RESEARCH ARTICLE

The vitamin D-vitamin D receptor axis in uterine leiomyomas: A scoping review of clinical, molecular, and genetic evidence

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Abstract

Uterine leiomyomas are the most common benign tumours of the female reproductive tract and a major cause of gynaecological morbidity worldwide. Observational and experimental studies have linked vitamin D and the vitamin D receptor (VDR) separately to uterine leiomyoma biology, including effects on cell proliferation and Wnt/β-catenin signalling in vitro; however, the breadth of this evidence has not been comprehensively mapped across clinical, molecular, and genetic domains. We conducted a scoping review following Joanna Briggs Institute (JBI) methodology and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar were searched from January 2016 to December 2025. Forty-two studies were included: 31 clinical, seven molecular, and four genetic. Most clinical studies reported lower circulating 25-hydroxyvitamin D concentrations among women with uterine leiomyomas compared with controls, with several demonstrating inverse associations with fibroid size, volume, or number; however, fewer than half adjusted for BMI and only one study adjusted for ethnicity, limiting causal inference. Seven molecular studies examined the vitamin D-VDR axis in leiomyoma tissue and cells: three demonstrated reduced VDR expression, two demonstrated upregulated CYP24A1 expression, and two demonstrated calcitriol-mediated suppression of Wnt/β-catenin signalling (and, in one study, mTOR signalling). Four genetic studies showed inconsistent associations between VDR and vitamin D metabolism gene polymorphisms and leiomyoma susceptibility across populations. The evidence maps parallel associations of lower circulating vitamin D, lower VDR expression and higher CYP24A1 expression in leiomyoma tissue with the disease; no included study tested whether VDR mediates or modifies the relationship between vitamin D and

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leiomyoma. Findings remain heterogeneous and largely observational. Well-designed prospective cohort studies incorporating LC-MS/MS vitamin D measurement, concurrent tissue sampling, and full confounder adjustment are needed to clarify the clinical and mechanistic significance of this pathway.

Introduction

Uterine leiomyomas (UL), commonly referred to as fibroids, are the most prevalent benign tumours of the female reproductive tract, and contribute substantially to gynaecological morbidity worldwide [1–3]. They affect a large proportion of women of reproductive age, and may present with abnormal uterine bleeding, pelvic pain, infertility, and adverse pregnancy outcomes [4–6]. The burden of UL varies across populations, with higher prevalence, earlier onset, and greater disease severity reported among women of African descent [7,8], suggesting the influence of both biological and contextual factors.

The pathogenesis of UL is complex, and not fully understood. The current evidence suggests multifactorial interactions involving genetic susceptibility, ovarian steroid hormones, growth factor signalling, and extracellular matrix remodelling [9,10]. While oestrogen and progesterone play central roles in the tumour growth and maintenance, additional endocrine and environmental factors have been proposed, to contribute to disease initiation and progression [11]. However, the relative contribution of these factors, and their interactions remain areas of ongoing investigation. Vitamin D has been explored as one potential factor of interest in UL biology [12]. Beyond its classical role in calcium homeostasis, vitamin D functions as a steroid hormone with diverse effects on cellular proliferation, differentiation, immune modulation, and fibrotic processes [10,12,13]. These actions are mediated primarily through the vitamin D receptor (VDR) [14], which is expressed in reproductive tissues, including the myometrium. The mechanistic basis for vitamin D's potential role in UL biology is increasingly well-characterized. Experimental studies have demonstrated that calcitriol suppresses key pathways implicated in UL pathogenesis including transforming growth factor-beta (*TGF-β*), *Wnt/β-catenin* signalling, and extracellular matrix regulation, independent of the *MED12* mutation status that defines the dominant molecular subtype of UL [15–17]. Critically, VDR expression is itself reduced in UL tissue relative to adjacent myometrium, while *CYP24A1*-mediated inactivation of calcitriol is simultaneously upregulated, which has been proposed to attenuate local vitamin D signalling and may thereby sustain the pro-proliferative and pro-fibrotic phenotype of fibroid cell [18]. Calcitriol has further been shown to upregulate VDR expression in cultured leiomyoma cells in a dose-dependent manner, a pattern consistent with ligand-induced transcriptional autoregulation of VDR, through which exogenous vitamin D may partially restore signalling capacity in VDR-depleted fibroid tissue [19]. These observations position the vitamin D-VDR axis not merely as a correlate of UL biology, but as a plausible upstream modulator of core pathogenic pathways, operating in parallel with, and potentially interacting with the established oestrogen and

progesterone signalling that drives tumour growth and maintenance [9]. The mechanistic pathway of the Vitamin D-VDR axis in UL is demonstrated in Fig 1.

In parallel, epidemiological studies have examined associations between circulating vitamin D levels and UL, with some reporting lower serum 25-hydroxyvitamin D (25(OH)D concentrations among women with UL [15–17,20,21]. However, findings across studies are not entirely consistent, and many investigations are limited by cross-sectional or case-control designs. In addition, studies differ in definitions of vitamin D deficiency, methods of measurement, and the clinical characteristics of UL, making comparisons challenging. Molecular and genetic studies, including investigations of VDR expression and polymorphisms have also been conducted [22,23], but this body of evidence remains heterogeneous and relatively limited. Importantly, the relative contribution of vitamin D in comparison to established hormonal and genetic drivers remains uncertain, and alternative explanations for observed associations have been proposed. Given the conceptual and methodological heterogeneity across clinical, molecular, and genetic studies, as well as variation in exposure definitions and outcome measures, a scoping review is therefore well suited to map the breadth and characteristics of this emerging field. To our knowledge, this is the first review to jointly map clinical, molecular, and genetic evidence on the

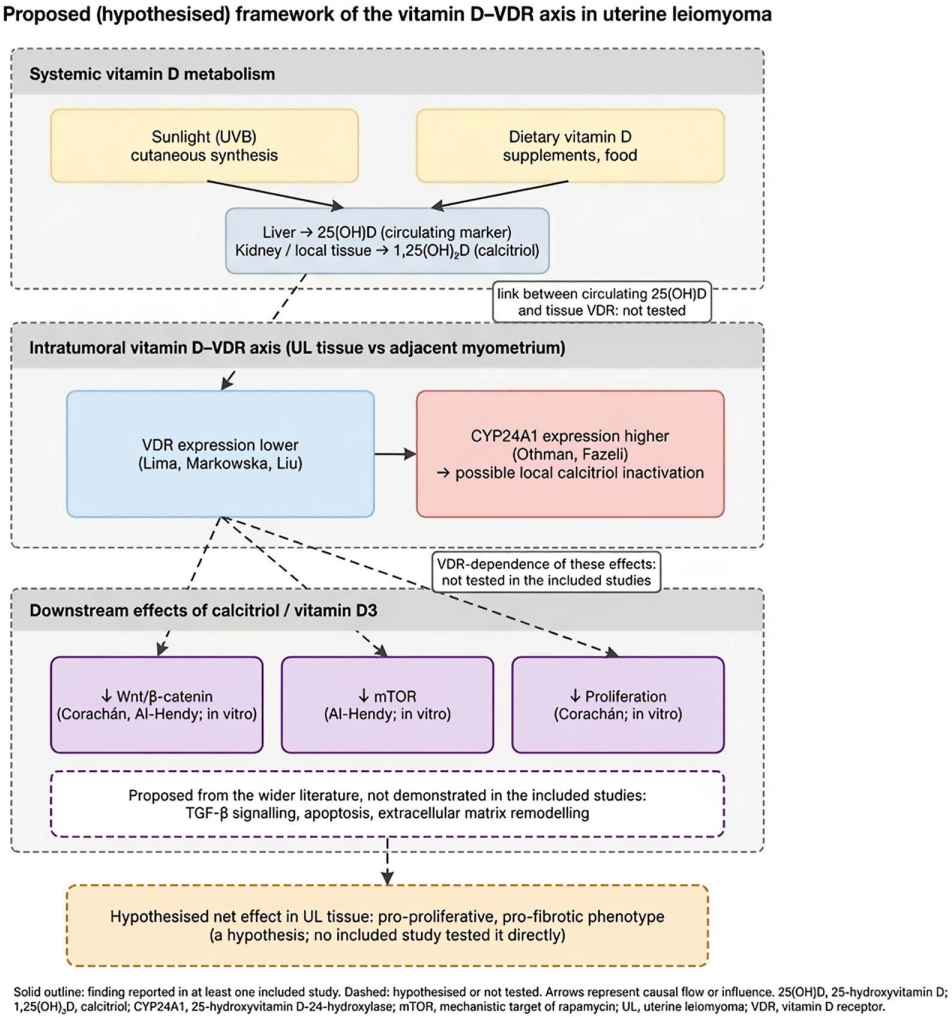

Fig 1. Proposed (hypothesised) mechanistic framework of the vitamin D-VDR axis in uterine leiomyoma biology.

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vitamin D-VDR axis in UL within a single PRISMA-ScR-adherent framework, in contrast to prior work that has addressed these evidence domains separately. The objective of this review was to map clinical, molecular, and genetic evidence on the vitamin D-VDR axis in UL, identify prevailing themes and knowledge gaps, and inform future research directions.

Materials and Methods

Study design and reporting framework

This scoping review was conducted to map and synthesize the breadth of clinical, molecular and genetic evidence on the role of the vitamin D-vitamin D receptor (VDR) axis in the pathogenesis and phenotypic heterogeneity of UL. The review was conducted in accordance with the Joanna Briggs Institute (JBI) methodology for scoping reviews [24] and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). A completed PRISMA-ScR checklist is provided as Supplementary File 1. A scoping review approach was selected due to the heterogeneity in study designs, exposures, and outcomes, and the inclusion of diverse evidence types, which precluded meaningful quantitative synthesis.

Protocol registration

The review protocol was prospectively registered on the Open Science Framework (OSF) https://osf.io/ya86m, prior to commencement of the literature search (registration date: 15 August 2025). The protocol details the objectives, eligibility criteria, search strategy, and planned methods for study selection and data charting.

Review questions

The review was guided by the following questions:

1. What clinical associations between vitamin D status and ULs have been reported in the literature?
2. What molecular and genetic mechanisms involving vitamin D and the vitamin D receptor have been investigated in relation to leiomyoma development, growth, or phenotypic characteristics?
3. What methodological approaches and study designs have been used to investigate the vitamin D-VDR axis in ULs?

Eligibility criteria

Eligibility criteria were defined a priori using the Population-Concept-Context (PCC) framework.

- Population: Women of reproductive age diagnosed with ULs, as well as human leiomyoma tissues or cells investigated in experimental studies.
- Concept: Vitamin D status, vitamin D binding protein (VDBP), VDR expression or polymorphisms, and downstream molecular pathways relevant to leiomyoma biology.
- Context: Clinical, translational, and laboratory-based studies conducted in any geographical setting.

The review included original peer-reviewed studies employing observational or experimental designs. Reviews, editorials, commentaries, conference abstracts without full text and animal-only studies were excluded. Animal-only studies were excluded because the PCC framework was scoped specifically to human clinical and tissue-level evidence, to maximise direct translational relevance to UL patients; readers seeking mechanistic evidence from established animal models (e.g., Eker rat, MED12-mutant mouse) are directed to the existing preclinical synthesis by Combs et al. [25], which specifically addresses that evidence base. Studies using secondary datasets such as large epidemiological databases, were included where they provided relevant clinical or molecular insights into the vitamin D-VDR axis in ULs. Mendelian randomisation

studies based solely on publicly available GWAS summary statistics, which do not report individual-level clinical, tissue, or genotype data, were not considered to meet these primary-study eligibility criteria and were instead discussed narratively where relevant. Only articles published in English were included; the rationale and implications of this restriction are discussed in the Information sources and search strategy section below.

Information sources and search strategy

A comprehensive literature search was conducted in the following electronic databases: PubMed/MEDLINE, Scopus, and Web of Science were selected for their broad coverage of biomedical, clinical and translational research. Additionally, to enhance retrieval of studies not indexed in these databases, Google Scholar was used as supplementary source. However, due to large volume of results retrieved from Google Scholar in addition to its limited filtering abilities and the absence of advanced Boolean operator support, screening was restricted to the first 300 results per search string, sorted by relevance. This threshold was applied across both search strings per database, yielding a maximum of 600 Google Scholar records for consideration. While this approach risks missing records ranked beyond position 300, empirical evidence and methodological guidance indicate that relevance-ranked Google Scholar results show steep decay in pertinence beyond the first 200–300 records, and that the primary databases (PubMed, Scopus, Web of Science) provide substantially more reliable and comprehensive retrieval for structured biomedical queries. The Google Scholar component was therefore treated as a supplementary rather than primary retrieval source, consistent with its recommended role in scoping review methodology. Only articles published in English were included. This restriction was applied for practical reasons of reviewer capacity and resource availability. It is acknowledged that this decision may have led to the exclusion of relevant studies published in other languages, particularly Arabic, Chinese, Portuguese, and French languages in which research from the Middle East, East Asia, Latin America, and francophone Africa may be disseminated. Given the disproportionate burden of ULs in African and low- and middle-income country populations, and the underrepresentation of these regions already noted in the included literature, the English-language restriction may have compounded existing geographic gaps in the evidence base. This methodological guidance on optimal database combinations for systematic and scoping reviews informed our search design [26] Searches covered all publications from January 1, 2016, to December 31, 2025, and the search was last executed on 8 January 2026. This lower bound was selected for three reasons: (1) it post-dates the establishment of MED12 mutation status as the dominant molecular framework defining UL subtypes in the early 2010s, allowing post-2016 molecular and genetic findings to be interpreted within a consistent contemporary mutational framework; (2) it coincides with the broader international shift toward standardised, automated immunoassay platforms for 25(OH)D measurement, which improved cross-study measurement comparability relative to older radioimmunoassay techniques; and (3) it reflected reviewer capacity and resource constraints. To mitigate the risk of omitting key foundational pre-2016 evidence, reference lists of all included studies and of relevant prior reviews were hand-searched for landmark earlier publications; studies identified through this backward citation-screening process and meeting eligibility criteria were incorporated into the included set. This process is how Al-Hendy et al. (2016) [27] was identified and added to Table 6. The search strategies combined controlled vocabulary and free-text terms related to ULs, vitamin D, vitamin D binding protein and the vitamin D receptor. The full reproducible search strategies for each database are provided in Table 1.

Only articles published in English were included. This restriction was applied for practical reasons of reviewer capacity and resource availability. It is acknowledged that this decision may have led to the exclusion of relevant studies published in other languages, particularly Arabic, Chinese, Portuguese, and French languages in which research from the Middle East, East Asia, Latin America, and francophone Africa may be disseminated. Given the disproportionate burden of ULs in African and low- and middle-income country populations, and the underrepresentation of these regions already noted in the included literature, the English-language restriction may have compounded existing geographic gaps in the evidence base. This methodological guidance on optimal database combinations for systematic and scoping reviews informed our search design [26]

Table 1. Literature search strategy.

Database	Step 1: Vitamin D Metabolites AND ULs	Step 2: Vitamin D-VDR Axis AND ULs
PubMed	((“Vitamin D”[Mesh] OR “Vitamin D”[tiab] OR “25-hydroxyvitamin D”[tiab] OR “25(OH)D”[tiab] OR “Calcitriol”[tiab] OR “Calcidiol”[tiab] OR “Cholecalciferol”[tiab] OR “1,25-dihydroxyvitamin D”[tiab])) AND ((“Leiomyoma”[Mesh] OR “ULs”[tiab] OR “UL”[tiab] OR myoma[tiab] OR leiomyomata[tiab] OR fibromyoma[tiab] OR “uterine smooth muscle tumor”[tiab])) AND (“2016/01/01”[PDAT]: “2025/12/31”[PDAT]) NOT(animals[mh] NOT humans[mh]) NOT (review[pt])	((“Vitamin D”[Mesh] OR “Vitamin D”[tiab] OR “Calcitriol”[tiab] OR “25(OH)D”[tiab] OR “1,25-dihydroxyvitamin D”[tiab]) AND (“Vitamin D Receptor”[Mesh] OR “VDR”[tiab] OR “vitamin D receptor”[tiab] OR “CYP24A1”[tiab] OR “CYP27B1”[tiab] OR “Vitamin D binding protein”[tiab] OR “VDBP”[tiab] OR “DBP”[tiab]) AND (“Leiomyoma”[Mesh] OR “ULs”[tiab] OR “UL”[tiab] OR myoma[tiab] OR leiomyomata[tiab] OR fibromyoma[tiab] OR “uterine smooth muscle tumor”[tiab])) AND (“2016/01/01”[PDAT]: “2025/12/31”[PDAT]) NOT (animals[mh] NOT humans[mh]) NOT (review[pt])
Scopus	TITLE-ABS-KEY(“vitamin d” OR “25-hydroxyvitamin d” OR “25(oh)d” OR calcitriol OR calcidiol OR cholecalciferol OR “1,25-dihydroxyvitamin d”) AND TITLE-ABS-KEY(“uterine fibroid*” OR “UL*” OR myoma OR leiomyomata OR fibromyoma OR “uterine smooth muscle tumor”) AND (PUBYEAR > 2015 AND PUBYEAR < 2026) AND NOT (DOCTYPE(review))	TITLE-ABS-KEY(“vitamin d” OR calcitriol OR “25(oh)d” OR “1,25-dihydroxyvitamin d”) AND TITLE-ABS-KEY(“vitamin d receptor” OR vdr OR cyp24a1 OR cyp27b1 OR “vitamin d binding protein” OR vdbp OR dbp) AND TITLE-ABS-KEY(“uterine fibroid*” OR “UL*” OR myoma OR leiomyomata OR fibromyoma OR “uterine smooth muscle tumor”) AND (PUBYEAR > 2015 AND PUBYEAR < 2026) AND NOT (DOCTYPE(review))
Web of science	TS=((“Vitamin D” OR “25-hydroxyvitamin D” OR “25(OH)D” OR Calcitriol OR Calcidiol OR Cholecalciferol OR “1,25-dihydroxyvitamin D”) AND (Leiomyoma OR “ULs” OR “UL” OR myoma OR leiomyomata OR fibromyoma OR “uterine smooth muscle tumor”)) and 2016 OR 2017 OR 2018 OR 2019 OR 2020 OR 2021 OR 2022 OR 2023 OR 2024 OR 2025 (Publication Years)	TS=((“vitamin d” OR calcitriol OR “25(oh)d” OR “1,25-dihydroxyvitamin d”) AND (“vitamin d receptor” OR vdr OR cyp24a1 OR cyp27b1OR “vitamin d binding protein” OR vdbp OR dbp) AND (“uterine fibroid*” OR “UL*” OR myoma OR leiomyomata OR fibromyoma OR “uterine smooth muscle tumor”)) and 2016 OR 2017 OR 2018 OR 2019 OR 2020 OR 2021 OR 2022 OR 2023 OR 2024 OR 2025 (Publication Years)
Google scholar	“vitamin D” OR “25(OH)D” OR “25-hydroxyvitamin D” OR “1,25-dihydroxyvitamin D” OR “1,25(OH)$_2$D” OR calcitriol “ULs” OR “UL” OR myoma Custom range: 2016–2025	“vitamin D receptor” OR VDR OR VDBP OR DBP OR CYP24A1 OR CYP27B1 OR “ULs” OR “UL” OR myoma Custom range: 2016–2025

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Study selection

All records retrieved from the searches were imported into Zotero (Corporation for Digital Scholarship, Vienna, VA, USA; version 7.0.32) subsequently uploaded into Rayyan (Rayyan Systems Inc., Qatar), for de-duplication and stepwise manual screening. Titles and abstracts were screened independently by two reviewers (GK and MAK), with discrepancies resolved through discussion and consensus. Full-text articles were retrieved for records deemed potentially eligible by either reviewer and were assessed independently for inclusion. Guo et al. [23], a Mendelian randomisation study using publicly available GWAS summary statistics for vitamin D and UL, was assessed at the full-text stage and excluded because it did not report individual-level clinical, tissue, or genotype data meeting the PCC eligibility criteria applied to primary observational/experimental studies; this exclusion is reflected under ‘wrong study design’ in Fig 2, and the study

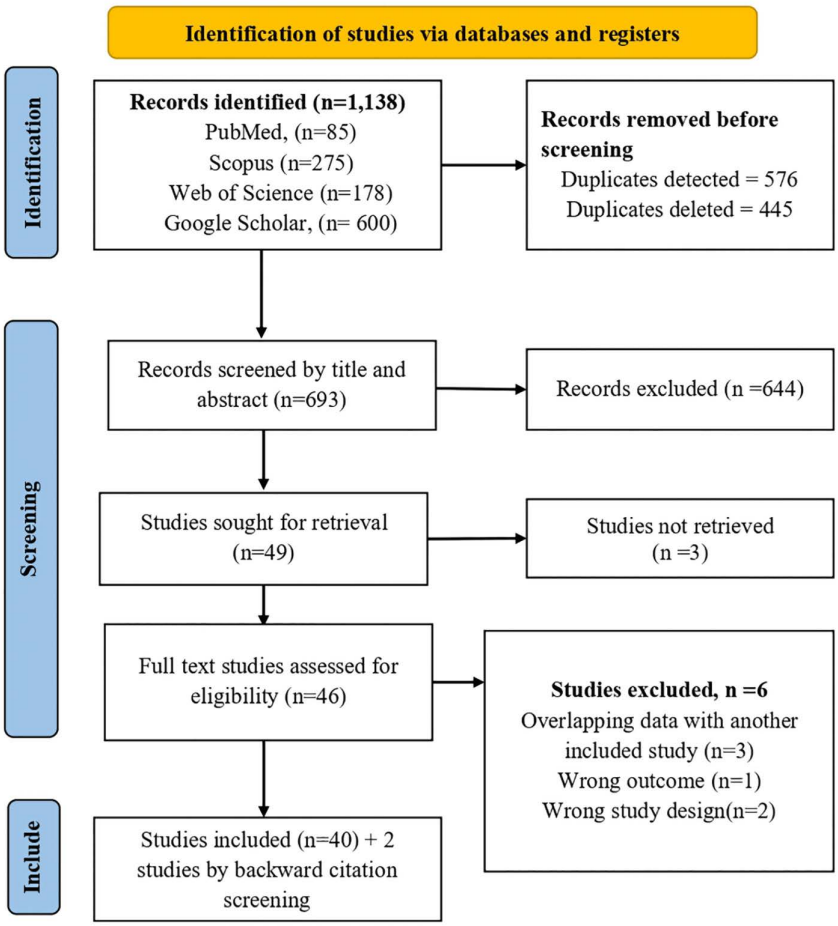

Fig 2. PRISMA-ScR flow diagram for selection of studies.

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is instead discussed narratively in the Introduction and Discussion as complementary evidence. Two further records, Corachán et al. [19] and Al-Hendy et al. [27], were identified through backward citation screening of included studies (see Information sources and search strategy) rather than through the primary database search, were assessed as meeting full eligibility criteria, and were added at the full-text stage; this is reflected in the updated PRISMA-ScR flow diagram (Fig 2), which now shows 42 included studies (40 from database searching, 2 from citation screening). Discrepancies at any stage were resolved through discussion and consensus.

Data charting process

A standardized data charting form was developed to extract key information from included studies, including publication characteristics, study design, population details, vitamin D-related exposures or measurements, leiomyoma outcomes, and key clinical or molecular findings. The data charting form was piloted on a subset of included studies and refined iteratively. Data were charted independently by one reviewer (GK) and cross-checked by a second reviewer (MAK) to ensure accuracy and completeness. Extracted variables included: author and year of publication; country or region; study design; sample size; participant characteristics; assessment of vitamin D status or VDR expression or genotype;

leiomyoma-related outcomes and reported clinical, molecular, or genetic associations. To support reproducibility, the full search strings for each database are reported verbatim in Table 1, the review protocol is prospectively registered and publicly accessible, and the completed PRISMA-ScR checklist is provided as Supplementary File 1; the data charting form and the extracted dataset underlying Tables 4–6 are available from the corresponding author upon reasonable request, consistent with the Data Availability Statement accompanying this submission.

Synthesis of results

Consistent with scoping review methodology, findings were synthesized descriptively rather than quantitatively. Extracted data were summarized using tables and narrative synthesis to map the range, nature, and focus of existing evidence. Studies were grouped thematically into clinical associations, molecular mechanisms, and genetic or epigenetic investigations (Table 2).

Critical appraisal

In accordance with PRISMA-ScR and JBI guidance, no formal assessment of methodological quality or risk of bias was undertaken, as the primary objective of the review was to map the extent and characteristics of the available evidence rather than to assess effect estimates or certainty of evidence. Sample size, method of exposure measurement and adjustment for confounders were charted descriptively (Tables 3–6) to aid interpretation. These descriptors were not used to grade, weight, rank or exclude studies, and sample size alone is not taken to indicate statistical power or methodological robustness.

Ethics statement

This scoping review did not involve direct use of human participants, human tissue, or identifiable personal data. All data were derived from previously published and publicly accessible studies. Ethical approval and informed consent were therefore not required for the conduct of this review.

Results

Selection of sources of evidence

The database search yielded a total of 1,138 records, as described in Table 2. After removal of duplicates, 693 unique records remained (Rayyan flagged 575 records belonging to 130 duplicate clusters; one record per cluster was retained and the remaining 445 duplicate records were removed, so that 1,138–445 = 693) and were screened at the title and

Table 2. Summary of the data bases and the number of articles obtained from each data base.

Database	Records obtained	Comments
PubMed/ MEDLINE	85	The search returned 72 records in step 1 and 13 in step 2. All records were considered
Scopus	275	The search returned 237 records in step 1 and 38 in step 2. All records were considered.
Web of Science	178	The search returned 157 records in step 1 and 21 records in step 2. All records were considered
Google scholar	600	The search retrieved > 10,000 records in step 1 and > 600,000 records in step 2. The first 300 in each step sorted by relevance were considered. This threshold was selected based on methodological guidance, suggesting that relevance ranking captures the most pertinent records [26].
Total	1,138	These were all imported into Rayyan for deduplication and step-wise manual screening

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Table 3. Methodological and outcome mapping for clinical studies (N = 31).

Variable	Frequency n (%)
Clinical outcomes assessed	
Presence or prevalence of UL	25 (80.6)
Size or volume of UL	16 (51.6)
Symptom severity	6 (19.4)
Number of UL lesions	5 (16.1)
Deficiency thresholds	
<20 ng/mL	19 (61.3)
<10ng/mL	3 (9.7)
Not defined	6 (19.4)
Other threshold	3 (9.7)
Adjustment for confounders	
Body mass index (BMI)	13 (41.9)
Ethnicity	1 (3.2)
Seasonality	2 (6.5)
Age	7 (22.6)
Parity	2 (6.5)
Any confounder adjustment	13 (41.9)
No confounder adjustment	18 (58.1)

25(OH)D, 25-hydroxyvitamin D; BMI, Body mass index; LC-MS/MS, Liquid Chromatography Tandem Mass Spectrometry; UL, Uterine leiomyoma; ROC, Receiver Operating Characteristic. Deficiency threshold categories reflect the cut-off applied by study authors; studies using ≥ 30 ng/mL as a sufficiency threshold [31], < 12 ng/mL [32], or a ROC-derived optimal threshold [37] are grouped as "Other threshold". Confounder adjustment categories and clinical outcomes assessed are not mutually exclusive; a single study may be counted under multiple confounder rows.

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abstract level. Of these, 644 were excluded for not meeting the eligibility criteria. A total of 49 full-text articles were sought for retrieval; 3 could not be retrieved and 46 were assessed for eligibility. Of these, 6 articles were excluded at the full-text stage due to reasons including wrong outcome (1), wrong study design (2), and overlapping data with an included study (3). In addition, two further records, Corachán et al. [19] and Al-Hendy et al. [27] meeting full eligibility criteria were identified through backward citation screening of included studies and added at the full-text stage. Forty-two studies met the inclusion criteria and were included in the final synthesis. The study selection process is summarized in a PRISMA-ScR flow diagram in Fig 2.

Characteristics of included studies

Forty-two studies were included, comprising predominantly clinical observational studies (73.8%), followed by molecular (16.7%) and genetic or epigenetic investigations (9.5%) in Fig 3. Geographically, most studies were conducted in Asia (42.9%) and Europe (21.4%), with limited representation from Africa (14.3%). The majority of studies employed case-control (50.0%) and cross-sectional (33.3%) designs, with relatively few longitudinal studies. Vitamin D status was primarily assessed using immunoassay-based methods (71.4%), while LC-MS/MS was rarely used (4.8%). Uterine leiomyoma diagnosis was most commonly based on ultrasonography (73.8%). Percentages are calculated on all 42 included studies; tissue, cell-culture and genetic studies without a circulating vitamin D assay (n = 10) and in vitro studies without a clinical UL diagnosis (n = 2) are shown as separate categories in Fig 3.

Table 4. Clinical studies (n = 31).

Author (Year) [Ref]	Study design	Sample size (n)	Key exposure and method of measurement	Main outcome	Summary findings	Con-founder adjustment
Ciebiera et al. (2016) [45]	Retrospec-tive cohort	105 UL cases vs 83 controls;	Serum 25(OH)D; Immunoassay Immunoassay	UL risk	Significantly lower 25(OH)D in UL cases vs controls	Partial (BMI and family history)
Oskovi Kaplan et al. (2018) [46]	Cross-sectional	68 UL cases vs 56 controls, premenopausal	Serum 25(OH)D; Immunoassay Immunoassay	UL presence and size	Lower 25(OH)D in UL cases; no correlation with size or volume	None
Sersam and Najeeb (2018) [47]	Prospective case-control	75 UL cases vs 75 controls	Serum 25(OH)D; Immunoassay Immunoassay	UL volume and number	Lower 25(OH)D in cases; inverse correla-tion with total volume and number	None
Ajmani et al. (2018) [48]	Prospective case-control	75 UL cases vs 75 controls	Serum 25(OH)D; Immunoassay	UL risk	Lower 25(OH)D in cases; 42.7% deficient in cases vs 20% controls	None
Singh et al. (2019) [49]	Cross-sectional	72 UL cases vs 72 controls	Serum 25(OH)D; Immunoassay	UL presence	Lower 25(OH)D in UL cases	None
Srivastava et al. (2020) [50]	Cross-sectional	45 UL cases vs 45 controls	Serum 25(OH)D; by Immunoassay	UL presence	Lower 25(OH)D in UL cases	None
Farzaneh et al. (2020) [51]	Case-control	71 UL cases vs 77 controls	Serum 25(OH)D Immunoassay	UL presence	Lower 25(OH)D in UL cases	None
Li et al. (2020) [32]	Case-control	279 UL cases vs 267 controls	Serum 25(OH)D; Immunoassay	UL presence	Lower 25(OH)D in UL cases	Partial (BMI and age);
Sarkar et al. (2020) [52]	Case-control	50 UL cases vs 50 controls	Serum 25(OH)D; Immunoassay	UL presence	44% deficient in cases vs 14% controls	None
Xu et al. (2021) [37]	Cross-sectional	133 asymptom-atic UL cases vs 80 controls	Serum 25(OH)D; Immunoassay	Asymptom-atic UL risk	Low 25(OH)D associated with higher UL risk	Partial (BMI and age);
Sarbhai et al. (2021) [53]	Case-control	75 UL cases vs 75 controls	Serum 25(OH)D; Immunoassay	Fibroid volume	Inverse correlation between 25(OH)D and UL volume	None
Choudhary et al. (2021) [54]	Cross-sectional	70 UL cases vs 70 controls	Serum 25(OH)D; Immunoassay	UL occurrence	Lower 25(OH)D in UL cases	None
Kumari et al. (2022) [34]	Case-control	102 UL cases vs 208 controls;	Serum 25(OH)D; Immunoassay	UL number and volume	Lower 25(OH)D in cases (14.52 ± 7.89 vs 26.6 ± 14.36 ng/mL, $p < 0.05$); inverse asso-ciation with fibroid number and volume	Partial (BMI and parity)
Al-azzawi et al. (2022) [38]	Cross-sectional	70 UL cases	Serum 25(OH)D; Immunoassay	UL size and number	Lower 25(OH)D levels observed in women with larger or multiple UL (within-case analysis; no control group)	None
Pradhan et al. (2022) [55]	Prospective case-control	100 UL cases vs 100 controls;	Serum 25(OH)D; Immunoassay	UL presence and volume	Lower 25(OH)D; associated with larger volume and multiple UL	None
Harmon et al. (2022) [31]	Prospective cohort	1,610 women	Serum 25(OH)D; LC-MS/MS	Fibroid growth and incidence/ loss	Higher 25(OH)D (≥30 ng/mL) associated with increased UL loss	Yes (BMI, season and race)
Chen et al. (2023) [20]	Case-control	55 UL cases vs 55 controls	Serum 25(OH)D; Immunoassay	UL presence and volume	Lower 25(OH)D in cases; negative correla-tion with volume	None
Kapoor and Maheshwari (2023) [35]	Case-control	150 UL cases vs 150 controls	Serum 25(OH)D; Immunoassay	UL occur-rence and volume	Low 25(OH)D was an independent risk factor	Partial (BMI)
Thomas et al. (2023) [36]	Case-control	183 UL cases vs 183 controls	Serum 25(OH)D; Immunoassay	UL presence	No direct association between low 25(OH) D and UL presence	Partial (BMI and age)

(Continued)

Table 4. (Continued)

Author (Year) [Ref]	Study design	Sample size (n)	Key exposure and method of measurement	Main outcome	Summary findings	Confounder adjustment
Dutta et al. (2023) [56]	Cross-sectional	100 UL cases vs 100 controls	Serum 25(OH)D; Immunoassay	UL presence	Lower 25(OH)D in UL cases; 83.3% deficient (<20 ng/mL)	None
Ahmad et al. (2024) [17]	Cross-sectional	80 UL cases vs 80 controls	Serum 25(OH)D; Immunoassay	UL presence and number	Lower 25(OH)D; inverse association with number of fibroids	None
Mahachiraphat and Lertsiripanich (2025) [16]	Cross-sectional	90 UL cases	Serum 25(OH)D; Immunoassay	Fibroid volume	Weak inverse correlation between 25(OH)D and fibroid volume (within-case analysis; no control group)	None
Cetin et al. (2025) [29]	Retrospective case-control	954 UL cases vs 668 controls	Serum 25(OH)D; Immunoassay	UL presence	Lower 25(OH)D in UL cases; lower in multiple fibroids	Partial (BMI and age)
Onaran et al. (2025) [57]	Retrospective case-control	74 UL cases vs 74 controls	Serum 25(OH)D; Immunoassay	UL presence (infertility context)	Lower 25(OH)D in UL cases; no association with size, number and location	Partial (BMI and season)
Hassanzadeh et al. (2025) [58]	Cross-sectional	67 UL cases vs 50 controls	Serum 25(OH)D; Immunoassay	UL presence and symptoms	Lower 25(OH)D in UL cases; deficiency more prevalent in cases	None
Ingala et al. (2016) [33]	Case-control	216 UL cases vs 216 controls	Serum 25(OH)D; Immunoassay (IRMA)	UL risk	Vitamin D deficiency significantly higher in UL cases	Partial (age, parity and BMI);
All Ansary and Abd El Megeed (2021) [59]	Case-control	75 UL cases vs 75 controls	Serum 25(OH)D; Immunoassay	UL presence	Significant association between vitamin D deficiency and UL	None
Tunau et al. (2021) [15]	Analytical cross-sectional	49 UL cases vs 48 controls	Plasma 25(OH)D; Immunoassay	UL risk	Lower 25(OH)D in UL cases; 1-unit increase reduces risk by 8%	Partial (BMI and age)
Abdel-Kader et al. (2022) [28]	Case-control	30 UL cases vs 30 controls	Serum 25(OH)D; Immunoassay	Small UL presence	Lower 25(OH)D in cases	None
Okoro et al. (2024) [21]	Case-control	75 UL cases vs 75 controls	Serum 25(OH)D; Immunoassay	UL volume	Significant negative correlation between 25(OH)D and UL volume	Partial (BMI and age)
Latifi et al. (2024) [30]	Case-control	55 UL cases vs 50 controls	Serum free and total 25(OH)D and vitamin D binding protein; Immunoassay	Serum biomarkers and fibroid size	Lower free vitamin D and higher DBP in UL cases; negative correlation with largest fibroid size	Partial (BMI)

25(OH)D, 25-hydroxyvitamin D; BMI, Body mass index; LC-MS/MS, Liquid Chromatography Tandem Mass Spectrometry; IRMA, Immunoradiometric Assay; DBP, Vitamin D binding protein; UL, Uterine leiomyoma. Sample size is the number of cases and controls as reported (total participants for cohort studies). It is shown for description only and was not used to rank, weight or exclude studies.

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Clinical associations between vitamin D and Uterine leiomyomas

Among the 31 clinical studies (Table 4), most (80.6%) assessed the association between vitamin D status and the presence of ULs, while fewer examined fibroid size or volume (51.6%) and only a minority assessed symptom severity (19.4%) (Table 3). Studies varied substantially in sample size, ranging from 60 participants by Abdel-Kader et al., (2022) [28] to 1,622 participants (954 cases and 668 controls) by Cetin et al.,(2025) [29], with important implications for the reliability and generalisability of their findings. Overall, the majority of studies reported lower circulating 25(OH)D concentrations among women with ULs compared with controls, with several demonstrating inverse associations between vitamin D levels and fibroid size, volume, or number. Latifi et al. [30] additionally measured vitamin D binding protein (DBP) in serum, reporting lower free vitamin D and higher DBP concentrations in women with ULs, with DBP negatively correlated with the largest fibroid diameter. The prospective cohort by Harmon et al.,(2022) [31] (n = 1,610), the only study that used LC-MS/

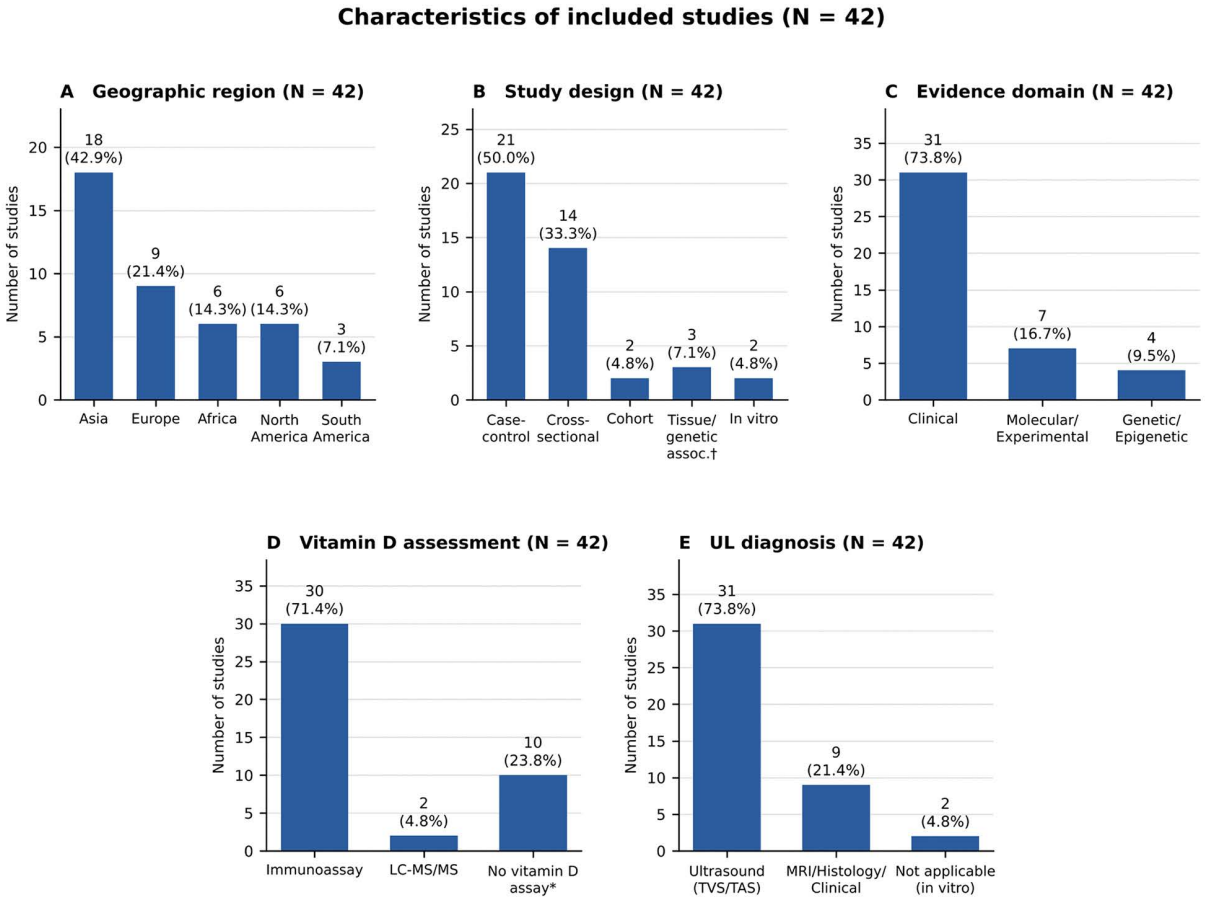

Fig 3. Characteristics of included studies (N = 42). ELISA, Enzyme linked immunosorbent assay; ECLIA, Electrochemiluminescence Immunoassay; CLIA, Chemiluminescence Immunoassay; IRMA, Immunoradiometric Assay; HPLC, High Performance Liquid Chromatography; LC-MS/MS, Liquid Chromatography Tandem Mass Spectrometry; RT-PCR-Real time Polymerase Chain Reaction; MRI, Magnetic Resonance Imaging; TVS, Transvaginal sonography; TAS, Transabdominal sonography. Percentages are calculated on N = 42 studies and may not sum to 100% because of rounding.

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MS measurement and adjusted fully for BMI, seasonality, and race, reported that higher 25(OH)D levels (≥30 ng/mL) were associated with increased fibroid loss; the associated reduction in fibroid incidence (aHR = 0.78; 95% CI: 0.47–1.30) did not reach statistical significance, underscoring that prospective evidence remains suggestive rather than conclusive. Among studies with 200 or more participants, Cetin et al.[29], (n = 1,622), Li et al. [32] (n = 546), Ingala et al.[33], (n = 432), Kumari et al.[34], (n = 310), Kapoor and Maheshwari [35] (n = 300), Thomas et al.[36], (n = 366) and Xu et al. [37] (n = 213, cross-sectional) mostly reported lower 25(OH)D in women with ULs, though Thomas et al.[36], found no significant association after adjustment for confounders. Smaller studies (n < 100), including Abdel-Kader et al. [28] (n = 60) and Al-azzawi et al. [38] (n = 70) reported similar directional findings. Sample size is reported here for description only: it was not used to weight or rank studies, because sample size alone does not establish statistical power or methodological robustness, and no formal appraisal was undertaken. Overall, the pattern of lower circulating vitamin D in women with ULs is broadly consistent across study sizes, but the strength and independence of this association remain uncertain, particularly given inconsistent adjustment for confounding variables. Fewer than half of the studies accounted for BMI, and fewer still adjusted for ethnicity, sun exposure, or seasonality, hence limiting interpretability of observed associations. Definitions of

Table 5. Molecular or experimental studies (n = 7).

Author (Year) [Ref]	Study design	Population or model and sample size	Key exposure/ Method of measurement	Main outcome	Summary findings	Confounder adjustment
Lima et al. (2021) [60]	Ex-vivo cross-sectional	40 women (30–35 y); UL tissue vs adjacent myometrium (paired samples from the same women)	VDR protein expression; IHC/Western blot	VDR levels in tissue	VDR expression significantly lower in UL tissue (60.22%) vs myometrium (79.52%)	N/A (tissue study)
Markowska et al. (2022) [39]	Ex-vivo cross-sectional	98 UL samples vs periphery muscle (paired samples)	VDR protein expression; IHC	VDR levels in tissue	VDR-positive cells highest in normal muscle, lowest in fibroid centre	N/A (tissue study)
Othman et al. (2018) [41]	Ex-vivo tissue analysis	40 UL vs matched myometrium (paired) and 40 normal controls	Vitamin D metabolising enzymes (*CYP27B1*/*CYP24A1*) and tissue $1,25(OH)_2D_3$; LC-MS/MS and PCR	Intra-tumoral vitamin D metabolism	Lower tissue $1,25(OH)_2D_3$ and higher *CYP24A1* in UL	N/A (tissue study)
Liu et al. (2018) [40]	Ex-vivo cross-sectional	21 UL vs adjacent myometrium (paired)	VDR and COX-2 expression; IHC and PCR	VDR/COX-2 levels	Decreased VDR and increased *COX-2* expression in UL tissue	N/A (tissue study)
Fazeli et al. (2020) [18]	Molecular genetic	61 UL tissue vs 51 adjacent myometrium samples (paired)	*CYP24A1* expression (*MED12* mutation profile); RT-PCR	*CYP24A1* expression	Significantly higher *CYP24A1* expression in UL (independent of *MED12* mutation)	N/A (tissue study)
Corachán (2019) [19]	In-vitro experimental	Primary human UL cell cultures	Calcitriol dose-response; Wnt/β-catenin markers; WB/qPCR	Proliferation, Wnt/β-catenin activity	Calcitriol inhibited UL cell proliferation via Wnt/β-catenin suppression, dose-dependent	N/A (in vitro study)
Al-Hendy (2016) [27]	In-vitro experimental	Human UL cell lines	Vitamin D3 treatment; Wnt/β-catenin, mTOR markers; WB; VDR knockdown in myometrial cells	Wnt/β-catenin, mTOR activity	Vitamin D3 significantly suppressed Wnt/β-catenin and mTOR signalling	N/A (in vitro study)

VDR, Vitamin D receptor; IHC, Immunohistochemistry; WB, Western blot; LC-MS/MS, Liquid Chromatography Tandem Mass Spectrometry; RT-PCR, Real-time Polymerase Chain Reaction; CYP24A1, Cytochrome P450 family 24 subfamily A member 1; CYP27B1, Cytochrome P450 family 27 subfamily B member 1; MED12, Mediator Complex Subunit 12; UL, Uterine leiomyoma; BMI, Body mass index; N/A, Not applicable (tissue-based or molecular study; individual-level confounder adjustment not applicable). For tissue studies, n is the number of women or tissue samples as reported; paired samples (UL and adjacent myometrium) are not independent observations. Sample size is shown for description only.

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vitamin D deficiency also varied widely across studies, with thresholds ranging from <10 ng/mL to <20 ng/mL, and measurement techniques were predominantly immunoassay-based, which may contribute to inter-study variability.

Molecular mechanisms involving the vitamin D-VDR axis

Seven studies investigated molecular mechanisms (Table 5), primarily using human UL tissues or cell line models. Of these, three examined VDR protein expression, two examined CYP24A1 expression and two directly examined calcitriol-mediated pathway suppression. Three studies examined VDR protein expression in UL tissue: Lima et al. reported significantly lower VDR expression in UL tissue (60.2%) compared with adjacent myometrium (79.5%); Markowska et al. [39] confirmed this gradient, with VDR-positive cell density highest in normal myometrium and lowest in the fibroid centre; and Liu et al. [40] additionally documented upregulation of *COX-2* in VDR-deficient fibroid tissue. Two studies examined CYP24A1: Othman et al. [41] demonstrated lower intratumoral 1,25-dihydroxyvitamin D3 levels alongside upregulated CYP24A1 expression in UL tissue, while Fazeli et al. [18] confirmed elevated CYP24A1 expression independently of MED12 mutation status; together suggesting active local inactivation of calcitriol within fibroid tissue. Two further studies directly assessed calcitriol-mediated suppression of pathogenic signalling: Corachán et al. [19] demonstrated that calcitriol inhibited leiomyoma cell proliferation via suppression of Wnt/β-catenin signalling in human UL cell cultures, and Al-Hendy et al. [27] demonstrated that vitamin D3 suppressed both Wnt/β-catenin and mTOR signalling in human leiomyoma cells. These two studies, rather than the VDR- or CYP24A1-focused studies described above, provide the direct

Table 6. Genetic or epigenetic studies (n = 4).

Author (Year) [Ref]	Study design	Population or model and sample size	Key exposure and method of measurement	Main outcome	Summary findings	Confounder adjustment
Ciebiera et al. (2021) [22]	Genetic case-control	114 UL cases vs 83 controls	VDR gene SNPs (rs731236, rs1544410, rs2228570); Genotyping	Genetic susceptibility	No significant association between selected VDR polymorphisms and UL	Partial (BMI, age)
Yilmaz et al. (2018) [42]	Genetic case-control	27 UL cases vs 33 controls	VDR Fok1 polymorphism (rs2228570); Genotyping	Genetic susceptibility	T allele (Fok1) significantly higher in UL cases as a risk factor	None
Xie et al. (2022) [43]	Case-control genetic	450 UL cases vs 450 controls	Vitamin D anabolism gene polymorphisms (*DHCR7* rs1044482, *NADSYN1* rs2276360); Genotyping	Genetic susceptibility	Polymorphisms in *DHCR7* rs1044482 and *NADSYN1* rs2276360 associated with UL susceptibility	Partial (age, BMI)
Tiwari et al. (2025) [44]	Genetic association	100 UL cases vs 100 controls	VDR intronic polymorphisms (ApaI/BsmI) and mRNA; Genotyping with RT-PCR	Genetic susceptibility and expression	ApaI variant (rs7975232) significantly associated with UL and VDR mRNA expression	Partial (age, BMI)

VDR, Vitamin D receptor; SNP, Single Nucleotide Polymorphism; TaqI, restriction enzyme identifying VDR rs731236; BsmI, restriction enzyme identifying VDR rs1544410; FokI, restriction enzyme identifying VDR rs2228570; ApaI, restriction enzyme identifying VDR rs7975232; DHCR7, 7-Dehydrocholesterol Reductase; NADSYN1, NAD Synthetase 1; UL, Uterine leiomyoma; BMI, Body mass index; mRNA, messenger RNA; RT-PCR, Real-time Polymerase Chain Reaction. Confounder adjustment refers to the statistical adjustment applied in the association analysis. Sample size is the number of cases and controls as reported and is shown for description only.

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evidence in this review for calcitriol-mediated pathway suppression; TGF-β pathway suppression by calcitriol is discussed in prior mechanistic literature but was not independently re-demonstrated among the studies charted here. Collectively, across these seven studies, calcitriol or vitamin D3 reduced proliferation and suppressed Wnt/β-catenin signalling (and, in one study, mTOR signalling) in leiomyoma cells in vitro, suggesting potential antiproliferative effects, while tissue studies reported lower VDR and higher CYP24A1 expression in leiomyoma than in adjacent myometrium. However, most findings derive from in vitro or ex vivo tissue models, limiting direct clinical applicability.

Genetic and epigenetic findings

Four genetic studies examined VDR gene polymorphisms and vitamin D metabolism genes in relation to UL susceptibility (Table 6). Ciebiera et al. [22] found no significant association between three common VDR single nucleotide polymorphisms *(rs731236, rs1544410, rs2228570)* and UL incidence in a Polish Caucasian population. In contrast, Yilmaz et al. [42] reported that the T allele of the *FokI* polymorphism *(rs2228570)* was significantly more frequent in Turkish women with UL, suggesting a population-specific susceptibility effect. Xie et al. [43] extended the genetic analysis to vitamin D metabolism genes, finding that polymorphisms in *DHCR7 (rs1044482) and NADSYN1 (rs2276360), genes involved in vitamin D synthesis,* were associated with UL susceptibility in a large Chinese case-control study (n = 900). Most recently, Tiwari et al. [44] reported that the *ApaI* intronic variant *(rs7975232)* was significantly associated with UL risk in North Indian women and was also linked to reduced VDR mRNA expression, providing a functional link between genotype and receptor activity. Collectively, these inconsistent findings across four populations likely reflect differences in genetic architecture, linkage disequilibrium patterns, and the modifying influence of environmental vitamin D exposure, rather than the absence of a genetic contribution.

Studies testing the link between vitamin D status and VDR

Across the 42 included studies, vitamin D status (circulating or tissue vitamin D) and VDR (expression or genotype) were examined in separate bodies of evidence. No included study analysed circulating 25(OH)D together with VDR expression

or VDR genotype in the same participants, and none reported an interaction or mediation analysis. Two in vitro studies examined the connection experimentally (Table 7). Al-Hendy et al. [27] knocked down VDR in myometrial cells, which increased Wnt/β-catenin and mTOR signalling, but did not test vitamin D3 in VDR-silenced cells. Corachán et al. [19] reported that calcitriol increased VDR expression in leiomyoma cells alongside suppression of Wnt/β-catenin signalling, without testing whether the antiproliferative effect required VDR. Othman et al. [41] measured tissue 1,25(OH)2D3 and CYP24A1 but not VDR, and Tiwari et al. [44] linked VDR genotype to VDR mRNA expression but did not measure vitamin D. The evidence for a VDR-dependent action of vitamin D in leiomyoma therefore rests on indirect and parallel findings rather than on direct tests.

Summary of evidence gaps

The mapped evidence highlights several key gaps. First, there is limited representation of African populations despite a high disease burden. Second, there is a lack of integration between clinical and molecular data, with few studies correlating serum vitamin D levels with tissue-level findings, hindering a comprehensive understanding of the vitamin D-VDR axis across biological scales. Third, the predominance of cross-sectional designs limits causal inference as temporal relationships between vitamin D status and leiomyoma development remain unclear. In addition, substantial variability in vitamin D measurement methods, deficiency thresholds, and adjustment for confounding factors complicates comparison across studies and may contribute to inconsistent findings. Finally, no included study tested whether VDR mediates or modifies the association between vitamin D status and UL (Table 7).

Discussion

This scoping review mapped the breadth and characteristics of clinical, molecular, and genetic evidence relating to the vitamin D-vitamin D receptor axis in ULs. The findings indicate that the field is dominated by observational clinical studies, complemented by a smaller body of experimental and limited genetic research. Across these domains, a consistent pattern emerges: lower circulating vitamin D levels are frequently reported among women with uterine leiomyomas, alongside mechanistic evidence suggesting that vitamin D signalling may influence key biological processes relevant to leiomyoma

Table 7. Included studies that examined both a vitamin D component and VDR, and what they show.

Study [Ref]	Vitamin D component	VDR component	Design	What the study shows, and what it does not
Al-Hendy et al. (2016) [27]	Vitamin D3 treatment of fibroid cells	VDR knockdown in myometrial cells	In vitro	VDR loss increased Wnt/β-catenin and mTOR signalling; vitamin D3 effects were not tested in VDR-silenced cells, so VDR-dependence is not shown
Corachán et al. (2019) [19]	Calcitriol dose-response	VDR expression in leiomyoma cells	In vitro	Calcitriol increased VDR expression and suppressed Wnt/β-catenin signalling; VDR-dependence of the antiproliferative effect was not tested
Othman et al. (2018) [41]	Tissue 1,25(OH)2D3	Not measured (CYP27B1/CYP24A1 expression)	Ex vivo tissue	Lower tissue calcitriol with higher CYP24A1 in UL; VDR signalling not assessed
Tiwari et al. (2025) [44]	Not measured	VDR genotype and VDR mRNA	Genetic association	Genotype was linked to VDR expression; no vitamin D measure, so no vitamin D-VDR interaction can be inferred
All other included studies (n = 38)	Serum vitamin D in the 31 clinical studies	VDR expression or genotype in the tissue and genetic studies	Various	Each study examined vitamin D status or a VDR/vitamin D-pathway component, not both; no joint, interaction or mediation analysis

UL, uterine leiomyoma; VDR, vitamin D receptor. The table lists studies that measured or manipulated both a vitamin D component and VDR, or a closely related component, and states whether the relationship between them was tested. VDR-dependence is taken to require VDR silencing or blockade combined with vitamin D treatment, or a joint, interaction or mediation analysis in the same participants.

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development. However, these findings should be interpreted cautiously. When two reporting features are considered together, namely adjustment for at least one major confounder (BMI, ethnicity, or seasonality) and a sample of at least 200 participants, only eight of the 31 clinical studies report both features: Harmon et al. (n = 1,610; full confounder adjustment; LC-MS/MS) [31], Cetin et al. (n = 1,622; BMI and age adjusted) [29], Thomas et al. (n = 366; BMI and age adjusted) [36], Kapoor and Maheshwari (n = 300; BMI adjusted) [35], Li et al. (n = 546; BMI and age adjusted) [32], Ingala et al. (n = 432; age, parity and BMI adjusted) [33], Kumari et al. (n = 310; BMI and parity adjusted) [34], and Xu et al. (n = 213; BMI and age adjusted) [37]. Of these eight, only Harmon et al. used the reference-standard LC-MS/MS measurement method [31]. These descriptors characterise reporting only: the threshold of 200 participants is arbitrary, and neither it nor sample size in general is a measure of statistical power or methodological robustness. The directional consistency of the overall evidence should therefore be read alongside the limited and heterogeneous reporting of confounder adjustment. The predominance of cross-sectional and case-control designs further limits the ability to establish temporality or causality, and the observed associations may partly reflect underlying confounding rather than a direct etiological role of vitamin D deficiency.

Most clinical studies included in this review reported inverse associations between serum 25(OH)D levels and the presence of ULs, with some demonstrating relationships with UL size, volume or number. These findings were observed across diverse populations, suggesting a potentially consistent epidemiological pattern. Nevertheless, the validity of these associations is substantially limited by inconsistent and often absent adjustment for key confounders. These confounders are not merely methodological footnotes; each operates through a distinct biological mechanism that can independently produce the observed pattern of lower vitamin D in women with ULs, and their differential handling across studies is a primary source of heterogeneity in this literature. Body mass index (BMI) is the most consequential confounder in this body of evidence. Vitamin D is a fat-soluble molecule that undergoes volumetric dilution and sequestration in adipose tissue, such that women with higher adiposity exhibit lower circulating 25(OH)D independently of sun exposure or dietary intake. Simultaneously, increased adiposity promotes oestrogen biosynthesis in peripheral adipose tissue and drives chronic low-grade inflammation, both of which are established drivers of UL growth. Fewer than half of the clinical studies in this review adjusted for BMI, meaning that in many studies the observed vitamin D deficiency may partly reflect adiposity-related dilution rather than a direct relationship with UL biology. Ethnicity introduces a separate confounding pathway. Women of African descent have both a higher prevalence and greater severity of UL, and also tend to have lower circulating 25(OH)D due to higher skin melanin content, which reduces the efficiency of cutaneous vitamin D synthesis. Only one of the 31 clinical studies (3.2%), Harmon et al. [31], explicitly adjusted for race or ethnicity, meaning that studies conducted in ethnically heterogeneous populations may be conflating a racial disparity in UL burden with a racial disparity in vitamin D status. The same issue extends beyond women of African descent. In a large integrated health care system in the United States, Mitro et al. [61] reported higher fibroid diagnosis rates among South Asian (71% higher), East Asian (47% higher) and Southeast Asian (29% higher) women than among non-Hispanic White women, indicating that ethnicity-related differences in UL burden also apply to Asian populations. Asia contributed the largest share of the included studies (18 of 42), yet none of these studies adjusted for ethnicity, and vitamin D research in Southeast Asia is comparatively limited and less diversified; Buana et al. [62], although focused on osteoporosis, documented this pattern in a bibliometric analysis. Ethnic differences in vitamin D status and UL risk within Asian populations therefore remain poorly characterised. Sun exposure and seasonality are functionally linked: cutaneous synthesis of vitamin D, the dominant source in most populations is driven by ultraviolet B radiation, which varies by latitude, season, and time of day. Only two studies (6.5%) adjusted for seasonality as reported in Table 3, of which Harmon et al. [31] and Onaran et al. [57] had confirmed ANCOVA-based seasonal adjustment, and none explicitly accounted for latitude or individual sun exposure behaviour. This is particularly relevant because several of the included studies were conducted in countries with highly variable solar radiation across seasons (Turkey, India, Nigeria). A 25(OH)D measurement taken in winter may reflect transient seasonal nadir, rather than habitual vitamin D status, and failure to account for this introduces non-differential

misclassification that could either attenuate, or spuriously inflate observed associations. Beyond BMI, ethnicity, and seasonality, several additional variables plausibly confound the relationship between vitamin D status and UL that were rarely addressed across the included studies. Physical activity increases outdoor sun exposure and independently influences adiposity and inflammatory tone; dietary vitamin D intake and use of vitamin D or calcium supplements directly alter circulating 25(OH)D independently of UL-related biology; renal disease impairs 1α-hydroxylation of 25(OH)D to its active metabolite and can itself arise secondarily to UL-related anaemia or urinary tract compression; parathyroid hormone exists in a reciprocal regulatory relationship with vitamin D and may itself be altered by chronic blood loss; oral contraceptive use and pregnancy history alter oestrogen and progesterone exposure; the dominant hormonal drivers of UL, while some evidence suggests hormonal contraceptives may also modestly influence circulating 25(OH)D; and latitude, individual UV exposure behaviour, and skin pigmentation jointly determine cutaneous vitamin D synthesis capacity, overlapping substantially with the ethnicity-related confounding discussed above. Socioeconomic status may act as a further, more distal confounder, influencing diet, outdoor occupation and leisure time, and access to healthcare and diagnostic imaging for UL. None of the included clinical studies adjusted for this full set of variables, and most adjusted for none of them; this represents a substantial and largely unaddressed source of potential confounding in the reviewed literature, and future prospective studies should prioritise their systematic measurement.

An additional interpretive consideration is the possibility of reverse causation: rather than vitamin D deficiency contributing to UL development, ULs themselves particularly through heavy menstrual bleeding, chronic anaemia, and low-grade pelvic inflammation; may lower circulating vitamin D status. Supporting this possibility, Oscanoa et al.[63], reported that serum 25(OH)D concentrations fell sharply following an acute inflammatory stimulus, independent of vitamin D intake, while Waldron et al. [64] observed a similar postoperative pattern in which 25(OH)D declined as C-reactive protein rose. Both observations are consistent with 25(OH)D behaving, in part, as a negative acute-phase reactant. Because ULs are associated with chronic low-grade inflammation and, in a subset of women, recurrent heavy bleeding, the cross-sectional design used by the great majority of included clinical studies cannot exclude the possibility that observed vitamin D deficiency is, at least partly, a consequence rather than a cause of UL-related pathology. This reverse-causation pathway is not mutually exclusive with a modulatory role of the vitamin D-VDR axis in UL biology; rather, it introduces an additional layer of complexity that only prospective, pre-symptomatic cohort studies with serial vitamin D measurement can resolve.

Experimental studies provide important mechanistic insights that support the plausibility of a role for vitamin D in leiomyoma biology. Two in vitro studies showed that calcitriol or vitamin D3 reduced proliferation and Wnt/β-catenin signalling (and mTOR signalling in one) in leiomyoma cells, processes relevant to UL pathogenesis. In particular, interactions between vitamin D signalling and Wnt/β-catenin signalling were reported in both in vitro studies, with mTOR signalling also suppressed in one [19,27]. These pathways are known to play critical roles in fibrogenesis and tumour growth. Separately, Ciebiera et al. [45] reported an inverse association between serum vitamin D and TGF-β3 concentrations in a clinical cohort, providing indirect clinical-level support for a link between the vitamin D axis and TGF-β-mediated fibrotic signalling, though this was a serum-based correlation rather than a direct tissue-level demonstration of pathway suppression, and should not be conflated with the Wnt/β-catenin evidence above. Comprehensive reviews of UL pathogenesis, have identified the vitamin D-VDR axis as one of several candidate endocrine modulators that may interact with the core oestrogen-progesterone signalling network driving UL growth [65]. Notably, a systematic review of vitamin D and fibroids by Combs et al. [25] synthesising 23 preclinical studies concluded that preclinical evidence consistently showed decreased VDR expression in fibroid cells, and that calcitriol exerted antiproliferative effects across multiple experimental models, providing an important mechanistic complement to the clinical evidence mapped in this review. Our findings are broadly consistent with, and extend, these two prior evidence syntheses. Yang et al.'s comprehensive review of UL pathogenesis identified the vitamin D-VDR axis as one of several candidate endocrine modulators without dedicated systematic mapping of the supporting evidenc [65], while Combs et al.'s systematic review addressed preclinical (largely animal and cell-line) evidence only, without extending to clinical epidemiology or genetic association data [25]. By contrast, the

present review is, to our knowledge, the first to jointly map clinical, molecular, and genetic evidence within a single PRISMA-ScR-adherent framework, allowing explicit identification of the gap between epidemiological association and tissue-level mechanism that neither prior synthesis addressed directly.

A particularly clinically relevant mechanistic finding is that calcitriol's antiproliferative effects on leiomyoma cells appear to be independent of *MED12* mutation status, the somatic mutation identified in approximately 70% of ULs, and previously thought to define distinct molecular subtypes with differing treatment responsiveness. This suggests that vitamin D-VDR signalling may represent a pathway accessible for therapeutic modulation across the full molecular spectrum of UL, not only in *MED12* wild-type tumours. A recurrent finding across the molecular studies included in this review was reduced VDR expression in UL tissue compared with adjacent myometrium, alongside upregulated *CYP24A1*. This bidirectional attenuation, reduced receptor expression and accelerated ligand inactivation raises the possibility of a self-sustaining cycle of vitamin D unresponsiveness within UL tissue, which may contribute to altered cellular behaviour although this has not been directly tested. However, most molecular studies were conducted in vitro or in ex vivo tissue models, and the translation of these mechanistic findings to the in vivo human context requires validation through integrative clinical-tissue studies [27,66]

Considered together, findings across the clinical, molecular, and genetic domains reveal parallel but separately established findings that warrant careful cross-domain interpretation. The pattern of lower circulating 25(OH)D in women with ULs and the finding of reduced VDR expression within fibroid tissue were established in different studies and populations, and no included study examined them together; the two findings are compatible with, but do not demonstrate, a shared mechanism. Critically, this reduced intratumoral VDR expression as reported by Lima et al. [60], Markowska et al. [39], and Liu et al.[40] across independent tissue cohorts, raises the possibility that a tissue-level difference exists in addition to any systemic difference. Even where circulating vitamin D levels are sufficient, UL tissue may exhibit impaired responsiveness to vitamin D signalling, a hypothesis that the included studies cannot test. Upregulated CYP24A1 expression in UL tissue, documented by Othman et al. [41] and Fazeli et al. [18], is consistent with increased local inactivation of 1,25-dihydroxyvitamin D3, although VDR signalling was not measured in these studies. In vitro, calcitriol or vitamin D3 suppressed Wnt/β-catenin signalling (and mTOR signalling in one study) in leiomyoma cells [19,27]; effects on TGF-β, apoptosis and extracellular matrix were not independently demonstrated among the studies charted here. The genetic findings are inconsistent and may reflect differences in population, sample size and study design. VDR polymorphisms may alter receptor expression or function, but no included study tested whether genotype modifies the relationship between vitamin D status and UL. The absence of studies that simultaneously measure serum 25(OH)D, tissue VDR expression, *CYP24A1* activity, and clinical outcomes in the same cohort is therefore the central gap in this literature. Until such integrative studies, or experiments showing VDR-dependent effects of vitamin D, are available, the three domains of evidence will remain separate, and the proposition that VDR mediates or modifies the relationship between vitamin D and UL will remain a hypothesis.

Genetic investigations of the vitamin D-VDR axis in UL remain limited. Studies examining VDR gene polymorphisms reported inconsistent associations with UL susceptibility, often varying by population and ethnic background. Notably, Xie et al.[43] examined vitamin D anabolism genes rather than VDR itself, finding that polymorphisms in DHCR7 (rs1044482) and NADSYN1 (rs2276360) were associated with UL susceptibility in a large Chinese case-control study (n = 900), suggesting that upstream genetic variation in vitamin D biosynthesis may be as relevant as receptor-level variation. Guo et al. [23], a Mendelian randomisation study using publicly available GWAS summary statistics for both vitamin D and UL, was identified during the search and is discussed in the Introduction as complementary evidence relevant to the causal question this review addresses; however, it was not charted as an included study because it did not report individual-level clinical, tissue, or genotype data meeting this review's PCC eligibility criteria for primary observational or experimental studies. This exclusion is noted explicitly here, and in the Methods, to avoid ambiguity given the study's relevance to the broader evidence base. These inconsistencies may reflect differences in genetic architecture, sample size, and study

design. Emerging evidence suggests that epigenetic mechanisms may also influence VDR expression and function within UL tissue. However, this area remains underexplored, and current evidence is insufficient to draw meaningful conclusions or support a consistent or population-independent genetic association. The limited integration of genetic, molecular, and clinical data represents a key gap in the literature. An important consideration in interpreting the available evidence is the biological heterogeneity of UL. Uterine leiomyomas vary widely in size, number, anatomical location (submucosal, intramural, subserosal), growth patterns, and molecular characteristics. These differences may influence both clinical presentation and underlying pathophysiology. Few studies stratified analyses based on fibroid characteristics, which may obscure subtype-specific associations with vitamin D status. For example, rapidly growing or highly fibrotic UL may be more strongly influenced by pathways modulated by vitamin D signalling. Failure to account for this heterogeneity may obscure subtype-specific associations and contribute to inconsistent findings across studies.

Methodological patterns and research gaps

This review highlights several important gaps in the existing literature. First, there is a clear predominance of observational studies, with relatively few longitudinal or interventional investigations. This limits the ability to establish temporal relationships and assess causality. Second, there is a notable lack of integrative studies linking systemic vitamin D status with tissue-level molecular changes and genetic variation within the same population. Bridging this gap would provide a more comprehensive understanding of the vitamin D-VDR axis in leiomyoma biology. Third, geographic representation is uneven, with limited data from African populations despite a disproportionately high burden of disease. This represents a critical gap, particularly given potential interactions between vitamin D status, skin pigmentation, and genetic susceptibility. Finally, methodological inconsistencies including variation in vitamin D assays, deficiency thresholds, outcome definitions, and confounder adjustment, limit comparability across studies and highlight the need for standardized research approaches.

Strengths and limitations

This review provides a comprehensive mapping of a diverse and multidisciplinary body of literature, integrating clinical, molecular, and genetic evidence. The use of a transparent, protocol-driven methodology and adherence to PRISMA-ScR guidelines, enhances the reproducibility and clarity of the review process. However, several limitations should be acknowledged. The review did not include formal quality appraisal, consistent with scoping review methodology, and therefore cannot assess the strength or certainty of the evidence. Sample size, assay method and confounder adjustment were charted descriptively only. Sample size alone does not establish power or robustness across clinical, genetic and tissue studies, and paired tissue samples from the same woman are not independent observations; the review therefore cannot judge the adequacy of individual studies. Additional limitations include restriction to English-language publications and the use of Google Scholar as a supplementary database with screening limited to the first 300 results per search string. The English-language restriction may have excluded relevant studies published in Arabic, Chinese, Portuguese, or French, potentially underrepresenting evidence from the Middle East, East Asia, Latin America, and francophone Africa regions, where UL research is growing but may be published in local-language journals. The Google Scholar restriction, while methodologically justified by relevance decay beyond 300 records, introduces a non-zero risk of missing records indexed in Google Scholar but not in the three primary databases. We additionally acknowledge that our search terms did not explicitly incorporate intervention-related terminology (vitamin D supplementation, analogues), such that trial-based literature on vitamin D as a treatment for UL may be incompletely captured by this review, which was scoped to map observational and mechanistic evidence rather than interventional evidence; a dedicated future review of supplementation trials is recommended. Similarly, the exclusion of animal-only studies, while consistent with this review's human-focused PCC framework, means that mechanistic insights from established preclinical models are not directly represented here and are instead available in existing preclinical syntheses [25]. Considered together, search constraints combined with inherent

heterogeneity in study designs, exposure definitions, and outcome measures, mean that the mapped evidence base may not be fully exhaustive. Furthermore, the underrepresentation of studies adjusting for ethnicity and environmental factors such as sunlight exposure limits interpretation, particularly in populations with high disease burden.

Conclusions

This scoping review mapped heterogeneous, largely observational evidence that lower circulating vitamin D levels are associated with UL presence, that VDR expression is lower and CYP24A1 expression higher in UL tissue than in adjacent myometrium, and that calcitriol or vitamin D3 suppresses Wnt/β-catenin signalling in leiomyoma cells in vitro. These findings come from separate studies. No included study tested whether VDR mediates or modifies the relationship between vitamin D status and UL, so the evidence does not allow conclusions about whether any effect operates through intratumoral signalling, systemic status, or both. Consistent with the observational nature of nearly all included evidence, and with the possibility of reverse causation discussed above, these associations should be interpreted as hypothesis-generating rather than as evidence of a direct causal or therapeutic relationship between vitamin D status and UL risk or progression. The central methodological gap that limits causal inference, is the absence of integrative studies that simultaneously characterise systemic 25(OH)D status, intratumoral VDR expression, CYP24A1 activity, and clinical fibroid outcomes within the same cohort. Future research should therefore prioritise prospective cohort studies with the following design features: (1) vitamin D measurement by LC-MS/MS rather than immunoassay to eliminate inter-assay variability; (2) concurrent tissue collection for VDR immunohistochemistry and *CYP24A1* expression quantification at the time of surgical intervention; (3) pre-specified stratification by fibroid molecular subtype (MED12-mutated vs. wild-type), anatomical location, and fibroid burden; (4) full adjustment for BMI, ethnicity, seasonality, and sun exposure behaviour; (5) a pre-specified sample size calculation based on the effect sizes reported to date, with paired clinical and tissue data; and (6) deliberate recruitment from African and South Asian populations, where UL burden is highest and vitamin D-related genetic and environmental interactions are least well characterised. As a staged roadmap: near-term work should prioritise integrative clinical-tissue cohort studies of the type above; medium-term work should pursue mechanistic validation and, where ethically appropriate, early-phase interventional (RCT) evidence on vitamin D repletion in women with confirmed VDR-attenuated tissue; and only once this evidence base matures should clinical translation into risk-stratification or adjunctive therapeutic use be considered.

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