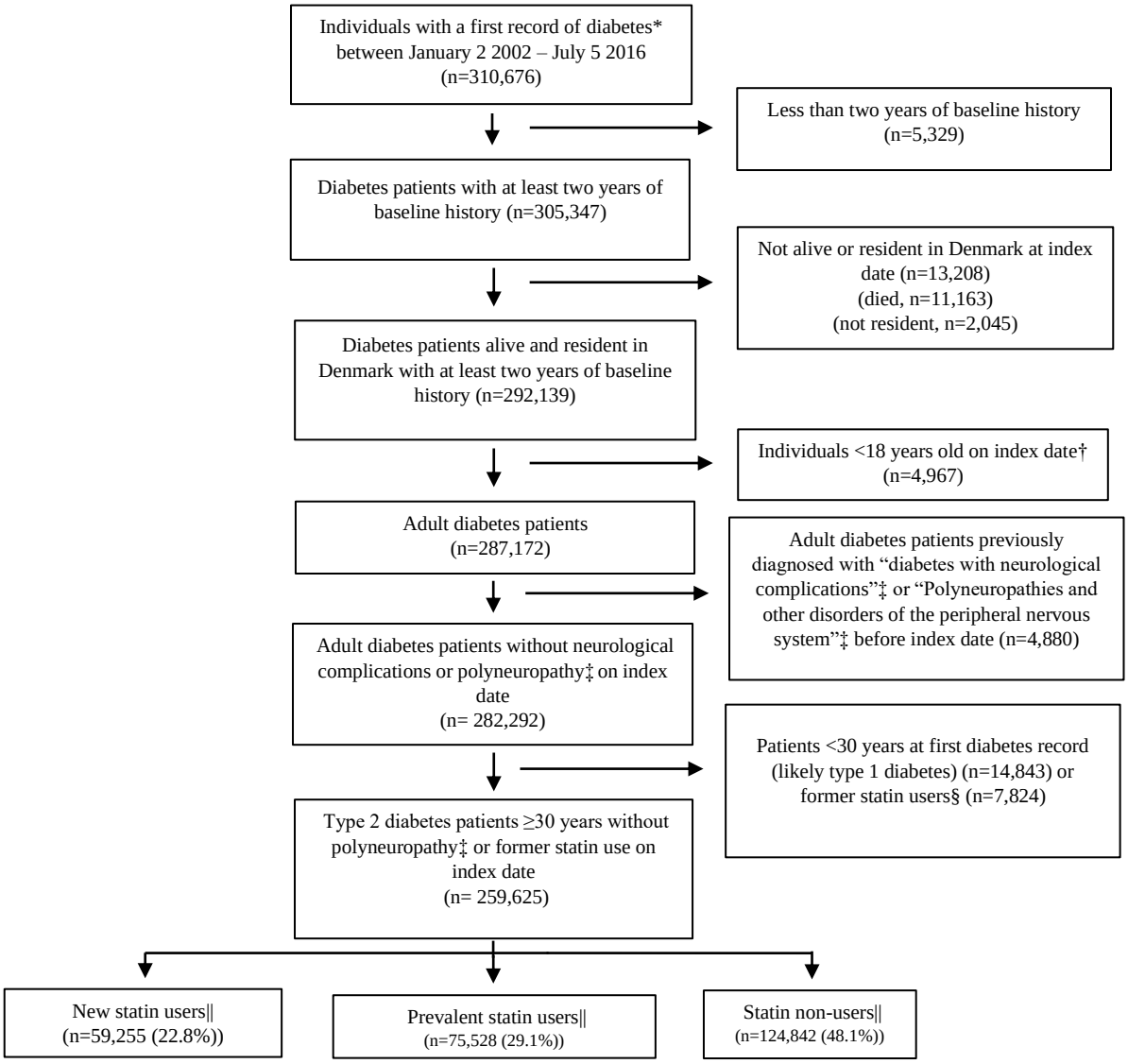
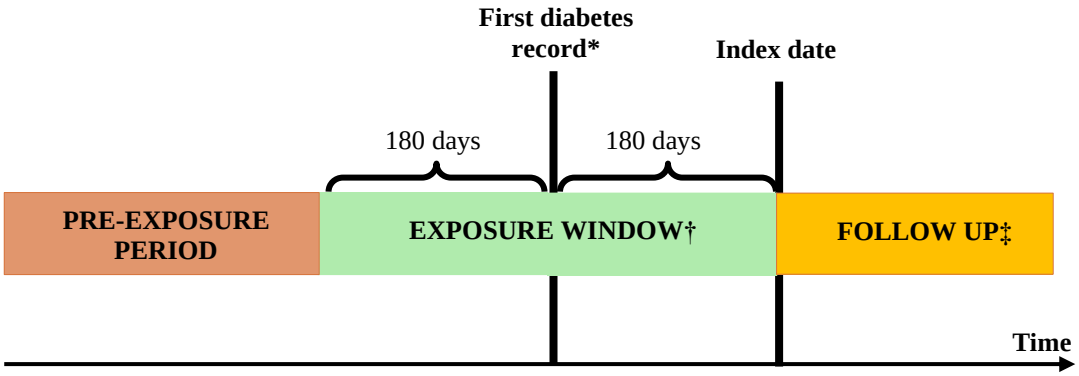
Data supplement

Supplementary Figure 1. Flowchart of the study population.



* Diabetes diagnosis defined as either a first-time hospital inpatient admission or hospital outpatient clinic contact yielding a diagnosis of diabetes at any hospital in Denmark, or a first-time redemption of a prescription for a glucose-lowering drug at any community pharmacy in Denmark from January 2, 2002 to July 5, 2016.
† Index date: 180 days after first diabetes record.
‡ Diabetes patients were excluded if they were diagnosed with DPN (algorithm defined in the main text) or received an ICD-10 diagnosis of "Polyneuropathies and other disorders of the peripheral nervous system" (G60-G64) before the index date (start of follow-up).
§ Former statin users filled their first statin prescription before the exposure window and did not fill additional statin prescription within the exposure window.
‖ New statin users redeemed their first-ever statin prescription within the exposure window (from 180 days before to 180 days after the first record of diabetes). Prevalent statin users filled their first-ever statin prescription before the exposure window and filled at least one prescription for a statin within the exposure window. Statin non-users filled no prescriptions for a statin before their index date.

Supplementary Figure 2. Outline of the study design and exposure definition.



*Diabetes diagnosis defined as either a first-time hospital inpatient admission or hospital outpatient clinic contact yielding a diagnosis of diabetes at any hospital in Denmark, or a first-time redemption of a prescription for a glucose-lowering drug at any community pharmacy in Denmark from January 2, 2002 to July 5, 2016.
† New statin users redeemed their first-ever statin prescription within the exposure window (from 180 days before to 180 days after the first record of diabetes). Prevalent statin users filled their first-ever statin prescription before the exposure window and filled at least one prescription for a statin within the exposure window. Statin non-users filled no prescriptions for a statin before their index date.
‡ The follow-up period started on the index date. Patients were followed until a first-time diabetic polyneuropathy diagnosis, death, emigration, or end of study period (January 1, 2018).

Supplementary Table 1. Codes used to define exposures, outcomes, and baseline covariates.

Variable	ICD-10/procedure/surgical codes	ICD-8 codes	ATC codes
Diabetes definition	ICD-10: E10-E14, O24 [except O24.4], G62.3, H36.0, N08.3		A10
Statin (exposure)			C10AA, C10BA, C10BX
Diabetic polyneuropathy (outcome)	Either (1) a primary or secondary hospital discharge diagnosis of polyneuropathy (G62.9) or diabetic polyneuropathy (G63.2) or (2) a primary discharge diagnosis of diabetes with neurological complications (E10.4, 11.4, 12.4, 13.4, 14.4)		
Other polyneuropathies or disorders of the peripheral nervous system (used in the sample process to exclude those patients with a previous diagnosis of neuropathy before index date)	G60-G64		
Diabetic neuropathy defined by Nielsen *et al*.(1)	E10.4-E13.4		
Smoking (proxy)	Z587, Z720, J40-J44	491, 492	R03BB, R03AC, R03AK, R03CC, R03DB, R03DA, R03AL, R03BA
Obesity	E65, E66, E68	27799	
B12 and other deficiencies	D51, D52, E51 DE52, E53	28119, 261, 262, 26380, 26381, 26699	A11D, B03BA
Alcohol-related disorders	E244, E529, F10, G312, G621, G721, I426, K70, K852, K860, L278A, K292, R780, T51, Z714, Z721, I85, I86.4, I98.2	29109-29199, 30309-30329, 30391, 30399, 979, 57710, 57110, 57109, 45600-45609	N07BB
Hyperlipidemia	E780, E781, E782, E783A, E784, E785, E786, E789	272, 279.00, 279.01	
Hypertension: Defined as: either ≥1 hypertension-related ICD-10/8 code or a prescription for ≥2 different anti-hypertensive drug classes.	I10-I15	401, 402, 403, 404	Adrenergic antihypertensive: C02 Non-loop diuretics and potassium-sparing agents: C03A, C03B, C03D, C03EA Beta-blockers: C07 Ca-antagonists: C08 Inhibition of RAAS-system: C09A, C09B, C09X C09C, C09D
Hypothyroidism	E03, E06	243, 244, 245	H03A
HIV/AIDS	B20-B24, F024	07983, Y4049, Y4149	
Cancer	C00-C99 Z082, Z542, Z092, Z926, K529B1, T808E	14009 - 20909	
Chemotherapy	Procedure code: ZZ0153A3 BWHA		L01, L04
Connective tissue disease	M06, M08, M09, M30-M36, D86, E85, L990	712, 71494, 71495, 71496, 71492, 276, 446, ,13599, 69549,	
Neuropathy-related infections	B15-B19, B20-B24 A368, B022, B279, A692D, A504, A30, A521, A178.	070, 053, 07983, Y4049, Y4149, 013, 072, 075, 032, 030, 095, 096	
Microvascular eye complications	E103, E113, E123, E133, E143, H330, H332, H333, H334, H335, DH36.0, H340, H341, H342, H348, H349 H450, H360 H46, H540, H541, H542, H543, H544, H547, H25, H268, DH281, H282, H269, H430, H431, H438 H439, DI708A	25001, 24901 36101, 36102, 37402/3/4/7/8/9, 377, 37909, 37919	

	Surgical codes: KCKC10, KCKC15, KCKD65		
Microvascular renal complications	E102, E112, DE122, E132, E142, I120, I131, I132, N083, N06, N17, N18, N19, R809. Z992, BJFD	25002, 24902, 403, 404	
Heart Failure	I500, I501, I502, DI503, I508, I509, I110, I130, I132, I420, I426 I427, I428, I429	42709, 42710, 42711, 42719, 42899, 78249	
Ischemic heart disease diagnosis (acute/chronic) including angina pectoris or coronary surgery	I21, I23, I24, T822A, T823D, T823E, I20, I25 Surgical codes: KFNA, KFNB, KFNC, KFND, KFNE, KFNF, KFNG, KFNH, KFNW, KFLF	410, 411, 412, 413, 414, 78209	
Cerebrovascular disease	I60, I61, I62, I63, I64, I65, I66 G45, I67, I68, I69, G80 Surgical codes: KAAL10, KAAL11	432, 433, 434, 435, 436, 437	
Atherosclerotic peripheral vascular disease including peripheral vascular surgery or limb amputation	E105, E115, E125, E135, E145 (A-D) I702, I708 I739, I742, I743, I744, I748, I749, I72 (without DI722) Surgical codes: KPBE, KPBF, KPBH, KPBN, KPBP, KPBQ, KPBW, KPEE, KPEF, KPEH, KPEN, KPEP, KPEQ, KPEU74, KPEU82, KPEU83, KPEU84, KPEW, KPFE, KPFH, KPFN, KPFP, KPFQ, KPFU74, KPFU82, KPFU83, KPFU84, KPFW (KPGH10, KPGH20, KPGH21, KPGH22, KPGH23, KPGH30, KPGH31, KPGH40, KPGH99, KPGU74, KPGU83, KPGU84, KPGU99, KPGW, KPWG I700, I701, I709, I71, I740, I741, I745 N280, K550, K551, I709, I722	25004, 25005, 24904, 24905, 445, 440, 443, [44440-41-42-43-44-48-49-90-99]	
Aortic, renal, and intestinal atherosclerotic disease	Surgical codes: KPAE, KPAF, KPAH, KPAN, KPAP, KPAQ, KPAW99, KPAU74,KPCE, KPCF, KPCH, KPCN, KPCP, KPCQ, KPCW99, KPCW20, KPCU74, KPCU82, KPCU83, KPCU84, KPDE, KPDF, KPDH, KPDN, KPDP, KPDQ, KPDU74, KPDU82, KPDU83, KPDU84, KPDW99, KPDW20	441, [44400-44439]	
Charlson Comorbidity Index diseases not listed as individual diseases above			
Gastrointestinal and liver disease	K22.1, K25-K28, B15.0, B16.0, B16.2, B18, B19.0, K71-K74, K76.0, K76.6 I85	530.91, 530.98 531-534, 573, 070	
Chronic pulmonary disease (excluding COPD)	J45-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3	490, 493, 515-518	
Dementia	F00-F03, F051, G30	290, 29309	
Medications			
Insulin			A10A
Fibrates			C10AB, B04AC
Other-lipid lowering drugs			C10AC B04AD, C10AD B04AE, C10AX B04AX

The look-back period was 10 years prior to the index date for all ICD discharge diagnosis codes, surgical codes, and procedure codes and 1 year for all ATC code

Supplementary Table 2. Extensively adjusted model: Risk of diabetic polyneuropathy associated with statin use.

Statin use	Number at risk	Events	Incidence rate per 1000 person-years (95% CI)	Crude HR (95% CI)	Adjusted HR* (95% CI)	Extensively adjusted HR† (95% CI)
Non-users	124,842	3357	3.8 (3.7-4.0)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
New users	59,255	1675	4.0 (3.8-4.2)	1.07 (1.01-1.14)	1.05 (0.98-1.11)	1.06 (1.00-1.13)
Prevalent users	75,528	1645	3.8 (3.6-3.9)	1.03 (0.97-1.09)	0.97 (0.91-1.04)	0.99 (0.92-1.06)

* The main model was adjusted for age, sex, index year, diagnoses of obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, alcohol-related disorders, and smoking.
† Adjusted for the same baseline variables as in the main model and additionally for other lipid-lowering drugs, disorders causing neuropathy symptoms (B12 and other B vitamin deficiencies, infections causing neuropathy symptoms, hypothyroidism, HIV, chemotherapy treatment, cancer, and connective tissue disease), chronic pulmonary disease, gastrointestinal and liver disease, dementia, number of inpatient hospitalizations, and total number of inpatient hospitalization days as a frailty marker.
Abbreviations: HR: hazard ratio; aHR: adjusted hazard ratio; CI: confidence interval; ref: reference

Supplementary Table 3. The risk of diabetic polyneuropathy in a propensity score matched population* (n=91,922).

	Number at risk	Events	Incidence rate per 1000 person-years (95% CI)	Hazard ratio (95% CI)
Non-users	45,961	1242	4.0 (3.8-4.2)	1.0 (reference)
New users	45,961	1293	3.9 (3.7-4.1)	1.02 (0.93-1.12)

*All baseline covariates listed in Table 1 were used in a logistic regression model to predict the propensity of being a new statin user. After trimming the propensity score, new statin users and statin non-users were matched on their propensity score in a 1:1 ratio with their nearest neighbor and no replacement using 0.2 times the standard deviation of the logit propensity score as the caliper. All covariates were well-balanced after matching.

Supplementary Table 4. Risk of diabetic polyneuropathy for new statin users adjusted for baseline lipid levels.

	Number at risk	Events	Incidence rate per 1000 person-years (95% CI)	Crude HR (95% CI)	Main model adjusted HR* (95% CI)	Main model + baseline lipid† aHR (95% CI)
Non-users	26,845	610	3.5 (3.2-3.8)	1.0 (ref)	1.0 (ref)	1.0 (ref)
New users	16,568	340	3.1 (2.8-3.5)	0.90 (0.79-1.03)	0.94 (0.82-1.08)	0.98 (0.84-1.14)

*Adjusted for age, sex, index year, diagnoses of obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, alcohol-related disorders, and smoking.
† Adjusted for the same baseline variables as in the main model including baseline LDL-c, triglycerides, and HDL-c adjusted as continues variables. The baseline lipid level was defined as the most recent lipid test before statin initiation for new statin users or the most recent lipid test before the index date for statin non-users.
Abbreviations: HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; ref: reference

Supplementary Table 5. Most recent lipid test for new and statin non-users in a geographic subpopulation.

	New statin users, n= 16,568 (38%)	Statin non-users n= 26,845 (62%)	Total
Most recent baseline lipid test*			
LDL-Cholesterol (mmol/L), median (IQR)	3.6 (3.1-4.3)	2.9 (2.4-3.5)	3.2 (2.6-3.8)
HDL-Cholesterol (mmol/L), median (IQR)	1.2 (1.0-1.4)	1.2 (1.0-1.5)	1.2 (1.0-1.4)
Triglycerides (mmol/L), median (IQR)	2.0 (1.4-2.9)	1.5 (1.1-2.2)	1.7 (1.2-2.5)
Most recent lipid test after 1 year of follow-up			
LDL-Cholesterol (mmol/L), median (IQR)	2.0 (1.6-2.6)	2.7 (2.2-3.3)	2.5 (1.9-3.1)
HDL-Cholesterol (mmol/L), median (IQR)	1.2 (1.0-1.5)	1.2 (1.0-1.5)	1.2 (1.0-1.5)
Triglycerides (mmol/L), median (IQR)	1.5 (1.1-2.1)	1.5 (1.1-2.1)	1.5 (1.1-2.1)

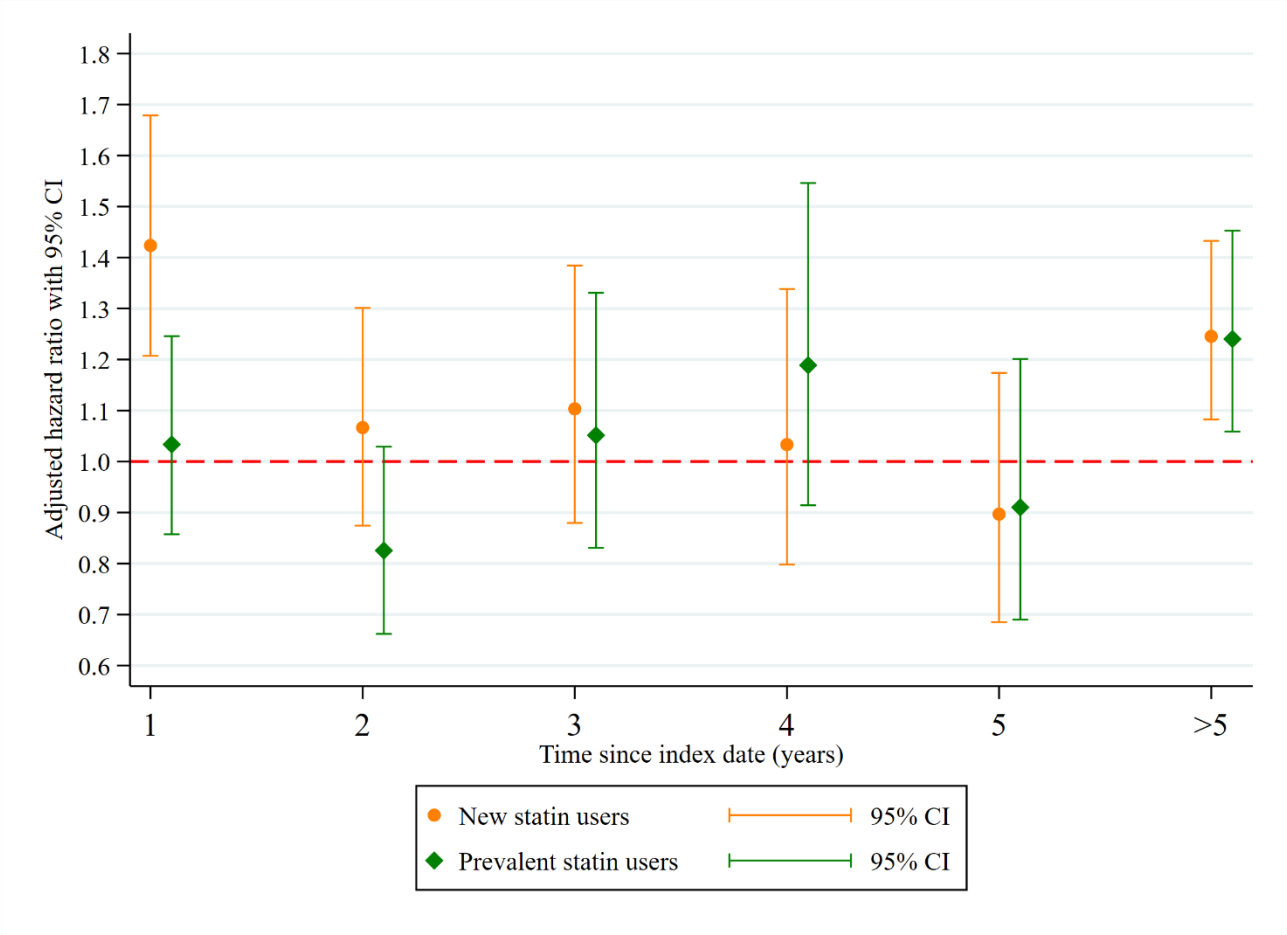
*Within a subpopulation of type 2 diabetes patients from the Northern and the Central Danish regions with available lipid tests before and during follow-up, we identified the most recent lipid test for new statin users before statin initiation and the most recent lipid test before index date for statin non-users. After 1 year of follow-up, we identified the most recent lipid test for both new users and statin non-users to show that statin therapy may have lowered the lipid level compared with the baseline level before the index date. Please see supplementary figure 1 for a description of the sampling for the complete case population.
Abbreviations: LDL-C: low density lipoprotein-cholesterol, HDL-C: high density lipoprotein-cholesterol

Supplementary Table 6. Using on-treatment censoring criteria* to calculate the risk of diabetic polyneuropathy by statin use.

Statin use	Number at risk	Events	Incidence rate per 1000 person-years (95% CI)	Adjusted Hazard ratio† (95% CI)
Non-users	124,842	1,588	3.0 (2.8-3.1)	1.0
New users	59,255	1,158	3.7 (3.5-3.9)	1.17 (1.09-1.27)
Prevalent users	75,528	1,299	3.5 (3.3-3.7)	1.06 (0.98-1.16)

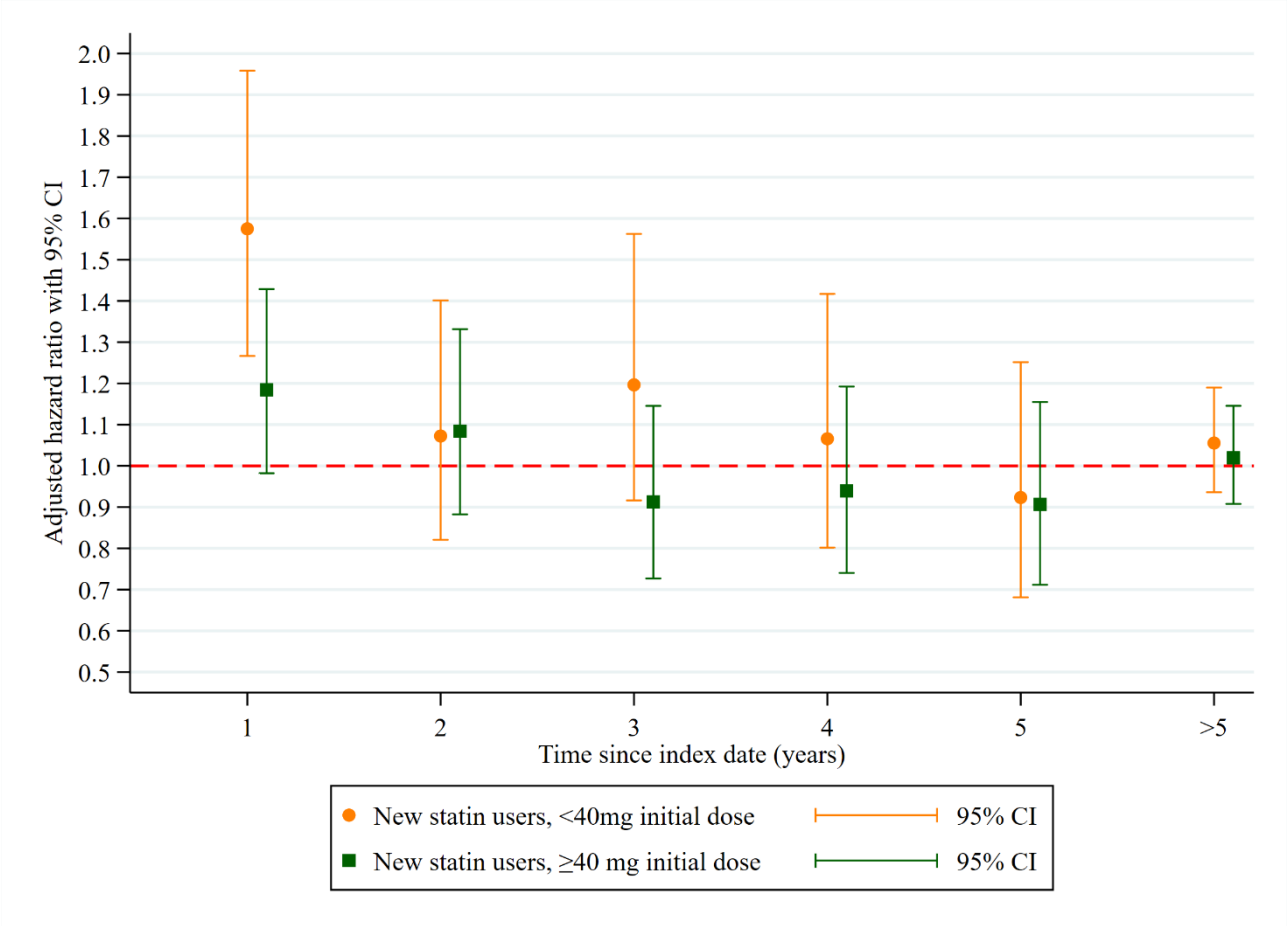
*Besides the censoring criteria (death, emigration, or study end), on-treatment censoring criteria were applied to new and prevalent users and statin non-users. Non-users were censored on the date they initiated statin therapy. Both new and prevalent statin users were censored if statin treatment was discontinued; this was defined as no refilled prescriptions for statins within a period corresponding to the "number of defined daily doses for the previous filled statin prescription" plus a 180-day grace period.
† Adjusted for age, sex, index year, diagnoses of obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, alcohol-related disorders, and smoking.

Supplementary Figure 3. Using on-treatment censoring criteria* to calculate the risk of diabetic polyneuropathy in one-year follow-up intervals by statin use.



*Besides the censoring criteria (death, emigration, or study end), on-treatment censoring criteria were applied to new and prevalent users and statin non-users. Non-users were censored on the date they initiated statin therapy. Both new and prevalent statin users were censored if statin treatment was discontinued; this was defined as no refilled prescriptions for statins within a period corresponding to the "number of defined daily doses for the previous filled statin prescription" plus a 180-day grace period. Patients were followed from 180 days after record of diabetes (index date) until an event of either diabetic polyneuropathy, death, emigration, or study end (Jan 1st 2018) and if the event happened during the one year interval, the patient did not contribute in the next one-year interval.
Adjusted for age, sex, index year, diagnoses of obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, alcohol-related disorders, and smoking.
Abbreviation: CI: confidence interval

Supplementary Figure 4. One-year follow-up intervals: Risk of diabetic polyneuropathy for new statin users stratified on initial statin dose*.



*New statin users had received their first-ever statin prescription within 180 days before to 180 days after first diabetes record. Simvastatin and atorvastatin were the most common represented subtypes. 51,684 (87.2% out of 59,255 total new statin users) filled a simvastatin prescription as their latest filled statin prescription before their index date. 6811 (11.5% out of 59,255 total new statin users) filled an atorvastatin prescription as their latest filled statin prescription before their index date. Since the two groups used similar dosages, we combined the two statin subgroups. The patients were followed from 180 days after their first diabetes record (index date) until a diabetic polyneuropathy diagnosis, death, emigration, or study end (Jan 1st 2018). If an event happened during a given one-year interval, the patient did not contribute to the next one-year interval.
Adjusted for age, sex, index year, diagnoses of obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, alcohol-related disorders, and smoking-related-disorders.

Supplementary Table 7. Association of all-cause mortality with statin use.

	Number at risk	Events	Incidence rate per 1000 person-years (95% CI)	Crude HR (95% CI)	Main model adjusted HR* (95% CI)	Extensively adjusted HR† (95% CI)
Non-users	124,842	33,378	38 (38-39)	1.0 (ref)	1.0 (ref)	1.0 (ref)
New users	59,255	10,461	25 (25-26)	0.67 (0.65-0.68)	0.70 (0.68-0.71)	0.74 (0.72-0.76)
Prevalent users	75,528	16,789	38 (38-39)	1.03 (1.00-1.05)	0.69 (0.68-0.70)	0.77 (0.76-0.79)

*Main model was adjusted for age, sex, index year, diagnoses of obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, alcohol-related disorders, and smoking-related-disorders.
† Adjusted for the same baseline variables as in the main model and additionally for other lipid-lowering drugs, disorders causing neuropathy symptoms (B12 and other B vitamin deficiencies, infections causing neuropathy symptoms, hypothyroidism, HIV, chemotherapy treatment, cancer, and connective tissue disease), chronic pulmonary disease, gastrointestinal and liver disease, dementia, number of inpatient hospitalizations, and total number of inpatient hospitalization days as a frailty marker.
Abbreviations: HR, Hazard ratio; CI, confidence interval; ref, reference

References

1. Nielsen SF, Nordestgaard BG. Statin use before diabetes diagnosis and risk of microvascular disease: a nationwide nested matched study. The lancet Diabetes & endocrinology. 2014;2(11):894-900.