Supplementary Material:

Ethical approval:

We made secondary use of a research database of medical claims records that is safeguarded and maintained by the Main Association of Austrian Social Security Institutions (HVB) and where it has been ensured that no individual is identifiable. This is a consolidated research database that is only accessible for selected partners under a strict data protection policy. Use of the data takes place in agreement and cooperation with the HVB. The data contains no names of individual patients or health care provider. All unique identifiers, such as the social security number, have been removed along with postal codes and the date of birth for the patients. Only district information and year of birth is available. All team members working with the data have signed a confidentiality agreement and declaration of commitment ensuring that research will be undertaken in accordance with the applicable data protection regulations. A security clearance for this database signed by MUV's legal department that states that individuals are not identifiable is enclosed in this submission.

Supplementary table S1:
Baseline characteristics of the osteoporotic population stratified by sex

	All	male	female
N	80,400	12,175	68,225
Age (mean +/- SD)	73.26 +/- 11.89	68.52 +/- 13.97	74.11 +/- 11.28
Statins	11,701 (14.55%)	1,765 (14.50%)	9,936 (14.56%)
Corticosteroids (Z92.241 and Z79.52)	1,311 (1.63%)	204 (1.68%)	1,107 (1.62%)
Insulin	2,489 (3.10%)	407 (3.34%)	2,082 (3.05%)
Oral antidiabetics	4,899 (6.09%)	786 (6.46%)	4,113 (6.03%)
Fibrates	864 (1.07%)	107 (0.88%)	757 (1.11%)
Arthritis (M06)	3,096 (3.85%)	386 (3.18%)	2,710 (3.97%)
CVD (I20–I25)	18,725 (23.29%)	3,423 (28.11%)	15,302 (22.43%)

Stroke (I63, I64)	4,045 (5.03%)	678 (5.57%)	3,367 (4.94%)
Diseases of arteries (I70–I79)	9,660 (12.01%)	1,988 (16.33%)	7,672 (11.25%)
Renal failure (N17–N19)	9,630 (11.98%)	1,818 (14.93%)	7,812 (11.45%)
Overweight and Obesity (E66)	6,318 (7.86%)	1,002 (8.23%)	5,315 (7.79%)
Nicotine abuse (F17)	2,108 (2.62%)	872 (7.16%)	1.236 (1.81%)
Fractures	12,879 (16.02%)	2,065 (16.96%)	10.814 (15.85%)

Supplementary table S2:
Baseline characteristics of the osteoporotic population with fracture stratified by sex

	All	male	female
N	12,879	2,065	10,814
Age (mean +/- SD)	75.68 +/- 10.77	71.16 +/- 13.14	76.55 +/- 10.03
Statins	1,678 (13.03%)	259 (12.54%)	1,419 (13.12%)
Insulin	419 (3.25%)	84 (4.07%)	335 (3.10%)
Oral antidiabetics	766 (5.95%)	146 (7.07%)	620 (5.73%)
Corticosteroids (Z92.241 and Z79.52)	287 (2.23%)	54 (2.62%)	233 (2.15%)
Fibrates	109 (0.85%)	12 (0.58%)	97 (0.90%)
Arthritis (M06)	517 (4.01%)	53 (2.57%)	464 (4.29%)
CVD (I20–I25)	3,485 (27.06%)	639 (30.94%)	2,846 (26.32%)

Stroke (I63, I64)	755 (5.86%)	122 (5.91%)	633 (5.85%)
Diseases of arteries (I70–I79)	1,831 (14.22%)	402 (19.47%)	1,429 (13.21%)
Renal failure (N17–N19)	1,986 (15,42%)	364 (17,63%)	1,622 (15.00%)
Overweight and Obesity (E66)	999 (7.76%)	158 (7.65%)	841 (7.78%)
Nicotine abuse (F17)	411 (3.19%)	191 (9.25%)	220 (2.03%)

Supplementary table S3:

	Statin	**Control**
Age (years)	Odds (95%-CI)	Odds (95%-CI)
40-50	3.27 ** (2.22—4.84)	1.99** (1.82—2.18)
50-60	3.42** (2.91—4.04)	2.81** (2.66—2.97)
60-70	4.67** (4.23—5.16)	3.84** (3.67—4.01)
70-80	5.11** (4.71—5.55)	4.57** (4.40—4.75)
80-90	4.67** (4.16—5.25)	3.94** (3.77—4.12)

** p<0.01; *p<0.05

In supplementary table S3 we present a different view on the data by comparing the odds of being diagnosed with osteoporosis with the odds of being female in the statin-treated and the control group, compared to males, respectively. This analysis confirms that female sex is significantly associated with increased odds of osteoporosis across all ages in both groups. By comparing the effect sizes between the statin-treated and the control group, we see that statin treatment coincides with significantly increased odds in females when compared to males, i.e. the statin—osteoporosis association is stronger in females than males. For instance, in the age group 40—50 years we find that females with statins have a 3.27-fold (p<0.01) increased risk

to be diagnosed with osteoporosis when compared to men, whereas females without statin treatment (control group) only have a 1.99-fold ($p<0.01$) increased risk for osteoporosis compared to males. In younger age groups (below 70 years), this effect was particularly strong. Furthermore, OR-intra increases as a function of age in both groups.

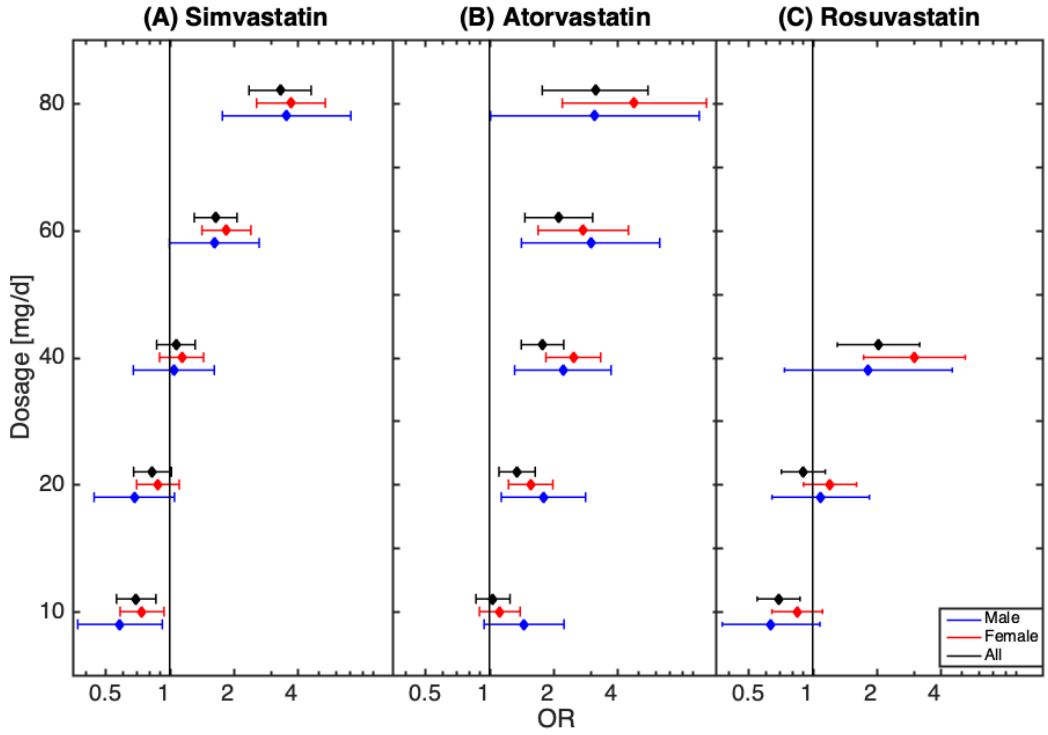
Supplementary table S4: Individual statin dosage-dependent ORs of osteoporosis with fracture (95% CI) obtained from the logistic regression model

All	**Lovastatin**	**Fluvastatin**	**Pravastatin**	**Simvastatin**	**Atorvastatin**	**Rosuvastatin**
0–10 mg	0.86	1.00	1.00	0.84	1.32	1.00
CI	0.15–4.83	1.00–1.00	0.56–1.77	0.54–1.30	0.85–2.05	0.57–1.75
10–20 mg	1.43	0.67	1.02	0.97	**2.03****	1.43
CI	0.53–3.87	0.31–1.47	0.63–1.63	0.64–1.47	1.27–3.26	0.75–2.71
20–40 mg	1.66	1.02	1.34	1.16	**2.35****	1.46
CI	0.38–7.26	0.62–1.68	0.82–2.17	0.75–1.77	1.35–4.10	0.49–4.31
40–60 mg		1.27		**2.63****	**3.75****	
CI		0.78–2.06		1.63–4.23	1.63–8.65	
60–80 mg		**1.60***		**4.73****	**8.68****	
CI		0.94–2.73		2.41–9.28	2.39–31.56	

** p<0.01; *p<0.05

Supplementary table S4 shows that increased doses of Fluvastatin (>60mg), Simvastatin (>40mg) and Atorvastatin (>10mg) are related to an overrepresentation of diagnosed osteoporosis with fracture.

Supplementary Figure S1: Dosage dependency of the statin—osteoporosis association. While low doses of statin can even be related to decreased osteoporosis risks, the disease risk clearly increases for higher doses



Supplementary table S5: Individual statin dosage-dependent ORs of osteoporosis (95% CI) obtained from the logistic regression model for females (pink) and males (blue):

Female	Lovastatin	Fluvastatin	Pravastatin	Simvastatin	Atorvastatin	Rosuvastatin
0-10 mg	**0.41***	1.00	**0.73***	**0.74***	1.12	0.85
CI	0.18--0.89	1.00--1.00	0.53--1.00	0.59--0.94	0.90--1.39	0.64--1.11
10-20 mg	0.95	**0.59****	0.88	0.88	**1.56****	1.21
CI	0.61--1.48	0.40--0.87	0.68--1.14	0.70--1.11	1.23--1.99	0.91--1.61
20-40 mg	1.80	0.93	1.05	1.14	**2.48****	**3.01****
CI	0.93--3.48	0.73--1.19	0.81--1.37	0.90--1.44	1.84--3.33	1.73--5.21
40-60 mg		0.98		**1.85****	**2.76****	
CI		0.77--1.24		1.42--2.41	1.69--4.50	
60-80 mg		1.09		**3.72****	**4.80****	
CI		0.85--1.42		2.56--5.39	2.20--10.48	
Adj. R^2	0.96	0.95	0.95	0.94	0.96	0.96
max.VIF	4.21	3.26	3.04	2.74	2.87	3.29

Male	Lovastatin	Fluvastatin	Pravastatin	Simvastatin	Atorvastatin	Rosuvastatin
0-10 mg	1.00	1.00	0.71	**0.58***	1.45	0.64
CI	1.00--1.00	1.00-1.00	0.40--1.24	0.37--0.92	0.94--2.22	0.38--1.08
10-20 mg	1.05	0.65	0.94	0.68	**1.79***	1.09
CI	0.35--3.09	0.30--1.37	0.59--1.48	0.44--1.05	1.14--2.83	0.64--1.85
20-40 mg	1.00	0.68	1.08	1.05	**2.21****	1.83
CI	1.00--1.00	0.43--1.08	0.68--1.71	0.67--1.62	1.31--3.73	0.74--4.53
40-60 mg		0.90		1.62	**2.99****	
CI		0.57--1.43		1.00--2.63	1.41--6.31	
60-80 mg		1.52		**3.54****	**3.13***	
CI		0.93--2.49		1.77--7.11	1.01--9.67	
Adj. R^2	0.72	0.72	0.73	0.77	0.72	0.71
max. VIF	4.21	3.26	3.04	2.74	2.87	3.29

** p<0.01; *p<0.05

Interpretation:

In the sex-specific analysis only low dose simvastatin treatment is related to an underrepresentation of diagnosed osteoporosis in males [0-10mg: OR(m):0.58, 95%CI:0.37—0.92, p<0.05] and a low dose lovastatin [0-10mg: OR(f):0.41, CI:0.18—0.89, p<0.05], fluvastatin [10-20mg: OR(f):0.59, CI:0.40—0.87, p<0.01], pravastatin [0-10mg: OR(f):0.73, CI:0.53—1, p<0.05] and simvastatin [0-10mg: OR(f):0.74, CI:0.59—0.94, p<0.05] treatment in females. With increased dosage, however the relationship between statin treatment and osteoporosis reverses. In both females and males, the increase in dose of simvastatin and atorvastatin is related to a higher occurrence of osteoporosis, whereas for rosuvastatin this relationship only remains significant in female patients (see supplementary table S5 and supplementary figure S1).

Supplementary table S6: Average age of the individual dosage groups for each statin regression model

All	Lovastatin	Fluvastatin	Pravastatin	Simvastatin	Atorvastatin	Rosuvastatin
0-10 mg	69.86	66.43	67.55	66.01	66.26	62.16
SD	10.79	11.49	10.83	10.88	10.88	10.89
10-20 mg	71.93	65.54	68.57	66.79	66.85	63
SD	9.74	11.44	10.61	10.81	10.99	10.35
20-40 mg	71.83	66.24	69.08	67.49	64.76	62.61
SD	9.59	11.09	10.45	10.72	11.05	10.90
40-60 mg		66.71		68.18	64.32	
SD		10.93		10.69	11.36	
60-80 mg		66.66		70.05	63.57	
SD		10.88		10.67	11.67	

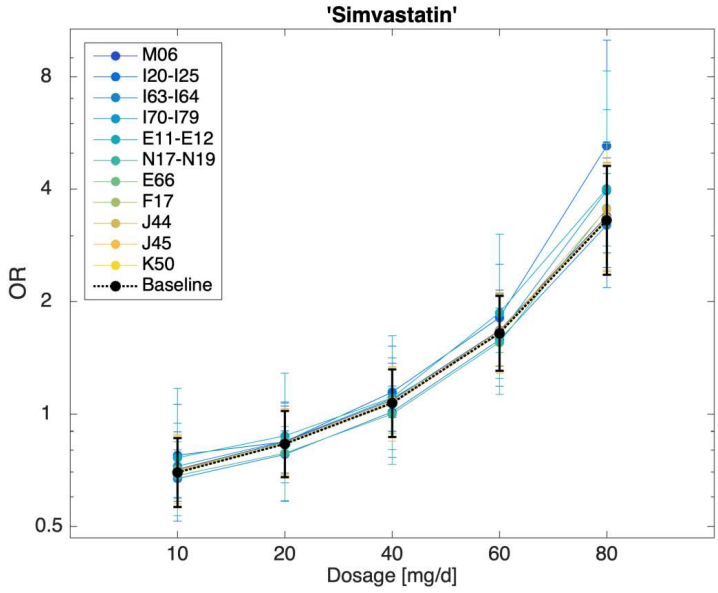
(SD: standard deviation)

Baseline-Tests:

1. Rheumatoid arthritis (ICD-code: M06)
2. Ischaemic heart diseases (ICD-code: I20-I25)
3. Diseases of arteries including arterioles and capillaries (ICD-code: I70-I79)
4. Stroke (ICD-code: I63, I64)
5. Diabetes mellitus type 1 and 2 (ICD-code: E10, E11)
6. Chronic renal insufficiency (ICD-code: N17-N19)
7. Chronic obstructive pulmonary disease (ICD-code: J44)
8. Asthma (ICD-code: J45)
9. Crohn disease (ICD-code: K50)
10. Nicotine dependence (ICD-code: F17)
11. Overweight and obesity (ICD-code: E66)

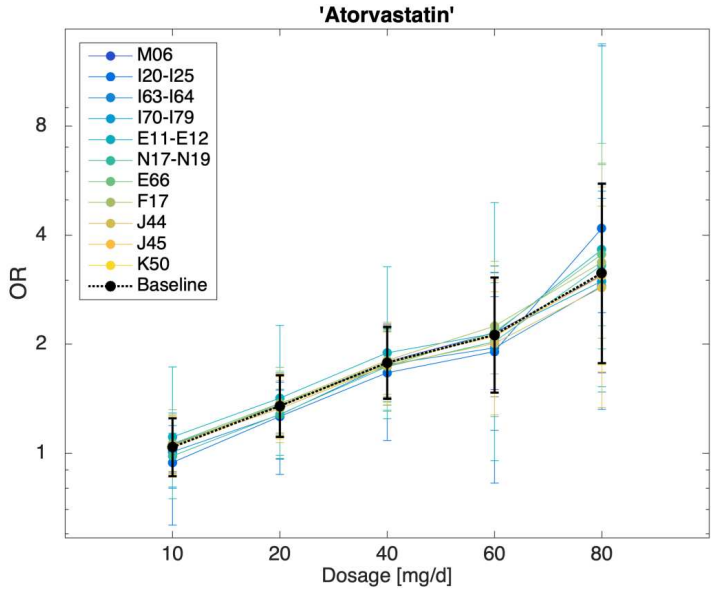
To test whether or not the observed dosage-dependent trend is independent of the identified comorbidity groups, we performed a multiple logistic regression analysis with the difference that the patients of the respective confounding disease group were excluded to investigate their influence on ORs development. The obtained results of each regression were visualized as one graphic, to compare the individual risk trajectories.

Supplementary figure S2: Dosage-dependent osteoporosis risk trajectories for the individual diseases groups of simvastatin.

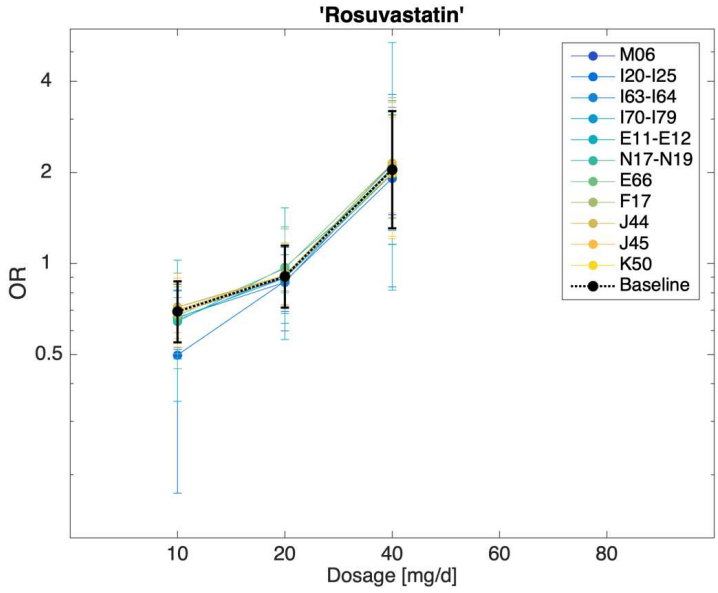


The figure above presents the dosage-dependent osteoporosis risk trajectories for the individual disease groups of simvastatin. The baseline (black) denote all individuals treated with simvastatin and their dosage-dependent osteoporosis risk development. The other 11 trajectories display how the risk develops when patients of a particular disease group are excluded. The figure shows that all trajectories follow the same trend that a higher dose is associated with higher incidence of osteoporosis diagnosis. Although we observe a higher variance of ORs in the highest dosage category (>60-80 mg), the differences can be neglected as they are likely to result from the small case numbers of this dosage category. This is indicated by the large confidence intervals. The interpretation of the results is further confirmed by the results of other statins as shown in supplementary figure S3,S4,S5,S6,S7.

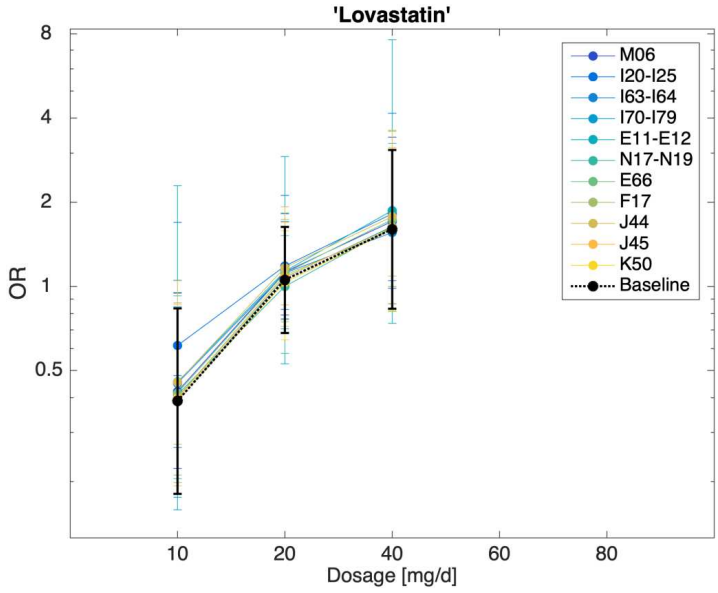
Supplementary figure S3: Dosage-dependent osteoporosis risk trajectories for the individual diseases groups of atorvastatin.



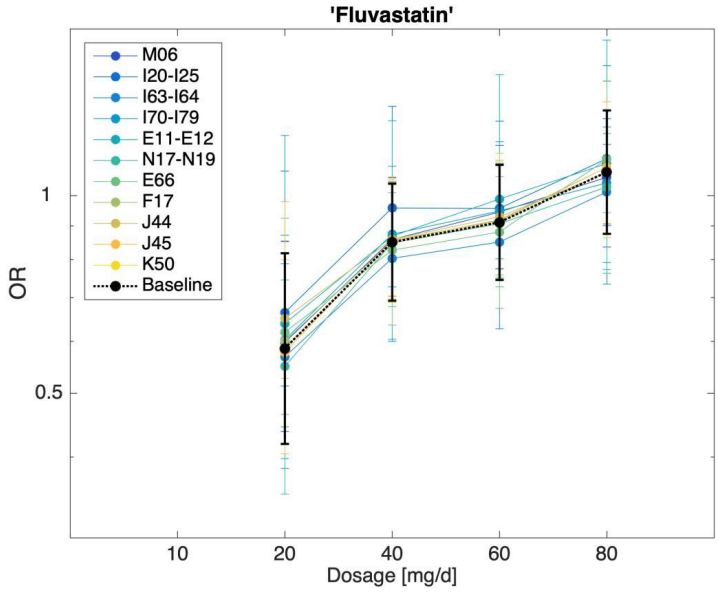
Supplementary figure S4: Dosage-dependent osteoporosis risk trajectories for the individual diseases groups of rosuvastatin.



Supplementary figure S5: Dosage-dependent osteoporosis risk trajectories for the individual diseases groups of lovastatin.



Supplementary figure S6: Dosage-dependent osteoporosis risk trajectories for the individual diseases groups of fluvastatin.



Supplementary figure S7: Dosage-dependent osteoporosis risk trajectories for the individual diseases groups of pravastatin.