Statin Medication: Systematic Review with ☸SAIMSARA.

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Abstract: The aim of this paper is to systematically review and synthesize current scientific literature on statin medication, leveraging a multilayer AI research agent for keyword normalization, retrieval and structuring, and paper synthesis (see SAIMSARA About section for details). The review utilises 1928 studies with 26142367 total participants (naïve ΣN). This comprehensive review highlights the indispensable role of statin medication in modern healthcare, primarily for cardiovascular risk reduction, but also revealing a growing understanding of its pleiotropic effects across various disease states, including sepsis, certain cancers, and Graves' disease. Despite these broad benefits, statin adherence remains a significant challenge, with a median reported rate of 63.9%, underscoring the need for improved patient-centered strategies. A key limitation is the reliance on observational data for many emerging benefits and risks. Future research should prioritize large-scale randomized controlled trials to confirm non-cardiovascular benefits and risks, alongside pharmacogenomic studies and real-world implementation research to optimize personalized statin therapy and enhance adherence, particularly in underserved populations.

Keywords: Statin therapy; Statin adherence; LDL-C levels; Cardiovascular disease; Statin intolerance; Statin side effects; Stroke recurrence; Sepsis mortality; Gut microbiota; Restenosis risk

Review Stats

- Generated: 2026-02-16 22:03:25 CET
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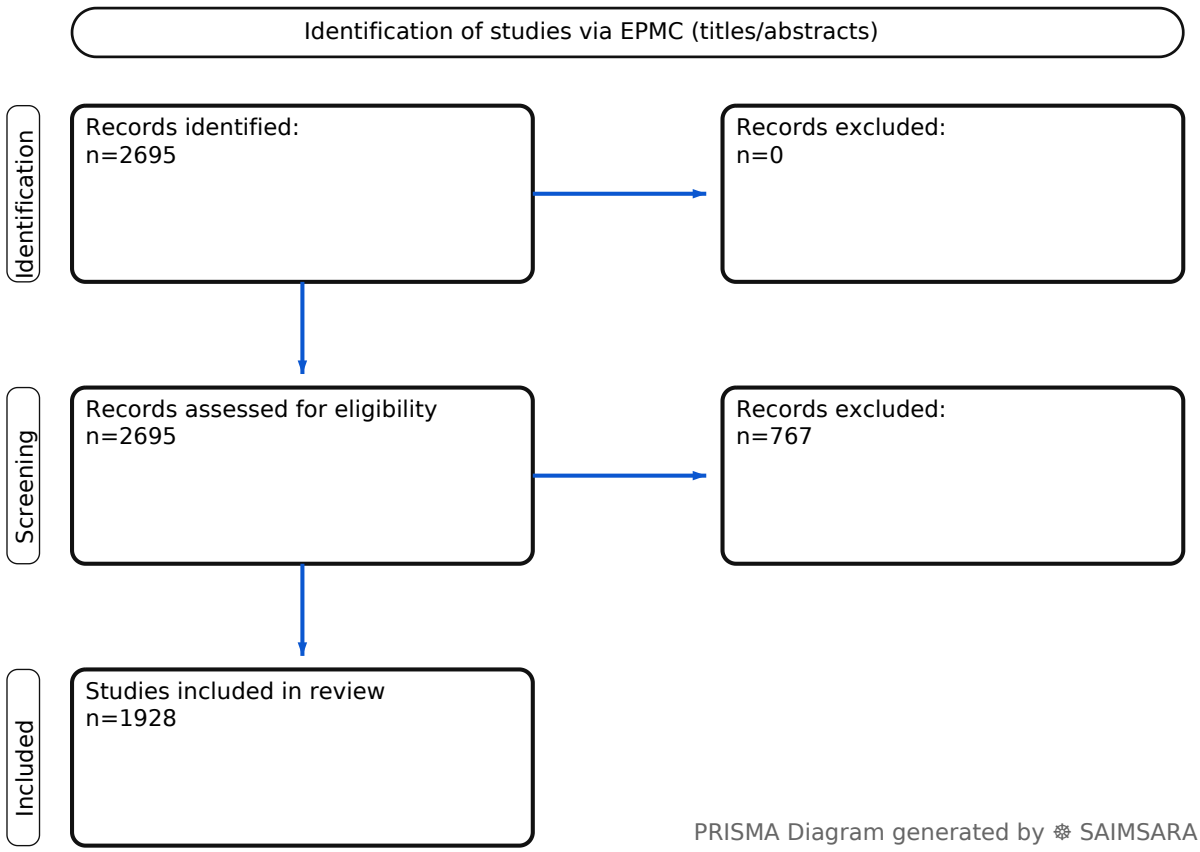
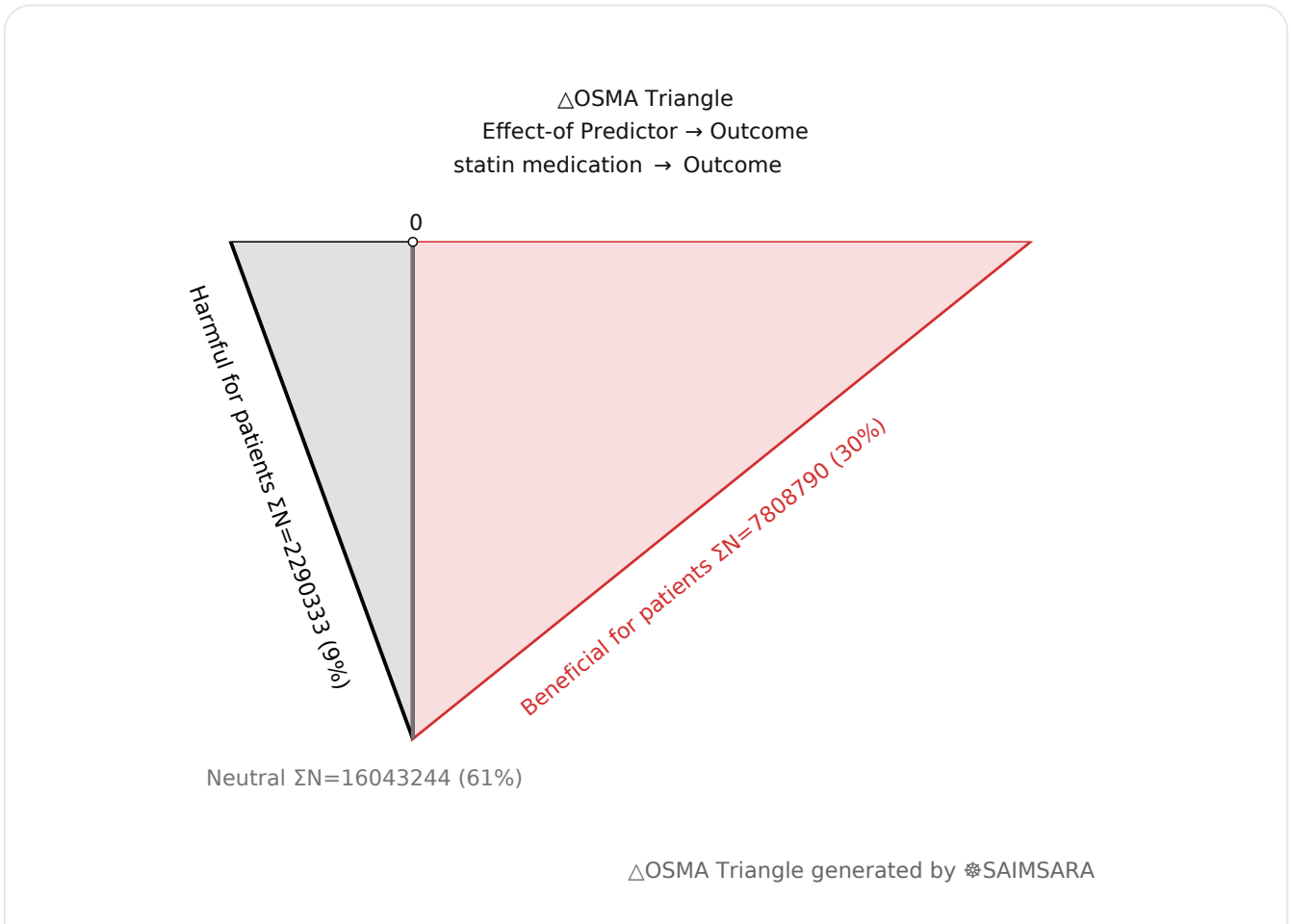
- Source: Europe PMC
- Scope: Titles/Abstracts (tiab)
- Keyword Gate: Fuzzy (≥60% of required terms, minimum 2 terms matched in title/abstract)
- Total Abstracts/Papers: 2695
- Downloaded Abstracts/Papers: 2695
- Included original Abstracts/Papers: 1928
- Total study participants (naïve ΣN): 26142367


Identification of studies via EPMC (titles/abstracts)
Identification
Records identified:
n=2695
Records excluded:
n=0
Screening
Records assessed for eligibility
n=2695
Records excluded:
n=767
Included
Studies included in review
n=1928
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
statin medication → Outcome
0
Harmful for patients ΣN=2290333 (9%)
Beneficial for patients ΣN=7808790 (30%)
Neutral ΣN=16043244 (61%)
△OSMA Triangle generated by ☸SAIMSARA

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

Frame: Effect-of Predictor → Outcome • *Source*: Europe PMC

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

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

Predictor: statin medication — exposure/predictor. Doses/units seen: 50 mg, 70 mg, 40 mg, 80 mg, 190 mg, 20 mg…. Routes seen: oral, intravenous. Typical comparator: control, non-target lesion, nonrecipients, usual care on adherence to et….

- **1) Beneficial for patients** — Outcome with statin medication — [3], [5], [8], [9], [10], [11], [14], [27], [29], [32], [33], [35], [36], [38], [39], [43], [50], [68], [71], [74], [79], [96], [97], [105], [117], [118], [121], [123], [124], [127], [130], [138], [140], [142], [144], [145], [161], [170], [175], [180], [186], [187], [189], [193], [195], [199], [201], [208], [210], [228], [230], [232], [236], [239], [243], [247], [249], [256], [259], [264], [265], [269], [287], [293], [303], [304], [317], [324], [329], [332], [334], [341], [348], [349], [352], [354], [359], [367], [368], [369], [373], [376], [377], [390], [393], [394], [399], [402], [407], [409], [410], [422], [423], [428], [446], [447], [450], [452], [454], [460], [463], [465], [468], [472], [475], [482], [484], [486], [488], [491], [497], [503], [506], [510], [512], [529], [533], [534], [537], [539], [544], [546], [547], [548], [549], [552], [554], [564], [570], [573], [578], [580], [583], [585], [589], [591], [594], [598], [603], [606], [611], [612], [614], [636], [640], [642], [650], [658], [661], [666], [670], [671], [673], [676], [677], [679], [680], [685], [690], [692], [697], [699], [709], [713], [720], [725], [727], [730], [736], [740], [741], [750], [759], [766], [778], [779], [785], [787], [789], [796], [806], [812], [820], [824], [832], [835], [837], [845], [847], [852], [853], [854], [855], [869], [870], [874], [875], [879], [892], [896], [900], [901], [903], [908], [915], [920], [921], [922], [927], [935], [948], [952], [954], [957], [963], [972], [974], [991], [997], [999], [1003], [1007], [1008], [1021], [1022], [1023], [1033], [1039], [1044], [1045], [1047], [1052], [1054], [1055], [1064], [1068], [1080], [1103], [1110], [1111], [1112], [1114], [1120], [1130], [1133], [1134], [1135], [1142], [1143], [1160], [1165], [1169], [1173], [1176], [1181], [1185], [1189], [1197], [1198], [1199], [1202], [1208], [1217], [1225], [1227], [1229], [1236], [1237], [1240], [1247], [1254], [1258], [1262], [1269], [1270], [1274], [1280], [1296], [1304], [1307], [1310], [1313], [1321], [1325], [1326], [1327], [1328], [1329], [1336], [1338], [1349], [1351], [1363], [1370], [1373], [1375], [1381], [1382], [1397], [1399], [1401], [1406], [1407], [1409], [1410], [1411], [1412], [1413], [1418], [1422], [1425], [1435], [1438], [1442], [1452], [1458], [1462], [1463], [1467], [1474], [1486], [1495], [1499], [1501], [1503], [1504], [1511], [1513], [1515], [1531], [1533], [1534], [1537], [1538], [1540], [1542], [1546], [1548], [1551], [1556], [1561], [1570], [1577], [1582], [1585], [1589], [1591],

[1594], [1604], [1605], [1611], [1612], [1622], [1625], [1626], [1630], [1636], [1639], [1644], [1650], [1651], [1652], [1653], [1654], [1655], [1656], [1657], [1662], [1664], [1666], [1669], [1675], [1676], [1677], [1696], [1699], [1701], [1704], [1708], [1710], [1728], [1736], [1742], [1748], [1751], [1754], [1757], [1776], [1781], [1800], [1804], [1811], [1815], [1842], [1847], [1849], [1856], [1858], [1859], [1861], [1871], [1873], [1876], [1882], [1883], [1888], [1889], [1893], [1894], [1897], [1898], [1901], [1906], [1912], [1914], [1922] — ΣN=7808790

- **2) Harmful for patients** — Outcome with statin medication — [15], [17], [30], [45], [65], [85], [86], [92], [93], [101], [120], [128], [141], [143], [156], [159], [160], [163], [166], [181], [190], [191], [207], [212], [248], [253], [254], [263], [267], [268], [271], [285], [298], [308], [314], [315], [335], [337], [363], [400], [405], [413], [435], [436], [439], [451], [477], [485], [515], [516], [521], [526], [538], [579], [582], [609], [621], [622], [632], [641], [665], [674], [675], [702], [703], [731], [739], [744], [749], [756], [765], [788], [818], [825], [827], [828], [836], [838], [864], [890], [910], [912], [934], [950], [955], [962], [966], [967], [992], [1009], [1048], [1075], [1081], [1086], [1104], [1106], [1132], [1154], [1207], [1215], [1218], [1233], [1287], [1331], [1337], [1342], [1366], [1379], [1387], [1388], [1389], [1393], [1394], [1395], [1417], [1427], [1430], [1432], [1440], [1448], [1450], [1451], [1464], [1553], [1555], [1567], [1571], [1574], [1581], [1592], [1600], [1607], [1629], [1658], [1688], [1689], [1705], [1713], [1768], [1829], [1848], [1890] — ΣN=2290333
- **3) No clear effect** — Outcome with statin medication — [1], [2], [4], [6], [7], [12], [13], [16], [18], [19], [20], [21], [22], [23], [24], [25], [26], [28], [31], [34], [37], [40], [41], [42], [44], [46], [47], [48], [49], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60], [61], [62], [63], [64], [66], [67], [69], [70], [72], [73], [75], [76], [77], [78], [80], [81], [82], [83], [84], [87], [88], [89], [90], [91], [94], [95], [98], [99], [100], [102], [103], [104], [106], [107], [108], [109], [110], [111], [112], [113], [114], [115], [116], [119], [122], [125], [126], [129], [131], [132], [133], [134], [135], [136], [137], [139], [146], [147], [148], [149], [150], [151], [152], [153], [154], [155], [157], [158], [162], [164], [165], [167], [168], [169], [171], [172], [173], [174], [176], [177], [178], [179], [182], [183], [184], [185], [188], [192], [194], [196], [197], [198], [200], [202], [203], [204], [205], [206], [209], [211], [213], [214], [215], [216], [217], [218], [219], [220], [221], [222], [223], [224], [225], [226], [227], [229], [231], [233], [234], [235], [237], [238], [240], [241], [242], [244], [245], [246], [250], [251], [252], [255], [257], [258], [260], [261], [262], [266], [270], [272], [273], [274], [275], [276], [277], [278], [279], [280], [281], [282], [283], [284], [286], [288], [289], [290], [291], [292], [294], [295], [296], [297], [299], [300], [301], [302], [305], [306], [307], [309], [310], [311], [312], [313], [316], [318], [319], [320], [321], [322], [323], [325], [326], [327], [328], [330], [331], [333], [336], [338], [339], [340], [342], [343], [344], [345], [346], [347], [350],

[351], [353], [355], [356], [357], [358], [360], [361], [362], [364], [365], [366], [370], [371], [372], [374], [375], [378], [379], [380], [381], [382], [383], [384], [385], [386], [387], [388], [389], [391], [392], [395], [396], [397], [398], [401], [403], [404], [406], [408], [411], [412], [414], [415], [416], [417], [418], [419], [420], [421], [424], [425], [426], [427], [429], [430], [431], [432], [433], [434], [437], [438], [440], [441], [442], [443], [444], [445], [448], [449], [453], [455], [456], [457], [458], [459], [461], [462], [464], [466], [467], [469], [470], [471], [473], [474], [476], [478], [479], [480], [481], [483], [487], [489], [490], [492], [493], [494], [495], [496], [498], [499], [500], [501], [502], [504], [505], [507], [508], [509], [511], [513], [514], [517], [518], [519], [520], [522], [523], [524], [525], [527], [528], [530], [531], [532], [535], [536], [540], [541], [542], [543], [545], [550], [551], [553], [555], [556], [557], [558], [559], [560], [561], [562], [563], [565], [566], [567], [568], [569], [571], [572], [574], [575], [576], [577], [581], [584], [586], [587], [588], [590], [592], [593], [595], [596], [597], [599], [600], [601], [602], [604], [605], [607], [608], [610], [613], [615], [616], [617], [618], [619], [620], [623], [624], [625], [626], [627], [628], [629], [630], [631], [633], [634], [635], [637], [638], [639], [643], [644], [645], [646], [647], [648], [649], [651], [652], [653], [654], [655], [656], [657], [659], [660], [662], [663], [664], [667], [668], [669], [672], [678], [681], [682], [683], [684], [686], [687], [688], [689], [691], [693], [694], [695], [696], [698], [700], [701], [704], [705], [706], [707], [708], [710], [711], [712], [714], [715], [716], [717], [718], [719], [721], [722], [723], [724], [726], [728], [729], [732], [733], [734], [735], [737], [738], [742], [743], [745], [746], [747], [748], [751], [752], [753], [754], [755], [757], [758], [760], [761], [762], [763], [764], [767], [768], [769], [770], [771], [772], [773], [774], [775], [776], [777], [780], [781], [782], [783], [784], [786], [790], [791], [792], [793], [794], [795], [797], [798], [799], [800], [801], [802], [803], [804], [805], [807], [808], [809], [810], [811], [813], [814], [815], [816], [817], [819], [821], [822], [823], [826], [829], [830], [831], [833], [834], [839], [840], [841], [842], [843], [844], [846], [848], [849], [850], [851], [856], [857], [858], [859], [860], [861], [862], [863], [865], [866], [867], [868], [871], [872], [873], [876], [877], [878], [880], [881], [882], [883], [884], [885], [886], [887], [888], [889], [891], [893], [894], [895], [897], [898], [899], [902], [904], [905], [906], [907], [909], [911], [913], [914], [916], [917], [918], [919], [923], [924], [925], [926], [928], [929], [930], [931], [932], [933], [936], [937], [938], [939], [940], [941], [942], [943], [944], [945], [946], [947], [949], [951], [953], [956], [958], [959], [960], [961], [964], [965], [968], [969], [970], [971], [973], [975], [976], [977], [978], [979], [980], [981], [982], [983], [984], [985], [986], [987], [988], [989], [990], [993], [994], [995], [996], [998], [1000], [1001], [1002], [1004], [1005], [1006], [1010], [1011], [1012], [1013], [1014], [1015], [1016], [1017], [1018], [1019], [1020], [1024], [1025], [1026], [1027], [1028], [1029], [1030], [1031], [1032], [1034], [1035], [1036], [1037], [1038], [1040], [1041], [1042], [1043],

[1046], [1049], [1050], [1051], [1053], [1056], [1057], [1058], [1059], [1060], [1061], [1062], [1063], [1065], [1066], [1067], [1069], [1070], [1071], [1072], [1073], [1074], [1076], [1077], [1078], [1079], [1082], [1083], [1084], [1085], [1087], [1088], [1089], [1090], [1091], [1092], [1093], [1094], [1095], [1096], [1097], [1098], [1099], [1100], [1101], [1102], [1105], [1107], [1108], [1109], [1113], [1115], [1116], [1117], [1118], [1119], [1121], [1122], [1123], [1124], [1125], [1126], [1127], [1128], [1129], [1131], [1136], [1137], [1138], [1139], [1140], [1141], [1144], [1145], [1146], [1147], [1148], [1149], [1150], [1151], [1152], [1153], [1155], [1156], [1157], [1158], [1159], [1161], [1162], [1163], [1164], [1166], [1167], [1168], [1170], [1171], [1172], [1174], [1175], [1177], [1178], [1179], [1180], [1182], [1183], [1184], [1186], [1187], [1188], [1190], [1191], [1192], [1193], [1194], [1195], [1196], [1200], [1201], [1203], [1204], [1205], [1206], [1209], [1210], [1211], [1212], [1213], [1214], [1216], [1219], [1220], [1221], [1222], [1223], [1224], [1226], [1228], [1230], [1231], [1232], [1234], [1235], [1238], [1239], [1241], [1242], [1243], [1244], [1245], [1246], [1248], [1249], [1250], [1251], [1252], [1253], [1255], [1256], [1257], [1259], [1260], [1261], [1263], [1264], [1265], [1266], [1267], [1268], [1271], [1272], [1273], [1275], [1276], [1277], [1278], [1279], [1281], [1282], [1283], [1284], [1285], [1286], [1288], [1289], [1290], [1291], [1292], [1293], [1294], [1295], [1297], [1298], [1299], [1300], [1301], [1302], [1303], [1305], [1306], [1308], [1309], [1311], [1312], [1314], [1315], [1316], [1317], [1318], [1319], [1320], [1322], [1323], [1324], [1330], [1332], [1333], [1334], [1335], [1339], [1340], [1341], [1343], [1344], [1345], [1346], [1347], [1348], [1350], [1352], [1353], [1354], [1355], [1356], [1357], [1358], [1359], [1360], [1361], [1362], [1364], [1365], [1367], [1368], [1369], [1371], [1372], [1374], [1376], [1377], [1378], [1380], [1383], [1384], [1385], [1386], [1390], [1391], [1392], [1396], [1398], [1400], [1402], [1403], [1404], [1405], [1408], [1414], [1415], [1416], [1419], [1420], [1421], [1423], [1424], [1426], [1428], [1429], [1431], [1433], [1434], [1436], [1437], [1439], [1441], [1443], [1444], [1445], [1446], [1447], [1449], [1453], [1454], [1455], [1456], [1457], [1459], [1460], [1461], [1465], [1466], [1468], [1469], [1470], [1471], [1472], [1473], [1475], [1476], [1477], [1478], [1479], [1480], [1481], [1482], [1483], [1484], [1485], [1487], [1488], [1489], [1490], [1491], [1492], [1493], [1494], [1496], [1497], [1498], [1500], [1502], [1505], [1506], [1507], [1508], [1509], [1510], [1512], [1514], [1516], [1517], [1518], [1519], [1520], [1521], [1522], [1523], [1524], [1525], [1526], [1527], [1528], [1529], [1530], [1532], [1535], [1536], [1539], [1541], [1543], [1544], [1545], [1547], [1549], [1550], [1552], [1554], [1557], [1558], [1559], [1560], [1562], [1563], [1564], [1565], [1566], [1568], [1569], [1572], [1573], [1575], [1576], [1578], [1579], [1580], [1583], [1584], [1586], [1587], [1588], [1590], [1593], [1595], [1596], [1597], [1598], [1599], [1601], [1602], [1603], [1606], [1608], [1609], [1610], [1613], [1614], [1615], [1616], [1617], [1618], [1619], [1620], [1621], [1623], [1624], [1627], [1628], [1631], [1632],

[1633], [1634], [1635], [1637], [1638], [1640], [1641], [1642], [1643], [1645], [1646], [1647], [1648], [1649], [1659], [1660], [1661], [1663], [1665], [1667], [1668], [1670], [1671], [1672], [1673], [1674], [1678], [1679], [1680], [1681], [1682], [1683], [1684], [1685], [1686], [1687], [1690], [1691], [1692], [1693], [1694], [1695], [1697], [1698], [1700], [1702], [1703], [1706], [1707], [1709], [1711], [1712], [1714], [1715], [1716], [1717], [1718], [1719], [1720], [1721], [1722], [1723], [1724], [1725], [1726], [1727], [1729], [1730], [1731], [1732], [1733], [1734], [1735], [1737], [1738], [1739], [1740], [1741], [1743], [1744], [1745], [1746], [1747], [1749], [1750], [1752], [1753], [1755], [1756], [1758], [1759], [1760], [1761], [1762], [1763], [1764], [1765], [1766], [1767], [1769], [1770], [1771], [1772], [1773], [1774], [1775], [1777], [1778], [1779], [1780], [1782], [1783], [1784], [1785], [1786], [1787], [1788], [1789], [1790], [1791], [1792], [1793], [1794], [1795], [1796], [1797], [1798], [1799], [1801], [1802], [1803], [1805], [1806], [1807], [1808], [1809], [1810], [1812], [1813], [1814], [1816], [1817], [1818], [1819], [1820], [1821], [1822], [1823], [1824], [1825], [1826], [1827], [1828], [1830], [1831], [1832], [1833], [1834], [1835], [1836], [1837], [1838], [1839], [1840], [1841], [1843], [1844], [1845], [1846], [1850], [1851], [1852], [1853], [1854], [1855], [1857], [1860], [1862], [1863], [1864], [1865], [1866], [1867], [1868], [1869], [1870], [1872], [1874], [1875], [1877], [1878], [1879], [1880], [1881], [1884], [1885], [1886], [1887], [1891], [1892], [1895], [1896], [1899], [1900], [1902], [1903], [1904], [1905], [1907], [1908], [1909], [1910], [1911], [1913], [1915], [1916], [1917], [1918], [1919], [1920], [1921], [1923], [1924], [1925], [1926], [1927], [1928] — ΣN=16043244

1) Introduction

Statin medications, inhibitors of HMG-CoA reductase, are foundational in the management of dyslipidemia and the prevention of cardiovascular diseases (CVD). Their widespread use necessitates a comprehensive understanding of their efficacy, safety, adherence patterns, and broader impacts across diverse patient populations and clinical contexts. This paper synthesizes recent research on statin medication, exploring its multifaceted roles from primary prevention to complex disease management and its interactions with various physiological systems and healthcare delivery models.

2) Aim

The aim of this paper is to systematically review and synthesize current scientific literature on statin medication, leveraging a multilayer AI research agent for keyword normalization, retrieval and structuring, and paper synthesis (see SAIMSARA About section for details).

3) Methods

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

- **Bias:** Qualitatively inferred from study design fields. Randomized controlled trials (RCTs) generally offer the lowest risk of bias for intervention effects, while cohort and mixed-design studies may be susceptible to confounding and selection biases. Cross-sectional studies are limited in establishing causality. Studies with unspecified designs or directionality carry the highest uncertainty regarding potential biases.

4) Results

4.1 Study characteristics:

The included studies predominantly comprised cohort designs (both prospective and retrospective), RCTs, and mixed-design studies, with a notable number of cross-sectional and case-control investigations. Populations ranged from general adults and older adults with dyslipidemia or CVD to highly specific groups such as transplant recipients, cancer patients, and individuals with rare neurological conditions. Follow-up periods varied widely, from short-term (e.g., 2 weeks to 6 months) to long-term (e.g., 2 years, 5 years, 10 years, and even 41 years).

4.2 Main numerical result aligned to the query:

Statin medication adherence rates, when explicitly quantified (e.g., as Proportion of Days Covered (PDC) ≥ 80% or similar metrics), varied considerably across studies. The median reported adherence rate was 63.9% [551], with a wide range observed from 4% [442] to 100% [1720]. This heterogeneity reflects diverse populations, measurement methods, and intervention strategies, indicating that while high adherence is achievable in some settings, suboptimal adherence remains a significant challenge.

4.3 Topic synthesis:

- **Adherence and Persistence:** Statin adherence is frequently suboptimal, with a median reported rate of 63.9% [551] and a range from 4% [442] to 100% [1720]. Factors influencing adherence include age (lower in younger adults, higher in older adults) [18, 25, 26, 442], sex (lower in females) [25, 26, 455], cost/copayments [129, 323, 421], pill burden [416], and social needs like loneliness or lack of transportation [639]. Interventions such as pharmacist-led programs [247, 265, 608, 660, 884, 1111], daily alarms with feedback [391, 403], appointment-based medication synchronization (ABMS) [760, 833], and physician mailings [1013] have shown improvements in adherence. However, some interventions like consumer apps [969, 976] and text messaging [604, 656] have shown mixed or no significant effects.

Generic substitution may also impact persistence [1162, 1393].

- **Cardiovascular Outcomes and Efficacy:** Statins are effective in reducing LDL-C [168, 205, 208, 259, 430, 1049, 1610, 1745], with a 40% reduction estimated for LDL cholesterol [168]. They are associated with reduced stroke recurrence [8, 195, 232], lower cardiovascular disease (CVD) risk [3, 564], reduced restenosis after angioplasty [10, 27], and decreased mortality after acute ischemic stroke (AIS) [230] and myocardial infarction (MI) [450, 491, 1463, 1728]. Statin use is also linked to reduced aneurysm diameter and growth rate [175, 127], improved endothelial function [338, 1781], and reduced risk of new-onset atrial fibrillation (NOAF) in hypertensive adults [68, 130].
- **Safety and Adverse Effects:** Statin-associated muscle symptoms (SAMS) are a significant concern, reported by physicians [15] and patients [254, 284, 405, 162, 151, 206, 207, 263, 385, 568, 890, 1071, 1689], with myalgias observed in 29.2% with rosuvastatin and 26.5% with atorvastatin [15]. Rare but severe adverse effects include necrotizing autoimmune myopathy [76, 181, 207, 385, 568, 890, 1071, 1689], rhabdomyolysis [250, 1640, 1848], and liver injury [128]. Statins may increase the risk of ocular hypertension and primary open-angle glaucoma (POAG) [17, 120, 439], and potentially diabetic nephropathy (DN) with long-term use [160]. Some studies suggest an increased risk of immune-related adverse events (irAEs) [93] and postoperative pneumonia [30]. No causal relationship was found with Achilles tendinopathy [51].
- **Impact on Other Conditions:** Statins have shown diverse effects beyond lipid lowering. They are associated with reduced mortality in sepsis patients [9, 39, 249, 486, 1747], improved survival in head and neck cancer [32], breast cancer [38, 666], ovarian cancer [539], oral squamous cell carcinoma [349], and hepatocellular carcinoma (HCC) [161, 264, 465]. They may also reduce Graves' orbitopathy (GO) risk [33, 43] and fracture risk in older males [79]. However, statin use has been linked to increased risk of Parkinson's disease [632, 756] and potentially amyotrophic lateral sclerosis (ALS) [308].
- **Implementation and Healthcare Delivery:** Gaps exist in statin prescribing, especially in low-income [42, 80, 90, 481, 690, 724, 290], incarcerated [23], and minority populations [42, 282, 1355]. Coronary computed tomography angiography (CCTA) can increase statin initiation/intensification [176, 1350, 462]. Shared decision-making (SDM) is crucial for older adults regarding continuation/discontinuation [119, 64, 937]. Pharmacist interventions [245, 247, 265, 483, 500, 584, 608, 660, 661, 884, 1037, 1089, 1111] and technology-assisted tools [144, 1650] can improve adherence and goal attainment.
- **Mechanistic Insights and Biomarkers:** Statins can alter gut microbiota composition [4, 252], with negative correlations observed for five species and positive for one [4]. They influence inflammatory markers like IL-6 and CRP [339, 653, 1681, 1777, 1827]. Genetic variants (e.g., SLCO1B1*5, NAT2) are associated with statin response and side effects [135, 151, 206, 242, 263, 557]. Statin therapy can also increase PCSK9 levels [415].

- **Co-medications and Interactions:** Combined statin and antiplatelet therapy may reduce the risk of cerebral cavernous malformation hemorrhage [11]. Combination therapy with ezetimibe or PCSK9 inhibitors can achieve lower LDL-C targets, especially in statin-intolerant patients or those with suboptimal response [109, 179, 214, 215, 219, 269, 292, 430, 700, 1054, 1855]. Drug-drug interactions (DDIs) can occur, such as with Danazol [209], Tribulus terrestris [250], or HIV antiretroviral therapy [521], potentially increasing myopathy risk [1492, 1848]. Metformin use may dampen vaccine responsiveness in diabetics [2] but enhance LDL-C response to statins [122].

5) Discussion

5.1 Principal finding:

The systematic review reveals that statin medication adherence is highly variable, with a median reported adherence rate of 63.9% [551] and a broad range from 4% [442] to 100% [1720], underscoring persistent challenges in patient compliance despite known benefits.

5.2 Clinical implications:

- **Personalized Adherence Strategies:** Given the wide range of adherence, individualized interventions (e.g., pharmacist-led counseling, digital reminders, addressing social needs) are crucial to improve statin uptake and persistence, particularly in vulnerable populations [247, 265, 391, 403, 639, 660, 833, 987].
- **Monitoring and Management of Side Effects:** Clinicians should actively inquire about and manage statin-associated muscle symptoms (SAMS) and other side effects, considering alternative statins (e.g., hydrophilic) or combination therapies (e.g., ezetimibe, PCSK9 inhibitors) for intolerant patients to maintain lipid-lowering goals [15, 109, 162, 179, 275, 292, 683].
- **Optimizing Prescribing Practices:** Despite clear guidelines, gaps in statin prescribing persist, especially in minority, low-income, and older adult populations, highlighting the need for enhanced clinician education, decision support tools, and health system interventions to ensure appropriate initiation and intensification of therapy [42, 80, 234, 282, 438, 455, 904, 1102, 1353, 1374, 1386].
- **Beyond Lipid Lowering:** The pleiotropic effects of statins extend to reduced mortality in sepsis and COVID-19, and improved outcomes in certain cancers and neurological conditions, suggesting broader therapeutic considerations beyond traditional cardiovascular risk reduction [9, 32, 33, 35, 38, 39, 43, 249, 349, 475, 486, 510, 539, 614, 666, 713, 789, 832, 870, 957, 974, 1225, 1269].

- **Caution with Specific Comorbidities:** Awareness of potential adverse effects in specific populations (e.g., increased glaucoma risk [17, 120, 439], diabetic nephropathy [160], or interactions with other medications [209, 250, 521, 1492, 1848]) is important for personalized care.

5.3 Research implications / key gaps:

- **Long-term Adherence Interventions:** Efficacy of sustained, tailored interventions to improve statin adherence across diverse socioeconomic and cultural contexts, particularly in low-income settings [90, 247, 460, 690].
- **Mechanistic Pathways in Non-CVD Benefits:** Elucidating the precise molecular mechanisms underlying statins' protective effects in conditions like sepsis, COVID-19, and various cancers, to inform new therapeutic targets [9, 32, 35, 39, 249, 475, 486, 510, 529, 539, 614, 666, 713, 789, 832, 870, 957, 974, 1225, 1269].
- **Pharmacogenomics and Personalized Therapy:** Prospective studies integrating pharmacogenomic testing (e.g., SLCO1B1, NAT2) to predict statin response, optimize dosing, and mitigate adverse effects like SAMS in diverse populations [135, 151, 206, 242, 263, 493, 557].
- **Statin Effects on Neurodegenerative Diseases:** Further investigation into the complex and sometimes conflicting associations between statin use and neurodegenerative diseases (e.g., Alzheimer's, Parkinson's, ALS), including specific statin types and long-term cognitive outcomes [121, 123, 124, 158, 201, 277, 308, 347, 444, 603, 606, 632, 635, 756].
- **Impact on Specific Organ Systems:** Dedicated research on the long-term effects of statins on ocular health (glaucoma, ocular hypertension) [17, 120, 439], bone density [28, 79, 216, 436, 1542], and male fertility [411], as these areas present conflicting or limited evidence.

5.4 Limitations:

- **Heterogeneity in Adherence Measurement** — Diverse methods (PDC, MPR, self-report, pill count, plasma levels) limit direct comparison and pooling of adherence rates, impacting the precision of central tendency estimates [220, 426, 495, 567, 627, 772, 913, 1434].
- **Observational Study Predominance** — Many findings, especially regarding non-CVD benefits and adverse events, derive from observational designs (cohort, case-control), which are susceptible to confounding and cannot establish causality [3, 9, 32, 38, 39, 160, 254, 308, 315, 485, 632, 756, 967].

- **Population Specificity and Generalizability** — Studies often focus on specific populations (e.g., older adults, diabetics, certain ethnicities), making it challenging to generalize findings across broader demographics or healthcare systems [18, 42, 282, 333, 455, 493, 724, 795, 840, 896, 1102, 1355, 1384, 1565].
- **Reporting Inconsistencies** — Variability in reporting specific statin types, dosages, and duration of use limits granular analysis of dose-response relationships or differences between individual statins [194, 208, 340, 375, 431, 1019, 1685].
- **Lack of Mechanistic Detail** — While associations are reported, underlying biological mechanisms for many pleiotropic effects or adverse events are often not fully elucidated, limiting a deeper understanding of statin action [4, 66, 206, 251, 252, 330, 411].

5.5 Future directions:

- **Standardize Adherence Metrics** — Implement consistent, validated adherence measures (e.g., MPR, PDC) in future clinical trials and observational studies to enable robust comparisons [220, 495, 567, 627].
- **RCTs for Pleiotropic Effects** — Conduct randomized controlled trials to definitively assess the causal impact of statins on non-cardiovascular outcomes (e.g., sepsis mortality, cancer survival) [9, 32, 35, 39, 249, 475, 486, 510, 539, 614, 666, 713, 789, 832, 870, 957, 974, 1225, 1269].
- **Pharmacogenomic-Guided Trials** — Design prospective studies to evaluate the clinical utility and cost-effectiveness of pharmacogenomic testing in guiding statin selection and dosing [135, 151, 206, 242, 263, 493, 557].
- **Longitudinal Safety Studies** — Establish long-term, large-scale prospective cohorts to monitor rare or delayed adverse effects, particularly on ocular health, bone, and neurological function [17, 28, 120, 160, 439, 442, 632, 756, 967].
- **Real-World Implementation Research** — Evaluate the effectiveness of integrated, multi-component interventions (e.g., pharmacist-led, digital health, policy changes) in improving statin prescribing, adherence, and outcomes in diverse, underserved populations [247, 265, 274, 290, 460, 500, 584, 660, 661, 884, 904, 1093].

6) Conclusion

This comprehensive review highlights the indispensable role of statin medication in modern healthcare, primarily for cardiovascular risk reduction, but also revealing a growing understanding of its pleiotropic effects across various disease states, including sepsis, certain cancers, and Graves' disease. Despite these broad benefits, statin adherence remains a significant challenge, with a

median reported rate of 63.9% [551], underscoring the need for improved patient-centered strategies. A key limitation is the reliance on observational data for many emerging benefits and risks. Future research should prioritize large-scale randomized controlled trials to confirm non-cardiovascular benefits and risks, alongside pharmacogenomic studies and real-world implementation research to optimize personalized statin therapy and enhance adherence, particularly in underserved populations.

References

SAIMSARA Session Index — session.json

Figure 1. Publication-year distribution of included originals

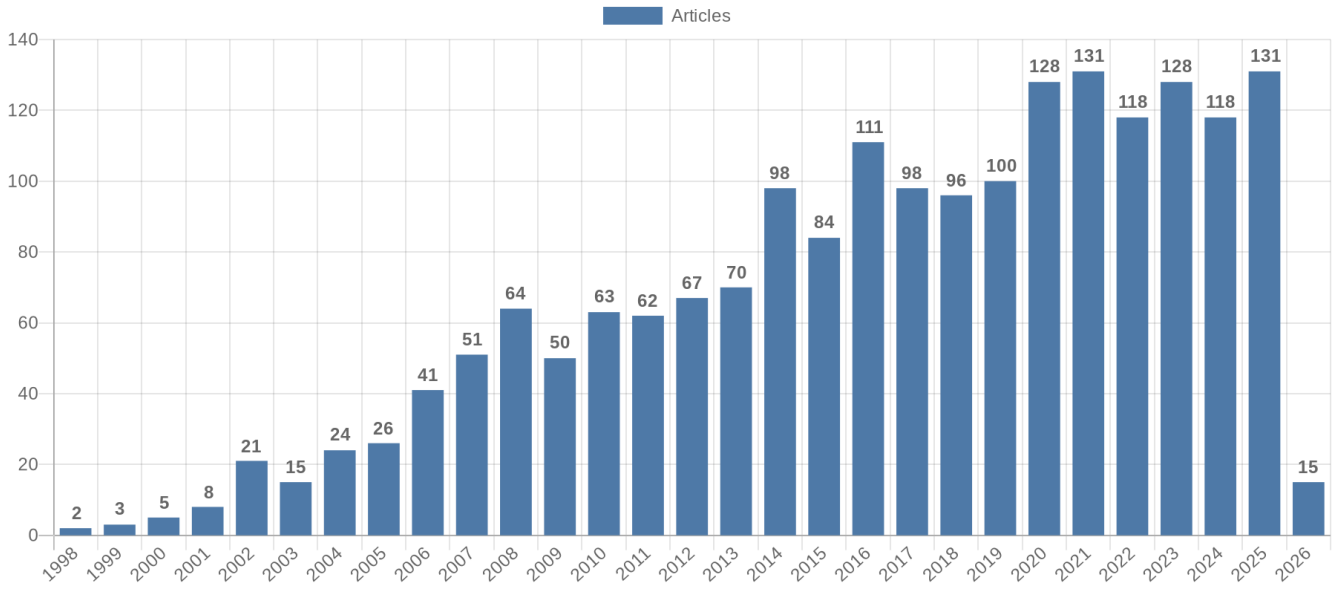


Figure 2. Study-design distribution of included originals

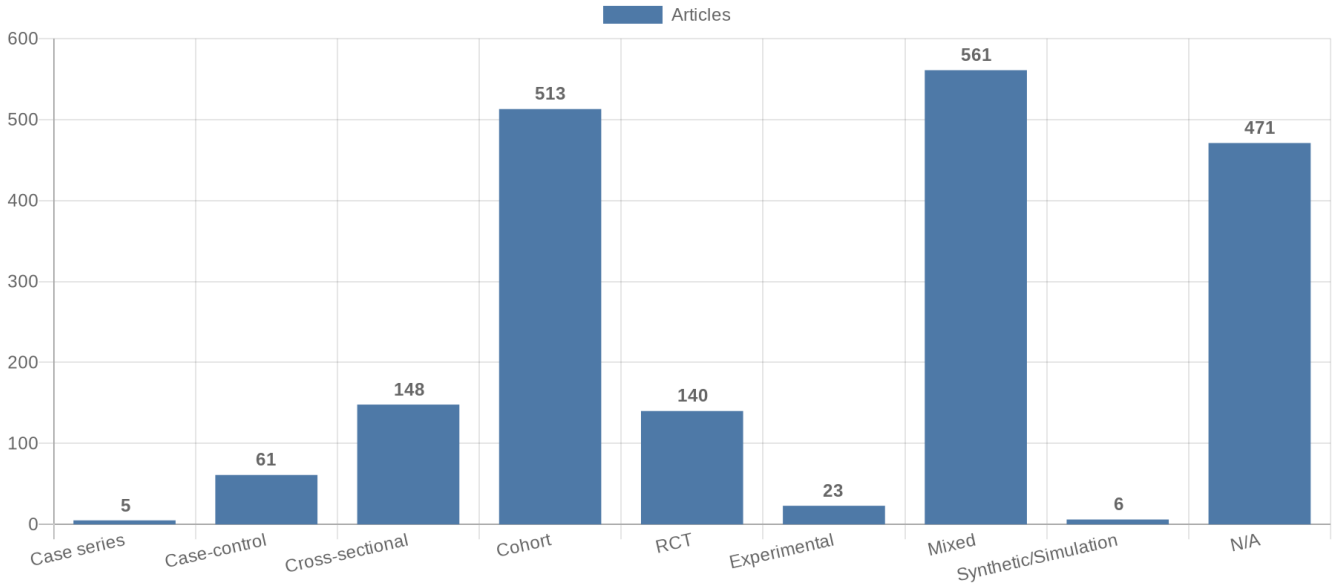


Figure 3. Study-type (directionality) distribution of included originals

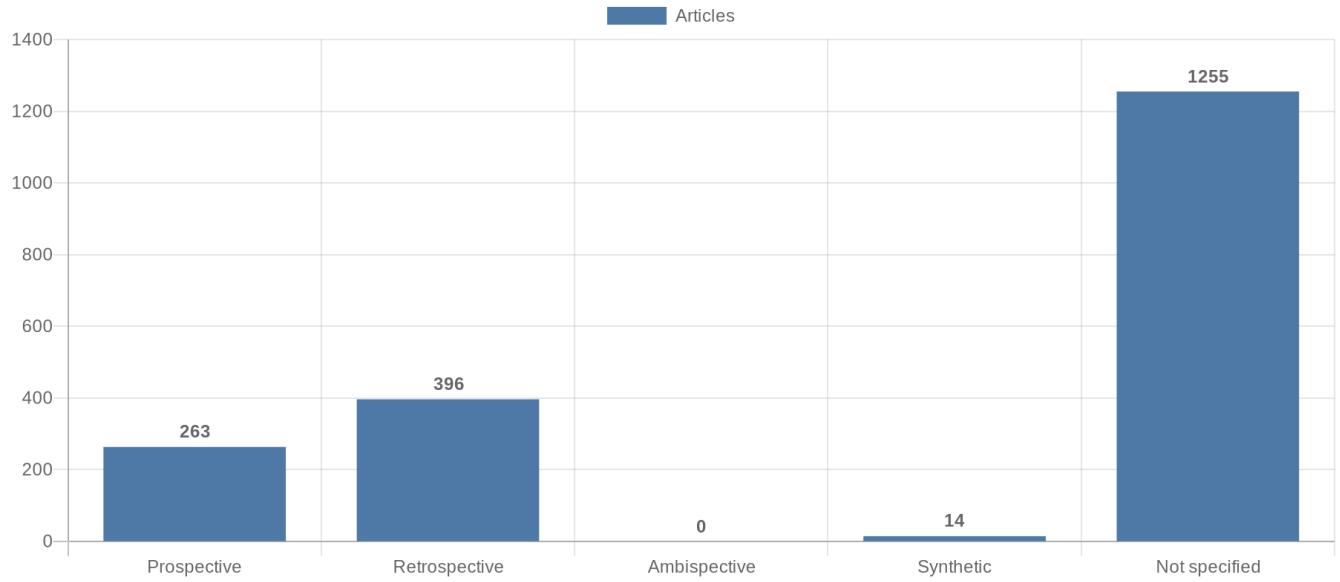


Figure 4. Main extracted research topics

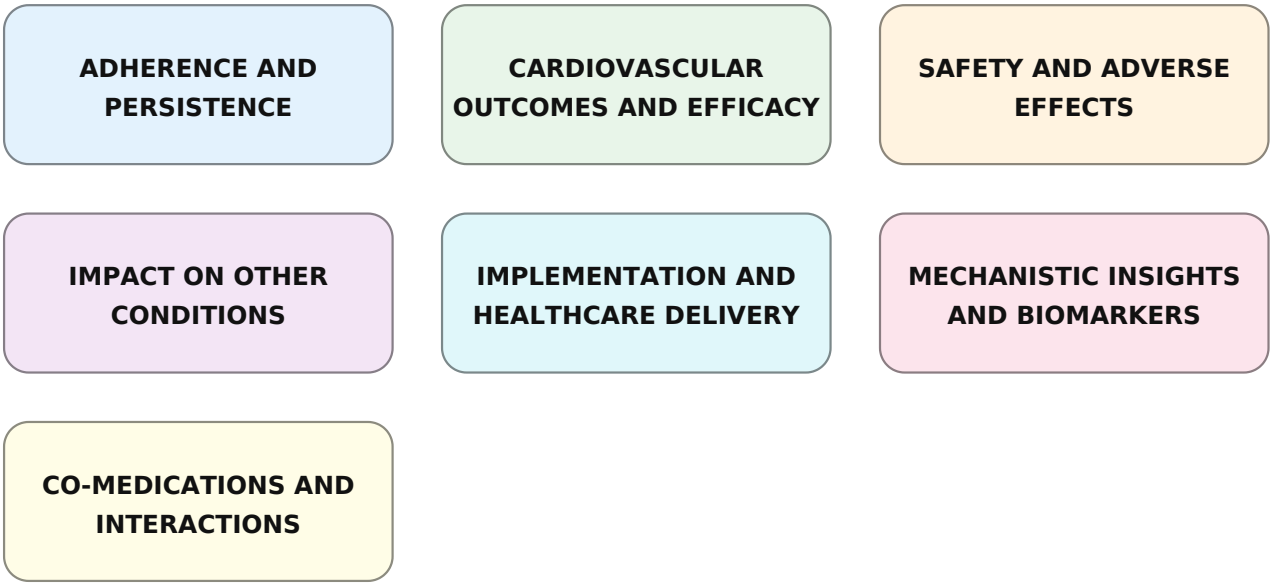


Figure 5. Limitations of current studies (topics)

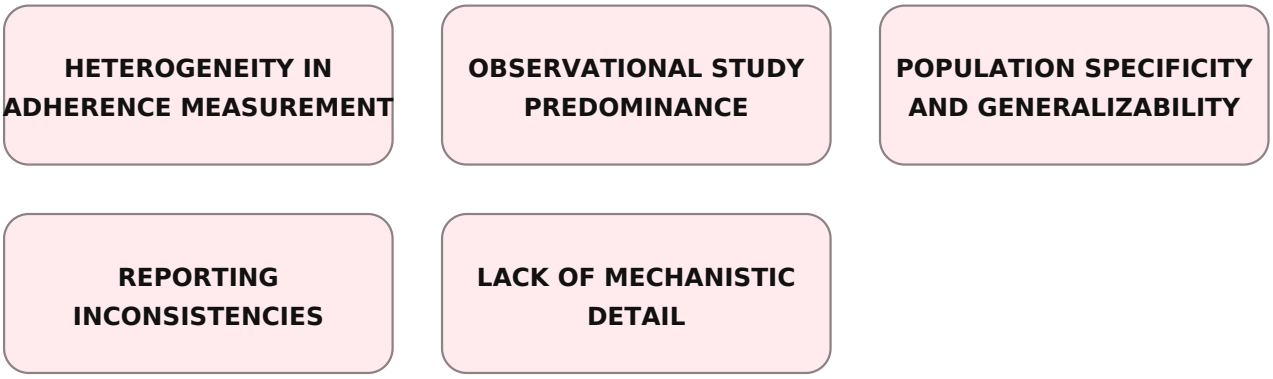


Figure 6. Future research directions (topics)

LONG-TERM ADHERENCE INTERVENTIONS

MECHANISTIC PATHWAYS IN NON-CVD BENEFITS

PHARMACOGENOMICS AND PERSONALIZED THERAPY

STATIN EFFECTS ON NEURODEGENERATIVE DISEASES

IMPACT ON SPECIFIC ORGAN SYSTEMS

RCTS FOR PLEIOTROPIC EFFECTS

REAL-WORLD IMPLEMENTATION RESEARCH