Varicose Veins and Risk Factors: Systematic Review with ☸SAIMSARA.

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Abstract: The aim of this paper is to systematically review and synthesize current research on varicose veins and their associated risk factors. The review utilises 716 studies with 8321642 total participants (naïve ΣN). This systematic review synthesized a vast body of literature on varicose veins, revealing a complex etiology driven by a multitude of interconnected risk factors. While the median prevalence of varicose veins across general adult populations was approximately 14.8%, this figure masks significant variability influenced by population characteristics and study methodologies. Key research topics include demographic factors (age, sex, BMI), lifestyle and occupational exposures (prolonged standing, physical inactivity), strong genetic and familial predispositions, hormonal influences (pregnancy, oral contraceptives), and a wide array of comorbidities (DVT/VTE, heart failure, diabetes, pelvic conditions). A significant limitation is the heterogeneity in study designs and outcome definitions, which complicates direct comparisons. Nevertheless, the findings underscore the importance of multifactorial risk assessment and lifestyle interventions, paving the way for future research to develop more precise predictive models and targeted therapeutic strategies.

Keywords: Varicose veins; Risk factors; Deep vein thrombosis; Obesity; Hypertension; Diabetes; Gender; Age; Genetic factors; Lifestyle factors

Review Stats

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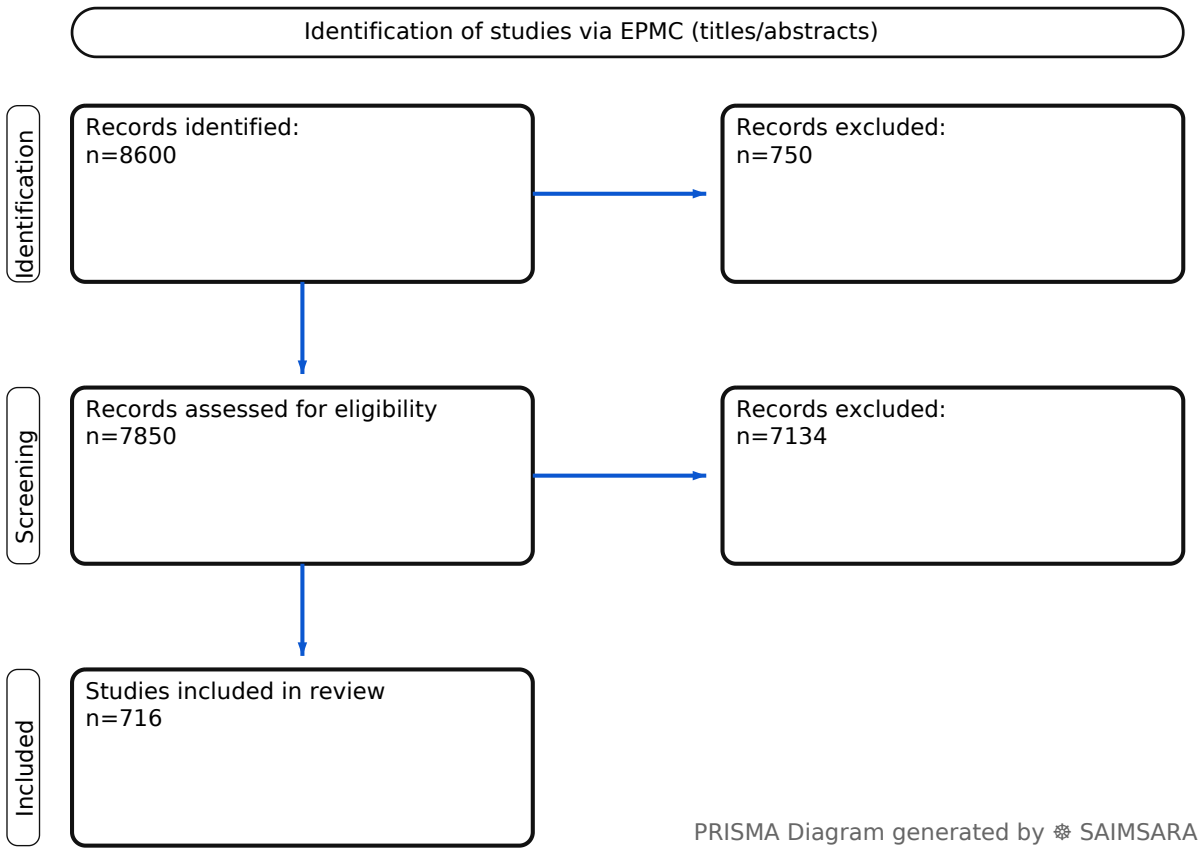
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Records excluded:
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Records assessed for eligibility
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Records excluded:
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Included
Studies included in review
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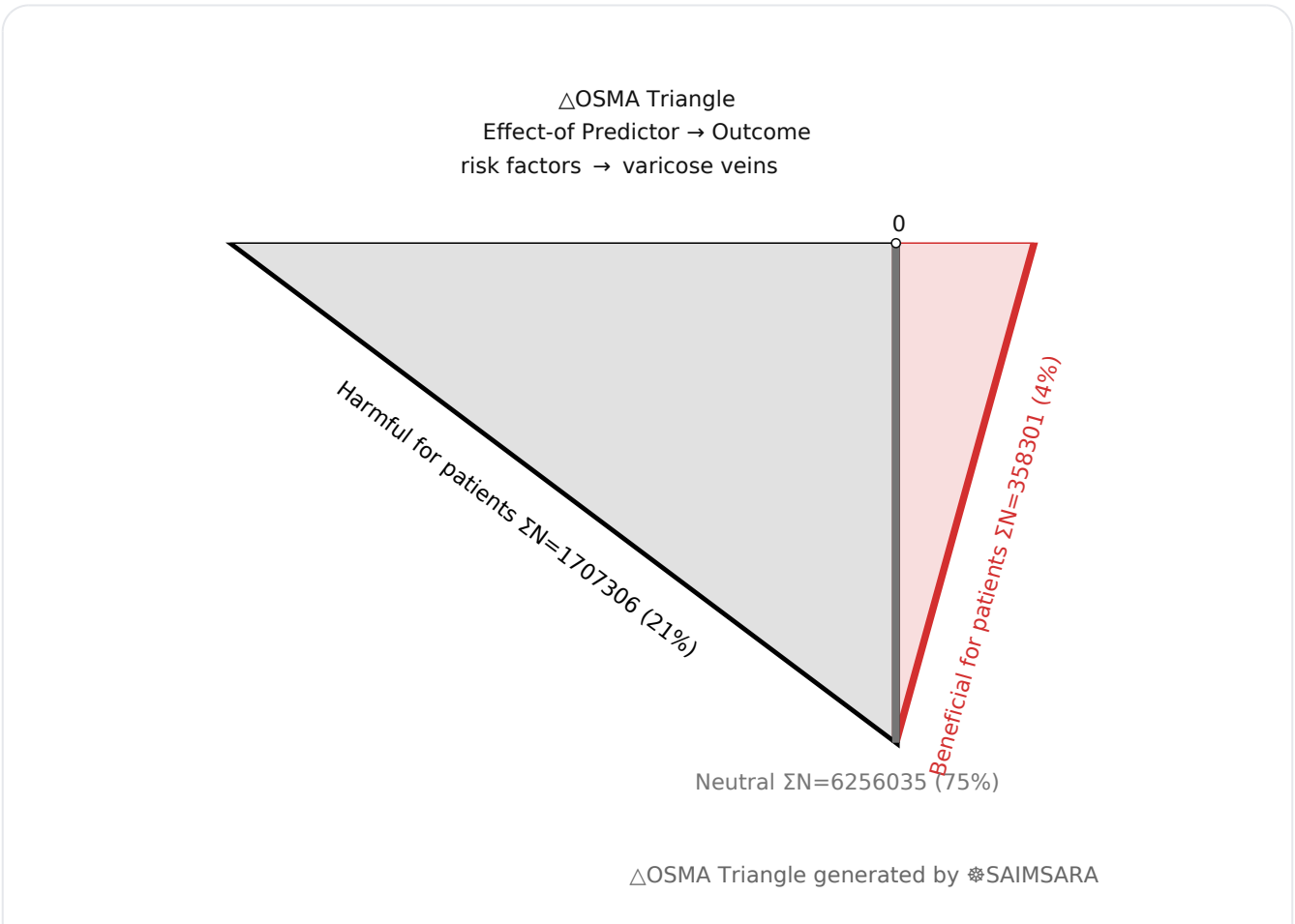
PRISMA Diagram generated by ☸ SAIMSARA


△OSMA Triangle
Effect-of Predictor → Outcome
risk factors → varicose veins
0
Harmful for patients ΣN=1707306 (21%)
Beneficial for patients ΣN=358301 (4%)
Neutral ΣN=6256035 (75%)
△OSMA Triangle generated by ☸SAIMSARA

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

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

Outcome: varicose veins Typical timepoints: peri/post-op, 5-y. Reported metrics: %, CI, p.

Common endpoints: Common endpoints: complications, recurrence, healing.

Predictor: risk factors — exposure/predictor. Doses/units seen: 10 ml, 10 g, 3.5 µg, 25 kg, 30 kg, 1639 g…. Routes seen: oral, subcutaneous, intravenous. Typical comparator: standard care, matched controls, other risk factors, healthy subjects….

- **1) Beneficial for patients** — varicose veins with risk factors — [152], [154], [168], [242], [249], [258], [259], [267], [308] — ΣN=358301
- **2) Harmful for patients** — varicose veins with risk factors — [3], [5], [7], [9], [13], [15], [20], [21], [26], [78], [89], [91], [92], [99], [105], [106], [110], [115], [116], [155], [156], [159], [163], [164], [166], [174], [175], [176], [177], [178], [181], [182], [184], [188], [195], [202], [203], [204], [207], [209], [213], [214], [216], [220], [224], [231], [233], [235], [238], [240], [271], [272], [273], [277], [287], [291], [294], [298], [302], [303], [304], [305], [309], [310], [311], [312], [313], [314], [316], [319], [320], [325], [326], [374], [375], [381], [382], [384], [385], [391], [400], [403], [406], [407], [409], [410], [414], [419], [420], [452], [458], [462] — ΣN=1707306
- **3) No clear effect** — varicose veins with risk factors — [1], [2], [4], [6], [8], [10], [11], [12], [14], [16], [17], [18], [19], [22], [23], [24], [25], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60], [61], [62], [63], [64], [65], [66], [67], [68], [69], [70], [71], [72], [73], [74], [75], [76], [77], [79], [80], [81], [82], [83], [84], [85], [86], [87], [88], [90], [93], [94], [95], [96], [97], [98], [100], [101], [102], [103], [104], [107], [108], [109], [111], [112], [113], [114], [117], [118], [119], [120], [121], [122], [123], [124], [125], [126], [127], [128], [129], [130], [131], [132], [133], [134], [135], [136], [137], [138], [139], [140], [141], [142], [143], [144], [145], [146], [147], [148], [149], [150], [151], [153], [157], [158], [160], [161], [162], [165], [167], [169], [170], [171], [172], [173], [179], [180], [183], [185], [186], [187], [189], [190], [191], [192], [193], [194], [196], [197], [198], [199], [200], [201], [205], [206], [208], [210], [211], [212], [215], [217], [218], [219], [221], [222], [223], [225], [226], [227], [228], [229], [230], [232], [234], [236], [237], [239], [241], [243], [244], [245], [246], [247], [248], [250], [251], [252], [253], [254], [255], [256], [257], [260], [261], [262], [263], [264], [265], [266], [268], [269], [270], [274], [275], [276], [278], [279], [280], [281], [282], [283], [284], [285], [286], [288], [289], [290], [292], [293], [295], [296], [297], [299], [300], [301], [306], [307], [315], [317], [318], [321], [322], [323], [324], [327], [328], [329], [330], [331], [332], [333], [334], [335], [336], [337],

[338], [339], [340], [341], [342], [343], [344], [345], [346], [347], [348], [349], [350], [351], [352], [353], [354], [355], [356], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [368], [369], [370], [371], [372], [373], [376], [377], [378], [379], [380], [383], [386], [387], [388], [389], [390], [392], [393], [394], [395], [396], [397], [398], [399], [401], [402], [404], [405], [408], [411], [412], [413], [415], [416], [417], [418], [421], [422], [423], [424], [425], [426], [427], [428], [429], [430], [431], [432], [433], [434], [435], [436], [437], [438], [439], [440], [441], [442], [443], [444], [445], [446], [447], [448], [449], [450], [451], [453], [454], [455], [456], [457], [459], [460], [461], [463], [464], [465], [466], [467], [468], [469], [470], [471], [472], [473], [474], [475], [476], [477], [478], [479], [480], [481], [482], [483], [484], [485], [486], [487], [488], [489], [490], [491], [492], [493], [494], [495], [496], [497], [498], [499], [500], [501], [502], [503], [504], [505], [506], [507], [508], [509], [510], [511], [512], [513], [514], [515], [516], [517], [518], [519], [520], [521], [522], [523], [524], [525], [526], [527], [528], [529], [530], [531], [532], [533], [534], [535], [536], [537], [538], [539], [540], [541], [542], [543], [544], [545], [546], [547], [548], [549], [550], [551], [552], [553], [554], [555], [556], [557], [558], [559], [560], [561], [562], [563], [564], [565], [566], [567], [568], [569], [570], [571], [572], [573], [574], [575], [576], [577], [578], [579], [580], [581], [582], [583], [584], [585], [586], [587], [588], [589], [590], [591], [592], [593], [594], [595], [596], [597], [598], [599], [600], [601], [602], [603], [604], [605], [606], [607], [608], [609], [610], [611], [612], [613], [614], [615], [616], [617], [618], [619], [620], [621], [622], [623], [624], [625], [626], [627], [628], [629], [630], [631], [632], [633], [634], [635], [636], [637], [638], [639], [640], [641], [642], [643], [644], [645], [646], [647], [648], [649], [650], [651], [652], [653], [654], [655], [656], [657], [658], [659], [660], [661], [662], [663], [664], [665], [666], [667], [668], [669], [670], [671], [672], [673], [674], [675], [676], [677], [678], [679], [680], [681], [682], [683], [684], [685], [686], [687], [688], [689], [690], [691], [692], [693], [694], [695], [696], [697], [698], [699], [700], [701], [702], [703], [704], [705], [706], [707], [708], [709], [710], [711], [712], [713], [714], [715], [716] — ΣN=6256035

1) Introduction

Varicose veins (VVs) are a prevalent and often progressive vascular condition characterized by dilated, tortuous veins, predominantly affecting the lower extremities. Beyond cosmetic concerns, VVs are associated with a range of symptoms, complications, and comorbidities, significantly impacting patient quality of life and healthcare burden. Understanding the diverse risk factors contributing to their development and progression is crucial for effective prevention, early diagnosis, and targeted therapeutic strategies. This paper synthesizes current research on the multifactorial

etiology of VVs, encompassing demographic, lifestyle, genetic, hormonal, and pathophysiological elements, as well as their clinical implications and associated health outcomes.

2) Aim

The aim of this paper is to systematically review and synthesize current research on varicose veins and their associated risk factors.

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.

4) Results

4.1 Study characteristics

The review encompassed a broad range of study designs, predominantly cross-sectional, cohort, and mixed-method approaches, with a notable number of retrospective analyses. Populations varied widely, including general adult populations, specific occupational groups (e.g., nurses, teachers, surgeons), pregnant women, older adults, and patients with existing VVs or other comorbidities. Follow-up periods, when specified, ranged from short-term (e.g., 1 month) to long-term (e.g., 13 years).

4.2 Main numerical result aligned to the query

The prevalence of varicose veins varied significantly across different populations and settings, precluding a single unified metric. Among general or mixed adult populations, the median prevalence of varicose veins was 14.8% [577], with a reported range from 1.28% in a South Korean health screening cohort [43] to 43.2% in an adult population from Northern Spain [160]. In specific occupational groups, prevalence rates ranged from 5.5% among healthcare professionals [568] to 24.2% in hairdressers [287] and 18.8% among teaching professionals [9]. For severely obese individuals, prevalence could be as high as 58.7% [174].

4.3 Topic synthesis

- **Demographic Risk Factors:**
- **Age:** Increasing age is a consistent risk factor for VVs [7, 13, 91, 114, 145, 149, 184, 195, 235, 252, 258, 260, 275, 291, 303, 304, 313, 336, 349, 350, 358, 373, 378, 384, 385, 409, 411, 422, 440, 464, 486, 487, 489, 491, 492, 500, 505, 518, 567, 576, 577, 579, 613, 616, 626, 631, 640, 643, 701, 707, 712], with older patients often presenting with more advanced

disease [336, 411].

- **Sex:** Female sex is frequently associated with VVs [7, 9, 10, 13, 72, 76, 78, 91, 114, 135, 145, 147, 149, 184, 195, 220, 241, 258, 260, 267, 275, 291, 294, 303, 313, 336, 349, 355, 358, 375, 398, 400, 422, 440, 464, 473, 477, 486, 489, 491, 492, 500, 505, 518, 527, 563, 567, 579, 611, 616, 626, 627, 631, 632, 639, 640, 647, 652, 653, 689, 696, 703, 706, 707, 711], with women having up to 7 times higher risk than men [358]. However, some studies note higher prevalence in men for trunk varices [464] or more severe disease [336].
- **Body Mass Index (BMI) / Weight / Height:** Higher BMI and obesity are significant risk factors [7, 13, 34, 36, 68, 78, 89, 91, 110, 118, 121, 149, 174, 181, 182, 188, 220, 223, 231, 235, 243, 248, 258, 263, 274, 298, 303, 304, 314, 320, 325, 342, 349, 350, 355, 358, 373, 381, 384, 385, 415, 420, 422, 424, 432, 434, 440, 471, 473, 489, 492, 506, 518, 526, 567, 569, 586, 588, 593, 609, 611, 613, 631, 634, 637, 689, 696, 701, 707], with higher BMI associated with increased complication rates [3] and less improvement post-treatment [118]. Taller height is also associated with increased risk [13, 89, 110, 349, 355, 611].
- **Lifestyle & Occupational Factors:**
- **Prolonged Standing/Static Postures:** Consistently identified as a significant risk factor [9, 66, 72, 91, 105, 138, 163, 175, 182, 195, 207, 235, 242, 273, 277, 287, 294, 349, 362, 375, 409, 432, 440, 473, 476, 489, 502, 506, 527, 552, 566, 577, 582, 611, 614, 627, 643, 646, 647], with some studies reporting high odds ratios (ORs) up to 27.44 [105] or 31.8 [287] in specific populations.
- **Physical Activity/Sedentary Lifestyle:** Lack of exercise increases risk [48, 81, 138, 155, 391, 526, 545, 611, 646], while regular exercise can be protective [94, 155]. Sedentarism is a risk factor for recurrent varices [391] and leg edema [426].
- **Smoking & Alcohol:** Smoking is associated with increased risk [7, 89, 138, 249, 266, 312, 410, 424, 434, 518, 545, 569, 611, 637, 672, 707] and impaired endothelial function [672]. Mild/regular alcohol consumption may be associated with lower risk [151], but other studies suggest increased risk [249].
- **Genetic & Familial Predisposition:**
- **Family History:** A strong and consistent risk factor [7, 29, 36, 48, 70, 73, 91, 128, 181, 209, 228, 238, 244, 271, 287, 291, 294, 349, 385, 432, 440, 465, 473, 477, 489, 491, 498, 502, 504, 526, 560, 564, 597, 616, 633, 643, 657, 659, 688, 703], with genetic factors contributing significantly to familial transmission [238, 465, 597].
- **Specific Genetic Variants:** Multiple genetic loci and variants are associated with VVs, including PTPRB [15], HADHA, BCL2L1, PARK7 [16], CASZ1 [39, 224], KRTAP5-AS1, PLEKHA5, CBWD1, CRIM1 [44], IRF3, LUM, POSTN, RSPO3, SARS2 [45], PIEZO1 [92, 413], EFEMP1 [83, 99], GJD3 (protective) [64], and MHC class III genomic region [172]. Genetically predicted higher sex hormone-binding globulin (SHBG) levels also increase risk, especially in females [46, 267].

- **Hormonal & Reproductive Factors:**
- **Pregnancy & Parity:** Pregnancy is a significant risk factor for VVs development and recurrence [7, 72, 81, 88, 91, 113, 114, 116, 124, 128, 131, 136, 164, 178, 195, 196, 214, 216, 228, 259, 268, 269, 278, 291, 294, 295, 306, 313, 324, 349, 362, 365, 399, 422, 427, 429, 432, 456, 461, 473, 477, 486, 489, 493, 501, 507, 526, 611, 652, 698, 704], with increasing parity being a key factor [116, 124, 195, 313, 349, 432].
- **Oral Contraceptives (OCs) & Hormone Replacement Therapy (HRT):** Use of OCs is identified as a risk factor in some studies [72, 81, 106, 138, 196, 315, 363, 427, 507, 609, 611, 632, 697], while HRT showed an increased risk in one study [313].
- **Comorbidities & Associated Conditions:**
- **Deep Vein Thrombosis (DVT) / Venous Thromboembolism (VTE):** VVs are a significant risk factor for DVT and VTE [19, 55, 58, 87, 93, 102, 104, 107, 109, 111, 113, 117, 120, 127, 130, 134, 135, 143, 144, 145, 150, 155, 164, 171, 176, 177, 181, 185, 188, 191, 194, 201, 205, 206, 215, 217, 223, 225, 226, 230, 232, 241, 243, 248, 254, 260, 261, 262, 263, 264, 265, 266, 268, 272, 279, 283, 292, 297, 304, 314, 315, 322, 327, 329, 331, 333, 338, 352, 353, 356, 361, 363, 365, 367, 370, 373, 376, 377, 379, 380, 383, 386, 387, 389, 393, 395, 399, 405, 415, 421, 423, 427, 434, 441, 442, 450, 451, 458, 459, 460, 461, 482, 493, 496, 498, 499, 504, 505, 507, 510, 513, 517, 518, 521, 522, 524, 525, 528, 532, 533, 536, 538, 540, 542, 544, 550, 551, 554, 556, 557, 560, 569, 570, 571, 583, 585, 586, 587, 588, 589, 590, 594, 596, 600, 601, 602, 603, 605, 606, 607, 608, 609, 612, 613, 617, 618, 619, 620, 621, 622, 625, 628, 629, 630, 631, 635, 636, 638, 641, 642, 645, 648, 649, 654, 656, 660, 662, 667, 668, 670, 671, 674, 675, 676, 677, 678, 679, 683, 684, 687, 690, 692, 693, 694, 697, 698, 700, 701, 702, 705, 707, 708, 709, 710, 712, 713], with ORs up to 5.30 [127] and 16.8 [513].
- **Heart Failure & Cardiovascular Disease:** VVs are associated with an increased risk of heart failure [13, 30, 38, 43, 145] and other cardiovascular risk factors [348].
- **Metabolic Conditions:** Hypertension [3, 7, 13, 252], diabetes [3, 7, 36, 71, 97, 410, 424, 426, 545, 704], and dyslipidemia [232, 410] are associated with VVs or their complications.
- **Neurological & Cognitive Conditions:** VVs are linked to increased incidence of sensorineural hearing loss [22], potential risk for Alzheimer's disease [51], and increased risk of all-cause dementia [95]. Restless legs syndrome (RLS) is associated with VVs [97, 412, 545], though one study suggests RLS may reduce VV risk [152].
- **Other Comorbidities:** Hydroceles [2], hemorrhoidal disease [33, 234], pelvic varicose veins/pelvic congestion syndrome [31, 204, 372, 429, 516, 549, 578, 633], cirrhosis/portal hypertension [77, 101, 170, 179, 281, 289, 310, 321, 326, 424, 512, 565, 615], cellulitis/infection [3, 40, 42, 48, 90, 160, 162, 170, 175, 279, 302, 417, 480, 519, 534, 542, 604, 613], connective tissue disorders [339, 351, 414, 419, 562, 559, 371], and even schizophrenia [137, 305] have shown associations with VVs.

- **Pathophysiological Mechanisms:**
- **Valvular Dysfunction & Venous Reflux:** Central to VV pathogenesis, involving fewer venous valves [21], saphenous vein incompetence [3, 19, 34, 114, 123, 124, 132, 133, 141, 193, 208, 213, 214, 216, 240, 258, 276, 290, 301, 311, 312, 334, 354, 357, 372, 378, 385, 390, 396, 406, 408, 418, 447, 448, 458, 470, 481, 503, 506, 509, 511, 520, 521, 525, 546, 553, 561, 563, 567, 576, 580, 593, 598, 614, 634, 639, 640, 652, 665, 666, 703, 709, 716], and disturbed venous shear stress [35].
- **Inflammation & Endothelial Dysfunction:** Involves dysregulations in angiogenesis- and inflammation-related factors [40, 42, 62, 63, 123, 129, 266, 280, 282, 300, 302, 316, 322, 332, 359, 364, 366, 397, 401, 402, 453, 472, 484, 488, 530, 574, 584, 610, 614, 672], activation of ETS1-NOTCH4/DLL4 signaling [35], and increased superoxide production [239].
- **Hypoxia:** Increased activation of hypoxia-inducible factor (HIF) pathway [123, 229, 316, 425, 474, 584] is implicated in VV pathogenesis.
- **Extracellular Matrix (ECM) Remodeling:** Alterations in smooth muscle cells, collagen, and elastin [397, 401, 445, 453, 539, 584, 650, 665, 703], and increased matrix metalloproteinases (MMPs) expression/activity [123, 332, 343, 366, 453, 472, 584] contribute to vein wall dilation.
- **Outcomes & Complications of Varicose Veins:**
- **Postoperative Complications & Recurrence:** Factors like larger vein diameter [132, 213, 214, 231, 320, 553], previous DVT [8, 111, 600], specific surgical techniques [173, 276, 390, 403, 448, 457, 479, 520, 537, 541, 598], and patient characteristics (e.g., male gender [217], advanced age [140], obesity [350]) influence postoperative outcomes and recurrence rates.
- **Quality of Life & Functional Impairment:** VVs negatively impact quality of life [9, 98, 147, 149, 198, 360, 400, 407, 435, 485, 523, 548, 643], with symptoms like pain and dysfunction [435] and limitations in daily activities [247].
- **Ulceration:** Risk factors for venous ulceration in VV patients include male sex, obesity, longer VV duration, deep venous valve insufficiency, low lymphocyte counts, high fibrinogen [34], and certain inflammatory markers [63, 155, 274, 342, 396, 467, 487, 561, 598, 663, 680, 686].
- **Associated Health Conditions:** VVs are linked to various conditions, including hydroceles [2], sensorineural hearing loss [22], breathing difficulties and hypotension [25], heart failure [13, 30, 38, 43, 145], dementia [51, 95], atrial fibrillation [61], mitral valve regurgitation [96], chronic pelvic pain [31, 202], cellulitis [417, 480, 519], and specific thrombophilic factors [205, 232].

5) Discussion

5.1 Principal finding

This systematic review highlights that varicose veins are a common vascular condition with a median prevalence of 14.8% in general or mixed adult populations [577], although rates vary widely depending on the specific cohort studied. The etiology is profoundly multifactorial, involving a complex interplay of demographic, lifestyle, genetic, and pathophysiological elements.

5.2 Clinical implications

- **Targeted Screening & Prevention:** Given the strong association with age, female sex, and family history [13, 91, 149, 228, 349, 385, 477], screening efforts could be prioritized for individuals with these characteristics.
- **Lifestyle Modification:** Counseling on modifiable risk factors like obesity [78, 188, 420], prolonged standing [105, 138, 207, 375, 409], and physical inactivity [48, 94, 155] is crucial for both prevention and managing disease progression.
- **Comorbidity Management:** Awareness of the increased risk for DVT/VTE [127, 130, 191, 230, 331, 461, 513, 569], heart failure [30, 43], and other conditions [22, 95, 202, 416] in VV patients should guide comprehensive patient care and monitoring.
- **Post-Procedural Care:** Factors influencing postoperative complications and recurrence, such as vein diameter [132, 213, 214, 320, 553], previous DVT [8, 111, 600], and adherence to compression therapy [10, 187, 531], should be integrated into treatment planning and patient education.

5.3 Research implications / key gaps

- **Standardized Epidemiology:** Future studies should adopt standardized definitions and reporting metrics for VV prevalence and incidence across diverse populations to enable more robust meta-analyses and comparative studies.
- **Mechanistic Pathways:** Further research is needed to fully elucidate the complex interplay between identified genetic variants [15, 39, 64, 83, 92], hormonal influences [46, 267], and molecular mechanisms (e.g., inflammation, hypoxia, ECM remodeling) [35, 40, 123, 316, 453] in VV pathogenesis.
- **Longitudinal Intervention Studies:** Prospective randomized controlled trials are required to evaluate the effectiveness of targeted interventions for modifiable risk factors (e.g., weight management, ergonomic workplace interventions, specific exercise regimens) on the incidence and progression of VVs.
- **Risk Stratification Models:** Development and validation of comprehensive risk prediction models that integrate genetic, demographic, lifestyle, and comorbidity data are needed to identify individuals at highest risk for VV development and associated complications.

5.4 Limitations

- **Heterogeneous Study Designs** — The included studies varied significantly in design, from cross-sectional to cohort studies, limiting direct comparisons and meta-analysis.
- **Inferred Bias** — Bias was qualitatively inferred from study designs, without a formal risk-of-bias assessment for each individual study.
- **Variable Outcome Definitions** — Definitions and diagnostic criteria for varicose veins and associated conditions were not always consistent across studies, affecting comparability.
- **Limited Causal Inference** — Many studies identified associations rather than causal relationships, particularly for lifestyle and comorbidity factors.
- **Geographic and Ethnic Specificity** — Prevalence and risk factor profiles often showed geographic or ethnic specificity, limiting generalizability to broader populations.

5.5 Future directions

- **Harmonize Diagnostic Criteria**
- **Investigate Genetic-Environment Interactions**
- **Develop Predictive Biomarkers**
- **Assess Long-term Intervention Efficacy**
- **Integrate Patient-Reported Outcomes**

6) Conclusion

This systematic review synthesized a vast body of literature on varicose veins, revealing a complex etiology driven by a multitude of interconnected risk factors. While the median prevalence of varicose veins across general adult populations was approximately 14.8% [577], this figure masks significant variability influenced by population characteristics and study methodologies. Key research topics include demographic factors (age, sex, BMI), lifestyle and occupational exposures (prolonged standing, physical inactivity), strong genetic and familial predispositions, hormonal influences (pregnancy, oral contraceptives), and a wide array of comorbidities (DVT/VTE, heart failure, diabetes, pelvic conditions). A significant limitation is the heterogeneity in study designs and outcome definitions, which complicates direct comparisons. Nevertheless, the findings underscore the importance of multifactorial risk assessment and lifestyle interventions, paving the way for future research to develop more precise predictive models and targeted therapeutic strategies.

References

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Figure 1. Publication-year distribution of included originals

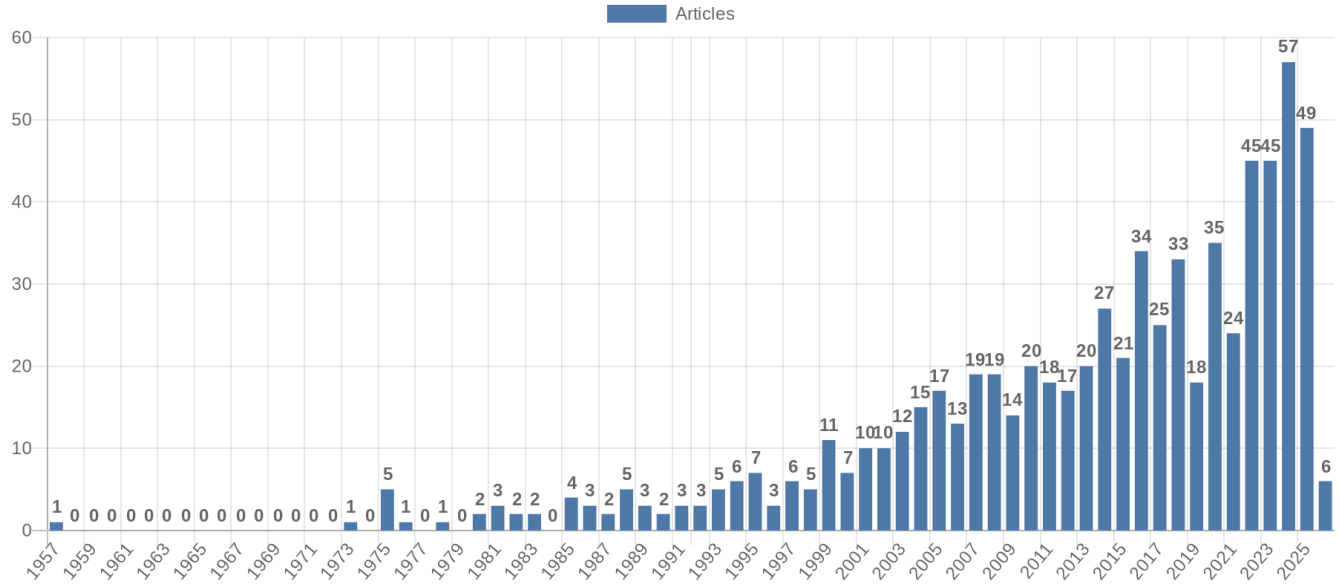

Figure 2. Study-design distribution of included originals

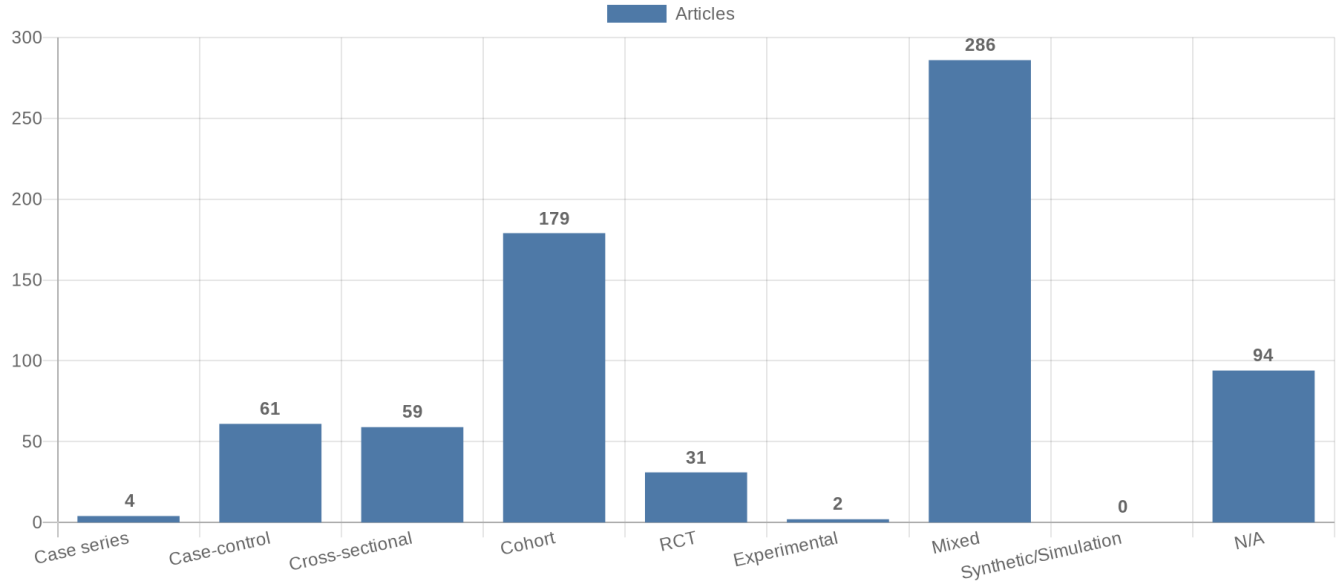

Figure 3. Study-type (directionality) distribution of included originals

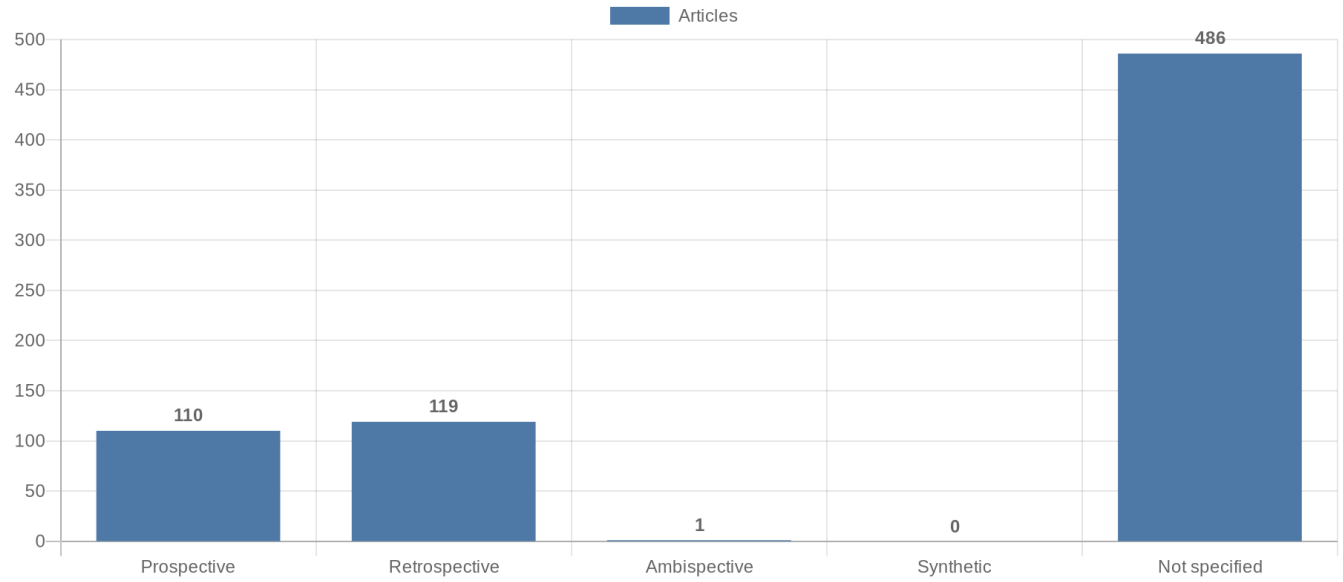

Figure 4. Main extracted research topics

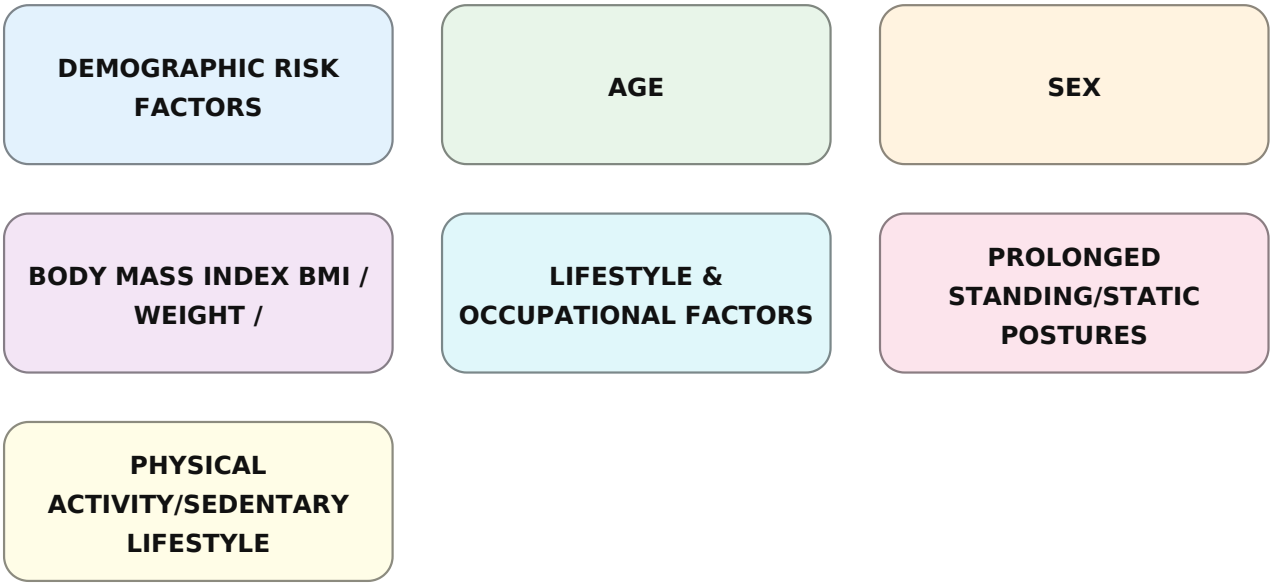

Figure 5. Limitations of current studies (topics)

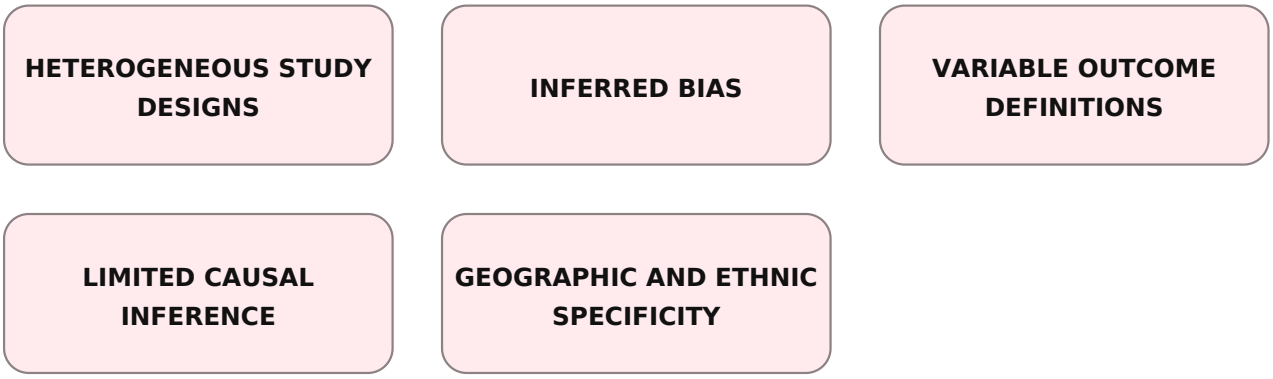

Figure 6. Future research directions (topics)

STANDARDIZED EPIDEMIOLOGY

MECHANISTIC PATHWAYS

LONGITUDINAL INTERVENTION STUDIES

RISK STRATIFICATION MODELS

HARMONIZE DIAGNOSTIC CRITERIA

INVESTIGATE GENETIC-ENVIRONMENT INTERACTIONS

DEVELOP PREDICTIVE BIOMARKERS