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

Marlena Broncel[1], Paulina Gorzelak-Pabiś[1], Amirhossein Sahebkar[2,3], Katarzyna Serejko[1], Sorin Ursoniu[4], Jacek Rysz[5], Maria Corina Serban[6,7], Monika Możdżan[1], Maciej Banach[8]; Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group

[1]Department of Internal Diseases and Clinical Pharmacology, Medical University of Lodz, Lodz, Poland
[2]Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Metabolic Research Centre, Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Perth, Australia
[4]Department of Functional Sciences, Discipline of Public Health, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[5]Department of Nephrology, Hypertension and Family Medicine, Chair of Nephrology and Hypertension, Medical University of Lodz, Lodz, Poland
[6]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA
[7]Department of Functional Sciences, Discipline of Pathophysiology, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[8]Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Lodz, Poland

Corresponding author:
Prof. Maciej Banach MD, PhD, FNLA, FAHA, FESC, FASA
Department of Hypertension
WAM University Hospital
Medical University of Lodz
113 Zeromskiego St
90-549 Lodz, Poland
Phone: +48 42 639 37 71
Fax: +48 42 639 37 71
E-mail:
maciejbanach@aol.co.uk

Submitted: 27 August 2015
Accepted: 27 August 2015

Arch Med Sci 2015; 11, 5: 915–926
DOI: 10.5114/aoms.2015.54841

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 few 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 and number of weakness. These results based on polysomnography (PSG) were not significantly correlated with the post-sleep questionnaire completed by patients [7]. Males with coronary artery disease (CAD) during 12-month observation slept less and had greater sleep disturbances due to simvastatin therapy compared to those using pravastatin [11].

However, no conclusive evidence exists that a particular statin is more likely to be associated with sleep disturbances over others, and whether statin therapy itself indeed influences sleep changes. Most of the studies were short-term observations, incorporated small cohorts, or did not have placebo control groups [7, 9, 10, 13]. In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, rates of adverse sleep events were similar in the placebo and rosuvastatin groups, and in subjects with and without low-density lipoprotein cholesterol (LDL-C) below 50 mg/dl [16]. Similar results were obtained in a prospective cohort of 149 patients followed for 6 months; self-reported sleep disturbances were not significantly different between the simvastatin, lovastatin, and placebo groups [17].

In the majority, data examining statins and sleep by using the most objective method, which is PSG, are limited and mixed [12, 18–21]; therefore there is still very limited knowledge on the effects of statins on sleep quality. The electroencephalogram (EEG), electrooculogram (EOG), and skeletal muscle electromyogram (EMG) provide measures characterizing the states of sleep and wakefulness [20]. Polysomnography can be summarized according to specific scoring criteria such as stages (1 to 4) of non-rapid eye movement (NREM), 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 reported after treatment. Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, 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 (I^2) value was < 50% and ≥ 50%, respectively. Heterogeneity was quantitatively assessed using the I^2 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

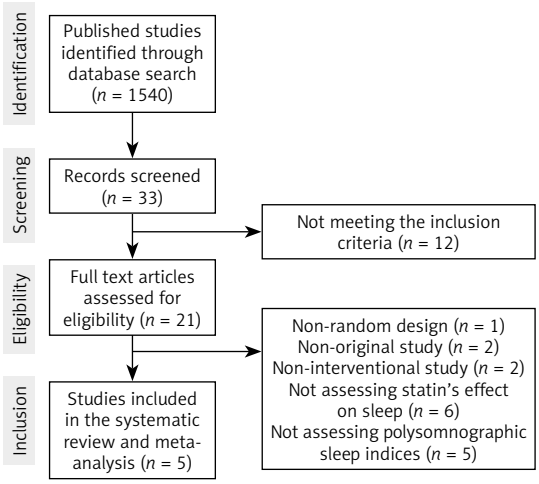


Figure 1. Flow chart of the number of studies identified and included in the meta-analysis

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, $t = 1.37$, d$f = 5$, 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, $t = 0.86$, d$f = 5$, 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-

Table I. Demographic characteristics and baseline parameters of the included studies

Parameter		Study				
		Kostis *et al.*	**Eckernas *et al.***	**Roth *et al.***	**Partinen *et al.***	**Kamei *et al.***
Year		1994	1993	1992	1994	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
		Pravastatin	Pravastatin	Pravastatin	Pravastatin	
Statin intervention		40 mg/day	20 mg/day	40 mg/day	40 mg/day	20 mg/day
		40 mg/day	40 mg/day	40 mg/day	40 mg/day	
Participants	Case	22	16	20	16	5
		22	16	19	16	
	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					
Total sleep duration [min]	Case	366.4#	404.5 ±30.6	436 ±6**	402 ±26	392.6 ±9.6**
		361.9#	402.1 ±30.6	434 ±6**	391 ±26	
	Control	361.9#	389.5 ±30.6	429 ±5**	400 ±26	406.3 ±19.3**
Sleep efficiency (%)	Case	NS	88.2 ±5.9	NS	90 ±8	NS
		NS	90.1 ±5.9	NS	84 ±8	
	Control	NS	87.5 ±5.9	NS	87 ±8	NS

Table I. Cont.

Parameter		Study				
		Kostis *et al.*	Eckernas *et al.*	Roth *et al.*	Partinen *et al.*	Kamei *et al.*
Entries to stage I	Case	NS	4.5 ±3.8	NS	20.8 ±5.7	NS
		NS	2.1 ±1.8	NS	23.7 ±5.7	
	Control	NS	2.2 ±1.9	NS	22.6 ±5.7	NS
Latency to stage I [min]	Case	NS	39.0 ±68.3	18 ±4**	8.7 ±6	28.3 ±13.5**
		NS	58.6 ±105.3	16 ±4**	9.6 ±6	
	Control	NS	11.4 ±20.3	26 ±4**	22.0 ±11	14.6 ±3.7**
Wake time during sleep [min]	Case	NS	26.1 ±18.5	24 ±5**	15.7 ±32.8	5.9 ±3.3**
		NS	27.4 ±19.3	23 ±5**	46.6 ±32.8	
	Control	NS	26.5 ±18.7	22 ±4**	39.5 ±32.8	19.7 ±15.6**
Number of awakenings	Case	NS	4.8 ±2.4	0.9 ±0.2**	2.9 ±0.1	1 ±0.5**
		NS	4.4 ±2.2	0.9 ±0.2**	2.9 ±0.1	
	Control	NS	4.7 ±2.4	0.9 ±0.17**	2.5 ±0.1	2.2 ±2.0**

*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.*

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

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	L
Eckernäs *et al.* 1993	L	L	L	L	L	L	L
Roth *et al.* 1992	U	U	L	L	L	L	L
Partinen *et al.* 1994	L	L	L	L	L	L	L
Kamei *et al.* 1993	U	U	L	L	L	L	L

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

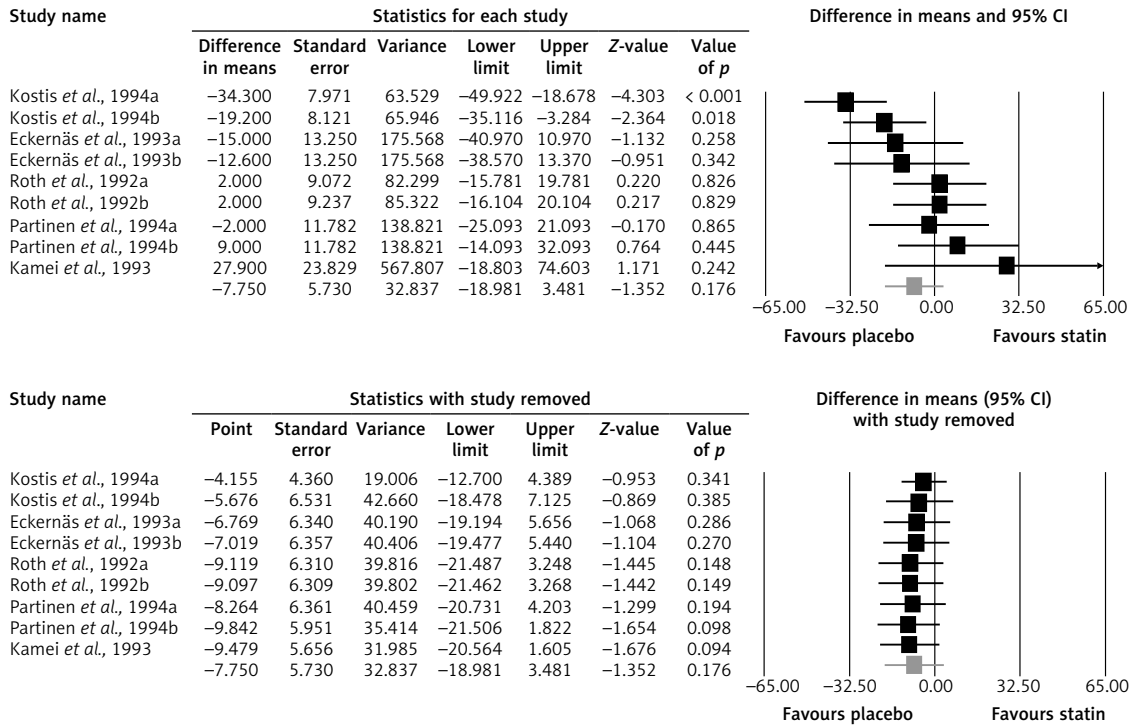
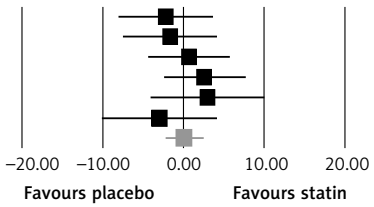


Figure 2. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of statin therapy on total sleep duration. Lower plot shows leave-one-out sensitivity analysis

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 and slows wave sleep [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 β-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 [18]. 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

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	*Z*-value	Value of *p*
Kostis *et al*., 1994a	–2.200	2.978	8.866	–8.036	3.636	–0.739	0.460
Kostis *et al*., 1994b	–1.700	2.954	8.727	–7.490	4.090	–0.575	0.565
Eckernäs *et al*., 1993a	0.700	2.555	6.527	–4.307	5.707	0.274	0.784
Eckernäs *et al*., 1993b	2.600	2.555	6.527	–2.407	7.607	1.018	0.309
Partinen *et al.,* 1994a	3.000	3.625	13.143	–4.105	10.105	0.828	0.408
Partinen *et al.,* 1994b	–3.000	3.625	13.143	–10.105	4.105	–0.828	0.408
	0.091	1.207	1.458	–2.275	2.458	0.076	0.940



Study name	Point	Standard error	Variance	Lower limit	Upper limit	*Z*-value	Value of *p*
Kostis *et al*., 1994a	0.542	1.321	1.745	–2.047	3.131	0.411	0.681
Kostis *et al*., 1994b	0.451	1.323	1.750	–2.142	3.043	0.341	0.733
Eckernäs *et al*., 1993a	–0.084	1.370	1.877	–2.769	2.602	–0.061	0.951
Eckernäs *et al*., 1993b	–0.630	1.370	1.877	–3.315	2.055	–0.460	0.646
Partinen *et al*., 1994a	–0.272	1.280	1.640	–2.781	2.238	–0.212	0.832
Partinen *et al*., 1994b	0.477	1.280	1.640	–2.033	2.987	0.373	0.710
	0.091	1.207	1.458	–2.275	2.458	0.076	0.940

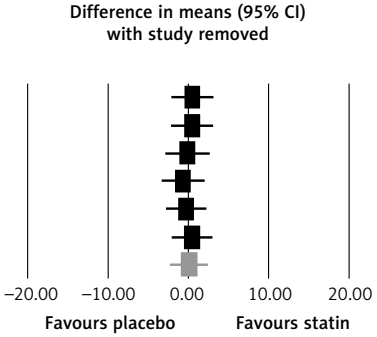
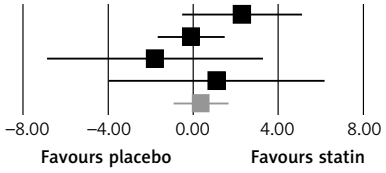


Figure 3. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of statin therapy on sleep efficiency. Lower plot shows leave-one-out sensitivity analysis

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	*Z*-value	Value of *p*
Eckernäs *et al*., 1993a	2.300	1.436	2.061	–0.514	5.114	1.602	0.109
Eckernäs *et al*., 1993b	–0.100	0.793	0.630	–1.655	1.455	–0.126	0.900
Partinen *et al*., 1994a	–1.800	2.583	6.672	–6.863	3.263	–0.697	0.486
Partinen *et al*., 1994b	1.100	2.583	6.672	–3.963	6.163	0.426	0.670
	0.359	0.649	0.421	–0.913	1.631	0.553	0.580



Study name	Point	Standard error	Variance	Lower limit	Upper limit	*Z*-value	Value of *p*
Eckernäs *et al*., 1993a	–0.140	0.728	0.530	–1.566	1.287	–0.192	0.848
Eckernäs *et al*., 1993b	1.288	1.129	1.274	–0.924	3.500	1.141	0.254
Partinen *et al*., 1994a	0.505	0.671	0.450	–0.810	1.819	0.752	0.452
Partinen *et al*., 1994b	0.309	0.671	0.450	–1.005	1.623	0.461	0.645
	0.359	0.649	0.421	–0.913	1.631	0.553	0580

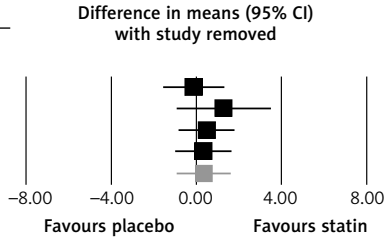
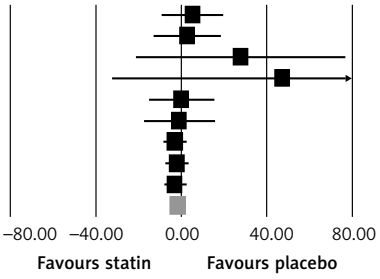


Figure 4. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of statin therapy on entries to stage I sleep. Lower plot shows leave-one-out sensitivity analysis

clear. 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]. Anal-

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	*Z*-value	Value of *p*
Kostis *et al.*, 1994a	5.200	7.345	53.944	–9.195	19.595	0.708	0.479
Kostis *et al.*, 1994b	2.700	7.964	63.427	–12.909	18.309	0.339	0.735
Eckernäs *et al.*, 1993a	27.600	24.919	620.949	–21.240	76.440	1.108	0.268
Eckernäs *et al.*, 1993b	47.200	40.664	1653.583	–32.501	126.901	1.161	0.246
Roth *et al.*, 1992a	0.000	7.709	59.436	–15.110	15.110	0.000	1.000
Roth *et al.*, 1992b	–1.000	8.351	69.746	–17.368	15.368	–0.120	0.905
Partinen *et al.*, 1994a	–3.000	2.719	7.393	–8.329	2.329	–1.103	0.270
Partinen *et al.*, 1994b	–2.100	2.719	7.393	–7.429	3.229	–0.772	0.440
Kamei *et al.*, 1993	–3.000	2.616	6.845	–8.128	2.128	–1.147	0.252
	–1.921	1.437	2.065	–4.738	0.895	–1.337	0.181



Study name	Point	Standard error	Variance	Lower limit	Upper limit	*Z*-value	Value of *p*
Kostis *et al.*, 1994a	–2.205	1.465	2.147	–5.077	0.667	–1.505	0.132
Kostis *et al.*, 1994b	–2.077	1.461	2.134	–4.940	0.786	–1.422	0.155
Eckernäs *et al.*, 1993a	–2.020	1.439	2.072	–4.841	0.801	–1.403	0.161
Eckernäs *et al.*, 1993b	–1.983	1.438	2.067	–4.801	0.835	–1.379	0.168
Roth *et al.*, 1992a	–1.991	1.463	2.139	–4.857	0.876	–1.361	0.174
Roth *et al.*, 1992b	–1.949	1.459	2.128	–4.808	0.910	–1.336	0.181
Partinen *et al.*, 1994a	–1.503	1.693	2.865	–4.821	1.814	–0.888	0.374
Partinen *et al.*, 1994b	–1.852	1.693	2.865	–5.170	1.465	–1.094	0.274
Kamei *et al.*, 1993	–1.455	1.720	2.957	–4.826	1.915	–0.846	0.397
	–1.921	1.437	2.065	–4.738	0.895	–1.337	0.181

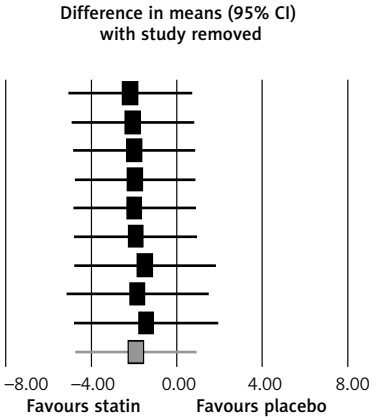
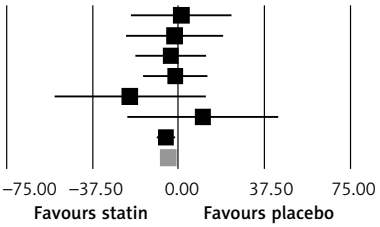


Figure 5. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of statin therapy on latency to stage I sleep. Lower plot shows leave-one-out sensitivity analysis

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	*Z*-value	Value of *p*
Eckernäs *et al.*, 1993a	1.500	11.279	127.220	–20.607	23.607	0.133	0.894
Eckernäs *et al.*, 1993b	–1.500	10.778	116.158	–22.624	19.624	–0.139	0.889
Roth *et al.*, 1992a	–3.000	7.845	61.545	–18.376	12.376	–0.382	0.702
Roth *et al.*, 1992b	–1.000	7.157	51.217	–15.027	13.027	–0.140	0.889
Partinen *et al.*, 1994a	–21.000	16.767	281.134	–53.863	11.863	–1.252	0.210
Partinen *et al.*, 1994b	–11.000	16.767	281.134	–21.863	43.863	0.656	0.512
Kamei *et al.*, 1993	–4.900	1.943	3.774	–8.707	–1.093	–2.522	0.012
	–4.327	1.756	3.083	–7.768	–0.885	–2.464	0.014



Study name	Point	Standard error	Variance	Lower limit	Upper limit	*Z*-value	Value of *p*
Eckernäs *et al.*, 1993a	–4.472	1.778	3.160	–7.956	–0.988	–2.516	0.012
Eckernäs *et al.*, 1993b	–4.404	1.780	3.167	–7.892	–0.916	–2.475	0.013
Roth *et al.*, 1992a	–4.397	1.802	3.246	–7.928	–0.866	–2.441	0.015
Roth *et al.*, 1992b	–4.540	1.811	3.281	–8.090	–0.990	–2.507	0.012
Partinen *et al.*, 1994a	–4.142	1.766	3.117	–7.602	–0.682	–2.346	0.019
Partinen *et al.*, 1994b	–4.497	1.766	3.117	–7.957	–1.036	–2.547	0.011
Kamei *et al.*, 1993	–1.768	4.105	16.847	–9.813	6.276	–0.431	0.667
	–4.327	1.756	3.083	–7.768	–0.885	–2.464	0.014

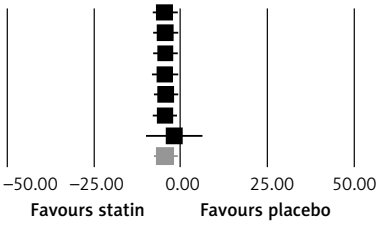
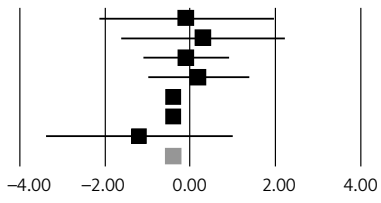


Figure 6. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of statin therapy on total wake time. Lower plot shows leave-one-out sensitivity analysis

ysis of sleep EEG measures relevant to insomnia provided no evidence of significant differences between these three treatments, except for entries and latency to stage I sleep [12]. The number of entries to stage I sleep was significantly 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

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	1.378	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
	–0.397	0.032	0.001	–0.459	–0.334	–12.442	< 0.001



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	–0.306	–8.769	< 0.001
Kamei *et al.,* 1993	–0.396	0.032	0.001	–0.459	–0.334	–12.416	< 0.001
	–0.397	0.032	0.001	–0.459	–0.334	–12.442	< 0.001

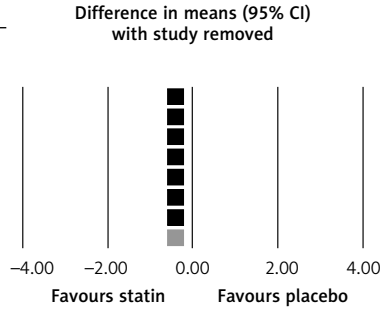


Figure 7. Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of statin therapy on number of awakenings. Lower plot shows leave-one-out sensitivity analysis

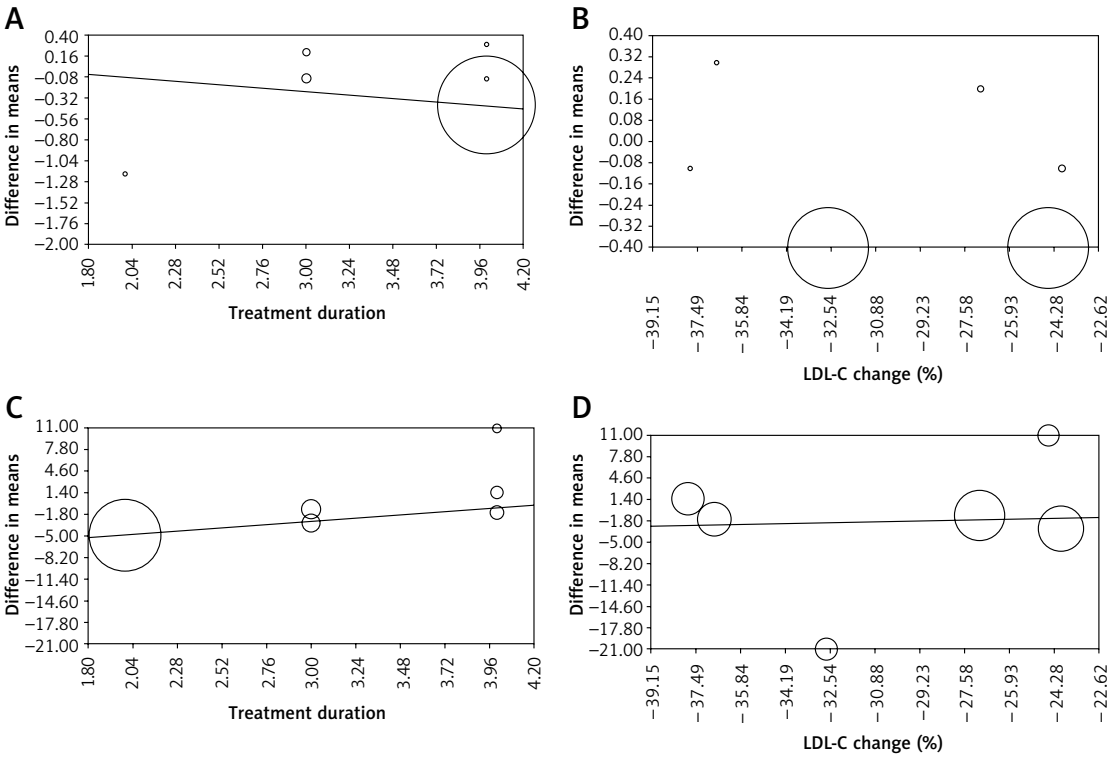


Figure 8. Meta-regression plots of the association between mean changes in the number of awakenings (**A**, **B**) and wake time (**C**, **D**) with duration of statin therapy and magnitude of LDL-C reduction

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].

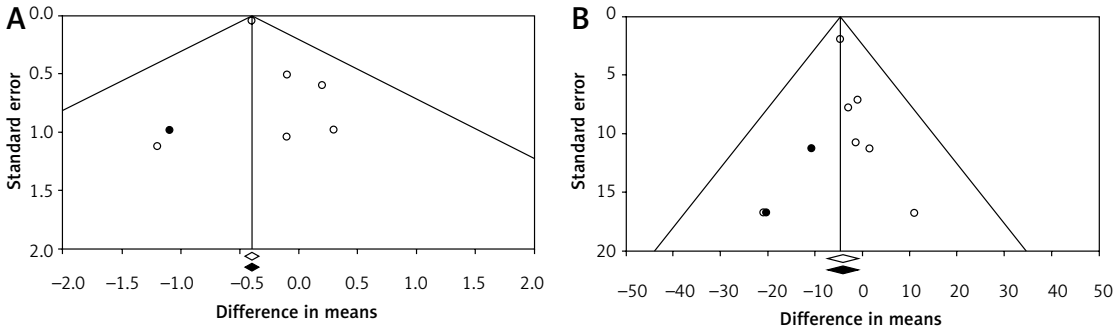


Figure 9. Funnel plots detailing publication bias in the meta-analyses of statins' effects on the number of awakenings (**A**) and wake time (**B**)

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.

References

1. Catapano AL, Reiner Ž, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis 2011; 217: 1-44.
2. Banach M, Rizzo M, Toth PP, et al. Statin intolerance – an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Expert Opin Drug Saf 2015; 14: 935-55.
3. Banach M, Rizzo M, Toth PP, et al. Statin intolerance – an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Arch Med Sci 2015; 11: 1-23.
4. Banach M, Malodobra-Mazur M, Gluba A, Katsiki N, Rysz J, Dobrzyn A. Statin therapy and new-onset diabetes: molecular mechanisms and clinical relevance. Curr Pharm Des 2013; 19: 4904-12.
5. Golomb BA, Evans MA, Dimsdale JE, White HL. Effects of statins on energy and fatigue with exertion: results from a randomized controlled trial. Arch Intern Med 2012; 172: 1180-2.
6. Tuccori M, Lapi F, Testi A, et al. Statin-associated psychiatric adverse events. Drug Safety 2008; 31: 1115-23.
7. Boriani G, Biffi M, Strocchi E, Branzi A. Nightmares and sleep disturbances with simvastatin and metoprolol. Ann Pharmacother 2001; 35: 1292.
8. Takada M, Fujimoto M, Yamazaki K, Takamoto M, Hosomi K. Association of statin use with sleep disturbances: data mining of a spontaneous reporting database and a prescription database. Drug Safety 2014; 37: 421-31.
9. Vgontzas AN, Kales A, Bixler EO, Manfredi RL, Tyson KL. Effects of lovastatin and pravastatin on sleep efficiency and sleep stages. Clin Pharmacol Therap 1991; 50: 730-7.
10. Harrison R, Ashton C. Do cholesterol-lowering agents affect brain activity? A comparison of simvastatin,

pravastatin, and placebo in healthy volunteers. Br J Clin Pharmacol 1994; 37: 231-6.
11. Barth JD, Kruisbrink O, Van Dijk AL. Inhibitors of hydroxymethylglutaryl coenzyme A reductase for treating hypercholesterolaemia. BMJ 1990; 301: 669.
12. Eckernäs S, Roos B, Kvidal P, et al. The effects of simvastatin and pravastatin on objective and subjective measures of nocturnal sleep: a comparison of two structurally different HMG CoA reductase inhibitors in patients with primary moderate hypercholesterolaemia. Br J Clin Pharmacol 1993; 35: 284-9.
13. Carlsson CM, Papcke-Benson K, Carnes M, McBride PE, Stein JH. Health-related quality of life and long-term therapy with pravastatin and tocopherol (vitamin E) in older adults. Drugs Aging 2002; 19: 793-805.
14. Saheki A, Terasaki T, Tamai I, Tsuji A. In vivo and in vitro blood–brain barrier transport of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Pharmaceut Res 1994; 11: 305-11.
15. Tobert JA, Leslie B, Schaefer E, et al. HMG-CoA reductase inhibitors for hypercholesterolemia. N Engl J Med 1988; 319: 1222-3.
16. Hsia J, MacFadyen JG, Monyak J, Ridker PM. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol < 50 mg/dl with rosuvastatin: the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). J Am Coll Cardiol 2011; 57: 1666-75.
17. Ditschuneit H, Kuhn K. Comparison of different HMG-CoA reductase inhibitors. Eur J Clin Pharmacol 1991; 40: S27-32.
18. Roth T, Richardson GR, Sullivan JP, Lee RM, Merlotti L, Roehrs T. Comparative effects of pravastatin and lovastatin on nighttime sleep and daytime performance. Clin Cardiol 1992; 15: 426-32.
19. Kostis JB, Rosen RC, Wilson AC. Central nervous system effects of HMG CoA reductase inhibitors: lovastatin and pravastatin on sleep and cognitive performance in patients with hypercholesterolemia. J Clin Pharmacol 1994; 34: 989-96.
20. Partinen M, Pihl S, Strandberg T, et al. Comparison of effects on sleep of lovastatin and pravastatin in hypercholesterolemia. Am J Cardiol 1994; 73: 876-80.
21. Kamei Y, Shirakawa S, Ishizuka Y, et al. Effect of pravastatin on human sleep. Psychiatry Clin Neurosci 1993; 47: 643-6.
22. Higgins J, Green S. Cochrane Handbook for systematic reviews of interventions version 5.0. 2 [updated September 2009]. The Cochrane Collaboration, 2009. www cochrane-handbook org/(accessed 18 May 2009). 2013.
23. Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive meta-analysis version 2. Englewood, NJ: Biostat 2005; 104.
24. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5: 1-10.
25. Duval S, Tweedie R. Trim and fill: a simple funnel plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; 56: 455-63.
26. Swiger KJ, Manalac RJ, Blaha MJ, Blumenthal RS, Martin SS. Statins, mood, sleep, and physical function: a systematic review. Eur J Clin Pharmacol 2014; 70: 1413-22.
27. Black DM, Lamkin G, Olivera EH, Laskarzewski PM, Stein EA. Sleep disturbance and HMG CoA reductase inhibitors. JAMA 1990; 264: 1105.
28. Ueno R, Honda K, Inoue S, Hayaishi O. Prostaglandin D2, a cerebral sleep-inducing substance in rats. Proc Natl Acad Sci USA 1983; 80: 1735-7.
29. Bielecka-Dabrowa A, Aronow WS, Rysz J, Banach M. Current place of beta-blockers in the treatment of hypertension. Curr Vasc Pharmacol 2010; 8: 733-41.
30. Galatti L, Polimeni G, Salvo F, Romani M, Sessa A, Spina E. Short-term memory loss associated with rosuvastatin. Pharmacotherapy 2006; 26: 1190-2.
31. King DS, Wilburn AJ, Wofford MR, Harrell TK, Lindley BJ, Jones DW. Cognitive impairment associated with atorvastatin and simvastatin. Pharmacotherapy 2003; 23: 1663-7.
32. Padala KP, Padala PR, Potter JF. Simvastatin-induced decline in cognition. Ann Pharmacother 2006; 40: 1880-3.
33. Banach M, Aronow WS, Serban C, et al. Lipids, blood pressure and kidney update 2014. Pharmacol Res 2015; 95: 111-25.
34. Banach M, Mikhailidis DP, Kjeldsen SE, Rysz J. Time for new indications for statins? Med Sci Monit 2009; 15: MS1-5.
35. Banach M, Serban C, Aronow WS, et al. Lipid, blood pressure and kidney update 2013. Int Urol Nephrol 2014; 46: 947-61.