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Coffee, caffeine, and sleep: A systematic review of epidemiological studies and randomized controlled trials

Clark, Ian ; Landolt, Hans Peter

Abstract: Caffeine is the most widely consumed psychoactive substance in the world. It is readily available in coffee and other foods and beverages, and is used to mitigate sleepiness, enhance performance, and treat apnea in premature infants. This review systematically explores evidence from epidemiological studies and randomized controlled trials as to whether coffee and caffeine have deleterious effects on sleep. Caffeine typically prolonged sleep latency, reduced total sleep time and sleep efficiency, and worsened perceived sleep quality. Slow-wave sleep and electroencephalographic (EEG) slow-wave activity were typically reduced, whereas stage-1, wakefulness, and arousals were increased. Dose- and timing-response relationships were established. The sleep of older adults may be more sensitive to caffeine compared to younger adults. Pronounced individual differences are also present in young people, and genetic studies isolated functional polymorphisms of genes implicated in adenosine neurotransmission and metabolism contributing to individual sensitivity to sleep disruption by caffeine. Most studies were conducted in male adults of Western countries, which limits the generalizability of the findings. Given the importance of good sleep for general health and functioning, longitudinal investigations aimed at establishing possible causal relationships among coffee- and caffeine-induced changes in sleep quality and health development are warranted.

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Ian Clark, B.Sc., Hans Peter Landolt, Ph.D., Prof. Dr.

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COFFEE, CAFFEINE, AND SLEEP:

A SYSTEMATIC REVIEW OF EPIDEMIOLOGICAL STUDIES AND RANDOMIZED CONTROLLED TRIALS

Ian Clark, B.Sc.¹ and Hans Peter Landolt, Ph.D.^{1,2}

¹Institute of Pharmacology & Toxicology, University of Zürich, Zürich, Switzerland

²Zürich Center for interdisciplinary Sleep Research (ZiS), University of Zürich, Switzerland

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Addresses for correspondence:

Prof. Dr. Hans Peter Landolt

Institute of Pharmacology & Toxicology

University of Zürich

Winterthurerstrasse 190

8057 Zürich

Switzerland

Tel. + 41 - 44 - 635 59 53

Fax. + 41 - 44 - 635 57 07

e-mail: landolt@pharma.uzh.ch

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Summary

Caffeine is the most widely consumed psychoactive substance in the world. It is readily available in coffee and other foods and beverages, and is used to mitigate sleepiness, enhance performance, and treat apnea in premature infants. This review systematically explores evidence from epidemiological studies and randomized controlled trials whether coffee and caffeine have deleterious effects on sleep. Caffeine typically prolonged sleep latency, reduced total sleep time and sleep efficiency, and worsened perceived sleep quality. Slow-wave sleep and electroencephalographic (EEG) slow-wave activity were typically reduced, whereas stage 1, wakefulness, and arousals were increased. Dose- and timing-response relationships were established. The sleep of older adults may be more sensitive to caffeine compared to younger adults. Pronounced individual differences are also present in young people, and genetic studies isolated functional polymorphisms of genes implicated in adenosine neurotransmission and metabolism contributing to individual sensitivity to sleep disruption by caffeine. Most studies were conducted in male adults of Western countries, which limits the generalizability of the findings. Given the importance of good sleep for general health and functioning, longitudinal investigations aimed at establishing possible causal relationships among coffee- and caffeine-induced changes in sleep quality and health development are warranted.

Keywords:

Sleepiness; sleep disruption; insomnia; stimulant; public health; caffeine sensitivity; adenosine; development; aging; genetics

Abbreviations:

ADA adenosine deaminase gene

ADORA2A adenosine A_{2A} receptor gene

CYP1A2 cytochrome P450 isoenzyme 1A2

DARPP-32 dopamine- and cAMP-regulated phosphoprotein of 32 kDa gene

GABA_A γ -amino-butyrac acid type-A

GBP4 gunylate binding protein 4 gene

EEG electroencephalography

MTNR1B melatonin receptor 1 β gene

NREM non-rapid-eye-movement

PRIMA1 proline rich membrane anchor 1 gene

REM rapid-eye-movement

SNP single nucleotide polymorphism

SWA slow-wave activity

SWS slow wave sleep

WASO wake time after sleep onset

Introduction

Caffeine is the most widely consumed psychoactive substance in the world, which is reflected in the estimated 85 % of the US population drinking least 1 caffeinated beverage each day [1]. It is a xanthine alkaloid and is found in a variety of foods and beverages, such as chocolate, coffee, and tea. Coffee is the primary dietary caffeine source in Western Europe and the United States [2], although among adolescents, soda appears to have emerged as the caffeinated beverage of choice [3] and energy drinks are growing in popularity [4, 5]. Caffeine is used to treat apnea of prematurity [6] and is found in several over-the-counter medications against headache or to suppress appetite [7]. Caffeine is also used to enhance performance among university athletes [8] and as a fatigue countermeasure, for example by truck drivers [9] and shift workers [10], as well as by airline pilots [11].

It is generally accepted that caffeine promotes wakefulness by antagonizing adenosine A₁ and A_{2A} receptors in the brain [7]. A role for adenosine in sleep and arousal regulation has been established by studies in humans and in animals [12]. Adenosine receptor agonists generally promote sleep. Caffeine is metabolized in the liver almost entirely by the cytochrome P450 isoenzyme 1A2 (CYP1A2) [13].

The word “caffeine” is derived literally from the German word for coffee, “Kaffee,” and was coined in 1820 upon its chemical identification by Friedlieb Ferdinand Runge [14] at the encouragement of his contemporary, Johann Wolfgang von Goethe, who supplied him with the coffee beans for the experiments [15].

According to legend [7], the wake-promoting qualities of caffeine were once cleverly exploited by the abbot of a Yemenite monastery, who proscribed coffee to his monks to facilitate their nighttime prayers. The effects of caffeine on human sleep have been the focus of serious scientific inquiry since at least 1912, when Hollingworth [16] published a report on a series of his experiments involving “caffein” [*sic*] and subjective sleep quality in a sample of 16 adult men and

women. Subsequent research in the century since Hollingworth's writing has confirmed and extended his findings, which relate to dose- and timing-response relationships, as well as individual differences in caffeine sensitivity that mediate its disruptive effects on sleep. These subjective findings have been reproduced using objective measures, such as electroencephalography (EEG) and actigraphy, and genetic studies are beginning to uncover potential genetic substrates underlying individual differences in caffeine sensitivity and sleep disruption.

Despite their widespread and increasing use, and the general consensus that coffee and caffeine may interfere with the quality of sleep, there exists presently no comprehensive review of the effects of coffee and caffeine on sleep. The aim of this study was to produce one, and in doing so, address the major open questions relating to coffee, caffeine and human sleep. To this end, a systematic review of all pertinent literature published in peer-reviewed journals was conducted. In the interest of maximizing the utility and applicability of the review, an effort was made to be as inclusive as possible, and both epidemiological as well as controlled clinical trials were examined.

Methods

Study selection

A computerized literature search was conducted with the Web-of-Science and MEDLINE (PubMed) electronic databases that have a comprehensive catalogue of scientific articles in the fields of psychology and medicine. Three search terms were used: "*coffee*," "*caffeine*," and "*sleep*." The search was conducted on all citations published until August 2014. The computerized search was then complemented by manual search through the references of the selected studies.

Articles chosen for review met the following inclusion criteria: the article was 1) published in a peer-reviewed journal; 2) written in English or German; 3) investigated human beings; 4) reported original data; 5) utilized a clinical trial or randomized controlled design; or 6) reported cross sectional or prospective data. Articles were excluded from review based on the following criteria: 1) case-

studies, reviews, and meta-analyses; 2) sleep and associated outcomes were not the primary focus; 3) healthy participant controls were not included if patients suffering from sleep disorders were investigated; 4) additional independent variables prevented reliable interpretation of results.

Figure 1 illustrates the reference selection process. Of the 232 citations identified in the original search, 189 were rejected based on the full title or abstract. Rejected articles did not report original data or were unrelated to the present review. In the remaining 43 citations, 18 were rejected after full-text examination. Manual search of the references in these papers produced 38 additional citations, of which five were rejected after full-text examination. Fifty-seven of the final 58 accepted studies were in English; one was in German [17]. These 58 studies consisted of 19 epidemiological studies, of which three investigated genetic aspects of caffeine sensitivity, two genome-wide association studies, 32 placebo-controlled clinical trials, four open clinical trials, and one observational study..

Insert **Fig. 1** around here

Results

Studies associating caffeine with variables of sleep quality in infants

The currently available evidence suggests that caffeine hardly influences variables related to sleep quality in infants (Table S1, supplementary information). The children of 177 high caffeine-consuming mothers ($\geq 300\text{mg/d}$) did not awaken more frequently than those of low-consuming mothers during pregnancy, as well as three months postpartum [18]. Similarly, no significant differences in heart rate and sleep duration estimated from heart rate were observed in breast-fed

infants from mothers ingesting decaffeinated or caffeine containing coffee over 5 d [19]. No effect was found in the sleep of 15 healthy, yet premature, infants treated with caffeine citrate (5mg/kg) to prevent or reduce apneas of prematurity [20].

Surveys associating caffeine with variables of sleep quality in adolescents

It is estimated that almost 30 % of American adolescents consume caffeinated beverages on a daily basis [21], and soda appears to be the beverage of choice [22], followed by coffee. Energy drinks are gaining popularity [4]. Data from a nationally representative survey [3] with 15'686 respondents revealed that more than two-thirds drank soda once a day or more. Respondents drank coffee less frequently, with over one half not drinking coffee at all and two thirds drinking it once a week or less. Adolescents reporting high caffeine intake (defined as a frequency of consumption > 1 drink/d; n = 4'243) were 1.9 times more likely to have difficulty sleeping and were 1.8 times more likely to experience sleepiness in the morning compared to adolescents reporting low caffeine intake. Besides short sleep duration [23-25], daytime sleepiness has been associated with high and moderate caffeine intake among adolescents [26, 27].

Based on survey data of 625 children aged 6-10 y, it was suggested that children who habitually drink on average 0.4 caffeinated beverages/d lose approximately 15 min in sleep duration [21]. Using a diary to record sleep and caffeine habits over approximately 21 d in 191 adolescents aged 12-15 y, caffeine consumption was associated with increased wake time after sleep onset (WASO), shorter sleep duration, and longer daytime sleep both within and between respondents [22]. The sleep of higher caffeine consumers (100-150 mg/day) was more interrupted than that of lower consumers (0-50 mg/d), and sleep was more interrupted on nights after increased consumption. Respondents consumed a mean of 1.1 caffeinated beverages/d, resulting in an individual mean daily consumption of 52.7 mg. Intake increased on weekends, reaching its peak (77.1 mg) on Saturday and falling to its lowest point (54.0 mg) on Wednesday, possibly reflecting

greater use due to social opportunity. Soda with modest caffeine content (≤ 40 mg) represented the most common (64 %) and most consumed (53 %) source.

Among 100 adolescents 12-18 years of age, only 20.6 % of respondents slept the recommended 8-10 h on school nights [28]; the rest slept less than eight h, although exact sleep durations were not specified. A median daily caffeine intake of 144 mg (range: 23-1'458 mg) was reported [29]. Intake typically occurred before or after school hours. Whereas caffeine consumption tended to be lower in the group sleeping 8-10 h, it did not reach significance. Tea and soda were the most frequently consumed caffeinated beverages in this sample. Consumption times were not reported.

Despite limitations in the available literature (e.g., different sources, unreported intake time, different age groups), associations between caffeine consumption and sleep in adolescents emerge (Table S2, supplementary information). Already at moderate dose, caffeine was associated with the perception of shorter sleep duration, delayed sleep onset, and increased perceived WASO, daytime sleep and daytime sleepiness. Studies employing objective measures of sleep-wake quality are required to confirm these findings.

Studies associating caffeine with variables of sleep quality in adults

Subjective sleep quality and reported sleep duration (epidemiological studies)

In a sample of 144 male prison inmates, subjective sleep quality was poorer in high (> 500 mg/d) than in low (< 500 mg/d) habitual caffeine consumers [30]. In one survey with 183 female respondents, however, those who reported higher caffeine intake (≥ 5 cups/d) typically reported less caffeine-attributed sleep disturbance, whereas those reporting lower caffeine intake (1-2 cups/d) reported more such disturbance [31].

One survey of 2'696 respondents reported that moderate coffee consumers (1-4 cups/d within 6 h of bedtime), constituting 40 % of the sample, had a shorter sleep latency, fewer awakenings, and were more satisfied with their sleep than heavy consumers (4 %) or those who abstained from caffeine (54 %) [32]. In a survey of 170 college students, those reporting habitual short sleep duration (< 6h) consumed 3.6 times more caffeine each day than long sleepers (> 8 h) [33]. Subjective sleep quality in this sample was found to be worse in heavy consumers (> 8 cups/d) compared to light (0-1 cup/d), although it did not reach significance. Nevertheless, in a larger sample, reported sleep duration decreased by 40 min on average when caffeine intake exceeded 8 cups/d [34] (Table S3, supplementary information).

Sleep latency, wake time after sleep onset, and sleep duration (laboratory and field studies)

An overwhelming majority of controlled laboratory studies with EEG [35-50] or actimetry [51-52] measures of sleep, in addition to one EEG field study [53], suggests that caffeine impacts human sleep quality. Sleep latency and WASO were prolonged and sleep duration was reduced. Only one actimetry study [54] with 10 participants and one polysomnography study [55] with 30 participants in a five-day shift work paradigm reported no effect of caffeine on any sleep variable. Sleep efficiency (i.e., percentage of total time asleep per total time in bed) was reduced in 10 of the 11 studies reporting this variable (Tables S4 & S5, supplementary information).

Daily caffeine doses ranged from 37.5 to 1'200 mg, in some cases administered in a pre-defined ratio to body weight. Of six studies with a focus on dose-response effects of caffeine on sleep, three [44, 52, 57] showed progressive worsening of sleep quality with increasing dose as quantified by sleep latency, WASO, sleep duration and sleep efficiency. Two studies [42, 56] showed no dose-related increase in sleep latency, whereas one study [54] found no effect on any of these variables. Although two reports suggested that caffeine clearance was greatest among participants

reporting the least sleep disruption [58], no consistent differences in pharmacokinetics were found between “sensitive” and “insensitive” subjects.

Habitual caffeine intake represents one potential index of individual sensitivity and may be a confounding variable when not appropriately controlled for. Of the 24 studies reviewed in this section, intake was specified in all but four [39, 42, 43, 45] and was typically moderate. One study stated vaguely “minimal drug use” [43]. One study [51] did not report pre-study habitual intake *per se*, but administration during the at-home field study was *ad libitum*, and hence intake during the study may have reflected actual habitual intake. Moderate intake was sometimes part of the inclusion criteria, in order to minimize variance attributable to individual differences. Individual differences in habitual intake were reported in one study [52], in which greater habitual intake was associated with less sleep disruption. One study [40], in which participants were grouped by high or low score on a measure of vulnerability to stress-related sleep disturbance, only the sleep of those in the high vulnerability group was affected by caffeine. The two groups did not differ on habitual intake.

The timing of administration may influence the magnitude of effects on sleep, such that administration close to habitual bedtime has the greatest potential for disruption, although there are only three studies [46, 52, 53], in which the timing of administration was systematically varied as a specific focus of the experiment. Typically, caffeine was administered in a single dose ≤ 60 min of habitual bedtime. This method tended to induce the greatest disruption, but may not reflect actual dietary patterns. Attempts at simulation of more naturalistic intake patterns (i.e., consumption at several intervals throughout the day) were made in five studies [51-54, 57]. Two studies provided caffeine *ad libitum*, one [51] to a sample of medical students in which afternoon and evening intake habits were already established and one [54] to university students, who were also instructed to consume one cup of coffee with dinner in addition to normal consumption. A timing-response effect was supported.

Comparison between subjective and objective measures of sleep latency, wake time after sleep onset, and sleep duration

A general agreement exists between objective and subjective measures of sleep latency, WASO, and sleep duration in caffeine studies [42, 44, 46, 53, 55]. In two studies [35, 36], subjective measures did not reach significance, and in two other studies with only subjective measures [54, 59], no perceptible change was reported. Compared to objective variables, the influence of caffeine was systematically underestimated. Subtle abnormalities in sleep quality, such as sleep fragmentation, may contribute to the discrepancy between subjective and objective findings. These characteristics are not easily perceived by the sleeper, which may contribute to poor adherence to appropriate sleep hygiene [53].

Four studies [60-63] used subjective measures of sleep latency and sleep duration in substantially larger samples of young adults. Their findings do not differ markedly from objective measures in smaller samples [41, 55, 58]. In one report [62], fewer participants with high habitual caffeine (coffee) intake (≥ 5 cups/d) than with low intake (0-1 cups/d) believed evening coffee ingestion would disrupt their sleep. By contrast, objectively, their sleep was affected just as much as those reporting low intake. In a caffeine withdrawal protocol [64], participants rated sleep quality as better and reported falling asleep faster in the two nights immediately following cessation. In nine psychiatric patients, nocturnal enuresis, pharmacological restraint, or insomnia improved after systematic withdrawal [65] (Table S5, supplementary information).

Polysomnography-derived sleep macro-structure

Caffeine modifies visually-scored sleep-wake states, such that the duration and frequency of wakefulness, arousals and stage 1 sleep increase earlier in the night at the expense of slow wave sleep (SWS; i.e., NREM sleep stages 3 and 4), which is reduced in duration and occupies

proportionately less of sleep time [56], especially within the first six h [36, 42, 44, 47]. Increased arousals and awakenings at the expense of reductions in both stage 2 and stage 4 sleep were shown [46]. While these findings may not necessarily mean that caffeine reduces physiological sleep propensity [36, 38], accumulating evidence supports the hypothesis that mechanisms of sleep homeostasis and caffeine interact [35-37, 47-49].

Stage 4 sleep over the entire sleep episode reverted back to baseline levels the night after cessation, although stage 2 sleep was still decreased [36]. Caffeine did not affect sleep structure in the recovery night after sleep deprivation [37]. Recovery sleep during the biological day after a night of sleep deprivation contained less SWS compared to baseline in two studies [47, 48]. No effect was found on any stages during daytime sleep after simulated night shift work [55].

There is some evidence for a dose-response relationship between caffeine and sleep structure. Progressively higher bedtime doses reduced the percentage of SWS [44], which initiated later, whereas lower doses increased latency to stage 2 sleep. The time spent in SWS decreased with progressive dose increase, whereas the duration of wakefulness in the first 6 h of the sleep episode progressively increased [53]. No clear dose-response relationship was found on REM sleep [41, 45]. Nevertheless, one experiment [44] suggested that after large doses (4.6 mg/kg), the proportion of REM sleep was increased in the first third of the night, whereas in the final third of the night, this effect on REM sleep occurred after comparatively moderate doses (2.3 mg/kg).

In only two studies, bedtime caffeine produced no significant effects in any stages [35, 45]. No differential response in sleep stages to caffeine administered at three different times of the night was found [53]. No studies reported any variability associated with sex. The pattern of caffeine effects on heart rate and QT variability in REM sleep may suggest increased risk of adverse cardiovascular events [66]. Slow-wave sleep was reduced in individuals with high vulnerability for stress-related sleep disturbance compared to those with low vulnerability [40].

EEG power spectra during sleep

The EEG power spectra during nighttime sleep [36, 37, 39, 67], daytime naps [48, 49], and daytime waking [37] are more sensitive to caffeine than sleep architecture. The most reliable changes were a reduction in slow-wave activity (SWA; ~ 0.75 -4.5 Hz) or delta frequencies, and an increase in sigma/beta frequencies (~ 13.0 -30.0 Hz) in NREM sleep [35-38, 48]. Reduced delta and enhanced sigma/beta activity in the NREM sleep EEG are well established neurophysiological markers of superficial sleep.

A 100-mg dose administered at habitual bedtime [36, 38] reduced SWA in the entire ensuing sleep episode, but reductions were particularly pronounced in the lower frequency range (0.25-2.0 Hz) and in the first NREM sleep episode. The accumulation of SWA was also attenuated in the first NREM sleep episode [36]. A higher early morning dose (200 mg at 7:15) induced similar changes on the ensuing nighttime sleep episode, such that spectral power density in the 0.25-0.5 Hz range in NREM sleep was reduced, even though saliva caffeine concentrations approached zero just before sleep [35]. Slow-wave activity was attenuated, and beta activity (11.25-20 Hz) was enhanced in recovery sleep after sleep deprivation despite undetectable salivary caffeine concentrations [37]. These findings suggest some longevity in the caffeine signature in these specific EEG frequency bands. Also sigma/beta ("spindle") frequency activity in NREM sleep [35-39] was increased, and a positive dose-response relationship was shown [39]. In REM sleep, activity in the 0.75-4.5 and 5.25-6.0 Hz ranges was also significantly reduced [35].

There is some evidence for topographical variability in caffeine-induced changes of the sleep EEG. Low-delta activity was reduced in all but occipital EEG derivations [36], whereas enhanced power in the spindle frequency range was found only in central and parietal derivations [36]. Also an age-dependent topographical EEG response to caffeine was reported. In older adults, SWA was most attenuated in the prefrontal cortex, while power in the high alpha (10-12 Hz) and beta (17-21, 23-25,

and 27-29 Hz) frequencies was elevated in parietal derivations [38]. No interaction between caffeine and younger and older adult age on quantitative EEG was shown, however [48].

Individual caffeine sensitivity

Not only individuals of different age, but also those of similar age are differently sensitive to sleep disruption by caffeine [16], and genetics influence caffeine consumption and the physiological response to caffeine in humans [68].

Of 4'329 young adult (mean age: 24 y) respondents to an internet questionnaire, symptoms of insomnia (> 20min time to fall asleep and "perception of frequent awakenings") were found to be more prevalent in self-rated caffeine sensitive than in insensitive respondents [69]. Within sensitive respondents, insomnia symptoms were also greater in habitual consumers than in non-consumers. No difference was observed between consumers and non-consumers in the insensitive respondents. Genetic variants in the adenosine A_{2A} receptor gene (ADORA2A) modulate individual differences in subjective response to the stimulating and anxiogenic properties of caffeine [67, 70, 71]. In addition, a ADORA2A polymorphism affects EEG activity in frequencies functionally related to sleep and wakefulness [67]. Thus, 142 of the male respondents to the internet questionnaire reporting caffeine sensitivity (n = 58) or insensitivity (n = 84) were genotyped for the single nucleotide polymorphism (SNP) c.176T>C (SNP identification number: rs5751876) of the ADORA2A gene. A higher proportion of participants reporting high sensitivity carried the C/C genotype, whereas a higher proportion of low sensitivity carried the T/T genotype. Heterozygosity was proportionately equal in high and low sensitivity groups. These findings were further supported in the laboratory, where 22 participants were given caffeine and placebo in a sleep deprivation protocol in double-blind, cross-over manner. The C/C-alleles carriers responded to caffeine with increased EEG beta (16-20 Hz) activity, whereas only half this increase was observed in the C/T group and no increase at all was found in T/T-alleles carriers. Importantly, haplotype and genome-wide linkage analyses

independently confirmed the impact of the ADORA2A gene on the effects of caffeine on the regulation of EEG SWA in NREM sleep and coffee-induced sleep disturbances [69, 72]. The frequencies of the C/C, C/T, and C/T genotypes in 142 healthy Caucasian individuals were 31.6 %, 54.2 %, and 14.1 % respectively [69].

Adenosine deaminase (ADA) is an enzyme which breaks down adenosine to inosine and regulates intra- and extracellular adenosine levels. The ADA gene encodes two electrophoretic variants of ADA (rs73598374), referred to as ADA*1 and ADA*2. The heterozygous ADA*1-2 (G/A) genotype shows reduced catalytic activity of ADA compared to homozygous carriers of the ADA*1 (G/G genotype) variant. EEG delta activity in NREM sleep is consistently enhanced in the G/A genotype [67, 73, 74]. An association was investigated between this functional polymorphism, sleep and caffeine intake [72]. Almost 1'000 participants (mean age: 43 y) were genotyped and homozygous G/G-alleles and A-allele carriers were stratified into two categories by caffeine consumption on the day of polysomnography (no caffeine vs. ≥ 1 cup). The A-allele carriers showed shorter sleep latency, higher sleep efficiency and proportion of REM sleep, and fewer min awake. No difference was found between genotypes among those who did not consume caffeine on the day prior to polysomnography. A linear model was then applied and demographic variables (age, sex, European ancestry) were adjusted for, which yielded a significant effect for sleep efficiency and REM sleep, such that G/G-alleles carriers of the c.22G>A polymorphism of ADA reported poorer sleep quality than A-allele carriers. The frequencies of ADA polymorphisms identified in 958 individuals were as follows: G/G 91.2 %; G/A 8.5 %; A/A 0.3 % [72], which are within the ranges expected in a healthy Caucasian population (G/G 88–92 %; G/A 8–12 %; A/A 1 %) [67].

One twin study [75] with 3'808 participants identified common genetic variants that predispose to general sleep disturbance attributed to caffeine. Heritability of self-reported coffee-attributed sleep disturbance was approximately 40 % in both sexes. A genome-wide linkage analysis of coffee attributed insomnia in 1'989 of the participants revealed significant linkage to a locus on chromosomal region 2q, which affected sibling pairs who were resilient to the disruptive effects of

caffeine on sleep. A region of suggestive linkage on chromosome 17q in caffeine-sensitive sibling pairs, which fell just short of significance, was also identified. Because the DARPP-32 (dopamine- and cAMP-regulated phosphoprotein of 32 kDa) gene resides within the chromosome 17q linkage peak, this region may be linked to caffeine-induced sleep disruption. Caffeine's stimulatory effect on motor activity in mice with DARPP-32 deletion is reduced [76]. Furthermore, adenosine represents a neuromodulator that stimulates phosphorylation of DARPP-32 protein. Nevertheless, it is still unclear to what extent the 17q region can be associated with caffeine's effects on sleep, if any.

A study of 2'402 twins [77] identified additional genes that showed evidence of association with caffeine-induced insomnia. Significant associations were identified with SNP rs6575353 of the gene encoding PRIMA1 (proline rich membrane anchor 1) located on chromosome 14, and with SNP rs521704 of the gene coding for GBP4 (guanylate binding protein 4) located on chromosome 1. The SNP rs10830964 near the MTNR1B (melatonin receptor 1 β) gene was also identified, which encodes a subunit of the melatonin receptor expressed mainly in the retina and the brain.

Polymorphisms of the gene CYP1A2 have been identified and may underlie individual variability in the hepatic metabolism of caffeine [78]. For example, the functional polymorphism c.-163C>A (rs762551) of CYP1A2 causes individual differences in the inducibility of CYP1A2 enzyme activity by caffeine, yet no association of this polymorphism with individual effects of caffeine on sleep has been investigated.

Melatonin secretion and metabolism

Melatonin, the "hormone of darkness" secreted by the pineal gland [79], is critically involved in the process of entraining the human sleep-wake cycle to the external 24-h solar day [80]. Both, melatonin and caffeine are metabolized by the liver enzyme CYP1A2 [81]. Coffee (5.3 cups/d) consumed in the "afternoon" and "evening" over seven days, compared with placebo, blunted the nightly (1:00-4:00) peak in melatonin secretion by 30 % [51]. By contrast, capsules containing 200 mg

caffeine administered in the evening to 12 participants on two occasions induced an increase in serum melatonin levels by 32 % [13].

Studies associating caffeine with sleep and sleep-associated variables in older individuals

Subjective insomnia and coffee consumption (epidemiological studies)

Lower plasma caffeine correlated with poorer sleep in an independently living group (n = 181) of older adults, but not in a hospitalized group (n = 53), leading to the speculation that the two distinct environments played a modulatory role on the association between caffeine consumption and sleep quality [82]. In a survey of 2'955 older adults [83], respondents who reported specific reasons for caffeine curtailment, one of the most-cited reasons was "sleep problems." Significantly more female (35 %) than male (27 %) respondents cited sleep problems for curtailed intake. Respondents who reported curtailment were also previously higher coffee consumers (3-3.5 cups/d) than respondents who did not curtail. (Table S6, supplementary information).

Sleep architecture and sleep EEG power spectra

Evening intake of 200 mg caffeine (divided evenly between 1 and 3 h before bedtime) increased sleep latency by 7 min, reduced sleep efficiency by 5 %, and decreased sleep duration and stage 2 sleep by 28 min in older (mean age: 50.3 y) and younger (23.8 y) adults [38]. The sleep EEG of both age groups was affected after caffeine, although only the older age group showed suppression of spectral power in the lower delta range (0.5-1.0 Hz) in the prefrontal cortex and an increase in the high alpha (10.00-12.00 Hz) and beta (17.00–21.00, 23.00–25.00, 27.00–29.00 Hz) ranges in parietal regions. No age-related differences in the effects of caffeine on the EEG during daytime recovery sleep after a night of sleep deprivation was found, however [48].

In a slightly older age group, 300 mg caffeine decreased total sleep time by an average of 2 h and increased mean sleep latency to 66 min [84]. The number of awakenings increased as did the mean total episodes of intervening wakefulness, particularly during the last three h of sleep. Stage 2 sleep was increased, whereas SWS was reduced in the first three h of sleep. No significant change was observed in REM sleep.

Discussion

An influence of caffeine on human sleep has been the focus of a considerable body of scientific research in the past century. In healthy adults, changes in sleep are well characterized, and experiments utilizing healthy adult samples yield reliable results. Other age groups have received less attention. This is unfortunate, because age may represent a mitigating factor in response to caffeine. The fewest studies were dedicated to infants, and no studies investigated young children.

Caffeine intake in infancy deserves more attention, as infants are regularly exposed to caffeine through maternal consumption and subsequent transmission during breastfeeding or during citrate therapy in the event of prematurity. Caffeine is furthermore present in select pharmaceutical compounds, which may be ingested during or following pregnancy and given to the infant. While caffeine may affect sleep and maturational markers in rats [85], the effects of caffeine on sleep and development of infants remains uninvestigated.

Adolescent sleep was the focus of several epidemiological studies, yet none were identified that experimentally investigated this age group in a controlled laboratory setting. Exposure to caffeine in this age group mainly in the form of soda is substantial [3] and may contribute to daytime sleepiness [27]. This, however, remains a correlational finding.

It is difficult to untangle caffeine use due to daytime sleepiness or daytime sleepiness due to disrupted sleep possibly caused by caffeine use. Individuals with poor sleep quality due to some other factor, such as shift work or a sleep disorder like narcolepsy, may, for instance, consume

caffeine to manage sleepiness [86, 87]. Nevertheless, it may be intriguing that chronic dietary caffeine consumption in rats increases the plasma concentration of adenosine [88], a biological signal thought to mediate sleepiness.

The sleep of older adults may respond differently to caffeine than the sleep of young adults when quantified with EEG spectral analysis. A recently published paper [89] not included in this review supports the hypothesis of heightened vulnerability to sleep disturbance induced by high caffeine doses in older adults. Older adults may also curtail intake due to perceived sleep problems. With the exception of infants, caffeine generally increased sleep latency, reduced sleep duration, and worsened sleep quality as assessed by subjective and objective measures across age groups.

Differences in dietary caffeine intake were associated with caffeine sensitivity [31], female sex [83], advanced age [38], vulnerability to stress-related sleep disturbance [52], as well as ADORA2A [69] and ADA [72] genotypes. The DARPP-32 [75] and PRIMA1 [77] genes were also implicated in caffeine sensitivity and caffeine induced insomnia, respectively. The efficiency of caffeine metabolism represents a further source of variance between individuals [58, 62, 90]. Caffeine exposure may also be altered as a function of body weight [62]. This is particularly relevant for adolescent and older adult caffeine consumption, as their dietary caffeine intake is comparable to that of adults, but these populations typically weigh less than adults.

Typically, the “lighter” sleep stages prevail at the expense of “deeper” stages, which occur less frequently, have a shorter duration and may be delayed to later NREM episodes after intake. In line with attenuated SWS, EEG delta frequencies are also typically reduced. An interaction between caffeine and sleep homeostasis has been hypothesized for this reason. Functional polymorphisms of the ADORA2A and ADA gene may underlie individual differences in caffeine’s reduction of SWS and SWA. Age may be a mitigating factor, such that older adults show greater decrease in delta frequencies above the prefrontal cortex compared to younger adults. This finding suggests topographical variance in response to caffeine.

Study limitations

The broad focus of this review resulted in the inclusion of scientific articles spanning the fields of medicine, genetics, neuroscience, and psychology. This demanded that some outcomes would be included at the expense of others, which were determined not to be directly related to the acute effects of coffee and caffeine on sleep, such as decrement in measures of vigilance, executive function, or changes in mood. These indirect or chronic effects of caffeine on sleep warrant independent review. There were only three epidemiological studies with a longitudinal design identified and these investigated only adolescents or infants. More longitudinal studies are necessary to characterize the caffeine habits of these and other populations. Almost without exception [18, 51, 54, 72], no studies were conducted in regions outside of North America or Western Europe. There were more males investigated than females. Thus, caution should be exercised in applying these findings to the inhabitants of other regions or women. Beverage type was not associated with systematic variability in sleep quality. There were 14 single- and 17 double-blind studies. Nevertheless, participants' expectations of the beverage could potentially influence their response to caffeine [52, 91].

Furthermore, sensory cues emanating from the autonomic nervous system [92] or the taste and odor [93] of the beverage could possibly influence response. Coffee and tea are composed of complex organic substances which may exude subtle and unique biological effects [52]. The flavonoids found in tea have been shown to interact with adenosine [94] and GABA_A (γ -aminobutyric acid type A) receptors [95], for instance, and tea may promote peripheral vasodilation [96].

Conclusions

This review presented reliable associations between altered sleep quality and dietary caffeine intake, which were reported in epidemiological studies. These observations were supported

by studies conducting experiments in controlled laboratory settings. By blocking the adenosine neuromodulator and receptor system, which contributes importantly to sleep-wake regulation, caffeine impairs nighttime sleep, at least in vulnerable individuals. The equivalent of caffeine contained in one or two double-essposos ingested up to 16 h before sleep induce reliable changes in the sleep EEG, indicative of more superficial sleep, although the caffeine level in saliva has virtually reverted to zero at the beginning of the sleep [35 37 69]. Average exposure to caffeine under non-controlled field conditions is likely to be as high, or higher, than to the amount of caffeine that impairs the quality of sleep in controlled laboratory studies (**Fig. 2**). We recently observed that the caffeine level in saliva at bedtime equaled roughly 12 $\mu\text{mol/l}$ in a random sample from a middle-aged urban population ($n = 336$; mean age: 63.9 y) (Urry et al., in review). This concentration is typically reached after intake of 200 mg caffeine in young and older adults after two weeks of abstinence [97]. It delays sleep onset and reduces SWS and neurophysiological markers of sleep intensity (Table S4, supplemental information). Thus, caffeine-induced sleep changes may not only underlie the daytime sleepiness it is meant to remedy, but also have negative consequences on key aspects of general health and functioning that depend on undisturbed sleep (see [98] for review). Indeed, poor sleep hygiene practices contribute to increased health risk, although awareness of these practices in the general public may be lacking [53].

Insert **Fig. 2** around here

On the other hand, it is common knowledge that caffeine promotes vigilance and reduces sleepiness. It is frequently consumed with this specific benefit in mind. Moreover, caffeine has demonstrated potency to restore performance in ecological situations such as highway-driving

during the night [99]. The majority of studies demonstrates that daily intake of 3-4 cups of coffee is not associated with a significant health risk. Even the opposite may be the case [100-102]. Nevertheless, it is currently unclear whether the reported associations among coffee, caffeine and health are causal or purely associative, and whether active ingredients of coffee other than caffeine have detrimental or beneficial health effects. Given that caffeine from coffee and other sources is the most widely used substance worldwide and that inadequate sleep has surpassed drugs and alcohol as the greatest identifiable and preventable cause of accidents in all modes of transportation [103], the relationships among coffee, caffeine and sleep have important public health impact and should be thoroughly explored with high priority in the future.

Practice points

- Sleep quality is altered by caffeine
- Expected consumption of caffeine in society is sufficient to interfere with sleep
- The magnitude of caffeine's effects on sleep are modulated by individual differences related to age, sex, weight, genetic predisposition, and possibly other factors

Research agenda

- Focus future epidemiological and experimental studies on currently under-investigated populations, including females, adolescents, young children, and adults living in non-Western societies
- Establish timing- and dose-response relationships relating to visually-scored and quantitative EEG sleep variables
- Investigate the effects of caffeine on circadian rhythms and the interaction of circadian and homeostatic sleep regulatory processes

- Establish possible causality among coffee and caffeine intake, sleep quality, and health development
- Further investigate genetic substrates predisposing individuals for caffeine-induced sleep changes

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References

* The most important references are denoted by an asterisk.

1. Mitchell DC, Knight CA, Hockenberry J, et al. Beverage caffeine intakes in the U.S. *Food Chem Toxicol* 2014;**63**:136-42
2. Barone JJ, Roberts HR. Caffeine consumption. *Food Chem Toxicol* 1996;**34**(1):119-29
3. Orbeta RL, Overpeck MD, Ramcharran D, et al. High caffeine intake in adolescents: associations with difficulty sleeping and feeling tired in the morning. *J Adolesc Health* 2006;**38**(4):451-3
4. Seifert SM, Schaechter JL, Hershorin ER, et al. Health effects of energy drinks on children, adolescents, and young adults. *Pediatrics* 2011;**127**(3):511-28
5. Van Batenburg-Eddes T, Lee NC, Weeda WD, et al. The potential adverse effect of energy drinks on executive functions in early adolescence. *Front Psychol* 2014;**5**:457
6. Calhoun LK. Pharmacologic management of apnea of prematurity. *J Perinat Neonatal Nurs* 1996;**9**(4):56-62
7. * Nehlig A, Daval JL, Debry G. Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. *Brain Res Brain Res Rev* 1992;**17**(2):139-70
8. Rosenbloom C. Energy drinks, caffeine, and athletes. *Nutrition Today* 2014;**49**(2):49-54
9. Ronen A, Oron-Gilad T, Gershon P. The combination of short rest and energy drink consumption as fatigue countermeasures during a prolonged drive of professional truck drivers. *J Safety Res* 2014;**49**:39-43
10. Dekker DK, Paley MJ, Popkin SM, et al. Locomotive engineers and their spouses: coffee consumption, mood, and sleep reports. *Ergonomics* 1993;**36**(1-3):233-8

11. Petrie KJ, Powell D, Broadbent E. Fatigue self-management strategies and reported fatigue in international pilots. *Ergonomics* 2004;**47**(5):461-8
12. Porkka-Heiskanen T, Kalinchuk AV. Adenosine, energy metabolism and sleep homeostasis. *Sleep Med Rev* 2011;**15**(2):123-35
13. Ursing C, Wikner J, Brismar K, et al. Caffeine raises the serum melatonin level in healthy subjects: an indication of melatonin metabolism by cytochrome P450(CYP)1A2. *J Endocrinol Invest* 2003;**26**(5):403-6
14. Runge FF. *Neueste phytochemische Entdeckungen zur Begründung einer wissenschaftlichen Phytochemie*. Berlin: G. Reimer, 1820.
15. Goethe JWv. *Anhang an Goethes Werke: Abteilung für Gespräche*. Leipzig: Biedermann, Woldemar Freiherr von, 1896.
16. Hollingworth HL. The Influence of Caffein Alkaloid on the Quality and Amount of Sleep (*sic*). *The American Journal of Psychology* 1912;**23**(1):89-100
17. Stradomsky N. [Studies of sleep movements following caffein-containing and caffein-free coffee]. *Med Klin* 1970;**65**(29):1372-6
18. Santos IS, Matijasevich A, Domingues MR. Maternal caffeine consumption and infant nighttime waking: prospective cohort study. *Pediatrics* 2012;**129**(5):860-8
19. Ryu JE. Effect of maternal caffeine consumption on heart rate and sleep time of breast-fed infants. *Dev Pharmacol Ther* 1985;**8**(6):355-63
20. Curzi-Dascalova L, Aujard Y, Gaultier C, et al. Sleep organization is unaffected by caffeine in premature infants. *J Pediatr* 2002;**140**(6):766-71
21. Calamaro CJ, Yang K, Ratcliffe S, et al. Wired at a young age: the effect of caffeine and technology on sleep duration and body mass index in school-aged children. *J Pediatr Health Care* 2012;**26**(4):276-82

22. Pollak CP, Bright D. Caffeine consumption and weekly sleep patterns in US seventh-, eighth-, and ninth-graders. *Pediatrics* 2003;**111**(1):42-6
23. Drescher AA, Goodwin JL, Silva GE, et al. Caffeine and screen time in adolescence: associations with short sleep and obesity. *J Clin Sleep Med* 2011;**7**(4):337-42
24. Lodato F, Araújo J, Barros H, et al. Caffeine intake reduces sleep duration in adolescents. *Nutr Res* 2013;**33**(9):726-32
25. Berkey CS, Rockett HR, Colditz GA. Weight gain in older adolescent females: the internet, sleep, coffee, and alcohol. *J Pediatr* 2008;**153**(5):635-9, 39.e1
26. * Roehrs T, Roth T. Caffeine: sleep and daytime sleepiness. *Sleep Med Rev* 2008;**12**(2): 153-62
27. Ludden AB, Wolfson AR. Understanding adolescent caffeine use: connecting use patterns with expectancies, reasons, and sleep. *Health Education and Behavior* 2009;**37**(3):330-42
28. US Department of Health and Human Services: Sleep health objectives. 2015; <https://www.healthypeople.gov/2020/topics-objectives/topic/sleep-health/objectives>.
29. Calamaro CJ, Mason TB, Ratcliffe SJ. Adolescents living the 24/7 lifestyle: effects of caffeine and technology on sleep duration and daytime functioning. *Pediatrics* 2009;**123**(6):e1005-10
30. Hughes GV, Boland FJ. The effects of caffeine and nicotine consumption on mood and somatic variables in a penitentiary inmate population. *Addict Behav* 1992;**17**(5):447-57
31. Goldstein A, Kaizer S. Psychotropic effects of caffeine in man. 3. A questionnaire survey of coffee drinking and its effects in a group of housewives. *Clin Pharmacol Ther* 1969;**10**(4):477-88

32. Mniszek DH. Brighton sleep survey: a study of sleep in 20-45-year olds. *J Int Med Res* 1988;**16**(1):61-5
33. Hicks RA, Hicks GJ, Reyes JR, et al. Daily caffeine use and the sleep of college students. *Bull Psychonom Soc* 1983;**21**(1):24-25
34. Sanchez-Ortuno M, Moore N, Taillard J, et al. Sleep duration and caffeine consumption in a French middle-aged working population. *Sleep Med* 2005;**6**(3):247-51
35. Landolt HP, Werth E, Borbély AA, et al. Caffeine intake (200 mg) in the morning affects human sleep and EEG power spectra at night. *Brain Res* 1995;**675**(1-2):67-74
36. Landolt HP, Dijk DJ, Gaus SE, et al. Caffeine reduces low-frequency delta activity in the human sleep EEG. *Neuropsychopharmacology* 1995;**12**(3):229-38
37. * Landolt HP, Rétey JV, Tönz K, et al. Caffeine attenuates waking and sleep electroencephalographic markers of sleep homeostasis in humans. *Neuropsychopharmacology* 2004;**29**(10):1933-9
38. Drapeau C, Hamel-Hébert I, Robillard R, et al. Challenging sleep in aging: the effects of 200 mg of caffeine during the evening in young and middle-aged moderate caffeine consumers. *J Sleep Res* 2006;**15**(2):133-41
39. * Hirshkowitz M, Thornby JI, Karacan I. Sleep spindles: pharmacological effects in humans. *Sleep* 1982;**5**(1):85-94
40. Drake CL, Jefferson C, Roehrs T, et al. Stress-related sleep disturbance and polysomnographic response to caffeine. *Sleep Med* 2006;**7**(7):567-72
41. Lin AS, Uhde TW, Slate SO, et al. Effects of intravenous caffeine administered to healthy males during sleep. *Depress Anxiety* 1997;**5**(1):21-8
42. Nicholson AN, Stone BM. Heterocyclic amphetamine derivatives and caffeine on sleep in man. *Br J Clin Pharmacol* 1980;**9**(2):195-203

43. Bonnet MH, Webb WB. The return to sleep. *Biol Psychol* 1979;**8**(3):225-33
44. * Karacan I, Thornby JI, Anch M, et al. Dose-related sleep disturbances induced by coffee and caffeine. *Clin Pharmacol Ther* 1976;**20**(6):682-9
45. Gresham SC, Webb WB, Williams RL. Alcohol and caffeine: effect on inferred visual dreaming. *Science* 1963;**140**(3572):1226-7
46. * Bonnet MH, Arand DL. Caffeine use as a model of acute and chronic insomnia. *Sleep* 1992;**15**(6):526-36
47. Carrier J, Fernandez-Bolanos M, Robillard R, et al. Effects of caffeine are more marked on daytime recovery sleep than on nocturnal sleep. *Neuropsychopharmacology* 2007;**32**(4):964-72
48. Carrier J, Paquet J, Fernandez-Bolanos M, et al. Effects of caffeine on daytime recovery sleep: A double challenge to the sleep-wake cycle in aging. *Sleep Med* 2009;**10**(9):1016-24
49. Van Dongen HP, Price NJ, Mullington JM, et al. Caffeine eliminates psychomotor vigilance deficits from sleep inertia. *Sleep* 2001;**24**(7):813-9
50. Kelly TL, Mitler MM, Bonnet MH. Sleep latency measures of caffeine effects during sleep deprivation. *Electroencephalogr Clin Neurophysiol* 1997;**102**(5):397-400
51. Shilo L, Sabbah H, Hadari R, et al. The effects of coffee consumption on sleep and melatonin secretion. *Sleep Med* 2002;**3**(3):271-3
52. * Hindmarch I, Rigney U, Stanley N, et al. A naturalistic investigation of the effects of day-long consumption of tea, coffee and water on alertness, sleep onset and sleep quality. *Psychopharmacology (Berl)* 2000;**149**(3):203-16
53. Drake C, Roehrs T, Shambroom J, et al. Caffeine effects on sleep taken 0, 3, or 6 hours before going to bed. *J Clin Sleep Med* 2013;**9**(11):1195-200

54. Ho SC, Chung JW. The effects of caffeine abstinence on sleep: a pilot study. *Appl Nurs Res* 2013;**26**(2):80-4
55. Muehlbach MJ, Walsh JK. The effects of caffeine on simulated night-shift work and subsequent daytime sleep. *Sleep* 1995;**18**(1):22-9
56. LaJambe CM, Kamimori GH, Belenky G, et al. Caffeine effects on recovery sleep following 27 h total sleep deprivation. *Aviat Space Environ Med* 2005;**76**(2):108-13
57. Rosenthal L, Roehrs T, Zwyghuizen-Doorenbos A, et al. Alerting effects of caffeine after normal and restricted sleep. *Neuropsychopharmacology* 1991;**4**(2):103-8
58. Levy M, Zylber-Katz E. Caffeine metabolism and coffee-attributed sleep disturbances. *Clin Pharmacol Ther* 1983;**33**(6):770-5
59. James JE. Acute and chronic effects of caffeine on performance, mood, headache, and sleep. *Neuropsychobiology* 1998;**38**(1):32-41
60. Höfer I, Bättig K. Cardiovascular, behavioral, and subjective effects of caffeine under field conditions. *Pharmacol Biochem Behav* 1994;**48**(4):899-908
61. Goldstein A. Wakefulness caused by caffeine. *Naunyn Schmiedebergs Arch Exp Pathol Pharmacol* 1964;**248**:269-78
62. * Goldstein A, Warren R, Kaizer S. Psychotropic effects of caffeine in man. I. Individual differences in sensitivity to caffeine induced wakefulness. *J Pharmacol Exp Ther* 1965;**149**:156-9
63. Smith AP, Maben A, Brockman P. The effects of caffeine and evening meals on sleep and performance, mood and cardiovascular functioning the following day. *J Psychopharmacol* 1993;**7**(2):203-6
64. Lader M, Cardwell C, Shine P, et al. Caffeine withdrawal symptoms and rate of metabolism. *J Psychopharmacol* 1996;**10**(2):110-8

65. Edelstein BA, Keaton-Brasted C, Burg MM. Effects of caffeine withdrawal on nocturnal enuresis, insomnia, and behavior restraints. *J Consult Clin Psychol* 1984;**52**(5):857-62
66. Bonnet M, Tancer M, Uhde T, et al. Effects of caffeine on heart rate and QT variability during sleep. *Depress Anxiety* 2005;**22**(3):150-5
67. Rétey JV, Adam M, Honegger E, et al. A functional genetic variation of adenosine deaminase affects the duration and intensity of deep sleep in humans. *Proc Natl Acad Sci USA* 2005;**102**(43):15676-81
68. Yang A, Palmer AA, de Wit H. Genetics of caffeine consumption and responses to caffeine. *Psychopharmacology (Berl)* 2010;**211**(3):245-57
69. * Rétey JV, Adam M, Khatami R, et al. A genetic variation in the adenosine A2A receptor gene (ADORA2A) contributes to individual sensitivity to caffeine effects on sleep. *Clin Pharmacol Ther* 2007;**81**(5):692-8
70. Huang ZL, Qu WM, Eguchi N, et al. Adenosine A2A, but not A1, receptors mediate the arousal effect of caffeine. *Nat Neurosci* 2005;**8**(7):858-9
71. Alsene K, Deckert J, Sand P, et al. Association between A2a receptor gene polymorphisms and caffeine-induced anxiety. *Neuropsychopharmacology* 2003;**28**(9):1694-702
72. Mazzotti DR, Guindalini C, Pellegrino R, et al. Effects of the adenosine deaminase polymorphism and caffeine intake on sleep parameters in a large population sample. *Sleep* 2011;**34**(3):399-402
73. Bachmann V, Klaus F, Bodenmann S, et al. Functional ADA polymorphism increases sleep depth and reduces vigilant attention in humans. *Cereb Cortex* 2012;**22**(4):962-70

74. Mazzotti DR, Guindalini C, de Souza AA, et al. Adenosine deaminase polymorphism affects sleep EEG spectral power in a large epidemiological sample. *PLoS One* 2012;**7**(8):e44154
75. * Luciano M, Zhu G, Kirk KM, et al. "No thanks, it keeps me awake": the genetics of coffee-attributed sleep disturbance. *Sleep* 2007;**30**(10):1378-86
76. Lindskog M, Svenningsson P, Pozzi L, et al. Involvement of DARPP-32 phosphorylation in the stimulant action of caffeine. *Nature* 2002;**418**(6899):774-8
77. Byrne EM, Johnson J, McRae AF, et al. A genome-wide association study of caffeine-related sleep disturbance: confirmation of a role for a common variant in the adenosine receptor. *Sleep* 2012;**35**(7):967-75
78. Sachse C, Brockmüller J, Bauer S, et al. Functional significance of a C→A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. *Br J Clin Pharmacol* 1999;**47**(4):445-9
79. Reppert SM, Weaver DR, Rivkees SA, et al. Putative melatonin receptors in a human biological clock. *Science* 1988;**242**(4875):78-81
80. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature* 2005;**437**(7063):1257-63
81. Härtter S, Nordmark A, Rose DM, et al. Effects of caffeine intake on the pharmacokinetics of melatonin, a probe drug for CYP1A2 activity. *Br J Clin Pharmacol* 2003;**56**(6):679-82
82. Curless R, French JM, James OF, et al. Is caffeine a factor in subjective insomnia of elderly people? *Age Ageing* 1993;**22**(1):41-5
83. Soroko S, Chang J, Barrett-Connor E. Reasons for changing caffeinated coffee consumption: the Rancho Bernardo Study. *J Am Coll Nutr* 1996;**15**(1):97-101

84. Březinová V. Effect of caffeine on sleep: EEG study in late middle age people. *Br J Clin Pharmacol* 1974;**1**(3):203-8
85. Olini N, Kurth S, Huber R. The effects of caffeine on sleep and maturational markers in the rat. *PLoS One* 2013;**8**(9):e72539
86. Akerstedt T, Wright KP. Sleep Loss and Fatigue in Shift Work and Shift Work Disorder. *Sleep Med Clin* 2009;**4**(2):257-71
87. Mitler MM, Walsleben J, Sangal RB, et al. Sleep latency on the maintenance of wakefulness test (MWT) for 530 patients with narcolepsy while free of psychoactive drugs. *Electroencephalogr Clin Neurophysiol* 1998;**107**(1):33-8
88. Conlay LA, Conant JA, deBros F, et al. Caffeine alters plasma adenosine levels. *Nature* 1997;**389**(6647):136
89. Robillard R, Bouchard M, Cartier A, et al. Sleep is more sensitive to high doses of caffeine in the middle years of life. *J Psychopharmacol* 2015;**29**(6):688-97
90. Tiffin P, Ashton H, Marsh R, et al. Pharmacokinetic and pharmacodynamic responses to caffeine in poor and normal sleepers. *Psychopharmacology (Berl)* 1995;**121**(4):494-502
91. Kirsch I, Weixel LJ. Double-blind versus deceptive administration of a placebo. *Behav Neurosci* 1988;**102**(2):319-23
92. Aspen J, Quinlan P. The immediate alerting effects of hot beverage ingestion: mediated by caffeine or sensory factors? *Chemical Senses* 1998;**23**:561-62
93. Alaoui-Ismaïli O, Robin O, Rada H, et al. Basic emotions evoked by odorants: comparison between autonomic responses and self-evaluation. *Physiol Behav* 1997;**62**(4):713-20

94. Ji XD, Melman N, Jacobson KA. Interactions of flavonoids and other phytochemicals with adenosine receptors. *J Med Chem* 1996;**39**(3):781-8
95. Medina JH, Viola H, Wolfman C, et al. Overview--flavonoids: a new family of benzodiazepine receptor ligands. *Neurochem Res* 1997;**22**(4):419-25
96. Quinlan P, Lane J, Aspinall L. Effects of hot tea, coffee and water ingestion on physiological responses and mood: the role of caffeine, water and beverage type. *Psychopharmacology (Berl)* 1997;**134**(2):164-73
97. Landolt HP, Rétey JV, Adam M. Reduced neurobehavioral impairment from sleep deprivation in older adults: contribution of adenosinergic mechanisms. *Front Neurol* 2012;**3**:62
98. Research IoMCoSMA. Extent and Health Consequences of Chronic Sleep Loss and Sleep Disorders. In: HR C, BM A, eds. *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem*. Washington (DC): National Academies Press (US), 2006.
99. Philip P, Taillard J, Moore N, et al. The effects of coffee and napping on nighttime highway driving: a randomized trial. *Ann Intern Med* 2006;**144**(11):785-91
100. Freedman ND, Park Y, Abnet CC, et al. Association of coffee drinking with total and cause-specific mortality. *N Engl J Med* 2012;**366**(20):1891-904
101. Chen JF, Eltzhig HK, Fredholm BB. Adenosine receptors as drug targets--what are the challenges? *Nat Rev Drug Discov* 2013;**12**(4):265-86
102. Butt MS, Sultan MT. Coffee and its consumption: benefits and risks. *Crit Rev Food Sci Nutr* 2011;**51**(4):363-73
103. Goel N, Rao H, Durmer JS, et al. Neurocognitive consequences of sleep deprivation. *Semin Neurol* 2009;**29**(4):320-39

104. Oellerich M. Enzyme immunoassays in clinical chemistry: present status and trends. J

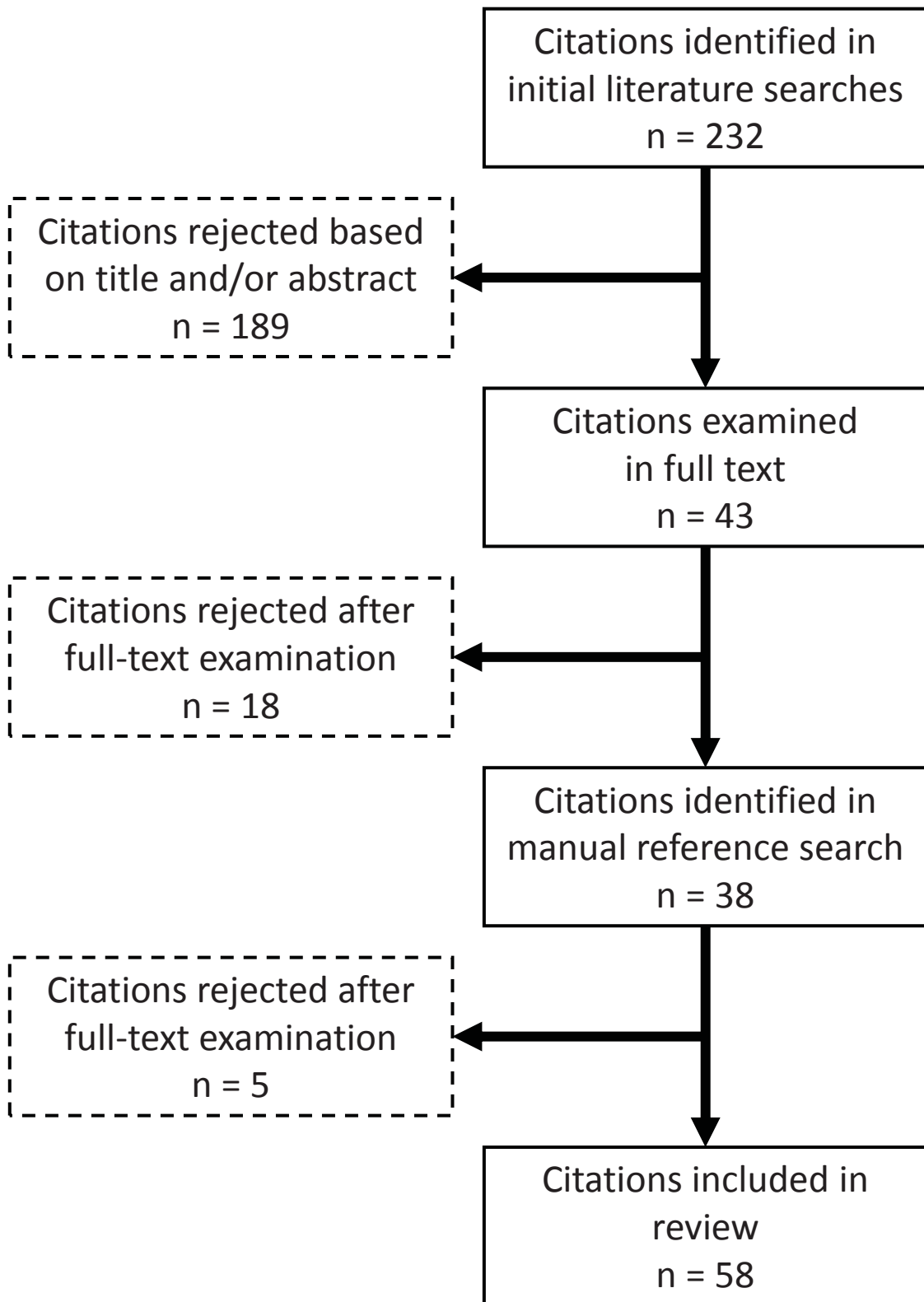
Clin Chem Clin Biochem 1980;**18**(4):197-208

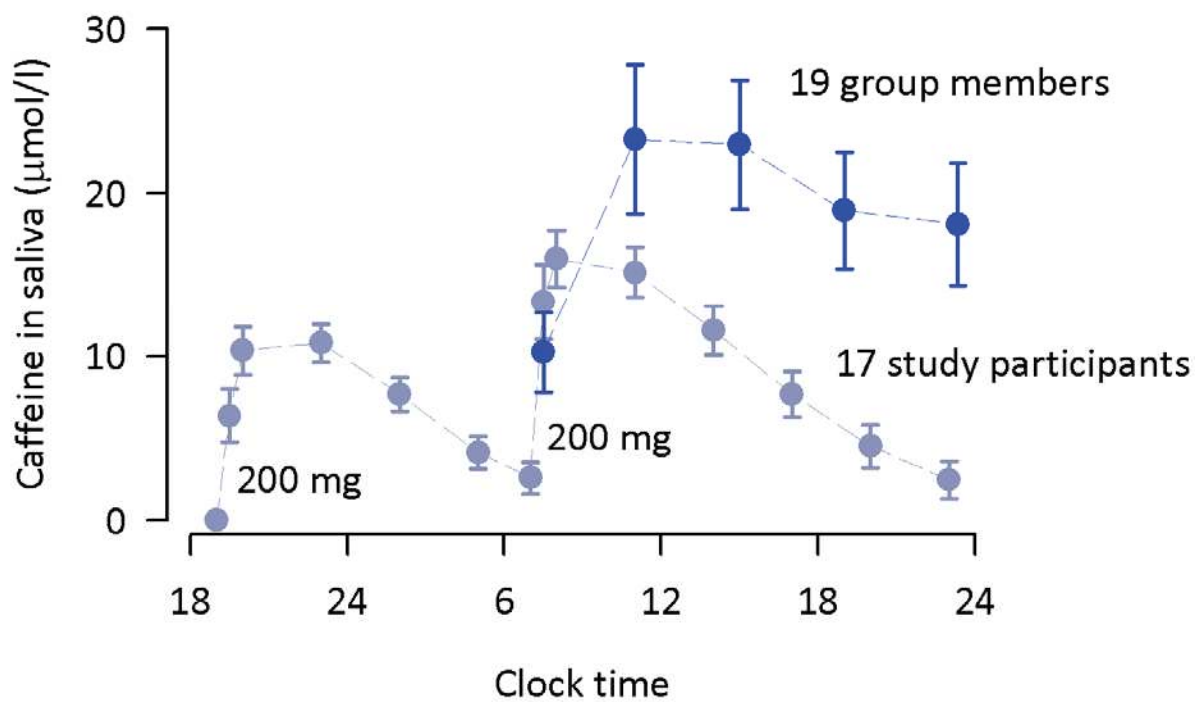
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Legends to Figures

Figure 1. Flowchart of reference selection process.

Figure 2. Time course of saliva caffeine concentration in 17 male participants of a controlled laboratory study after two weeks of caffeine abstinence (grey dots) [64] and 19 members of a sleep research group under non-controlled conditions (blue dots). In the laboratory study, 2 x 200 mg caffeine in capsules were administered at 20:00 and 08:00 during 40 hours prolonged wakefulness. All saliva samples were stored at -20 °C and later analyzed for caffeine with a homogenous enzyme immunoassay (Emit[®]-Caffeine Test, Syva Company, Palo Alto, CA)[104].





COFFEE, CAFFEINE, AND SLEEP:

A SYSTEMATIC REVIEW OF EPIDEMIOLOGICAL STUDIES AND RANDOMIZED CONTROLLED TRIALS

Ian Clark, B.Sc.¹ and Hans Peter Landolt, Ph.D.^{1,2}

¹Institute of Pharmacology & Toxicology, University of Zürich, Zürich, Switzerland

²Zürich Center for interdisciplinary Sleep Research (ZiS), University of Zürich, Switzerland

SUPPLEMENTARY INFORMATION

SLEEP MEDICINE REVIEWS

January 22, 2016

Addresses for correspondence:

Prof. Dr. Hans Peter Landolt

Institute of Pharmacology & Toxicology

University of Zürich

Winterthurerstrasse 190

8057 Zürich

Switzerland

Tel. + 41 - 44 - 635 59 53

Fax. + 41 - 44 - 635 57 07

e-mail: landolt@pharma.uzh.ch

Abbreviations

ACTH	adrenocorticotrophic hormone
d	day
f	female
m	male
mo	month
MSLT	multiple sleep latency test
n/s	not specified
PSG	polysomnography
SE	sleep efficiency (percentage of total time asleep per total time in bed)
SOL	sleep onset latency
SWA	slow-wave activity (EEG spectral power in the ~ 0.5-4.5 Hz range)
SWS	slow wave sleep
TST	total sleep time
WASO	wake time after sleep onset
wk	week
y	year

Table S1. Caffeine and sleep in infants.

Reference	Design	N	Method	Age	Caffeine source(s)	Dose/Intake	Sleep measure(s)	Sleep changes
Santos et al., 2012 ¹⁸	Longitudinal	885	Caregiver's-report	3 mo	Coffee, mate tea	≥ 300 mg/wk/trimester	Reported frequency of nocturnal awakening	↔
Ryu, 1985 ¹⁹	Double blind clinical trial	11	Heart rate measurement, breast milk and infant serum caffeine assays, parent-report	16 - 50 d	Coffee	100 mg x 5 d	Heart rate-derived sleep duration, milk and serum caffeine concentration, reported sleep duration	↔
Curzi-Dascalova et al., 2002 ²⁰	Clinical trial, use of placebo not specified	15	Polysomnography	33-34 wk postmenstrual age	Caffeine	5 mg/kg/d	Wake, active sleep, quiet sleep, intermediate sleep, TST, state transitions	↔

N = sample size. Caffeine source(s) = primary caffeine sources. ↔ = no consistent effect or association.

Table S2. Caffeine intake and sleep quality in adolescents (epidemiological studies).

Reference	Design	N	Sex	Method	Age/grade (range)	Caffeine source(s)	Intake	Sleep measure(s)	Sleep changes
Orbeta et al., 2006 ³	Cross sectional	15'686	m, f	Self-report	11 - 17 y	Soda, coffee	1-2 cups/d	Sleep latency and quality, morning tiredness	↓
Van Batenburg-Edes et al., 2014 ⁵	Cross sectional	509	m, f	Caregiver's-report	13.10 (11-16) y	Energy drinks, Coffee, cola	< 1 servings/d; ≥ 1-2 servings/d	Problems initiating and maintaining sleep	↓
Calamaro et al., 2012 ²¹	Cross sectional	625	m, f	Caregiver's-report	8.6 (6-10) y	n/s	0.4 cups/d	Sleep duration	↓
Pollack et al., 2003 ²²	Longitudinal	191	m, f	Self-report	7 th -9 th grades	Soda	≤ 0-50 mg/d; 50-100 mg/d; 100-150 mg/d; ≥ 150 mg/d	Sleep times and duration, WASO, daytime naps	↓
Drescher et al., 2011 ²³	Cross sectional	319	m, f	Caregiver's report, PSG	13.3 (19-17) y	n/s	n/s	Sleep duration	↓
Lodato et al., 2013 ²⁴	Cross sectional	1'522	m, f	Self-report	13 y	Ice tea, soda, chocolate snacks	22-27 mg/d	Sleep duration	↓
Berkey et al., 2008 ²⁵	Longitudinal	4'427	f	Self-report	14-21 y	Coffee	n/s	Sleep duration	↓
Ludden & Wolfson, 2010 ²⁷	Cross sectional	197	m, f	Self-report	9 th -12 th grades	Soda, coffee, energy drinks, tea, pills	0-4 servings/ 2 wk period	Sleep duration, daytime sleepiness	↓
Calamaro et al., 2009 ²⁹	Cross sectional	100	m, f	Self-report	15 (12-18) y	Tea, soda	144 mg	Sleep duration	↔

N = sample size. Caffeine source(s) = primary caffeine sources. ↓ = deterioration. ↔ = no consistent effect or association.

Table S3. Caffeine intake and sleep quality in adults (epidemiological studies).

Reference	Design	N	Sex	Method	Age/grade (range)	Caffeine source(s)	Intake	Sleep measure(s)	Sleep changes
Hughes & Boland, 1992 ³⁰	Cross sectional	144	m	Self-report	34 y	Coffee	Vendor record: 553 mg/d; consumer record: 805 mg/d	Reported sleep quality	↓
Goldstein & Kaizer, 1969 ³¹	Cross sectional	183	f	Self-report	20-29 y [74%]; 30-39 y [19%]	Coffee	Cups/d: 0; 1-2, 3-4, > 5	Reported interference with ability to fall asleep	↓
Mniszek, 1988 ³²	Cross sectional	2'696	m, f	Self-report	20-45 y	Coffee, tea	Cups/d: 1-4, > 4	Reported SOL, frequency of awakening, early awakening, satisfaction with perceived sleep duration	↔
Hicks et al., 1983 ³³	Cross sectional	170	m, f	Self-report	"University undergraduate students"	Not specified	≥ 8 cups/d	Reported sleep duration, satisfaction with sleep	↓
Sanchez-Ortuno et al., 2005 ³⁴	Cross sectional	1'498	m, f	Self-report	51 (44-58) y	Coffee	225 mg/d	Reported sleep quality and time in bed	↓

N = sample size. Caffeine source(s) = primary caffeine sources. ↓ = deterioration. ↔ = no consistent effect or association.

Table S4. Studies investigating objective measures of sleep latency, wake time after sleep onset (WASO), and sleep duration in adults.

Reference	N	Sex	Method	Blinding	Age (range)	Caffeine source	Dose	Sleep measure(s)	Sleep changes
Landolt et al., 1995 ³⁵	9	m	PSG, salivary caffeine assay, self-report	Double	22.4 (21-25) y	Capsule	200 mg	EEG spectral power, SOL, SE, TST, sleep stages, salivary caffeine concentration, reported sleep quality	↓
Landolt et al., 1995 ³⁶	8	m	PSG, salivary caffeine assay, self-report	Single	23.3 (20-25) y	Capsule	100 mg	EEG spectral power, SWA, sleep stages, SOL, reported sleep quality	↓
Landolt et al., 2004 ³⁷	12	m	PSG, salivary caffeine assay	Double	25.3 (20-30) y	Capsule	2 x 200 mg	EEG spectral power, sleep stages	↓
Drapeau et al., 2006 ³⁸	24	m, f	PSG, salivary caffeine assay	Double	23.8 y; 50.3 y	Capsule	200 mg	TST, SOL, SE, EEG spectral power, sleep stages	↓
Hirshkowitz et al., 1982 ³⁹	8	n/s	PSG	Double	n/s	Coffee*	1.1, 2.2, 4.4 mg/kg	Spindle length and density in stage 2 or in total NREM sleep	↔
Drake et al., 2006 ⁴⁰	21	m, f	PSG	Single	32.64 y (low anxiety); 34.20 y (high anxiety)	n/s	3 mg/kg	SOL, SE, SWS	↓
Lin et al., 1997 ⁴¹	15	m	PSG, self-report, cortisol and ACTH assay	Single	30 (25-43) y	Intravenous	5 mg/kg	TST, SE, SOL, REM sleep latency, cortisol and ACTH concentrations, reported frequency of awakenings	

Nicholson & Stone, 1980 ⁴²	6	m	PSG, self-report	Double	26 (20-30) y	Tablet	100, 200, 300 mg	TST, SOL, sleep stages latency to stage 3 and REM sleep, REM/NREM sleep ratio, self-reported sleep quality	↓
Bonnet & Webb, 1979 ⁴³	6	m	PSG	Single	21-23 y	Pill	400 mg	SOL, sleep stages	↓
Karacan et al., 1976 ⁴⁴	18	m	PSG, self-report	Double	20-30 y	Coffee, water*	1.1, 2.3, 4.6 mg/kg x d	SOL, TST, SE, sleep stages, reported sleep quality, duration, frequency of awakenings	↓
Gresham et al., 1963 ⁴⁵	7	n/s	PSG	n/s	23-28 y	Orange juice*	0.005 mg/kg	REM sleep	↔
Bonnet & Arand, 1992 ⁴⁶	12	m	PSG, self-report	n/s	18-30 y	Pill	3 x 400 mg /d	SOL, TST, sleep stages, self-reported sleep quality	↓
Carrier et al., 2007 ⁴⁷	24	m, f	PSG, salivary caffeine assay	Double	37.2 y (night sleep); 39.9 y (day sleep)	Capsule	200 mg	TST, SOL, SE, sleep stages	↓
Carrier et al., 2009 ⁴⁸	24	m, f	PSG, salivary caffeine assay	Double	20-30 y; 45-60 y	Capsule	200 mg	TST, SE, SOL, EEG spectral power, sleep stages, salivary caffeine concentration	↓
Van Dongen et al., 2001 ⁴⁹	28	m	PSG, plasma caffeine assay	Double	29 (21-47) y	Pill	66 x 0.3 mg/ kg	SOL, TST, sleep inertia, REM and NREM sleep, slow wave energy, plasma caffeine concentration	↓

Kelly et al., 1997 ⁵⁰	25	m	PSG	n/s	21 y (placebo); 19.5 y (caffeine)	Capsule	7 x 300 mg	MSLT	↓
Shilo et al., 2002 ⁵¹	6	m, f	Urinary melatonin assay	Double	32 y	Coffee	5 x 130 mg/d	Urinary melatonin concentration	↓
Hindmarch et al., 2000 ⁵²	30	m, f	Actigraphy, self-report	No placebo	27.3 (19-36) y	Coffee, tea	4 x 37.5, 75, 150 mg/d	Combined subjective and actigraphically-derived SOL, sleep quality and duration	↓
Drake et al., 2013 ⁵³	12	m, f	PSG, self-report	Double	29.3 y	Pill	400 mg	TST, SOL, sleep stages, reported sleep quality	↓
Ho et al., 2013 ⁵⁴	10	m, f	Actigraphy, self-report	Double	21.4 y	Coffee	60 mg	SOL, SE, reported sleep quality	↔
Muehlbach & Walsh, 1995 ⁵⁵	30	m, f	PSG, MSLT, self-report	Double	23.9 y (placebo); 24.7 y (caffeine)	Coffee*	4 x 300 mg/d	TST, SOL, TST, sleep stages, MSLT, reported sleep quality	↔
Lajambe et al., 2005 ⁵⁶	16	m, f	PSG	Single	18-35 y	Gum	100-400 mg	TST, SE, SOL, sleep stages	↓
Rosenthal et al., 1991 ⁵⁷	36	m	Actigraphy	n/s	19-35 y	Coffee*	2 x 75, 150 mg/ d	SOL	↓
Levy & Zylber-Katz, 1983 ⁵⁸	12	m, f	Self-report, salivary caffeine assay	n/s	36.2 y (caffeine sensitive); 30.3 y (caffeine insensitive)	Coffee	300 mg	Reported sleep quality, salivary caffeine concentration	↓

N = sample size. Caffeine source(s) = primary caffeine sources. ↓ = deterioration. ↔ = no consistent effect or association. * Caffeine added to decaffeinated or otherwise caffeine-free beverage.

Table S5. Caffeine intake and reported measures of sleep latency, wake time after sleep onset (WASO), and sleep duration in adults (laboratory studies).

Reference	N	Sex	Method	Blinding	Age (range)	Caffeine source	Dose	Sleep measure(s)	Sleep changes
James, 1998 ⁵⁹	36	m, f	Self-report, salivary caffeine	Double	23 (18-52) y	n/sd	1.75 mg/ kg	Sleep duration and quality, salivary caffeine concentration	↔
Höfer & Bättig, 1994 ⁶⁰	120	m, f	Self-report, salivary caffeine	n/s	31.0 [m], 32.4 [f] (20-45) y	Coffee	56 mg	Sleep duration, SOL, sleep quality, awakenings, salivary caffeine concentration	↔
Goldstein et al., 1964 ⁶¹	230	m, f	Self-report	Double	20-26 y	Capsule, coffee*	200, 150 mg	SOL and "soundness" of sleep	↓
Goldstein et al., 1965 ⁶²	20	m	Self-report, plasma caffeine	Double	n/s	Coffee*	300 mg	SOL and "soundness" of sleep, plasma caffeine concentration	↓
Smith et al., 1993 ⁶³	48	m, f	Self-report	Double	20.3 y	Coffee	2 x 3 mg/kg	SOL, frequency and duration of awakenings, sleep quality	↓
Lader et al., 1996 ⁶⁴	40	m, f	Self-report, salivary caffeine	Double	36 y	Capsule	500 mg	SOL, TST, feeling on awakening	↓
Edelstein et al., 1984 ⁶⁵	25	m, f	Clinician report	No placebo	n/s	n/s	750 mg	Insomnia, enuresis	↓

N = sample size. Caffeine source(s) = primary caffeine sources. ↓ = deterioration. ↔ = no consistent effect or association.

Table S6. Caffeine intake and subjective and objective measures of sleep quality in older adults.

Reference	Design	N	Sex	Methods	Age (range)	Caffeine source	Dose	Sleep measure(s)	Sleep changes
Curless et al., 1993 ⁸²	Cross sectional	234	m, f	Self-report, plasma caffeine	68 (44 - 98) y	Coffee, tea	90 - 240 mg/d	Reported sleep quality	↓
Soroko et al., 1996 ⁸³	Cross sectional	2'955	m, f	Self-report	64 (30 - 105) y	Coffee	3 - 3.5 cups/d	Reported "Sleep problems"	↓
Březinová, 1974 ⁸⁴	Clinical trial, blinding not specified	6	m, f	PSG, self-report	56 (50 - 63) y	Coffee*	291.3 mg/d	TST, SE, sleep stages, reported sleep quality	↓

N = sample size. Caffeine source(s) = primary caffeine sources. ↓ = deterioration. ↔ = no consistent effect or association.