Statin therapy and risk of diabetic polyneuropathy: A population-based cohort study

Research year report

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Abbreviations

DPN	Diabetic polyneuropathy
T2D	type 2 diabetes
T1D	type 1 diabetes
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
CPR	Central personal registration
ICD	International Classification of Diseases
ATC	Anatomical Therapeutic Chemical
HR	Hazard ratio
aHR	Adjusted hazard ratio
PPV	Positive predictive value
DDD	Defined daily dosage
ITT	Intention-to-treat
PS	Propensity score
CI	Confidence interval
LABKA	The Clinical Laboratory Information System
RCT	Randomized controlled clinical

Abstract

Background: Statins possess both anti-inflammatory and neurotoxic effects. Thus, the impact of statin therapy on DPN risk remains unclear.

Methods: We conducted a cohort study including all incident type 2 diabetes (T2D) patients in Denmark from 2002-2016. We categorized T2D patients into new, prevalent and never statin users. DPN was defined by previously validated hospital diagnosis codes. New, prevalent, and never statin users were followed from 180 days after their first diabetes record, using Cox proportional hazard analysis to estimate adjusted hazard ratios (aHR) for the risk DPN.

Results: The study population consisted of 59,255 (23%) new users, 75,528 (29%) prevalent users and 124,842 (48%) never statin users; patients were followed-up for a median of 6.7 years (IQR 3.4-9.6 years). The incidence rate of DPN per 1000 person-years was similar in new users (4.0 events), prevalent users (3.7 events) and never statin users (3.8 events). The aHR for DPN was 1.05 (95% CI, 0.98-1.11) in new users, and 0.97 (95% CI, 0.91-1.04) in prevalent users, as compared with never statin users.

Conclusion: Statin therapy was not associated with risk of subsequent DPN in T2D.

Dansk resumé

Baggrund: Statiner har både anti-inflammatorisk og neurotoksiske effekter. Statiners indflydelse på risikoen for diabetisk polyneuropathy (DPN) er derfor stadig uklar.

Metode: Dette kohortestudie brugte medicinske databaser til at inkludere alle incidente type 2 diabetes (T2D) patienter fra 2002-2016 i Danmark. Patienterne blev inddelt i nye, prævalente og aldrig-brugere af statiner. DPN blev defineret ud fra tidligere validerede diagnosekoder. Nye, prævalente og aldrig-brugere af statiner blev fulgt fra 180 dage efter første diabetes diagnose. Vi brugte en Cox proportional hazard model til at udregne en justeret hazard ratio (HR) for risikoen for at udvikle DPN.

Resultater: Studiepopulationen indeholdt 59.255 (23%) ny brugere, 75.528 (29%) prævalente og 124.842 (48%) aldrig-brugere af statiner. Patienter blev i alt fulgt i 6,7 median år (IQR: 3.4-9.6). Per 1000 person år var DPN incidensraten 4,0 for nye brugere, 3,7 for prævalente brugere og 3,8 for aldrig-brugere af statiner. Den justerede HR for DPN var sammenlignet med aldrig statin brugere; 1,05 (95% CI; 0,98-1,11) for nye brugere og 0,97 (95% CI, 0.91-1.04) for prævalente brugere.

Konklusion: Brug af statiner er ikke associeret med udvikling af DPN hos T2D patienter

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Introduction

Diabetic polyneuropathy (DPN) affects up to 50% of all type 2 diabetes (T2D) patients and associates with increased risk of falls, foot ulcers, amputations, and impaired quality of life.[1,2] Metabolic syndrome components including obesity, hypertension, increased levels of triglycerides, and low levels of high-density lipoprotein cholesterol (HDL-C) are highly prevalent in newly diagnosed T2D patients.[3] These metabolic components have all been associated with increased risk of DPN,[4-6] possibly through reactive oxygen species, local nerve inflammation, and impaired endoneurial capillary function.[1,2,7]

Statins primarily reduce low-density lipoprotein cholesterol (LDL-C) by inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase and further exert pleiotropic functions including endothelial activation, anti-inflammatory, and anti-oxidative effects.[8] These pleiotropic functions have been suggested as potential type 2 diabetic polyneuropathy protective effects.[9] However, animal and observational studies have also associated statin therapy with a neurotoxic effect through inhibition of neural cholesterol reuptake and further inhibition of neural regeneration and rebuilding of peripheral nerves.[10,11]

Findings from observational studies have supported the hypothesis of a DPN protective effect, first in a subgroup analysis of the Australia Fremantle cohort study from 2008, including 395 T2D patients showed a 35% reduced screen-detected diabetic neuropathy risk among statin users.[12] Similar findings were reported in 2014 in a Danish T2D cohort study of 15,679 prevalent statin users and 47,037 non statin users, showing a 34% reduced diabetic neuropathy risk among prevalent statin users.[13] In 2019, a Taiwanese propensity score matched cohort study of more than 35,000 T2D patients suggested a 15% risk reduction of diabetic neuropathy with prevalent versus no use of statins.[14] However, observational studies of non-diabetes patients have found mixed associations suggesting both an increased and no risk of neuropathy when treated with statins.[15,16] In addition, several small (<50 patients) Mexican clinical trials of patients with prevalent DPN have been unable to find any improvement in either neuropathy symptoms score, or nerve fiber conduction for new statin use compared with placebo treatment.[17,18]

Previous observational studies had limitations. The largest study by Nielsen et al.[13] used non-validated neuropathy codes, including codes that may represent events of stroke as recently documented in a

polyneuropathy diagnosis validation study[19], potentially overestimating any statin effect. Also, focusing on prevalent statin users may increase risk of healthy adherer bias.[20]

We therefore conducted a large population-based cohort study of all incident T2D patients in Denmark, applying a new-user design and diagnosis codes of DPN validated by us[19], to clarify whether statin treatment reduces the risk of developing DPN.

Methods

Study design and data setting

This population-based cohort study was based on prospectively collected health and administrative data in Denmark. The Danish National Health service provides free-of-charge health care service and partial reimbursement of prescribed medications to all Danish residents.[21] Since 1968, the Danish Civil Registration System has provided each Danish resident with a unique central personal registration (CPR) number, and recorded information about migration, and vital status allowing individual-level linkage across all Danish registries ensuring complete follow-up.[22]

The Danish National Patient Registry contains information on all non-psychiatric inpatient contacts since 1977 and all emergency department, hospital outpatient contacts, and all psychiatric hospital contacts since 1995. Discharge diagnoses are provided with a primary and secondary code according to International Classification of Diseases (ICD), 8th revision until the end of 1993 and 10th revision thereafter. Surgery codes have been classified according to the Nordic Medico-Statistical Committee since 1996.[23]

The Danish National Prescription Registry holds individual-level data on all prescribed medications filled in Denmark since 1995.[24] Information include patient- and product-related data (e.g. date of dispensing, type of drug according to the Anatomical Therapeutic Chemical [ATC] classification system, strength, defined daily dose (DDD) and amount of drug).

Type 2 diabetes cohort

The study population was obtained from The Danish National Patient Registry and The Danish National Prescription Registry consisting of all first-time incident drug-treated or hospital-diagnosed diabetes patients in Denmark between January 2 2002 and July 5 2016. For patients ≥30 years, T2D was defined as the first

coming of either in- or outpatient hospital discharge diabetes diagnosis, or a filled prescription of a glucose-lowering drug (positive predictive value (PPV) of 97% for discharge diagnosis and 95% for drug prescriptions[25]). Patients who were younger than 30 years at their first diabetes record were excluded as likely type 1 diabetes patients.[26]

We excluded diabetes patients with a previous diagnosis of DPN (algorithm defined below) or a diagnosis of other polyneuropathies and disorders of the peripheral nervous system (G60-G64) before the index date (figure 1). Finally, we excluded diabetes patients with former statin use (defined below) (figure 1-2).

Statin exposure assessment and index date of follow-up start

We obtained complete information on statin use from the Danish National Prescription Registry. Statin use was categorized into new, prevalent, and never use (figure 1-2). The statin exposure assessment window was 180 days before to 180 days after the first incident diabetes record, to allow some time for diagnostic work-up, blood lipid testing, and decision to start statin therapy. The advantages of the new-user approach are related to a mitigation in bias from confounding by healthy adherer effect and immortal time bias by aligning the patients to a specific point in time to start follow up.[20]

New statin users filled their first-ever statin prescription within the 360-day exposure assessment window (figure 2). Prevalent statin users also filled at least one statin prescription within this window but had also filled their first-ever statin prescription before that period. Former statin users filled a statin prescription before the exposure window but did not fill a prescription within the period. Never users did not fill a statin prescription since 1995 (onset of the Danish National Prescription Registry) and up till the end of the exposure window but could fill a statin prescription during follow up. Follow-up was initiated at the end of the exposure window i.e. 180 days after first diabetes record (index date) (figure 2).

Outcome

We identified DPN by using an ICD-10 diagnosis code algorithm recently validated among patients with T2D in the Danish National Patient Registry (PPV = 74%).[19] Accordingly, we defined hospital-diagnosed DPN as either 1) a primary or secondary discharge diagnosis of "Polyneuropathy, unspecified" (G62.9) or

"Diabetic polyneuropathy" (G63.2) or 2) a primary discharge diagnosis of "Diabetes with neurological complications" (E10.4-14.4). We used only primary E-chapter diagnosis codes since secondary E-chapter diagnosis codes often denote stroke or mononeuropathies rather than DPN.[19]

Covariates

We searched the Danish National Patient Registry and the Danish National Prescription Registry for covariates associated with statin therapy and DPN. We obtained information on sex, age, ICD-defined obesity and hyperlipidemia, other lipid-lowering drugs, hypertension and antihypertensive drugs, insulin therapy, macrovascular complications, microvascular complications, and smoking-related disorders.[1,4-6] We also included alcohol-related disorders, HIV/AIDS disease, cancer, chemotherapy treatment, hypothyroidism, B12 and other B-vitamin deficiencies, connective tissue disease, and neuropathy-related infections as other possible causes of neuropathy symptoms.[27] Also, chronic pulmonary disease, gastrointestinal and liver disease, and dementia were included, since these covariates could influence the choice of statin initiation. As a measure of frailty, we included the number of inpatient hospitalizations and inpatient hospitalization days within 1 year before index date. Codes and definitions are available in supplementary table 1.

Statistical analyses

We provided descriptive statistics obtained on index date. We followed all patients from index date until outcome (DPN), death, emigration, or study end (January 1, 2018) whichever came first. We plotted crude cumulative incidence curves for DPN stratified by statin use, treating death as competing risk.[28] In an intention-to-treat analysis, we used Cox proportional-hazard regression to compute crude and adjusted hazard ratios (aHRs) with 95% confidence intervals comparing new and prevalent users with never statin users. The underlying time scale was years after index date. The adjusted Cox regression analysis included age (continuous variable), sex, index year (continuous variable), ICD-defined hyperlipidemia and obesity, insulin use, macrovascular and other microvascular complications, hypertension, smoking-related disorders, and alcohol-related disorders.[1,4-6] The assumption of proportional hazards was verified by visual inspection

of log minus log plots. We stratified the analyses on sex and age groups (30-50 years, 50-70 years, and >70 years) in order to investigate potential effect measure modification.

Sensitivity analyses

We performed 10 sensitivity analyses to investigate confounding, misclassification and compliance problems. First, we performed an extended adjusted analysis including all covariates shown in table 1. Second, to balance confounding factors, we conducted a propensity score matched analysis (see the supplementary section "Conventional confounder adjustments versus Propensity score (PS) matching"). Third, to account for possible misclassification of statin use during follow-up, we conducted an on-treatment analysis (see supplementary section "Intention-to-treat versus on-treatment analytic approach"). Fourth, to reveal a potential protopathic bias, i.e. early symptoms of yet undiagnosed DPN triggering statin initiation, we repeated the analysis while 1) delaying the start of follow-up with 1 year and alternatively 2) stratifying the follow-up period in one-year intervals. Fifth, to examine a possible dose-response association among new statin users, we categorized new users of simvastatin (87% of all new statin users) and atorvastatin (12% of all new statin users) into low dose (<40 mg) and high dose (≥40 mg) statin users. Sixth, we improved the specificity of the new statin user definition by 1) stratifying new statin users by the number of prescriptions within the exposure assessment window (1; 2-3; or ≥4 filled statin prescriptions) and 2) restricting the exposure assessment window to the 180 days after first diabetes record. Seventh, we repeated the analysis using the neuropathy definition from the aforementioned paper by Nielsen et al.[13], and we examined the risk of DPN using E-chapter and G-chapter diagnosis codes separately. Eighth, assuming a DPN outcome misclassification of 26% (diagnostic PPV=74%[19]) and a completeness of polyneuropathy diagnoses as low as 20% when compared with patient questionnaires and clinical examination[29], while assuming both figures to be independent of exposure status, we used the website clepan.com to perform a bias analysis. Ninth, since new statin users may have higher baseline lipid values at diabetes diagnosis than never statin users, we repeated the new statin analysis with additional adjustment for baseline LDL-C, triglyceride, and HDL-C in a geographical subpopulation linkable to the clinical laboratory information system (LABKA) research database (see the supplementary sections "Baseline lipid levels and sampling subpopulation" and "Missing

data and multiple imputation"). Finally, as a positive control in our analysis, we repeated the main analysis using all-cause mortality as an outcome for which statins have a documented effect.

We used Stata version 14.0 (Statacorp, Texas, USA) for all analyses. According to Danish law, ethical approval was not required.

Results

Descriptive results

Between January 2 2002 and July 5 2016, we identified a total of 310,676 incident diabetes patients. 292,139 (94%) were living in Denmark and alive on index date. After applying excluding criteria; 259,625 patients remained of which 59,255 (22.8%) were new users, 75,528 (29.0%) were prevalent users, 124,842 (48.1%) were never statin users (figure 1).

Table 1 provides descriptive data for new, prevalent, and never statin users. 57.6% of all statin users were males. Prevalent statin users had a higher median age (67 years, IQR 60-74) than new (60 years, IQR 52-68) and never (59 years, IQR: 52-71) statin users (table 1) The median time from first statin prescription until index date was 180 days (IQR: 238-180 days) for new statin users and 1823 days (IQR: 1000-2986 days) for prevalent statin users.

Statin use and risk of diabetic polyneuropathy

During follow-up, we identified 6,677 patients with incident DPN, 60,628 patients died, and 1,606 patients emigrated. Total median follow-up time was 6.65 years (IQR 3.39-9.57); 6.75 years (IQR 4.08-9.79) for new users, 5.58 years (IQR 3.07-8.04) for prevalent users, and 6.52 years (IQR 3.30-10.50) for never statin users. The incidence rates of DPN were per 1000 years; 4.0 (95% CI, 3.8-4.2) for new users, 3.7 (95% CI, 3.5-3.9) for prevalent users, and 3.8 (95% CI, 3.7-3.9) for never statin users. New statin users tended to have the highest cumulative incidence of DPN (figure 3).

The aHRs for DPN were 1.05 (95% CI, 0.98-1.11) for new users and 0.97 (95% CI, 0.91-1.04) for prevalent users (table 2). New statin users had an increased risk of DPN during the first year of follow-up (aHR 1.30, 95% CI: 1.12-1.53) disappearing after ≥2 years of follow-up (figure 4 and supplementary table 2). Sex appeared to modify the association, thus, female new users (aHR 1.20 (95% CI, 1.08-1.33)) and

female prevalent users (aHR 1.11 (95% CI, 0.99-1.25)) had a moderately increased risk of DPN (table 2), however, this was, as for the overall cohort, mainly driven by the first year (figure 4 and supplementary table 2). Risk estimates slightly above one were also observed among patients aged 30-50 years with new statin use (aHR 1.21 (95% CI, 1.06-1.39)) and prevalent use (aHR 1.22 (95% CI, 0.98-1.51)) (table 2).

Sensitivity analyses

Additional adjustment for all variables in table 1 did not materially change the association (supplementary table 3).

Using a propensity score matched population yielded similar results (HR 1.02 (95% CI, 0.93-1.12)) (supplementary table 4-6 and figure 1-3).

45% of the never statin users initiated statin therapy during follow-up. Applying an on-treatment analytic approach yielded an increased risk of DPN for new statin users (aHR 1.17 (95% CI, 1.09-1.27)) in the main cohort (supplementary table 7) as well as in the propensity score matched cohort (aHR 1.15 (95% CI, 1.00-1.31)) (supplementary table 7 and figure 4). Using this analysis approach showed similar results for prevalent statin users as in the main analysis (aHR 1.06 (95% CI, 0.98-1.16)) (supplementary table 7 and figure 4).

Starting follow-up one year delayed after the index date moved the estimate towards the null for new statin users (aHR 1.01 (95% CI: 0.95-1.08) and left the estimate for prevalent statin users unchanged (supplementary table 8).

Investigating dose-response relationships of new statin users did not associate low-dose simvastatin users (aHR 1.05 (95% CI, 0.96-1.15) or high-dose simvastatin users (aHR 1.01 (95% CI, 0.94-1.09) with DPN, however, low-dose atorvastatin users associated with an increased risk of DPN (aHR 1.50 (95% CI, 1.24-1.80)); mainly driven by a high first-year risk (supplementary table 9 and figure 5).

Assessing statin prescriptions only 0-180 days after first diabetes record showed similar results as in the main analyses (supplementary table 10-11 and figure 6). Those new statin users filling one statin prescription had increased risk for DPN (aHR 1.16 (95% CI, 1.04-1.28), related to their single prescription typically being filled late in the 360 days exposure window (supplementary figure 7). However, in order to

increase compliance by restricting the analysis to those new statin users filling ≥2 statin prescriptions inside the exposure window did not change the association (supplementary table 10).

Using the outcomes defined by Nielsen *et al.*[13] did not associate prevalent statin use with diabetic neuropathy (aHR 0.96 (95% CI, 0.89-1.03)) (supplementary table 12). For new statin users, the modestly increased risk of DPN was particularly present for the diagnosis of "Diabetes with neurological complications" (E10.4-E14.4), or "Diabetic polyneuropathy" (G62.3) but not "Polyneuropathy, unspecified" (62.9) (supplementary table 12).

Using a bias analysis, investigating the impact of the possible 26% misclassification and down to 20% completeness of the outcome algorithm did not substantially change the estimate for new statin users (supplementary table 13).

Additional adjustment for baseline lipid levels in a geographic subpopulation (n= 55,176 (21.3%)), did not change the estimate for new statin users (aHR 1.04 (95% CI, 0.92-1.19)), even though new statin users had lowered the LDL-C level by more than 50% from baseline within 1 year of follow-up (2.0 mmol/L (IQR: 1.6-2.6)) (supplementary table 14-16 and supplementary figure 8)

Finally, as a positive control, we found that statin users had 25% decreased all-cause mortality, seen both in new and prevalent users and consistent with previous studies[30,31] (supplementary figure 9 and table 17).

Discussion

In this large Danish population-based cohort study, we found no evidence that statin therapy is likely associated with reduced or increased risk of DPN. A moderately increased risk of DPN was observed for new statin users during the first year of follow-up both in intention-to-treat and on-treatment analysis approach.

In contrast to our findings, three previous observational studies have associated statin therapy with a 15-35% risk reduction of diabetic neuropathy.[12-14] There are several possible explanations for these diverging findings: Firstly, previous observational studies used a prevalent statin user definition, we observed that prevalent statin use in general was associated with a lower risk of DPN than new statin use, a finding which

could point to healthy adherer bias.[20] Secondly, in contrast to Nielsen *et al.*[13] and Kang *et al.*[14], we applied a validated outcome algorithm to increase the likelihood of only including true polyneuropathy and not other types of neuropathy, e.g. mononeuropathy[19]. However, changing our outcome definition to the codes used in Nielsen *et al.* did not materially change the association for prevalent users, thus, the different outcome algorithms alone do not explain the different results for prevalent users in Nielsen *et al.* and our study. Thirdly, Nielsen *et al.* initiated follow-up on first diabetes date, which may cause a misclassification of non-users; we showed that 80% of all new statin users initiated statin therapy within 180 days after first diabetes record. According to our data showing a modestly increased early risk of DPN in new statin users, any misclassification of new users as non-users may cause a false protective association when comparing prevalent users with non-users.

The time-varying risk of DPN for new statin users may possibly be explained by a protopathic bias i.e. new statin users may have had early signs of DPN triggering a contact with the health care system and then initiation of statin therapy; to diagnostic work-up time, the diagnosis of DPN may have been first recorded later. Another potential explanation may be pathophysiological, *i.e.*, an early toxic effect of statins. Statins may inhibit cholesterol production by the nerve cell body, creating a need for the neuron to use exogenous cholesterol to maintain peripheral nerve membrane-building and regeneration.[11] Hence, if exogenous LDL-C levels are low due to statin therapy, the growth and regeneration of peripheral nerve axons and consequently nerve conduction may be impaired.[10,11] Consistent with this explanation, a recent longitudinal analysis of the Anglo-Danish-Dutch study cohort found a lower risk of DPN with higher levels of LDL-C.[6] However, the small increased risk of DPN in new statin users in our study was driven by those initiating lower-dose statin (<40 mg), thus, speaking against a toxic effect. Also, the LDL-C levels 1 year after index date was within the recommended level for diabetic patients without cardiovascular risk factors and thus most likely not insufficient for nerve cholesterol supply.

We observed a stronger association of statin use with risk of DPN in females than males. This effect measure modification was not found[13] or tested in previous observational studies[12,14] and it has neither been found in cohort studies of non-diabetes patients.[15,16] This could be explained by either females being more likely to report neuropathy symptoms than males,[32] or females initiating statin therapy at a later metabolic

stage having more components of the metabolic syndrome and then have a worse DPN risk profile compared with male statin initiators.[33,34] However, these findings should be considered as hypothesis generating.

The strength of this cohort study arises from the use of large-scale real-world population-based data from the Danish tax-supported health care system ensuring complete follow up, high generalizability and reduced selection bias. Our study has also limitations. First, the slow progression of neuropathy symptoms and the absence of a disease-specific treatment may lead to general underdiagnosing of DPN and thus to a likely overrepresentation of severe DPN cases in the medical databases. Accuracy of diagnosing DPN are further threatened by other disorders like mononeuropathies stemming from e.g. stroke, causing the same symptoms as DPN.[19] Using the documented positive predictive value of the DPN algorithm, and assuming a low sensitivity (≤20%) with a non-differential misclassification of DPN in a bias analysis moved the risk estimates towards the null, suggesting that our analyses were robust against potential misclassification of DPN. Second, a high proportion (45%) of the baseline never statin users initiated statin therapy during follow-up causing bias towards the null if assumed independent misclassification. We therefore supplemented with an on-treatment analysis resulting in a 17% increased risk of DPN for new statin users, particularly driven by the first year of the follow-up period. Third, as in any observational study, we cannot exclude unmeasured or residual confounding. Although hospital diagnosis codes for obesity have a high positive predictive value, their completeness is low. Misclassification of some obese patients as non-obese would possibly lead to an underestimation of a possible beneficial effect of statins on DPN[35], since obesity is associated both with statin use and DPN risk. We did not have data on exact smoking habits and other potential confounders like socioeconomic status and physical activity, but we were able to adjust for surrogate measures like use of respiratory medicine and chronic obstructive pulmonary disease. Although we used a new-user design to account for healthy adherer bias, healthy user effects may still have affected our results. However, Danish statin users are verified more comorbid and less healthy than non-statin users[36] and adjusting for a wide range of comorbid conditions as well as frailty markers in an extensively adjusted confounder model left the results virtually unchanged.

In conclusion, among newly diagnosed T2D patients, statin therapy was not associated with risk of subsequent DPN. It is likely that statin therapy does not have any positive or negative effect on DPN, and it

should be emphasized for clinicians that statin therapy is highly more important in cardiovascular risk factor management than a potentially discreetly increased risk of DPN among T2D patients.

Supplementary

The following section consists information on methodological and statistical considerations, a discussion of potential systemic and random error, and at last, perspectives and suggestion for future studies within the field of statins and DPN.

Methodological considerations

Choice of study design

This pharmacoepidemiology study of the association between statins and DPN was conducted in a cohort design. The basic principal of a cohort study is to assemble a cohort of people who have not experienced the event of interest before, but could experience the event later, and next classify individuals either as exposed or unexposed within this cohort.[37] This cohort is then observed over time to compare the rates of having the event between the two exposure groups.[37] Different cohort study designs exist: the historical cohort study based on already existing data (sometimes called a retrospective cohort study), and the prospectively designed and conducted cohort study. The retrospective cohort study is cheap and efficient since secondary collected data often are available, compared with prospectively designed cohort studies which require a beforehand prospective data collection phase before data analyses. However, a prospective planning of primary data collection may yield information about confounders that are more accurate collected than in a retrospective register-based cohort study based on secondary collected data.[37] Both cohort study designs can measure multiple outcomes in relation to a single exposure and calculate disease occurrence.[37]

Another study design for consideration is the case-control design. A case-control study identifies patients with the event of interest within a study population (cases) and samples patients without the event from the same study population (controls).[38] There are different subtypes of case-control study designs each representing a way of sampling controls, however, in general, this sampling has to be independent of the exposure status.[37,38] After the sampling, a case-control study categorizes each patient according to their exposure status, before the event, and compares the probability of being exposed between the case and the control group.[37] This study design is therefore recommend 1) when studying many exposures in relation to a single disease, 2) if the outcome is rare and 3) if a long latency period from exposure to outcome is

expected.[38] Compared with a cohort study, the case-control study only obtain ratio measurements, whereas person-time or absolute measures of an outcome are not assessable.[38]

The present study was designed as a cohort study for several reasons. First, a cohort study may be easier to understand for non-epidemiologists: i) exposure groups are assigned at a clear baseline where the distribution of covariates between exposure groups can be assessed, ii) follow-up starts at baseline and runs forward, and iii) outcome is assessed after exposure assessment. Thus, the cohort study may mimic a randomized controlled clinical trial (RCT) setting familiar to clinicians.[37] Secondly, we considered the ability to calculate person-time and report absolute measurements an advantage of the cohort study design instead of only reporting relative measurements (odds ratios) in case-control studies.[37]

A RCT is considered as the golden standard study design when investigating drug associations. However, ethical restrictions, high expenses of doing a RCT, and the requirement of a large sample for statistical precession purposes, hindered the ability to make a RCT.[38,39] Compared with a RCT, which allocate patients to a specific treatment group by randomization, our cohort study used secondary collected data recorded by physicians who selected the treatment for the patients. This major difference in treatment allocation may introduce biases in observational studies. I will pursue a discussion on how the study tried to limit the impact of these biases and further discuss the limitations of this study below.

Study population and period of inclusion

We used population-based pharmacy collected prescription data and in- and outpatient hospital diagnosis to define our study population consisting of all newly diagnosed diabetes patients from January 2 2002 to July 5 2016. See the main article for further details of the sampling process.

To secure a complete inclusion of all T2D patients in Denmark, we used both type 1 and type 2 specific diabetes discharge diagnosis codes and specific type 1 and type 2 antihyperglycemic drugs since both the ICD discharge diagnosis codes and diabetes drugs are considered inaccurate for distinguishing between T1D and T2D.[25,26] Interestingly, we observed that diabetes patients <30 years (n=14,843) mainly consisted of women prescribed metformin, which is used for T2D and not T1D. T2D is rare before age 30 years. This indicates therefore a high proportion of women suffering from polycystic ovary syndrome and not real T2D patients (data not shown). Thus, since proper algorithms to distinguish between T1D, T2D and

gestational diabetes patients have not been developed and validated yet, we excluded those patients with diagnosed diabetes before age 30 to increase the probability of only including T2D patients.[26]

The specific inclusion period was chosen for several reasons. Firstly, statins were introduced in the preventive cardiovascular treatment guideline of diabetes in 2002.[40] In addition, in Denmark from 1996 to 2015, we observed a 62-fold increase of use of statins[41] and our data showed that only a minor proportion of diabetes patients were treated with statins in the late 90's and early 00's. Thus, to increase the likelihood of including statin users and making guideline indications homogeneous within our study population, we excluded patients diagnosed with diabetes before 2002. Secondly, diagnostic activity of DPN may have changed over time with a higher focus on DPN work-up in the recent study years, thus, restricting the study period to the later periods would thereby potentially limit misclassification of DPN (false negative). Thirdly, we used the Laboratory Clinical Information System to obtain information of lipid tests in a subgroup analysis, this database is considered complete from 2002 and onwards.[42].

Statin use and new user design

We used the Danish National Prescription Registry to obtain information about filled prescriptions of statins from the Danish pharmacies. To distinguish new statin use from prevalent statin use, we established an exposure assessment window defined as 180 days before to 180 days after first diabetes record (figure 2) (see the main article for further definition). The following provides information about the advantage of the exposure assessment window and the new user study design.

According to diabetes guidelines, statin therapy is not required for all type 2 diabetes patients. Lifestyle and diet changes may be enough to reach the goal of LDL-C <2.6 mmol/L for T2D patients without prevalent cardiovascular risk factors or < 1.8 mmol/l in T2D patients with cardiovascular risk factors.[43] A diagnosis of diabetes is therefore an indication for having a lipid test performed, which may be followed by initiation of statin therapy. Thus, we would expect that T2D patients often switch from never users to new statin users at time of their first diabetes record and shortly after a diagnostic work period used by the physician to observe if the lipid level changes because of lifestyle interventions. This exposure switch was also observed in our data since 80% of the new statin users had their first statin prescription after their first

diabetes record. Including the first 180 days after first diabetes record as exposure window would thereby reduce misclassification of statin users.

By separating new statin users from prevalent statin users, we tried to limit the risk of healthy adherer bias associated with prevalent drug use which often overemphasized the effect of a drug.[20,44,45] Prevalent or longer-term users are associated with those surviving before study initiation, and may have a higher compliance for taking a drug which relates to higher health literacy and self-care,[44,45] We would therefore a priori expect that prevalent statin users had a lower risk of DPN compared with new statin users caused by healthy adherer bias.

We performed several sensitivity analyses to test the robustness of the statin use definition for both prevalent and new statin users. For example, restricting the exposure assessment window for new statin users to the 180 days after first diabetes record only increased the specificity of being a new statin user. However, this maneuver also caused a decreased sensitivity, since this definition implicate that the new statin users with the longest lasting prescriptions (>180 days) were allocated as prevalent statin users. Another example, we restricted new statin users to those filling at least two prescriptions of statins within the exposure window in order to increase compliant to statin use. Both sensitivity analysis showed similar results as the main results suggesting a robust exposure definition (supplementary table 10). Although altering the baseline exposure definition will test the robustness of the exposure definition, these sensitivity analyses still cannot prevent limitations due to compliance, adherence or to misclassification of statin use during follow-up. These limitations will be discussed in the section of "Intention to treat versus on-treatment analysis" and "limitations".

Diabetic polyneuropathy

The outcome of interest was DPN identified by ICD-10 diagnosis code. Compared to previous studies[12-14], the present study used a validated outcome algorithm to identify patients with DPN. See the main article and supplementary table 1 for a further definition.

A main limitation of identifying definite DPN in both a clinical and research setting is related to the complex and insidious nature of DPN development. DPN is caused by a chronic, slowing progressive loss of small sensory peripheral nerve fibers.[46] 50% of all diabetes patients will develop DPN during the course of

diabetes and it may be asymptomatic in 50% of those with DPN.[1,47] This unawareness by the patient may affect the physician's ability to initiate diagnostic work and hence accurately classify patients with DPN. In addition, the neglect of diagnosing DPN by the physician could stem from the treatment options which are limited to symptomatic pain treatment and not specific DPN treatment.[1,46] Underdiagnosing of DPN is potentially present in the Danish medical databases: Using a non-validated and broader DPN algorithm, a Danish T2D observational study showed a low proportion of patients diagnosed DPN (3.8%) in the DD2 cohort,[29] compared with the prevalence of screen-detected DPN observed at study entry among Danish screen-detected T2D patients (13%).[6] This lack of DPN diagnoses in the medical databases could be explained by either a true lack of DPN patient examinations or by the physicians forgetting to record a diagnosis of DPN in the medical databases causing a reduced sensitivity of our DPN algorithm. Finally, the medical databases could also be overrepresented by severe cases. Thus, our study could have a problem with misclassification of DPN (see information bias for a further discussion)

Baseline lipid levels and sampling the subpopulation

Statin therapy leads to lower levels of LDL-C and plasma triglyceride, and potentially an increase in HDL-C levels.[43] These lipid levels associate with development of DPN and the baseline lipid level may therefore act as a confounder between statin use and DPN.[5] Patients with a high baseline lipid level before statin initiation may theoretically have a worse nerve micro environment associate with a higher risk of DPN. In order to investigate this further, we performed additional analyses in a geographical subpopulation with data on lipid tests available from the clinical laboratory information system (LABKA). LABKA records clinical biochemistry data from primary and secondary health care within the Central and Northern Danish Regions starting in 1997 (see supplementary figure 8 for a flowchart of the subpopulation).[42]

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 index date for never statin users. The difference in baseline lipid definition between new and never statin users required an assumption of a small fluctuation of the lipid level for never statin users back in time i.e. we assumed that baseline lipid level for the never statin users represented the lipid levels within the whole exposure assessment window. In this sensitivity analysis, we

excluded prevalent statin users since these patients often initiated statin therapy before a recorded lipid test in LABKA – the baseline lipid level would therefore be lacking.

Supplementary figure 8 represents the sampling process of the subpopulation with available LABKA data. Within this geographic subpopulation (n=55,176 (21.3%), we found a high completeness of LABKA data: only 533 (0.1%) were unregistered within LABKA. 11.763 (21.3 %) of the subpopulation had missing baseline lipid levels (either missing LDL-C, triglyceride or HDL-C) but available lipid data after index date. As expected, never users more often had a missing baseline lipid value compared with new statin users (9.083 (77.2 %) vs 2680 (22.8 %)). To account for missing data, we used multiple imputation (see statistical considerations for more information).

Statistical considerations

Time-to-event analysis and competing risk

We used a Cox proportional hazards regression model (Cox regression model) to compute the hazard ratio of having DPN for both new and prevalent statin users compared with never statin users (see the main article for further details)

The main statistical assumption of a Cox regression model is a constant proportional hazard ratio between two exposure groups over time.[48] Thus, a single hazard of an exposure group may vary over time, however, the ratio between two groups (e.g. new users vs never statin users) should be constant to fulfill the assumption. There are several ways to check the assumption of a proportional hazard ratio. We used log minus log plots for binary variables and plotted the scaled Schoenfeld residuals against time for continues variables. Using these methods, we concluded that the assumption was fulfilled. Alternatively, stratifying the results on follow-up time may confirm that our model fulfilled the assumption: all 1-year-interval hazard ratios are within the same 95% confidence interval (figure 4).

We had to acknowledge that patients could experience a competing event before diagnosed DPN. A competing event occurs when a patient is at risk of an event other than the main outcome, and if this event occurs, the patient is no longer at risk of experiencing the outcome of interest.[37] Statin therapy associates with risk of death, we therefore assumed that the probability of dying within each exposure group may differ and death may act as a competing event. Thus, patients who died during follow up should be censored,

however, still contribute with risk time until they die. The Cox regression model account for competing risks through considering the risk sets of patients still being followed-up at each time a main event occurs.[48] With other words, patients are withdrawn from the total risk set if they experience a competing event, but they still contribute with risk time until the occurrence of this event. Importantly, regarding competing risk, the naïve Kaplan Meier curve assumes that censored patients are still at risk, however, this assumed independency between two outcomes are not present in our study: the patient cannot experiences DPN if the patient is dead.[49] Thus, instead of using Kaplan Meier curve for graphic incidence plots, we plotted the crude cumulative incidence curves to account for death as a competing event.[28]

Conventional confounder adjustments versus Propensity score (PS) matching

We used the Cox regression model to account for confounding factors through adjustment. We established a main model including all covariates that in the literature particularly have shown to predict DPN risk. However, as an attempt to exclude those patients with potential contraindications for statin therapy, to mimic a study cohort of a RCT and to balance confounding factors[44], we repeated the Cox regression model in a propensity score matched cohort.

In a sensitivity analysis, we used logistic regression including all covariates from table 1 as predictors of being a new statin user to compute the PS. To account for bias stemming from matching in non-overlapping PS intervals, we used an asymmetrical 5%- and 95% percentile PS trimming (outlined in figure A; supplementary figure 1-3 shows the PS distribution in the present study).[50,51] New users and never statin users were then matched on their PS in a 1:1 ratio with nearest-neighbor and no replacement using 0.2 times of the standard deviation of the logit of propensity score as the caliper width.[52] After PS matching, all covariates were well balanced with a standard difference <0.1 (Supplementary table 4-5).

Under the assumption that information on every predictor of new statin use have been sufficient collected, excluding outliers and patients with a contraindication for statins through trimming and matching may cause a higher homogeneous distribution of measured confounding factors, and yield a more unbiased result than using adjustments.[38,50,51] Another advantage, PS matching limits the possibility of overfitting a regression model. When adjusting for covariates, which comprise less than 10 outcomes, the regression model would be heavily influenced by random error and consequently cause an overfitted regression model.

Since PS computation is related to the probability of being a new statin user and not related to the outcome, overfitting may not be a problem when using PS matching to deal with confounding factors.[38] However, using PS matching comes at the cost of a lower generalizability.

The PS matched analysis showed the same result as the main analysis and confirmed that the main result may be robust against unbalanced confounding factors. This finding is in line with simulation studies showing that conventional adjustment and PS analyses often yield the same results.[51]

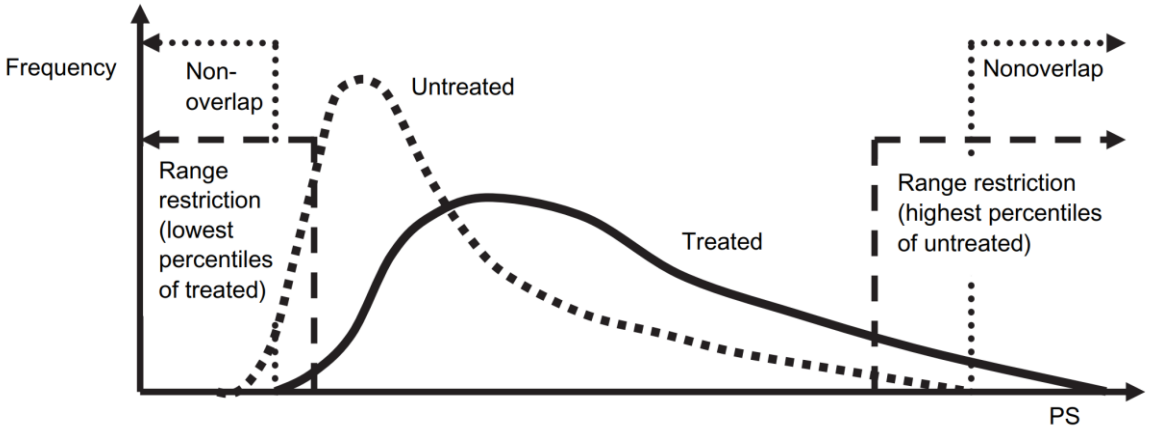

Figure A: Outline of the asymmetric PS range restrictions from Stürmer et al.[50]. Abbreviations: PS: propensity score

Missing data and multiple imputation

Missing data are unavoidable in clinical epidemiology research. Patients with missing data may differ in terms of prognosis and outcome compared with those without missing data and consequently introduce selection bias.[53] Using multiple imputation, to account for missing values, may both increase statistical power and reduce selection bias compared with complete case analysis.[53,54] We used multivariate normal imputation (MVNI) to impute missing values of baseline lipid levels within the geographic subpopulation.

A crucial assumption behind multiple imputation is to determine what category missing data belong: missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR).[53] Multiple imputation assumes that missing data is MAR; the probability that data are missing depends only on observed data and not on unobserved data[53] The assumption of MAR is difficult to test because the association of missing data with unobserved data is unknown, however, including more variables in the multiple imputation model may make the assumption plausible.[53]

For the imputation model, we included all covariates from table 1 since proxies for frailty may predict both missingness and the value of the incomplete covarariate.[55] The outcome indicator and the Nelson-Aalen estimator were additionally included in the imputation model to reduce the probability of a biased estimate when using a Cox regression model.[56] The imputation method assumes that all variables in the model follows a normal distribution; this was achieved by log transforming the lipid values with zero skewness followed by a back-transforming after running the imputation model.[54] The number of imputed dataset was decided by the percentage of incompleteness (21.3%)[53], thus, the number of dataset was 20.

Intention-to-treat (ITT) versus on-treatment analytic approach

The main analysis was an ITT approach. The ITT approach emphasizes that patients are analyzed in the treatment groups, they were assigned to, even though adherence to treatment may differ in the exposure groups during follow-up.[37] ITT is often implemented in observational study analyses to mimic a RCT and estimate "the effect of assigned treatment".[57] However, associations of this approach are often considered conservative since the results may be biased towards the null by an accepted non-differential misclassification of the exposure during follow-up.[57] Since the direction and magnitude of the effect of assigned treatment depends on the adherence pattern, the *true* effect of treatment may be even higher or lower.[57]

We found that 45% of the never statin users initiated statin therapy during follow-up. To minimize the effect of non-adherence and misclassification of exposure status during follow-up, we did an on-treatment analysis. Besides the censoring criteria; death, emigration and study end, the on-treatment analysis included new censoring criteria. Never statin users were censored on the date they initiated statin therapy during follow-up. New and prevalent statin users were both censored on the date their statin therapy was discontinued defined as no refilled statin prescriptions during the time corresponding to the total number of defined daily dosages (DDD) in the last prescribed statin package plus the following 180 days as grace period. DDD is defined as the average drug dosage per day by WHO and found on their website (https://www.whocc.no/). Using these additional criteria, every time a DPN event happened we would compare actually never statin users with actually baseline new or prevalent statin users; only comparing those who adhere to the treatment.

The on-treatment analysis approach is often referred to as "the effect of treatment",[57] and potentially mimics the *ideal*-world better than ITT because of fully adherence to treatment.[58] However, the *real*-world estimate may be in between the ITT and the on-treatment estimate because lacking adherence to treatment is present in the clinic.

A limitation of the on-treatment approach is the risk of introducing selection bias through the prognostic factors that predict adherence to statin use e.g. prognosis of death.[57,58] We would therefore have to adjust for predictors of adherence to limit selection bias. To make a valid non-biased on-treatment analysis, we should use G-methods such as inverse probability weighting by propensity score estimation.[58] This propensity score should be estimated by use of time-varying confounding factors that predict adherence to prevent selection bias in on-treatment analyses.[58] Working with time-varying exposure status and time-varying confounding factors are beyond my statistical capacity which suggest that our on-treatment analysis is influenced by selection bias. However, at least we provided an on-treatment analysis within a propensity score matched cohort, which may overcome some of the selection bias introduced by the additional censoring criteria.

Strengths

The strengths of this cohort study arise firstly from the use of large-scale real-world population-based data from the Danish tax-supported health care system ensuring complete follow-up and hence reduced selection bias, and high generalizability. Secondly, we used a recommend new user study design to account for potential healthy adherer effect. Thirdly, we used different analytic approaches such as both 1) adjustment and propensity score matching and 2) ITT analyses versus on-treatment analyses. Finally, we were able to adjust for baseline lipid levels as important confounders of the association between statin therapy and DPN and use all-cause mortality as a positive control.

Limitations: Systemic and random error

All studies are in danger of both systematic and random error potential affecting the internal validity and hence the external validity. Random error is associated with statistical precision. This precision is validated by looking at the 95% confidence interval of a point estimate rather than the p-value.[38] Random error is often

reduced when the study population becomes larger while the proportion of systematic error remains steady.[38] In this large study, we provided narrow confidence intervals which indicate a low amount of random error. Systematic error includes three commonly described sources of bias in observational studies: selection bias, information bias and confounding.[38] Assuming the amount of random error is close to zero, I will pursue a discussion of the potential systematic errors of this study.

Selection bias

Selection bias arises from the procedure of selecting participants being influenced by factors that associate with the probability of study participation.[38] In order to cause biased relative estimates such factors should both be related to the exposure and the outcome.[38]

In cohort studies, selection bias is usually occurring in the sampling process or the follow-up period. As stated above using the Danish medical databases which prospectively and irrespectively of diseases collects information, only censoring patients on emigration or death, ensured complete follow and thereby reduced selection bias.[21]

On the other side, even though the diabetes identification algorithm had a high positive predictive value, the study population may be underrepresented by T2D patients with risk factors of DPN stemming from the metabolic syndrome (e.g. hypertension or dyslipidemia) but maintain a diet controlled T2D. These patients were not included in our study population. According to the cohort profile of newly diagnosed T2D patients from the DD2 cohort this proportion is 15%, however, the real proportion is probably lower since the proportion from that study is estimated on the date of their first diabetes diagnosis and a large proportion of those having a diet-controlled diabetes will probably initiate anti-hyperglycemia later.[59] In addition, as described above, the younger proportion of our study population may be treated with antihyperglycemic drugs for other reasons than diabetes. We believe that in both cases, the threat of losing representativeness and introduce selection bias is minimal since it is small proportions and the selection is unrelated to the future DPN outcome.

Information bias

Information bias arises when either exposure or outcome is systematically misclassified. This misclassification is divided into non-differential (e.g. the outcome misclassification is independent of the

exposure status) and differential misclassification (e.g. the outcome misclassification depends on the exposure status).[38]

We believe that statin use was accurately classified at baseline since we were able to obtain complete information of redeemed filled statin prescriptions from the Danish National Prescription Registry and since statins are not sold over the counter in Denmark.[41] However, during follow-up we experienced that 45% of the never statin users initiated statin therapy early in the follow-up; an assumed non-differential misclassification causing biased estimates towards the null. Depending on the definition of non-adherence, this problem may be less present in the statin user groups since a Danish study showed a persistence to statin therapy of 84% for new statin users.[60] To prevent exposure misclassification during follow-up, we did an on-treatment analysis (see the intention to treat versus on-treatment for a further discussion) yielding a slightly increased risk for new statin users, mainly driven by an increased first-year risk.

Misclassification of the outcome was also present in our study. As stated above, the neglection of diagnosing DPN causes an underrepresentation of diagnosed DPN in the medical registries and lower the sensitivity of the DPN algorithm (a high proportion of false negative). Accuracy of diagnosing DPN are further threatened by other disorders like mononeuropathies stemming from e.g. stroke causing the same symptoms as DPN.[19] Assuming this misclassification is independently associated with statin treatment may cause a bias towards the null. Using both a low sensitivity (<20%), the present positive predictive value of 74% and assuming that the misclassification is independently associated with statin treatment, yield, in a bias analysis using clepan.com, a similar DPN risk as in the main result.

On the other side, statin users may have a higher probability of being diagnosed with DPN since filling a statin prescription may be a marker of adherence to health care and statin users could therefore be more closely monitored for DPN than the never statin user group. Using this argument would introduce detection bias into the results of our study causing a differential misclassification of DPN.[61] This bias may cause either an overestimation or underestimation of the results depending on the real association between statins and DPN. However, most clinicians are unaware about the relationship between statins and DPN, which may lower the probability that a statin user is more screened for DPN than a never statin user.

Furthermore, indications for DPN-screening are eventually the same for all incident T2D patients within the study population.

Confounding

A confounding factor is associated with both the outcome and the exposure and not an intermediate step of the exposure effect on the outcome.[38] Dealing with confounding can be done in the design phase of the study (matching, restriction and randomization) or in the analyzing phase (standardization, adjusting or stratification). We used both adjusting in the main analysis and a restriction by matching on a propensity score in a sensitivity analysis (see statistical considerations).

Obesity is known as an independent risk factor of DPN[4], associated with statin therapy[36] and not an intermediate step between statin therapy and DPN risk. Hence, obesity is a confounder between statin therapy and DPN. As stated in the main article, misclassification of patients as non-obese patients may underestimate an eventually risk decreasing effect of DPN when treated with statins. Furthermore, due to data availability our results may be biased by unmeasured confounders such as socioeconomic factors and physical activity not considered in the statistical models. Finally, since we only adjusted for confounders at baseline; time-varying confounding may as well be a problem.

Other potential sources of confounding in our study are the healthy user bias (combination of healthy initiator and healthy adherer effect[20]) and confounding by indication/contraindication.[20]

The healthy user bias arises from the preventive effect of patients initiating statin therapy also living a healthier life than non-initiators. This may cause an overestimation of an eventually preventive effect of statins on DPN. Using the never user group as the control group may not be sufficient to account for healthy user bias, thus, to ensure less impact of healthy user bias, we could use an active comparator drug.[44] Such drug has been suggested to be another secondary preventative drug like topical glaucoma medication or thyroid hormone substitution which could cause a mitigation in the amount of healthy user bias.[20,44] However, using such drug would cause a significant decrease in the size of the study cohort and hence reduce power and increase the probability of random error.

The confounding by indication arises if the indication for statin treatment also associate with the risk of DPN, which is likely to cause false adverse associations if not controlled for.[20,62] This is also known as

confounding by contraindication; never statin use may associate with contraindications against statin therapy such as 1) frailty markers, 2) near the end of life or 3) T2D patients who maintain the right lipid level through diet.[62] Table 1 shows that never statin users are both older and younger, more comorbid and associate with higher proportions of frailty markers such as inpatient hospitalizations than both new and prevalent statin users, which could associate with confounding by contraindication. Confounding by contraindication may lead to spurious adverse associations, since never statin users will not experience DPN due to short follow-up time. Likewise, confounding by indication may cause adverse associations of statin use since T2D statin users potentially have a worse prognosis of experiencing DPN due to worse metabolic status at statin initiation compared with never statin users. To overcome confounding by indication, we established a propensity score matched cohort to balance at least measured confounders (see "Conventional confounder adjustments vs Propensity score matching") which yield a point estimate similar to the one in the main analysis. However, the present study could still be biased by unmeasured confounding.

Clinical implications, future studies and perspectives

We are the first to show no association between statin use and risk of DPN. Particularly, new statin users associated with a 30% increased first-year risk of DPN followed by no association the subsequent years compared with never statin users. This could be explained by either protopathic bias or a nerve toxic effect of statins for some patients (see discussion section in the main article). The association was robust in several sensitivity analyses when adjusting for baseline lipid levels, using propensity score matching and on-treatment analyses.

These results emphasize for clinicians that statin therapy alone is not enough to prevent DPN and that previous studies may have been biased by misclassification of exposure status and the outcome. Likely, statins do not associate with any positive or negative effect related to DPN risk. The importance of statin therapy is further highlighted by the reduction in all-cause mortality which emphasizes that T2D patients should still be treated with statins despite a possible discreetly increased risk of DPN.

The overall evidence is still uncertain about the association of statin therapy, lipid levels and risk of DPN and our study rises future research questions: how associate baseline and time-varying lipid levels of

LDL-C, HDL-C and triglycerides with DPN in long-term follow-up studies? How does sex affect the association between statins and DPN? Obesity is an independent risk factor of polyneuropathy[4], what is the effect of statins and risk of polyneuropathy within a confirmed obese cohort? If statins affect the peripheral nerve system, could this effect also be present in the central nerve system and potentially prevent cognitive impairments observed in obese populations?[63]

Interestingly, recent research in mice found that free fatty acids and dyslipidemia induce mitochondrial dysfunction causing impaired nerve conduction. Reversing the diet from a saturated free fatty acid rich diet to a diet of unsaturated free fatty acids yield an improvement in nerve conduction.[64] The role of diet and blood lipid composition are therefore crucial to understand – this could as well associate with the effect of statins and a change in the blood lipid composition.

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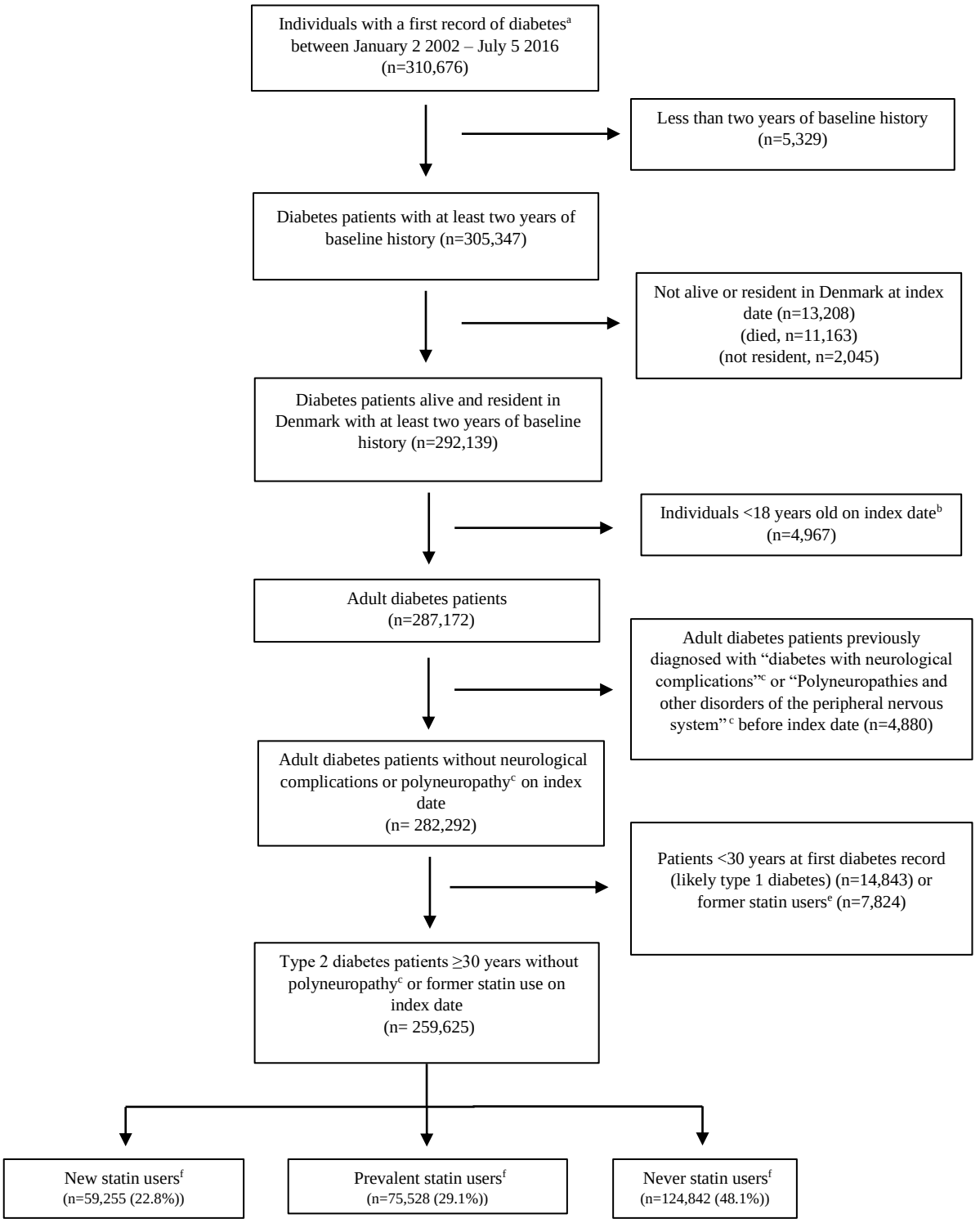
Main tables and figures

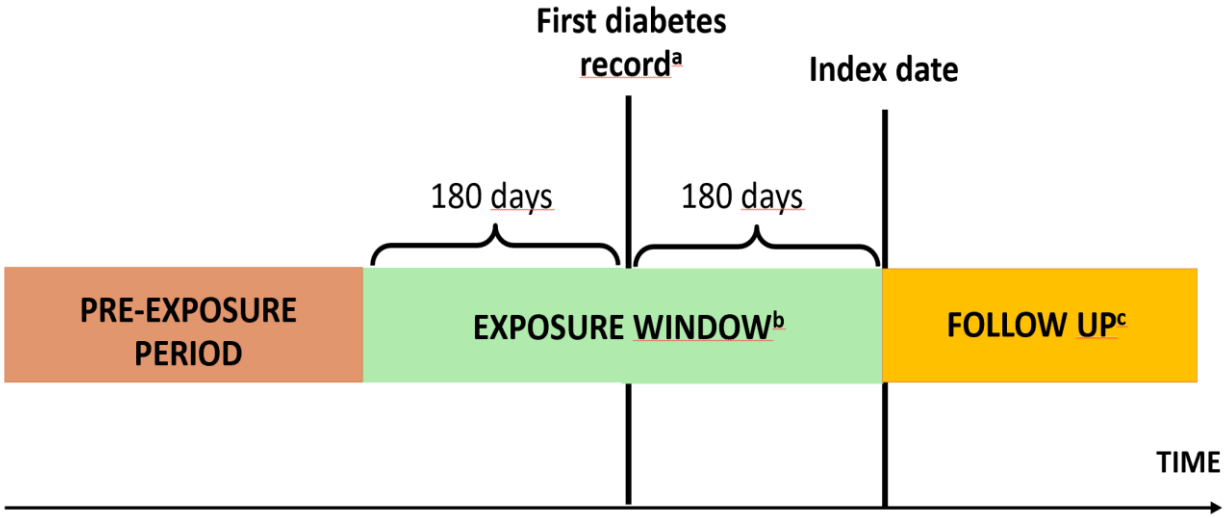
Figure 1. Flowchart of the study population.



[a]Diabetes diagnosis defined as either a first-time filled prescription for a glucose-lowering drug at any community pharmacy in Denmark, or a first-time hospital inpatient admission or hospital outpatient clinic contact with a diagnosis of diabetes at any hospital in Denmark.

[b]Index date: 180 days after first diabetes record.
[c]We excluded diabetes patients with a previous ICD-10 diagnosis of "diabetes with neurological complications" (E10.4-14.4), or ICD-10 diagnosis of "Polyneuropathies and other disorders of the peripheral nervous system" (G60-G64) before the index date of follow-up start. Other disorders of the peripheral nervous system causing polyneuropathy included idiopathic and hereditary polyneuropathy, inflammation induced polyneuropathy, alcohol induces polyneuropathy, medicine induced polyneuropathy, radiation induced polyneuropathy, and unspecific polyneuropathy.
[e]Former statin users had their first statin prescription before the exposure window and no additionally statin prescription inside the exposure window.
[f]New statin users: First-ever filled statin prescription within the exposure window (180 days before and 180 days after first diabetes record). Prevalent statin users had their first-ever filled statin prescription before the exposure window and at least one prescription of statins filled within the exposure window. Never statin users had no prescription of statin before index date.

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



[a]Diabetes diagnosis defined as either a first-time filled prescription for a glucose-lowering drug at any community pharmacy in Denmark, or a first-time hospital inpatient admission or hospital outpatient clinic contact with a diagnosis of diabetes at any hospital in Denmark from January 2 2002 to July 5 2016.
[b]New statin users: First-ever filled statin prescription within the exposure window (180 days before and 180 days after first diabetes record). Prevalent statin users had their first-ever filled statin prescription before the exposure window and at least one prescription of statins filled within the exposure window. Former statin users had their first statin prescription before the exposure window and no additionally statin prescription inside the exposure window. Never statin users had no prescription of statin before index date.
[c]The follow-up period started on index date: Patients were followed until first-time diabetic polyneuropathy diagnosis, death, emigration, or end of study period (Jan 1st 2018).

Table 1. Baseline characteristics of 259,625 incident type 2 diabetes patients by new, prevalent, or never statin use.

Characteristics at start of follow-up 180 days after first diabetes record	New users n (%)	Prevalent users n (%)	Never users n (%)	Total n (%)
Number of participants	**59,255 (22.9)**	**75,528 (29.0)**	**124,842 (48.1)**	**259,625 (100.0)**
Male sex	34,800 (58.7)	42,871 (56.8)	62,234 (49.9)	139,905 (53.9)
Age, median (IQR)	60 (52-68)	67 (60-74)	59 (52-71)	62 (52-72)
Age groups				
30-39	2,301 (3.9)	521 (0.7)	18,172 (14.6)	20,994 (8.1)
40-49	8,995 (15.2)	3,833 (5.1)	19,359 (15.5)	32,187 (12.4)
50-59	16,837 (28.4)	13,903 (18.4)	25,631 (20.5)	56,371 (21.7)
60-69	18,313 (30.9)	26,618 (35.2)	27,121 (21.7)	72,052 (27.8)
70-79	9,739 (16.4)	22,078 (29.2)	19,606 (15.7)	51,423 (19.8)
≥80	3,070 (5.2)	8,575 (11.4)	14,953 (12.0)	26,598 (10.2)
Index year				
2002-2005	10,862 (18.3)	6,980 (9.2)	37,362 (29.9)	55,204 (21.3)
2006-2009	18,969 (32.0)	20,011 (26.5)	34,074 (27.3)	73,054 (28.1)
2010-2013	19,600 (33.1)	31,956 (42.3)	33,160 (26.6)	84,716 (32.6)
2014-2017	9,824 (16.6)	16,581 (22.0)	20,246 (16.2)	46,651 (18.0)
Smoking[a]	8,298 (14.0)	13,916 (18.4)	18,732 (15.0)	40,946 (15.8)
Hypertension[b]	25,650 (43.3)	50,688 (67.1)	40,873 (32.7)	117,211 (45.1)
Hyperlipidemia (ICD-registered)	5,067 (8.6)	17,619 (23.3)	1,186 (1.0)	23,872 (9.2)
Obesity (ICD-registered)	4,789 (8.1)	6,629 (8.8)	12,591 (10.1)	24,009 (9.2)
Microvascular complications	4,855 (8.2)	10,721 (14.2)	12,714 (10.2)	28,290 (10.9)
Eye complications	4,187 (7.1)	8,955 (11.9)	10,662 (8.5)	23,804 (9.2)
Renal complications	788 (1.3)	2,224 (2.9)	2,436 (2.0)	5,448 (2.1)
Macrovascular complications	12,636 (21.3)	34,023 (45.0)	17,051 (13.7)	63,710 (24.5)
Aortic, renal and intestinal atherosclerotic disease	740 (1.2)	3,535 (4.7)	1,015 (0.8)	5,290 (2.0)
Cerebrovascular disease	4,253 (7.2)	9,518 (12.6)	5,778 (4.6)	19,549 (7.5)
Heart failure	2,518 (4.2)	7,195 (9.5)	5,258 (4.2)	14,971 (5.8)
Ischemic heart disease	6,807 (11.5)	23,426 (31.0)	6,954 (5.6)	37,187 (14.3)
Peripheral vascular disease	1,834 (3.1)	5,870 (7.8)	2,918 (2.3)	10,622 (4.1)
Disorders causing neuropathy symptoms				
Alcohol-related disorders	2,142 (3.6)	2,773 (3.7)	6,506 (5.2)	11,421 (4.4)
B12 and B-vitamin deficiencies	1,297 (2.2)	2,713 (3.6)	4,198 (3.4)	8,208 (3.2)
Infections causing neuropathy symptoms[c]	202 (0.3)	166 (0.2)	866 (0.7)	1,234 (0.5)
Hypothyroidism	2,347 (4.0)	4,574 (6.1)	5,687 (4.6)	12,608 (4.9)
HIV/AIDS	39 (0.1)	35 (0.0)	102 (0.1)	176 (0.1)
Chemotherapy treatment	1,450 (2.4)	2,779 (3.7)	5,104 (4.1)	9,333 (3.6)
Cancer[d]	3,491 (5.9)	7,340 (9.7)	10,592 (8.5)	21,423 (8.3)
Connective tissue disease	1,162 (2.0)	2,160 (2.9)	3,636 (2.9)	6,958 (2.7)
Additional comorbidities from the Charlson Comorbity index				
Gastrointestinal and liver disease	1,711 (2.9)	3,133 (4.1)	5,533 (4.4)	10,377 (4.0)
Dementia	301 (0.5)	972 (1.3)	1,894 (1.5)	3,167 (1.2)
Chronic pulmonary disease (excl. COPD)	1,800 (3.0)	2,683 (3.6)	4,780 (3.8)	9,263 (3.6)
Medications				
Insulin use[e]	3,440 (5.8)	2,398 (3.2)	11,651 (9.3)	17,489 (6.7)
Fibrates	251 (0.4)	882 (1.2)	278 (0.2)	1,411 (0.5)
Other lipid lowering agents	200 (0.3)	1,580 (2.1)	225 (0.2)	2,005 (0.8)
Adrenergic antihypertensives	655 (1.1)	1,468 (1.9)	1,261 (1.0)	3,384 (1.3)
Beta blockers	13,883 (23.4)	31,808 (42.1)	20,678 (16.6)	66,369 (25.6)
Calcium channel antagonists	13,380 (22.6)	26,668 (35.3)	20,699 (16.6)	60,747 (23.4)
Non-loop antihypertensives	14,671 (24.8)	25,633 (33.9)	28,895 (23.1)	69,199 (26.7)
RAAS antagonists	32,308 (54.5)	49,473 (65.5)	41,677 (33.4)	123,458 (47.6)
Received inpatient hospital care[f]				
Number of inpatient hospitalizations				
None	41,297 (69.7)	53,778 (71.2)	82,372 (66.0)	177,447 (68.3)
1-2	15,674 (26.5)	17,710 (23.4)	35,195 (28.2)	68,579 (26.4)
>2	2,284 (3.9)	4,040 (5.3)	7,275 (5.8)	13,599 (5.2)
Total number of inpatient hospitalization days				
None	41,297 (69.7)	53,778 (71.2)	82,372 (66.0)	177,447 (68.3)
1-5	8,388 (14.2)	10,628 (14.1)	18,310 (14.7)	37,326 (14.4)
>5	9,570 (16.2)	11,122 (14.7)	24,160 (19.4)	44,852 (17.3)

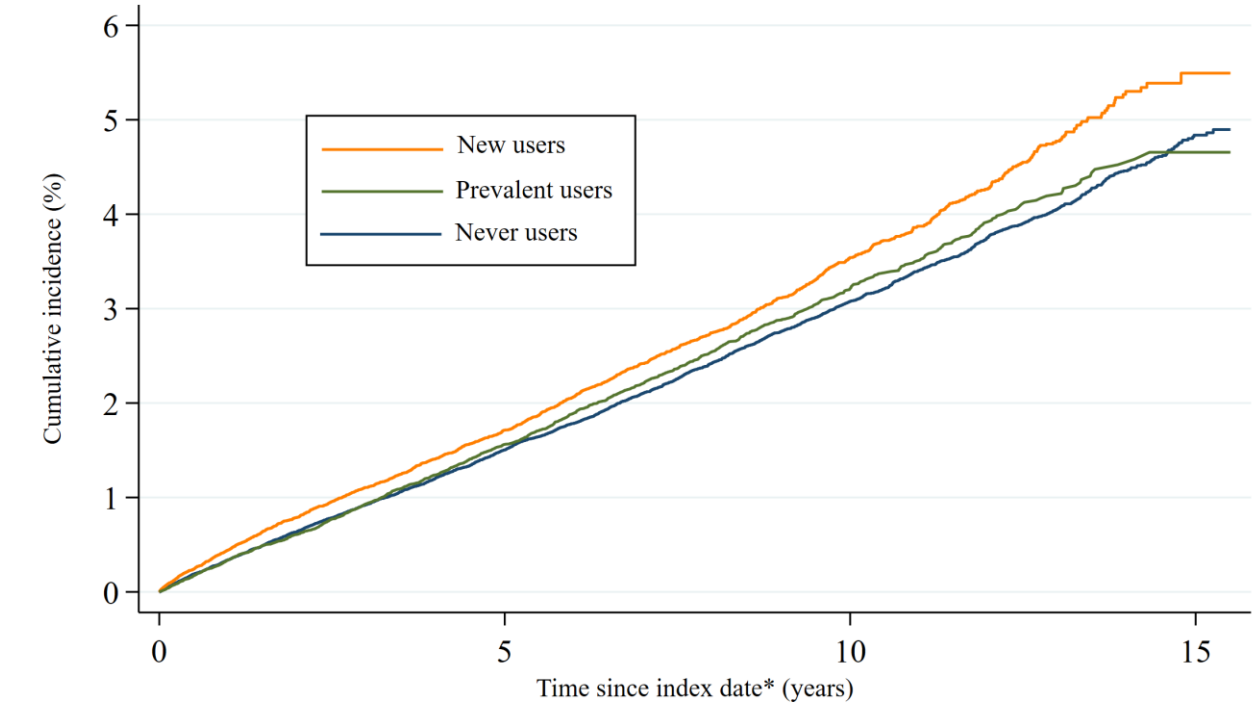
[a]Proxy measure defined by ICD-10/8 diagnosis codes for chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), and medication used for COPD.

[b]Hypertension was defined as either ≥1 ICD-10/8 diagnosis code or use of ≥2 different anti-hypertensive drug-classes prior to the index date.

[c]Hepatitis, herpes zoster, mononucleosis, lyme disease, leprosy, tertiary syphilis, tuberculosis, diphtheria.

[d]All malignant cancers including skin cancers but excluding carcinoma in situ and benign cancers.
[e]≥1 prescription of insulin within 180 days before the index date.
[f]Information about inpatient hospital care was obtained within 1 year prior to index date.

Figure 3.Crude cumulative incidence of diabetic polyneuropathy by statin use treating death as a competing risk.



Number at risk

New users	59,255	39,805	14,055	345
Prevalent users	75,528	43,104	9,366	253
Never users	124,842	77,808	35,079	2,813

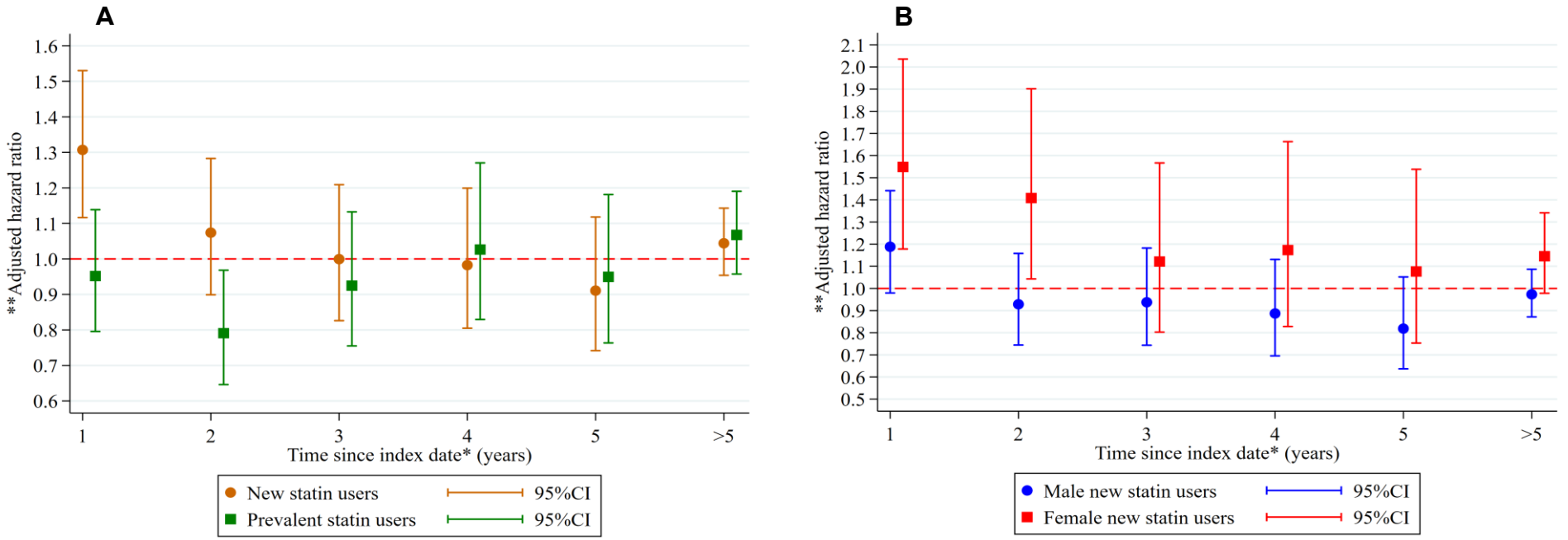
*Type 2 diabetes patients were followed from 180 days after first diabetes record (index date) until first-time diabetic polyneuropathy diagnosis, death, emigration, or study end (January 1st 2018). New statin users had their first-ever prescription of statins within the exposure window (180 days before and after first diabetes record). Prevalent statin users had their first-ever filled statin prescription before the exposure window and at least one additional prescription of statins filled within the exposure window. Never statin users had no prescription of statin before index date.

Table 2. Crude and adjusted hazard ratios of diabetic polyneuropathy risk 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)[a]
Never users (ref.)	124,842	3357	3.8 (3.7-3.9)	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)
Prevalent users	75,528	1645	3.7 (3.5-3.9)	1.03 (0.97-1.09)	0.97 (0.91-1.04)
Stratification on sex and age groups					
Men					
Never users (ref.)	62,334	2221	5.2 (5.0-5.4)	1.0 (ref.)	1.0 (ref.)
New users	34,800	1128	4.7 (4.4-5.0)	0.93 (0.86-0.99)	0.96 (0.89-1.03)
Prevalent users	42,871	1077	4.4 (4.1-4.6)	0.89 (0.83-0.96)	0.90 (0.82-0.98)
Women					
Never users (ref.)	62,608	1136	2.5 (2.4-2.7)	1.0 (ref.)	1.0 (ref.)
New users	24,455	547	3.1 (2.9-3.4)	1.25 (1.13-1.39)	1.20 (1.08-1.33)
Prevalent users	32,657	568	2.9 (2.7-3.2)	1.22 (1.10-1.35)	1.11 (0.99-1.25)
30-49 years					
Never users (ref.)	37,531	823	2.8 (2.6-3.0)	1.0 (ref.)	1.0 (ref.)
New users	11,296	319	3.4 (3.4-4.4)	1.52 (1.34-1.74)	1.21 (1.06-1.39)
Prevalent users	4,354	118	4.1 (3.5-5.0)	1.67 (1.37-2.02)	1.22 (0.98-1.51)
50-70 years					
Never users (ref.)	52,752	1869	4.8 (4.5-5.0)	1.0 (ref.)	1.0 (ref.)
New users	35,150	1060	4.3 (3.9-4.4)	0.89 (0.83-0.97)	0.92 (0.85-0.99)
Prevalent users	40,521	956	3.7 (3.5-4.0)	0.82 (0.76-0.88)	0.82 (0.75-0.90)
>70 years					
Never users (ref.)	34,559	665	3.7 (3.4-3.9)	1.0 (ref.)	1.0 (ref.)
New users	12,809	296	3.7 (3.3-4.2)	1.01 (0.88-1.16)	0.97 (0.84-1.12)
Prevalent users	30,653	571	(3.7-3.4-4.1)	1.03 (0.92-1.16)	0.99 (0.87-1.12)

[a]Adjusted for the main variables that, in the literature, have been shown to predict risk of diabetic polyneuropathy: age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, alcohol-related disorders and smoking-related disorders.
Abbreviations: HR: Hazard ratio, CI: confidence interval, ref.: reference

Figure 4. Risk of diabetic polyneuropathy in 1-year follow-up intervals comparing new and prevalent statin users with never statin users(A) and new statin users stratified on sex(B)



*Patients were followed from 180 days after first diabetes record (index date) until 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. For both figures see supplementary table 2 for more information about numbers at risk, incidence rates and numbers of events during each one-year intervals.

**Adjusted for: age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, alcohol-related disorders and smoking-related disorders.
Abbreviations: CI: confidence interval

Supplementary tables and figures

Supplementary table 1. ICD-8/10 diagnosis codes and ATC codes used to define exposure, outcome 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), and no simultaneous diagnosis of G59.0, G99.0, or G73.0.		
Diabetic neuropathy defined by Nielsen et al.[13]	E10.4-E13.4		
Smoking (proxy)	Z587, Z720, J40-J44	491 492	R03BB, R03AC, R03AK, R03CC, R03DB, R03DA, R03AL, R03BA
Obesity (ICD-registred)	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 (ICD-registred)	E780, E781, E782, E783A, E784, E785, E786, E789	272 279.00, 279.01	
Hypertension: Defined as: either ≥1 hypertension-related ICD-10/8 or a prescription of ≥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 (excluded: carcinoma in situ, benign cancers)	C00-C99	14009 - 20909	
Chemotherapy	Z082, Z542, Z092, Z926, K529B1,T808E Procedure code ZZ0153A3 BWHA		L01, L04

Connective tissue disease	M06, M08, M09, M30-M36 , D86, E85, L990	712, 71494, 71495, 71496, 71492, 71199 446, 13599, 69549., 276, 716,734
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 Surgical codes: KCKC10, KCKC15, KCKD65	25001, 24901 36101/02, 37402/3/4/7/8/9, 377, 37909, 37919
Microvascular renal complications	E102, E112, DE122, E132,E142,I120, I131, I132, N083, N06, N17, N18, N19, R809. Z992, BJFD (dialysis)	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 incl. 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	25004, 25005, 24904, 24905, 445, 440 443, [44440-41-42-43-44-48-49-90-99]
Aortic, renal and intestinal atherosclerotic disease	I700, I701, I709, I71, I740, I741, I745 N280, K550, K551 I709 I722 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 (excluded 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	
Medication			
Insulin:			A10A
Fibrates			C10AB B04AC
Other lipid lowering drugs			C10AC B04AD C10AD B04AE C10AX B04AX

The look back period was 10 years prior to index date for all ICD/surgical/procedure-codes and 1 year for all ATC-codes.

Supplementary table 2. 1-year follow-up intervals: Adjusted[a] risk of diabetic polyneuropathy risk associated with statin use

Statin user status	Number at risk/events	0-1 year follow-up aHR (95% CI)	Number at risk/events	1-2 years follow-up aHR (95% CI)	Number at risk/events	2-3 years follow-up aHR (95% CI)	Number at risk/events	3-4 years follow-up aHR (95% CI)	Number at risk/events	4-5 years follow-up aHR (95% CI)	Number at risk/events	>5 years follow-up aHR (95% CI)
Never users	124,842/425	1.0 (ref.)	118,484/365	1.0 (ref.)	106,558/318	1.0 (ref.)	96,578/301	1.0 (ref.)	87,527/297	1.0 (ref.)	77,808/1,651	1.0 (ref.)
New users	59,255/263	1.30 (1.12-1.53)	57,851/198	1.07 (0.89-1.28)	53,285/172	0.99 (0.82-1.20)	49,016/154	0.98 (0.80-1.20)	44,790/143	0.91 (0.74-1.12)	39,805/745	1.04 (0.95-1.14)
Prevalent users	75,528/255	0.95 (0.79-1.14)	72,655/196	0.79 (0.64-0.96)	64,364/215	0.92 (0.75-1.13)	57,145/188	1.03 (0.83-1.27)	50,675/180	0.95 (0.76-1.18)	43,104/611	1.06 (0.96-1.19)
Stratification on sex												
Men												
Never users	62,234/284	1.0 (ref)	58,763/246	1.0 (ref)	52,559/210	1.0 (ref)	47,418/204	1.0 (ref)	42,821/199	1.0 (ref)	37,968/1,078	1.0 (ref)
New users	34,800/176	1.19 (0.98-1.44)	33,927/126	0.92 (0.74-1.16)	31,164/118	0.93 (0.74-1.18)	28,511/104	0.89 (70-1.13)	25,989/96	0.82 (0.64-1.05)	23,007/508	0.97 (0.87-1.09)
Prevalent users	42,871/168	0.90 (0.72-1.12)	41,115/135	0.77 (0.60-0.99)	36,249/141	0.85 (0.66-1.09)	32,094/120	0.90 (0.69-1.80)	28,367/108	0.80 (0.60-1.04)	24,112/405	0.99 (0.87-1.14)
Women												
Never users	62,608/141	1.0 (ref)	59,721/119	1.0 (ref)	53,999/108	1.0 (ref)	49,160/97	1.0 (ref)	44,706/98	1.0 (ref)	39,840/573	1.0 (ref)
New users	24,455/87	1.54 (1.18-2.04)	23,924/72	1.41 (1.04-1.90)	22,221/54	1.12 (0.80-1.57	20,505/50	1.17 (0.83-1.66)	18,801/47	1.08 (0.75-1.54)	16,798/237	1.15 (0.98-1.34)
Prevalent users	32,657/87	1.06 (0.78-1.44)	31,540/61	0.82 (0.58-1.17)	28,115/74	1.08 (0.77-1.52)	25,051/68	1.29 (0.91-1.84)	22,308/72	1.28 (0.90-1.83)	18,992/206	1.20 (1.00-1.44)

[a]Adjusted for: age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, alcohol-related disorders and smoking-related disorders.
Abbreviations: aHR: adjusted hazard ratio, CI: confidence interval, ref: reference

Supplementary table 3. Extensively adjusted model: Risk of diabetic polyneuropathy risk associated with statin use

Statin use	Number at risk	Events	Incidence rate per 1000 person-years (95% CI)	Crude HR (95% CI)	[a]Adjusted HR (95% CI)	Extensively adjusted[b] HR (95% CI)
Never users (ref.)	124,842	3357	3.8 (3.7-3.9)	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	3.7 (3.5-3.9)	1.03 (0.97-1.09)	0.97 (0.91-1.04)	0.99 (0.92-1.06)
Stratification on sex and age groups						
Men						
Never users (ref.)	62,334	2221	5.2 (5.0-5.4)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
New users	34,800	1128	4.7 (4.4-5.0)	0.93 (0.86-0.99)	0.96 (0.89-1.03)	0.97 (0.90-1.05)
Prevalent users	42,871	1077	4.4 (4.1-4.6)	0.89 (0.83-0.96)	0.90 (0.82-0.98)	0.91 (0.83-0.99)
Women						
Never users (ref.)	62,608	1136	2.5 (2.4-2.7)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
New users	24,455	547	3.1 (2.9-3.4)	1.25 (1.13-1.39)	1.20 (1.08-1.33)	1.13 (1.10-1.36)
Prevalent users	32,657	568	2.9 (2.7-3.2)	1.22 (1.10-1.35)	1.11 (0.99-1.25)	1.13 (1.01-1.27)
30-49 years						
Never users (ref.)	37,531	823	2.8 (2.6-3.0)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
New users	11,296	319	3.4 (3.4-4.4)	1.52 (1.34-1.74)	1.21 (1.06-1.39)	1.24 (1.08-1.43)
Prevalent users	4,354	118	4.1 (3.5-5.0)	1.67 (1.37-2.02)	1.22 (0.98-1.51)	1.23 (0.98-1.53)
50-70 years						
Never users (ref.)	52,752	1869	4.8 (4.5-5.0)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
New users	35,150	1060	4.3 (3.9-4.4)	0.89 (0.83-0.97)	0.92 (0.85-0.99)	0.93 (0.86-1.01)
Prevalent users	40,521	956	3.7 (3.5-4.0)	0.82 (0.76-0.88)	0.82 (0.75-0.90)	0.84 (0.76-0.92)
>70 years						
Never users (ref.)	34,559	665	3.7 (3.4-3.9)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
New users	12,809	296	3.7 (3.3-4.2)	1.01 (0.88-1.16)	0.97 (0.84-1.12)	0.98 (0.85-1.13)
Prevalent users	30,653	571	(3.7-3.4-4.1)	1.03 (0.92-1.16)	0.99 (0.87-1.12)	0.99 (0.87-1.13)

[a]The main model was adjusted for the main variables that, in the literature, have been shown to predict risk of diabetic polyneuropathy: age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, alcohol-related disorders and smoking-related disorders.

[b]Adjusted for the same baseline variables as in the main model and additionally 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 4. Baseline characteristics of new and never statin users <u>before</u> propensity score matching

Characteristics at start of follow-up: 180 days after diabetes diagnosis	**New users** n (%)	**Never users** n (%)	**Standard difference**
Number of participants	**59,255 (32.2%)**	**124,842 (67.8%)**	**Total: 184.097 (100 %)**
Male sex	34,800 (58.7)	62,234 (49.9)	0.179
Age, mean	60.15	59.02	0.080
Index year (mean)	2009.42	2008.61	0.204
Smoking[a]	8,298 (14.0)	18,732 (15.0)	-0.028
Hypertension[b]	25,650 (43.3)	40,873 (32.7)	0.219
Hyperlipidemia (ICD-registered)	5,067 (8.6)	1,186 (1.0)	0.363
Obesity (ICD-registered)	4,789 (8.1)	12,591 (10.1)	0.070
Microvascular complications	4,855 (8.2)	12,714 (10.2)	-0.069
Eye complications	4,187 (7.1)	10,662 (8.5)	-0.055
Renal complications	788 (1.3)	2,436 (2.0)	-0.049
Macrovascular complications	12,636 (21.3)	17,051 (13.7)	0.203
Aortic, renal and intestinal atherosclerotic disease	740 (1.2)	1,015 (0.8)	0.043
Cerebrovascular disease	4,253 (7.2)	5,778 (4.6)	0.108
Heart failure	2,518 (4.2)	5,258 (4.2)	0.002
Ischemic heart disease	6,807 (11.5)	6,954 (5.6)	0.213
Peripheral vascular disease	1,834 (3.1)	2,918 (2.3)	0.047
Disorders causing neuropathy symptoms			
Alcohol-related disorders	2,142 (3.6)	6,506 (5.2)	-0.078
B12 and B-vitamin deficiencies	1,297 (2.2)	4,198 (3.4)	-0.071
Infections causing neuropathy symptoms[c]	202 (0.3)	866 (0.7)	-0.049
Hypothyroidism	2,347 (4.0)	5,687 (4.6)	-0.029
HIV/AIDS	39 (0.1)	102 (0.1)	-0.006
Chemotherapy	1,450 (2.4)	5,104 (4.1)	-0.092
Cancer[d]	3,491 (5.9)	10,592 (8.5)	-0.101
Connective tissue disease	1,162 (2.0)	3,636 (2.9)	-0.062
Additional comorbidities within the Charlson Comorbity index			
Gastrointestinal and liver disease	1,711 (2.9)	5,533 (4.4)	-0.082
Dementia	301 (0.5)	1,894 (1.5)	-0.101
Chronic pulmonary disease (excl. COPD)	1,800 (3.0)	4,780 (3.8)	-0.043
Medications			
Insulin use[e]	3,440 (5.8)	11,651 (9.3)	-0.134
Fibrates	251 (0.4)	278 (0.2)	0.035
Other lipid lowering agents	200 (0.3)	225 (0.2)	0.031
Adrenergic antihypertensives	655 (1.1)	1,261 (1.0)	0.009
Beta blockers	13,883 (23.4)	20,678 (16.6)	0.172
Calcium channel antagonists	13,380 (22.6)	20,699 (16.6)	0.152
Non-loop antihypertensives	14,671 (24.8)	28,895 (23.1)	0.038
RAAS antagonists	32,308 (54.5)	41,677 (33.4)	0.436
Received inpatient hospital care[f]			
Number of inpatient hospitalizations (mean)	1.34	1.40	-0.099
Total number of inpatient hospitalization days (mean)	0.77	0.87	-0.087

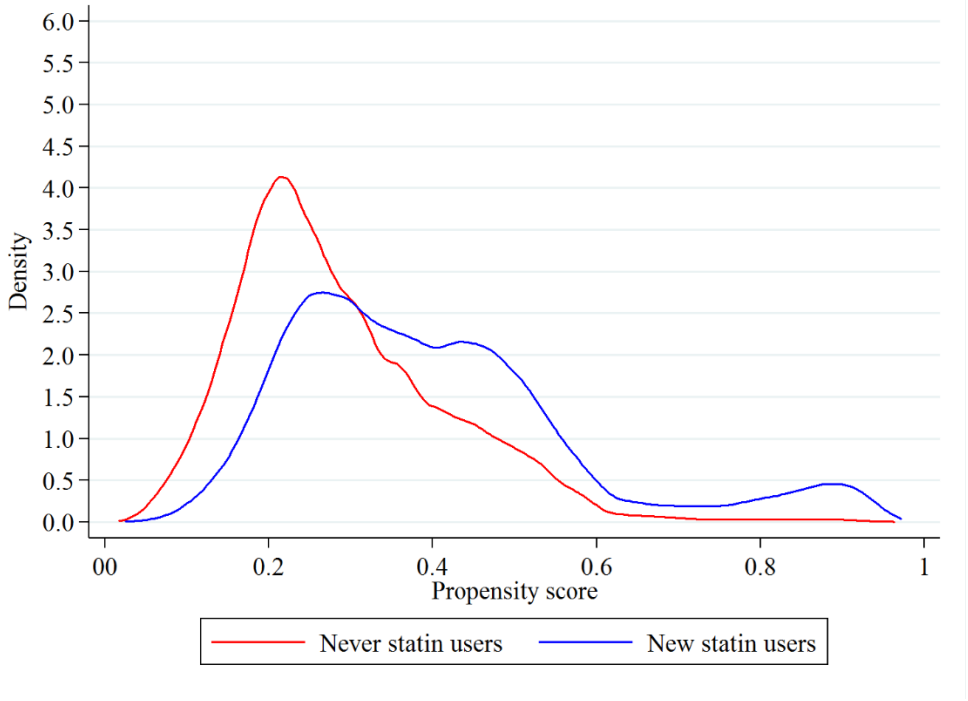
[a]Proxy measure defined by ICD-10/8 diagnosis codes for chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), and medication used for COPD.
[b]Hypertension was defined as either ≥1 ICD-10/8 diagnosis code or use of ≥2 different anti-hypertensive drug-classes prior to the index date.
[c]Hepatitis, herpes zoster, mononucleosis, lyme disease, leprosy, tertiary syphilis, tuberculosis, diphtheria.
[d]All malignant cancers including skin cancers but excluding carcinoma in situ and benign cancers.
[e]≥1 prescription of insulin within 180 days before the index date.
[f]Information about inpatient hospital care was obtained within 1 year prior to index date

Supplementary table 5. Baseline characteristics of new and never statin users after trimming and propensity score matching[a]

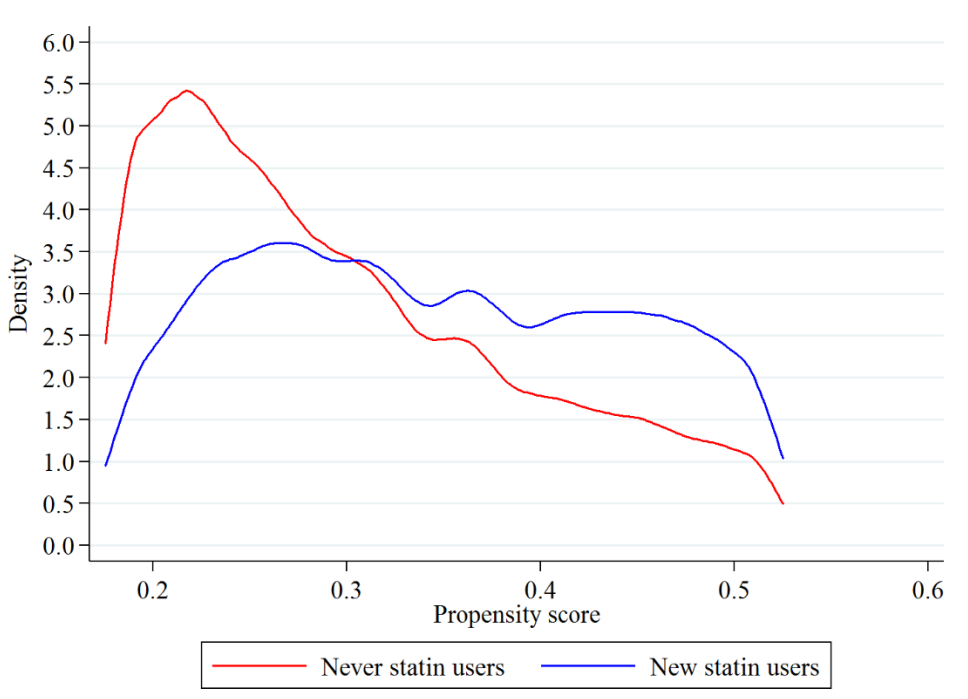
Characteristics at start of follow-up: 180 days after diabetes diagnosis	**New users** n (%)	**Never users** n (%)	**Standard difference**
Number of participants	**45,961 (50%)**	**45,961 (50%)**	**Total: 91,922 (100%)**
Male sex	26,124 (56.8)	26,97 (58.7)	-0.037
Age, mean	59.73	60.81	-0.084
Index year, mean	2009.35	2009.41	-0.015
Smoking[b]	6,173 (13.4)	6,315 (13.7)	-0.009
Hypertension[c]	18,085 (39.3)	18,095 (39.4)	-0.000
Hyperlipidemia (ICD-registered)	53 (0.1)	48 (0.1)	0.003
Obesity (ICD-registered)	3,211 (7.0)	3,023 (6.6)	0.016
Microvascular complications	3,446 (7.5)	3,518 (7.7)	-0.006
Eye complications	3,073 (6.7)	3,11 (6.8)	-0.003
Renal complications	448 (1.0)	487 (1.1)	-0.008
Macrovascular complications	6,315 (13.7)	6,202 (13.5)	0.007
Aortic, renal and intestinal atherosclerotic disease	399 (0.9)	410 (0.9)	-0.003
Cerebrovascular disease	2,155 (4.7)	2,123 (4.6)	0.003
Heart failure	1,597 (3.5)	1,606 (3.5)	-0.001
Ischemic heart disease	2,774 (6.0)	2,721 (5.9)	0.005
Peripheral vascular disease	1,1 (2.4)	1,036 (2.3)	0.009
Disorders causing neuropathy symptoms			
Alcohol-related disorders	1,547 (3.4)	1,415 (3.1)	0.016
B12 and B-vitamin deficiencies	907 (2.0)	853 (1.9)	0.009
Infections causing neuropathy symptoms[d]	115 (0.3)	107 (0.2)	0.004
Hypothyroidism	1,792 (3.9)	1,836 (4.0)	-0.005
HIV/AIDS	31 (0.1)	27 (0.1)	0.003
Chemotherapy	949 (2.1)	987 (2.1)	-0.006
Cancer[e]	2,481 (5.4)	2,497 (5.4)	-0.002
Connective tissue disease	724 (1.6)	813 (1.8)	-0.015
Additional comorbidities within the Charlson Comorbity index			
Gastrointestinal and liver disease	1,099 (2.4)	1,068 (2.3)	0.004
Dementia	115 (0.3)	116 (0.3)	-0.000
Chronic pulmonary disease (excl. COPD)	1,282 (2.8)	1,303 (2.8)	-0.003
Medications			
Insulin use[f]	2,216 (4.8)	2,004 (4.4)	0.022
Fibrates	151 (0.3)	104 (0.2)	0.019
Other lipid lowering agents	89 (0.2)	84 (0.2)	0.003
Adrenergic antihypertensives	476 (1.0)	453 (1.0)	0.005
Beta blockers	8,731 (19.0)	8,612 (18.7)	0.007
Calcium channel antagonists	9,562 (20.8)	9,41 (20.5)	0.008
Non-loop antihypertensives	11,004 (23.9)	11,123 (24.2)	-0.006
RAAS antagonists	23,733 (51.6)	23,243 (50.6)	0.021
Received inpatient hospital care[g]			
Number of inpatient hospitalizations (mean)	1.25	1.25	0.012
Total number of inpatient hospitalization days (mean)	0.57	0.56	0.007

[a]All baseline covariates from the main 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 never statin users were matched on their propensity score in a 1:1 ratio with nearest-neighbor and no replacement using 0.2 times of the standard deviation of the logit propensity score as the caliper. We considered a standard difference <0.1 as well-balanced. See the supplementary section "Conventional confounder adjustments versus Propensity score (PS) matching" for more information.
[b]Proxy measure defined by ICD-10/8 diagnosis codes for chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), and medication used for COPD.
[c]Hypertension was defined as either ≥1 ICD-10/8 diagnosis code or use of ≥2 different anti-hypertensive drug-classes prior to the index date.
[d]Hepatitis, herpes zoster, mononucleosis, lyme disease, leprosy, tertiary syphilis, tuberculosis, diphtheria.
[e]All malignant cancers including skin cancers but excluding carcinoma in situ and benign cancers.
[e]≥1 prescription of insulin within 180 days before the index date.
[g]Information about inpatient hospital care was obtained within 1 year prior to index date.

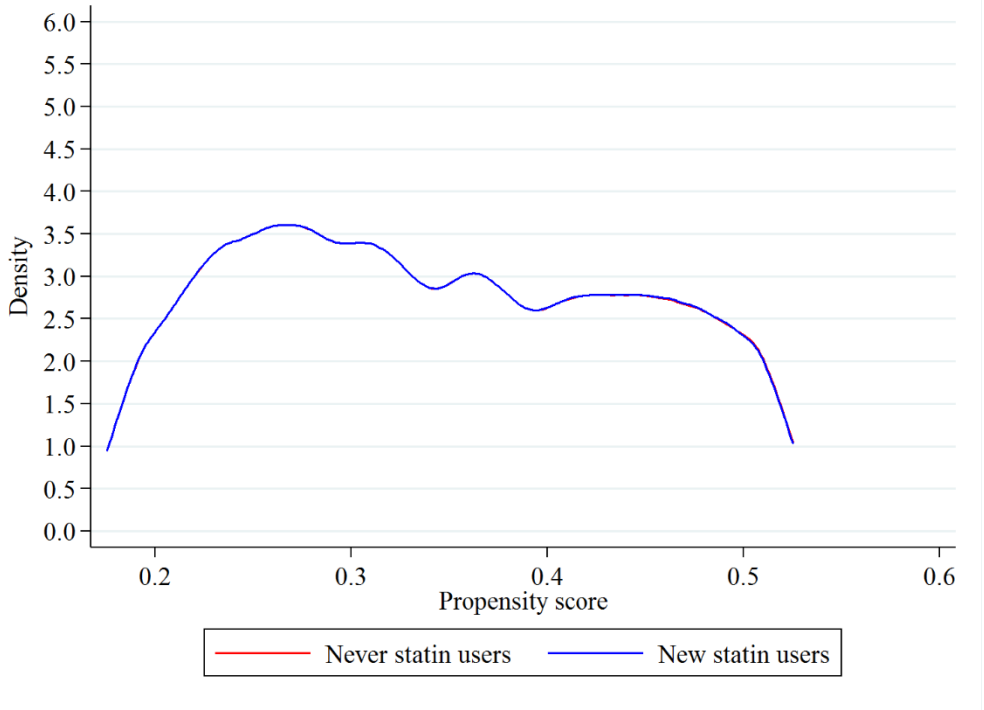
Supplementary figure 1. The distribution of the propensity score for new and never statin users before trimming and matching



Supplementary figure 2. The distribution of the propensity score for new and never statin users after asymmetrical trimming before matching



Supplementary figure 3. The distribution of the propensity score for new and never statin users after trimming and after propensity score matching



Supplementary table 6. The risk of diabetic polyneuropathy in a propensity score matched population[a] (n=91,922)

	Number at risk	Events	Incidence rate per 1000 year (95% CI)	Hazard ratio (95% CI)
Never 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)

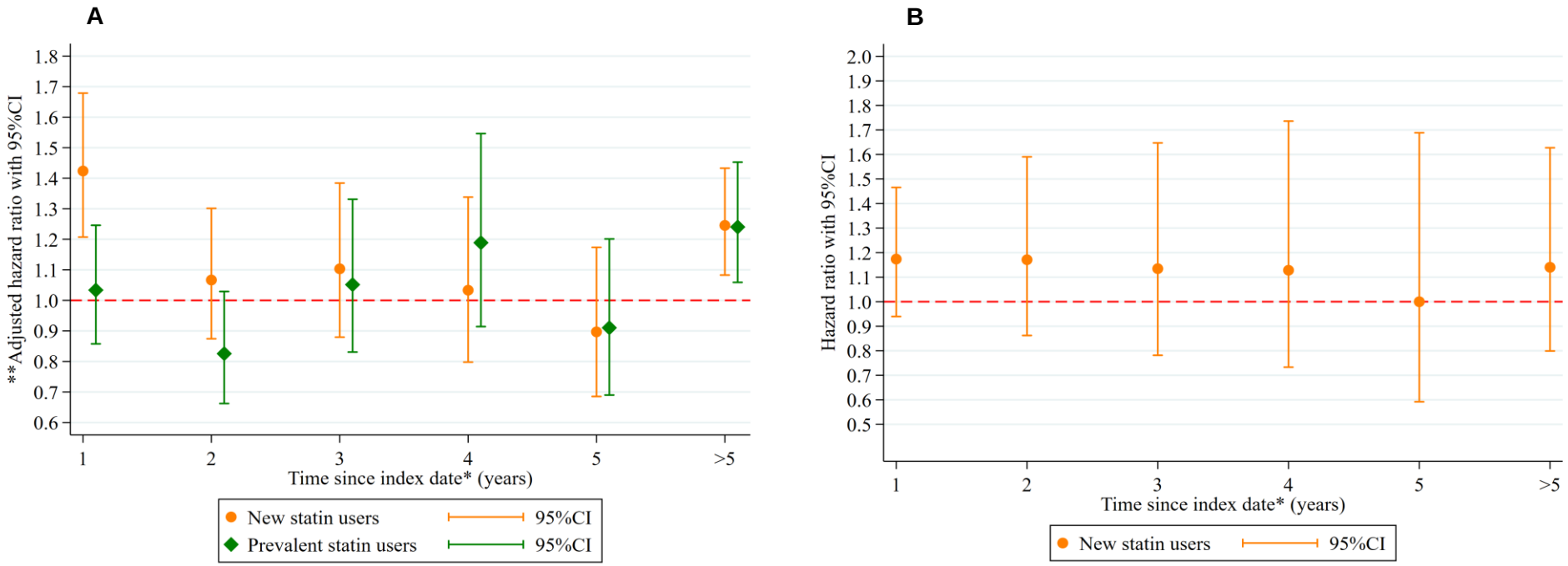
[a]All baseline covariates from table 1 were used in a logistic regression model to predict the propensity of being a new statin user. After trimming the propensity score, new statin users and never statin users were matched on their propensity score in a 1:1 ratio with nearest-neighbor and no replacement using 0.2 times of the standard deviation of the logit propensity score as the caliper. See the supplementary section "Conventional confounder adjustments versus Propensity score (PS) matching" for more information".
Abbreviations: CI: confidence interval

Supplementary table 7. Using on-treatment censoring criteria[a]: The risk of diabetic polyneuropathy by statin use within the main study population and within the propensity score matched cohort

Statin use	Number at risk	Events	Incidence rate per 1000 person-years (95% CI)	[b]Adjusted Hazard ratio (95% CI)
The main study population				
Never users	124,842	1,588	3.0 (2.8-3.1)	1.0 (reference)
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)
The propensity scores matched cohort[c]				
Never users	45,961	594	3.4 (3.1-3.7)	1.0 (reference)
New users	45,961	884	3.6 (3.4-3.9)	1.15 (1.00-1.31)

[a]Besides the censoring criteria; death, emigration or study end, on-treatment censoring criteria included censoring criteria for new and prevalent users and never statin users, respectively. Never statin users were censored on the date they initiate statin therapy. Both new and prevalent statin users were censored if statin treatment was discontinued defined as no refilled prescriptions of statins within a period corresponding to "number of defined daily dose for the previous filled statin prescription" plus a 180-day grace period.
[b]Adjusted for: age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, alcohol-related disorders and smoking-related disorders.
[c]All baseline covariates from 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 never statin users were matched on their propensity score in a 1:1 ratio with nearest-neighbor and no replacement using 0.2 times of the standard deviation of the logit propensity score as the caliper. See supplementary section "Conventional confounder adjustments versus Propensity score (PS) matching" for more information.
Abbreviations: CI: confidence interval

Supplementary figure 4. Using on-treatment censoring criteria[a]: The risk of diabetic polyneuropathy in one-year follow-up intervals by statin use within the main study population (A) and the propensity score matched cohort[b] (B)



[a]Besides the censoring criteria; death, emigration or study end, on-treatment censoring criteria included censoring criteria for new and prevalent users and never statin users, respectively. Never statin users were censored on the date they initiate statin therapy. Both new and prevalent statin users were censored if statin treatment was discontinued defined as no refilled prescriptions of statins within a period corresponding to "number of defined daily dose for the previous filled statin prescription" plus a 180-day grace period.
[b]All baseline covariates from 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 never statin users were matched on their propensity score in a 1:1 ratio with nearest-neighbor and no replacement using 0.2 times of the standard deviation of the logit propensity score as the caliper (n=91,922). See supplementary section "Conventional confounder adjustments versus Propensity score (PS) matching" for more information.
*Patients were followed from 180 days after first diabetes record (index date).
**Adjusted for: age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, alcohol-related disorders and smoking-related disorders. Abbreviations: CI: confidence interval

Supplementary table 8. Following new, prevalent and never statin users from a delayed start of follow-up 1 year after index date[a]

Statin user status	Number at risk	Events	Incidence rate per 1000 person-years (95% CI))	Crude HR (95% CI)	Adjusted HR[b] (95% CI)
Never users	118,484	2,932	3.9 (3.8-4.0)	1.0 (ref.)	1.0 (ref.)
New users	57,851	1,412	4.0 (3.8-4.2)	1.04 (0.98-1.11)	1.01 (0.95-1.08)
Prevalent users	72,655	1,390	3.8 (3.6-4.0)	1.04 (0.98-1.11)	0.97 (0.91-1.06)

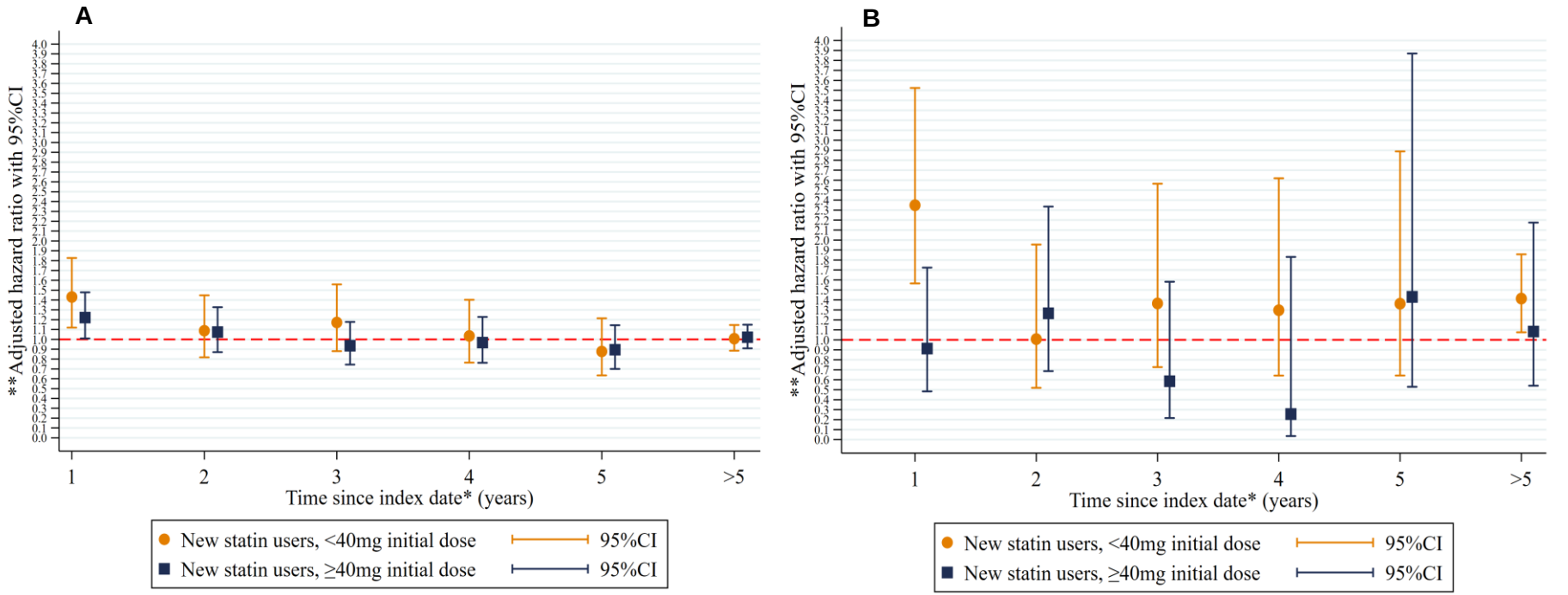
[a]We excluded patients who had a diagnosis of diabetic polyneuropathy, died, emigrated within the first year of follow, or had less than 1 year of follow-up time. Thus, we started the follow-up time from 1 year after the index date. However, the exposure window definition was still centered around the first diabetes record (180 days before and 180 days after first diabetes record) – the same as in the main analysis.
[b]Adjusted for: age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, alcohol-related disorders and smoking-related disorders.
Abbreviations: HR: Hazard ratio, CI: confidence interval, ref: reference.

Supplementary table 9. Risk of diabetic polyneuropathy stratified on initial statin dose of simvastatin or atorvastatin

New user, statin subtype[a]	Number at risk	Events	Incidence rate per 1000 person-years (95% CI)	Adjusted HR[b] (95% CI)
Simvastatin				
Never users	124,842	3,357	3.8 (3.7-4.0)	1.0 (reference)
New users, <40 mg	16,260	553	4.2 (3.8-4.5)	1.05 (0.96-1.15)
New users, ≥40 mg	35,425	935	3.8 (3.6-4.1)	1.01 (0.94-1.09)
Atorvastatin				
Never users	124,842	3,357	3.8 (3.7-4.0)	1.0 (reference)
New users, <40 mg	3,409	113	5.9 (4.9-7.1)	1.50 (1.24-1.80)
New users, ≥40 mg	3,402	38	3.2 (2.3-4.4)	0.95 (0.69-1.31)

[a]New statin users had their first-ever statin prescription within 180 days before – 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 the latest filled statin prescription before index date. 6811 (11.5% out of 59,255 total new statin users) filled an atorvastatin prescription as the latest filled statin prescription before index date.
[b]Adjusted for: age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, alcohol-related disorders and smoking-related disorders.
Abbreviations: HR: Hazard ratio, CI: confidence interval

Supplementary figure 5. Stratified on follow-up time: Risk of diabetic polyneuropathy for new statin users according to simvastatin dose (A) and atorvastatin dose (B)



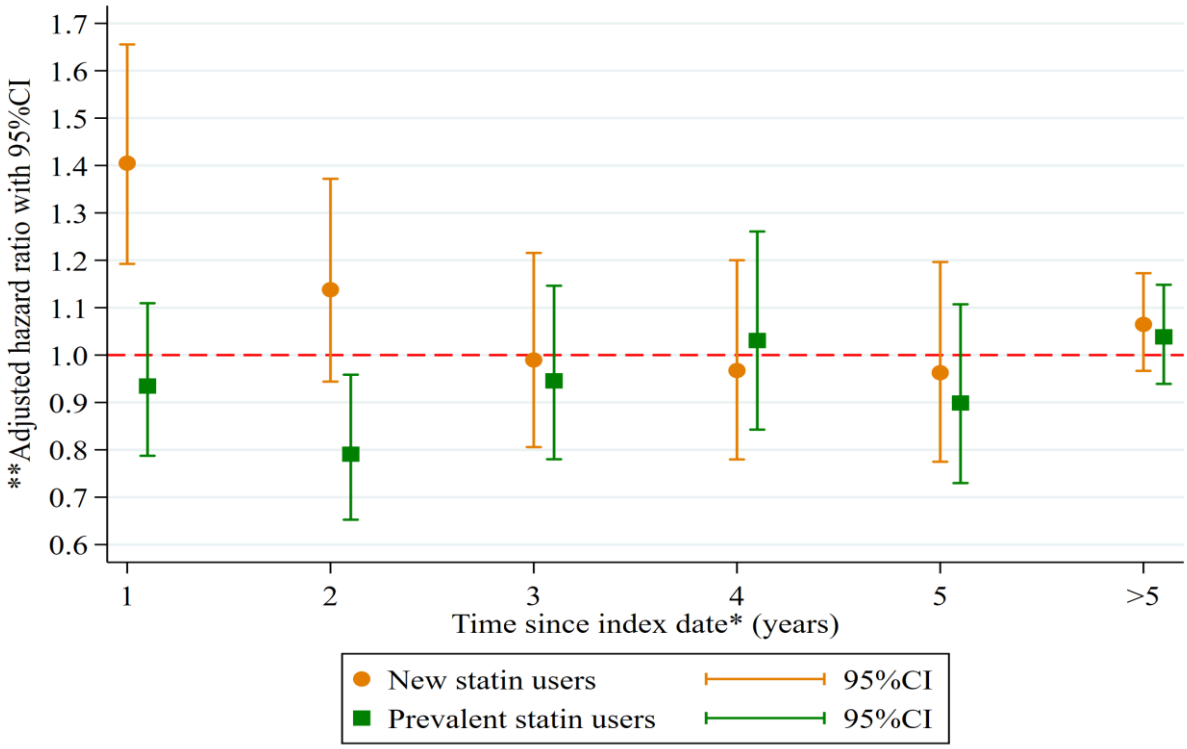
*Patients were followed from 180 days after first diabetes record (index date) until an event of either diabetic polyneuropathy, death, emigration, or study end (Jan 1st 2018) and if an event happened during the one year interval, the patient did not contribute in the next one-year interval.
**Adjusted for: age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, alcohol-related disorders and smoking-related disorders.
Abbreviations: CI: confidence interval

Supplementary table 10. Specifying the exposure assessment window and the definition of new and prevalent statin users and the risk of diabetic polyneuropathy.

Statin user status	Number at risk	Events	Incidence rate per 1000 person-years (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Stricter statin use definition: at least two prescriptions of statins within exposure assessment window required					
Never users	124,842	3,357	3.8 (3.7-3.9)	1.0 (ref)	1.0 (ref)
New users[b]	45,347	1258	3.9 (3.7-4.1)	1.05 (0.98-1.12)	1.02 (0.95-1.09)
Prevalent users[c]	71,090	1,520	3.6 (3.4-3.8)	1.01 (0.95-1.07)	0.94 (0.88-1.01)
Specifying exposure assessment window: using 180 days *after* first diabetes record[d]					
Never users	124,842	3,357	3.8 (3.7-3.9)	1.0 (ref.)	1.0 (ref.)
New users	47,512	1,365	4.1 (3.9-4.3)	1.11 (1.04-1.18)	1.08 (1.01-1.15)
Prevalent users	87,271	1,955	3.7 (3.5-3.8)	1.02 (0.96-1.08)	0.96 (0.90-1.02)
Stratifying prevalent statin users into shorter-term and longer-term prevalent users[e]					
Never users	124,842	3357	3.8 (3.7-3.9)	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)
Shorter-term prevalent users	11,627	286	3.4 (3.1-3.9)	0.93 (0.82-1.05)	0.90 (0.79-1.01)
Longer-term prevalent users	63,901	1359	3.8 (3.6-4.0)	1.06 (0.99-1.13)	0.99 (0.92-1.06)

[a]Adjusted for: age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, alcohol-related disorders and smoking-related disorders.
[b]New statin use were defined as at least two prescriptions of statins within the exposure window and no previous statin use.
[c]Prevalent statin users were defined as having a first statin prescription before the exposure assessment window and at least two prescriptions of statins within the exposure assessment window.
[d]New users had their first statin prescription within 180 days after first diabetes record (80 % of all new statin users). Prevalent statin users had their first statin prescription before first diabetes record.
[e]To account for a difference in diabetic polyneuropathy risk for prevalent statin users, we divided prevalent statin users (n=75,528) into shorter-term and longer-term prevalent statin users. Shorter-term prevalent statin users had their first-ever statin prescription within 547 days (1.5 year) before the exposure window (180 days before and 180 after first diabetes record) and at least one statin prescription within the exposure window. Longer-term prevalent statin users had their first statin prescription >547 days (1.5 year) before the exposure window and at least one statin prescription within the exposure window.
Abbreviations: HR: Hazard ratio, CI: confidence interval, ref: reference.

Supplementary figure 6. 1-year follow-up intervals: The risk of diabetic polyneuropathy for new and prevalent statin users within a *180 days exposure assessment window*



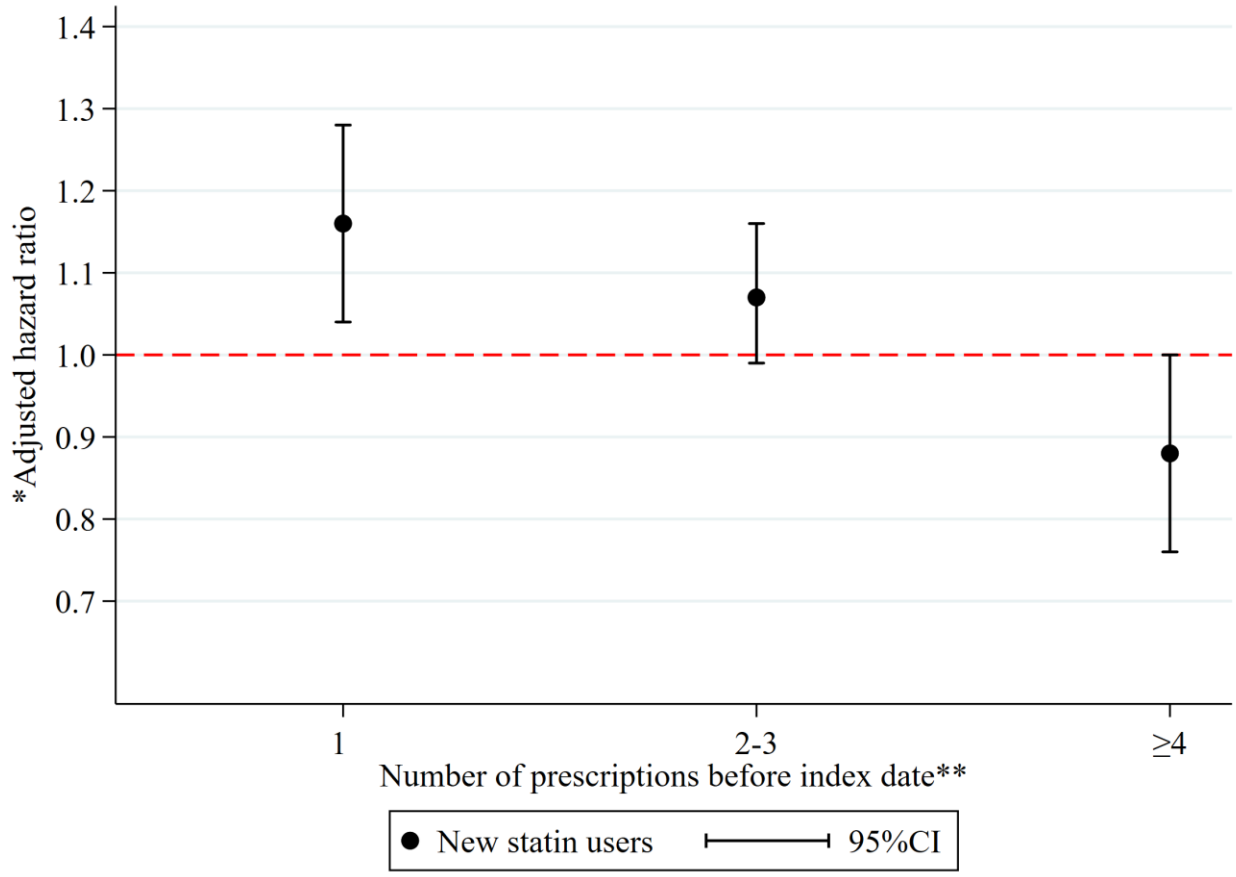
*Patients were followed from 180 days after first diabetes record (index date) until an event of either diabetic polyneuropathy, death, emigration, or study end (Jan 1st 2018) and if the event happened during the one year interval, the patient did not contribute in the next one-year interval.
**Adjusted for: age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, alcohol-related disorders and smoking-related disorders.
Please see supplementary table 11 for more information about numbers at risk, and numbers of event during each one-year intervals.
Abbreviations: CI: confidence interval

Supplementary table 11. 1-year follow-up intervals: The adjusted[a] risk of diabetic polyneuropathy for new and prevalent statin users within a *180 days exposure assessment window*

Statin user status	Number at risk/events	0-1 year follow-up aHR (95% CI)	Number at risk/events	1-2 years follow-up aHR (95% CI)	Number at risk/events	2-3 years follow-up aHR (95% CI)	Number at risk/events	3-4 years follow-up aHR (95% CI)	Number at risk/events	4-5 years follow-up aHR (95% CI)	Number at risk/events	>5 years follow-up aHR (95% CI)
Never users	124,842/425	1.0 (ref.)	118,484/365	1.0 (ref.)	106,558/318	1.0 (ref.)	96,578/301	1.0 (ref.)	87,527/297	1.0 (ref.)	77,808/1,651	1.0 (ref.)
New users	47,512/228	1.40 (1.19-1.66)	46,410/167	1.13 (0.94-1.37)	42,596/134	0.98 (0.80-1.21)	39,019/120	0.97 (0.77-1.20)	35,460/119	0.96 (0.77-1.20)	31,329/597	1.06 (0.96-1.17)
Prevalent users	87,271/290	0.93 (0.79-1.11)	84,096/227	0.79 (0.65-0.95)	75,053/253	0.95 (0.78-1.14)	67,142/222	1.03 (0.84-1.26)	60,005/204	0.89 (0.72-1.10)	51,580/759	1.04 (0.94-1.15)

[a]Adjusted for: age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, alcohol-related disorders and smoking-related disorders.
Abbreviations: HR: Hazard ratio, aHR: adjusted hazard ratio, CI: confidence interval, ref: reference

Supplementary figure 7. Number of prescriptions for new statin users and risk of diabetic polyneuropathy



***** Adjusted for: age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, alcohol-related disorders and smoking-related disorders.
**The number of prescriptions for new statin users was obtained within 180 days before and 180 days after first diabetes record.
Abbreviations: CI: confidence interval.

Supplementary table 12. The risk of diabetic polyneuropathy for statin users using diagnosis codes from Nielsen *et al.*[13] and within specific diagnosis codes of the validated outcome algorithm

Statin user status	Number at risk	Events	Incidence rate per 1000 person-years (95% CI)	Crude HR (95% CI)	Adjusted HR [a] (95% CI)
Alternative diabetic polyneuropathy definition[b]					
Never users	124,842	3,113	3.5 (3.4-3.6)	1.0 (ref.)	1.0 (ref.)
New users	59,255	1,511	3.6 (3.4-3.8)	1.04 (0.98-1.10)	1.09 (1.02-1.16)
Prevalent users	75,528	1,390	3.1 (3.0-3.3)	0.93 (0.87-0.99)	0.96 (0.89-1.03)
Diabetes with neurological complications[c]					
Never users	124,842	1,595	1.8 (1.7-1.9)	1.0 (ref.)	1.0 (ref.)
New users	59,255	801	1.9 (1.8-2.0)	1.07 (0.99-1.17)	1.13 (1.04-1.24)
Polyneuropathy unspecified[d]					
Never users	124,842	1263	1.4 (1.4-1.5)	1.0 (ref.)	1.0 (ref.)
New users	59,255	611	1.5 (1.3-1.6)	1.04 (0.94-1.14)	0.94 (0.85-1.04)
Diabetic Polyneuropathy[e]					
Never users	124,842	499	0.56 (0.52-0.61)	1.0 (ref.)	1.0 (ref.)
New users	59,255	263	0.62 (0.55-0.70)	1.15 (0.99-1.34)	1.13 (0.97-1.32)

[a]Adjusted for: age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, alcohol-related disorders and smoking-related disorders.
[b]We changed the diabetic polyneuropathy definition to the non-validated diabetic neuropathy definition used in Nielsen *et al.* which included diabetes with neurological complications (ICD-10 diagnosis codes E10.4-E13.4)[13]. This algorithm has previously been shown to include stroke, and mononeuropathies[19]. The statin exposure definition was the same as in the main analysis.
[c]E-Chapter diagnosis codes (ICD-10 E10.4-14.4)
[d]G-Chapter diagnosis codes (ICD-10 G62.9)
[e]G-Chapter diagnosis codes (ICD-10 G63.2)
Abbreviations: HR: Hazard ratio, CI: confidence interval, ref: reference.

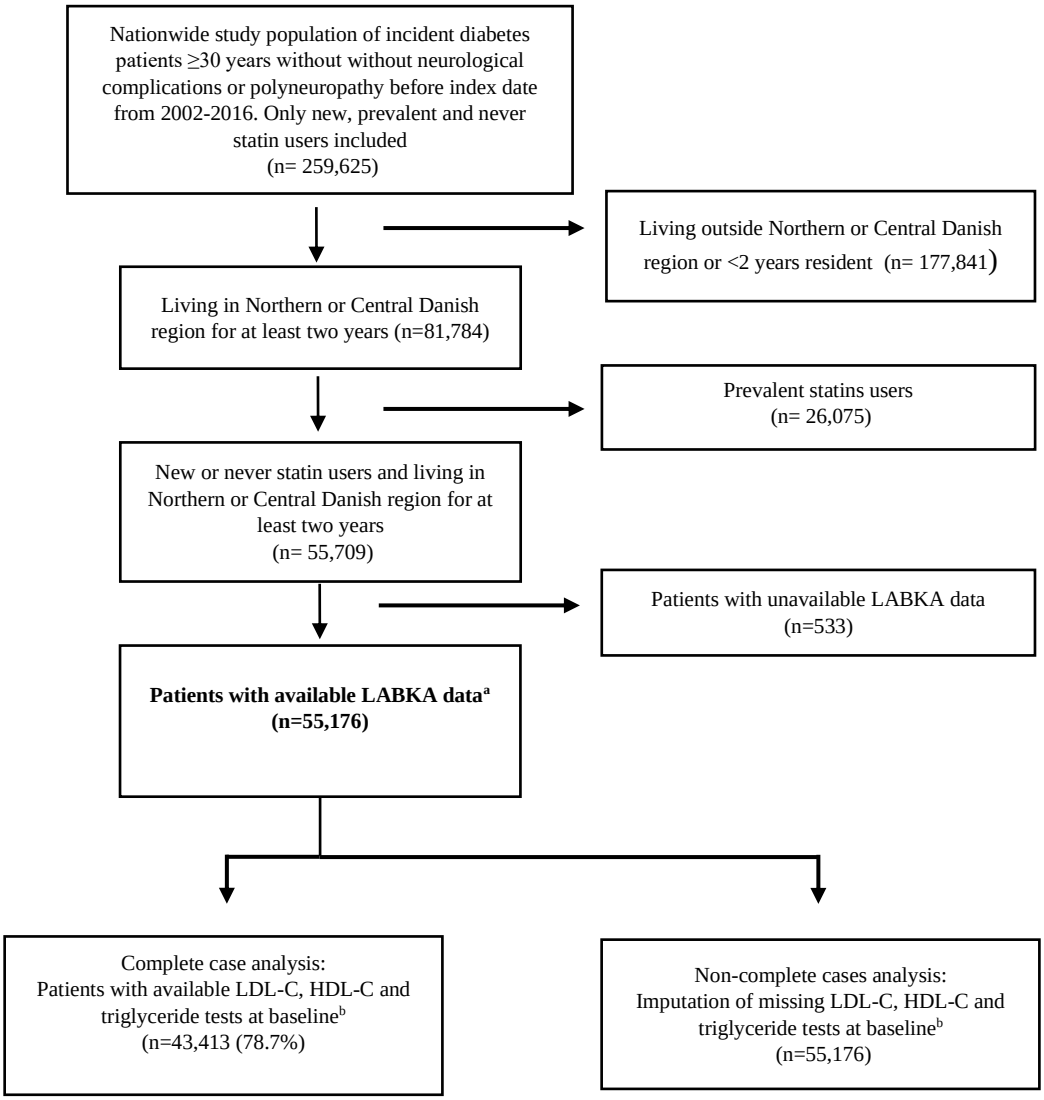
Supplementary table 13: Risk of diabetic polyneuropathy for new statin users uncorrected and corrected for misclassification of diabetic polyneuropathy

	DPN +	DPN -	Total
New statin users	1,675	57,580	59,255
Never statin users	3,357	121,485	124,842
Total	5,032	179,065	184,097
$RR_{new\ users} = 1.05$			
	DPN +	DPN -	Total
New statin users	13,082	46,173	59,255
Never statin users	27,436	97,406	124,842
Total	40,518	143,579	184,097
$RR_{New\ users;\ corrected^*} = 1.00$			

*Using both the moderate, 74%, positive predictive value, an assumed low sensitivity (<20%) and assumed independency of DPN misclassification between statin exposure groups, we performed an outcome misclassification bias analysis on website clepan.com

Abbreviations: DPN: Diabetic polyneuropathy

Supplementary figure 8. Flowchart of the Danish geographic subpopulation with available baseline lipid tests from the Clinical Laboratory Information System (LABKA)



[a]The Clinical Laboratory Information system (LABKA) records laboratory information from hospitals, general practitioners, and private clinics in Danish Northern and Central region. LABKA is expected to be complete from 2002 and onwards and can be linked to other medical databases with a Danish CPR identification number[42].
[b]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 index date for never statin users.
Abbreviations: LDL-C: low density lipoprotein-cholesterol, HDL-C: high density lipoprotein-cholesterol.

Supplementary table 14. Baseline characteristics of 55,176 incident type 2 diabetes patients from Northern and Central Danish Region with available baseline lipids by new and never statin use

Characteristics at start of follow-up: **180 days after diabetes diagnosis**	**New users** n (%)	**Never users** n (%)	**Total** n (%)
Number of participants	**19,248 (34.9)**	**35,928 (65.1)**	**55,176 (100.0)**
Male sex	11,182 (58.1)	18,253 (50.8)	29,435 (53.3)
Age, median (IQR)	60 (52-68)	59 (47-72)	60 (49-70)
Age groups			
30-39	799 (4.2)	5,336 (14.9)	6,135 (11.1)
40-49	3,010 (15.6)	5,465 (15.2)	8,475 (15.4)
50-59	5,422 (28.2)	7,326 (20.4)	12,748 (23.1)
60-69	5,845 (30.4)	7,474 (20.8)	13,319 (24.1)
70-79	3,172 (16.5)	5,782 (16.1)	8,954 (16.2)
≥80	1,000 (5.2)	4,545 (12.7)	5,545 (10.0)
Index year			
2002-2005	3,215 (16.7)	10,326 (28.7)	13,541 (24.5)
2006-2009	6,007 (31.2)	9,811 (27.3)	15,818 (28.7)
2010-2013	6,639 (34.5)	9,732 (27.1)	16,371 (29.7)
2014-2017	3,387 (17.6)	6,059 (16.9)	9,446 (17.1)
Baseline lipid levels[a]			
LDL-Cholesterol (mmol/L), median (IQR)	3.07 (2.41-3.73)	2.2 (1.66-2.80)	2.4 (1.79-3.08)
Triglycerids (mmol/L), median (IQR)	2.71 (1.70-4.65)	1.92 (1.29-2.95)	2.08 (1.37-3.30)
HDL-Cholesterol (mmol/L), median (IQR)	1.18 (0.94-1.42)	1.26 (1.02-1.55)	1.13 (1.00-1.52)
Smoking[b]	2,648 (13.8)	5,256 (14.6)	7,904 (14.3)
Hypertension[c]	8,394 (43.6)	12,090 (33.7)	20,484 (37.1)
Hyperlipidemia (ICD-registered)	1,380 (7.2)	390 (1.1)	1,770 (3.2)
Obesity (ICD-registered)	1,648 (8.6)	3,868 (10.8)	5,516 (10.0)
Microvascular complications	1,383 (7.2)	3,522 (9.8)	4,905 (8.9)
Eye complications	1,193 (6.2)	2,963 (8.2)	4,156 (7.5)
Renal complications	221 (1.1)	667 (1.9)	888 (1.6)
Macrovascular complications	3,857 (20.0)	4,904 (13.6)	8,761 (15.9)
Aortic, renal and intestinal atherosclerotic disease	232 (1.2)	317 (0.9)	549 (1.0)
Cerebrovascular disease	1,299 (6.7)	1,637 (4.6)	2,936 (5.3)
Heart failure	735 (3.8)	1,559 (4.3)	2,294 (4.2)
Ischemic heart disease	2,036 (10.6)	2,001 (5.6)	4,037 (7.3)
Peripheral vascular disease	558 (2.9)	800 (2.2)	1,358 (2.5)
Disorders causing neuropathy symptoms			
Alcohol-related disorders	617 (3.2)	1,703 (4.7)	2,320 (4.2)
B12 and B-vitamin deficiencies	554 (2.9)	1,633 (4.5)	2,187 (4.0)
Infections causing neuropathy symptoms[d]	47 (0.2)	219 (0.6)	266 (0.5)
Hypothyroidism	744 (3.9)	1,567 (4.4)	2,311 (4.2)
HIV/AIDS	8 (0.0)	20 (0.1)	28 (0.1)
Chemotherapy	459 (2.4)	1,517 (4.2)	1,976 (3.6)
Cancer[e]	1,042 (5.4)	2,943 (8.2)	3,985 (7.2)
Connective tissue disease	378 (2.0)	1,074 (3.0)	1,452 (2.6)
Additional comorbidities within the Charlson Comorbity index			
Gastrointestinal and liver disease	511 (2.7)	1,508 (4.2)	2,019 (3.7)
Dementia	77 (0.4)	413 (1.1)	490 (0.9)
Chronic pulmonary disease (excl. COPD)	600 (3.1)	1,325 (3.7)	1,925 (3.5)
Medications			
Insulin use[f]	1,172 (6.1)	3,465 (9.6)	4,637 (8.4)
Fibrates	73 (0.4)	118 (0.3)	191 (0.3)
Other lipid lowering agents	50 (0.3)	85 (0.2)	135 (0.2)
Adrenergic antihypertensives	176 (0.9)	278 (0.8)	454 (0.8)
Beta blockers	4,662 (24.2)	6,709 (18.7)	11,371 (20.6)
Calcium channel antagonists	4,366 (22.7)	6,043 (16.8)	10,409 (18.9)
Non-loop antihypertensives	4,781 (24.8)	8,469 (23.6)	13,250 (24.0)
RAAS antagonists	10,769 (55.9)	12,675 (35.3)	23,444 (42.5)
Received inpatient hospital care[g]			
Numbers of inpatient hospitalizations			
None	13,491 (70.1)	23,313 (64.9)	36,804 (66.7)
1-2	5,044 (26.2)	10,576 (29.4)	15,620 (28.3)
>2	713 (3.7)	2,039 (5.7)	2,752 (5.0)
Total number of inpatient hospitalization days			
None	13,491 (70.1)	23,313 (64.9)	36,804 (66.7)
1-5	2,739 (14.2)	5,440 (15.1)	8,179 (14.8)
>5	3,018 (15.7)	7,175 (20.0)	10,193 (18.5)

[a]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 index date for never statin users. 11,763 of the study population (21.3 %) did not have baseline lipid level and we therefore used multiple imputation to account for those values.

[b]Proxy measure defined by ICD-10/8 diagnosis codes for chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), and medication used for COPD.
[c]Hypertension was defined as either ≥ 1 ICD-10/8 diagnosis code or use of ≥2 different anti-hypertensive drug-classes prior to the index date.
[d]Hepatitis, herpes zoster, mononucleosis, lyme disease, leprosy, tertiary syphilis, tuberculosis, diphtheria.
[e]All malignant cancers including skin cancers but excluding carcinoma in situ and benign cancers.
[f]≥1 prescription of insulin within 180 days before the index date.
[g]Information about inpatient hospital care was obtained within 1 year prior to index date.

Supplementary table 15. Adjusted for baseline lipid levels: Risk of diabetic polyneuropathy for new statin users

	Number at risk	Events	Incidence rate per 1000 person-years (95% CI)	Crude HR (95% CI)	Main model aHR[a] (95% CI)	Main model + baseline lipid[b] aHR (95% CI)
Never users	35,928	848	3.4 (3.2-3.6)	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
New users	19,248	444	3.3 (3.0-3.6)	0.99 (0.89-1.12)	1.02 (0.90-1.15)	1.04 (0.92-1.19)

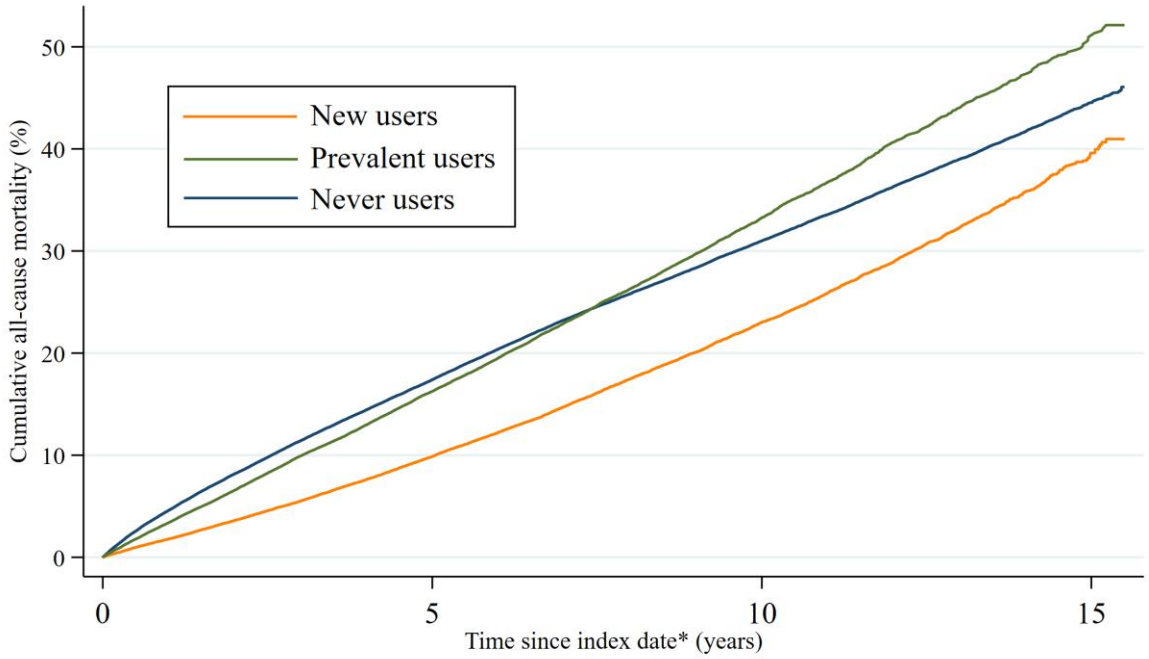
[a]Adjusted for: age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, hyperlipidemia, alcohol-related disorders and smoking-related disorders.
[b]Adjusted for the same baseline variables as in the main model 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 index date for never statin users. 11,763 of the study population (21.3 %) did not have baseline lipid level and we therefore used multiple imputation to account for those values.
Abbreviations: HR: Hazard ratio, aHR: adjusted hazard ratio, CI: confidence interval, ref.: reference

Supplementary table 16. Most recent lipid test for new and never statin users

	New statin users	Never statin users	Total
Most recent baseline lipid test within complete case[a] population			
Number with a LDL-C test	16,773 (38.1%)	27,222 (61.9%)	43,995
LDL-Cholesterol (mmol/L), median (IQR)	3.7 (3.1-4.3)	2.9 (2.4-3.5)	3.2 (2.6-3.8)
Number with a HDL-C test	17,403 (38.3%)	28,050 (61.7%)	45,453
HDL-Cholesterol (mmol/L), median (IQR)	1.2 (0.9-1.4)	1.2 (1.0-1.4)	1.2 (1.0-1.4)
Number with a triglyceride test	17,158 (38.6%)	27,335 (61.4%)	44,493
Triglycerides (mmol/L), median (IQR)	2.0 (1.4-3.0)	1.59 (1.1-2.2)	1.7 (1.2-2.5)
Most recent lipid test within complete case[a] population after 1 year of follow-up			
Number with a LDL-C test	18,028 (38.4%)	28,934 (61.6%)	46,962
LDL-Cholesterol (mmol/L), median (IQR)	2.0 (1.6-2.6)	2.7 (2.2-3.3)	2.5 (1.9-3.1)
Number with a HDL-C test	18,140 (38.0%)	29,573 (62.0%)	47,713
HDL-Cholesterol (mmol/L), median (IQR)	1.1 (1.0-1.5)	1.1 (1.0-1.5)	1.1 (1.0-1.5)
Number with a triglyceride test	18,021 (38.3%)	28,999 (61.7%)	47,020
Triglycerides (mmol/L), median (IQR)	1.5 (1.1-2.2)	1.5 (1.09-2.2)	1.5 (1.1-2.2)

[a]Within a population of type 2 diabetes patients from the Northern and the Central Danish region with available lipid tests before and during follow-up, we found the most recent lipid test for new statin users before statin initiation and the most recent lipid test before index date for never statin users. After 1 year of follow-up, we found the most recent lipid test for both new users and never statin 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 8 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 figure 9. Crude cumulative all-cause mortality by statin use



Number at risk

New users	59,255	40,509	14,640	375
Prevalent users	75,528	43,826	9,755	272
Never users	124,842	79,130	36,436	3,011

*Type 2 diabetes patients were followed from 180 days after first diabetes record (index date) until death, emigration, or study end (January 1st 2018). New statin users had their first-ever prescription of statins within the exposure window (180 days before to 180 days after first diabetes record). Prevalent statin users had their first-ever filled prescription of statins before the exposure window and at least one additional prescription of statins filled within the exposure window. Never statin users had no prescription of statin before index date.

Supplementary table 17. The 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[a] HR (95% CI)	Extensively adjusted HR[b] (95% CI)
Never 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 (37-39)	1.03 (1.00-1.05)	0.69 (0.68-0.70)	0.77 (0.76-0.79)

[a]Main model was adjusted for age, sex, index year, ICD-defined obesity and hyperlipidemia, insulin use, macrovascular complications, microvascular complications, hypertension, alcohol-related disorders, and smoking-related-disorders.
[b]Adjusted for the same baseline variables as in the main model and additionally 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