Supplementary material to:

Use of statins and risk of myeloproliferative neoplasms – a Danish nationwide case-control study

Kristensen D.T. *et al*

CONTENTS:

Danish nationwide registers

The Personal Identification number (CPR number) and linkage of registers
Since 1968 all Danish residents have been given a unique 10-digit Personal Identification number (CPR number) at birth or immigration.[1,2] The CPR number is used to register data from all contacts with the health care system, including hospitals. Data is registered at and governed by different Danish health institutions and a generalized division includes:

- The Danish Health Data Authority (Danish, Sundhedsdatastyrelsen: https://sundhedsdatastyrelsen.dk/da/english) contains administrative health care data.
- The Danish Clinical Quality Program – National Clinical Registries (Danish, Regionernes Kliniske Kvalitetsudviklingsprogram [RKKP]: https://www.rkkp.dk/in-english/) contains data regarding specific diseases and treatment.
- Statistics Denmark (Danish, Danmarks Statistik: https://www.dst.dk/en) holds data on socioeconomic data for the entire Danish population.

Danish Civil Registration System (CRS)
The CRS contains data on all Danish residents since 1968 and allows for matching cases to population-based controls. The register holds information on CPR number, age, date of birth, continuously updated information on vital status along with 150 other variables.[1,2] This register was used to follow all subjects during the study period.

The National Patient Register (NPR)
The NPR holds data on all non-psychiatric hospitalizations (inpatient-, outpatient-, and emergency department visits) for all Danish residents since 1977 and uses ICD-10 for coding diagnoses at discharge or the diagnose leading to the contract with the health care system.[3,4] Additionally, procedure and treatment codes are registered.

The Danish National Chronic Myeloid Neoplasia Registry (DCMR)
The DCMR is a population-based clinical quality database aimed to evaluate the diagnosis and treatment of MPNs in Denmark[5]. The register holds prospectively collected information on the diagnoses: essential thrombocythemia (ET), polycythemia vera (PV), myelofibrosis (MF), MPN-unclassifiable (MPN-U), chronic myeloid leukemia (CML), and chronic myelomonocytic leukemia (CMML). Since January 1, 2010, all hematology departments in Denmark are obliged to collect and enter data on newly diagnosed cases of MPN to the DCMR at least six months after the diagnosis. Patients diagnosed or treated outside Denmark are included only if their treatment is continued in Denmark. Patients diagnosed before January 1, 2010, are not entered in the register. For each patient up to four registration forms may be collected on predefined intervals (primary registration form, 2-year registration form, 5-year registration form, and follow-up form at the end of follow-up defined as death or progression to acute leukemia). A study found a coverage ≥90% of all Danish MPN cases and a data completeness of ≥88% of the DCMR, but no formal validation has been done.[5] However, the DCMR is a part of the joint Danish clinical hematology databases generally known to have great validity.[6,7]

The Danish National Prescription Register (DNPR)
The DNPR has recorded all prescription drug fillings redeemed by Danish residents since 1995[8,9]. Drugs in the register are categorized the hierarchical classification Anatomic Therapeutic Chemical (ATC) index proposed by the World Health Organization. The register holds information on drug name, date of filling, quantity of filling (i.e., package size) and dose of each entity (i.e., tablet). However, it does not hold information in indication or prescribed daily dose. All registrations are from pharmacies and drugs given at hospitals are not registered in DNPR.

The Danish Education Registers (DERs)
The DERs contains several registers regarding various aspects of education[10]. Most used is the Populations Education Register (PER) that covers information on highest achieved education coded as eight-digit code easy to transform into the International Standard Classification of Education (ISCED) codes. Overall, the coverage is excellent with ≥96% of the Danish population aged 15–69 having complete information on education.

Codes and definitions

TABLE S1: Codes and definitions for exclusion criteria and confounding		
Exclusion criteria		
Any cancer, except non-melanoma skin cancer	ICD-8 codes	140-199, 204-207, 200-203
	ICD-10 codes	C00-97, except C44.
Prior diagnoses (diagnostic code or drug use as a marker)		
Alcohol abuse	ICD-8 codes	291, 303, 425.5, 571.0, 571.1, 571.2, 571.3, 577.1
	ICD-10 codes	F10, K70, K86.0, K29.2, G31.2, G62.1, G72.1, I42.6, Z72.1A, T51.9
	ATC code	N07BB
Chronic obstructive pulmonary diseases (COPD)	ICD-8 codes	490.0, 491.00, 491.01,491.03
	ICD-10 codes	J42, J43, J44
	ATC code	R03BB, R03AL
Diabetes melitus	ICD-8 codes	249.00–250.09
	ICD-10 codes	E10.0–14.9
	ATC code	A10
Obesity	ICD-8 codes	277.99
	ICD-10 codes	E66.0–66.9
Autoimmune disease	ICD-8 codes	135, 245.2, 279.0, 279.4, 283.0, 287.31, 284.01, 284.09, 284.81, 284.9, 340, 555, 571.42, 696.0, 696.1, 696.3, 696.4, 709.01, 714, 710.0, 710.1, 710.2, 710.3, 710.4, 725, 729.1, 729.2.
	ICD-10 codes	M32-M34, M05-M09, M351, M353, M360, M315, M359, M358, M601, M609, M791, M797, M541, M7923, E062, E063, E065, D80, D899, D898, D590, D591, D599A, D693, D6101, D6109, D600, D601, D608, D609, D60, D619, D61, G35, K50, K51, K52, K754, L40, L41, L42, L44, L80, H027C
	ATC codes	L04
ICD-8 and 10 codes from the National Patient Register (NPR)		

Supplementary analyses

TABLE S2: Association between exposure to different statins and risk of myeloproliferative neoplasm according to duration of treatment.

Subgroup	Exposure pattern	Cases, n	Controls, n	OR[†] (95% CI)	Adjusted OR[‡] (95% CI)
Simvastatin	**Never-use**	2593	13103	1.0 (reference)	1.0 (reference)
	Ever-use	1223	5977	1.04 (0.96-1.12)	0.86 (0.78-0.94)
	Long-term use[§]	538	2957	0.88 (0.79-0.98)	0.72 (0.64-0.82)
	CTD				
	<1 year	229	991	1.17 (1.01-1.36)	0.93 (0.79-1.09)
	1-4.99 years	456	2029	1.14 (1.02-1.27)	0.94 (0.84-1.06)
	5-9.99 years	344	1751	0.99 (0.88-1.13)	0.83 (0.73-0.95)
	≥10 years	194	1206	0.81 (0.69-0.95)	0.64 (0.54-0.76)
Atorvastatin	**Never-use**	3501	17327	1.0 (reference)	1.0 (reference)
	Ever-use	315	1753	0.89 (0.78-1.01)	0.72 (0.63-0.83)
	Long-term use[§]	70	410	0.86 (0.66-1.11)	0.71 (0.55-0.93)
	CTD				
	<1 year	104	574	0.89 (0.72-1.11)	0.72 (0.58-0.90)
	1-4.99 years	141	769	0.90 (0.75-1.09)	0.73 (0.60-0.88)
	5-9.99 years	44	254	0.85 (0.62-1.18)	0.70 (0.51-0.98)
	≥10 years	26	156	0.82 (0.54-1.25)	0.71 (0.47-1.09)
Other statins[#]	**Never-use**	3629	18112	1.0 (reference)	1.0 (reference)
	Ever-use	187	968	0.96 (0.82-1.13)	0.82 (0.70-0.97)
	Long-term use[§]	50	308	0.81 (0.60-1.09)	0.65 (0.48-0.88)
	CTD				
	<1 year	69	318	1.05 (0.81-1.37)	0.93 (0.71-1.22)
	1-4.99 years	69	342	1.02 (0.79-1.32)	0.89 (0.68-1.15)
	5-9.99 years	33	194	0.90 (0.63-1.29)	0.72 (0.50-1.04)
	≥10 years	15	114	0.66 (0.38-1.13)	0.54 (0.31-0.94)

Abbreviations: CTD, cumulative treatment duration; OR, odds ratio; 95% CI, 95% confidence interval.

[§]Long-term use: ≥5 years.

[#]Other statins include lovastatin, pravastatin, fluvastatin and rosuvastatin.

[†] Adjusted for age, sex, and calendar time (by matching design).

[‡] Adjusted for ([†]) in addition to i) education level (primary school; high school; short/intermediate education; long education), ii) Charlson Comorbidity Index (0; 1; ≥2) iii) previous use of aspirin, other NSAIDs; alendronate; immunosuppressants and metformin, vi) previous history of alcohol related diagnoses, overweight and obesity related diagnoses, chronic obstructive pulmonary disease, autoimmune disease, and diabetes.

TABLE S3: Effect of adjustment for single potential confounders on the association between ever-use of statins and risk of myeloproliferative neoplasm.

Potential confounder	Adjusted OR (95% CI)
No adjustment	1.07 (0.99-1.16)
Full adjustment	0.87 (0.80-0.96)
Highest achieved education	1.07 (0.99-1.16)
Charlson Comorbidity Index	1.00 (0.92-1.08)
Medical history	
Alcohol related diseases	1.07 (0.99-1.16)
Overweight and obesity related diagnoses	1.08 (1.00-1.17)
COPD	1.07 (0.99-1.15)
Autoimmune disease	1.07 (0.99-1.16)
Diabetes	1.12 (1.03-1.22)
All diagnosis	1.12 (1.03-1.21)
Previous drug use	
Aspirin	0.86 (0.79-0.94)
Other NSAIDs	1.07 (0.99-1.15)
Alendronate	1.07 (0.99-1.16)
Metformin	1.11 (1.03-1.21)
Immunosuppressants	1.07 (0.99-1.16)
Any drugs	0.89 (0.82-0.98)

Abbreviations: COPD, chronic obstructive pulmonary disease; NSAIDs, Non-steroidal anti-inflammatory drugs; OR, odds ratio; 95% CI, 95% confidence interval.

TABLE S4: Effect of various lag time periods (disregarded period of exposure prior to index date) on the association between long-term statin use (≥5 years) and the risk of myeloproliferative neoplasm.

Lag time (months)	Adjusted OR (95% CI)[†]
0	0.51 (0.45-0.57)
6	0.71 (0.63-0.79)
12[§]	0.72 (0.64-0.81)
18	0.72 (0.64-0.81)
24	0.73 (0.64-0.82)
30	0.72 (0.63-0.82)
36	0.73 (0.64-0.83)

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.
[§]12 months corresponds to the primary analysis.
[†] Adjusted for i) age, sex, and calendar time (by matching design), ii) education level (primary school; high school; short/intermediate education; long education), iii) Charlson Comorbidity Index (0; 1; ≥2), vi) previous use of aspirin, other NSAIDs, alendronate, immunosuppressants and metformin, v) previous history of alcohol related diagnoses, overweight and obesity related diagnoses, chronic obstructive pulmonary disease, autoimmune disease, and diabetes.

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