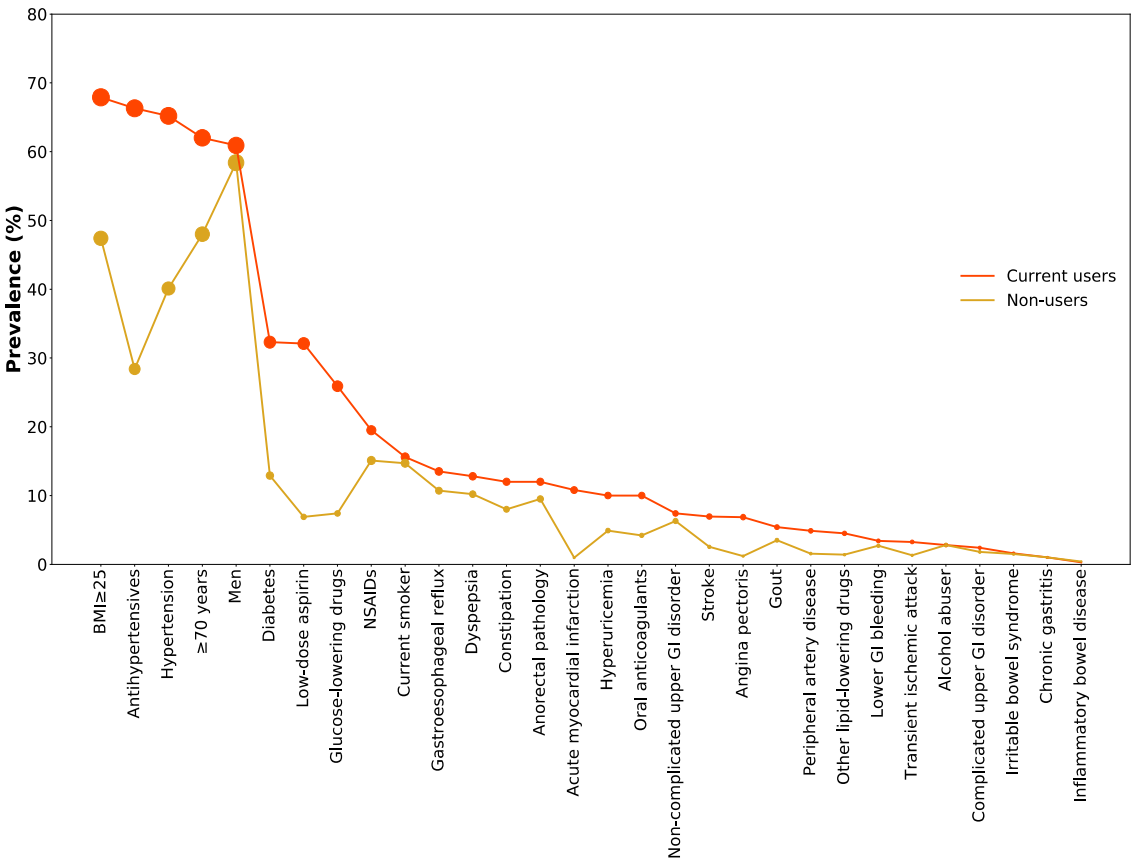


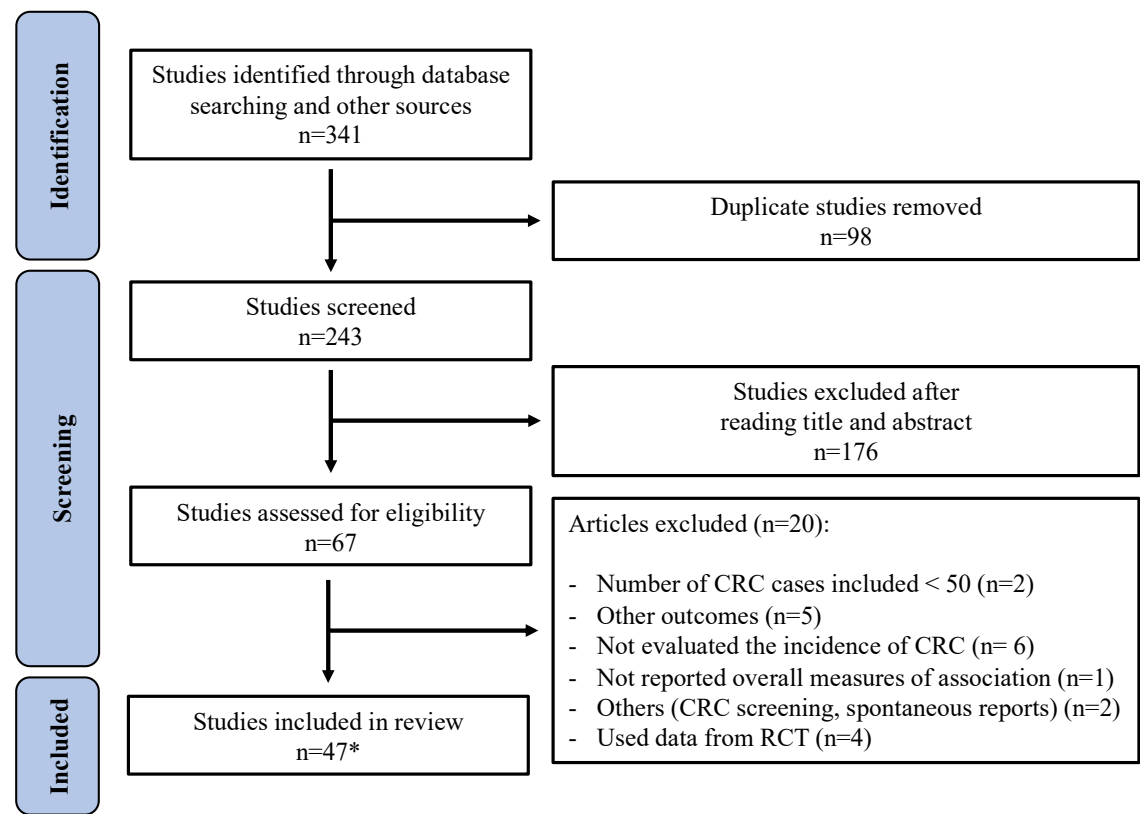
Supplementary Materials

Figure S1. Vascular risk factors, comorbidity and comedication associated with current use of statins as compared to non-use, among controls



BMI: body mass index; NSAID: nonsteroidal anti-inflammatory drugs; GI: gastrointestinal

Figure S2. Flow diagram for systematic review



CRC: colorectal cancer; RCT: randomized clinical trials

*48 studies finally included in the meta-analysis: 47 selected after systematic review plus the present study.

Table S1. Summary evidence from studies included in review

a) Case-control studies

Author (year, country)	Data source/ Study period	Exposure/ Active principles studied	Outcome/ Definition-confirmation	Definition of population	N	Cases	Site, sex	AOR (95% CI)	Matching/ Adjustment variables
Blais <i>et al</i> (2000, Canada)	Database (Régie de l'Assurance-Maladie du Québec), January 1, 1988-December 31,1994	Prevalent statin users (at least 1 prescription). Reference category: bile acid-binding resins/ Simvastatin, Lovastatin, Pravastatin	Diagnosis of cancer/ ICD-9 (codes 153.0-154.9)	General population. Range age: ≥ 65 - ≥ 85	5962	56	Colon, both sexes	0.83 (0.37-1.89)	No/ 1,2,10, 16,57,58
Graaf <i>et al</i> (2004, Netherlands)	Database (PHARMO), January 1, 1985-December 31, 1998	Prevalent statin users (threshold of at least 6 months)/ Simvastatin, Atorvastatin, Fluvastatin, Cerivastatin, Pravastatin	First diagnosis of cancer/ ICD9-CM (codes 140 to 208)	Population with one or more prescriptions for cardiovascular drugs. Range age: ≤ 64 - ≥ 85	20105	292	Colon, both sexes	0.87 (0.48-1.57)	Yes/1-5,8-16
						148	Rectum, both sexes	0.48 (0.16-1.48)	
Kaye <i>et al</i> (2004, United Kingdom)	Database (GPRD), 1990-2002	Prevalent statin users (1 prescription within the year before cancer diagnosis, first prescription more than 1 year). Reference category: non-statin (fibrates, cholestyramine, colestipol, nicotinic acid, and acipimox). Hyperlipidemia not treated separate category/ Not defined	First diagnosis of cancer/ Not defined	Population with use of antihyperlipidemic drugs or diagnosis of untreated hyperlipidemia. Range age: 50-89	18088	329	Colon, both sexes	1.00 (0.60-1.70)	Yes/1-3,5,7, 17,18,28
						183	Rectum, both sexes	1.60 (0.90-2.80)	
Khurana <i>et al</i> (2004, United States)	Database (VISN 16 VA), 1998-2004	Prevalent statin users / Not defined	Diagnosis of cancer/ Not defined	General population. Mean age: 61.1 (SD ± 14.4)	534273	5339	Colon, both sexes	0.94 (0.89-1.00)	No/1,2,6,14, 17-19
Poynter <i>et al</i> (2005, Israel)	Interview/ questionnaire, Database (Clalit Health Services), May 31, 1998- March 31, 2004	Prevalent statin users (use at least for 5 years). Reference category: less than 5 years or no use/ Simvastatin, Pravastatin	Diagnosis of cancer/ Standardized pathological review	General population. Mean age cases: 69.9 (SD ± 11.7)	3968	1953	Colorectal, both sexes	0.53 (0.38-0.74)	Yes/1-3,6, 14,20-23

Author (year, country)	Data source/ Study period	Exposure/ Active principles studied	Outcome/ Definition-confirmation	Definition of population	N	Cases	Site, sex	AOR (95% CI)	Matching/ Adjustment variables
Rubin <i>et al</i> (2005, Denmark)	Database (administrative claims), January 1, 2001- December 31, 2003	Prevalent statin users (statin use measured during a 12-month period prior to diagnosis)/ Not defined	First diagnosis of cancer/ Colonoscopy, bowel surgery	Patients with inflammatory bowel disease (IBD- ulcerative colitis and/or Crohn's disease). Age ≥ 18	1536	364	Colorectal, both sexes	0.74 (0.52-1.05)	Yes/1,2,5,7, 14,24-28
				Patients without IBD. Age ≥ 18 years	385704	18076	Colorectal, both sexes	0.92 (0.89-0.96)	
Coogan <i>et al</i> (2007, United States)^a	Interview/ questionnaire, 1991-2005	Prevalent statin users (use at least 4 times a week for at least 3 continuous months)/ Simvastatin, Lovastatin, Fluvastatin, Pravastatin	First diagnosis of cancer/ Not defined	General population. Range age: 40-79	8813	726	Colorectal, both sexes	0.80 (0.50-1.20)	No/1.1-3, 6, 14,17-19, 22,28,29
						467	Colon, both sexes	0.70 (0.40-1.10)	
						259	Rectum, both sexes	1.10 (0.60-2.00)	
Coogan <i>et al</i> (2007, United States)^b	Interview/ questionnaire, Database (Massachusetts Cancer Registry) January 1, 2001- November 30, 2004	Prevalent statin users (use at least 3 times a week for at least 3 continuous months)/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Cerivastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ Not defined	General population. Range age: 50-74	3618	1809	Colorectal, both sexes	0.92 (0.78-1.09)	Yes/1.1-3,6, 14, 17-19, 20,22,27,29-31
						187	Colorectal, women	1.02 (0.78-1.32)	
						270	Colorectal, men	0.86 (0.68-1.08)	
						320	Colon, both sexes	1.07 (0.87-1.32)	
						136	Rectum, both	0.70 (0.51-0.95)	
Hoffmeister <i>et al</i> (2007, Germany)	Interview/ questionnaire, January, 2003- June, 2004	Prevalent statin users (use at least 2 times a week for at least 1 year)/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Cerivastatin, Pravastatin	First diagnosis of cancer/ ICD 10 pos. C18-C20	General population. Mean age cases: 68 Range age: ≥ 30 - ≥ 80	1154	540	Colorectal, both sexes	0.69 (0.45-1.06)	Yes/1.1-3,8, 14,15,17-19, 21-23,27, 29
						324	Colon, both sexes	0.64 (0.39-1.04)	
						216	Rectum, both sexes	0.69 (0.37-1.28)	

Author (year, country)	Data source/ Study period	Exposure/ Active principles studied	Outcome/ Definition-confirmation	Definition of population	N	Cases	Site, sex	AOR (95% CI)	Matching/ Adjustment variables
Vinogradova <i>et al</i> (2007, United Kingdom)	Database (QRESEARCH database), January 1, 1995- July 31, 2005	Prevalent statin users (at least 1 prescription during 13– 48 months before index date)/ Simvastatin, Atorvastatin, Fluvastatin, Cerivastatin, Pravastatin	First diagnosis of cancer/ Not defined	General population. Mean age cases: 72 (IQR 64-79) Range age: <55-≥85	30668	5686	Colorectal, both sexes	0.93 (0.83-1.04)	Yes/1,2,5,7, 8,10,14,17, 18,32,39,42-44
Boudreau <i>et al</i> (2008, United States)	Database (Group Health Cooperative, Washington Surveillance, Epidemiology, and End Results cancer registry), January 1, 2000- December 31, 2003	Prevalent statin users (at least 2 prescriptions during a 6 months period)/ Not defined/ Prevalent users	First diagnosis of cancer/ Not defined	General population. Mean age cases: 69.9 (SD± 12.3) Range age: ≥ 40	1330	665	Colorectal, both sexes	1.02 (0.65-1.59)	Yes/1,2,4,8, 11-18
						512	Colon, both sexes	0.91 (0.55-1.50)	
						153	Rectum, both sexes	1.47 (0.50-4.29)	
Yang <i>et al</i> (2008, United Kingdom)	Database (GPRD), May, 1987- April, 2002	Prevalent statin users (at least 5 years)/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Cerivastatin, Pravastatin	First diagnosis of cancer/ Diagnostic codes for CRC in the GPRD	General population. Mean age cases: 67.5 (SD± 8.9)	48724	4432	Colorectal, both sexes	1.10 (0.50-2.20)	Yes/3,4,7, 14,15,17,18, 27,28
Hachem <i>et al</i> (2009, United States)	Database (Department of Veterans Affairs), 1997-2002	Prevalent statin users (at least 2 years before index date)/ Simvastatin	First diagnosis of cancer/ ICD-9 (codes 153.0/9, 154.0 /1/8, 230.3/4)	Population with diabetes mellitus. Mean age: 74	30400	6080	Colorectal, both sexes	0.91 (0.86-0.96)	Yes/1,2,14, 28,31,33-36
Shadman <i>et al</i> (2009, United States)	Interview/ questionnaire, database (Wisconsin cancer reporting system), 1999-2001	Prevalent statin users (at least 1 month within one year before cancer diagnosis)/ Simvastatin, Lovastatin, Fluvastatin, Pravastatin	Diagnosis of cancer/ Not defined	General female population. Range age: 50-74	2044	669	Colorectal, women	1.17 (0.74-1.85)	Yes/1,15,17, 18,22,27-29

Author (year, country)	Data source/ Study period	Exposure/ Active principles studied	Outcome/ Definition-confirmation	Definition of population	N	Cases	Site, sex	AOR (95% CI)	Matching/ Adjustment variables
Robertson <i>et al</i> (2010, Denmark)	Database (National Health Service), January 1, 1991- December 31, 2008	Prevalent statin users (at least 2 prescriptions)/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Pitavastatin, Cerivastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ ICD-8: 153.00/99 154.00 /19; ICD-10: C18.0/9, C19.9, C20.9	General population. Mean age: 71.20	109769	9979	Colorectal, both sexes	0.87 (0.80-0.96)	Yes/1-3,8, 14,19,31,37-39
Cheng <i>et al</i> (2011, Taiwan)	Database (National Health Insurance), January, 1996- December, 2008	Prevalent statin users (at least 1 prescription within one year before cancer diagnosis)/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ ICD-9-CM: Code 153-154	General population. Mean age cases: 68.34 (SD±10.40) Range age: ≥50	5780	1156	Colorectal, both sexes	1.09 (0.91-1.30)	Yes/1,2,5,8, 9,14,16,27, 31,33,35,40, 41
Samadder <i>et al</i> (2011, Israel)	Interview/ questionnaire, Database (Clalit Health Services) 1998- 2004	Prevalent statin users (use at least for 5 years). Reference category: less than 5 years or no use/ Simvastatin, Pravastatin	Diagnosis of cancer/ Standardized pathological review	Patients with IBD. Mean age cases: 69.8 (SD±11.8)	3842	39	Colorectal, both sexes	0.10 (0.01, 1.31)	Yes/1-3,6, 17,20, 22,23
				Patients without IBD. Mean age cases: 69.8 (SD±11.8)		1882	Colorectal, both sexes	0.55 (0.43-0.70)	
Vinogradova <i>et al</i> (2011, United Kingdom)	Database (QResearch database), January 1, 1998- July 1, 2008	Prevalent statin users (at least 2 prescriptions in 2 months)/ Simvastatin, Atorvastatin, Fluvastatin, Cerivastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ READ codes (B13, B14)	General population. Mean age cases: 69 (IQR 60-77) Range age: ≥ 30	60373	11749	Colorectal, both sexes	1.07 (1.00-1.15)	Yes/1,2,5,7, 8,14,17,18, 26,37,39,42, 43,44
Broughton <i>et al</i> (2012, United Kingdom)	Interview/ questionnaire, September 1, 2009- May 31, 2010	Prevalent statin users/ Simvastatin, Atorvastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ Histological confirmation	Population of Gastroenterology Department. Mean age cases: 70.3 (SD±10.2) Range age: ≥ 18	233 (62.40)	101	Colorectal, both sexes	0.43 (0.25-0.80)	No/1,2,8,14, 19,36

Author (year, country)	Data source/ Study period	Exposure/ Active principles studied	Outcome/ Definition-confirmation	Definition of population	N	Cases	Site, sex	AOR (95% CI)	Matching/ Adjustment variables
Lakha <i>et al</i> (2012, United Kingdom)	Interview/ questionnaire, Database (Health Informatics Centre), 1999-2009	Prevalent statin users (1/2 prescriptions in 2 months pre-recruitment; 1/2 prescriptions in 7 months pre-recruitment)/Not defined	First diagnosis of cancer/ Surgical units	General population. Statin use: ≥ 2 p at least 2 months pre-recruitment. Mean age cases: 60.0 (SD \pm 11.8). Range: 16–79	603	309*	Colorectal, both sexes	0.42 (0.19-0.92)	Yes/1-3,14, 17,18,20,22, 33
				General population. Statin use: ≥ 2 p at least 7 months pre-recruitment. Mean age cases: 60.0 (SD \pm 11.8). Range: 16–79		309*	Colorectal, both sexes	0.49 (0.22-1.08)	
Deshpande <i>et al</i> (2013, United States)	Database (HealthCore Integrated Research Database), January 1, 2001- January 30, 2011	Prevalent statin users (at least one prescription)/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Cerivastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ ICD-9 (codes 153.xx, 230.3 or 230.4)	General population. Mean age cases: 60.7 (SD \pm 13.2) Range age: ≥ 18	73472	36736	Colon, both sexes	0.96 (0.89-1.05)	Yes/1,2,4,5, 27,33
Björkhem-Bergman <i>et al</i> (2014, Sweden)	Database (Swedish Cancer Register, Swedish Prescribed Drug Register), July 1, 2006- December 31, 2010	Prevalent statin users (at least 9 months during the year before of index date)/ Simvastatin, Atorvastatin, Fluvastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ ICD-0/3 code C18	General population. Range age: 40– ≥ 90	126858	21143	Colon, both sexes	1.04 (1.00-1.08)	Yes/1,2,5,14 ,24,29,33,45
Sehdev <i>et al</i> (2014, United States)	Database (MarketScan), 2004-2010	Prevalent statin users (statin use measured during a 12-month period prior to diagnosis)/ Simvastatin, Lovastatin, Atorvastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ ICD9-CM codes (153.0-9, 154.0/1/8)	General population. Mean age cases: 54.44 (SD \pm 7.5)	357702	32616	Colorectal, both sexes	0.74 (0.72-0.77)	Yes/1.1-3,5, 7-10,14,18, 33,36,42,46

Author (year, country)	Data source/ Study period	Exposure/ Active principles studied	Outcome/ Definition-confirmation	Definition of population	N	Cases	Site, sex	AOR (95% CI)	Matching/ Adjustment variables
Mamtani <i>et al</i> (2016, United Kingdom)	Database (THIN), 1995-2013	Prevalent statin users / Not defined	First diagnosis of cancer/ READ codes (B13x, B803x, B804x, B14x)	General population. Short-term (< 1 yr). Mean age cases: 72.3 (IQR 63.8-79.6)	108701	904	Colorectal, both sexes	0.92 (0.85-0.99)	Yes/1.1-4, 8,14-19,27, 28
				General population. Long-term (> 1 yr). Mean age cases: 72.3 (IQR 63.8-79.6)		4936	Colorectal, both sexes	0.95 (0.91-0.99)	
Horibe <i>et al</i> (2017, Japan)	Interview/ questionnaire, August 2012, June 2014	Prevalent statin users / Simvastatin, Atorvastatin, Fluvastatin, Pitavastatin, Pravastatin, Rosuvastatin	Diagnosis of cancer/ Colonoscopy	Population with diabetes mellitus who underwent total colonoscopy. Mean age: 71.6 (SD±10.1)	168	70	Colorectal, both sexes	4.59 (1.69-13.43)	No/1,2,13, 14,16-19,36, 48,59,60
Renman <i>et al</i> (2017, Sweden)	Database (electronic health records), January 1, 2012-December 31, 2015	Prevalent statin users (at least 2 prescriptions, one of them more than 1-year prior cancer diagnosis)/ Simvastatin, Atorvastatin	First diagnosis of cancer/ ICD-10 (codes C18-C20)	General population. Mean age cases: 70.4 (SD± 12.7)	325	107	Colorectal, both sexes	1.12 (0.64-1.96)	Yes/1,8
Ibáñez-Sanz <i>et al</i> (2019, Spain)	Database (SIDIAP), January 1, 2010-December 31,2015	Prevalent statin users (at least one prescription)/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ ICD-10 (C18, C19, C20)	General population. Mean age users: 74.0 Range age: 18-90	154928	25811	Colorectal, both sexes	0.98 (0.95-1.01)	Yes/1.1-3,5, 10,14,17-19,32
						21242	Colon, both sexes	1.00 (0.97-1.03)	
						4569	Rectum, both sexes	0.87 (0.81-0.92)	
Dickerman <i>et al</i> (2020, United Kingdom)	Database (Clinical Practice Research Database), January, 1999 – February, 2016	New statin users (no statin prescriptions within the past year)/ Not defined	First diagnosis of cancer/ Read codes in primary care and as ICD-10 codes in hospitals	General population. Mean age cases: 68.5 (SD± 10.7)	359959 6	3596	Colorectal, both sexes	1.00 (0.86-1.16)	No/1,2,7,14, 15,17,18,21, 42,43,47

1: year of birth, 1.1: 5-year age-group, 2: sex, 3: geographic region, 4: duration of follow up, 5: index date, 6: ethnic group/race, 7: practice, 8: diabetes mellitus, 9: hospitalization, 10: comorbidity, 11: diuretics, 12: ACE inhibitors, 13: calcium-channel blockers, 14: NSAIDs, 15: hormone therapy, 16: other lipid-lowering therapies, 17: smoking, 18: BMI, 19: alcohol use, 20: exercise, 21: hypercholesterolemia/hyperlipidemia, 22: family history of colorectal cancer, 23: diet (vegetable consumption/red meat), 24: glucocorticosteroids, 25: immunomodulators, 26: 5-ASAs, 27: colorectal cancer endoscopic screening, 28: calendar year, 29: educational level, 30: vitamins and calcium supplements, 31: cholecystectomy, 32: socioeconomic status, 33: inflammatory bowel disease, 34: nephropathy, 35: liver disease, 36: antidiabetics agents, 37: Myocardial infarction, 38: Atherosclerosis, 39: Stroke, 40: polyps, 41: fecal occult blood, 42: coronary heart disease, 43: hypertension, 44: rheumatoid arthritis, 45: chemotherapy, 46: polycystic ovary disease, 47: cerebrovascular disease, 48: other

cardiovascular drugs, 49: thyroid disease. 50: mental illness, 51: lung disease 52: gastrointestinal disease 53: prostate disease 54: immunomodulator, 55: anti-TNF biologic exposure, 56: glucose, 57: previous benign neoplasm, 58: year of cohort entry, 59: HbA1c values, 60: fecal immunochemical test
*Number of exposed cases

b) Cohort studies

Author (year, country)	Data source/ Study period	Exposure/ Active principles studied	Outcome/ Definition-confirmation	Definition of population	N	Cases	Site, sex	RR/HR/IRR/OR (95% CI)	Matching/ Adjustment variables
Friis <i>et al</i> (2005, Denmark)	Database (Central Population Register, Pharmacoeptide- Prescription Database), January 1, 1989- December 31, 2002	Prevalent statin users. Reference category: non-statin lipid-lowering drugs users (at least 2 prescriptions). Subjects are allowed to change exposure variables/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Cerivastatin, Pravastatin	First diagnosis of cancer/ Not defined	General population. Mean age statin users: 60.7 Range age: 30-80	334754	3006	Colorectal, both sexes	RR: 0.85 (0.65-1.11)	No/1,2,12-15,28,48
Jacobs <i>et al</i> (2006, United States)	Interview/ questionnaire, 1997-2001	Prevalent statin users/ Simvastatin, Lovastatin, Fluvastatin, Pravastatin	First diagnosis of cancer/ Not defined	General population. Range age: ≤50 ≥80	132136	815	Colorectal, both sexes	RR: 1.03 (0.85-1.26)	No/1,2,6,14, 15,18,20,21, 23,27,29,37
Setoguchi <i>et al</i> (2007, United States)	Database (Pharmaceutical Assistance Contract for the Elderly, Medicare and Pennsylvania State Cancer Registry, Medicare Current Beneficiary Survey), January 1,1994- May 31, 2003	New statin users (no statin prescriptions within the past year) (at least 3 prescriptions in 6 months). Non-exposed: Users of glaucoma drugs/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Cerivastatin, Pravastatin	First diagnosis of cancer/ Not defined	General population. Mean age statin users: 76.4 (SD± 6.0) Range age: ≥65	31723	249	Colorectal, both sexes	HR: 0.96 (0.70-1.31)	No/1,2,6-10, 14,15,17,18, 27,33,40,44
Farwell <i>et al</i> (2008, United States)	Database (VA VISN-1), January 1, 1997- December 31, 2005	Prevalent users of statin and antihypertensive drug use (at least 2 prescriptions within 1 year). Non-exposed: Nonusers of statins, but users of antihypertensive drugs/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Pravastatin	First diagnosis of cancer/ ICD-9-CM (codes 140.XX – 208.XX)	General population. Mean age statin users: 66.6 (SD± 10) Range age: ≥18	62842	687	Colorectal, both sexes	HR: 0.65 (0.55-0.78)	No/1,8,14,17 -19,21,27, 34,42,43,49-53

Author (year, country)	Data source/ Study period	Exposure/ Active principles studied	Outcome/ Definition-confirmation	Definition of population	N	Cases	Site, sex	RR/HR/IRR/OR (95% CI)	Matching/ Adjustment variables
Friedman <i>et al</i> (2008, United States)	Database (Kaiser Permanente Medical Care Program, Pharmacy Information Management System), August, 1994 -December, 2003	New statin users (all persons were considered to be non-users of statins until one was dispensed to them) (2 years before diagnosis)/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Cerivastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ Not defined	General male population. Range age: 20-79	2097474	292*	Colon, men	RR: 0.88 (0.78-1.00)	No/28
						129*	Rectum, men	RR: 0.93 (0.77-1.12)	
				General female population. Range age: 20-79	2145593	243*	Colon, women	RR: 0.97 (0.85-1.11)	
						69*	Rectum, women	RR: 0.97 (0.76-1.25)	
Flick <i>et al</i> (2009, United States)	Interview/ questionnaire, 1991-2005	Prevalent statin users (at least 1 prescription in 3 months)/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Cerivastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ Not defined	General male population. Mean age: 58 Range age: 45–69	69115	171	Colorectal, men	HR: 0.89 (0.61-1.30)	No/1,14,17-23,27,30,40,42
						123	Colon, men	HR: 0.90 (0.58-1.40)	
						48	Rectum, men	HR: 0.86 (0.41-1.78)	
Singh <i>et al</i> (2009, United States)	Database (Manitoba Cancer Registry and Drug Program Information, MHHL Population Registry and Hospital Discharge Abstract and Medical Claims database), April 1,1995- December 31, 2005	Prevalent statin users (at least 2 prescriptions in 3 months)/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Cerivastatin, Pravastatin, Rosuvastatin	Diagnosis of cancer/ Not defined	General population. Mean age: 62 Range age: ≥40	423558	6637	Colorectal, both sexes	IRR: 1.13 (1.02-1.25)	No/1,2,8,10,14,15,27,32,33,42

Author (year, country)	Data source/ Study period	Exposure/ Active principles studied	Outcome/ Definition-confirmation	Definition of population	N	Cases	Site, sex	RR/HR/IRR/OR (95% CI)	Matching/ Adjustment variables
Haukka <i>et al</i> (2010, Finland)	Database (Social Insurance Institution, Finnish Cancer Registry), January 1, 1996- December 31, 2005	Prevalent statin users (at least one prescription)/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Cerivastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ ICD-7 (153, 154)	General population. Mean age: 60 (IQR 52.6- 67.9)	472481	2950	Colon, both sexes	RR: 0.99 (0.92-1.06)	Yes/1-3,4
						2066	Rectum, both sexes	RR: 1.07 (0.98-1.17)	
Jacobs <i>et al</i> (2011, United States)	Interview/ questionnaire, database (state cancer registries) 1997-2007	Prevalent statin users/ Simvastatin, Lovastatin, Fluvastatin, Pravastatin	First diagnosis of cancer/ Not defined	General population. Statin use: <5 years Range age: <60- ≥80	133255	270*	Colorectal, both sexes	RR: 0.96 (0.82-1.12)	No/1,2,6,8, 14,15,17,18, 20,21,27,29, 42,43
				General population. Statin use: ≥5 years Range age: <60- ≥80		259*	Colorectal, both sexes	RR: 0.93 (0.80-1.07)	
Lee <i>et al</i> (2011, United States)	Interview/ questionnaire, database (National Death Index), 1990-2006	Prevalent statin users/ Not defined	First diagnosis of cancer/ Standardized pathological review	General population. Mean age men: 67.4-68.7 Mean age women: 67.7-69.9	131922	1680	Colorectal, both sexes	RR: 0.97 (0.84-1.12)	No/1,14,17-19, 22,23,27, 28,29
						1282	Colon, both sexes	RR: 1.10 (0.94-1.29)	
						398	Rectum, both sexes	RR: 0.59 (0.41-0.84)	
Clancy <i>et al</i> (2013, Italy)	Database (Emilia-Romagna Region (RER) health care database), 2003-2010	New statin users (no prescriptions within the past year) (at least 3 prescriptions in 6 months). Non-exposed: new users of glaucoma drugs (no prescriptions within the past year) / Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Pitavastatin, Cerivastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ ICD-9 (codes 153.xx, 230.3 or 230.4)	General population. Mean age statin users: 64.6 (SD±11.4)	266109	2420	Colorectal, both sexes	HR: 0.84 (0.76-0.93)	Yes (Propensity score)/1,2,9, 10,14,27,33, 48

Author (year, country)	Data source/ Study period	Exposure/ Active principles studied	Outcome/ Definition-confirmation	Definition of population	N	Cases	Site, sex	RR/HR/IRR/OR (95% CI)	Matching/ Adjustment variables
Leung <i>et al</i> (2013, Taiwan)	Database (National Health Insurance Research Database), January 1, 2000- December 31, 2008	Prevalent statin users (continuously use for at least 6 months)/ Simvastatin, Atorvastatin, Fluvastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ ICD-9-CM (153.xx, 154.xx)	General population. Mean age: 58.31 (SD±12.12)	34205	458	Colon, both sexes	HR: 1.11 (0.77-1.60)	Yes/1,2,5,8, 10,14-16
						196	Rectum, both sexes	HR: 0.54 (0.27-1.12)	
Ananthakrishnan <i>et al</i> (2016, United States)	Database (electronic health records), 1998-2010	Prevalent statin users (at least one prescription)/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Pitavastatin, Pravastatin, Rosuvastatin	Diagnosis of cancer/ ICD-9-CM (153.x – 154.x)	Patients with IBD. Mean age statin users: 67 (IQR 58-76)	11001	317	Colorectal, both sexes	OR: 0.42 (0.28-0.62)	No/1,2,4,6, 17,27,33,54, 55
Liu <i>et al</i> (2016, Taiwan)	Database (National Health Insurance Research Database), January 1, 2001- December 31, 2012	Prevalent statin users/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ ICD-9-CM (codes 153.0–153.9)	Patients with Chronic Obstructive Pulmonary Disease. Mean age: 62.92 (SD±13.18)	43802	946	Colon, both sexes	HR: 0.52 (0.44-0.62)	Yes (Propensity score)/1,2,8, 10,21,32,43
						591	Colon, men	HR: 0.49 (0.39-0.63)	
						355	Colon, women	HR: 0.55 (0.42-0.72)	
Lee <i>et al</i> (2019, Korea)	Database (National Health Insurance Service-Health Screening) 2002-2015	Prevalent statin users (statin use during 2002-2003). Non-exposed: nonusers of statins despite having hypercholesterolemia/ Simvastatin, Lovastatin, Atorvastatin, Fluvastatin, Cerivastatin, Pitavastatin, Pravastatin, Rosuvastatin	First diagnosis of cancer/ ICD-10 (code C18.0-C20.0)	Hypercholesterolemia (cholesterol ≥250 mg/dL). Low users (statin usage). Mean age: 53.4 (SD±0.1)	31149	617 [†]	Colorectal, both sexes	HR: 1.10 (0.86-1.40)	No/1,8,17-21, 32,43,56
				Hypercholesterolemia (cholesterol ≥250 mg/dL). High users (statin usage). Mean age: 54.5 (SD±0.1)		617 [†]	Colorectal, both sexes	HR: 0.60 (0.45-0.80)	

Author (year, study location)	Data source/ Study period	Exposure/ Active principles studied	Outcome/ Definition-confirmation	Definition of population	N	Cases	Site, sex	RR/HR/IRR/OR (95% CI)	Matching/ Adjustment variables
Erkinantti <i>et al</i> (2021, Finland)	Database (FinDM-Diabetes in Finland database)/ January 1, 1996- December 31, 2011	Prevalent statin users/Not defined	First diagnosis of cancer/ ICD-10 (C18) ICD-O-3 (M-8140/3)	Patients with type 2 Diabetes. Range age: 40-107 years	306317	1349	Colon, both sexes	HR: 0.94 (0.84-1.05)	No/1,2,8
Han <i>et al</i> (2021, Korea)	Database (National Health Insurance Service of South Korea)/2009-2011	Prevalent statin users/Not defined	First diagnosis of cancer/ ICD-10 (C18-C20)	General population. Mean age: 70.75 (SD± 2.26)	131266	1552	Colorectal, both sexes	HR: 0.80 (0.67-0.95)	No/1-3,8,17-19,22,61
Yeh <i>et al</i> (2021, Taiwan)	Database (Taiwan's National Health Insurance)/ January 1, 2000- December 31, 2013	Prevalent and new users (use less than 3 months)/ Not defined	First diagnosis of cancer/ ICD-9-CM (codes 153-154)	Patients with Interstitial lung disease and pulmonary fibrosis. Mean age: 55.3 (SD±16.7)	20072	380	Colorectal, both sexes	HR: 0.73 (0.59-0.89)	Yes (propensity score)/1,2,8, 10,18,21,24, 34,39,43,50
Zhang <i>et al</i> (2022, United States)	Interview/ questionnaire, database (National Death Index)/1990-2016	Prevalent statin users/Not defined	First diagnosis of cancer/ Medical and pathology reports, state cancer registries	General population. Mean age women: 67.0 (SD±9.0)- 78.6 (SD±6.4) (duration of statin use) Mean age men: 65.0 (SD±10.8)- 76.7 (SD±7.6) (duration of statin use)	148291	2924	Colorectal, both sexes	HR: 1.05 (0.95-1.16)	No/1,2,6,8,14,17-22,23, 30

1: year of birth, 1.1: 5-year age-group, 2: sex, 3: geographic region, 4: duration of follow up, 5: index date, 6: ethnic group/race, 7: practice, 8: diabetes mellitus, 9: hospitalization, 10: comorbidity, 11: diuretics, 12: ACE inhibitors, 13: calcium-channel blockers, 14: NSAID, 15: hormone therapy, 16: other lipid-lowering therapies, 17: smoking, 18: BMI, 19: alcohol use, 20: exercise, 21: hypercholesterolemia/hyperlipidemia, 22: family history of colorectal cancer, 23: diet (vegetable consumption/red meat), 24: glucocorticosteroids, 25: immunomodulators, 26: 5-ASAs, 27: colorectal cancer endoscopic screening, 28: calendar year, 29: educational level, 30: vitamins and calcium supplements, 31: cholecystectomy, 32: socioeconomic status, 33: inflammatory bowel disease, 34: nephropathy, 35: liver disease, 36: antidiabetics agents, 37: Myocardial infarction, 38: Atherosclerosis, 39: Stroke, 40: polyps, 41: fecal occult blood, 42: coronary heart disease, 43: hypertension, 44: rheumatoid arthritis, 45: chemotherapy, 46: polycystic ovary disease, 47: cerebrovascular disease, 48: other cardiovascular drugs, 49: thyroid disease. 50: mental illness, 51: lung disease 52: gastrointestinal disease 53: prostate disease 54: immunomodulator, 55: anti-TNF biologic exposure, 56: glucose, 57: previous benign neoplasm, 58: year of cohort entry, 59: HbA1c values, 60: fecal immunochemical test, 61: insurance

*Number of exposed cases

†Total number of cases (not disaggregated)

Table S2. Reported subgroup analyses from studies included in review

a) Case-control studies

Author (year, country)	Sex categories		Age categories	Duration categories			Intensity categories	Lipophilicity/ Active principle categories	
Blais <i>et al</i> (2000, Canada)	Not reported		Not reported	Not reported			Not reported	Not reported	
Graaf <i>et al</i> (2004, Netherlands)	Not reported		Not reported	Not reported			Not reported	Not reported	
Kaye <i>et al</i> (2004, United Kingdom)	Not reported		Not reported	Colon	<2 years	0.80 (0.40-1.90)	Not reported	Not reported	
					2-5 years	0.90 (0.40-1.80)			
					≥5 years	3.50 (1.10-10.90)			
				Rectum	<2 years	1.20 (0.50-3.00)			
					2-5 years	1.40 (0.60-3.20)			
					≥5 years	4.20 (1.10-16.60)			
Khurana <i>et al</i> (2004, United States)	Not reported		Not reported	Not reported			Not reported	Not reported	
Poynter <i>et al</i> (2005, Israel)	Not reported		Not reported	≥5 years	0.55 (0.40-0.74)	Not reported	Simvastatin	0.49 (0.36-0.67)*	
							Pravastatin	0.44 (0.31-0.63)*	
Rubin <i>et al</i> (2005, Denmark)	Not reported		Not reported	Not reported			Not reported	Not reported	
Coogan <i>et al</i> (2007, United States)a	Not reported		Not reported	≤1 year		0.70 (0.30-1.50)	Not reported	Not reported	
				>1-<5 years		0.70 (0.40-1.30)			
				≥5 years		1.10 (0.60-2.20)			
Coogan <i>et al</i> (2007, United States)b	Both sexes	0.92 (0.78-1.09)	Not reported	Regular use	0.92 (0.78-1.09)	Not reported	Simvastatin	0.81 (0.59-1.12)	
							Lovastatin	1.73 (1.03-2.88)	
							Atorvastatin	0.93 (0.76-1.14)	

							Pravastatin	0.94 (0.60-1.46)	
				≤1 year	0.57 (0.27-1.24)				
				>1-4 years	0.94 (0.77-1.15)				
				5-9 years	0.95 (0.71-1.27)				
				≥ 10 years	0.86 (0.51-1.45)				
	Women	1.02 (0.78-1.32)							
	Men	0.86 (0.68-1.08)							
Hoffmeister <i>et al</i> (2007, Germany)	Not reported		Not reported	1-4 years	0.58 (0.33-1.04)	Not reported	Simvastatin	0.50 (0.24-1.02)	
				≥5 years	0.71 (0.39-1.28)		Atorvastatin	0.84 (0.46-1.53)	
							Pravastatin	0.61 (0.21-1.81)	
Vinogradova <i>et al</i> (2007, United Kingdom)	Not reported		Not reported	< 1 year	0.84 (0.71-1.00)	Not reported	Simvastatin	0.83 (0.72-0.96)	
				1-2 years	0.99 (0.80-1.22)		Atorvastatin	1.11 (0.95-1.30)	
				> 2 years	0.99 (0.84-1.16)		Fluvastatin	1.21 (0.85-1.74)	
							Cerivastatin	1.34 (0.97-1.86)	
Boudreau <i>et al</i> (2008, United States)	Not reported		Not reported	< 2 years	0.80 (0.40-1.59)	Not reported	Not reported		
				≥2 years	1.22 (0.70-2.12)				
Yang <i>et al</i> (2008, United Kingdom)	Not reported		Not reported	≥5 years	1.10 (0.50-2.20)	Not reported	Not reported		
				≥10 years	1.30 (0.60-2.70)				
Hachem <i>et al</i> (2009, United States)	Not reported		≥65 years	0.90 (0.85-0.96)	< 0.5 year	0.86 (0.77-0.95)	Not reported	Simvastatin	0.91 (0.86-0.97)
					0.5-1 year	0.98 (0.89-1.09)			
					>1-1.5 year	0.91 (0.82-1.02)			
					1.5-2 years	0.93 (0.84-1.04)			
					> 2 years	0.87 (0.80-0.95)			
Shadman <i>et al</i> (2009, United States)	Women	1.17 (0.74 -1.85)	Not reported		< 3 years	1.07 (0.56-2.03)	Not reported	Lipophilicity	1.20 (0.72-2.00)
					≥ 3 years	1.27 (0.68-2.38)		Hydrophilicity	1.10 (0.44-2.77)
Robertson <i>et al</i> (2010, Denmark)	Not reported		Not reported		0-3 years	0.84 (0.75-0.95)	Not reported	Simvastatin	0.88 (0.79-0.98)
					3-5 years	0.88 (0.74-1.04)		Lovastatin	0.78 (0.45-1.35)
					> 5 years	0.95 (0.80-1.12)		Atorvastatin	0.73 (0.52-1.01)
								Pravastatin	0.85 (0.61-1.20)
Cheng <i>et al</i> (2011, Taiwan)	Not reported		Not reported		Not reported		Not reported	Not reported	

Author (year, country)	Sex categories	Age categories		Duration categories		Intensity categories	Lipophilicity/ Active principle categories	
Samadder <i>et al</i> (2011, Israel)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Simvastatin, IBD	0.05 (0.004-0.54)
							Pravastatin, IBD	0.11 (0.004-3.00)
							Simvastatin, Non-IBD	0.36 (0.30-0.42)
							Pravastatin, Non- IBD	0.41 (0.31-0.52)
Vinogradova <i>et al</i> (2011, United Kingdom)	Not reported	Not reported	<1 year	1.05 (0.95-1.17)	Not reported	Not reported	Simvastatin	0.96 (0.88-1.04)
			>1-2 years	1.04 (0.92-1.17)			Atorvastatin	1.17 (1.07-1.28)
			>2-4 years	1.02 (0.92-1.14)			Pravastatin	1.09 (0.93-1.28)
			>4 years	1.23 (1.10-1.38)				
Broughton <i>et al</i> (2012, United Kingdom)	Not reported	Not reported	<2 years	0.66 (0.21-1.69)	Not reported	Not reported	Simvastatin	0.43 (0.10-0.73)
			2-5 years	0.38 (0.14-1.01)				
			>5 years	0.18 (0.06-0.55)				
Lakha <i>et al</i> (2012, United Kingdom)	Not reported	Not reported	Not reported		Not reported	Not reported	Not reported	
Deshpande <i>et al</i> (2013, United States)	Not reported	Not reported	<0.5 years	0.84 (0.75-1.24)	Not reported	Not reported	Simvastatin	0.94 (0.89-0.99)
			<1 year	0.86 (0.83-0.89)			Fluvastatin	0.84 (0.67-1.05)
							Cerivastatin	1.05 (0.75-1.48)
							Pravastatin	0.91 (0.84-0.99)
							Rosuvastatin	0.97 (0.87-1.08)
Björkhem-Bergman <i>et al</i> (2014, Sweden)	Not reported	Not reported	Not reported		Not reported	Not reported	Not reported	
Sehdev <i>et al</i> (2014, United States)	Not reported	≤ 55 years	0.67 (0.63-0.71)	91-217 days	0.77 (0.62-0.95)	Not reported	Simvastatin	0.79 (0.75-0.83)
		> 55 years	0.79 (0.76-0.82)	218-303 days	0.93 (0.67-1.02)			
				304-365 days	0.80 (0.65-0.99)			

Author (year, country)	Sex categories		Age categories		Duration categories		Intensity categories		Lipophilicity/ Active principle categories	
Mamtani <i>et al</i> (2016, United Kingdom)	Not reported		Not reported		< 1 year	0.92 (0.85-0.99)	Not reported		Not reported	
					> 1 year	0.95 (0.91-0.99)				
Horibe <i>et al</i> (2017, Japan)	Not reported		Not reported		Not reported		Not reported		Not reported	
Renman <i>et al</i> (2017, Sweden)	Not reported		Not reported		Not reported		Not reported		Not reported	
Ibáñez-Sanz <i>et al</i> (2019, Spain)	Women	1.01 (0.97-1.05)	18-55 years	1.07 (0.95-1.20)	< 5 years	1.11 (1.04-1.08)	Low	0.98 (0.94-1.01)	Lipophilicity	0.98 (0.95-1.01)
			55-65 years	0.98 (0.91-1.04)					Hydrophilicity	0.96 (0.87-1.05)
									Simvastatin	0.97 (0.94-0.99)
									Lovastatin	1.04 (0.96-1.13)
	Men	0.95 (0.91-0.98)	65-75 years	1.00 (0.95-1.06)	> 5 years	0.96 (0.93-1.00)	High	1.01 (0.96-1.07)	Atorvastatin	0.99 (0.96-1.03)
			75-85 years	0.96 (0.92-1.01)					Fluvastatin	0.98 (0.90-1.06)
									Pitavastatin	1.03 (0.76-1.34)
									Pravastatin	0.98 (0.93-1.04)
85-95 years	0.96 (0.88-1.05)	Rosuvastatin	0.92 (0.82-1.03)							
Dickerman <i>et al</i> (2020, United Kingdom)	Not reported		Not reported		Not reported		Not reported		Not reported	

*Non-adjusted odds ratios

Coogan et al (2007, United States)a: Statin Use and the Risk of 10 Cancers. DOI: 10.1097/01.ede.0000254694.03027.a1

Coogan et al (2007, United States)b: Statin Use and Risk of Colorectal Cancer. DOI: 10.1093/jnci/djk003

b) Cohort studies

Author (year, country)	Sex categories		Age categories	Duration categories		Intensity categories	Lipophilicity/ Active principle categories	
Friis <i>et al</i> (2005, Denmark)	Not reported		Not reported	Not reported		Not reported	Not reported	
Jacobs <i>et al</i> (2006, United States)	Not reported		Not reported	<5 years	1.00 (0.80-1.25)	Not reported	Not reported	
				≥5 years	1.09 (0.83-1.43)			
Setoguchi <i>et al</i> (2007, United States)	Not reported		Not reported	< 3 years	0.93 (0.57-1.51)	Not reported	Not reported	
				≥ 3 years	0.97 (0.65-1.46)			
Farwell <i>et al</i> (2008, United States)	Not reported		Not reported	Not reported		Not reported	Not reported	
Friedman <i>et al</i> (2008, United States)	Colon, women	0.97 (0.85-1.11)	Not reported	> 5 years	1.02 (0.75-1.38)	Not reported	Not reported	
	Rectum, women	0.97 (0.76-1.25)		> 5 years	1.15 (0.66-2.01)			
	Colon, men	0.88 (0.78-1.00)		> 5 years	1.00 (0.78-1.30)			
	Rectum, men	0.93 (0.77-1.12)		> 5 years	1.09 (0.74-1.61)			
Flick <i>et al</i> (2009, United States)	Men	0.89 (0.61-1.30)	Not reported	101 days-<5 years	0.91 (0.61-1.34)	Not reported	Not reported	
				> 5 years	0.83 (0.43-1.63)			
Singh <i>et al</i> (2009, United States)	Not reported		Not reported	≥5 years	0.89 (0.70-1.13)	Not reported	Not reported	
Haukka <i>et al</i> (2010, Finland)	Not reported	Not reported	Colon, 1 year	1.01 (0.98-1.04)	Not reported	Simvastatin	0.99 (0.96-1.01)	
						Lovastatin	0.97 (0.94-1.00)	
						Atorvastatin	1.03 (1.00-1.06)	
						Fluvastatin	0.98 (0.94-1.02)	
			Rectum, 1 year	0.96 (0.92-0.99)		Pravastatin	1.02 (0.97-1.08)	
						Simvastatin	1.00 (0.97-1.03)	
						Lovastatin	0.94 (0.90-0.98)	
						Atorvastatin	1.02 (0.98-1.06)	
						Fluvastatin	0.98 (0.93-1.03)	

								Pravastatin	0.91 (0.84-0.99)
Author (year, country)	Sex categories		Age categories		Duration categories		Intensity categories	Lipophilicity/ Active principle categories	
Jacobs <i>et al</i> (2011, United States)	Not reported		Not reported		< 5 years	0.93 (0.80-1.07)	Not reported	Not reported	
					≥ 5 years	0.96 (0.82-1.12)			
Lee <i>et al</i> (2011, United States)	Not reported		Not reported		0-2 years	0.99 (0.82-1.20)	Not reported	Not reported	
					3-5 years	1.01 (0.79-1.28)			
					≥6 years	0.97 (0.75-1.25)			
Clancy <i>et al</i> (2013, Italy)	Both sexes	0.84 (0.76-0.93)	Not reported		Not reported		Not reported	Lipophilicity	0.84 (0.76-0.94)
								Hydrophilicity	0.85 (0.75-0.96)
	Women	0.95 (0.82-1.10)						Lipophilicity	0.93 (0.79-1.08)
								Hydrophilicity	0.99 (0.82-1.19)
	Men	0.77 (0.67-0.88)	Lipophilicity	0.79 (0.69-0.90)					
			Hydrophilicity	0.75 (0.63-0.89)					
Leung <i>et al</i> (2013, Taiwan)	Not reported		Not reported		Not reported		Not reported	Not reported	
Ananthakrishnan <i>et al</i> (2016, United States)	Women	0.36 (0.18-0.75)	Not reported		Not reported		Not reported	Not reported	
	Men	0.35 (0.21-0.59)						Not reported	
Liu <i>et al</i> (2016, Taiwan)	Both sexes	0.52 (0.44-0.62)	40-64 years	0.47 (0.36-0.62)	Not reported		Not reported	Lipophilicity	0.64 (0.53-0.77)
								Hydrophilicity	0.48 (0.35-0.66)
								Simvastatin	0.64 (0.47-0.87)
								Lovastatin	1.02 (0.75-1.38)
								Atorvastatin	0.65 (0.52-0.83)
								Fluvastatin	0.93 (0.63-1.35)
			Pravastatin	0.89 (0.60-1.32)					
			Rosuvastatin	0.28 (0.17-0.45)					
Lee <i>et al</i> (2019, Korea)	Women	0.64 (0.46-0.90)	Not reported		Not reported		Not reported	Not reported	
	Men	0.56 (0.42-0.75)						Not reported	
Yeh <i>et al</i> (2021, Taiwan)	Women	0.87 (0.69-1.11)	≤ 49 years	0.65 (0.34-1.25)	Not reported		Not reported	Not reported	

	Men	0.70 (0.56-0.87)	≥ 50 years	0.75 (0.64-0.89)				
Author (year, country)	Sex categories		Age categories		Duration categories		Intensity categories	Lipophilicity/ Active principle categories
Han <i>et al</i> (2021, Korea)	Not reported		Not reported		Not reported		Not reported	Not reported
Erkinantti <i>et al</i> (2021, Finland)	Not reported		Not reported		Not reported		Not reported	Not reported
Zhang <i>et al</i> (2022, United States)	Not reported		Not reported		1-5 years	1.03 (0.92-1.16)	Not reported	Not reported
					6-10 years	1.05 (0.91-1.20)		
					11-15 years	1.03 (0.80-1.32)		
					> 15 years	1.43 (1.04-1.99)		

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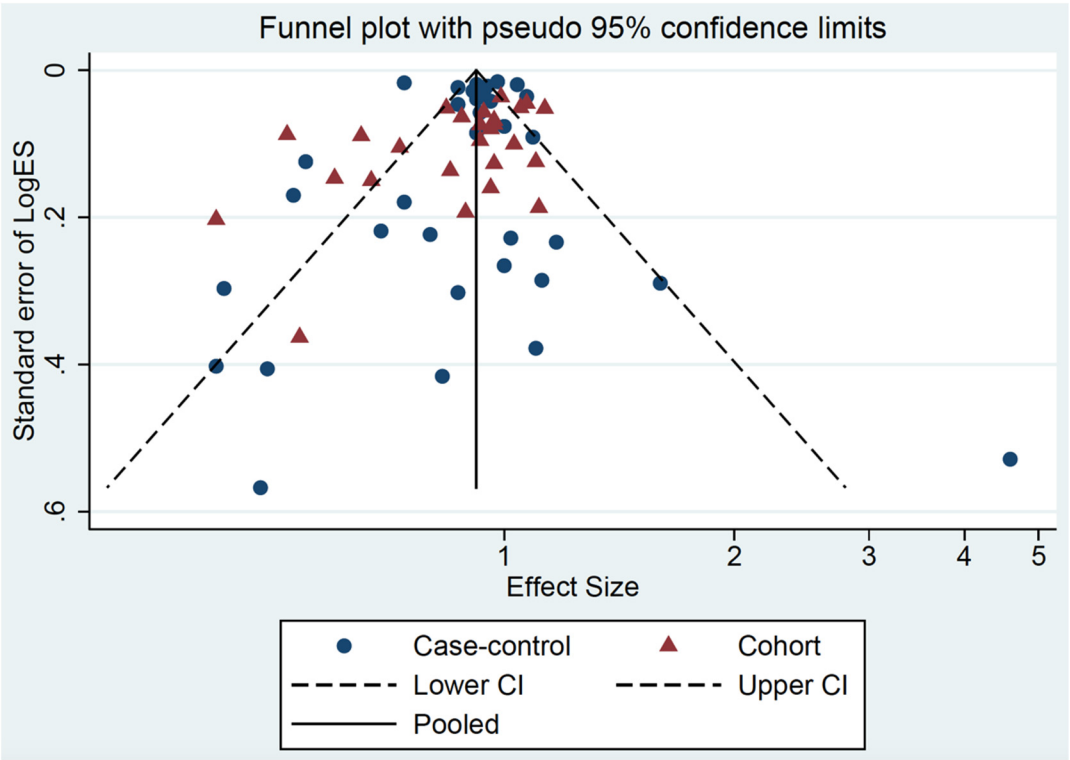
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Figure S3. Funnel plot



ES: standard error; CI: confidence interval