anesthetic drugs used, and duration of general anesthesia are listed in Table 1. Surgical characteristics and length of hospital stay are listed in Supplementary Table 3.

***Fig. 1. Flowchart denoting recruitment of patients into study.***



The midpoint of sleep (SD) three nights before surgery was 03:33 (55 min) and showed a phase advance to 02:53 (67 min) on the night after surgery ($P < 0.001$). The phase advance correlated with midpoint of sleep three nights before surgery ($P < 0.001$) with an $R^2$ of 0.143 and a regression coefficient (95% CI) of 0.38 (0.20 – 0.67) (Fig. 2), and was not associated with age ($P = 0.83$), sex ($P = 0.81$), length of general anesthesia ($P = 0.32$) or intra operative dexamethasone use ($P = 0.82$). This means that the later a patient's midpoint of sleep is normally, the more phase advance is to be expected after surgery and general anesthesia. In contrast, the earlier a patient's midpoint of sleep normally is, the smaller the phase advance, and in very early chronotypes surgery may induce a phase delay (Fig. 2).

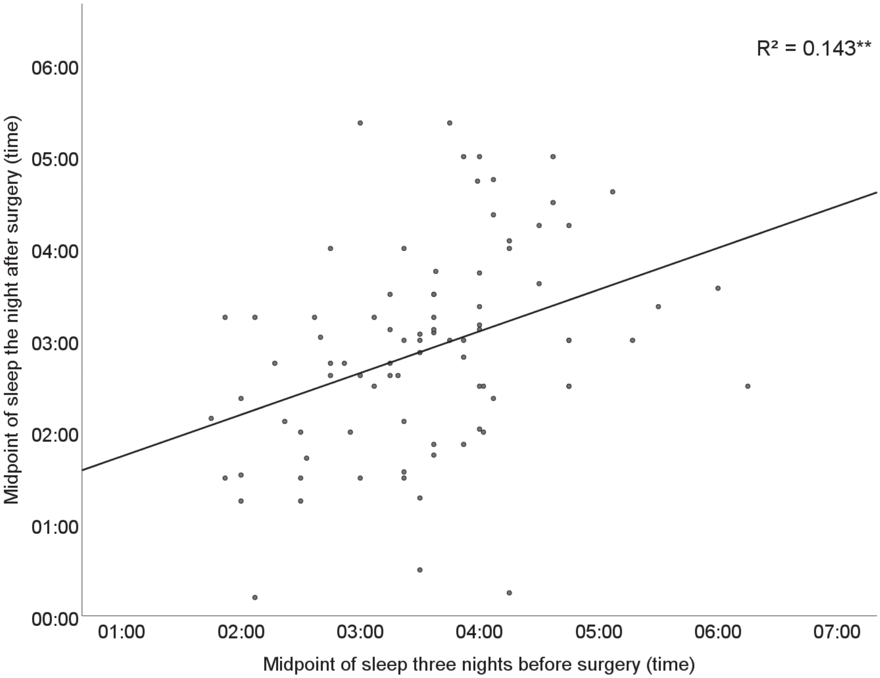
*Table 1. Participant characteristics.*

| **Baseline characteristics (n=94)** | | |
|---|---|---|
| | **Age, years** | 52 (16.9) |
| | **Female sex** | 56 (59.6%) |
| | **ASA physical status classification** | |
| | I | 33 (35.1%) |
| | II | 61 (64.9%) |
| | **Surgical risk stratification** | |
| | Minor | 49 (52.1%) |
| | Moderate | 43 (45.7%) |
| | Major | 2 (2.1%) |
| | **Anesthetic induction agent** | |
| | Propofol | 92 (97.8%) |
| | Sevoflurane | 1 (1.1%) |
| | Thiopentone | 1 (1.1%) |
| | **Anesthetic maintenance agent** | |
| | Propofol | 85 (90.4%) |
| | Sevoflurane | 7 (7.4%) |
| | Propofol+sevoflurane | 2 (2.1%) |
| | **Duration of general anesthesia** | |
| | 30 min - 1 h | 12 (12.8%) |
| | 1-2 h | 40 (42.5%) |
| | 2-4 h | 27 (28.7%) |
| | ≥4 h | 15 (16.0%) |
| **Sleep parameter characteristics** | | |
| | **Number of workdays per week** | |
| | 0 workdays | 26 (27.7%) |
| | 1-3 workdays | 27 (28.7%) |
| | 4-6 workdays | 41 (43.6%) |
| | **Shift work in previous 3 months** | 6 (6.4%) |
| | **Sleep variables, workdays** | |
| | Sleep onset time | 23:15 (23:00 - 00:00 [20:45 - 2:15]) |
| | Sleep latency, min | 15 (10 – 15 [0 – 120]) |
| | Time of awakening | 07:00 (06:11 – 07:45 [04:45 – 10:00]) |
| | Sleep inertia, min | 15 (5 - 30 [0 – 165]) |
| | Use of alarm clock | 45 (47.9%) |
| | Total duration of sleep, h and min | 7h 45m (1h13m) |
| | Patients taking a regular nap | 15 (16.0%) |
| | Total nap time, min | 45 (30 – 75 [15 – 180]) |
| | Total time spent outside in daylight, min | 180 (88 - 300 [0 – 650]) |

| **Baseline characteristics (n=94)** | | |
|---|---|---|
| | **Sleep variables, work-free days** | |
| | Sleep onset time | 23:45 (23:15 – 00:45 [21:15 – 02:30]) |
| | Sleep latency, min | 15 (15 – 15 [0 – 120]) |
| | Time of awakening | 08:00 (07:00 – 08:30 [05:00 – 11:30]) |
| | Sleep inertia, min | 30 (15 – 49 [0 – 150]) |
| | Use of alarm clock | 10 (10.6%) |
| | Total duration of sleep, h and min | 8h (2h4m) |
| | Patients taking a regular nap | 20 (21.3%) |
| | Total nap time, min | 60 (34 – 90 [15 – 240]) |
| | Total time spent outside in daylight, min | 240 (150 – 350 [10 – 720]) |
| | **Chronotype (MSFsc)[a], hh:mm** | 03:35 (55m) |

*Values are mean (SD), number (proportion) or median (IQR [Range]).*
*a = midpoint sleep on work-free days corrected for sleep deficit on workdays*
*ASA = American Society of Anesthesiologists*

***Fig. 2. Correlation of midpoint of sleep the night after surgery with midpoint of sleep three nights before surgery.***



*** P ≤ 0.01*

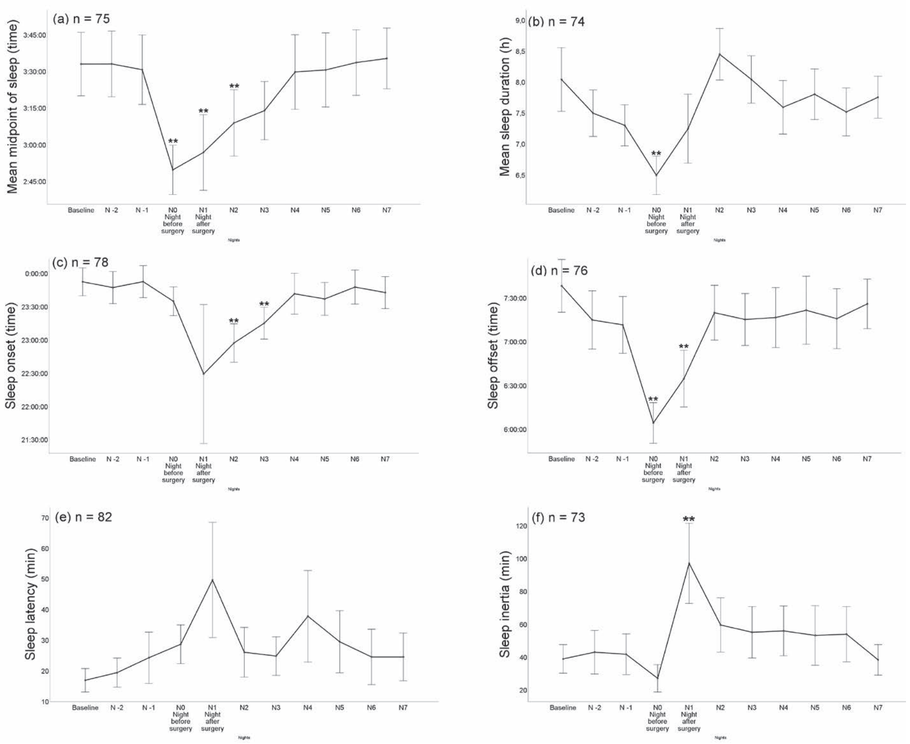
A phase advance of sleep timing compared to three nights before surgery was observed from the night before surgery, up to one night after surgery (F (7.27, 538.18) = 12.13; $P < 0.001$) (Fig. 3a). Time of sleep offset and sleep duration, also significantly changed from the night before surgery, which persisted until the night after surgery (Figs. 3b and 3d).

An increased use of an alarm clock the days preceding surgery, compared to baseline alarm clock use, was observed (Fig. 4a). Surgery with general anesthesia elicited an increase in the percentage of patients taking naps on the first day after surgery, which was not associated with the duration of general anesthesia ($P = 0.80$), age ($P = 0.783$), intra-operative dexamethasone use ($P = 0.557$) and sex ($P = 0.28$), and this increase lasted until the sixth day after surgery (Fig. 4b). Time of sleep onset, sleep latency and sleep inertia also significantly changed from baseline after surgery and did not normalize up until two days postoperatively (Figs. 3c, 3e and 3f). There were no between-group differences in sleep variables in the nights immediately following surgery when comparing day surgery with inpatient surgery.

In patients undergoing surgery under general anesthesia, Δ-NAS increased when patients had surgery during the afternoon compared to the morning ($r_s = 0.29$; $P = 0.01$) or with an increased Δ-induction (i.e. midpoint of sleep three days before surgery subtracted from time of induction of anesthesia) ($r_s = 0.209$; $P = 0.043$). Thus, the later surgery or induction took place, the larger the observed phase advance. Conversely, there was a moderate negative correlation between the Δ-NAS and patients' baseline chronotype ($r_s = -0.43$; $P < 0.001$), meaning that later chronotypes have smaller phase shifts (Supplementary Table 4). No significant correlations were found between Δ-NAS and patient characteristics or perioperative data (Supplementary Table 5).

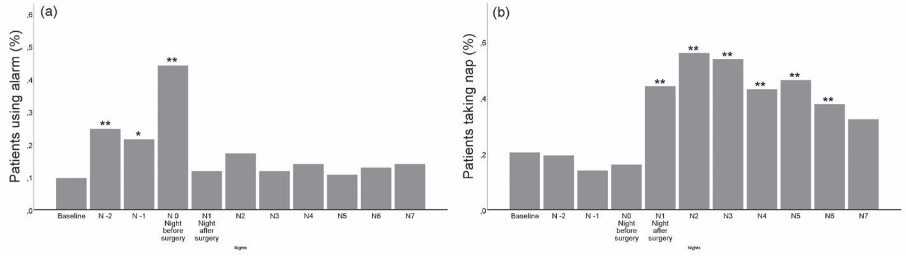
Pre- and postoperative total PSQI scores were correlated with question 6 of the PSQI ("How would you rate your own sleep quality in the last month?"), showing that a high total score corresponds to poor subjective sleep quality ($r_s = 0.75$; $P < 0.001$ and $r_s = 0.77$; $P < 0.001$). Pre- and postoperative PSQI scores and multiple subscales were compared. Total PSQI scores (SD) rose from 6.43 (3.98) to 9.06 (4.38) ($P < 0.001$). Several components of the PSQI were significantly different after surgery and general anesthesia: patients went to bed earlier; had a shorter total sleep duration; worse sleep efficiency; more sleep disturbance; increased sleep latency; more daytime fatigue; used more sleep medications; and had a lower subjective sleep quality (Table 2). Finally, the data show a more negative Δ-NAS is associated with worse subjective sleep quality after surgery ($r_s = -0.326$; $P = 0.002$).

***Fig. 3. Perioperative sleep variables over time (baseline to 7 nights after surgery).***



*(a) Midpoint of sleep (b) Sleep duration (c) Sleep onset (d) Sleep offset (e) Sleep latency (f) Sleep inertia (g) Percentage of patients using an alarm clock. Greenhouse-Geisser corrected.*
*** P ≤ 0.01. The number of patients completing each item is shown in the upper left corner.*

***Fig. 4. (a) Percentage of patients using an alarm clock or (b) taking naps over time (baseline to 7 nights after surgery).***



** P ≤ 0.05 / ** P ≤ 0.01*

***Table 2. Comparison between pre- and post operative PSQI-scores. Values are mean (SD) or median (IQR [Range]).***

| | **Pre operative** | **1 week post-operative** | ***P*-value** |
|---|---|---|---|
| Total PSQI score (all 7 subscales) | 6.43 (3.98) | 9.06 (4.38) | < 0.001 |
| Time patient went to bed | 22:53 (0:54) | 22:40 (0:52) | 0.006 |
| Time patient got out of bed | 7:43 (1:32) | 7:58 (1:05) | 0.10 |
| Sleep duration | 7h 20m (1h 21m) | 6h 57m (1h 31m) | 0.013 |
| Time spent in bed, h | 9h13m (2h 26m) | 9h 34m (2h 1m) | 0.19 |
| Percentage sleep efficiency | 82.0 (15.4) | 74.4 (17.2) | < 0.001 |
| Subscale 'Sleep Disturbance' (range 0-3) | 1 (1 - 2 [0 – 2]) | 1 (1 - 2 [1 – 3]) | 0.007 |
| Subscale 'Latency' (range 0-3) | 1 (1 - 2 [0 – 3]) | 1 (0 - 2 [0 – 3]) | 0.02 |
| Subscale 'Daytime Fatigue' (range 0-3) | 1 (0 - 1 [0 – 3]) | 1 (1 - 2 [0 – 3]) | < 0.001 |
| Use of sleep medication (range 0-3) | 0 (0 - 0 [0 – 3]) | 0 (0 - 2 [0 – 3]) | < 0.001 |
| Subjective sleep quality (range 0-3) | 1 (1 - 1 [0 – 3]) | 1 (1 - 2 [0 – 3]) | < 0.001 |

*PSQI = Pittsburgh Sleep Quality Index*

## DISCUSSION

In this prospective cohort study we observed a significant perioperative diurnal phase advance in patients undergoing surgery and general anesthesia. This phase advance correlated with midpoint of sleep three nights before surgery, Δ-induction (midpoint of sleep three days before surgery subtracted from time of induction of anesthesia) and time of surgery, but not with other baseline and perioperative patient characteristics, and was associated with lower subjective sleep quality in the week after surgery.

Interestingly, midpoint of sleep on the night prior to surgery was already advanced compared to three nights before surgery. Our data suggest that the phase advance before surgery can be explained by a shorter sleep duration, earlier wake up time, and alarm clock use. Other possible factors such as pre operative fasting and stress from the impending surgery might also play a role. Conversely, the phase advance in the nights after surgery was associated with higher sleep latency and inertia. Other postoperative sleep alterations were observed, such as an increased sleep duration. The changes in sleep variables immediately after surgery were independent of whether a patient had undergone day surgery or had been hospitalized overnight.

Our results support earlier research showing that sleep and sleep-wake rhythms can be negatively affected by surgery. Patients' pre operative diurnal rhythm of physical activity may be associated with an increased risk of developing postoperative delirium

[39] Other studies have described associations between surgery and reduced night-time melatonin levels [68]; reduced sleep duration and sleep efficiency; reduced day-time physical activity; more frequent and lengthy night-time awakenings; and increased numbers of naps during the daytime [183]. Reduced postoperative sleep quality has also been linked to worse post-surgical recovery [184]. Although daytime napping in non-surgical populations has been linked to better cognitive function [185], unintentional napping is associated with worse cognitive functioning [186]. In our study, subjective sleep quality deteriorated in the nights after surgery despite an increased sleep duration. This reduced subjective sleep quality after surgery may be due to physical recovery from surgery and pain [187].

Two smaller studies have previously revealed a phase delay, rather than an advance, after surgery [66, 67]. However, these studies had very small sample sizes and did not examine sleep-wake timing, but rather assessed core body temperature and melatonin release. Nonetheless, it is possible that rather than phase advancing the whole circadian system, surgery with general anesthesia creates internal desynchronisation. The increased percentage of patients taking naps after surgery and the deteriorated sleep efficiency at night observed in the present study might be an expression of this.

Our findings suggest that perioperative sleep interventions to fasten postoperative recovery should not only entail improving sleep quality and duration, but should also focus on circadian realignment. However, means of preventing this perioperative phase shift and improving sleep quality, need to be examined in clinical intervention studies.

Prior studies have found propofol to cause a phase shift dependent upon the timing of administration, with the largest phase advance observed when administered close to the end of the light period [188]. Most of our patients (98%) received propofol, therefore, the observed correlation between phase shift and Δ-induction might be explained with a time of induction closer to the end of the light period [189]. Perioperative stress [190] on the suprachiasmatic nucleus or exposure to bright light [177] may also contribute to diurnal phase shifts. Furthermore, dexamethasone administration has timing-dependent circadian effects [191] and a large proportion of patients in this study (88%) received intra-operative dexamethasone. This was not associated with a larger phase advance; however, our sample size was not calculated to detect these changes.

A limitation of our study was the considerable loss to follow-up, as often experienced with studies using questionnaires sent through email [192]. This may have caused bias, as patients with sleeping difficulties may have been more inclined to fill in the questionnaires. A total of 45 patients withdrew their consent before the first questionnaires were completed, for the most part because patients thought it would take them too long to complete the questionnaires around a surgical procedure. The ongoing COVID-19 pandemic may also have played a role in this. It cannot be excluded that this may have caused some bias, but the group of patients who withdrew their informed consent did not differ significantly from the other patients (both in- and exclusions). Also, only patients undergoing elective surgery with general anesthesia were included to test the hypothesis. As such, we did not include patients undergoing elective surgery with regional anesthesia in the cohort, and therefore cannot distinguish the role of surgery from that of general anesthesia. Nonetheless, this is the first adequately powered study in humans that examined the role of surgery and general anesthesia on sleep-wake timing.

Due to our sample size and the included low-risk surgical population we cannot draw conclusions on the relation between perioperative phase shifts and postoperative surgical recovery or postoperative complications. Tracking diurnal phase shifts and sleeping patterns in a control group of patients scheduled for elective surgery under regional anesthesia may further delineate the specific effects of surgery and general anesthesia on sleep-wake behaviour. Future research should also focus on the question whether surgery and/or general anesthesia cause a phase advance of the entire circadian system or a desynchronisation of the circadian rhythm by simultaneously assessing central and peripheral clock rhythms [188].

This study showed that surgery with general anesthesia causes a significant phase shift of diurnal sleep- wake rhythms and deteriorates sleep quality. Potential mechanisms include timing-dependent effects of propofol administration or effects of perioperative stress on the suprachiasmatic nucleus. It is important that future studies distinguish the role of surgery in diurnal phase shifts from that of general anesthesia. In the future, we will further investigate the role of perioperative phase shifts in surgical recovery and postoperative complications.