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ORIGINAL RESEARCH ARTICLE

Association Between Statin Use and Bell's Palsy: A Population-Based Study

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Abstract

Background Several reports mention that statin (HMG-CoA reductase inhibitor) use seems to be associated with several neurologic disorders and that the lipid-lowering effect of statins may contribute to some neural toxicity.

Objective This study aimed to evaluate the association between statin use and Bell's palsy using a population-based health insurance database.

Methods This case-control study identified 1,977 subjects with Bell's palsy as cases and 5,931 sex- and age-matched subjects without Bell's palsy as controls from the Taiwan Longitudinal Health Insurance Database 2000. Conditional logistic regressions was used to estimate the odds ratio (OR) and 95 % confidence interval (CI) for previous use of statins between the cases and controls. The associations of regular and irregular statin users with Bell's palsy were further analyzed.

Results By Chi-square test, there was a significant difference in the prevalence of statin use between cases and controls (23.2 vs. 16.4 %, $p < 0.001$). Conditional logistic regression analysis revealed that after adjusting for diabetes mellitus, hypertension, and hyperlipidemia, the OR for prior statin use was 1.47 (95 % CI 1.28–1.69) for cases compared with controls. Bell's palsy was significantly associated with previous regular statin use (≥60 days within 6 months) (adjusted OR: 1.46, 95 % CI 1.28–1.67). However, there was no increased adjusted OR of irregular statin use (<60 days within 6 months) for cases compared with controls (OR: 1.09, 95 % CI 0.82–1.46).

Conclusions Our present data suggest a potential association between regular statin use and Bell's palsy.

Key Points

There is a significant difference in the prevalence of statin use between subjects with Bell's palsy and healthy controls (23.2 vs. 16.4 %; $p < 0.001$)

The adjusted odds ratio (OR) for prior statin use was 1.47 (95 % CI 1.28–1.69) for subjects with Bell's palsy, compared with controls

Bell's palsy is significantly associated with previous regular statin use (≥60 days within 6 months) (adjusted OR: 1.46)

There is no increased adjusted OR of irregular statin use (<60 days within 6 months) for subjects with Bell's palsy compared with controls

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1 Introduction

Statins (3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitors) are used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. Increased cholesterol levels have been associated with cardiovascular diseases (CVDs) [1–3] and research has found that statins are effective in preventing and treating CVDs [4–7???].

Aside from their cholesterol-lowering effect and primary and secondary prevention of CVDs, statins have recently been associated with other benefits involving various body systems. Tonelli et al. [8] reported that statins may be of some benefit in preserving renal function in patients with moderate chronic renal insufficiency. Statin use has even been reported to improve outcomes of patients with sepsis and infections [9, 10]. Simvastatin, in particular, has been found to strongly reduce levels of β-amyloid peptides associated with Alzheimer's disease and, possibly, to have some potential in preventing the development of dementia [11]. However, there are also reports in which statins seem to be associated with several neurologic disorders [12–15]. It is believed that the lipid-lowering effect of statins may contribute to some neural toxicity [16]. Interestingly, most reports on statin neurotoxicity are regarding effects on the peripheral nervous system [17, 18]. In our previous study, we found that sudden sensorineural hearing loss (SSNHL) was significantly associated with previous statin use [19], suggesting that the central nervous system (CNS) can also be affected. However, associations between statin use and cranial nerve neuropathy, such as Bell's palsy, remain unknown.

Bell's palsy is commonly used to describe an acute peripheral facial palsy of unknown cause [20]. Currently, this condition is suspected to mostly originate from a herpes simplex-mediated viral inflammatory/immune mechanism [21, 22]. Although other mechanisms such as genetic predisposition or facial nerve ischemia have been proposed, only the multi-factorial nature of the disease is certain [23, 24]. The present study aimed to evaluate the association of statin use with Bell's palsy using a population-based coverage database.

2 Methods

2.1 Database

The study sample for this case-control study was retrieved from the Longitudinal Health Insurance Database 2000 (LHID2000). The LHID2000, derived from the Taiwan National Health Insurance (NHI) program, was provided to scientists in Taiwan for research purposes. The LHID2000 mainly included the medical claims of 1,000,000 enrollees, who were randomly selected from all enrollees under the NHI program, and has been used to publish studies in internationally peer-reviewed journals [25]. It provides researchers with an opportunity to trace all medical utilizations of these 1,000,000 enrollees since the start of the NHI program in 1995.

This study was exempt from full review by the Institutional Review Board of Taipei Medical University because the LHID2000 consisted of de-identified secondary data released to the public for research purposes.

2.2 Selection of Cases and Controls

Cases were selected by identifying 1,977 subjects aged ≥40 years with a first-time principal diagnosis of Bell's palsy [International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 351.0] in an ambulatory care visit (including the outpatient departments of hospitals and clinics) from 1 January 2008 to 31 December 2011. Subjects aged <40 years were not included because of the low prevalence of statin use in this age group. The first ambulatory care visit for treatment of facial nerve disorders was assigned as the index date for cases.

Three controls for each case were selected from the remaining beneficiaries of the LHID2000. First, all subjects who had received a diagnosis of Bell's palsy since the beginning of the NHI program were excluded. Then, 5,931 controls were randomly selected to match the cases in terms of age, sex, and index year. For cases, the year of index date was the year in which the cases received their first diagnosis of Bell's palsy; for controls, the year of index date was simply a matched year in which controls had a medical utilization. For the controls, the first utilization of medical care occurring in the index year was also defined as the index date.

2.3 Exposure Assessment

From the file of ambulatory care medical orders, prior use of simvastatin, lovastatin, atorvastatin, fluvastatin, pravastatin, and rosuvastatin before the index date was selected. We defined those subjects who had ever received statin prescriptions within 1 year before the index date as statin users. Therefore, all statin users included in this study are considered as current users. Those subjects who had never received statin prescriptions within 1 year before the index date were defined as non-users in this study. Since most statin use is continuous, we also found that all non-users

had never received statin prescriptions since the start of the NHI program in 1995. In addition, the information on prescription date and duration was recorded in the file of ambulatory care medical orders. This allows us to understand the continuity and duration of prescription for each subject. Subjects who had received continuous statin prescriptions for ≥60 days within 6 months before the index date were further defined as regular statin users in accordance with a prior study [26]. The remaining subjects who had been prescribed statins for <60 days within 6 months before the index date were regarded as irregular statin users.

In this study, we also took the variables of monthly income [new Taiwan dollars ($NT) 0–15,840, 15,841–25,000, and ≥25,001), urbanization level, geographic location (northern, central, eastern, and southern Taiwan), diabetes mellitus, hypertension, hyperlipidemia, coronary heart disease, obesity, and tobacco use disorder into consideration. The method of monthly income classification was based on a previous study [27]. $NT15,840 was used as the first income level cutoff point since that is the Government's definition of minimum wage for full-time employees in Taiwan.

2.4 Statistical Analysis

SAS® for Windows, version 8.2 (SAS Institute, Cary, NC, USA) was used to perform all statistical analyses. Chi-square tests were conducted to compare statistical differences in monthly income, urbanization level, geographic location, diabetes, hypertension, hyperlipidemia, coronary heart disease, obesity, and tobacco use disorder between cases and controls. Conditional logistic regression analysis (conditioned on age, sex, and index year) was also used to estimate the odds ratio (OR) and 95 % confidence interval (CI) for previous statin use between cases and controls after adjusting for medical co-morbidities. We only took medical co-morbidities that were significantly associated with Bell's palsy into consideration in the regression models. The associations of regular and irregular statin users with Bell's palsy were also further analyzed. Statistical significance was set at $p \leq 0.05$.

Table 1 Demographic characteristics of patients with Bell's palsy and controls ($N = 7,908$)

Variable	Patients with Bell's palsy ($n = 1,977$)		Controls ($n = 5,931$)		p value
	Total no.	%	Total no.	%	
Age (years)	58.1 (±11.9)		58.1 (±11.9)		>0.999
Sex					>0.999
Male	942	47.6	2,826	47.6	
Female	1,035	52.4	3,105	52.4	
Monthly income ($NT)[a]					0.284
≤15,840	696	35.2	2,131	35.9	
15,841–25,000	784	39.7	2,237	37.7	
≥25,001	497	25.1	1,563	26.4	
Geographic region					0.278
Northern	899	45.5	2,807	47.3	
Central	459	23.2	1,258	21.2	
Southern	564	28.5	1,701	28.7	
Eastern	55	2.8	165	2.8	
Urbanization level					0.645
1 (most urbanized)	589	29.8	1,819	30.7	
2	615	31.1	1,753	29.6	
3	279	14.1	845	14.2	
4	263	13.3	772	13.0	
5 (least urbanized)	231	11.7	742	12.5	
Diabetes mellitus	478	24.2	904	15.2	<0.001
Hypertension	708	35.8	1,734	29.2	<0.001
Hyperlipidemia	570	28.8	1,425	24.0	<0.001
Tobacco use disorder	70	3.5	192	3.2	0.680
Obesity	28	1.4	63	1.1	0.201
Coronary heart disease	168	8.5	500	5,931	0.926

$NT New Taiwan dollars

[a] The average exchange rate in 2010 was US$1.00 ≈ $NT30.0

3 Results

Among the 1,977 cases and 5,931 controls, the mean age was 58.1 ± 11.9 years and 52.4 % were females. After matching for age, sex, and index year, there were no significant differences between cases and controls in terms of monthly income, geographic region, or urbanization level (Table 1). However, cases were more likely to have diabetes (24.2 vs. 15.2 %), hypertension (35.8 vs. 29.2 %), and hyperlipidemia (28.8 vs. 24.0 %) than the controls.

In terms of the distribution of prior statin use in the 7,908-person study sample, 1,431 (18.1 %) were statin users prior to the index date (Table 2). Chi-square test further demonstrated a significant difference in the prevalence of prior statin use in cases and controls (23.2 vs. 16.4 %, $p < 0.001$). Conditional logistic regression analysis (conditioned on age, sex, and index year) also revealed that the OR for prior statin use among cases was 1.54 (95 % CI 1.36–1.74, $p < 0.001$) compared with controls. After adjusting for diabetes, hypertension, and hyperlipidemia, the OR for prior statin use was 1.47 (95 % CI 1.28–1.69) for cases.

Tables 3 and 4 present the association of Bell's palsy with statin use stratified by diabetes and hypertension. The results all suggested that there was a significant association between Bell's palsy and statin use regardless of the status of diabetes or hypertension.

In terms of the association of Bell's palsy with regular/irregular statin use (Table 5), Bell's palsy was statistically and significantly associated with previous regular statin use (OR: 1.46, 95 % CI 1.28–1.67) after adjusting for diabetes, hypertension, and hyperlipidemia. However, there was no increase in the adjusted OR of irregular statin use for cases compared with controls (OR: 1.09, 95 % CI 0.82–1.46).

4 Discussion

To date, this is the first study to report an association between statin use and Bell's palsy. This study demonstrates that Bell's palsy is significantly associated with previous statin use and the adjusted OR of statin use before the index date of diagnosis of Bell's palsy is 1.47 (95 % CI 1.28–1.69) for cases compared with controls. This suggests that possible neurotoxicity associated with statin use may not be limited to the peripheral nervous system as previously reported in literature and may instead also affect the facial nerve, with an increasing incidence of developing Bell's palsy [14].

The earliest study regarding statin use and peripheral neuropathy was published in 1995 by Phan et al. [28], who reported four cases that developed sensori-motor neuropathy while under treatment with simvastatin and who had complete or partial resolution of the clinical abnormalities after cessation of treatment. A few years later, Ziajka and Wehmeier [29] reported another case that further demonstrated the cross-reactivity of neuropathic processes to different statins. As more evidence emerged from many subsequent studies, researchers mostly agreed that physicians should be alert to the potential risk of peripheral neuropathy in patients receiving any of the statins and that statins should be considered the cause of peripheral neuropathy when other etiologies have been excluded [14].

It has been proposed that statins interfere with cholesterol synthesis, thereby altering myelin and nerve membrane functions, and preventing mitochondrial respiratory chain enzyme synthesis, which may disturb neuron energy use [16]. If these proposed mechanisms are correct, then the CNS can also be affected in the same way. Interestingly, there are some reports regarding certain mental and depressive symptoms associated with statin use [30–32]. Symptoms including behavioral alterations, cognitive and memory impairments, sleep disturbance, and sexual dysfunction were reported to be associated with statin treatment [33]. However, involvement of the cranial nerves after statin use has never been reported.

In a previous study, SSNHL was significantly associated with previous statin use [19]. The adjusted OR of statin use before the index date of an SSNHL diagnosis was 1.43 (95 % CI 1.23–1.67) for cases compared with controls.

Table 2 Prevalence, odds ratios, and 95 % confidence intervals for statin use among sampled patients

Variable	Patients with Bell's palsy (n = 1,263) [n (%)]	Controls (n = 6,315) [n (%)]	Crude OR (95 % CI)	Adjusted OR[a] (95 % CI)
Presence of prior statin use				
Yes	344 (27.2)	1,344 (21.3)	1.54*** (1.36–1.74)	1.47*** (1.28–1.69)
No	919 (72.8)	4,971 (78.7)		

The OR was calculated using a conditional logistic regression conditioned on age and sex

CI confidence interval, *OR* odds ratio

*** $p < 0.001$

[a] Adjusted for diabetes mellitus, hypertension, and hyperlipidemia

Table 3 Prevalence, odds ratios, and 95 % confidence intervals for statin use among sampled patients stratified by diabetes mellitus

Variable	Patients with Bell's palsy (n = 1,263) [n (%)]	Controls (n = 6,315) [n (%)]	Crude OR (95 % CI)	Adjusted OR[a] (95 % CI)
With diabetes				
Presence of prior statin use				
Yes	227 (47.5)	373 (41.3)	1.32* (1.06–1.66)	1.31* (1.10–1.57)
No	251 (52.5)	531 (58.7)		
Without diabetes				
Presence of prior statin use				
Yes	231 (15.4)	600 (11.9)	1.36*** (1.15–1.60)	1.34*** (1.14–1.55)
No	1,268 (84.6)	4,427 (88.1)		

The OR was calculated using a conditional logistic regression conditioned on age and sex

CI confidence interval, *OR* odds ratio

* $p < 0.05$; *** $p < 0.001$

[a] Adjusted for hypertension

Table 4 Prevalence, odds ratios, and 95 % confidence intervals for statin use among sampled patients stratified by hypertension

Variable	Patients with Bell's palsy (n = 1,263) [n (%)]	Controls (n = 6,315) [n (%)]	Crude OR (95 % CI)	Adjusted OR[a] (95 % CI)
With hypertension				
Presence of prior statin use				
Yes	235 (33.2)	479 (27.6)	1.34** (1.11–1.63)	1.30** (1.08–1.57)
No	473 (66.8)	1,255 (72.4)		
Without hypertension				
Presence of prior statin use				
Yes	223 (17.6)	494 (11.8)	1.63*** (1.36–1.94)	1.60*** (1.35–1.90)
No	1,046 (82.4)	3,703 (88.2)		

The OR was calculated using a conditional logistic regression conditioned on age and sex

CI confidence interval, *OR* odds ratio

** $p < 0.01$; *** $p < 0.001$

[a] Adjusted for diabetes mellitus

Table 5 Odds ratios and 95 % confidence intervals for statin use among patients with Bell's palsy and controls

Use of statin	Total (N = 7,908)	Patients with Bell's palsy (n = 1,977)	Controls (n = 5,931)
Regular use of statin (≥60 days within 6 months)			
Yes [n (%)]	1,172 (14.8)	383 (19.4)	789 (13.3)
Crude OR (95 % CI)		1.57*** (1.37–1.79)	1.00
Adjusted OR (95 % CI)[a]		1.46*** (1.28–1.67)	1.00
Irregular use of statin (<60 days within 6 months)			
Yes [n (%)]	259 (3.3)	75 (3.8)	184 (3.1)
Crude OR (95 % CI)		1.23 (0.94–1.62)	1.00
Adjusted OR (95 % CI)[a]		1.09 (0.82–1.46)	1.00

The OR was calculated using a conditional logistic regression conditioned on age and sex

CI confidence interval, *OR* odds ratio

*** $p < 0.001$

[a] Adjusted for diabetes mellitus, hypertension, and hyperlipidemia

This implied that the CNS was also susceptible to the adverse effects of statins.

There are several possible mechanisms that can explain the increased incidence of Bell's palsy under regular statin use. First, statins have been reported to induce a disturbance in neurite outgrowth and/or maintenance. Schulz et al. [34] reported that atorvastatin treatment caused a profound reduction in neurite length, neurite loss, and, ultimately, cell death in undifferentiated and pre-differentiated PC12 cells and in rat primary cortical neurons. Interestingly, many others reported that statins might have certain neuroprotective effects for treating specific neurodegenerative diseases such as Parkinson's and Alzheimer's disease [35]. While seemingly paradoxical, if Bell's palsy is considered to be a peripheral type of facial nerve disorder, it is possible that the neuroprotective effect of statins is mostly restricted to neuron bodies but not to nerve sheaths [36]. This hypothesis is further supported by several studies reporting that statins might negatively impact oligodendrocytes and myelin formation [37, 38]. Miron et al. [39] even reported that simvastatin inhibited CNS remyelination by blocking progenitor differentiation,

implying that patients using statins might be more vulnerable to demyelination of nerves induced by viral infections, as seen in Bell's palsy.

Second, statins are commonly reported to have anti-inflammatory effects such as decreased plasma levels of the acute-phase inflammatory marker C-reactive protein [15]. However, there are also reports showing that statins are capable of stimulating pro-inflammatory responses, which appears to be undesirable in the pathogenesis of Bell's palsy [40, 41].

Lastly, statins can trigger autoimmunity. Mammen et al. [42] described a novel autoantibody that recognizes ~200- and ~100-kDa proteins associated with autoimmune myopathy and statin use. Two other reports also showed that statins induced systemic immune reactions, including dermatomyositis, polymyalgia rheumatica, and serum anti-neutrophil cytoplasmic antibody-associated systemic vasculitis [43, 44]. Although the role of autoimmunity in the development of Bell's palsy remains unclear, it is possible that statin-triggered autoimmune reactions may contribute to the development of Bell's palsy.

While evidence might indirectly support the role of statin facial palsy effect, considering the marginal increase in risk, this contribution of statin use might actually not be causal. As stated previously, Bell's palsy is a disease of multifactorial nature with predisposing conditions including viral infections, inflammations, genetic predisposition, and ischemia of the facial nerve. Therefore, it is difficult to include all the co-morbidities and adjust these covariates. Diabetes was reported to be associated with the severity of Bell's palsy and therefore was adjusted [45]. The CVDs and hyperlipidemia, which are commonly seen in statin users, were also adjusted. However, it remained difficult to include and adjust factors such as genetic predisposition and definite herpes infections based on our health insurance databases.

This study has several limitations. First, the study was performed on the Taiwanese population and it is possible that the study findings cannot be extended to different ethnic groups. Second, limited by the data retrieved from the health insurance database, the actual administered doses of statins might have been inconsistent among these patients. Moreover, the statin concentrations in patients' plasma were unavailable and there was no information on the severity of or recovery from Bell's palsy. Thus, a dose-dependent relationship cannot be assessed and this may compromise the significance of the findings. Although we tried to control for diseases factors such as hypertension and diabetes, we were not able to control and adjust for the severity of these diseases. In addition, the LHID2000 data provides no information on the patients' body mass index, race/ethnicity, smoking habits, alcohol consumption, physical activity, or non-prescription medication use. Although Bell's palsy was recently reported to be associated with hepatitis B vaccination administration [46], information of previous vaccinations was also unavailable. Thus, the impacts of these factors on Bell's palsy have not been evaluated.

Third, like most research that utilizes health insurance databases, there is a possibility of a surveillance bias, which means that it is possible that patients who used statins visited doctors more often. However, this bias may have a limited impact on the conclusions since Bell's palsy appears to be an acute event easily noticed by affected individuals. Bell's palsy is unlikely to have been diagnosed in a medical visit related to hyperlipidemia and statin use.

Fourth, the dataset used in this study only included the medical claims of 1,000,000 enrollees. In the present study, controls have been selected to match the cases in terms of age and sex. We do not have enough of a sample population to allow us to match each control to case in terms of age, sex, and exact index day of the case.

Lastly, 'regular use' of statins is difficult to define. To establish a more direct, causal relationship, subjects who had received continuous statin prescriptions for $\geq$60 days within 6 months prior to the index date were defined as regular statin users. However, the duration of statin use sufficient to affect the development of Bell's palsy or other related facial nerve neuropathy remains unknown. Furthermore, this study is designed as a case-control study. It is difficult to obtain reliable information about an individual's exposure duration to statins over time; therefore, this study did not examine the association between drug duration and Bell's palsy.

Nevertheless, this study provides an understanding of the adverse effects of statins greater than before. Although more studies are needed to further clarify the true relationship between statin use and the development of Bell's palsy, it can be recommend that physicians be more alert in managing patients under regular statin use, as this popular therapy may cause more problems than previously thought.

5 Conclusions

Our present data suggest the possible relationship between regular statin use and Bell's palsy. Further studies are needed to clarify and confirm the significance of our findings.

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References

1. Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet. 2007;370(9602):1829–39.
2. Goldstein JL, Hazzard WR, Schrott HG, et al. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. J Clin Invest. 1973;52(7):1533–43.
3. Cohn PF, Gabbay SI, Weglicki WB. Serum lipid levels in angiographically defined coronary artery disease. Ann Intern Med. 1976;84(3):241–5.
4. Taylor F, Ward K, Moore TH, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2011;(1):CD004816.
5. Chang CH, Lee YC, Tsai CT, et al. Continuation of statin therapy and a decreased risk of atrial fibrillation/flutter in patients with and without chronic kidney disease. Atherosclerosis. 2014;232(1):224–30.
6. Kawahara T, Nishikawa M, Kawahara C, et al. Atorvastatin, etidronate, or both in patients at high risk for atherosclerotic aortic plaques: a randomized, controlled trial. Circulation. 2013;127(23):2327–35.
7. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013;1:CD004816.
8. Tonelli M, Sacks FM, Cole T, Curhan GC, Cholesterol and Recurrent Events Trial Investigators. Effect of pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease. J Am Soc Nephrol. 2003;14(6):1605–13.
9. Stefanec T. The effects of statins on mortality rates among bacteremic patients [letter]. Clin Infect Dis. 2002;34(8):1158.
10. Almog Y, Shefer A, Novack V, et al. Prior statin therapy is associated with a decreased rate of severe sepsis. Circulation. 2004;110(7):880–5.
11. Fassbender K, Simons M, Bergmann C, et al. Simvastatin strongly reduces levels of Alzheimer's disease β-amyloid peptides Aβ42 and Aβ40 in vitro and in vivo. Proc Natl Acad Sci U S A. 2001;98(10):5856–61.
12. Vaughan TB, Bell DS. Statin neuropathy masquerading as diabetic autoimmune polyneuropathy. Diabetes Care. 2005;28(8):2082.
13. Baker SK, Tarnopolsky MA. Statin-associated neuromyotoxicity. Timely Top Med Cardiovasc Dis. 2005;9:E26.
14. Chong PH, Boskovich A, Stevkovic N, et al. Statin-associated peripheral neuropathy: review of the literature. Pharmacotherapy. 2004;24(9):1194–203.
15. Lo YL, Leoh TH, Loh LM, et al. Statin therapy and small fibre neuropathy: a serial electrophysiological study. J Neurol Sci. 2003;208(1–2):105–8.
16. Formaglio M, Vial C. Statin induced neuropathy: myth or reality? [in French]. Rev Neurol (Paris). 2006;162(12):1286–9.
17. West B, Williams CM, Jilbert E, et al. Statin use and peripheral sensory perception: a pilot study. Somatosens Mot Res. 2014;31(2):57–61.
18. Tierney EF, Thurman DJ, Beckles GL, et al. Association of statin use with peripheral neuropathy in the U.S. population 40 years of age or older. J Diabetes. 2013;5(2):207–15.
19. Chung SD, Chen CH, Hung SH et al. A population-based study on the association between statin use and sudden sensorineural hearing loss. Otolaryngol Head Neck Surg (in press).
20. May M, Klein SR. Differential diagnosis of facial nerve palsy. Otolaryngol Clin North Am. 1991;24(3):613–45.
21. Murakami S, Mizobuchi M, Nakashiro Y, et al. Bell palsy and herpes simplex virus: identification of viral DNA in endoneurial fluid and muscle. Ann Intern Med. 1996;124(1 Pt 1):27–30.
22. Schirm J, Mulkens PS. Bell's palsy and herpes simplex virus. APMIS. 1997;105(11):815–23.
23. Hageman G, Ippel PF, Jansen EN, et al. Familial, alternating Bell's palsy with dominant inheritance. Eur Neurol. 1990;30(6):310–3.
24. Kanoh N, Nomura J, Satomi F. Nocturnal onset and development of Bell's palsy. Laryngoscope. 2005;115(1):99–100.
25. Chen Y-C, Yeh H-Y, Wu J-C, et al. Taiwan's National Health Insurance Research Database: administrative health care database as study object in bibliometrics. Scientometrics. 2011;86(2):365–80.
26. Chung SD, Tsai MC, Lin HC, et al. Statin use and clinical outcomes among pneumonia patients. Clin Microbiol Infect. Epub 2014 Jan 23. doi: 10.1111/1469-0691.12544
27. Sheu JJ, Kang JH, Lou HY, et al. Reflux esophagitis and the risk of stroke in young adults: a 1-year population-based follow-up study. Stroke. 2010;41(9):2033–7.
28. Phan T, McLeod G, Pollard JD, et al. Peripheral neuropathy associated with simvastatin. J Neurol Neurosurg Psychiatry. 1995;58(5):625–8.
29. Ziajka PE, Wehmeier T. Peripheral neuropathy and lipid-lowering therapy. South Med J. 1998;91(7):667–8.
30. Buajordet I, Madsen S, Olsen H. Statins—the pattern of adverse effects with empahsis on mental reactions. Data from a national and an international database [in Norwegian]. Tidsskr Nor Laegeforen. 1997;117(22):3210–3.
31. Duits N, Bos FM. Psychiatric disorders with use of simvastatin [in Dutch]. Ned Tijdschr Geneeskd. 1993;137(26):1312–5.
32. Lechleitner M, Hoppichler F, Konwalinka G, et al. Depressive symptoms in hypercholesterolaemic patients treated with pravastatin [letter]. Lancet. 1992;340(8824):910.
33. Tuccori M, Montagnani S, Mantarro S, et al. Neuropsychiatric adverse events associated with statins: epidemiology, pathophysiology, prevention and management. CNS Drugs. 2014;28(3):249–72.
34. Schulz JG, Bösel J, Stoeckel M, et al. HMG-CoA reductase inhibition causes neurite loss by interfering with geranylgeranylpyrophosphate synthesis. J Neurochem. 2004;89(1):24–32.
35. Wood WG, Eckert GP, Igbavboa U, et al. Statins and neuroprotection: a prescription to move the field forward. Ann N Y Acad Sci. 2010;1199:69–76.
36. Xu X, Gao W, Dou S, et al. Simvastatin inhibited the apoptosis of PC12 cells induced by 1-methyl-4-phenylpyridinium ion via inhibiting reactive oxygen species production. Cell Mol Neurobiol. 2013;33(1):69–73.
37. Sim FJ, Lang JK, Ali TA, et al. Statin treatment of adult human glial progenitors induces PPAR gamma-mediated oligodendrocytic differentiation. Glia. 2008;56(9):954–62.
38. Klopfleisch S, Merkler D, Schmitz M, et al. Negative impact of statins on oligodendrocytes and myelin formation in vitro and in vivo. J Neurosci. 2008;28(50):13609–14.
39. Miron VE, Zehntner SP, Kuhlmann T, et al. Statin therapy inhibits remyelination in the central nervous system. Am J Pathol. 2009;174(5):1880–90.

40. Garjani A, Andalib S, Ziaee M, et al. Biphasic effects of atorvastatin on inflammation. Pak J Pharm Sci. 2008;21(2):125–30.
41. Kiener PA, Davis PM, Murray JL, et al. Stimulation of inflammatory responses in vitro and in vivo by lipophilic HMG-CoA reductase inhibitors. Int Immunopharmacol. 2001;1(1):105–18.
42. Mammen AL, Chung T, Christopher-Stine L, et al. Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase in patients with statin-associated autoimmune myopathy. Arthritis Rheum. 2011;63(3):713–21.
43. Rudski L, Rabinovitch MA, Danoff D. Systemic immune reactions to HMG-CoA reductase inhibitors. Report of 4 cases and review of the literature. Medicine (Baltimore). 1998;77(6):378–83.
44. Haroon M, Devlin J. A case of ANCA-associated systemic vasculitis induced by atorvastatin. Clin Rheumatol. 2008;27(Suppl 2):S75–7.
45. Riga M, Kefalidis G, Danielides V. The role of diabetes mellitus in the clinical presentation and prognosis of Bell palsy. J Am Board Fam Med. 2012;25(6):819–26.
46. Paul R, Stassen LF. Transient facial nerve paralysis (Bell's palsy) following administration of hepatitis B recombinant vaccine: a case report. Br Dent J. 2014;216(2):69–71.