

SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Description of method used to determine the dose and treatment duration of statins.

The national prescription registry does not include information on prescribed daily dosage of the medication, but rather date of dispensing, strength and quantity. For each of the statins dispensed between 1 January 2004 and 31 December 2018, we created an algorithm in which a minimum, maximum and typical daily dosage of used medication was defined. For patients who had not been in treatment in the period preceding the day of a prescription claim, the typical daily dosage was assigned, and treatment length was calculated by dividing the amount of claimed medications by the daily dosage. For patients who were covered by a previous prescription claim at the time of claiming a new prescription, the daily dosage was reset and a new daily dosage was calculated as the amount of claimed medications during the preceding period divided by time between prescription claims. If calculated dosages exceeded the predefined highest daily dosages, patients were assigned the maximally dosages and exceeding tablets were assumed to be stored and consumed during the immediate period after duration of last prescription. Based on these assumptions, we calculated whether patients at any time had tablets available or not. We defined a patient as receiving treatment if tablets were available.

Table S1. ICD-8, ICD-10 and ATC codes used.

	ICD-8, ICD-10 and ATC codes	Comments
Outcomes of interest (ICD)		From the National Patient Registry and National Causes of Death Registry
Myocardial infarction	ICD-10: I21	
Ischemic stroke	ICD-8: 433, 443, 436 ICD-10: I63-64	
Comorbidities (ICD)		From the National Patient Registry
Coronary artery disease	ICD-8: 410-414 ICD-10: I20-25	
Congestive heart failure	ICD-8: 42709-42711, 42719, 42899, 78249 ICD-10: I110, I130, I132, I420, I426-429, I500-503, I508-509	
Peripheral arterial disease	ICD-8: 44389-44399 ICD-10: I73	
Chronic renal failure	ICD-8: 585, T858-859, Z992 ICD-10: N18, I12-13	
Atrial fibrillation	ICD-8: 42793, 42794 ICD-10: I48	
Chronic obstructive pulmonary disease	ICD-8: 490-492 ICD-10: J42, J44	
Cancer	ICD-8: 140-209 ICD-10: C00-99	
Medication (ATC)		From the National Prescription Registry. Medications at the index date were defined as dispensed prescriptions within 180 days prior to the index date. For the nested case-control population, medications were defined as dispensed prescriptions within 180 days prior to one year before the case date.
Exposure		
Statins	C10AA	
Antidiabetics		

Metformin	A10BA02, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD10, A10BD11, A10BD13, A10BD14, A10BD15, A10BD16, A10BD17, A10BD18, A10BD20, A10BD22, A10BD23, A10BD25	
Insulin	A10A	
Sulfonylureas	A10BB, A10BD02, A10BD04, A10BD06	
DPP4-inhibitors	A10BH, A10BD07, A10BD08, A10BD10, A10BD11, A10BD12, A10BD13, A10BD18, A10BD21, A10BD22, A10BD24	
GLP1-analogs	A10BJ, A10AE54, A10AE56	
Antithrombotic agents		
Aspirin	B01AC06, N02BA01	
ADP-receptor inhibitors	B01AC04, B01AC22, B01AC24	
Anticoagulants	BB01AA, BB01AE, BB01AF	
Other		
Cholesterol-lowering drugs (non-statins)	C10A, except C10AA	
RASi	C09	
Betablockers	C07, C09BX	
Calcium channel blockers	C08, C07F, C09BB, C09DB	
Thiazides	C03A, C07B, C07D, C09XA52, C03EA01	
Furosemide	C03C, C03EB01, C03EB02	
Aldosterone	C03DA	

Table S2. Variables standardized (main analysis) and adjusted (nested case-control) for in the models.

Models	Variables
Main analysis	Sex, age (1-year bands), atrial fibrillation, chronic obstructive pulmonary disease, ethnicity (Danish, 1 st generation immigrants, 2 nd generation immigrants), highest attained education (ground school, high school, vocational, bachelor, master/research), metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 analogues, aspirin, ADP inhibitors, anticoagulants, RASi, cholesterol-lowering drugs (non-statins), betablockers, calcium-channel blockers, thiazides, furosemide, aldosterone, year of type 2 diabetes diagnosis (2005, 2006, 2007, 2008, 2009, 2010, 2011).
Nested case-control	Matching variables: sex and age (10-year bands). Atrial fibrillation, chronic obstructive pulmonary disease, cancer, ethnicity (Danish, 1 st generation immigrants, 2 nd generation immigrants), highest attained education (ground school, high school, vocational, bachelor, master/research), metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 analogues, aspirin, ADP inhibitors, anticoagulants, RASi, cholesterol-lowering drugs (non-statins), betablockers, calcium-channel blockers, thiazides, furosemide, aldosterone, year of type 2 diabetes diagnosis (2005, 2006, 2007, 2008, 2009, 2010, 2011).

Table S3. Population characteristics according to coverage of statins in the nested case-control population.

	Coverage		PDC				
	Not treated	Treated	<20%	(20-40%]	(40-60%]	(60-80%]	≥80%
Count (%)	37625	73574	3956	3552	4241	9059	52766
Women	15,812 (42.0)	31,400 (42.7)	1,606 (40.6)	1,449 (40.8)	1,635 (38.6)	3,661 (40.4)	23,049 (43.7)
Age (Q₁-Q₃*)	71 [62, 81]	69 [62, 76]	68 [58, 77]	68 [59, 77]	68 [60, 76]	69 [61, 76]	70 [63, 77]
Ethnic Danish	34,744 (92.3)	69,051 (93.9)	3,552 (89.8)	3,210 (90.4)	3,851 (90.8)	8,303 (91.7)	50,135 (95.0)
Comorbidities							
Diabetes duration (Q ₁ -Q ₃ *)	3.9 [2.6, 5.1]	4 [2.8, 5.3]	3.6 [2.5, 5.0]	3.8 [2.6, 5.1]	3.8 [2.6, 5.1]	3.9 [2.7, 5.2]	4.1 [2.9, 5.3]
Coronary heart disease	416 (1.1)	1375 (1.9)	63 (1.6)	67 (1.9)	83 (2.0)	160 (1.8)	1002 (1.9)
Heart failure	411 (1.1)	590 (0.8)	32 (0.8)	25 (0.7)	30 (0.7)	91 (1.0)	412 (0.8)
PAD	160 (0.4)	537 (0.7)	28 (0.7)	36 (1.0)	42 (1.0)	65 (0.7)	366 (0.7)
Chronic renal failure	212 (0.6)	370 (0.5)	16 (0.4)	15 (0.4)	14 (0.3)	65 (0.7)	260 (0.5)
Atrial fibrillation	3130 (8.3)	5084 (6.9)	286 (7.2)	241 (6.8)	261 (6.2)	620 (6.8)	3676 (7.0)
COPD	2793 (7.4)	4264 (5.8)	230 (5.8)	217 (6.1)	250 (5.9)	579 (6.4)	2988 (5.7)
Cancer	3670 (9.8)	6187 (8.4)	359 (9.1)	267 (7.5)	372 (8.8)	783 (8.6)	4406 (8.4)
Highest attained education							
Basic school	18,130 (48.2)	33,715 (45.8)	1,764 (44.6)	1,611 (45.4)	1,809 (42.7)	3,879 (42.8)	24,652 (46.7)
Upper secondary	869 (2.3)	1394 (1.9)	98 (2.5)	78 (2.2)	97 (2.3)	209 (2.3)	912 (1.7)
Vocational	12747 (33.9)	27573 (37.5)	1491 (37.7)	1325 (37.3)	1652 (39.0)	3504 (38.7)	19601 (37.1)
Short or medium length higher education	4334 (11.5)	8568 (11.6)	464 (11.7)	382 (10.8)	522 (12.3)	1153 (12.7)	6047 (11.5)
Master's degree or higher	1545 (4.1)	2324 (3.2)	139 (3.5)	156 (4.4)	161 (3.8)	314 (3.5)	1554 (2.9)
Medication							
Metformin	22613 (60.1)	58368 (79.3)	2678 (67.7)	2534 (71.3)	3146 (74.2)	7192 (79.4)	42818 (81.1)
Insulin	2376 (6.3)	3908 (5.3)	277 (7.0)	238 (6.7)	268 (6.3)	493 (5.4)	2632 (5.0)

Sulfonylureas	8174 (21.7)	14668 (19.9)	788 (19.9)	751 (21.1)	883 (20.8)	1800 (19.9)	10446 (19.8)
DPP-4 inhibitor	1548 (4.1)	4736 (6.4)	238 (6.0)	213 (6.0)	259 (6.1)	616 (6.8)	3410 (6.5)
GLP-1 analogue	488 (1.3)	1540 (2.1)	74 (1.9)	77 (2.2)	92 (2.2)	207 (2.3)	1090 (2.1)
Aspirin	7538 (20.0)	24409 (33.2)	906 (22.9)	943 (26.5)	1144 (27.0)	2772 (30.6)	18644 (35.3)
ADP inhibitor	155 (0.4)	844 (1.1)	32 (0.8)	39 (1.1)	41 (1.0)	102 (1.1)	630 (1.2)
Anticoagulants	2398 (6.4)	4467 (6.1)	222 (5.6)	175 (4.9)	207 (4.9)	521 (5.8)	3342 (6.3)
RAS inhibitor	16378 (43.5)	47010 (63.9)	1943 (49.1)	1930 (54.3)	2356 (55.6)	5454 (60.2)	35327 (67.0)
Non-statin lipid-lowering drugs	487 (1.3)	264 (0.4)	75 (1.9)	50 (1.4)	37 (0.9)	34 (0.4)	68 (0.1)
Beta blocker	6751 (17.9)	15915 (21.6)	657 (16.6)	652 (18.4)	769 (18.1)	1820 (20.1)	12017 (22.8)
CCB	8251 (21.9)	22343 (30.4)	859 (21.7)	871 (24.5)	1080 (25.5)	2507 (27.7)	17026 (32.3)
Thiazides	7383 (19.6)	16279 (22.1)	753 (19.0)	701 (19.7)	832 (19.6)	1843 (20.3)	12150 (23.0)
Furosemide	4960 (13.2)	7788 (10.6)	347 (8.8)	301 (8.5)	382 (9.0)	958 (10.6)	5800 (11.0)
Aldosterone	1436 (3.8)	1971 (2.7)	96 (2.4)	75 (2.1)	102 (2.4)	226 (2.5)	1472 (2.8)

PDC = proportion of days covered, Q₁-Q₃ = 25th percentile-75th percentile, PAD = peripheral arterial disease, COPD = chronic obstructive pulmonary disease, DPP4 = dipeptidyl peptidase 4, GLP1 = glucagon-like peptide 1, ADP = adenosine diphosphate, NOAC = novel oral anticoagulant, RAS inhibitor = renin-angiotensin system inhibitor, CCB = calcium channel blockers.

Highest attained education: Basic school (primary, lower secondary; 9 years); Upper secondary (general secondary, technical secondary; "high-school"); Vocational (e.g., electrician or chef); Short or medium length higher education (academy professional degree, professional bachelor's degree, university bachelor's degree; 2 to 4 years following upper secondary); Master's degree or higher.

Table S4. Hazard ratios of adjustment variables used for the main analysis according to coverage (reference = risk_{treated}).

Variable	Units	Hazard ratio	P-value
Sex	Men vs. women	1.46 [1.40;1.52]	< 0.001
Age		1.06 [1.06;1.07]	< 0.001
Atrial fibrillation	Yes vs. no	1.30 [1.19;1.43]	< 0.001
COPD	Yes vs. no	1.98 [1.86;2.11]	< 0.001
Ethnicity	1st generation immigrant vs. Danish	0.78 [0.71;0.85]	< 0.001
	2nd generation immigrant vs. Danish	0.56 [0.27;1.17]	0.121
Highest attained education	Highschool vs. ground school	1.03 [0.89;1.18]	0.73
	Vocational vs. ground school	0.90 [0.86;0.94]	< 0.001
	Bachelor vs. ground school	0.82 [0.77;0.88]	< 0.001
	Master vs. ground school	0.72 [0.64;0.81]	< 0.001
Metformin	Yes vs. no	0.86 [0.82;0.90]	< 0.001
Insulin	Yes vs. no	1.72 [1.59;1.86]	< 0.001
Sulfonylurea	Yes vs. no	1.06 [1.01;1.12]	0.023
DPP4 inhibitor	Yes vs. no	1.04 [0.94;1.16]	0.465
GLP-1 analog	Yes vs. no	0.92 [0.74;1.14]	0.436
Aspirin	Yes vs. no	1.06 [1.01;1.11]	0.01
ADP-inhibitor	Yes vs. no	2.09 [1.67;2.61]	< 0.001
Anticoagulants	Yes vs. no	0.92 [0.83;1.02]	0.13
Non-statin lipid-lowering drugs	Yes vs. no	1.05 [0.81;1.36]	0.701
RASi	Yes vs. no	0.85 [0.81;0.88]	< 0.001
Betablocker	Yes vs. no	1.07 [1.02;1.13]	0.007
Calcium channel blocker	Yes vs. no	1.03 [0.98;1.07]	0.288
Thiazide	Yes vs. no	1.08 [1.03;1.13]	0.003
Furosemide	Yes vs. no	1.61 [1.52;1.71]	< 0.001
Aldosterone	Yes vs. no	1.50 [1.37;1.65]	< 0.001
Year	2006 vs. 2005	1.00 [0.93;1.08]	0.93

2007 vs. 2005	0.97 [0.90;1.05]	0.452
2008 vs. 2005	0.92 [0.85;0.99]	0.035
2009 vs. 2005	0.90 [0.83;0.97]	0.009
2010 vs. 2005	0.87 [0.81;0.94]	< 0.001
2011 vs. 2005	0.89 [0.83;0.96]	0.003

Table S5. Hazard ratios of adjustment variables used for the main analysis according to proportion of days covered (reference = risk_{PDC 80-100%}).

Variable	Units	Hazard ratio	P-value
Sex	Men vs. women	1.45 [1.37;1.54]	< 0.001
Age		1.06 [1.06;1.07]	< 0.001
Atrial fibrillation	Yes vs. no	1.33 [1.15;1.53]	< 0.001
COPD	Yes vs. no	2.06 [1.87;2.27]	< 0.001
Ethnicity	1st generation immigrant vs. Danish	0.77 [0.67;0.88]	< 0.001
	2nd generation immigrant vs. Danish	0.48 [0.12;1.91]	0.294
Highest attained education	Highschool vs. ground school	0.96 [0.77;1.19]	0.688
	Vocational vs. ground school	0.87 [0.81;0.93]	< 0.001
	Bachelor vs. ground school	0.83 [0.75;0.92]	< 0.001
	Master vs. ground school	0.78 [0.66;0.93]	0.006
Metformin	Yes vs. no	0.91 [0.85;0.99]	0.02
Insulin	Yes vs. no	1.75 [1.54;1.99]	< 0.001
Sulfonylurea	Yes vs. no	1.09 [1.00;1.18]	0.039
DPP4 inhibitor	Yes vs. no	1.12 [0.98;1.29]	0.108
GLP-1 analog	Yes vs. no	1.10 [0.84;1.45]	0.48
Aspirin	Yes vs. no	1.07 [1.01;1.14]	0.026
ADP-inhibitor	Yes vs. no	2.13 [1.64;2.78]	< 0.001
Anticoagulants	Yes vs. no	1.07 [0.92;1.24]	0.394
Non-statin lipid-lowering drugs	Yes vs. no	1.13 [0.78;1.63]	0.529
RASi	Yes vs. no	0.93 [0.87;0.98]	0.014
Betablocker	Yes vs. no	1.08 [1.01;1.16]	0.032
Calcium channel blocker	Yes vs. no	1.05 [0.99;1.12]	0.118
Thiazide	Yes vs. no	1.08 [1.01;1.16]	0.029
Furosemide	Yes vs. no	1.63 [1.49;1.77]	< 0.001
Aldosterone	Yes vs. no	1.10 [0.94;1.29]	0.246
Year	2006 vs. 2005	1.01 [0.89;1.14]	0.901

2007 vs. 2005	0.91 [0.80;1.03]	0.129
2008 vs. 2005	0.88 [0.78;0.99]	0.037
2009 vs. 2005	0.83 [0.73;0.94]	0.002
2010 vs. 2005	0.81 [0.72;0.91]	< 0.001
2011 vs. 2005	0.84 [0.75;0.95]	0.004

Table S6. Hazard ratios of adjustment variables used for the nested case control population according to coverage (reference = risk_{treated}).

Variable	Units	Hazard ratio	P-value
Atrial fibrillation	Yes vs. no	1.11 [1.01;1.22]	0.027
COPD	Yes vs. no	1.91 [1.78;2.04]	<0.001
Ethnicity	1st generation immigrant vs. Danish	0.71 [0.65;0.78]	<0.001
	2nd generation immigrant vs. Danish	0.44 [0.20;0.95]	0.036
Highest attained education	Highschool vs. ground school	0.95 [0.82;1.10]	0.502
	Vocational vs. ground school	0.86 [0.82;0.90]	<0.001
	Bachelor vs. ground school	0.78 [0.72;0.83]	<0.001
	Master vs. ground school	0.71 [0.62;0.80]	<0.001
Metformin	Yes vs. no	0.91 [0.86;0.96]	<0.001
Insulin	Yes vs. no	1.49 [1.38;1.62]	<0.001
Sulfonylurea	Yes vs. no	1.15 [1.09;1.21]	<0.001
DPP4 inhibitor	Yes vs. no	0.79 [0.72;0.88]	<0.001
GLP-1 analog	Yes vs. no	0.62 [0.51;0.74]	<0.001
Aspirin	Yes vs. no	1.09 [1.03;1.14]	<0.001
ADP-inhibitor	Yes vs. no	1.50 [1.23;1.82]	<0.001
Anticoagulants	Yes vs. no	1.07 [0.97;1.18]	0.205
Non-statin lipid-lowering drugs	Yes vs. no	0.76 [0.58;0.99]	0.045
RASi	Yes vs. no	0.83 [0.79;0.87]	<0.001
Betablocker	Yes vs. no	1.06 [1.01;1.12]	0.027
Calcium channel blocker	Yes vs. no	1.02 [0.97;1.07]	0.526
Thiazide	Yes vs. no	1.12 [1.06;1.18]	<0.001
Furosemide	Yes vs. no	1.59 [1.49;1.69]	<0.001
Aldosterone	Yes vs. no	1.32 [1.20;1.46]	<0.001
Year	2006 vs. 2005	1.00 [0.92;1.09]	0.983
	2007 vs. 2005	0.92 [0.84;1.01]	0.072
	2008 vs. 2005	0.82 [0.75;0.91]	<0.001

2009 vs. 2005	0.77 [0.70;0.86]	<0.001
2010 vs. 2005	0.72 [0.65;0.81]	<0.001
2011 vs. 2005	0.70 [0.62;0.79]	<0.001

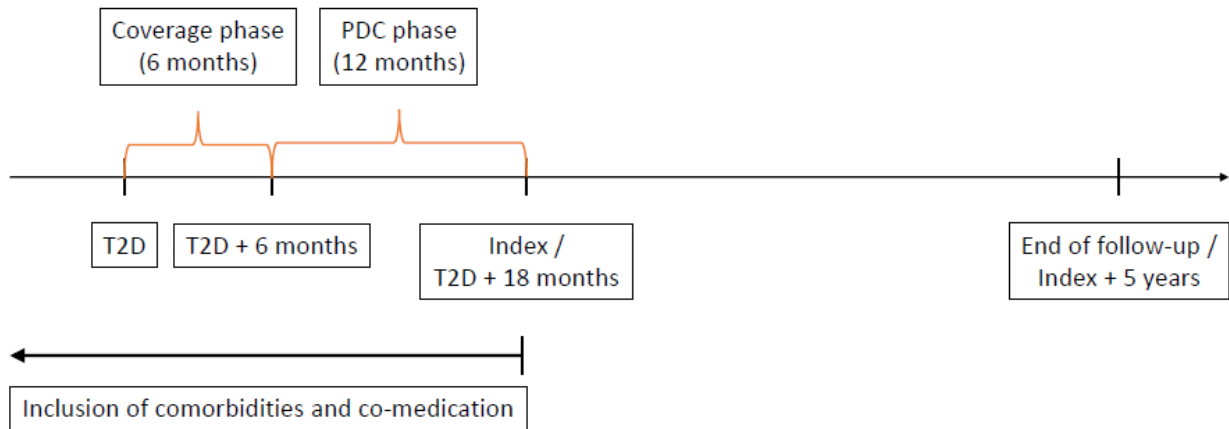
Table S7. Hazard ratios of adjustment variables used for the nested case control population according to proportion of days covered (reference = risk_{PDC 80-100%}).

Variable	Units	Hazard ratio	P-value
Atrial fibrillation	Yes vs. no	1.09 [0.95;1.24]	0.227
COPD	Yes vs. no	1.96 [1.77;2.16]	< 0.001
Ethnicity	1st generation immigrant vs. Danish	0.69 [0.60;0.80]	< 0.001
	2nd generation immigrant vs. Danish	0.34 [0.08;1.44]	0.144
Highest attained education	Highschool vs. ground school	0.87 [0.70;1.09]	0.234
	Vocational vs. ground school	0.85 [0.80;0.91]	< 0.001
	Bachelor vs. ground school	0.77 [0.70;0.85]	< 0.001
	Master vs. ground school	0.75 [0.62;0.90]	0.002
Metformin	Yes vs. no	0.92 [0.85;0.99]	0.031
Insulin	Yes vs. no	1.40 [1.24;1.57]	< 0.001
Sulfonylurea	Yes vs. no	1.14 [1.05;1.23]	0.001
DPP4 inhibitor	Yes vs. no	0.85 [0.75;0.96]	0.01
GLP-1 analog	Yes vs. no	0.65 [0.52;0.82]	< 0.001
Aspirin	Yes vs. no	1.14 [1.07;1.21]	< 0.001
ADP-inhibitor	Yes vs. no	1.56 [1.24;1.96]	< 0.001
Anticoagulants	Yes vs. no	1.25 [1.08;1.43]	0.002
Non-statin lipid-lowering drugs	Yes vs. no	0.69 [0.42;1.13]	0.142
RASi	Yes vs. no	0.91 [0.86;0.97]	0.004
Betablocker	Yes vs. no	1.10 [1.02;1.18]	0.01
Calcium channel blocker	Yes vs. no	1.07 [1.00;1.14]	0.049
Thiazide	Yes vs. no	1.09 [1.02;1.17]	0.012
Furosemide	Yes vs. no	1.55 [1.42;1.69]	< 0.001
Aldosterone	Yes vs. no	1.26 [1.08;1.47]	0.003
Year	2006 vs. 2005	0.90 [0.79;1.02]	0.094
	2007 vs. 2005	0.86 [0.76;0.98]	0.025
	2008 vs. 2005	0.74 [0.65;0.85]	< 0.001

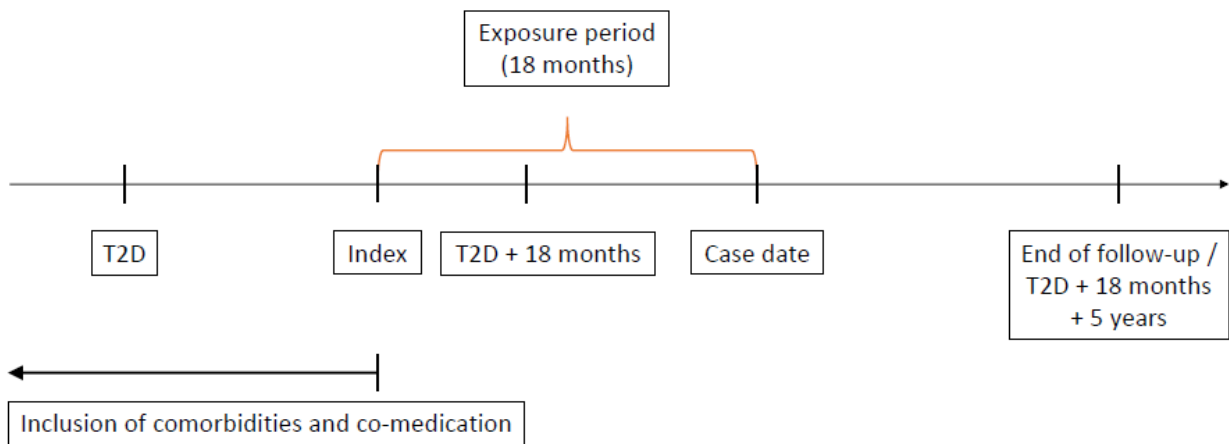
2009 vs. 2005	0.67 [0.58;0.78]	< 0.001
2010 vs. 2005	0.63 [0.54;0.73]	< 0.001
2011 vs. 2005	0.62 [0.53;0.73]	< 0.001

Figure S1. Illustration of the study setup in the main analysis (A) and in the nested case control population (B).

A) Main analysis



B) Nested case control analysis



T2D = Type 2 diabetes, PDC = proportion of days covered.

Figure S2. Flowchart.

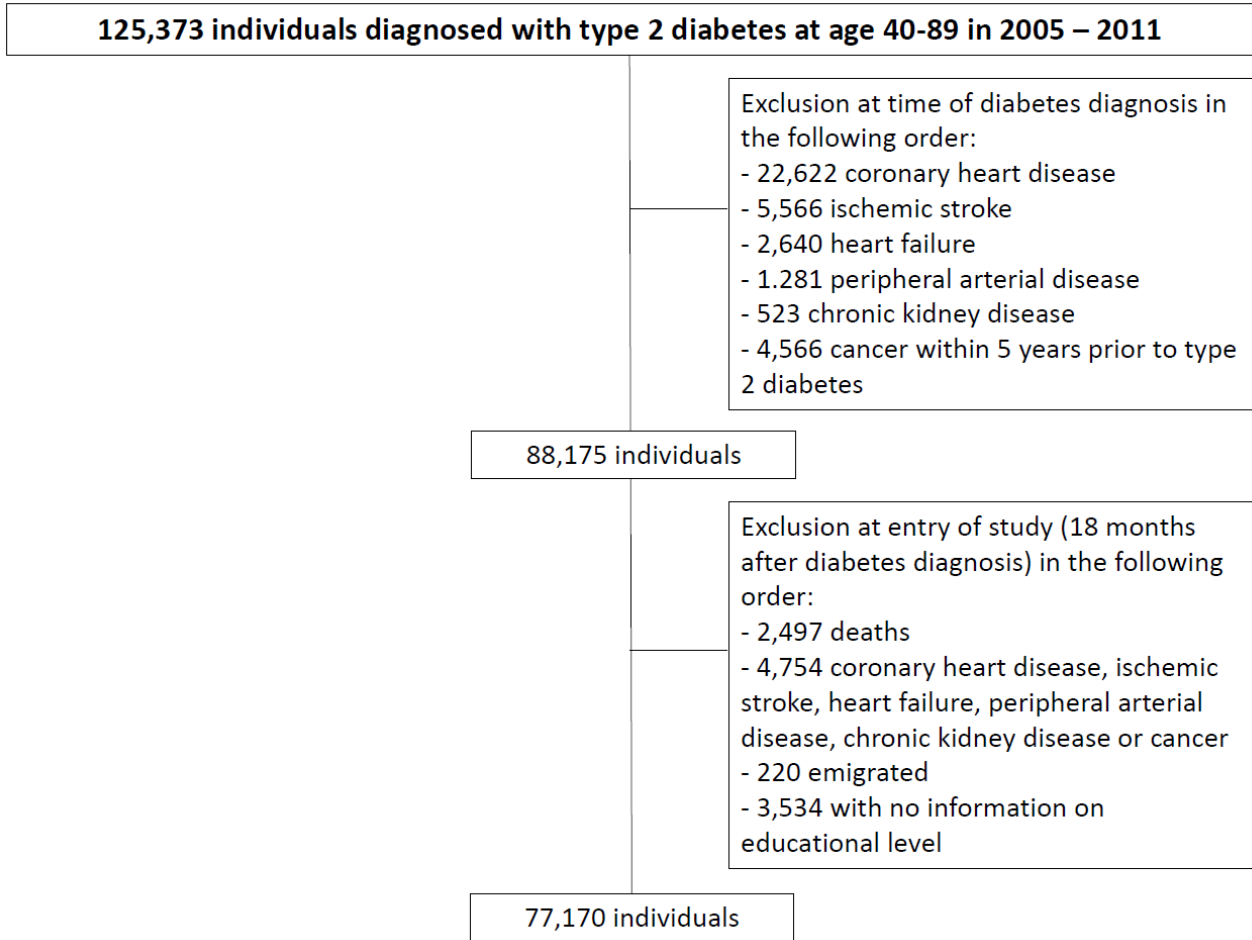
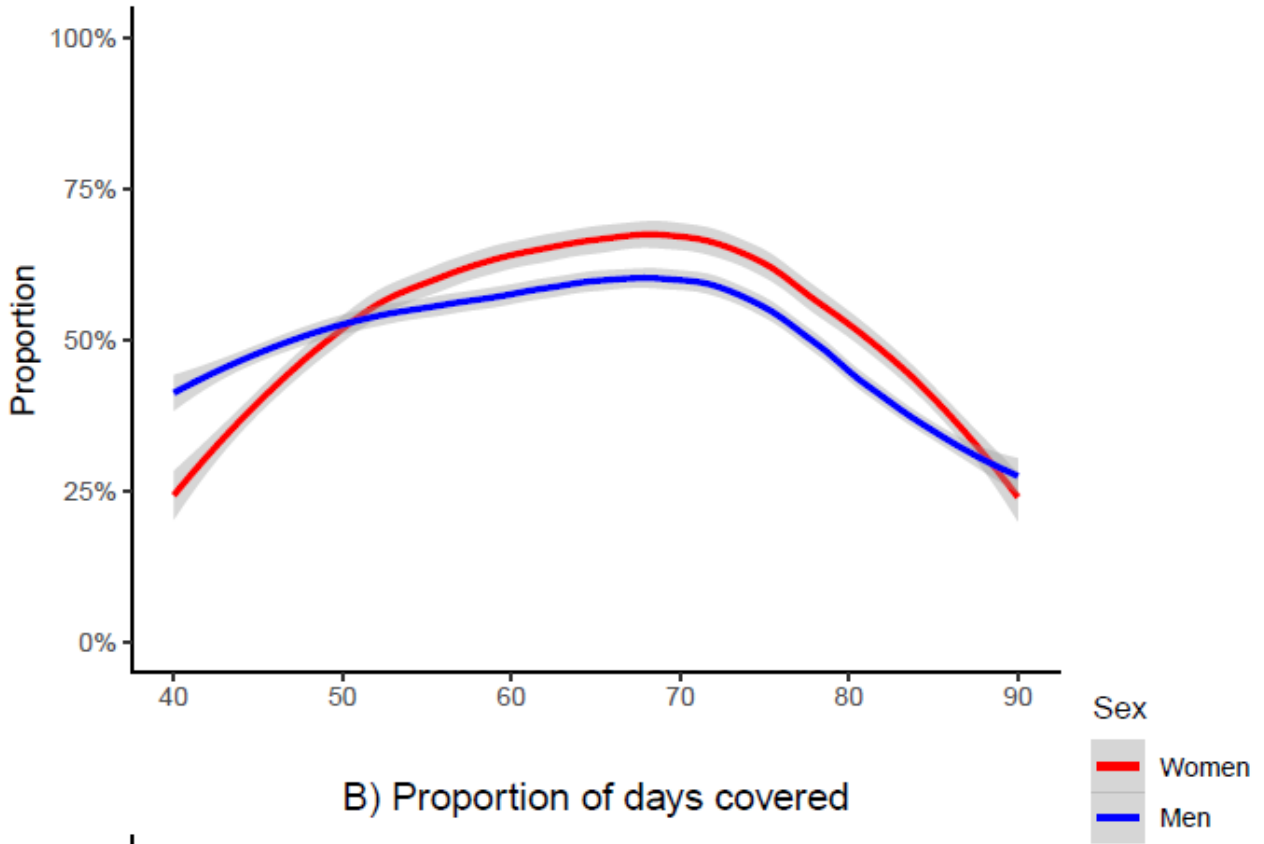


Figure S3. A) Proportion of patients treated with statins at index by age and sex, and B) mean proportion of days covered at index by age and sex in patients treated with statins at index.

A) Initiated treatment with statins



B) Proportion of days covered

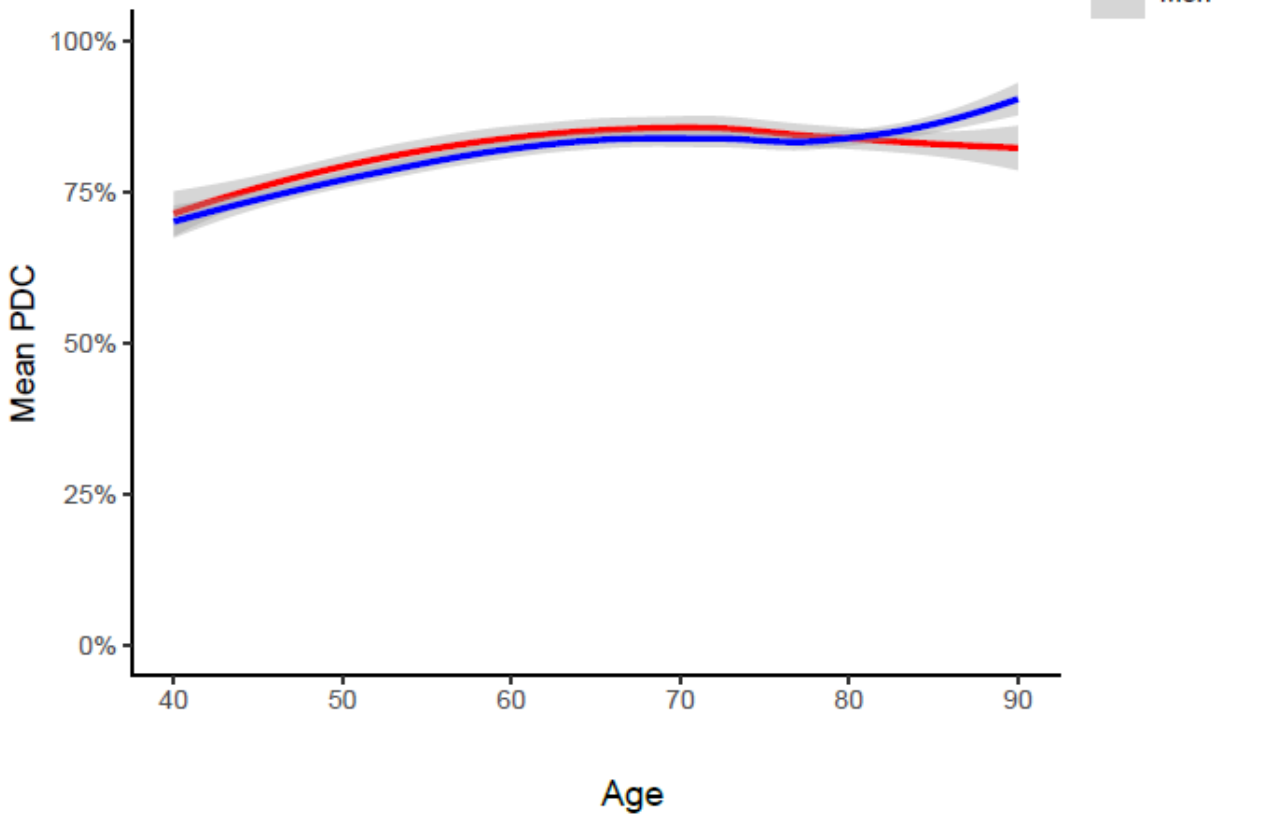


Figure S4. Crude and standardized 5-year risk of myocardial infarction, ischemic stroke or all-cause death according to sex, coverage and proportion of days covered.

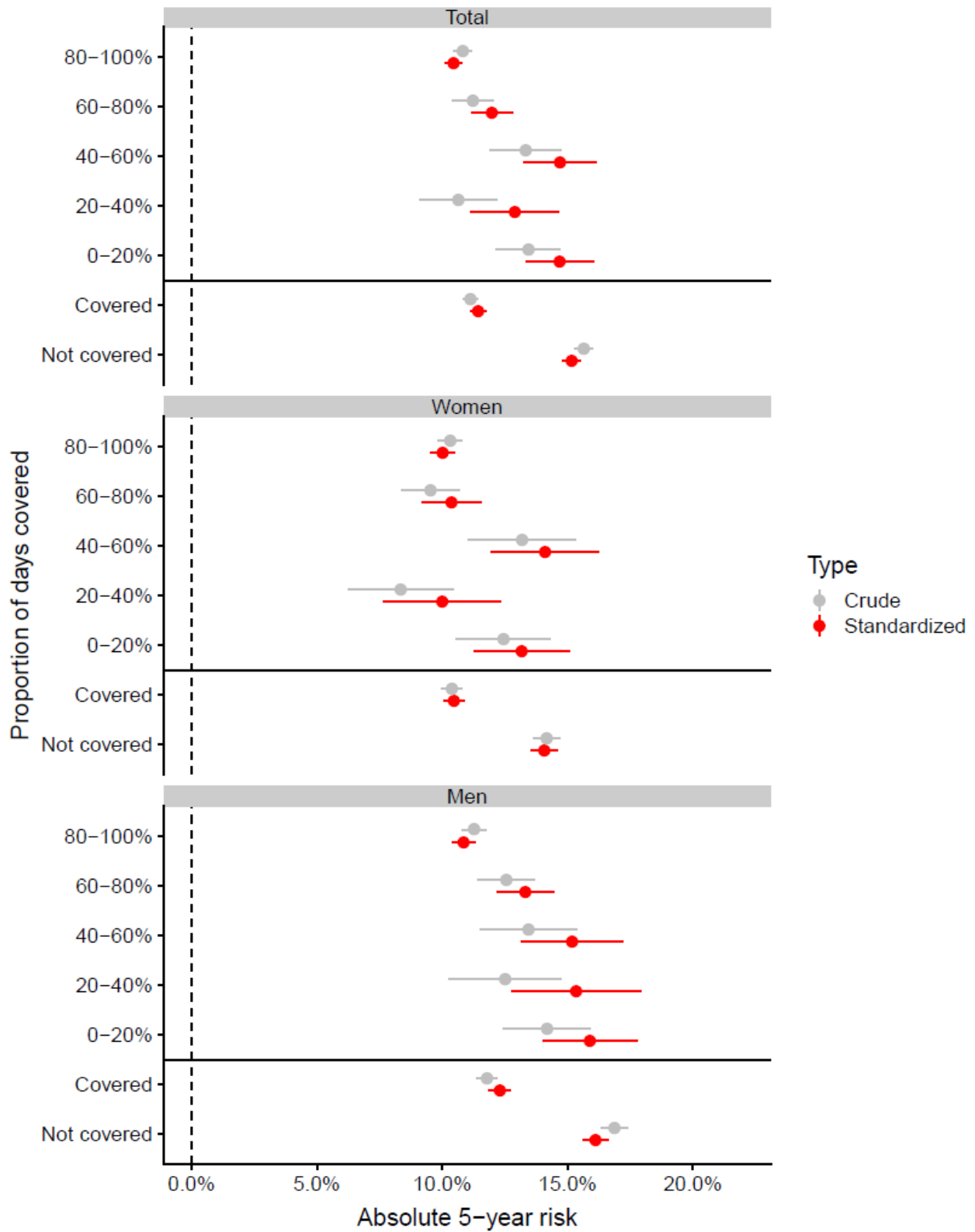
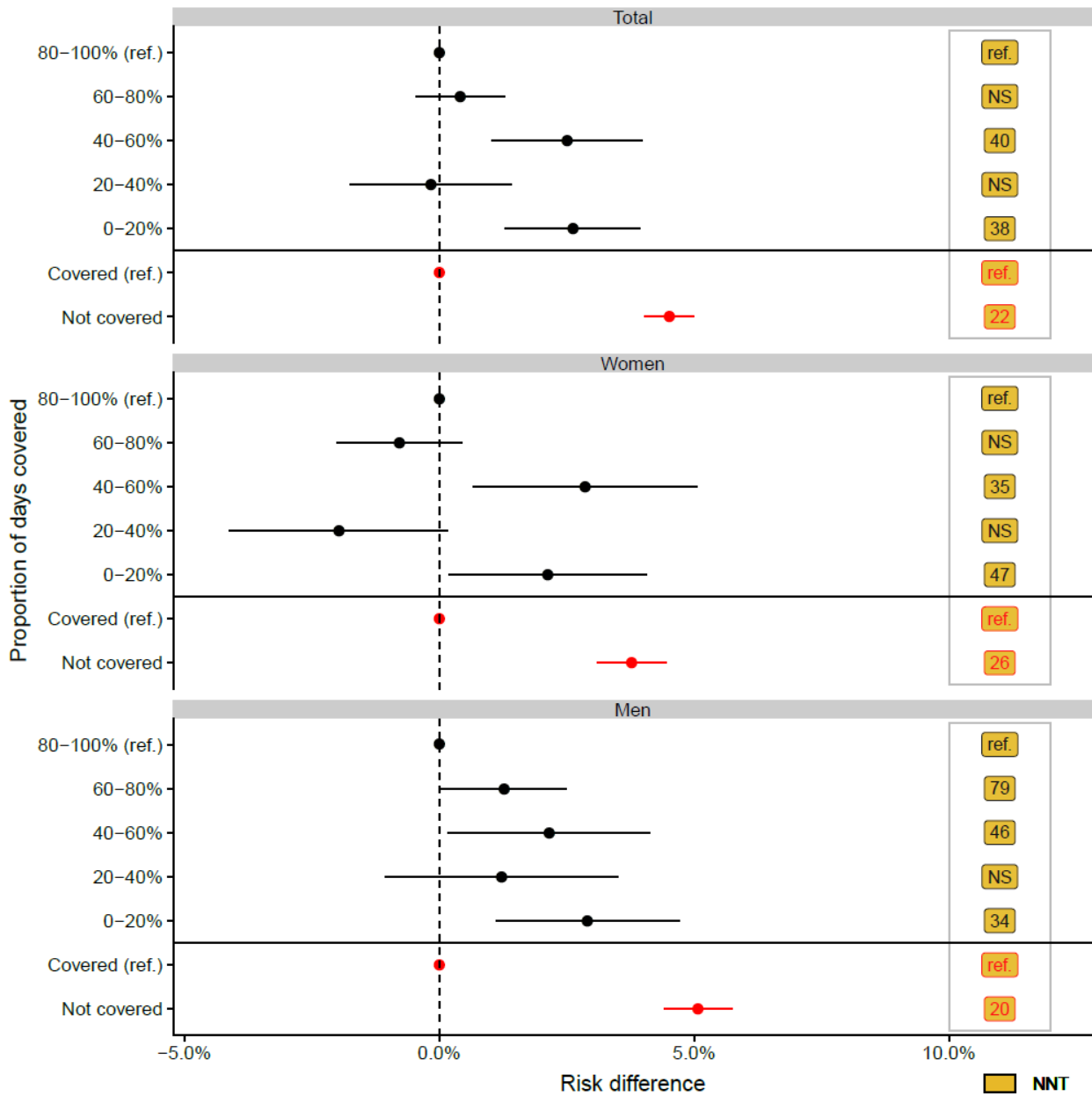


Figure S5. Crude 5-year risk difference of myocardial infarction, ischemic stroke or all-cause death according to sex, coverage of statins (reference = risk_{treated}) and proportion of days covered (reference = risk_{PDC 80-100%}).



NNT = Numbers needed to treat, NS = Not significant.

Figure S6. Standardized 5-year risk of myocardial infarction, ischemic stroke or all-cause death according to sex, age and coverage.

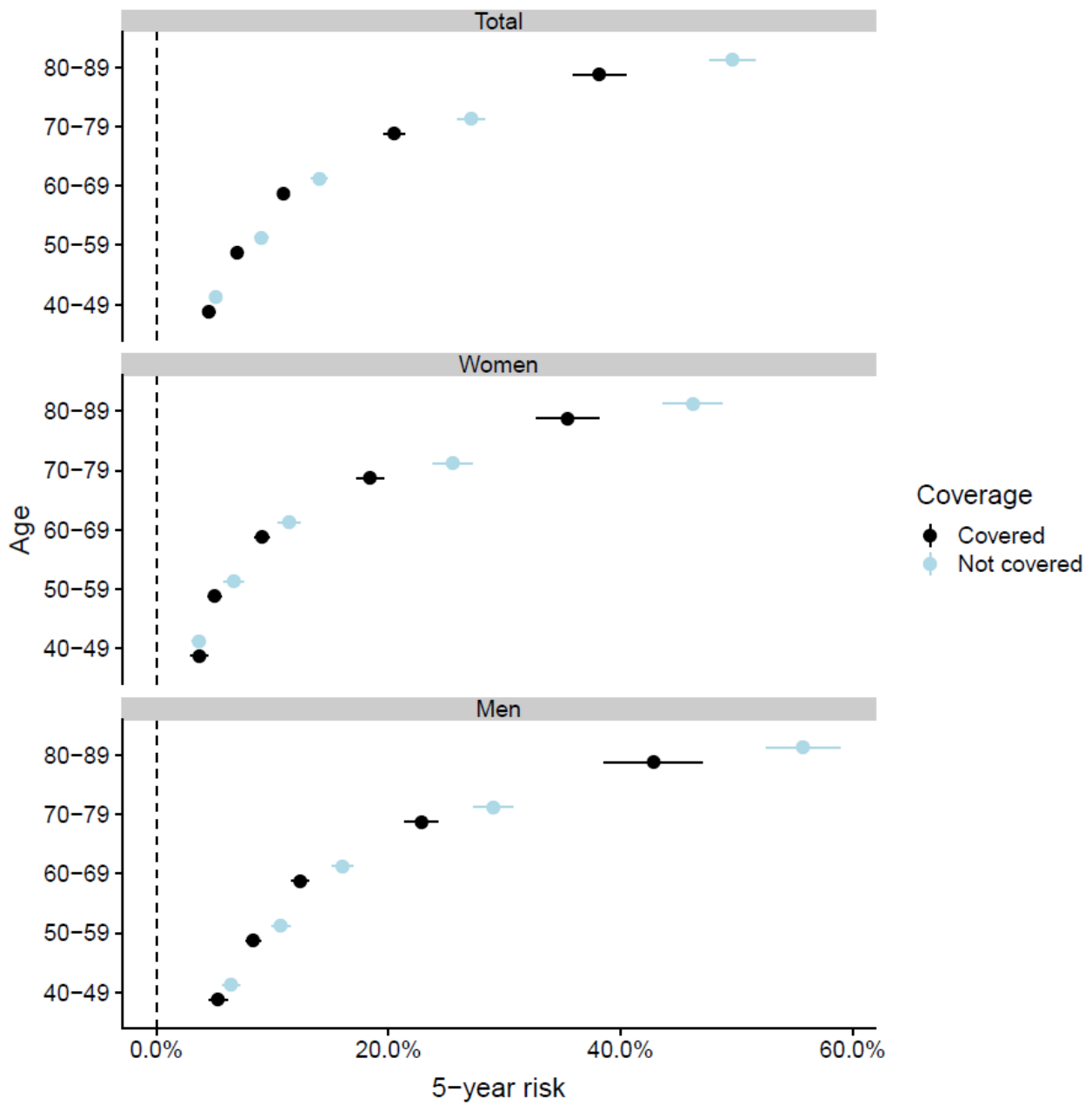


Figure S7. A) Crude and standardized 5-year risk of hospital discharge due to any skin lesion according to sex, coverage of statins and proportion of days covered. B) Standardized 5-year risk of hospital discharge due to any skin lesion according to sex, age-group and coverage of statins.

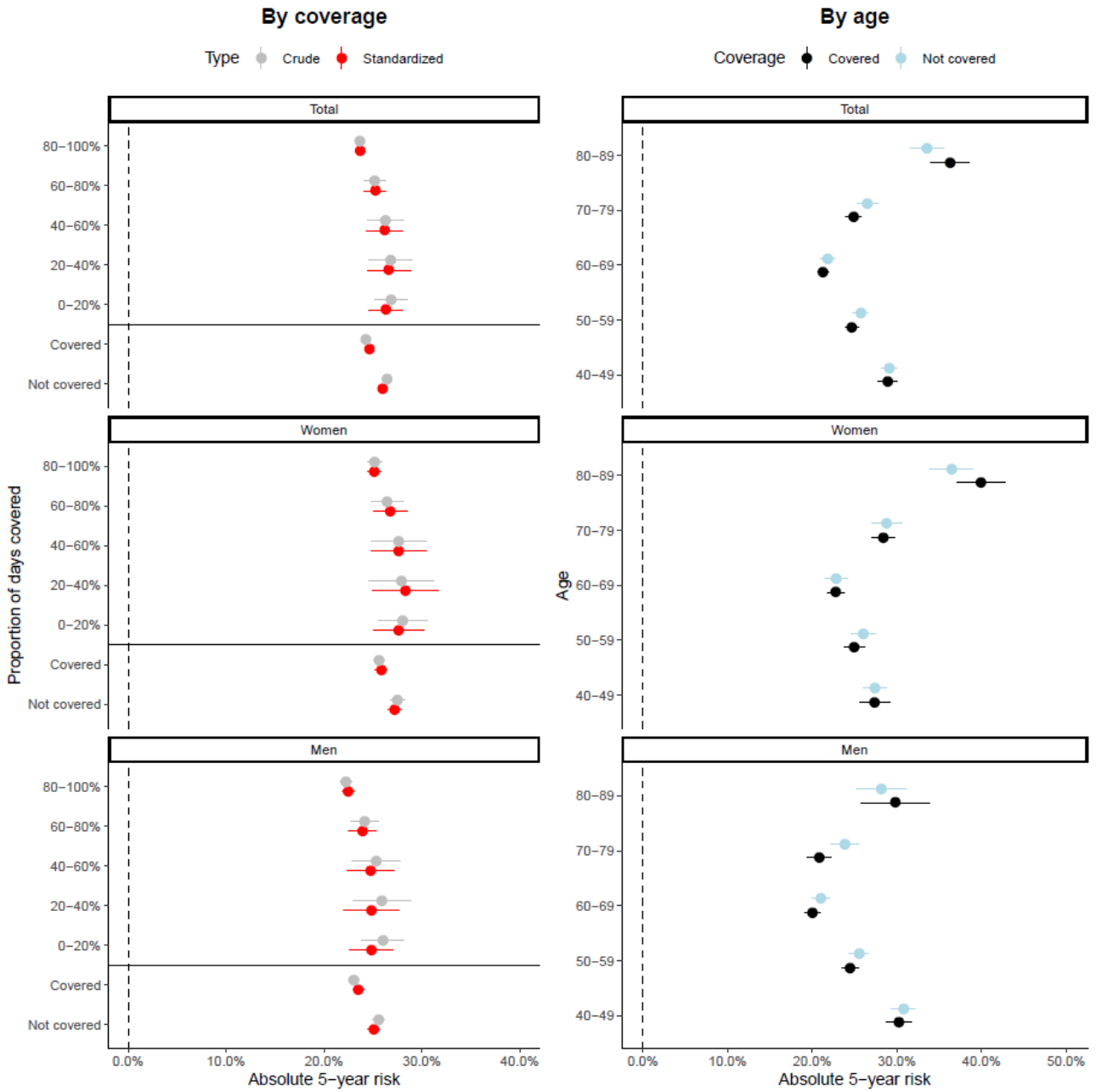
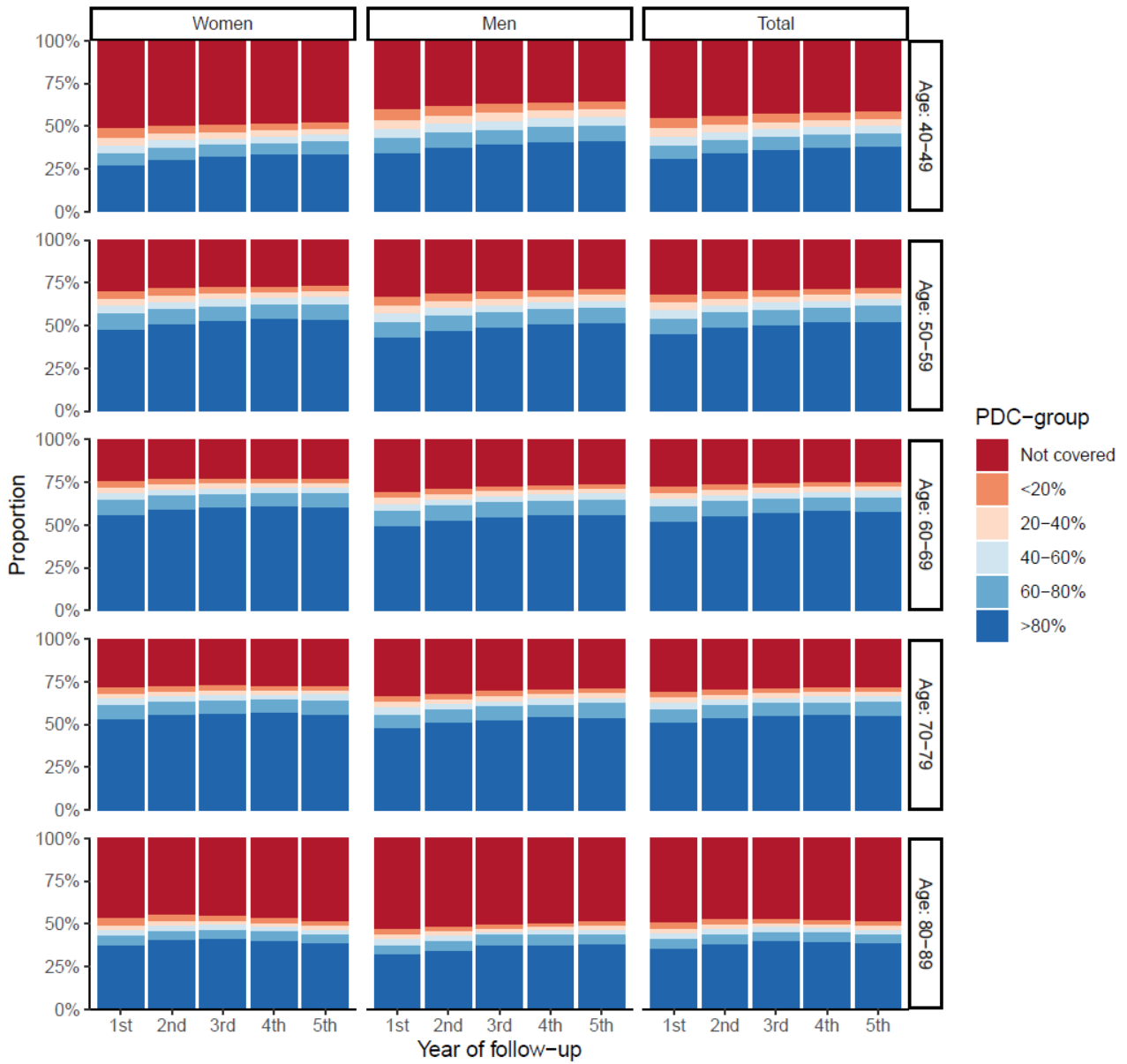
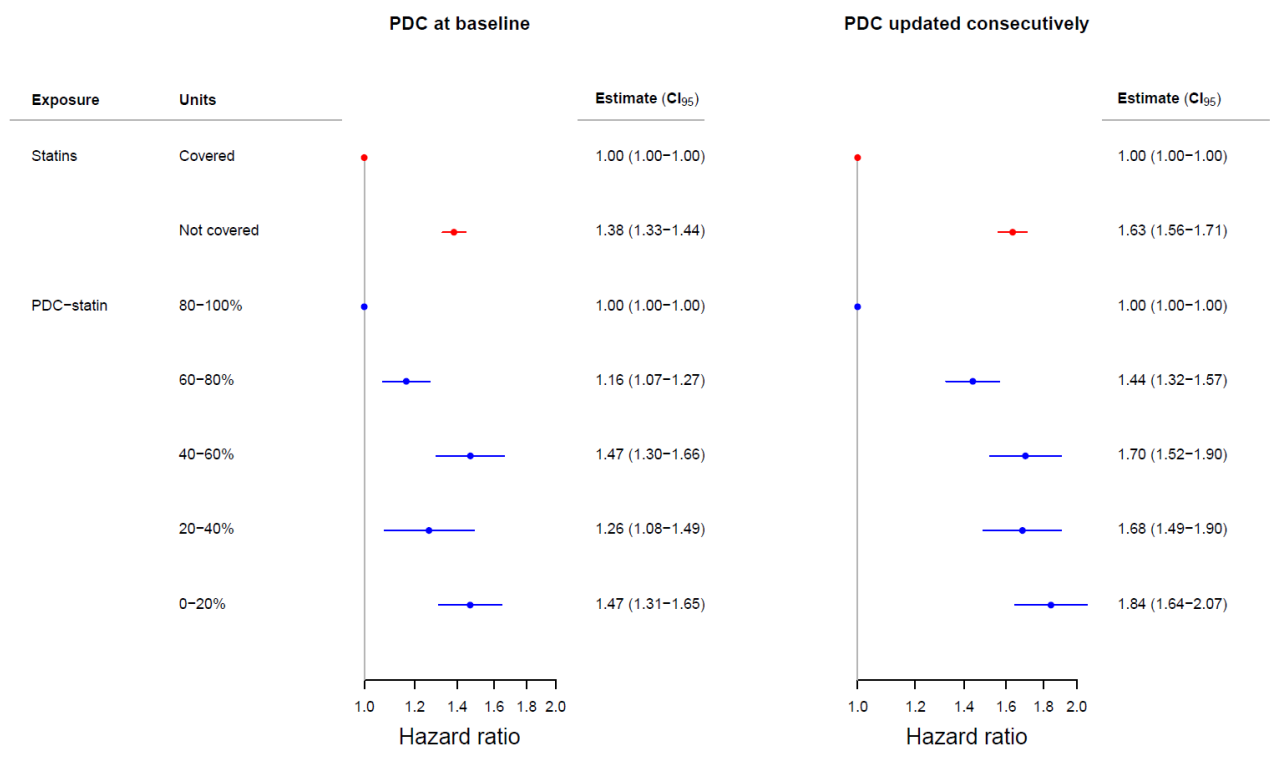


Figure S8. Coverage of statins according to sex, age group at time of type 2 diabetes diagnosis and year of follow-up in event-free individuals.



PDC = Proportion of days covered.

Figure S9. Adjusted Hazard ratios of myocardial infarction, ischemic stroke or all-cause death according to coverage (red) and proportion of days covered (blue) of statins in the main analysis and the nested case-control population.



PDC = proportion of days covered.