The effect of caffeine on subsequent sleep: A systematic review and meta-analysis

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ABSTRACT

The consumption of caffeine in response to insufficient sleep may impair the onset and maintenance of subsequent sleep. This systematic review and meta-analysis investigated the effect of caffeine on the characteristics of night-time sleep, with the intent to identify the time after which caffeine should not be consumed prior to bedtime. A systematic search of the literature was undertaken with 24 studies included in the analysis. Caffeine consumption reduced total sleep time by 45 min and sleep efficiency by 7%, with an increase in sleep onset latency of 9 min and wake after sleep onset of 12 min. Duration (+6.1 min) and proportion (+1.7%) of light sleep (N1) increased with caffeine intake and the duration (−11.4 min) and proportion (−1.4%) of deep sleep (N3 and N4) decreased with caffeine intake. To avoid reductions in total sleep time, coffee (107 mg per 250 mL) should be consumed at least 8.8 h prior to bedtime and a standard serve of pre-workout supplement (217.5 mg) should be consumed at least 13.2 h prior to bedtime. The results of the present study provide evidence-based guidance for the appropriate consumption of caffeine to mitigate the deleterious effects on sleep.

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1. Introduction

Sleep is an essential component of physical and emotional wellbeing [1]. Current recommendations outline the need for healthy adults to achieve seven to nine h of sleep per night [2]. Despite the innate requirement to attain healthy sleep, insufficient sleep is a growing public health challenge. It is estimated that 20–45% of the population around the world are sleep deprived [3–6]. Short and fragmented sleep bouts may result in impaired cognitive functioning, diminished mood, and increased risk of accident or injury [1]. When sustained chronically, insufficient sleep contributes to the risk of health epidemics with a heightened probability of cardiometabolic disease and mental health disorders [7,8]. Negative outcomes of this nature carry a significant cost to the individual and society, through compromised health and reduced productivity [9]. As such, recommendations for positive sleep behaviours have been developed to provide individuals with strategies to optimise their sleep quantity and quality [10].

A common behavioural recommendation to optimise sleep is to avoid caffeine in close proximity to bedtime [10]. Caffeine is a widely accessible psychostimulant found in foods, supplements, and medications [11]. With its status as a socially acceptable drug, caffeine is consumed by approximately 80% of the world's population [12]. Caffeine is an adenosine antagonist suggested to acutely reduce sleep pressure through action on the homeostatic component of sleep-wake regulation [13]. This action stimulates the central nervous system with a resulting decrease in the perception of fatigue and sleepiness [14]. For this reason, caffeine is commonly consumed throughout the day in response to insufficient sleep to promote a state of wakefulness [15]. However, the use of caffeine to stimulate wakefulness may result in impaired onset and maintenance of subsequent sleep [16], potentially creating a cycle of diminished sleep and subsequent caffeine reliance [17].

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Abbreviations

CI	confidence interval
EEG	electroencephalogram
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
N1	non-rapid eye movement stage one
N2	non-rapid eye movement stage two
N3	non-rapid eye movement stage three
N4	non-rapid eye movement stage four
NREM	non-rapid eye movement
REM	rapid eye movement

The half-life of caffeine displays large variation across healthy adults (two to 10 h) [18], making it difficult to identify the appropriate time of day to discontinue caffeine intake to minimise disruptions to sleep. Currently, recommendations for positive sleep behaviours display a lack of precision in terminology. For example, the American Academy of Sleep Medicine warns that caffeine may cause sleep disruption if taken "too close to bedtime" [19], while the Sleep Health Foundation suggests consumers should "avoid caffeine close to bedtime" [20]. The lack of precision in these recommendations may limit the ability of consumers to make evidence-based decisions regarding the timing of their caffeine intake. A previous systematic review by Clark and Landolt [21] confirmed the negative association between caffeine and subsequent sleep. However, this review did not include a quantitative synthesis of the findings. In particular, the impact of the dose and timing of caffeine intake on subsequent sleep has yet to be quantified systematically. The aims of this systematic review and meta-analysis are to: 1) establish the level of evidence for the effect of caffeine intake on the characteristics of subsequent sleep (i.e., total sleep time, sleep onset latency, rapid eye movement (REM) onset latency, wake after sleep onset, sleep efficiency, sleep architecture, and subjective sleep quality; 2) quantify the effect of caffeine intake on the characteristics of subsequent sleep; and 3) quantify the influence of the dose and timing of caffeine intake on the characteristics of subsequent sleep. The review will provide evidence-based guidance to support recommendations regarding caffeine consumption to minimise decrements in subsequent sleep.

2. Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) 2020 guidelines [22]. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42021267812).

2.1. Databases and search strategy

Four electronic databases were systematically searched from their inception until June 2021. These databases were CINAHL, MEDLINE, SPORTDiscus, and Web of Science. The search strategy was developed using the PICO (Population, Intervention, Comparison, and Outcome) framework [22] and the search terms are detailed in Table 1. The terms employed within each component were searched using the Boolean operator "OR" and each component was linked together through the Boolean operator "AND" to run the search. Results were limited to peer-reviewed journal articles published in the English language that examined humans

only. All search records were exported to the Endnote reference managing software (V20, Thomson Reuters, Philadelphia, USA).

2.2. Study screening and selection

Duplicate results were removed, and the remaining articles were screened by two independent reviewers (CG and JW) using the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Discrepancies in decisions were resolved by a third reviewer (SH) when necessary. Title and abstract screening were initially completed to remove articles outside the scope of the review. For all remaining articles, full-text versions were located for screening. Studies were included if they: 1) employed a healthy adult population aged 18–65 years; 2) used a controlled experimental design; 3) administered a measured caffeine dose; and 4) implemented a protocol involving a measured sleep episode initiated in the subsequent evening with a morning waking. In instances where additional interventions were examined, such as exercise, studies were included if the effect of caffeine could be isolated. Studies were excluded if: 1) the duration of measured sleep was <90 min (defined as a napping protocol); 2) the caffeine dose was administered >18 h prior to the scheduled sleep episode; 3) the caffeine dose was administered after the onset of the scheduled sleep episode; or 4) measures of sleep were not reported.

2.3. Assessment of reporting quality

The methodological reporting quality of included studies was assessed using the Cochrane Risk of Bias (RoB 2) tool for crossover trials [23]. The tool specifies six domains to assess potential sources of bias including that arising from the randomisation process, period and carryover effects, deviations from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain is comprised of signalling questions that can be answered as "yes", "probably yes", "no", "probably no", or "no information". A risk of bias judgement is generated for each domain by a pre-determined algorithm with classifications of "low risk", "some concern", or "high risk". Judgements across domains are used to classify the overall risk of bias. A study was deemed to be "low risk" only if this was true for all domains. If not, a study was assessed for overall risk in accordance with the highest risk of bias recorded across each domain.

2.4. Data extraction and synthesis

For each study, data were extracted into a pre-defined Microsoft Excel (V2201, Microsoft, Washington, USA) template under the categories of study details, characteristics of the participants, study protocol, objective measurement tools, subjective measurement tools, and sleep outcome measures. For the purpose of this review, time in bed was defined as the period between lights off and lights on with total sleep time defined as the time spent asleep during this period. Sleep efficiency was calculated as the percentage of time in bed spent asleep. Sleep onset latency was accepted as the time from lights out to the first epoch of sleep, except where the author defined this to occur beyond non-rapid eye movement (NREM) stage one (N1) [24–30]. Where activity monitoring was employed [31–33], sleep onset latency was accepted as the period between bedtime and the start of sleep. REM onset latency was accepted as the time from sleep onset to the first occurrence of REM, except in one study where it was defined as the first occurrence of REM from the first occurrence of NREM stage two (N2) [30]. Wake after sleep onset was defined as the duration of time spent awake after the onset of sleep and before the final awakening. Outcome data

Table 1
Search strategy.

	Population or Problem	Intervention	Comparison	Outcome
Keywords	"sleep" NOT "deprivation" NOT "dementia" NOT "Parkinson*" NOT "sclerosis" NOT "cancer" NOT "infant" NOT "neonate" NOT "child*" NOT "mice" NOT "mouse" NOT "rat" NOT "rats" NOT "macaque*"	"caffeine" OR "caffeinated" OR "1,3,7-trimethylxanthine" OR "coffee"	N/A	"sleep quality" OR "quality of sleep" OR "sleep quantity" OR "sleep duration" OR "sleep time" OR "time in bed" OR "sleep efficiency" OR "sleep latency" OR "sleep onset" OR "sleep stage" OR "sleep architecture" OR "slow wave" OR "non rapid eye movement" OR "NREM" OR "rapid eye movement" OR "REM" OR "sleep-wake" OR "sleep maintenance" OR "sleep satisfaction" OR "wake after sleep" OR "sleep arousal" OR "sleep disturbance" OR "awakening from sleep" OR "EEG" OR "electroencephalogram"

reported as NREM stage three (N3) and NREM stage four (N4) [28–30,34–36] or slow wave sleep [25,27,37–41] were classified as N3 sleep in line with the current American Academy of Sleep Medicine guidelines [42], except for two studies [24,43] where N3 and N4 were reported independently. Outcome data reported as a combination of distinctly different sleep stages [27,36] were excluded from the meta-analysis. All data were extracted as the mean and standard deviation for each study condition. Where mean data were reported with the standard error of the mean [24,30,31,34,37,40,44–46], confidence interval (CI) [25], or coefficient of variability [35], calculations were performed to transform these measures into standard deviations. One study [26] did not report a measure of variance and was not included in the quantitative synthesis of the review. Where necessary, corresponding authors were contacted for further information.

2.5. Meta-analysis and meta-regression

Meta-analysis was performed using the "metafor" [47] and "clubSandwich" [48] packages in the R programming language (R Core Team, 2021). For each outcome variable, the mean difference effect size and sampling variance for each study were calculated. Since all included studies utilised a cross-over design, dependency was accounted for when computing sampling variance using previously described methods [49]. However, none of the included studies reported the required correlation between outcomes in the two conditions (control and caffeine). Through author contact, correlation data were obtained for four studies [41,45,46,50], which were included in the computations. For the remaining studies, the pooled correlation value was used from the four studies where correlation data were obtained. Due to the uncertainty from deriving the correlation from a subset of studies, a sensitivity analysis was conducted to ensure the results were robust. Further details of handling of correlation data and the sensitivity analysis can be found in Supplementary Fig. S1.

Effect sizes were then pooled across studies using a random effects model, with a restricted maximum likelihood method used to estimate between-study variance. It was noted that some studies included more than one caffeine condition, and therefore provided multiple effect sizes estimates, where both the effect sizes and standard errors were correlated. To account for these dependencies, a nested random effects structure was used and a covariance matrix was imputed. Since there is uncertainty around the correlation value used for imputation, robust inference methods with an adjustment for small samples was used, so that the interpretation of fixed effects were unbiased [51]. Where additional data were available related to the dose of caffeine and the timing of intake, moderator (meta-regression) analysis was performed to assess the influence of these potential effect modifiers on sleep outcomes. Where a significant effect for timing of intake was found, the meta-regression model was used to estimate

the cut-off time (i.e., the latest time at which caffeine can be consumed without having a statistically significant effect on the sleep outcome of interest). Since the meta-regression model estimates the effect size and 95% CI for any given dose and timing of caffeine, the cut-off time was determined as the first timepoint at which the 95% CI of the effect size did not cross the null effect for a given dose. Dosages were selected to reflect commonly consumed caffeine products – a cup of black tea (typical caffeine content: 47 mg per 250 mL [55]), a cup of coffee (typical caffeine content: 107 mg per 250 mL [56]), and a standard serve of pre-workout supplement (typical caffeine content: 217.5 mg [57]). Additionally, the number of effect sizes (k) and participants (n) included in each meta-analytic model are reported. A full summary of all meta-analytical models is provided in Supplementary Tables S1–S4.

3. Results

3.1. Study selection and characteristics

The screening process identified 24 studies for inclusion in the review as outlined in the PRISMA flow diagram (Fig. 1). All included studies employed a controlled crossover design with the intervention administered as an acute daily dose on the day of the measured sleep bout, except for five studies where the daily dose was administered for consecutive days including four [32,40], six [52], nine [37], and 14 [46] days. The key characteristics of each included study are presented in Table 2.

3.2. Assessment of reporting quality

Five studies were deemed to be at a high risk of bias. Two of these studies [35,36] presented sleep staging data for the first portion of the sleep bout (i.e., six and three h, respectively) without providing context for this decision in the introduction or method, and three of these studies [26,43,53] did not implement a washout period with conditions administered across consecutive nights. Without a wash-out period, the results may be confounded by carryover effects from exposure to the prior condition. Three additional studies [30,34,40] were deemed to be of some concern with the absence of appropriate randomisation of interventions with all participants exposed to the control condition followed by the caffeine condition. The remaining 16 studies were deemed to be of low risk of bias. A summary of the risk of bias assessment is displayed in Table 3.

3.3. Objective sleep outcomes

3.3.1. Total sleep time

Twenty studies [24–27,29–37,40,41,43–46,50] reported measures of objective total sleep time. Caffeine consumption was associated with 45.3 min less total sleep time compared to the
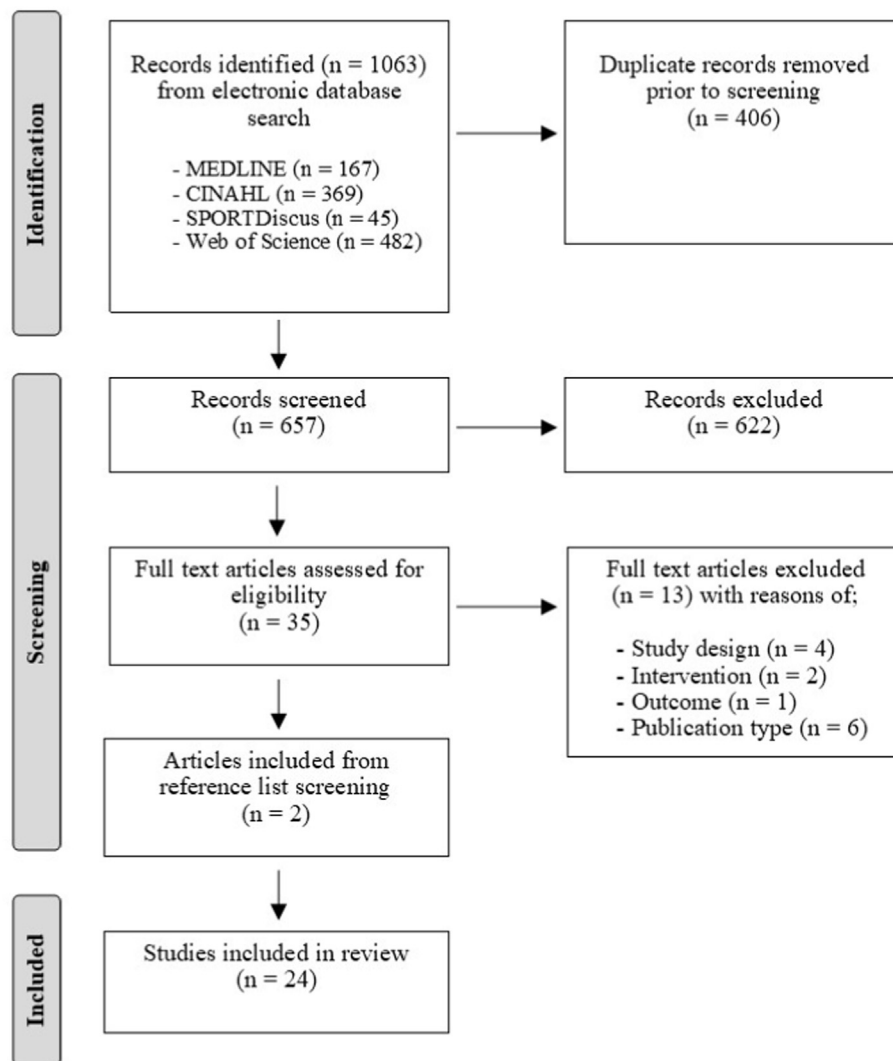
Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) flow diagram outlining the process for selection of studies.

control condition (Fig. 2a; 95%CI = 29.0 to 61.5 min, k = 37, n = 340, p < 0.001). Meta-regression analysis (k = 30, n = 262) revealed a significant influence of timing of intake (p = 0.032) and the final dose of caffeine (p = 0.037) on total sleep time. The mean difference in total sleep time between the control condition and a given dose of caffeine decreased by 2.8 min (95%CI = 0.4 to 5.2 min) for every additional hour that caffeine was consumed prior to bedtime. In addition, the mean difference in total sleep time between groups increased by 0.2 min (95%CI = 0.01 to 0.31 min) for every 1-mg increase in caffeine dose.

3.3.2. Sleep onset latency

Nineteen studies [24–30,33–37,40,41,43–46,50] reported measures of objective sleep onset latency. Sleep onset latency was 9.1 min longer in the caffeine condition compared to the control condition (Fig. 2a; 95%CI = 3.8 to 14.4 min, k = 32, n = 280, p = 0.002). This effect was not moderated by the timing of intake (p = 0.071) or the final dose of caffeine (p = 0.960) (k = 26, n = 232).

3.3.3. REM onset latency

Ten studies [24,29,30,34,35,37,40,44,46,50] reported measures of objective REM onset latency. No significant differences in REM onset latency were observed between the caffeine condition and the control condition (Fig. 2a; mean difference = −1.5 min, 95%CI = −8.1 to 5.2 min, k = 14, n = 114, p = 0.581). This effect was not moderated by the timing of intake (p = 0.364) or the final dose of caffeine (p = 0.279) (k = 13, n = 108).

3.3.4. Wake after sleep onset

Thirteen studies [24,25,27,29,30,34,35,37,40,43,44,46,50] reported measures of objective wake after sleep onset. The duration of wake after sleep onset was 11.8 min longer in the caffeine condition compared to the control condition (Fig. 2a; 95%CI = 2.5 to 21.0 min, k = 17, n = 148, p = 0.019). This effect was not moderated by the timing of intake (p = 0.205) or the final dose of caffeine (p = 0.419) (k = 13, n = 121).

3.3.5. Sleep efficiency

Eighteen studies [24–30,33–35,37,40,41,43–46,50] reported measures of objective sleep efficiency. Sleep efficiency was reduced by 7.0% in the caffeine condition compared to the control condition

Table 2
Summary characteristics of the included studies.

Study	Sample (n)	Age (years)	Habitual caffeine intake (per day)	Caffeine dose (mg)	Proximity to bedtime (min)	Method of sleep measurement	Reported sleep outcomes of interest	Significant findings (compared to control)
Alford et al., 1996 [24]	3 M; 3 F	23.8[b]	Undisclosed *Abstain across study*	4 & 8 kg^{-1}	~20	PSG LSEQ	TST, SE, WASO, SOL, sleep stages GTS, QOS, AFS	↑SOL, WASO ↓TST, SE, N3 ↑GTS ↓QOS
Ali et al., 2015 [53]	10 F	23.6 ± 4.2	<300 mg *Abstain within 48 h prior to intervention*	6 kg^{-1}	Undisclosed	LSEQ	GTS, QOS, AFS	↑GTS ↓QOS
Bonnet & Arand, 2003 [41]	35 M & F	18 to 39[a]	<250 mg *Abstain across study*	400	30	PSG	TST, SE, WASO, SOL, sleep stages	↑WASO, N1 ↓TST, SE, N2, N3, N4, REM
Brezinova, 1974 [42]	2 M; 4 F	56[b]	150–440 mg *No abstinence period*	300	15	PSG VAS	TST, SOL, awake & sleep stages [d] Subjective quality	↑SOL, awake & N1, N2 ↓TST, N3, REM ↓Quality
Carrier et al., 2007 [43]	7 M; 10 F	37.2 ± 14.4	1 to 3 beverages *Abstain on day of intervention*	200 As *2 equal doses*	60 & 180	PSG	TST, SE, WASO, SOL, ROL, sleep stages	↑SOL, N1 ↓SE, N2, N3
Drake et al., 2013 [26]	6 M; 6 F	29.3 ± 7.6	<5 beverages *Abstain on day of intervention*	400	0, 180, & 360	In-home PSG Sleep diary	TST, SE, WASO, SOL, sleep stages Subjective TST, WASO, SOL, quality	↑SOL, WASO ↓TST, SE, N1 & N2, N3 ↑SOL ↓TST
Drake et al., 2006 [27]	6 M; 4 F 4 M; 6 F	32.6 ± 15.5 34.2 ± 13.7	<3 beverages *Abstain on day of intervention*	3 kg^{-1}	60	PSG	SE, SOL, sleep stages	↑SOL ↓SE
Drapeau et al., 2006 [44]	6 M; 6 F 5 M; 7 F	23.8 ± 2.3 50.3 ± 5.6	1 to 3 beverages *Abstain on day of intervention*	200 As *2 equal doses*	60 & 180	PSG	TST, SE, SOL, sleep stages, qEEG	↑SOL, sigma frequency ↓TST, SE, N2, delta frequency
Hindmarch et al., 2000 [30]	15 M; 15 F	27.3 ± 1.64	160 mg–710 mg *Abstain within 48 h prior to intervention*	150, 300 & 600 As *4 equal doses*	120, 360, 600, & 840	Activity monitoring LSEQ	TST GTS, QOS	↓TST ↑GTS ↓QOS
James, 1998 [51]	18 M; 18 F	23[b]	3 to 5 beverages *Abstain across study*	5.2 kg^{-1} As *3 equal doses*	Undisclosed	Sleep diary & VAS	Subjective TST, quality	No significant change
Júdice et al., 2013 [31]	30 M	24.5 ± 4.8	<100 mg *Abstain within 48 h prior to intervention*	5 kg^{-1} As *2 equal doses*	Undisclosed	Activity monitoring	TST	↓TST
Karacan et al., 1976 [25]	18 M	20 to 30[a]	1 to 4 beverages *Abstain on day of intervention*	1.1, 2.,3 & 4.6 kg^{-1}	30	PSG Sleep diary	TST, SE, SOL, sleep stages Subjective TST, SOL, quality	↑SOL, N1, REM ↓TST, SE, N3 ↑SOL ↓TST, quality
Landolt et al., 1995 [29]	9 M	22.4 ± 1.2	1 to 2 beverages *Abstain across study*	200	950	PSG	TST, SE WASO, SOL, ROL, sleep stages, qEEG	↑SOL, sigma frequency ↓TST, SE, delta frequency
Landolt et al., 1995 [33]	8 M	23.3 ± 0.9	1 to 3 beverages *Abstain on day of intervention*	100	0	PSG	TST, SE, WASO, SOL, ROL, sleep stages, qEEG	↑SOL, sigma frequency ↓TST, SE, delta frequency
Lloret-Linares et al., 2012 [52]	26 M; 37 F	30.5 ± 12	<3 beverages *No abstinence period*	4.5 & 90	~122	Sleep diary & VAS	Subjective SOL, quality	↑SOL ↓Quality
Miller et al., 2014 [49]	6 M	27.5 ± 6.9	<300 mg *Abstain within 48 h prior to intervention*	6 kg^{-1} As *2 equal doses*	Undisclosed	PSG	TST, SE, WASO, SOL, ROL, sleep stages	↑SOL, WASO ↓TST, SE, REM
Nicholson & Stone, 1980 [34]	6 M 6 M	26[b] 24[b]	Undisclosed *Abstain across study*	100, 200, & 300	0	PSG VAS	TST, SE, SOL, ROL, WASO, sleep stages [e] Subjective SOL, quality	↑WASO, N1 ↓TST, SE, N3 ↓Quality
Okuma et al., 1982 [28]	8 M	21.1[b]	1 to 2 beverages *Abstain within 48 h prior to intervention*	150	30	PSG	TST, SE, WASO, SOL, ROL, sleep stages	↑SOL, WASO ↓TST, SE, N2
Paterson et al., 2009 [23]	12 M	24.9[b]	<600 mg *Abstain on day of intervention*	150	60	In-home PSG	TST, SE, SOL, ROL, WASO, sleep stages, qEEG	↑SOL ↓TST, SE, N2
Ramos-Campos et al., 2019 [32]	15 M	23.7 ± 8.2	250–572 mg *Abstain within 48 h prior to intervention*	6 kg^{-1}	Undisclosed	Activity monitoring KSD	TST, SE, SOL Quality, EOFA	↓SE ↓Quality, EOFA
Robillard et al., 2015 [39]	10 M; 12 F 12 M; 13 F	23.5 ± 1.9 51.7 ± 11.5	1 to 3 beverages *Abstain on day of intervention*	200 & 400 As *2 equal doses*	60 & 180	PSG	TST, SE, SOL, sleep stages, qEEG	↑SOL, N1, sigma frequency ↓TST, SE, N2, N3, REM, delta frequency
Weibel et al., 2021 [35]	20 M	26.4 ± 4	300–600 mg	150 & 450	480, 700, & 910	PSG	TST, SE, WASO, SOL, ROL, sleep stages, qEEG	↓ Sigma frequency

(*continued on next page*)

Table 2 (*continued*)

Study	Sample (n)	Age (years)	Habitual caffeine intake (per day)	Caffeine dose (mg)	Proximity to bedtime (min)	Method of sleep measurement	Reported sleep outcomes of interest	Significant findings (compared to control)
			Abstain across study	*As 3 equal doses*[c]		LSEQ	GTS, QOS, AFS	No significant change
Youngstedt et al., 2000 [38]	8 M	24.5 ± 4.3	100−400 mg	1200	120, ~465, & ~960	PSG	TST, SE, WASO, SOL, ROL, sleep stages	↑SOL ↓TST, N3
			Abstain across study	*As 3 equal doses*		Sleep diary	Subjective WASO, SOL, quality	No significant change
Zhang et al., 2020 [45]	12 M	37.1 ± 14.9	<300 mg	103.6	660 & 900	PSG	TST, SE, WASO, SOL, ROL, sleep stages	No significant change
			Abstain across study	*As 2 equal doses*				

Abbreviations: AFS- awake following sleep; EOFA-ease of falling asleep; GTS- getting to sleep; KSD- Karolinska sleep diary; LSEQ- Leeds sleep evaluation questionnaire; PSG-polysomnography; N1- non-rapid eye movement (NREM) stage 1 sleep; N2- NREM stage 2 sleep; N3-: NREM stage 3 sleep; N4- NREM stage 4 sleep; qEEG-quantitative electroencephalogram; QOS- quality of sleep; REM-rapid-eye movement (REM) sleep; ROL- REM onset latency; SE-sleep efficiency; SOL-sleep onset latency; TST-total sleep time; VAS- visual analogue scale; WASO- wake after sleep onset.
~Approximate timing reported.
 [a] Mean not reported.
 [b] Standard deviation not reported.
 [c] 150 mg as one dose with remaining two doses containing placebo.
 [d] First 3 h of sleep recording only.
 [e] First 6 h of sleep recording only.

(Fig. 2b; 95%CI = 4.0 to 10.0%, k = 31, n = 274, p < 0.001). This effect was not moderated by the timing of intake (p = 0.058) or the final dose of caffeine (p = 0.193) (k = 25, n = 226).

3.3.6. Sleep architecture

Eighteen studies [24−30,34−37,40,41,43−46,50] reported measures of objective sleep architecture. Compared to the control condition, caffeine consumption increased (+6.1 min) the duration of sleep in N1 (Fig. 2c; 95%CI = 2.3 to 9.9 min, p = 0.012), had no effect on the duration of sleep in N2 (Fig. 2c; mean difference = −23.3 min, 95%CI = −56.1 to 9.6 min, p = 0.120), reduced (−11.4 min) the duration of sleep in the combined stages N3 and N4 (Fig. 2c; 95%CI = −4.3 to −18.5 min, p = 0.012) (k = 35, n = 127), and had no effect on the duration of REM sleep (Fig. 2c; mean difference = −4.4 min, 95%CI = −10.5 to 1.6 min, k = 17, n = 163, p = 0.127). Compared to the control condition, caffeine consumption increased (+1.7%) the proportion of sleep in N1 (Fig. 2b; 95%CI = 0.2 to 3.1%, p = 0.033), had no effect on the proportion of sleep in N2 (Fig. 2b; mean difference = −2.8%, 95% CI = −6.4 to 0.4%, p = 0.080), reduced (−1.4%) the proportion of sleep in the combined stages N3 and N4 (Fig. 2b; 95%CI = 0.2 to 2.6%, p = 0.028) (k = 48, n = 172), and had no effect on the proportion of REM sleep (Fig. 2b; mean difference = −0.02%, 95% CI = −1.67 to 1.6%, k = 19, n = 172, p = 0.980).

3.3.7. Quantitative electroencephalogram (EEG)

Six studies [24,30,34,37,41,45] reported measures of EEG spectral power during NREM sleep. A meta-analysis was not conducted for EEG spectral power given the limited number of studies reporting this outcome. Four studies [30,34,41,45] reported a significant reduction in spectral power within the delta frequency range (~0.5−4 Hz) in the caffeine condition compared to the control condition and two studies [24,37] reported no significant change compared to the control condition. Four studies [30,34,41,45] reported a significant increase in spectral power within the sigma frequency range (~12−16 Hz) in the caffeine condition compared to the control condition, one study [37] reported a significant decrease within the sigma frequency range compared to the control condition, and one study [24] reported no significant change compared to the control condition.

3.3.8. Subjective sleep outcomes

Twelve studies [25−27,31,33,35−37,40,52−54] reported measures of subjective sleep through varying self-report tools detailed

in Table 2. A meta-analysis was not conducted for subjective sleep due to a lack of homogeneity in the measured outcomes. Three studies reported measures of subjective total sleep time with two [26,27] identifying a significant reduction in the perceived duration of sleep in the caffeine condition compared to the control condition and one [52] reporting no significant change in comparison to the control condition. Ten studies reported measures of subjective sleep onset latency with seven [25−27,31,33,53,54] identifying a significant increase in the perceived time to fall asleep in the caffeine condition and three [35,37,40] reporting no significant change in comparison to the control condition. Five studies [25,27,37,40,54] reported no difference in perceived wake duration after sleep onset between the caffeine condition and the control condition. Twelve studies reported measures of subjective sleep quality, with eight [25,26,31,33,35,36,53,54] identifying a significant reduction in perceived sleep quality in the caffeine condition compared to the control condition and four [27,37,40,52] reporting no difference in perceived sleep quality between conditions.

3.3.9. Caffeine cut-off times for avoiding reductions in total sleep time

The meta-regression analysis revealed a significant influence of the timing of intake and the final dose of caffeine on total sleep time. The model identified a cut-off time of 13.2 h prior to bedtime for a standard serve of pre-workout supplement, a cut-off time of 8.8 h prior to bedtime for a cup of coffee, and no cut-off time for a cup of black tea. Using a 10 p.m. bedtime as an example, the model indicates that a cup of black tea can be consumed at any time prior to bedtime without significantly reducing total sleep time, a cup of coffee must be consumed before 1:12 p.m. to avoid a significant reduction in total sleep time, and a pre-workout supplement must be consumed before 8:50 a.m. to avoid a significant reduction in total sleep time (Fig. 3). The model predicts that a significant reduction in total sleep time will occur if caffeine is consumed after these cut-off times in a time-dependent manner − i.e., the closer consumption occurs to bedtime, the greater reduction in total sleep time.

4. Discussion

This meta-analysis summarised and quantified the adverse effects of caffeine intake on the characteristics of subsequent night-time sleep. Specifically, caffeine consumption reduced total sleep time by 45 min, increased sleep onset latency by 9 min, and

Table 3
Results of the Cochrane Risk of Bias (RoB 2) tool.

Study	D1	DS	D2	D3	D4	D5	Overall Bias
Alford et al., 1996 [24]	+	+	+	+	+	+	+
Ali et al., 2015 [53]	+	+	+	+	+	+	+
Bonnet & Arand, 2003 [41]	+	−	+	+	+	+	−
Brezinova, 1974 [42]	+	+	+	+	+	−	−
Carrier et al., 2007 [43]	+	+	+	+	+	+	+
Drake et al., 2013 [26]	+	+	+	+	+	+	+
Drake et al, 2006 [27]	+	+	+	+	+	+	+
Drapeau et al., 2006 [44]	+	+	+	+	+	+	+
Hindmarch et al., 2000 [30]	+	+	+	+	+	+	+
James, 1998 [51]	+	+	+	+	+	+	+
Júdice et al., 2013 [31]	+	+	+	+	+	+	+
Karacan et al., 1976 [25]	+	−	+	+	+	+	−
Landolt et al 1995a [29]	!	+	+	+	+	+	!
Landolt et al 1995b [33]	!	+	+	+	+	+	!
Lloret-Linares et al., 2012 [52]	+	−	+	+	+	+	−
Miller et al, 2014 [49]	+	+	+	+	+	+	+
Nicholson & Stone, 1980 [34]	+	+	+	+	+	−	−
Okuma et al., 1982 [28]	+	+	+	+	+	+	+
Paterson et al., 2009 [23]	+	+	+	+	+	+	+
Ramos-Campos et al., 2019 [32]	+	+	+	+	+	+	+
Robillard et al., 2015 [39]	+	+	+	+	+	+	+
Weibel et al., 2021 [35]	+	+	+	+	+	+	+
Youngstedt et al., 2000 [38]	!	+	+	+	+	+	!
Zhang et al., 2020 [45]	+	+	+	+	+	+	+

D1: Randomisation process, DS: Period and carryover effects, D2: Deviations from intended interventions,

D3: Missing outcome data, D4: Measurement of outcome, D5: Selection of reported result

+ Low risk   ! Some concerns   − High risk

increased wake after sleep onset by 12 min. These changes were accompanied by a 7% reduction in sleep efficiency. Alterations in sleep architecture were also identified; the duration (+6.1 min) and relative proportion (+1.7%) of light sleep (i.e., N1) increased with caffeine intake and the duration (−11.4 min) and relative proportion (−1.4%) of deep sleep (i.e., N3 and N4) decreased with caffeine intake. The impact of dose and timing of caffeine intake on subsequent sleep was also examined. The amount and timing of the final caffeine dose reduced total sleep time. Specifically, the closer to bedtime that high doses of caffeine were consumed, the greater reduction in total sleep time. However, this relationship was not

identified for any other sleep outcomes. Importantly, by quantifying the influence of the dose and timing of caffeine intake on subsequent sleep, cut-off times for caffeine intake prior to bedtime can be established. For example, one cup of black tea (typical caffeine content: 47 mg per 250 mL [55]) can be consumed up until bedtime without a significant effect on total sleep time. To avoid reductions in total sleep time, a cup of coffee (typical caffeine content: 107 mg per 250 mL [56]) must be consumed at least 8.8 h prior to bedtime and a standard serve of pre-workout supplement (typical caffeine content: 217.5 mg [57]) must be consumed at least 13.2 h prior to bedtime. Consuming a cup of coffee or a standard
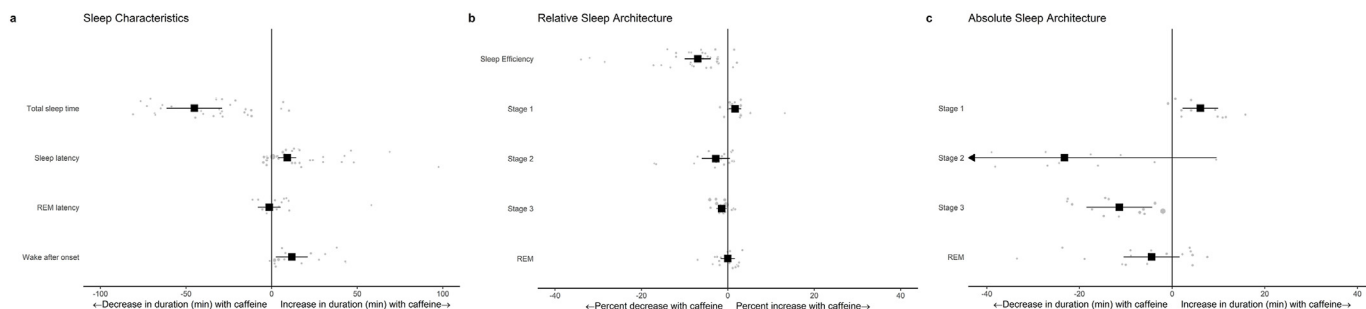
Fig. 2. Forest plot a) displays the sleep characteristics of total sleep time, sleep onset latency, rapid eye movement (REM) onset latency, and wake after sleep onset as absolute measures (min). Forest plot b) displays sleep architecture outcomes of sleep efficiency, non-rapid eye movement (NREM) stage one, NREM stage two, NREM stage three, and REM as relative measures (%). Forest plot c) displays sleep architecture outcomes of NREM stage one, NREM stage two, NREM stage three, and REM as absolute measures (min). Each circle represents the mean difference between the control and caffeine condition, with the size of the circle representing the statistical weight of the effect size.
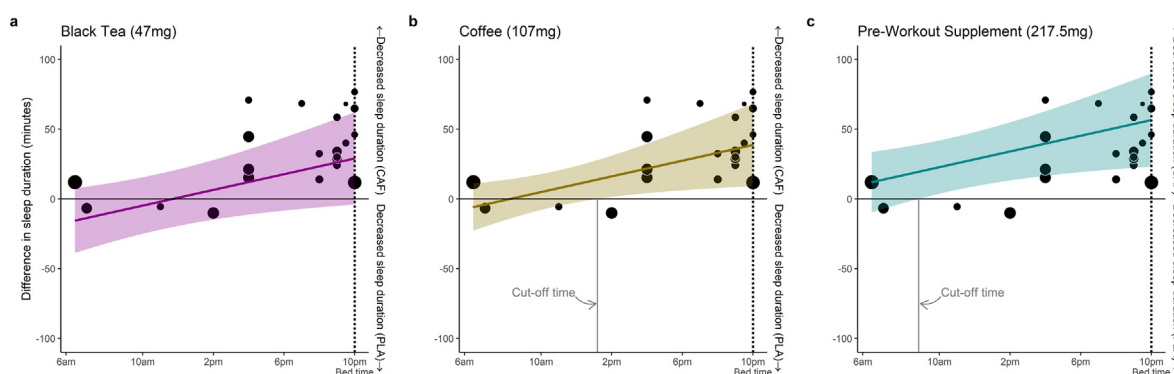

Fig. 3. Meta-analytic model accounting for both the timing and the amount of the final caffeine dose. With this, estimated caffeine cut off times for a) a cup of black tea (typical caffeine content: 47 mg per 250 mL [55]), b) a cup of coffee (typical caffeine content: 107 mg per 250 mL [56]), and c) a standard serve of pre-workout supplement (typical caffeine content: 217.5 mg [57]) are modelled for a 10 p.m. bedtime (x-axis). Each circle represents the mean difference (y-axis) between the control and caffeine condition, with the size of the circle proportional to the statistical weight of the effect size. When looking at the zero reference line, any value above this indicates the caffeine group exhibited less total sleep time compared to the control. The 95% confidence intervals are represented by the shaded band, and the estimated cut-off time occurs where this crosses the zero reference line. As such, no clear cut off is identified for black tea (a). However, the cut off for coffee (b) occurs at 1:12 p.m. and for pre-workout supplement (c) at 8:50 a.m. Consumption of caffeine anytime beyond these cut-offs is estimated to reduce total sleep time, with this reduction greater as consumption occurs closer to bedtime. Model parameters (estimate [95%CI]): intercept, 21.02 [-8.53 to 50.57]; coefficient for time, −0.05 [-0.09 to −0.01]; coefficient for dose, 0.16 [0.01 to 0.31].

serve of pre-workout supplement within this proximity to bedtime is estimated to reduce total sleep time, with greater reductions the closer consumption occurs to bedtime.

4.1. Objective sleep outcomes

4.1.1. Total sleep time

Across the 20 studies investigating the effect of caffeine on total sleep time, 16 [24−27,29−32,34−36,40,41,43,45,50] demonstrated a significant reduction. Of the four studies [33,37,44,46] that did not report a significant effect (final caffeine intake ranging from 60 to 660 min prior to bedtime), two administered caffeine for nine [37] and 14 [46] days consecutively prior to the measured sleep bout. This sustained administration across numerous days may have promoted tolerance to the acute effect of caffeine through an upregulation of cerebral adenosine receptors. However, evidence of this is currently limited to animal studies [58−61], with greater uncertainty underpinning caffeine tolerance in humans [62]. Additionally, six studies [25,26,31,35,37,41] investigated a potential dose-response relationship between caffeine intake and subsequent sleep, with five studies [25,26,31,35,41] demonstrating substantially less sleep (ranging from 24 to 114 min) when larger doses of caffeine were consumed. The remaining study [37] that did not report a dose-response effect administered 150 mg or 450 mg of caffeine on the day of the measured sleep bout, with the lower dose

intended as a withdrawal from the prior eight days of caffeine administration. Regardless, no effect was found for either condition [37]. Finally, one study [27] investigated the timing relationship with a fixed dose of caffeine (400 mg). When consumed zero, three, or six h prior to bedtime, caffeine reduced total sleep time by ~1.2 h, irrespective of the timing of intake. As such, there was no clear relationship between the timing of caffeine consumption and total sleep time.

The consumption of caffeine is associated with a 45-min reduction in total sleep time over the subsequent evening. Furthermore, the extent of this sleep loss is dependent on the final amount of caffeine consumed and the proximity of this consumption to bedtime. Specifically, larger doses of caffeine and consumption closer to bedtime resulted in greater reductions in total sleep time. Currently, sleep behaviour recommendations do not account for the important influence of the dose and timing of caffeine intake [19,20]. For example, when applying the findings of this study to commonly consumed beverages, drinking a cup of coffee (typical caffeine content: 107 mg per 250 mL [56]) would likely equate to a 9-min greater reduction in total sleep time than a cup of black tea (typical caffeine content: 47 mg per 250 mL [55]). Alternatively, assuming a 10 p.m. bedtime, consumption of a fixed dose of caffeine at 3 p.m. would equate to a 16-min reduction in sleep than intake of the dose at 9 a.m. Given time in bed was comparable between conditions in all but four studies

[24,32,33,50], the observed reduction in total sleep time cannot be attributed to a reduced sleep opportunity but more likely disruption to the sleep bout. As homeostatic sleep pressure is suggested to increase with rising cerebral adenosine concentrations [14,63], the action of caffeine in blocking A1 and A2a receptors may reduce the propensity for sleep [64,65]. With a difference in total sleep time of 20 min identified as the threshold for clinically meaningful change [66], these findings suggest the intake of caffeine may substantially reduce the subsequent sleep duration of consumers.

4.1.2. Sleep onset latency

The effect of caffeine on sleep onset latency was investigated in 19 studies [24–30,33–37,40,41,43–46,50], with 14 [24–30,34,36,40,41,44,45,50] reporting a significant increase following caffeine consumption. Of interest, one study [35] reported no effect when caffeine was administered at bedtime, despite the consumption of moderate to high doses (100, 200, & 300 mg). Similarly, one study [43] found no effect when a high dose of caffeine (400 mg) was administered 30 min prior to bedtime. As plasma caffeine concentration typically peaks between 30 and 120 min post consumption [67–69], it is feasible that consumption in these studies was too close to bedtime to influence sleep onset. Of the included studies, five [25,26,35,37,41] investigated the dose-response relationship, with three [25,26,41] demonstrating substantially longer latencies (ranging from 13 to 62 min) with larger doses of caffeine. Lastly, one study [27] investigated the relationship between timing of consumption and sleep onset latency. In comparison to the control condition (20.6 ± 9.8 min), a significant increase of 17.2 min was observed when 400 mg of caffeine was consumed three hours (37.8 ± 29.9 min) prior to bedtime. Although similar mean increases were observed when caffeine was administered zero (43.0 ± 38.9 min) and six (44.7 ± 54.6 min) hours prior to bedtime, there was no significant effect of these timings on sleep onset latency, with greater variation in individual response. Therefore, it appears there is a peak effect of caffeine on sleep onset latency occurring approximately three hours post consumption.

Caffeine consumption increased sleep onset latency by 9.1 min. Unexpectedly, this increase was not moderated by the amount or the timing of the final caffeine dose. Given seven of the included studies administered the caffeine as a split dose across two [41,44–46,50] or three [37,40] time points, the moderating influence of each may be understated as the meta-regression modelling accounted for the amount and timing of the final dose only. Even though the influence of dose and timing could not be determined, the adverse effect of caffeine on sleep onset latency was evident. Given the action of caffeine on the central nervous system [64,70], a heightened state of arousal may pose a substantial challenge to the initiation of sleep. Thus, the findings emphasise the consumption of caffeine prolongs the onset of subsequent sleep, with these delays approaching the 10-min threshold of clinically meaningful change [66]. It remains unclear whether this increase in sleep onset latency is affected by the amount or timing of the final caffeine dose.

4.1.3. REM onset latency

Ten studies [24,29,30,34,35,37,40,44,46,50] investigated the effects of caffeine on REM onset latency, however none demonstrated significant effects. Of the included studies, two [35,37] examined the dose-response relationship with various doses of caffeine. There was no meaningful change in REM onset latency when larger doses of caffeine were consumed. It should be noted that no study has systematically varied the timing of consumption using a fixed caffeine dose. Therefore, no data were available on the relationship between caffeine timing and REM onset latency.

The results of the current analysis showed a non-significant effect of caffeine on REM onset latency (−1.5 min). Furthermore,

the amount and timing of the final caffeine dose were not shown to be moderating factors. As REM onset latency is measured from sleep onset and not lights out, it remained largely unaffected by the delayed initiation of sleep following caffeine consumption. Consequently, the consumption of caffeine likely has no meaningful effect on REM onset latency. It appears this lack of effect is not influenced by the amount or timing of the final caffeine dose.

4.1.4. Wake after sleep onset

Wake after sleep onset was investigated in 13 studies [24,25,27,29,30,34,35,37,40,43,44,46,50], with six [25,27,29,35,43,50] demonstrating a significant increase when caffeine was consumed. In one study [24], there was a non-significant increase in wake after sleep onset when caffeine was consumed (49.0 ± 8.7 min v 43.0 ± 6.4 min). Alternatively, another study [30] showed no effect following the administration of a 200-mg dose of caffeine in the morning. This may have been due to the ~16-h time frame between caffeine consumption and bedtime [30]. Of the included studies, three [25,35,37] investigated the dose-response relationship, with one [25] demonstrating considerably greater wake after sleep onset when larger doses of caffeine were consumed. In this instance, increasing the dose from 4 mg kg^{-1} to 8 mg kg^{-1} resulted in a 29.6-min mean increase in wake after sleep onset [25]. Finally, one study [27] investigated the relationship between timing of caffeine consumption and wake after sleep onset. In comparison to the control condition (9.6 ± 14.7 min), caffeine (400 mg) caused a significant increase when consumed three (37.2 ± 43.0 min) and six (17.6 ± 22.3 min) hours prior to bedtime. Although demonstrating a similar mean increase in wake after sleep onset, no significant effect was found when caffeine was consumed at bedtime (27.0 ± 40.1 min). As such, no clear timing relationship was identified for the effect of caffeine on wake after sleep onset.

The findings from the current analysis demonstrate an 11.8-min increase in wake after sleep onset following the consumption of caffeine. It was not apparent whether this increase was moderated by the amount or the timing of the final caffeine dose. The observed increase in wake after sleep onset indicates that the consumption of caffeine disrupts sleep maintenance. Caffeine may cause brief episodes of wake across the sleep bout by reducing homeostatic sleep propensity and heightening arousal state [64,65]. Consequently, sleep appears to be fragmented by recurrent awakenings following caffeine. These findings demonstrate that caffeine consumption increases periods of wakefulness during sleep. However, the observed increase in wake after sleep onset following caffeine consumption fails to meet the 20-min threshold of clinically meaningful change [66]. It could not be determined if the increase in wake after sleep onset was influenced by the amount or the timing of the final caffeine dose.

4.1.5. Sleep efficiency

Across the 18 studies assessing sleep efficiency, 15 [24–30,33–35,41,43–45,50] reported a significant reduction in sleep efficiency following caffeine consumption. Of the three studies [37,40,46] reporting no significant effect, two [37,46] administered the caffeine dose over numerous days. Additionally, one study [40] showed no effect following 1200 mg of caffeine administered in three equal doses across the morning, afternoon, and evening. In this instance, the authors attributed these findings to a lack of statistical power [40]. Of the included studies, five [25,26,35,37,41] investigated the dose-relationship with three [25,26,41] demonstrating greater reductions (ranging from 5 to 23%) in sleep efficiency when larger doses were consumed. Finally, one study investigated the timing relationship with significant reductions in sleep efficiency when 400 mg of caffeine was

administered zero, three, and six hours prior to bedtime [27]. In comparison to the control condition, reductions were similar across all time points (~8%) with no clear timing relationship identified.

The current analysis demonstrates a 7% reduction in sleep efficiency following the consumption of caffeine. However, this reduction was not moderated by the amount or the timing of the final caffeine dose. Although it may seem counterintuitive, not all time in bed is spent asleep. This discrepancy between total sleep time and time in bed is accounted for by the duration of wake between lights off and lights on [71]. When large periods of time in bed are spent awake, the duration of total sleep time is reduced with a subsequent reduction in sleep efficiency. As previously outlined, time in bed was comparable in all but four studies [24,32,33,50]. Therefore, it appears the consumption of caffeine reduces sleep efficiency through a reduction in total sleep time [72]. With the stimulating effect of caffeine, it is likely this reduction occurs largely through the impaired onset and maintenance of sleep [64]. The reduction in sleep efficiency following caffeine consumption exceeds the 5% threshold of clinically meaningful change [66], suggesting caffeine consumption causes considerable detriment to subsequent sleep efficiency. It is not clear if this reduction is influenced by the amount or the timing of the final caffeine dose.

4.1.6. Sleep architecture

The effect of caffeine on absolute (min) sleep architecture was investigated in 12 studies [24,27,30,34–36,40,41,44–46,50]. Of these, two [35,41] reported an increase in N1 sleep, one [36] reported an increase in N2 sleep, four [24,41,44,45] reported a decrease in N2 sleep, six [27,35,36,40,41,44] reported a decrease in N3 sleep, and three [36,41,50] reported a decrease in REM sleep. Of the included studies, two [35,41] investigated the dose-relationship between caffeine intake and absolute sleep architecture. Dose-dependent reductions in the duration of N3 sleep [35,41] and REM sleep [41] were identified, with greater reductions occurring at larger doses. Additionally, one study [27] investigated the timing relationship between caffeine intake and absolute sleep architecture with the administration of caffeine zero, three, and six hours prior to bedtime. Reductions in duration of the combined stages N1 and N2 sleep were comparable across time points of caffeine consumption (~40 min) when compared to the control condition. Similarly, the duration of N3 sleep was reduced in comparison to the control (71.5 ± 26.5 min) when caffeine was consumed zero (56.7 ± 21.5 min), three (57.0 ± 16.8 min), and six (48.9 ± 15.8 min) hours prior to bedtime, although the reduction observed with consumption 3 h prior to bedtime was not statistically significant. These findings suggest there is no relationship between the timing of caffeine intake and alterations in the duration of sleep stages.

The effect of caffeine on relative (%) sleep architecture was investigated in 11 studies [25–29,35,37,41,43,44,50]. Of these, five [26,35,41,43,44] reported an increase in N1 sleep, two [29,43] reported a decrease in N2 sleep, and five [25,26,35,41,43] reported a decrease in N3 sleep. There was no clear effect on the proportion of REM sleep with one study [26] reporting an increase and one study [43] reporting a decrease. Five studies [25,26,35,37,41] investigated the dose-relationship between caffeine intake and relative sleep architecture. Of these studies, three [26,35,41] reported a greater increase in the proportion of N1 sleep, while four [25,26,35,41] reported a greater reduction in the proportion of N3 sleep when larger caffeine doses were consumed. Lastly, one study [27] investigated the timing relationship between caffeine intake and relative sleep architecture with the administration of 400 mg of caffeine. Relative sleep architecture was not significantly altered when caffeine was consumed zero, three, or six h prior to bedtime. As

such, there was no evidence of a time-dependent effect of caffeine on relative sleep architecture.

From the results of the current analysis, caffeine consumption increased the duration (+6.1 min) and proportion (+1.7%) of N1 sleep and decreased the duration (−11.1 min) and proportion (−1.4%) of N3 (and N4) sleep. No significant effect of caffeine was shown on the duration or proportion of N2 or REM sleep. The increased occurrence of N1 sleep and the decreased occurrence of N3 sleep is indicative of a reduction in sleep depth. Through action as an adenosine receptor antagonist, caffeine may diminish homeostatic sleep pressure with a subsequent reduction in N3 sleep [73]. In addition, caffeine increased the duration of wake across the sleep bout. With increased awakenings, shifts between sleep stages occur with a tendency for N1 sleep to re-emerge at the expense of deeper stages of sleep [21]. Coupled together, these findings demonstrate the consumption of caffeine alters sleep architecture in a manner that increases light sleep (i.e., N1) and reduces deep sleep (i.e., N3 and N4). With deep sleep suggested to be essential to physiological restoration and memory processing [74,75], reductions in N3 sleep may have neurobehavioral and health implications. However, the changes observed in this analysis are unlikely to be sufficient to elicit clinically meaningful change in an individual's sleep architecture [72].

4.1.7. Quantitative EEG

The effect of caffeine on EEG spectral power was investigated in six studies [24,30,34,37,41,45] with four [30,34,41,45] reporting a significant reduction in spectral power within the delta frequency range (~0.5−4 Hz) and a significant increase in spectral power within the sigma frequency range (~12−16 Hz) during NREM sleep. Slow wave activity within the delta frequency range is a commonly reported marker of sleep intensity [14], and an increase in the expression of slow waves during NREM sleep is suggested to reflect an increase in homeostatic sleep pressure [76,77]. Findings from the included studies indicate that caffeine consumption may reduce subsequent sleep depth through attenuation of homeostatic sleep pressure. However, it has recently been highlighted that the kinetics of adenosine formation and breakdown appear to occur at a faster rate than diurnal changes in NREM sleep EEG slow wave activity [62]. Therefore, it remains unclear whether the observed reduction in sleep depth following the consumption of caffeine is due to the attenuation of homeostatic sleep pressure.

4.1.8. Subjective sleep outcomes

Twelve studies [25–27,31,33,35–37,40,52–54] investigated the effect of caffeine on the perceptions of sleep. Collectively, caffeine had an adverse effect on perceived total sleep time, sleep onset latency, sleep efficiency, and sleep quality. There was no effect of caffeine on perceived wake after sleep onset, even though concurrent increases in objective wake after sleep onset were reported [25,27]. These findings suggest transient periods of wake may go largely unnoticed. Of the five studies [25,26,31,35,37] investigating the dose-response relationship, four [25,26,31,35] reported heightened perceptions of sleep disruption with larger caffeine doses. Additionally, perceptions of sleep disturbance were reported when caffeine (400 mg) was administered zero and three h prior to bedtime [27]. However, no perceived effect was reported when this dose was consumed six h prior to bedtime, despite a significant effect on objective sleep parameters [27]. Such findings suggest the negative influence of caffeine on subsequent sleep is underestimated the further away from bedtime consumption occurs. In fact, the relationship between objective and subjective sleep quality is not well defined [78]. Regardless, perceptions of sleep capture individual outcomes, which have a strong influence in driving behavioural decision making [79]. Therefore, subjective

sleep outcomes are an important metric when evaluating the effect of caffeine on subsequent sleep and should be incorporated alongside objective measures.

4.1.9. Practical significance

Substantial changes in sleep quantity and quality were observed following the consumption of caffeine. Specifically, there was a 45-min reduction in total sleep time, a 9-min increase in sleep onset latency, a 12-min increase in wake after sleep onset, and a reduction of 7% in sleep efficiency. With the exception of wake after sleep onset, these changes are considered to be clinically significant suggesting caffeine consumption will substantially impair subsequent sleep [66]. Current sleep recommendations outline the need for healthy adults to achieve seven to nine h of sleep per night [2]. In addition, satisfactory sleep quality is indexed by a sleep onset latency less than 30 min, wake after sleep onset of less than 20 min, and a sleep efficiency of 85% or above [72]. With the extent of change observed in these outcomes in the present analysis, it is likely that the consumption of caffeine will increase the risk of insufficient sleep. It has been shown that mild sleep restriction (~1 h) can disrupt emotional regulation [80] and impair cognitive and behavioural function [81,82]. When mild sleep restriction is sustained over 14 days, the decrements in behavioural alertness and working memory are similar to those experienced after one night of sleep deprivation [82]. Given that decrements in performance associated with sleep restriction can accrue in a cumulative manner, the decrease in sleep quantity and quality resulting from the consumption of caffeine may impair cognitive and behavioural function over time. The consumption of caffeine increased the proportion of N1 sleep by 1.7% and decreased the proportion of N3 (and N4) sleep by 1.4%. Healthy sleep architecture is comprised of less than 5% of N1 sleep and 16−20% of N3 sleep [72]. Therefore, it appears the consumption of caffeine may result in considerable increases in the occurrence of N1 sleep relative to normative values. However, it is unlikely that the decrease in N3 (and N4) sleep would be of sufficient magnitude to alter normal sleep architecture [72].

The deleterious effect of caffeine on subsequent sleep may be lessened in habitual consumers due to a potential tolerance to the substance [62]. A pattern of regular caffeine intake exposes the central nervous system to the continuous presence of caffeine. Although evidence is scarce in humans [62], repeated caffeine exposure in rodents indicates an adaptive response in the adenosinergic system characterised by an increase in cerebral adenosine concentrations [83] and an upregulation in cerebral adenosine receptors [58−61]. Of the studies included in the present analysis, two involved the administration of caffeine for more than one week. The administration of 450 mg of caffeine for nine days [37] and 100 mg of caffeine for 14 days [46] resulted in no significant impairment to sleep. Rather, a reduction in spectral power within the sigma frequency range was reported [37], with reductions in this frequency band observed under conditions of increased sleep pressure [84,85]. Collectively, these findings suggest chronic caffeine exposure may elicit adaptation in the adenosinergic system that normalises function in response to the continual presence of caffeine and its metabolites. Even though tolerance has not been clearly established in humans [62], it is important to consider that the impairments to sleep reported in this analysis may be reduced with repeated caffeine consumption.

4.1.10. Practical recommendations

One of the aims of the present study was to quantify the influence of caffeine dose and timing on subsequent total sleep time. From the analysis, cut-off times of consumption (Fig. 3) to minimise the negative effect of caffeine were established for common caffeine products. Assuming a 10 p.m. bedtime, there is no clear cut off time for consumption of black tea (typical caffeine content: 47 mg per 250 mL [55]). This suggests a single cup of black tea may be consumed at any time prior to bedtime without a significant reduction in total sleep time. However, there is an estimated reduction in total sleep time if a cup of coffee (typical caffeine content: 107 mg per 250 mL [56]) is consumed after approximately 1 p.m. The reduction in total sleep time is greater as caffeine is consumed closer to bedtime (Fig. 3). Similarly, the consumption of a standard serve of a pre-workout supplement (typical caffeine content: 217.5 mg [57]) is predicted to reduce total sleep time if consumed at any point after 8:50 a.m. These findings suggest the cut-off time for doses of caffeine contained in a standard cup of coffee or a standard serve of pre-workout supplement occur substantially earlier than anecdotally expected, and well before timings based on the typical half-life of three to six h [18,86,87]. Given the prevalence of caffeine consumption [12], and the growing popularity of supplements aimed at enhancing physical and cognitive performance [57,88,89], awareness of these cut-off times is essential in minimising caffeine-induced sleep disturbance. With the half-life of caffeine reported to vary up to eight h across healthy adults [18], it is likely that the effect of caffeine on sleep will differ across individuals. Therefore, consumers should consider the cut-off times provided as a starting point and adjust the amount and timing of their caffeine intake in response to the effect on their subsequent sleep.

5. Limitations

This study presents novel insights into the effect of caffeine on subsequent sleep. However, there are several limitations to consider when interpreting the findings. First, it should be acknowledged that across studies assessing objective sleep outcomes, three studies [31−33] employed activity monitors. The use of activity monitors to assess sleep is a valid alternative to the gold-standard method of polysomnography, but the devices tend to overestimate sleep duration and underestimate wake duration [90]. As such, there may be variation in the calculation of some outcome measures with reduced sensitivity and confidence in the estimates reported. Second, across studies, caffeine was administered as either an acute daily dose or a sustained dose across multiple days. With numerous days of consumption, there is the potential for habituation to the dose being administered [62], which may reduce the acute effects of caffeine. Given the limited number of studies [32,37,40,46,52] in which caffeine was administered over several days, there were insufficient data to determine whether the effect of caffeine was altered with repeated exposure. Third, where caffeine was administered across multiple time points in one day, the meta-regression was performed using the amount and timing of the final dose only. Therefore, the influence of dose and timing may have been underestimated in the model. Fourth, the studies included in this review investigated healthy adults with a focus on low to moderate habitual caffeine consumers. As such, the results may not be generalisable to alternative populations including adolescents, older adults (>65 years), caffeine naïve individuals, or those with a high habitual caffeine intake. Lastly, a range of factors may influence the half-life of caffeine including antidepressants, oral contraceptives, smoking, alcohol, obesity, impaired liver function, age, and ethnicity [91]. As these factors were largely controlled across the included studies, their potential influence needs to be considered when interpreting the findings of the analysis. The cut-off times identified are based on statistical significance with the assumption that statistically significant reductions in total sleep time are equivalent to clinically significant reductions. In addition, caffeine can display a degree of inter-individual variability in half-life and effect attributed to genetic

predispositions [91]. Variation in the expression of genes such as cytochrome P450 1A2 (CYP1A2) [91] and adenosine A2A receptor (ADORA2A) [92] are suggested to modulate the rate of metabolism and sensitivity. Given the influence of genetic predispositions was not accounted for by studies included in the review, the demonstrated effects of caffeine on subsequent sleep appear to be largely robust in nature. Regardless, individual variation should be appreciated when applying the findings of this review.

6. Conclusion

The consumption of caffeine impairs subsequent total sleep time, sleep onset latency, wake after sleep onset, sleep efficiency, and sleep architecture. The reduction in total sleep time is dependent on the final dose of caffeine and the time of day that it is consumed relative to bedtime. Specifically, the closer to bedtime larger doses of caffeine are consumed, the greater the reduction in total sleep time. However, the relationship between caffeine dose and timing of intake remains unclear for outcomes other than total sleep time and further investigation is required. The results of the present study provide evidence-based guidance for the appropriate consumption of caffeine—with respect to both dose and timing of consumption—to mitigate the deleterious effects on sleep.

Practice points

1. Consuming caffeine prior to sleep reduces total sleep time and sleep efficiency, and increases sleep onset latency and wake after sleep onset.
2. Caffeine consumption alters subsequent sleep architecture with an increase in the occurrence of light sleep (N1) and a reduction in the occurrence of deep sleep (N3 and N4).
3. Reductions in total sleep time are dependent on the final dose of caffeine and the time of day that it is consumed relative to bedtime, with greater reductions occurring when larger doses are consumed closer to bedtime.
4. To avoid reductions in total sleep time, coffee (107 mg per 250 mL) should be consumed at least 8.8 h prior to bedtime and a standard serve of pre-workout supplement (217.5 mg) should be consumed at least 13.2 h prior to bedtime.

Research agenda

1. Investigate the influence of both caffeine dose and timing of intake on the characteristics of subsequent sleep through controlled experimental studies.
2. Establish cut-off times for common caffeinated products to minimise the negative effect of caffeine on the characteristics of subsequent sleep.
3. Identify how the effect of caffeine on subsequent sleep is moderated by genotype expression.

Declaration of competing interest

The authors do not have any conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2023.101764.

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