Sleep changes following statin therapy: a systematic review and meta-analysis of randomized placebo-controlled polysomnographic trials

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Abstract

Introduction: Statin use might be associated with an increased risk of sleep disturbances including insomnia, but the evidence regarding sleep changes following statin therapy has not been conclusive. Therefore we assessed the impact of statin therapy on sleep changes through a systematic review and meta-analysis of available randomized controlled trials (RCTs).

Material and methods: We searched MEDLINE and SCOPUS up to October 1, 2014 to identify placebo-controlled RCTs investigating the effect of statin therapy on sleep changes. A meta-analysis was performed using either a fixed-effects or a random-effect model according to the I² statistic. Effect size was expressed as weighted mean difference (WMD) and 95% confidence interval (CI).

Results: Overall, the impact of statin therapy on polysomnography (PSG) indices of sleep was reported in 5 trials comprising 9 treatment arms. Overall, statin therapy had no significant effect on total sleep duration (WMD: –7.75 min, 95% CI: –18.98, 3.48, p = 0.176), sleep efficiency (WMD: 0.09%, 95% CI: –2.27, 2.46, p = 0.940), entries to stage I (WMD: 0.36, 95% CI: –0.91, 1.63, p = 0.580), or latency to stage I (WMD: –1.92 min, 95% CI: –4.74, 0.89, p = 0.181). In contrast, statin therapy significantly reduced wake time (WMD: –4.43 min, 95% CI: –7.77, –0.88, p = 0.014) and number of awakenings (WMD: –0.40, 95% CI: –0.46, –0.33, p < 0.001). Meta-regression did not suggest any correlation between changes in wake time and awakening episodes with duration of treatment and LDL-lowering effect of statins.

Conclusions: The results indicated that statins have no significant adverse effect on sleep duration and efficiency, entry to stage I, or latency to stage I sleep, but significantly reduce wake time and number of awakenings.

Key words: statins, stain therapy, sleep, polysomnography, meta-analysis.
**Introduction**

Statin therapy is the cornerstone for primary and secondary prevention of cardiovascular diseases (CVD) and is generally safe and well tolerated [1]. Most adverse effects associated with these drugs are muscle symptoms (weakness, myalgia, myopathies and rhabdomyolysis), gastrointestinal discomfort and liver enzyme elevations [2, 3]. Diabetes mellitus, alopecia, hemorrhagic stroke, and cataract are rarely observed, and the causality has not always been confirmed [4]. Some reports have noted other side effects, which might reduce patients’ quality of life and might result in statin discontinuation [5–7]. Accumulating databases from the US Food and Drug Administration Adverse Event Reporting System (FAERS) suggest that statin use is associated with an increased risk of sleep disturbances including insomnia [8].

In other studies hallucinations and nightmares during statin therapy were also observed [6, 7]. There are fewer clinical trials evaluating the effect of statins on sleep as a primary outcome. Three of them suggested an essential effect of statins on sleep quality [9–11], while two others presented no impact of statin treatment on sleep [12, 13].

It has been suggested that statins with a high degree of lipophilicity (lovastatin, simvastatin) might be associated with a higher rate of central nervous system disturbances in comparison with hydrophilic statins (pravastatin) [9, 10, 14, 15]. Tobert et al. reported that 17% of subjects taking lovastatin complained of shortening sleep duration (by 1 to 3 h) compared to no reports from patients treated with pravastatin [15]. Vgontzas et al. [9] noted that lovastatin therapy in comparison to pravastatin was associated with increased time in stage 1, wake time during steep, total wakeings, latency to stage I sleep, sleep efficiency, and REM sleep [20]. Using PSG, the following sleep parameters can be evaluated: number of awakenings, latency to stage I sleep, sleep efficiency, entries to stage I, wake time during steep, total wake and total sleep time [20].

The data on the risk of sleep disturbances associated with statin use might be very important in clinical practice, especially with regard to the elderly population, in which sleep disorders are a common problem. Taking into account the divergent data, we performed a meta-analysis to investigate the effect of statin therapy on sleep parameters using the polysomnography method.

**Material and methods**

**Search strategy**

This study was designed according to the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [21]. SCOPUS (http://www.scopus.com) and MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed) databases were searched using the following search terms in titles and abstracts (also in combination with MESH terms): (atorvastatin OR simvastatin OR rosuvastatin OR fluvastatin OR pravastatin OR pitavastatin OR lovastatin OR cerivastatin OR “statin therapy” OR statins OR statin) AND (polysomnography OR sleep OR “statin disturbances” OR “sleep changes” OR insomnia OR parasomnia). The wild-card term “*” was used to increase the sensitivity of the search strategy. No language restriction was used in the literature search. The search was limited to studies in human. The literature was searched from inception to October 1, 2014.

**Study selection**

Original studies were included if they met the following inclusion criteria: (1) being a randomized controlled trial (RCT) with either parallel or crossover design, (2) using polysomnographic recording to assess at least one of the following measures:
total sleep time, sleep efficiency, latency to stage I, entries to stage I, number of awakenings and total wake time, (3) statin therapy duration of at least 2 weeks, (4) presentation of sufficient information on PSG indices at baseline and at the end of follow-up in each group or providing the net change values.

Exclusion criteria were (1) non-randomized trials, (2) lack of a control group in the study design, (3) case reports or observational studies with case-control, cross-sectional or cohort design, (4) employing subjective measures of sleep instead of PSG findings, and (5) lack of sufficient information on baseline or follow-up PSG indices.

Data extraction

Eligible studies were reviewed and the following data were abstracted: 1) first author’s name; 2) year of publication; 3) study location; 4) study design; 5) number of participants in the statin and control (in the case of randomized design) groups; 6) age of study participants; 7) type and duration of statin therapy; and 8) baseline and follow-up values of PSG indices.

Quality assessment

A systematic assessment of bias in the included studies was performed using the Cochrane criteria [22]. The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding, reporting of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of “yes” indicated low risk of bias, while “no” indicated high risk of bias. Labeling an item as “unclear” indicated an unclear or unknown risk of bias.

Quantitative data synthesis

The meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [23]. Net changes in measurements (change scores) were calculated as follows: measure at end of follow-up – measure at baseline. For single-arm cross-over trials, the net change in PSG parameters was calculated by subtracting the value after control intervention from that report- ed after treatment. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root [(SDpre-treatment)² + (SDpost-treatment)² – (2 × SDpre-treatment × SDpost-treatment)], assuming a correlation coefficient of R = 0.5. If the outcome measures were reported as the median and inter-quartile range, mean and standard SD values were estimated using the method described by Hozo et al. [24]. Where only the standard error of the mean (SEM) was reported, the SD was estimated using the following formula: SD = SEM × sqrt (n), where n is the number of subjects.

A fixed-effects or random-effects model (using the DerSimonian-Laird method) was applied when the heterogeneity (I²) value was < 50% and ≥ 50%, respectively. Heterogeneity was quantitatively assessed using the I² index. Effect sizes were expressed as the weighted mean difference (WMD) and 95% confidence interval (CI). In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the leave-one-out method, i.e. removing one study each time and repeating the analysis.

Meta-regression

Random-effects meta-regression was performed to evaluate the association between calculated WMD and potential confounders including duration of treatment with statins and changes in plasma LDL-C concentrations following treatment.

Publication bias

Potential publication bias was explored using visual inspection of Begg’s funnel plot asymmetry, Begg’s rank correlation, and Egger’s weighted regression. Duval and Tweedie “trim and fill” was used to adjust the analysis for the effects of publication bias [25].

Results

Flow and characteristics of included studies

Initial screening for potential relevance excluded articles whose titles or abstracts were clearly irrelevant. After assessment, 5 eligible studies equivalent to 9 treatment arms were selected for the final meta-analysis [12, 18–21]. Among 231 participants in the selected studies, 152 were allocated to statin intervention groups, and 79 to the control group. All participants were male. Three studies are focused on patients with primary hypercholesterolemia [12, 19, 20], 2 included healthy young people [18, 21], and 4 compare two different statins [12, 18–20]. Included studies were published between 1992 and 1994, and were conducted in the USA (2 studies), Sweden, Finland and Japan. The following statin doses were administered in the included trials: 20 mg to 40 mg/day pravastatin, 40 mg/day lovastatin and 20 mg/day simvastatin. Duration of statin intervention ranged between 16 days and 6 weeks. One study had a parallel group design, 2 studies had a two-period crossover trial design (i.e. each...
patient received two of the three possible treatments) and 2 studies were crossover studies.

A summary of the study selection process is shown in Figure 1 and the characteristics of studies in Table I.

Risk of bias assessment

A systematic assessment of bias in the included studies was carried out using the Cochrane criteria [22]. The items used for the assessment of each study were as follows: adequacy of sequence generation, allocation concealment, blinding, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. According to the recommendations of the Cochrane Handbook, a judgment of “yes” indicated low risk of bias, while “no” indicated high risk of bias. Labeling an item as “unclear” indicated an unclear or unknown risk of bias (Table II).

Effect of statin therapy on polysomnography findings

The impact of statin therapy on PSG indices of sleep was reported in 9 treatment arms. Overall, statin therapy had no significant effect on total sleep duration (WMD: –7.75 min, 95% CI: –18.98, 3.48, \( p = 0.176 \)) (Figure 2), sleep efficiency (WMD: 0.09%, 95% CI: –2.27, 2.46, \( p = 0.940 \)) (Figure 3), entries to stage I (WMD: 0.36, 95% CI: –0.91, 1.63, \( p = 0.580 \)) (Figure 4) or latency to stage I (WMD: –1.92 min, 95% CI: –4.74, 0.89, \( p = 0.181 \)) (Figure 5). These effect sizes were robust and iteratively removing each study from the meta-analysis did not change the significance of the results (Figures 2–5). In contrast, statin therapy significantly reduced wake time (WMD: –4.43 min, 95% CI: –7.77, –0.88, \( p = 0.014 \)) (Figure 6) and number of awakenings (WMD: –0.40, 95% CI: –0.46, –0.33, \( p < 0.001 \)) (Figure 7). These effect sizes were not sensitive to any single trial, apart from the sensitivity of pooled effect size for the wake time to the study by Kamei et al. (WMD: –1.77, 95% CI: –9.81, 6.28, \( p = 0.667 \)) (Figures 6 and 7).

Meta-regression

Meta-regression did not suggest any association between changes in wake time and awakening episodes following statin therapy with duration of treatment (slope: 1.99; 95% CI: –3.94, 7.93; \( p = 0.510 \) (wake time); slope: –0.16; 95% CI: –0.78, 0.47; \( p = 0.628 \) (awakening episodes)). Likewise, there was no association of either of the parameters with LDL-lowering effect of statins (slope: 0.08; 95% CI: –1.41, 1.57; \( p = 0.914 \) (wake time); slope: –0.00004; 95% CI: –0.02, 0.02; \( p = 0.996 \) (awakening episodes)) (Figure 8).

Publication bias

The funnel plots of the study standard error by effect size (mean difference) were slightly asymmetrical for the meta-analyses of statins’ effects on wake time and awakening episodes (Figure 9). Using Duval and Tweedie’s “trim and fill” method, these asymmetries were addressed by imputing 1 (for the meta-analysis of awakening episodes) and 2 (for the meta-analysis of wake time) potentially missing studies. Corrected effect sizes were –0.40 min (95% CI: –0.46, –0.34) (for the meta-analysis of awakening episodes) and –4.65 (95% CI: –8.03, –1.27) (for the meta-analysis of wake time). There was no evidence of publication bias according to the results of Begg’s rank correlation (Kendall’s Tau with continuity correction = 0, \( z = 0 \), two-tailed \( p-value = 1.000 \) (for the meta-analysis of awakening episodes); Kendall’s Tau with continuity correction = 0.24, \( z = 0.75 \), two-tailed \( p-value = 0.453 \) (for the meta-analysis of wake time)) and Egger’s linear regression (intercept = 0.39, standard error = 0.028; 95% CI = –0.34, 1.12, \( t = 1.37 \), \( df = 5 \), two-tailed \( p = 0.229 \) (for the meta-analysis of awakening episodes); intercept = 0.31, standard error = 0.36; 95% CI = –0.61, 1.23, \( t = 0.86 \), \( df = 5 \), two-tailed \( p = 0.431 \) (for the meta-analysis of wake time)) tests for either awakening episodes or wake time.

Discussion

The first reports about the effect of statins on sleep quality come from the 1990s [9–11, 15, 16]. Mainly they were case reports or small, retrospective, uncontrolled studies. The design, statistical methods and interpretation of results have been questioned [26]. Previous studies were performed on young normal volunteers rather than on hy-
| Parameter                          | Study                                      |
|-----------------------------------|--------------------------------------------|
| Year                              | Kostis et al. 1994, Eckernas et al. 1993, Roth et al. 1992, Partinen et al. 1994, Kamei et al. 1993 |
| Location                          | USA, Sweden, USA, Finland, Japan           |
| Design                            | Randomized double-blind placebo-controlled crossover trial, Randomized double-blind placebo-controlled two-period crossover trial (i.e. each patient received two of the three possible treatments), Randomized double-blind placebo-controlled parallel trial, Randomized double-blind placebo-controlled two-period crossover trial (i.e. each patient received two of the three possible treatments), Double-blind placebo-controlled crossover trial |
| Duration of therapy               | 6 weeks, 4 weeks, 3 weeks, 4 weeks, 16 days |
| Inclusion criteria                | Male patients aged 36 to 65 years with a diagnosis of hypercholesterolemia, Male patients with primary, moderate hypercholesterolemia as characterized by an LDL cholesterol level of 4–7 mmol/l and triglycerides ~3.9 mmol/l, Healthy men within 20% of ideal body weight, Male patients with primary hypercholesterolemia (low-density lipoprotein 4 to 7 mmol/l, and triglycerides ~3.8 mmol/l), Healthy male adults |
| Statin form                        | Lovastatin, Simvastatin, Lovastatin, Lovastatin, Pravastatin |
| Statin intervention               | 40 mg/day, 20 mg/day, 40 mg/day, 40 mg/day, 20 mg/day |
| Participants                      | Case 22, 16, 20, 16, 16, 20, 16, 5 |
|                                   | Control 22, 16, 20, 16, 5 |
| Age (years)                       | Case 36–65*, 52.9, 25.8 ±0.6**, 55 (34–70)*, 36.4 (29–49)** |
|                                   | Control NS, 84 ±8, 87 ±8 |
| Total sleep duration [min]        | Case 366.4*, 404.5 ±30.6, 436 ±6**, 402 ±26, 392.6 ±9.6** |
|                                   | Control 361.9*, 389.5 ±30.6, 429 ±5**, 400 ±26, 406.3 ±19.3** |
| Sleep efficiency (%)              | Case NS, 88.2 ±5.9, 90 ±8, NS |
|                                   | Control NS, 90.1 ±5.9, 84 ±8, 87 ±8, NS |
percholesterolemic [10, 11] or high cardiovascular (CV) risk patients with indications for statin therapy. Harrison and Ashton [10] using the Leeds Sleep Questionnaire claimed that simvastatin in healthy young people \((n = 25)\) may cause different difficulties in getting to sleep versus pravastatin, but not in comparison to the placebo group. Barth et al. [11] noted that 4 of 15 males with CAD complained of shorter sleep duration (approximately by 1 h) during a one-year period of simvastatin treatment (20 mg daily), and such effects were not observed in patients taking colestipol or a bile acid sequestrant [11]. In contrast to the above studies, Carlsson et al. found no impact of 6-month pravastatin treatment on sleep [13]. Black et al. used a questionnaire in 409 hyperlipidemic patients receiving a diet intervention, lovastatin, simvastatin, pravastatin, or other lipid-lowering drugs in a cross-sectional approach [27]. They found no significant differences in the prevalence of sleep disturbances between the groups [27].

It is, however, worth underlining that the above observations were based only on the patients’ subjective evaluation. The results are mixed, and no conclusive evidence exists that statin therapy is associated with sleep disturbances, and there is not enough data to confirm the causality of statin therapy on sleep disturbances [2, 3]. Insomnia might be due to the underlying diseases, rather than the drug alone; however, the effect of hypercholesterolemia on sleep quality remains unclear [21].

There are only a few studies which have objectively evaluated the effect of statin therapy on sleep parameters using PSG [12, 18–21]. Due to the time-consuming nature and high costs of PSG, the cohorts of patients involved in the study were usually small \((n = 5–59)\), with the duration of observation from 2 weeks to 6 months. Our meta-analysis represents the first attempt to systematically evaluate the effects of statin therapy versus placebo on sleep parameters estimated by PSG. Surprisingly, taking into account previous reports, our results indicate that statins have no significant adverse effect on sleep duration and efficiency, entry to stage I sleep, or latency to stage I. What is more, they might even have some beneficial effects, significantly reducing wake time and number of awakenings. Meta-regression did not suggest any correlation between changes in wake time and awakening episodes with duration of treatment and LDL-lowering effect of statins.

Kamei et al. [21] aimed to evaluate the effect of pravastatin on sleep in 5 healthy adults treated for 16 days. In comparison to placebo they found no significant differences in total sleep, arousal after sleep and sleep latency between the baseline night values and the acute or chronic phase values. The authors supposed that the cause of these results depended on the

| Parameter                | Study                  | Parameter Study | Parameter Study | Parameter Study | Parameter Study |
|--------------------------|------------------------|-----------------|-----------------|-----------------|-----------------|
| Entries to stage I      | Kostis et al.          | NS              | NS              | NS              | NS              |
| Latency to stage I [min]| Ecker et al.           | 4.5 ± 1.8       | 2.7 ± 1.8       | 2.7 ± 1.9       | 3.9 ± 1.4       |
| Sleep [min]             | Parrin et al.          | 26 ± 1.6        | 24 ± 1.5        | 23 ± 1.5        | 18 ± 1.4        |
| Number of awakenings    | Roth et al.            | 32 ± 1.4        | 24 ± 1.1        | 22 ± 1.4        | 16 ± 1.4        |
| Wake time during sleep [min] | Kamei et al. | 26 ± 1.6        | 22 ± 1.4        | 22 ± 1.4        | 16 ± 1.4        |
| Sleep latency [min]     | Control                | 26 ± 1.6        | 22 ± 1.4        | 22 ± 1.4        | 16 ± 1.4        |
| Wake time during sleep [min] | Control            | 26 ± 1.6        | 22 ± 1.4        | 22 ± 1.4        | 16 ± 1.4        |
| Number of awakenings    | Control                | 32 ± 1.4        | 24 ± 1.1        | 22 ± 1.4        | 16 ± 1.4        |
| Wake time during sleep [min] | Control            | 26 ± 1.6        | 22 ± 1.4        | 22 ± 1.4        | 16 ± 1.4        |
| Number of awakenings    | Control                | 32 ± 1.4        | 24 ± 1.1        | 22 ± 1.4        | 16 ± 1.4        |
| Wake time during sleep [min] | Control            | 26 ± 1.6        | 22 ± 1.4        | 22 ± 1.4        | 16 ± 1.4        |
| Number of awakenings    | Control                | 32 ± 1.4        | 24 ± 1.1        | 22 ± 1.4        | 16 ± 1.4        |

Values are expressed as mean ± SD; *only range; #only mean; **values are expressed as mean ± SEM; ***mean (range). SD – standard deviation, SEM – standard error of the mean, NS – not stated.
hydrophilic properties of pravastatin [21]. Due to not crossing the blood-brain barrier, pravastatin probably does not inhibit prostaglandin D \(_2\) (PGD\(_2\)) synthase, a sleep-inducing substance. An animal study reported that the intraventricular infusion of PGD\(_2\) increases the total sleep time [28]. There is also a hypothesis that sleep disorders during statin treatment may depend on their degree of lipophilicity [21, 28]. It is known that lipophilic drugs, such as \(\beta\)-blockers, penetrate the blood-brain barrier and may affect central nervous system function [29]. Thus, it is hypothesized that statins with a high degree of lipophilicity might be associated with a higher rate of central nervous system disturbances in comparison with hydrophilic statins [30]. In fact, the majority of available reports have referred to lipophilic statins, namely simvastatin and lovastatin [18, 31, 32]. However, no conclusive evidence exists that a particular statin is more likely to be associated with sleep disturbances over others [26, 33–35]. Roth et al. in a randomized, double-blind, placebo-controlled study showed that neither pravastatin nor lovastatin significantly affected nocturnal sleep or daytime sleepiness in healthy young men (n = 59), but lovastatin significantly affected daytime performance \(p < 0.001\). Two measures of performance – divided attention \((p < 0.05)\) and vigilance \((p < 0.001)\) – worsened significantly from baseline, as did global performance \((p < 0.001)\). The mechanism of these lovastatin effects is not

Table II. Assessment of risk of bias in the included studies using Cochrane criteria

| Study | Sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective outcome reporting | Other potential threats to validity |
|-------|---------------------|------------------------|----------------------------------------|-------------------------------|-------------------------|-----------------------------|----------------------------------|
| Kostis et al. 1994 | U | U | L | L | L | L |
| Eckernäs et al. 1993 | L | L | L | L | L | L |
| Roth et al. 1992 | U | U | L | L | L | L |
| Partinen et al. 1994 | L | L | L | L | L | L |
| Kamei et al. 1993 | U | U | L | L | L | L |

L – Low risk of bias, H – high risk of bias, U – unclear risk of bias.

Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of statin therapy on total sleep duration. Lower plot shows leave-one-out sensitivity analysis.
The authors eliminated the possibility that the performance effects resulted from changes in lipids since both lovastatin and pravastatin decreased LDL-C equivalently [18]. Partinen et al. reported significant differences between lovastatin and pravastatin treatment in sleep efficiency, total wake time, wake time during sleep, entries to wake and percentage of REM stage sleep in men with primary hypercholesterolemia [20]. All changes in PSG parameters indicated improved sleep with lovastatin compared with pravastatin. But neither lovastatin nor pravastatin had any effect on subjective, qualitative sleep ratings. Thus, the differences between these statins, reported based on PSG, were probably not clinically relevant [20]. Kostis et al. reported that lovastatin and pravastatin did not have significant effects on sleep or daytime performance measures in patients (n = 22, all men) with hypercholesterolemia [19]. They supposed that the patients with unstable sleep architecture may have been predisposed to disruptive effects on sleep, but such patients were not included in this study. Similar conclusions were observed in another study comparing simvastatin, pravastatin and placebo in patients with hypercholesterolemia [12].
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The number of entries to stage I sleep was significantly prolonged by pravastatin [12]. Eckernäs et al. [12], like Partinen et al. [20], found that subjective ratings of sleep

greater after simvastatin treatment than after either pravastatin or placebo (p < 0.05). The latency to stage I sleep was significantly prolonged by pravastatin [12], Eckernäs et al. [12], like Partinen et al. [20], found that subjective ratings of sleep
initiation and maintenance during and after therapy were not significantly different between the groups. In summary, the studies have shown that both simvastatin and lovastatin, despite the lipophilic properties, do not cause clinically significant sleep disorders. However, in 2014 Takada et al. [8] suggested that statin use is associated with an increased risk for sleep disturbances including insomnia. They examined the correlation between various statins and sleep disturbances using the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and database vendor from Japan (Japan Medical Information Research Institute, Inc. Japan [JMIRI]) [8].

### Table: Difference in means and 95% CI

| Study name | Difference in means | Standard error | Variance | Lower limit | Upper limit | Z-value | Value of p |
|------------|---------------------|----------------|----------|-------------|-------------|---------|-----------|
| Eckernäs et al., 1993a | –0.100 | 1.039 | 1.080 | –2.137 | 1.937 | –0.096 | 0.923 |
| Eckernäs et al., 1993b | 0.300 | 0.981 | 0.962 | –1.623 | 2.223 | 0.306 | 0.760 |
| Roth et al., 1992a | –0.100 | 0.509 | 0.259 | –1.097 | 0.897 | –0.197 | 0.844 |
| Roth et al., 1992b | 0.200 | 0.601 | 0.361 | –0.978 | 2.223 | 0.333 | 0.739 |
| Partinen et al., 1994a | –0.400 | 0.045 | 0.002 | –0.489 | –0.311 | –8.827 | < 0.001 |
| Partinen et al., 1994b | –0.400 | 0.045 | 0.002 | –0.489 | –0.311 | –8.827 | < 0.001 |
| Kamei et al., 1993 | –1.200 | 1.118 | 1.251 | –3.392 | 0.992 | –1.073 | 0.283 |

### Table: Difference in means with study removed

| Study name | Point | Standard error | Variance | Lower limit | Upper limit | Z-value | Value of p |
|------------|-------|----------------|----------|-------------|-------------|---------|-----------|
| Eckernäs et al., 1993a | –0.397 | 0.032 | 0.001 | –0.460 | –0.335 | –12.444 | < 0.001 |
| Eckernäs et al., 1993b | –0.397 | 0.032 | 0.001 | –0.460 | –0.335 | –12.458 | < 0.001 |
| Roth et al., 1992a | –0.398 | 0.032 | 0.001 | –0.461 | –0.335 | –12.454 | < 0.001 |
| Roth et al., 1992b | –0.398 | 0.032 | 0.001 | –0.461 | –0.336 | –12.477 | < 0.001 |
| Partinen et al., 1994a | –0.394 | 0.045 | 0.002 | –0.482 | –0.306 | –8.769 | < 0.001 |
| Partinen et al., 1994b | –0.394 | 0.045 | 0.002 | –0.482 | –0.334 | –8.769 | < 0.001 |
| Kamei et al., 1993 | –0.396 | 0.032 | 0.001 | –0.459 | –0.334 | –12.442 | < 0.001 |

### Figure 8. Meta-regression plots of the association between mean changes in the number of awakenings (A, B) and wake time (C, D) with duration of statin therapy and magnitude of LDL-C reduction
In this observational cohort study, significant evidence for disturbances in initiating and maintaining sleep was found for the whole class of statins in the analysis of the FAERS database, and a significant association was found between statin use and hypnotic drug use in the analysis of the JMIRI prescription database. However, in the analysis of individual statins, significant disturbances of sleep were found for simvastatin, rosuvastatin and lovastatin, but not for atorvastatin, fluvastatin, and pitavastatin. Additionally, it has been reported that switching to a different statin was able to resolve symptoms in some cases, but in other cases, switching to a different statin was not able to resolve symptoms [8]. The authors suggest that sleep disturbances related to statins should be closely monitored in clinical practice, but further prospective, long-term, large, randomized studies using validated outcome measures are needed to confirm the causality between sleep disturbances and statin therapy.

The present meta-analysis has some important limitations. There were only a few eligible randomized clinical trials (RCTs) with relatively small numbers of patients (n < 60, only men, mostly young; the average age does not exceed 55 years), and a short follow-up. The studies are also old, as they were performed between 1992 and 1994. It was also a reason that no trials with new statins – atorvastatin and rosuvastatin – were included in the analysis, which enables one to say whether the observed effects might be considered as class effects. The population was also very heterogeneous, as the included studies investigated both patients at CV risk with hypercholesterolemia and healthy subjects. Finally, the meta-analysis was limited by the lack of RCTs, which would evaluate the effects of statin therapy on sleep in elderly and high-risk patients.

In conclusion, the meta-analysis of available RCTs does not suggest any significant adverse effects of statin therapy on sleep duration and its efficiency. However, taking into account different results in observational cohort studies, there is still a substantial need for large, long-term, randomized studies using validated outcome measures to finally confirm (or not) the causality between sleep disturbances and statin therapy.

Acknowledgments

Drs Broncel and Banach contributed equally to this meta-analysis.

Conflict of interest

The authors declare no conflict of interest.

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