

Statin Medication: Systematic Review with SAIMSARA.

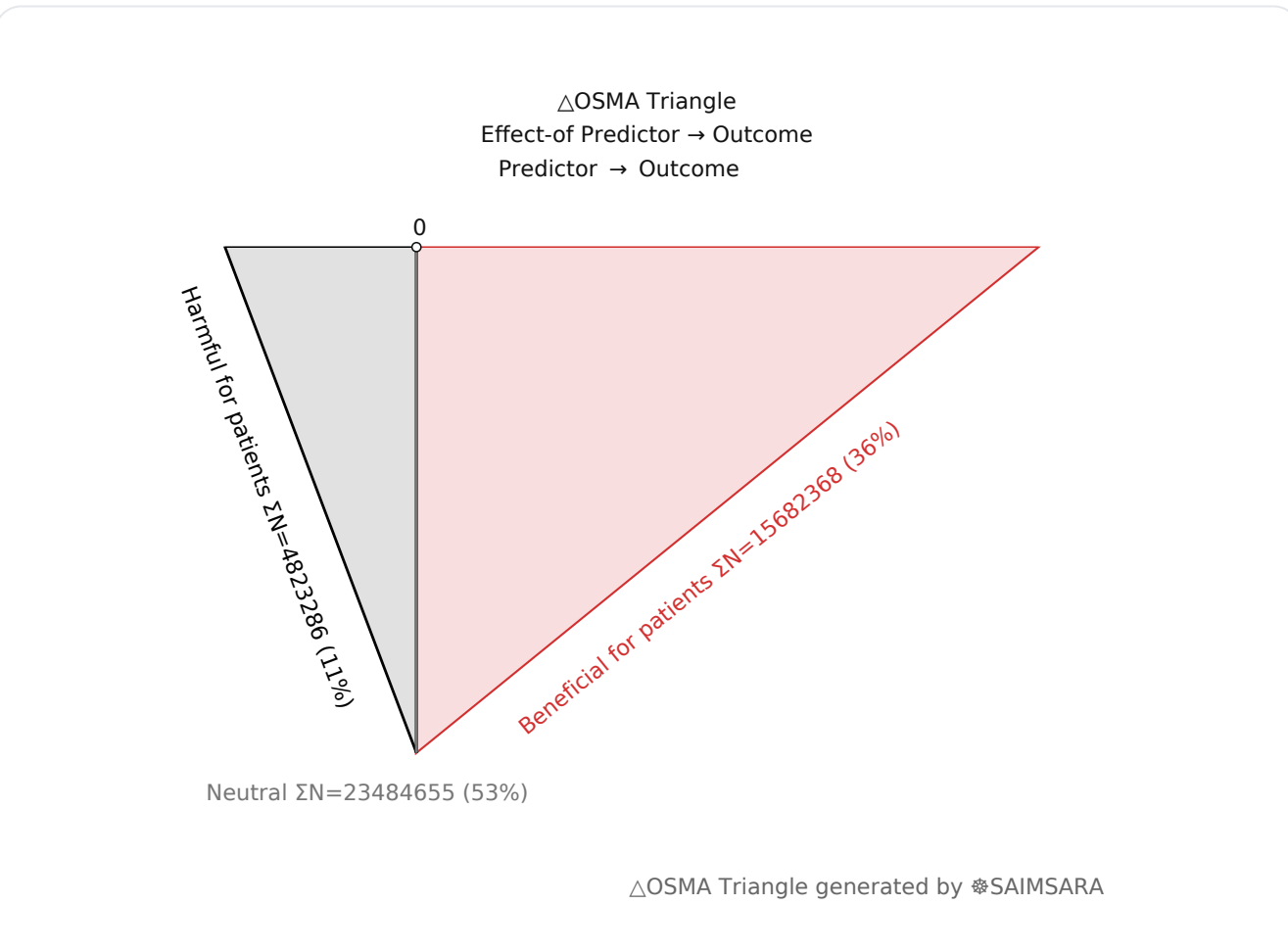
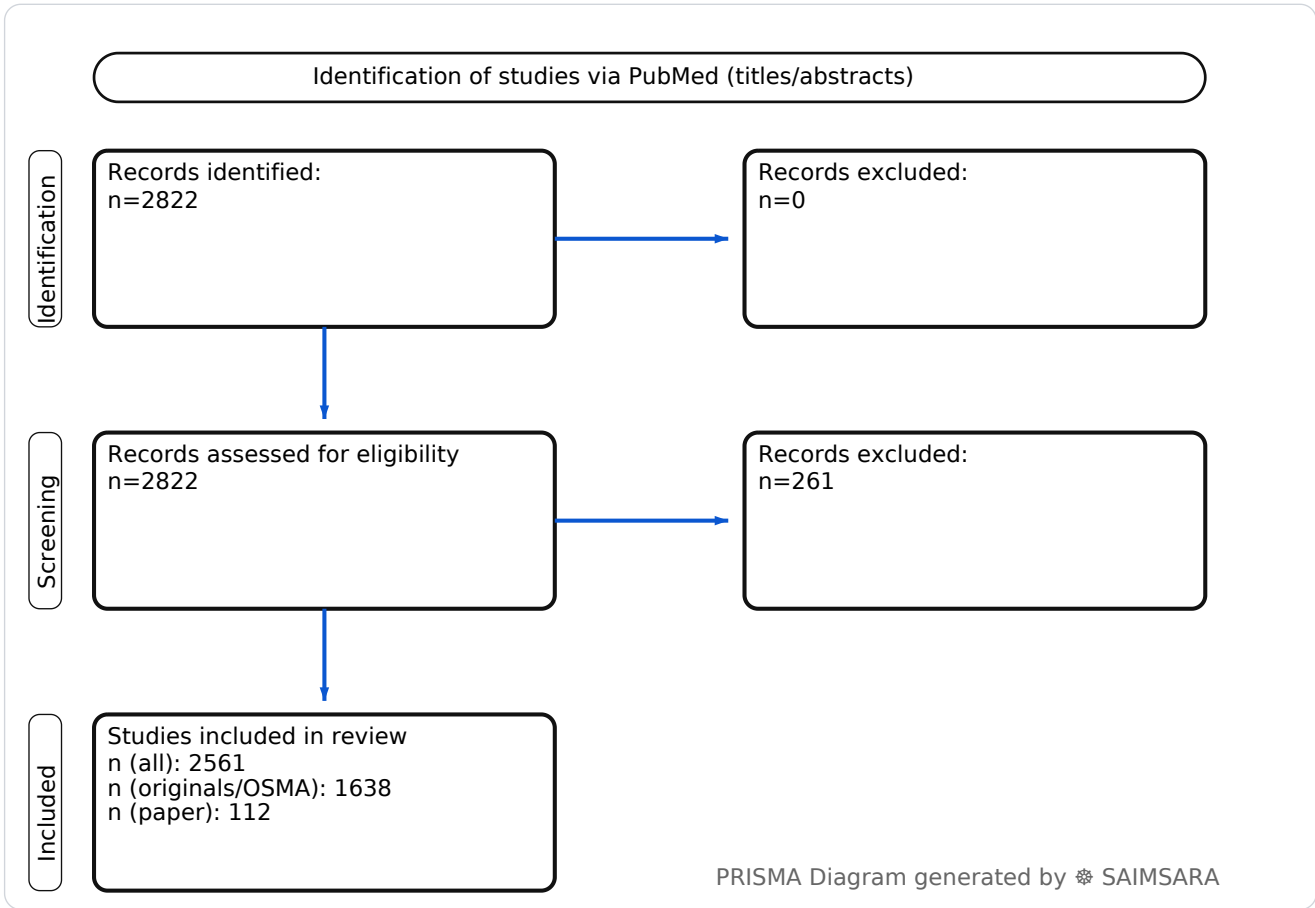
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Abstract: This systematic review aims to synthesize the evidence from the provided literature on statin medication. The review focuses on synthesizing key themes related to clinical outcomes, adverse effects, medication adherence, and the role of statins across a variety of patient populations and clinical contexts. The review utilises 1638 original studies with 43990309 total participants (naïve ΣN). This systematic review synthesizes a broad landscape of evidence on statin medication, confirming its central role in cardiovascular risk reduction while highlighting significant challenges and areas of ongoing investigation. Key research themes include the pervasive issue of suboptimal medication adherence, the complex spectrum of adverse effects dominated by myotoxicity, and the expanding understanding of statins' pleiotropic effects on cancer, metabolic health, and neurological conditions. Numerically, adherence remains a critical weakness, with a median rate of only 54.0% across studies, underscoring a major gap in real-world effectiveness. A primary limitation of the current evidence base is the heterogeneity of study designs, which complicates causal inference for many observed associations. A crucial clinical implication is the need for proactive, patient-centered strategies that focus on shared decision-making to improve adherence, manage side effects, and tailor therapy to individual risk profiles and goals of care.

Keywords: Medication adherence; Adverse effects; Myopathy; Cardiovascular disease; Statin intolerance; Primary prevention; Statin discontinuation; Gut microbiota; Cancer; Palliative care

Review Stats

- Generated: 2026-03-02 22:58:41 CET
- Plan: Pro (expanded craft tokens; source: PubMed)
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- Scope: Titles/Abstracts (tiab)
- Keyword Gate: Fuzzy ($\geq 60\%$ of required terms, minimum 2 terms matched in title/abstract)
- Total Abstracts/Papers: 2822
- Downloaded Abstracts/Papers: 2822
- Included original Abstracts/Papers (all): 2561
- Included original Abstracts/Papers (OSMA; excl. Mixed): 1638
- Reference Index (links used in paper): 112
- Total study participants (naïve ΣN): 43990309



Outcome-Sentiment Meta-Analysis (OSMA): (LLM-only)

Frame: Effect-of Predictor → Outcome • *Source:* PubMed

Outcome: Outcome Typical timepoints: 1-y, peri/post-op. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: mortality, complications, admission.

Predictor: Predictor — exposure/predictor. Concentrations seen: 95%. Doses/units seen: 100 mg, 190 mg, 70 mg, 600 mg, 150 mg, 40 mg.... Routes seen: oral, topical, intravenous. Typical comparator: non-hispanic whites. adherence, non-users, daily dosing instructions., those not receiving statin....

- **1) Beneficial for patients** — Outcome with Predictor — [28], [45], [74], [78], [81], [83], [94], [97], [105], [107], [114], [120], [122], [124], [139], [142], [156], [162], [164], [167], [172], [175], [176], [183], [203], [212], [221], [232], [233], [244], [250], [261], [262], [267], [271], [275], [279], [282], [290], [291], [294], [298], [299], [300], [303], [305], [316], [317], [322], [324], [326], [341], [348], [350], [351], [355], [358], [364], [365], [370], [402], [405], [406], [414], [427], [434], [438], [440], [443], [444], [448], [449], [450], [451], [452], [455], [458], [465], [466], [475], [477], [478], [479], [481], [484], [485], [486], [497], [498], [502], [505], [507], [508], [517], [520], [522], [523], [524], [529], [531], [532], [535], [539], [540], [548], [550], [552], [554], [557], [558], [559], [563], [566], [567], [573], [576], [577], [585], [589], [593], [600], [601], [604], [608], [610], [613], [616], [619], [625], [627], [630], [639], [645], [646], [656], [661], [664], [671], [677], [679], [685], [689], [692], [694], [698], [712], [714], [716], [721], [726], [735], [736], [740], [744], [751], [754], [756], [759], [767], [768], [778], [782], [783], [795], [798], [803], [811], [812], [814], [818], [819], [821], [824], [826], [829], [830], [831], [836], [838], [844], [849], [854], [887], [889], [890], [900], [901], [904], [905], [906], [909], [911], [913], [917], [923], [929], [931], [942], [943], [944], [956], [964], [968], [971], [972], [974], [976], [981], [987], [991], [996], [1006], [1012], [1017], [1019], [1026], [1027], [1028], [1030], [1035], [1050], [1052], [1055], [1058], [1061], [1063], [1079], [1089], [1095], [1096], [1097], [1105], [1110], [1111], [1112], [1116], [1118], [1124], [1125], [1127], [1131], [1138], [1141], [1142], [1153], [1155], [1157], [1159], [1162], [1169], [1172], [1173], [1174], [1181], [1192], [1197], [1201], [1205], [1207], [1208], [1220], [1221], [1222], [1223], [1226], [1228], [1235], [1238], [1241], [1251], [1262], [1263], [1268], [1269], [1273], [1280], [1284], [1286], [1288], [1291], [1297], [1298], [1300], [1305], [1311], [1312], [1329], [1334], [1337], [1341], [1352], [1353], [1369], [1372], [1374], [1376], [1378], [1379], [1388], [1390], [1392], [1394], [1397], [1399], [1404], [1407], [1429], [1431], [1432], [1437], [1438], [1441], [1442], [1443], [1456], [1458], [1460], [1461], [1470], [1477], [1487], [1491], [1494], [1499], [1505], [1511], [1512], [1513], [1515], [1518], [1528], [1529], [1531],

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• **2) Harmful for patients** — Outcome with Predictor — [36], [59], [125], [135], [168], [174], [193], [197], [200], [202], [209], [226], [242], [288], [295], [297], [302], [304], [310], [311], [333], [334], [338], [347], [352], [367], [445], [459], [462], [467], [480], [482], [487], [495], [500], [501], [525], [541], [564], [572], [584], [594], [599], [603], [606], [612], [634], [647], [663], [669], [678], [711], [713], [739], [743], [786], [802], [813], [815], [822], [834], [837], [851], [852], [894], [912], [924], [955], [963], [984], [998], [999], [1005], [1010], [1021], [1051], [1053], [1074], [1090], [1091], [1100], [1102], [1104], [1106], [1128], [1129], [1156], [1160], [1196], [1246], [1255], [1257], [1266], [1275], [1299], [1306], [1318], [1324], [1366], [1416], [1452], [1453], [1457], [1517], [1530], [1538], [1543], [1611], [1616], [1618], [1634], [1636], [1651], [1674], [1685], [1695], [1716], [1721], [1724], [1752], [1780], [1784], [1792], [1794], [1834], [1860], [1887], [1922], [1957], [2095], [2100], [2128], [2132], [2149], [2164], [2175], [2207], [2213], [2271], [2277], [2306], [2316], [2333], [2334], [2347], [2359], [2375], [2397], [2409], [2436], [2440], [2454], [2461], [2478], [2499], [2504], [2510], [2528], [2557] — $\Sigma N=4823286$

• **3) No clear effect** — Outcome with Predictor — [1], [3], [5], [6], [7], [8], [9], [10], [12], [16], [17], [21], [25], [26], [27], [32], [33], [35], [39], [40], [44], [46], [49], [53], [57], [62], [63], [64], [66], [67], [75], [77], [87], [88], [95], [99], [100], [102], [104], [106], [108], [112], [113], [115], [117], [127], [128], [129], [131], [134], [136], [137], [138], [140], [141], [147], [151], [152], [153], [154], [155], [157], [160], [163], [165], [166], [169], [170], [171], [173], [177], [179], [180], [181], [182], [186], [187], [188], [189], [191], [194], [195], [196], [198], [199], [201], [206], [208], [214], [216], [217], [225], [228], [230], [234], [235], [237], [239], [241], [243], [245], [246], [247], [256],

[257], [259], [260], [265], [266], [270], [272], [274], [276], [277], [281], [283], [286], [292], [293], [301], [307], [313], [314], [315], [318], [319], [321], [323], [327], [339], [343], [346], [353], [360], [361], [362], [363], [366], [368], [369], [372], [373], [374], [375], [376], [377], [379], [381], [386], [388], [389], [391], [398], [399], [404], [407], [408], [409], [411], [412], [420], [424], [425], [428], [439], [441], [442], [446], [454], [456], [461], [463], [469], [472], [473], [476], [483], [488], [489], [490], [491], [492], [493], [499], [503], [504], [506], [510], [511], [512], [513], [515], [527], [528], [530], [533], [536], [537], [542], [545], [547], [549], [553], [556], [560], [562], [565], [568], [569], [570], [571], [574], [575], [578], [580], [582], [587], [590], [592], [596], [597], [598], [602], [609], [611], [614], [615], [618], [621], [622], [626], [635], [637], [643], [644], [666], [668], [672], [676], [690], [693], [701], [702], [709], [710], [715], [717], [718], [720], [724], [725], [732], [737], [742], [750], [752], [753], [758], [760], [762], [763], [766], [771], [774], [780], [784], [792], [793], [794], [796], [797], [799], [801], [804], [805], [807], [809], [810], [816], [817], [820], [825], [827], [828], [833], [835], [839], [842], [845], [846], [848], [850], [853], [855], [860], [861], [862], [863], [864], [865], [866], [872], [874], [875], [876], [880], [881], [883], [885], [886], [888], [892], [895], [896], [897], [898], [899], [902], [903], [910], [914], [916], [918], [919], [921], [926], [927], [930], [932], [933], [937], [939], [940], [946], [947], [951], [954], [957], [960], [965], [967], [969], [975], [977], [978], [979], [980], [983], [985], [986], [988], [989], [992], [993], [994], [997], [1007], [1009], [1011], [1015], [1016], [1018], [1020], [1022], [1023], [1037], [1039], [1040], [1043], [1044], [1047], [1056], [1059], [1065], [1066], [1071], [1072], [1073], [1076], [1080], [1081], [1083], [1085], [1087], [1088], [1094], [1099], [1101], [1107], [1113], [1114], [1117], [1119], [1120], [1123], [1126], [1132], [1135], [1136], [1139], [1147], [1149], [1151], [1152], [1163], [1165], [1166], [1167], [1168], [1171], [1176], [1177], [1179], [1180], [1182], [1187], [1189], [1190], [1191], [1193], [1195], [1199], [1204], [1206], [1209], [1211], [1212], [1214], [1215], [1219], [1224], [1225], [1230], [1231], [1233], [1234], [1240], [1242], [1244], [1247], [1252], [1253], [1254], [1256], [1261], [1264], [1270], [1272], [1274], [1277], [1278], [1279], [1281], [1282], [1283], [1285], [1289], [1292], [1293], [1295], [1301], [1302], [1304], [1308], [1309], [1313], [1314], [1315], [1316], [1317], [1319], [1320], [1322], [1325], [1327], [1328], [1330], [1333], [1339], [1340], [1342], [1346], [1347], [1351], [1355], [1361], [1365], [1367], [1368], [1370], [1371], [1373], [1375], [1377], [1382], [1385], [1389], [1396], [1398], [1400], [1401], [1403], [1406], [1409], [1411], [1412], [1413], [1414], [1417], [1419], [1424], [1425], [1426], [1428], [1430], [1433], [1434], [1435], [1436], [1445], [1448], [1455], [1459], [1463], [1464], [1465], [1466], [1467], [1468], [1469], [1471], [1476], [1478], [1482], [1483], [1485], [1486], [1488], [1490], [1493], [1495], [1496], [1497], [1500], [1506], [1514], [1516], [1521], [1522], [1523], [1524], [1525], [1527], [1532], [1536], [1547], [1548], [1549], [1550], [1551],

[1552], [1554], [1556], [1557], [1558], [1559], [1560], [1561], [1563], [1564], [1568], [1571], [1573], [1575], [1576], [1577], [1582], [1583], [1584], [1586], [1587], [1589], [1590], [1591], [1592], [1593], [1594], [1601], [1609], [1613], [1619], [1620], [1626], [1628], [1629], [1632], [1633], [1635], [1638], [1640], [1641], [1643], [1644], [1645], [1649], [1650], [1653], [1655], [1657], [1658], [1659], [1660], [1661], [1664], [1665], [1669], [1672], [1673], [1675], [1676], [1680], [1683], [1684], [1686], [1688], [1689], [1690], [1693], [1694], [1696], [1698], [1699], [1701], [1702], [1704], [1705], [1706], [1709], [1710], [1719], [1728], [1731], [1734], [1740], [1741], [1743], [1746], [1747], [1748], [1749], [1750], [1751], [1754], [1755], [1756], [1757], [1758], [1763], [1765], [1768], [1769], [1770], [1771], [1772], [1773], [1774], [1775], [1776], [1777], [1778], [1779], [1781], [1783], [1786], [1787], [1788], [1791], [1793], [1795], [1796], [1797], [1798], [1800], [1802], [1804], [1805], [1806], [1809], [1818], [1819], [1821], [1824], [1826], [1827], [1828], [1830], [1831], [1833], [1835], [1838], [1840], [1842], [1846], [1847], [1848], [1852], [1854], [1856], [1858], [1859], [1862], [1867], [1870], [1871], [1872], [1874], [1876], [1877], [1879], [1880], [1883], [1888], [1890], [1891], [1895], [1896], [1901], [1903], [1906], [1911], [1912], [1913], [1914], [1915], [1930], [1931], [1936], [1937], [1938], [1939], [1941], [1946], [1950], [1953], [1955], [1958], [1961], [1965], [1970], [1979], [1985], [1992], [1993], [2002], [2003], [2010], [2013], [2020], [2028], [2044], [2058], [2076], [2077], [2078], [2080], [2081], [2082], [2085], [2086], [2087], [2089], [2090], [2092], [2093], [2094], [2096], [2099], [2101], [2102], [2103], [2107], [2110], [2112], [2113], [2114], [2115], [2116], [2119], [2121], [2123], [2124], [2125], [2126], [2127], [2129], [2133], [2134], [2140], [2142], [2144], [2145], [2147], [2148], [2150], [2151], [2152], [2153], [2154], [2157], [2158], [2159], [2160], [2161], [2165], [2168], [2169], [2170], [2172], [2173], [2174], [2177], [2179], [2180], [2193], [2194], [2196], [2198], [2224], [2233], [2236], [2244], [2250], [2254], [2255], [2256], [2260], [2263], [2265], [2266], [2268], [2269], [2270], [2272], [2274], [2276], [2278], [2279], [2280], [2281], [2282], [2283], [2285], [2286], [2287], [2288], [2289], [2290], [2291], [2292], [2298], [2301], [2303], [2305], [2311], [2313], [2317], [2318], [2319], [2321], [2322], [2324], [2327], [2328], [2329], [2330], [2331], [2332], [2335], [2338], [2339], [2341], [2343], [2344], [2349], [2350], [2351], [2352], [2354], [2355], [2356], [2357], [2358], [2361], [2362], [2363], [2364], [2366], [2368], [2369], [2370], [2371], [2373], [2374], [2376], [2377], [2378], [2379], [2380], [2383], [2385], [2386], [2390], [2391], [2394], [2395], [2396], [2398], [2400], [2401], [2402], [2404], [2412], [2414], [2416], [2419], [2424], [2427], [2428], [2432], [2434], [2438], [2439], [2443], [2444], [2448], [2457], [2458], [2460], [2463], [2464], [2465], [2466], [2467], [2469], [2470], [2473], [2474], [2475], [2479], [2480], [2481], [2483], [2488], [2491], [2492], [2493], [2496], [2497], [2500], [2501], [2503], [2505], [2506], [2512], [2514], [2517], [2518], [2523], [2526], [2529], [2530], [2531], [2532], [2535], [2536], [2537], [2539], [2543],

[2545], [2550], [2551], [2552], [2554], [2555], [2556], [2558], [2561] —
ΣN=23484655

1) Introduction

Statins, or HMG-CoA reductase inhibitors, are a cornerstone of modern medicine, primarily prescribed for the prevention of atherosclerotic cardiovascular disease (ASCVD) by lowering low-density lipoprotein (LDL) cholesterol levels [\[521\]](#). Their efficacy in both primary and secondary prevention settings is well-established, leading to their widespread use across diverse populations, including those with hypertension, diabetes, and a history of ischemic events [\[20\]](#), [\[110\]](#), [\[521\]](#). However, the clinical landscape of statin therapy is complex and extends far beyond lipid management. A growing body of research has illuminated a wide spectrum of pleiotropic effects, potential adverse events, and significant challenges related to medication adherence.

Adverse effects, particularly statin-associated muscle symptoms (SAMS), represent a major clinical concern and a primary driver of medication intolerance and discontinuation [\[4\]](#), [\[37\]](#), [\[50\]](#). These can range from mild myalgia to severe, life-threatening conditions like rhabdomyolysis and autoimmune necrotizing myopathy [\[4\]](#), [\[24\]](#), [\[65\]](#). Furthermore, metabolic consequences, such as an increased risk of new-onset diabetes mellitus (NODM) and hepatic insulin resistance, have been identified, adding another layer of complexity to risk-benefit discussions [\[10\]](#), [\[202\]](#), [\[304\]](#). Conversely, research has also explored potential benefits of statins beyond cardiovascular health, including associations with reduced cancer risk, improved survival in certain malignancies, and neuroprotective effects [\[17\]](#), [\[25\]](#), [\[481\]](#).

Despite their proven benefits, suboptimal adherence and premature discontinuation of statin therapy are pervasive issues that significantly undermine their effectiveness and lead to increased risks of adverse cardiovascular outcomes [\[48\]](#), [\[83\]](#), [\[156\]](#). Factors influencing adherence are multifactorial, encompassing patient-related aspects such as cost, beliefs, and fear of side effects, as well as system-level factors like provider communication and continuity of care [\[26\]](#), [\[66\]](#), [\[123\]](#), [\[195\]](#). This complex interplay of benefits, risks, and behavioral challenges necessitates a comprehensive understanding of the current evidence to optimize patient outcomes, guide clinical decision-making, and identify critical areas for future research.

2) Aim

This systematic review aims to synthesize the evidence from the provided literature on statin medication. The review focuses on synthesizing key themes related to clinical outcomes, adverse effects, medication adherence, and the role of statins across a variety of patient populations and clinical contexts.

3) Methods

Systematic review with multilayer AI research agent: keyword normalization, retrieval & structuring, and paper synthesis (see SAIMSARA About section for details).

- **Bias:** The included studies encompass a wide range of designs, from randomized controlled trials (RCTs) to retrospective cohorts, cross-sectional analyses, and experimental models. While RCTs provide high-quality evidence for specific interventions [3], [32], [67], the preponderance of observational studies introduces a potential for selection bias, confounding by indication, and recall bias, particularly in retrospective designs [5], [25], [28]. Mixed-method studies and reviews, while providing broad overviews, are subject to the biases of their primary sources [4], [18], [20].

4) Results

4.1 Study characteristics (1-2 sentences):

The synthesized literature includes a diverse array of study designs, including RCTs, prospective and retrospective cohort studies, cross-sectional analyses, case-control studies, and experimental models. Populations ranged from broad general and Medicare populations to specific cohorts such as patients with acute ischemic stroke, cancer, diabetes, and those in palliative care, with follow-up periods extending from short-term assessments to over 20 years.

4.2 Main numerical result aligned to the query (2-4 sentences):

Statin medication adherence is a central and frequently measured outcome, though rates vary substantially across different populations and settings. The median adherence rate reported across studies was 54.0%, with a range from 29.7% in diabetic patients in Saudi Arabia to 89% in a separate cohort of type 2 diabetes patients [7], [112], [300]. Several prospective cohort studies highlight a decline in adherence over time; for instance, adherence in older adults with diabetes decreased from 54.0% at 6 months to 37.0% at 9 years, and in patients post-ASCVD, it dropped from 71% at 6 months to 42% at 7 years [301], [794].

4.3 Topic synthesis (5-20 topics):

- **Medication Adherence and Discontinuation:** Adherence to statin therapy is suboptimal and highly variable, with reported rates ranging from 29.7% to 89% [112], [300]. Discontinuation is common, often occurring within the first year of initiation [26], [88]. Key predictors of poor adherence and discontinuation include high patient cost-sharing [26], [154], [200], female gender [42], [170], younger age [170], concerns about side effects [66], lower necessity beliefs [137], and racial/ethnic minority status [7], [333], [155]. Conversely, factors associated with better adherence include older age [341], [983], secondary prevention versus primary prevention [128], continuity of care with a physician [173], [195], [245], and the use of fixed-dose combinations [104].
- **Adverse Effects: Myotoxicity:** Statin-associated muscle symptoms (SAMS) are the most frequent cause of intolerance and discontinuation, with an estimated prevalence of around 10% [50], [178]. The spectrum of myotoxicity ranges from asymptomatic elevations in creatine kinase (CK) to myalgia, severe rhabdomyolysis, and rare but severe statin-induced autoimmune necrotizing myopathy (SIANM), which can persist after discontinuation and requires immunosuppressive treatment [4], [24], [65], [109], [133]. Risk factors include concomitant medication use (e.g., CYP3A4 inhibitors), medical conditions, and genetic predisposition [4], [310].
- **Metabolic Effects and Diabetes Risk:** Statin therapy is associated with an increased risk of new-onset diabetes mellitus (NODM) [202], [304], [311], [1106]. One large cohort study in postmenopausal women reported a hazard ratio (HR) of 1.48 for NODM among statin users [202]. Mechanistic studies in animal models suggest this may be mediated through the induction of hepatic insulin resistance via the HNF4 α /PAQR9/PPM1 α axis [10]. However, in pre-diabetic individuals, withdrawal of statin medication did not affect fasting or post-meal insulin resistance [165].
- **Cardiovascular Outcomes and Prevention:** Statins are associated with improved survival and reduced adverse events in numerous high-risk populations. This includes patients with lower extremity artery disease (improved overall and amputation-free survival) [122], those undergoing elective abdominal aortic aneurysm (AAA) repair [183], and post-ischemic stroke patients, where lack of treatment is associated with higher mortality (HR 1.74 at 1 year) [83]. Discontinuation, even briefly, is linked to harmful outcomes, including early neurological deterioration in stroke patients and increased mortality risk [48], [110], [156], [860].
- **Cancer Risk and Survival:** The relationship between statin use and cancer is complex and appears to vary by cancer type. Statin use was associated with a reduced risk of oral squamous cell carcinoma (OSCC) in betel nut chewers (adjusted HR 0.61) and stomach

cancer [17], [450]. Improved survival was noted in patients with head and neck cancer (HR 0.80) and resectable pancreatic ductal adenocarcinoma (PDAC) [25], [625]. In contrast, no significant association was found with overall or high-grade prostate cancer risk or with survival in patients with resected PDAC in another study [40], [35].

- **Statin Intolerance and Management:** SAMS are the primary driver of statin intolerance [50]. Management strategies include switching to hydrophilic statins, correcting metabolic abnormalities, using fixed-dose combinations, or initiating non-statin agents like ezetimibe, bempedoic acid, or PCSK9 inhibitors [41], [103], [296]. For patients with prior myalgia, pharmacogenetic testing for SLCO1B1 variants improved statin re-initiation [163]. N-of-1 trials, where patients alternate between statin and placebo, have been shown to increase statin uptake by demonstrating that many symptoms are attributable to a nocebo effect [355], [511], [930].
- **Pharmacogenomics and Drug Interactions:** Genetic predisposition influences the risk of statin-related side effects [4], [68]. Pharmacogenomics, such as testing for SLCO1B1 variants, can help mitigate the risk of SAMS and guide prescribing [163], [219], [330], [487]. Co-medication with drugs that inhibit CYP3A4-metabolized statins is a significant concern, with one study finding that 2.84% of patients were co-medicated with contraindicated drugs, often prescribed by different institutions [76], [310]. Interactions with other medications, such as Paxlovid™, require dose adjustments or temporary substitution of certain statins [92].
- **Neurological and Cognitive Effects:** Evidence is mixed. Good statin compliance was associated with a reduced risk of dementia in patients with chronic periodontitis (HR 0.57 for high compliance) [74], and another study found a lower risk of overall dementia in hypercholesterolemic individuals [481]. However, a large cohort study of older veterans found statin initiation was not associated with incident dementia [164]. Conversely, continuous pre- and post-stroke statin treatment was associated with a higher hazard of post-stroke depression (1.99 times higher) [36].
- **Combination Therapies and Novel Agents:** Combining statins with other lipid-lowering agents like ezetimibe can significantly enhance LDL-C reduction and increase target achievement compared to statin monotherapy [89], [90], [798]. Novel agents such as bempedoic acid and PCSK9 inhibitors (e.g., evolocumab, alirocumab, inclisiran) offer effective alternatives or adjuncts for patients with statin intolerance or those who fail to reach LDL-C goals on maximally tolerated statin therapy [103], [136], [217], [607].
- **Effects on Gut Microbiota:** Mendelian randomization analysis indicates a causal relationship between statin medication and changes in the abundance of six specific gut microbiota species. This suggests that long-term statin therapy alters the gut microbiome, which may have implications for health monitoring and understanding the pleiotropic effects of statins [6].

- **Deprescribing in Specific Populations:** Discontinuing statin medication is safe and beneficial in certain contexts. In patients with a limited life expectancy (1 month to 1 year) in a palliative care setting, discontinuing statins was associated with improved quality of life (mean score 7.11 vs 6.85, $P=.04$) and reduced medication costs without significantly affecting mortality within 60 days [3]. However, for older adults in primary prevention, there is uncertainty about the risk-benefit profile, and decisions are often deferred to physicians [231], [287].
- **Perioperative and Post-procedural Effects:** Statin use is associated with varied outcomes in surgical and procedural settings. Perioperative statin use was linked to a higher rate of postoperative pneumonia after esophagectomy (OR 3.022) [5]. In contrast, it was associated with reduced 30-day mortality in stented patients undergoing non-cardiac surgery and a reduced risk of sepsis after colorectal surgery [291], [378]. Pre-interventional statin use was also a predictor for risk reduction in patients undergoing carotid stent-angioplasty [70].
- **Impact on Periodontal Health:** Statins appear to have a dual effect on the periodontium. Studies show a negative association with periodontal infection and fewer signs of inflammatory injury in patients with plaque or gingival bleeding [32], [271]. However, one study noted an increased likelihood of deepened periodontal pockets in subjects without gingival bleeding [32]. Good statin compliance may also reduce the risk of stroke in older adults with chronic periodontitis [45].
- **Patient Awareness and Communication:** A significant proportion of statin users may be unaware of their hypercholesterolemia diagnosis or that they are taking a statin (17.6% in one study) [33]. Furthermore, provider-patient communication regarding potential drug-drug interactions and individualized statin selection appears inadequate, with few patients recalling such discussions [238].

5) Discussion

5.1 Principal finding (1-2 sentences):

The principal finding from this systematic review is the profound variability and general suboptimality of statin medication adherence, with a median reported rate of 54.0% across diverse populations [7], [112], [300]. This highlights a critical gap between the established efficacy of statins in clinical trials and their real-world effectiveness, which is significantly undermined by a complex web of factors leading to non-adherence and discontinuation.

5.2 Clinical implications (3-5 bullets):

- **Active Adherence Monitoring is Essential:** Given that adherence is often low and declines over time, clinicians should proactively monitor and regularly discuss medication-taking behavior with patients [8], [22], [99]. Interventions such as reminder messages, simplifying regimens, and frequent follow-up have been shown to be effective [22], [77].
- **Systematic Management of Adverse Effects:** Clinicians must be vigilant for SAMS and other adverse effects, as they are a primary reason for non-adherence [50], [161]. A patient-centered approach involving thorough evaluation, risk factor modulation, and consideration of alternative statins or non-statin therapies is crucial to optimize tolerability [37], [41], [269].
- **Informed Deprescribing in Palliative Care:** In patients with limited life expectancy, deprescribing statins should be considered as a safe and effective strategy to improve quality of life and reduce medication burden [3]. This requires careful, individualized discussion with patients and their families about the goals of care [231], [287].
- **Address Disparities and Patient Beliefs:** Significant disparities in adherence exist across racial, ethnic, and socioeconomic groups [7], [57], [333]. Effective clinical practice requires addressing these disparities and engaging in shared decision-making that acknowledges and explores patient concerns, beliefs about medication necessity, and fear of side effects [85], [123], [137].
- **Consider Pharmacogenomic Testing:** For patients with a history of SAMS or at high risk for myotoxicity, pharmacogenomic testing (e.g., for SLCO1B1 variants) can be a valuable tool to guide statin selection and dosing, potentially improving tolerance and re-initiation rates [163], [219], [330].

5.3 Research implications / key gaps (3-5 bullets):

- **Efficacy of SAMS Management Strategies:** While Coenzyme Q-10 (CoQ10) is often used for SAMS, its benefit has not been confirmed in randomized controlled trials, representing a key evidence gap that needs to be addressed [71].
- **Statins and Musculoskeletal Repair:** The observation that statin use may be associated with re-tear after arthroscopic rotator cuff repair is based on retrospective data and requires prospective studies to determine causality and inform clinical practice [464], [1051].
- **Long-term Statin Safety in Youth:** Despite the use of statins in pediatric populations with conditions like familial hypercholesterolemia, there is a need for extensive future studies on the long-term safety and most appropriate age for initiation [1360], [1999].
- **Clarifying the Role of Statins in Dementia:** Observational data on the association between statin use and dementia risk are conflicting, with some studies suggesting a

protective effect and others finding no association. Rigorous, long-term prospective studies are needed to clarify this relationship and the potential for statins in dementia prevention [\[74\]](#), [\[164\]](#), [\[471\]](#), [\[481\]](#).

- **Evidence for Non-Statin Combinations:** There is a noted lack of accurate evidence on the use of non-statin medications in patients already receiving high-intensity statin therapy, necessitating a re-evaluation of treatment recommendations and dedicated clinical trials [\[158\]](#).

5.4 Limitations (up to 5; parse-friendly):

- **Heterogeneity Of Evidence** — The synthesis is based on a wide variety of study designs, including observational studies with inherent risks of bias and confounding, which limits the ability to draw strong causal inferences for many associations.
- **Variability In Adherence Metrics** — Studies used different methods to assess medication adherence (e.g., medication possession ratio, self-report), which complicates direct comparison and calculation of a precise, pooled adherence rate.
- **Lack Of Meta Analysis** — This review provides a qualitative and thematic synthesis without performing a formal quantitative meta-analysis, precluding the generation of pooled effect estimates and statistical measures of heterogeneity.
- **Broad User Query** — The general query "statin medication" yielded a vast and diverse set of findings, which allows for a broad overview but prevents a deep, focused analysis of any single clinical question or outcome.
- **Potential For Publication Bias** — The review is constrained to the provided summaries, and it is possible that studies with null or negative findings were underrepresented, potentially skewing the overall impression of statin effects.

5.5 Future directions (up to 5; parse-friendly):

- **Standardize Adherence Interventions** — Future research should focus on developing and testing scalable, multi-component behavior change technique (BCT) interventions to identify the minimum effective dose required to sustainably improve statin adherence [\[52\]](#), [\[166\]](#).
- **Clarify Statin Role In Cancer** — Large-scale, prospective, randomized trials are needed to definitively establish the causal role of statins in the prevention or improved survival of

specific cancers, such as oral, head and neck, and colorectal cancers [\[17\]](#), [\[25\]](#), [\[232\]](#).

- **Investigate Mechanistic Pathways** — Further experimental and clinical research should aim to elucidate the biological mechanisms underlying both adverse effects (e.g., myopathy, insulin resistance) and pleiotropic benefits (e.g., gut microbiota modulation, anti-inflammatory effects) of statins [\[6\]](#), [\[10\]](#), [\[37\]](#).
- **Optimize Deprescribing Guidelines** — Prospective trials are required to develop evidence-based guidelines for statin deprescribing in older adults and other specific populations, focusing on key outcomes like quality of life, mortality, and cardiovascular events [\[3\]](#), [\[1092\]](#), [\[287\]](#).
- **Evaluate Novel Delivery Systems** — Clinical trials should be conducted to evaluate the real-world efficacy, safety, and cost-effectiveness of nanoparticle drug delivery technologies for statins, which have shown potential for dramatically improving oral bioavailability in preclinical models [\[30\]](#).

6) Conclusion (3-6 sentences)

This systematic review synthesizes a broad landscape of evidence on statin medication, confirming its central role in cardiovascular risk reduction while highlighting significant challenges and areas of ongoing investigation. Key research themes include the pervasive issue of suboptimal medication adherence, the complex spectrum of adverse effects dominated by myotoxicity, and the expanding understanding of statins' pleiotropic effects on cancer, metabolic health, and neurological conditions. Numerically, adherence remains a critical weakness, with a median rate of only 54.0% across studies, underscoring a major gap in real-world effectiveness. A primary limitation of the current evidence base is the heterogeneity of study designs, which complicates causal inference for many observed associations. A crucial clinical implication is the need for proactive, patient-centered strategies that focus on shared decision-making to improve adherence, manage side effects, and tailor therapy to individual risk profiles and goals of care.

Session data (all downloaded records)

SAIMSARA Session Index — [session.json](#)

Figure 1. Publication-year distribution of included originals

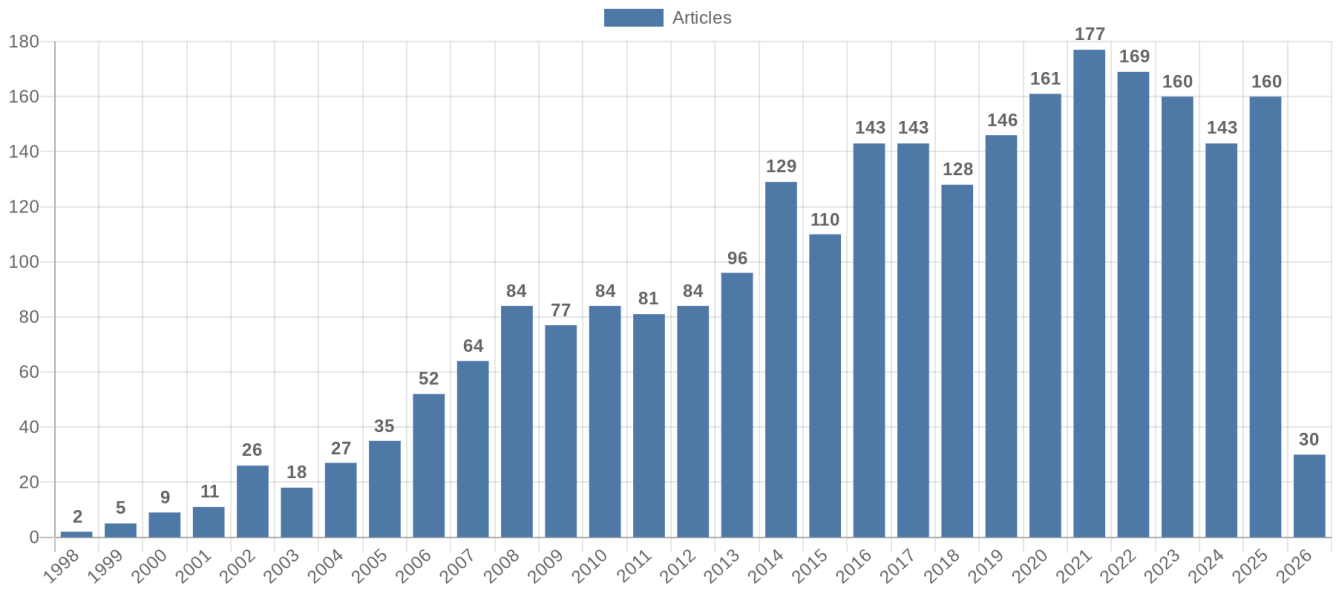


Figure 2. Study-design distribution of included originals

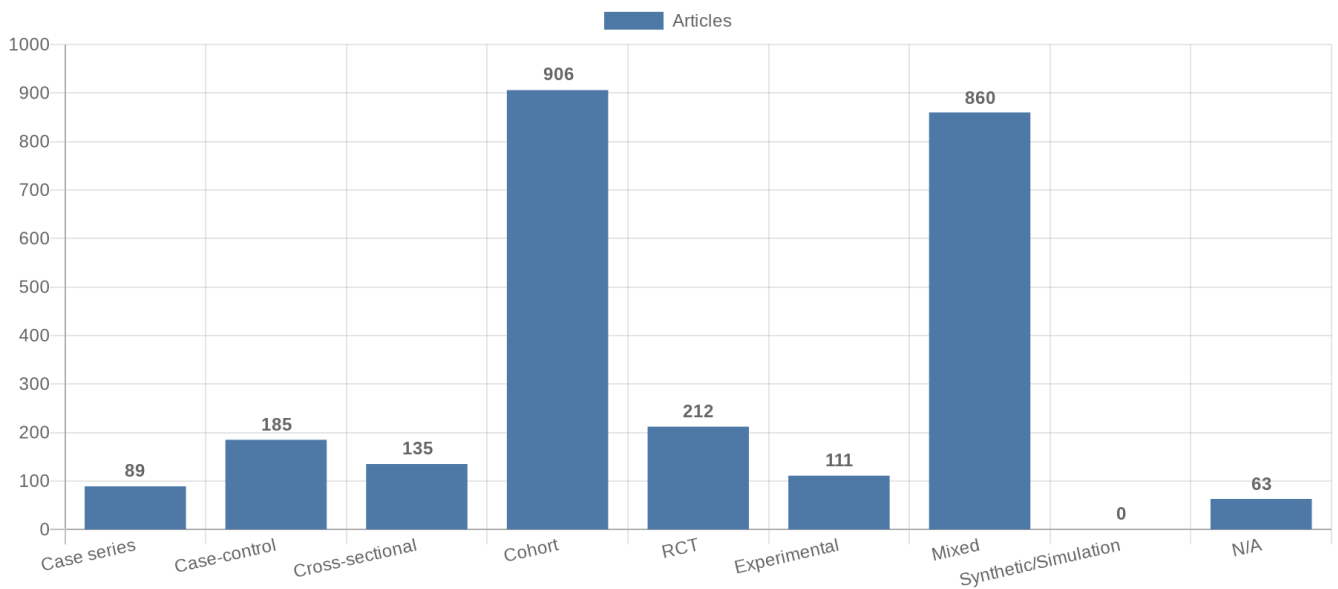


Figure 3. Study-type (directionality) distribution of included originals

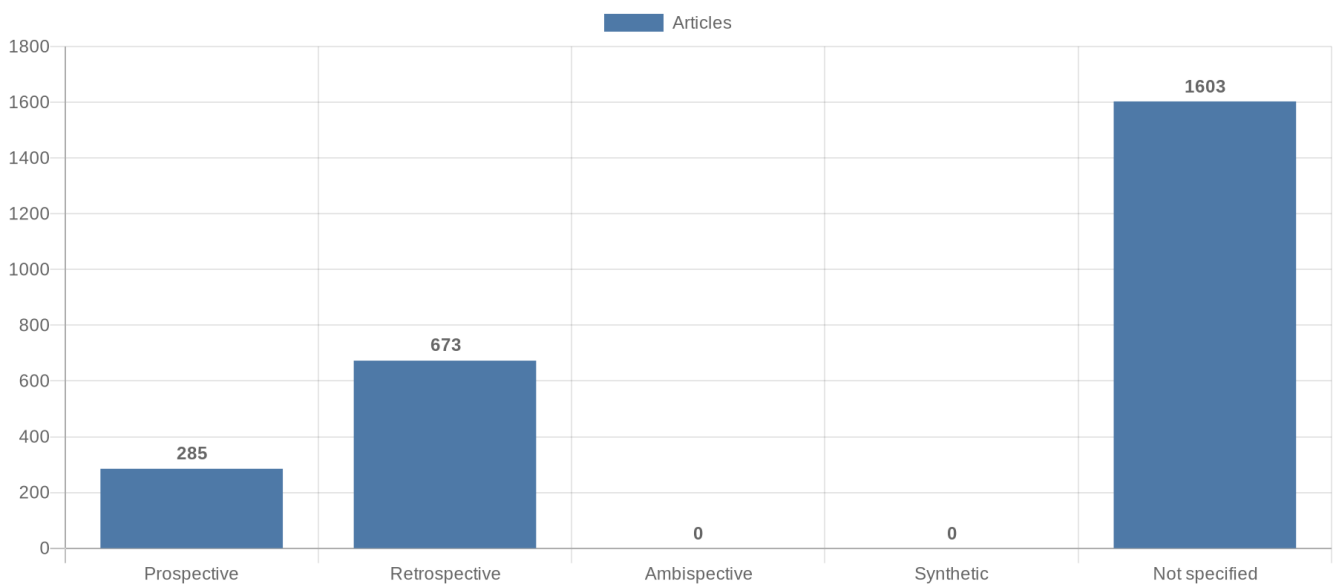


Figure 4. Main extracted research topics

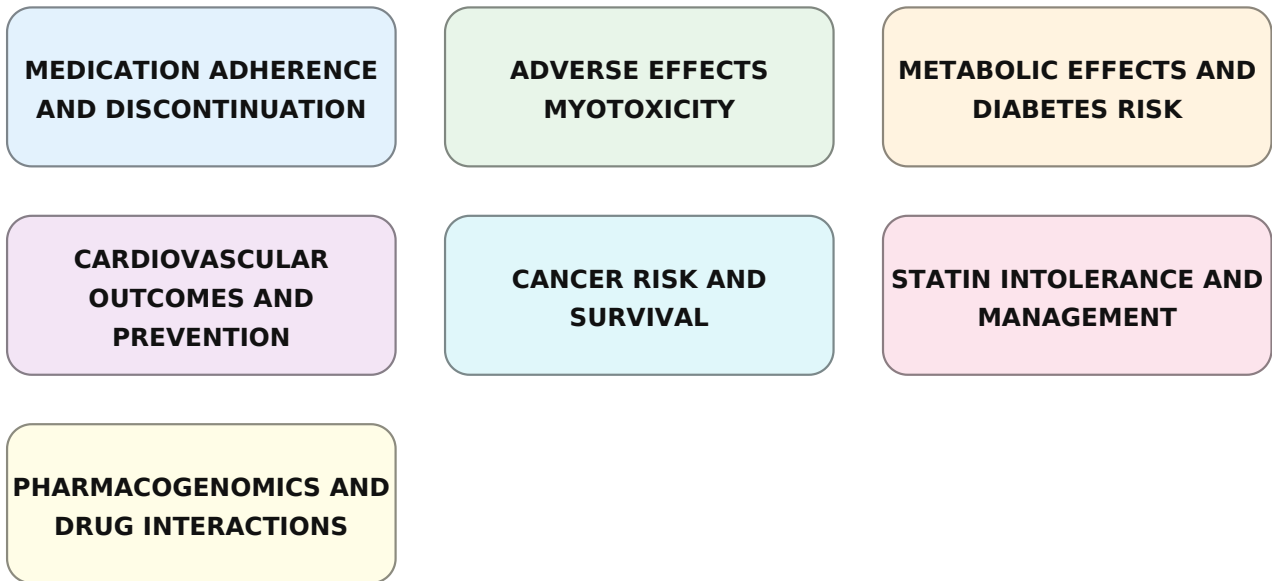


Figure 5. Limitations of current studies (topics)

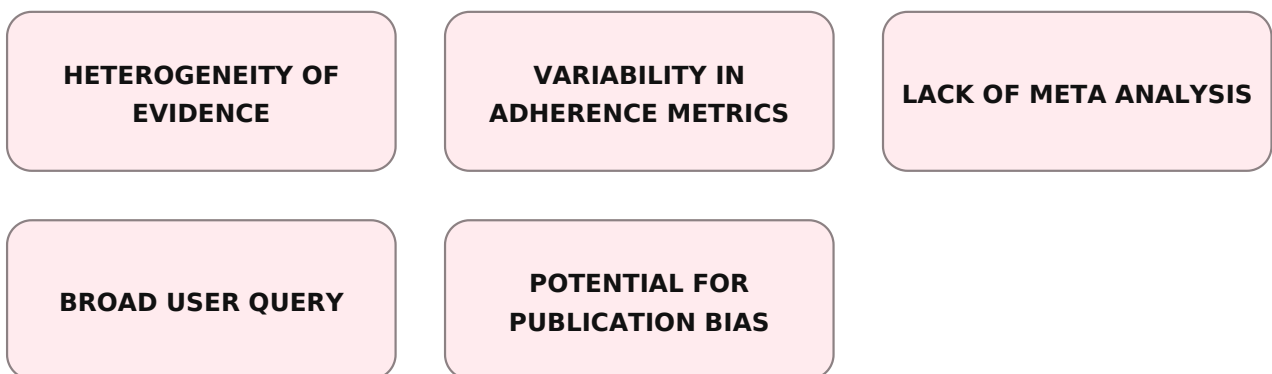
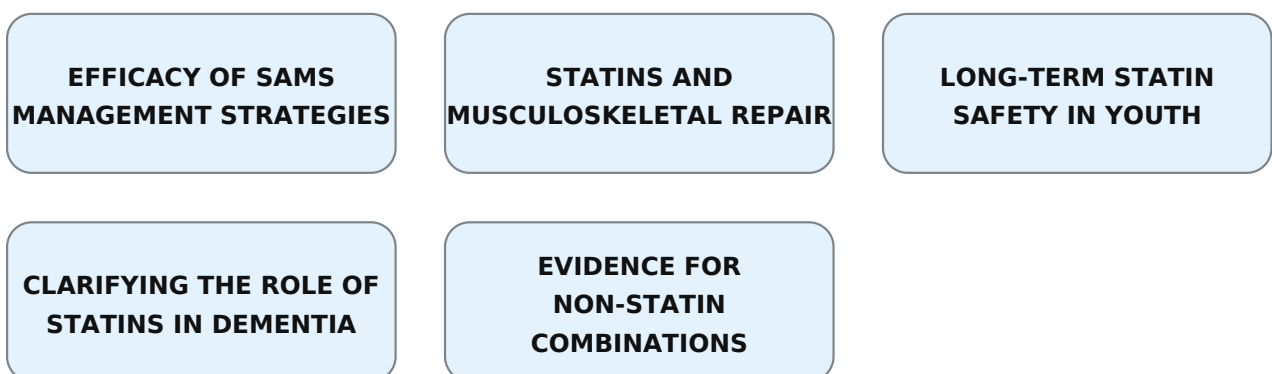


Figure 6. Future research directions (topics)



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