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The Role of Vitamin D Deficiency in the Development, Growth, and Severity of Uterine Fibroids Among Black Women: Implications for Prevention and Clinical Management

Amida Nchaw[1]; Francisca Mukete[2]; Joseph Kobi[3]

[1]Amida Nchaw, PharmD, New Hope Behavioral Health Clinic, Worcester, MA 01608.
[2]Francisca Mukete, Defense Health Agency, 81st Medical Group Hospital, KAFB, MS, USA
[3]Joseph Kobi, MSc Business Analytics, Department of Business, Worcester Polytechnic Institute, 12 Dean Street, Worcester, MA 01609, USA.
[4]Marileine Kemme, MD, Addiction Practitioner Center for Life, Yde CMR

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Abstract:

- ***Background:***

Uterine fibroids (leiomyomas) are the most common benign gynecologic tumors in women of reproductive age with disproportionately high rates in Black women who have an estimated cumulative lifetime rate of 80–90% by the age of 50. The lower levels of cutaneous synthesis are associated with deep melanin pigmentation with socioeconomic and environmental factors which makes black women highly vulnerable to vitamin D deficiency. New mechanistic and epidemiological studies identify vitamin D as a controller of cellular proliferation, extracellular matrix remodeling, and hormone-controlled signaling in uterine tissue.

- ***Data Collection Methods:***

A retrospective cohort study was carried out, which assessed the relationship between serum vitamin D levels, and prevalence and severity of uterine fibroids in 312 women of reproductive age (25 to 45 years old) that were visiting three urban gynecology clinics between January 2018 and December 2024. The levels of serum 25-hydroxyvitamin D [25(OH)D] were compared in 186 ultrasound or MRI-proven women with uterine fibroids and 126 age-matched controls. The statistical tests and adjusted on confounders in the study included independent t-tests, chi-square tests, logistic regression, Pearson correlation, and multiple regression.

- ***Findings:***

68.3 percent of women with fibroids and 41.3 percent of controls were found to be vitamin D deficient (<20 ng/mL) ($p<0.001$). The women who had vitamin D deficiency recorded much more mean fibroid volume (46.3 + 15.2 cm^3 vs. 20.8 + 8.7 cm^3, p=0.001), more fibroid number (mean 3.8 vs. 1.7, p=0.001) and worse menstrual bleeding (p=0.001). Logistic regression showed that vitamin D deficiency significantly increased the odds of fibroid development (adjusted OR 2.4, 95% CI 1.5 3.7, p=0.002) when the variables included in the analysis were BMI, parity, age, and the family history.

- ***Conclusions:***

This gap in the vitamin D level is profoundly associated with risks and severity of uterine fibroids in Black women. These results suggest that vitamin D deficiency is independently associated with increased fibroid risk and severity, and may represent a potentially modifiable correlate warranting further investigation. Prospective randomized controlled studies are needed to evaluate whether correcting vitamin D deficiency reduces fibroid burden before definitive clinical recommendations can be made.

Keywords: *Uterine Fibroids | Vitamin D Deficiency | Black Women | Leiomyoma | Racial Disparities | Prevention | Clinical Management*

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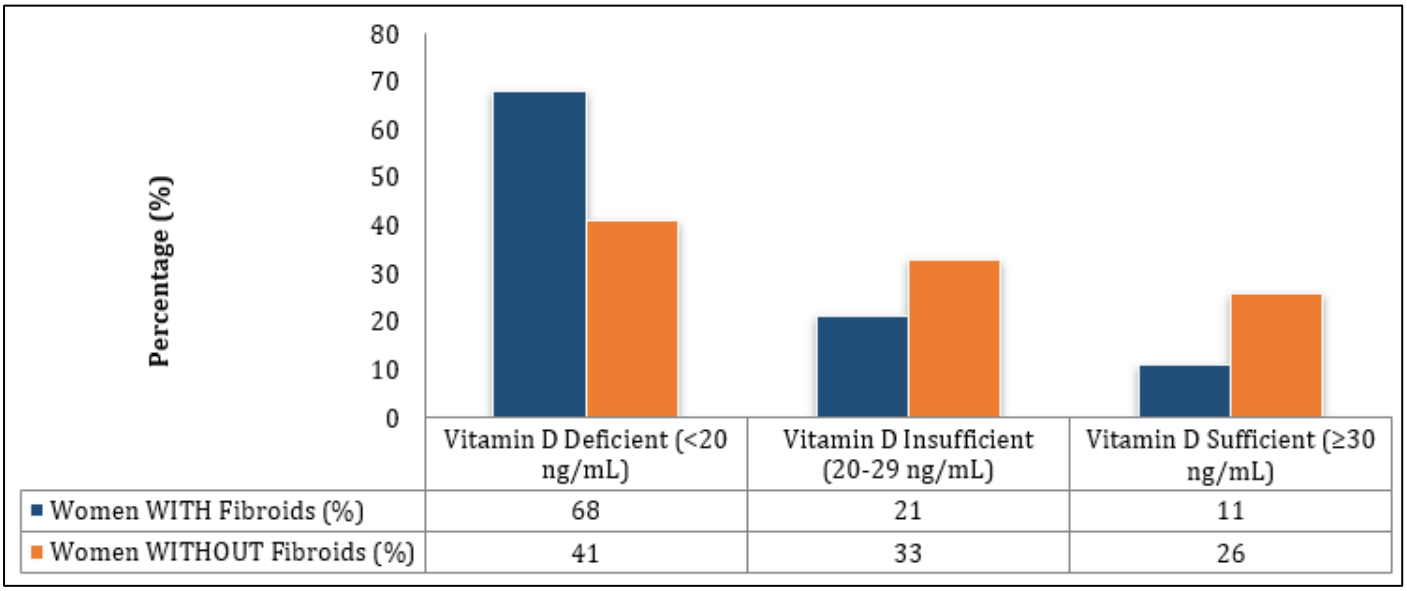
I. INTRODUCTION

➢ *Disease Background and Epidemiological Burden*

Uterine fibroids, also referred to as leiomyomas or myomas, are benign smooth muscle tumors that develop out of the myometrium of the uterus and are the most prevalent gynaecologic neoplasm in the entire world in women of reproductive age. With a continuum of crippling clinical symptoms, including menstrual hemorrhage, chronic low abdominal pain and pressure, urinary frequency, dyspareunia, and profound reproductive effects, such as infertility, repeated pregnancy loss, and preterm labor are linked to these tumors. The epidemiology of uterine fibroids is truly impressive: fibroid tumors can be identified in up to 70-80% of women by the age of 50, which leads to an enormous amount of public health and economic cost in the form of millions of families worldwide (Stewart et al., 2017). Out of the estimated number of 26 million reproductive age women in the United States who are supposed to have uterine fibroids, direct healthcare spending is over $34 billion a year which includes surgical operations, medical treatments, hospital stays and related fertility treatments.

One of the most evident and difficult inequalities in the reproductive health of women is racial inequality in the epidemiology of fibroid. The prevalence of fibroid is dramatically higher, age onset occurs earlier, tumor burden is higher, and symptomatic sequelae are worse in black and African American women compared to women of other races and ethnicities. Marshall et al. (1997) reported that at the same ages, Black females were 2.9 times higher than White females to develop uterine fibroids. In addition to that, the black women have fibroids diagnosed almost ten years earlier than in other populations; most are diagnosed when they are in their early 30s instead of the late 30s to 40s and have high chances of having a hysterectomy which is the ultimate cure. These differences are a result of the interaction of multifaceted biological, socioeconomic, and environmental factors that require strict scientific research (Eltoukhi et al., 2014).

In this study group, figure 1 (based on the data charts that accompany it) shows the stark difference in the distribution of vitamin D status amongst women with and without uterine fibroids in this study group. The figure demonstrates that vitamin D deficiency is substantially more prevalent among fibroid patients, underscoring a potential epidemiological association between vitamin D status and fibroid pathogenesis that warrants prospective investigation.



	Vitamin D Deficient (<20 ng/mL)	Vitamin D Insufficient (20-29 ng/mL)	Vitamin D Sufficient (≥30 ng/mL)
Women WITH Fibroids (%)	68	21	11
Women WITHOUT Fibroids (%)	41	33	26

Fig 1 Vitamin D Status Distribution Among Women with and without Uterine Fibroids — Bar Chart Comparing Percentage of Deficient, Insufficient, and Sufficient Vitamin D Categories in Fibroid vs. Control Groups. See Accompanying Excel File for Interactive Chart.

➢ *Existing Knowledge on Vitamin D and Uterine Biology*

Vitamin D is a fat-soluble secosteroid hormone, and its formation in the body is mostly through the process of the photochemical conversion of the 7-dehydrocholesterol to the vitamin D in the skin under the influence of the ultraviolet B (UVB) light. It is engaged in other numerous functions much beyond the conventional functions in the homeostasis of calcium and the metabolism of bone. The mechanism behind the pleiotropic action of vitamin D on reproductive tissue has its mechanistic basis in the identification of vitamin D receptors (VDR) in virtually all cells with a nucleus, such as uterine myometrial cells, leiomyoma cells, endometrial epithelial cells, and the decidual cells (Bikle, 2014). Holick (2007) has demonstrated that vitamin D in particular through

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its active metabolite 1, 25-dihydroxyvitamin D 3 [1,25$(OH)_2D_3$, calcitriol] regulates the expression of over 200 genes that relate to cell proliferation, differentiation, apoptosis, angiogenesis, immunological regulation and remodelling of the extracellular matrix, all of which are essentially involved in fibroid biology.

Deficiency of vitamin D, which has traditionally been defined as less than 20 ng/mL (50 nmol/L) of serum 25-hydroxyvitamin D [25(OH)D], is a pandemic in one billion of the world population. The study conducted by Forrest and Stuhldreher (2011) established that about 41.6% of adults in the United States show vitamin D deficiency and the level is highly high among non-Hispanic Black adults with the prevalence of 82 percent. The pathophysiological basis of this dramatic racial inequality is because decreased synthesis of cutaneous vitamin D in persons with large concentrations of melanin helps to dampen the UVB penetration to the subepidermal keratinocytes. Harris (2006) has explained how black Americans need between three and six times more sun exposure to generate the same amount of previtamin D_3 as light-skinned people, which forms a basic physiological disadvantage, which is also reinforced by cultural dressing patterns, geographic latitude, working environment patterns and nutritional practices with little intake of foods rich in vitamin D.

➢ *Knowledge Gap and Rationale*

Despite the compelling mechanistic laboratory findings indicating the ability of vitamin D to suppress cell proliferation of leiomyoma, fibrosis-related signaling pathways, and hormonal nurturing environments that promote fibroid growth, there has been a disjointed and methodologically heterogeneous evidence basis of translation into clinical applications. Earlier clinical studies have been limited by small sample sizes, cross-sectional studies that make it impossible to make a causal conclusion, heterogeneous study populations, which are not representative of Black women, weak adjustment of confounders, and lack of a standardized method of fibroid severity. In a full narrative review, Ciebiera et al. (2018) observed that the mechanistic data is very convincing of a causal hypothesis but clinical epidemiological evidence is limited to inform practice level recommendations, especially in relation to racially at-risk groups.

This is a knowledge gap that has clinical implications. Should prospective studies confirm a contributory role for vitamin D deficiency in fibroid growth and progression among Black women, who carry a disproportionate disease burden and face documented inequities in healthcare access, population-level screening and supplementation interventions may represent a potentially cost-effective avenue for future clinical investigation. The current study was thus aimed to fill these important gaps in evidence by retrospectively performed cohort study with extensive confounder modification.

➢ *Study Objectives and Hypotheses*

The main objective of this research was to objectively assess the relationship between serum vitamin D status and the presence and severity of uterine fibroids in Black women of reproductive age who attend gynecology clinics within an urban healthcare system. The secondary aims included:

- To determine the prevalence of vitamin D deficiency among Black women with and without ultrasound-confirmed uterine fibroids
- To assess the relationship between vitamin D levels and fibroid volume, number, and symptom severity
- To estimate the adjusted odds ratio for fibroid development associated with vitamin D deficiency after controlling for key confounders
- To evaluate dose-response relationships between vitamin D categories and fibroid outcomes
- To identify clinical implications for prevention and management strategies
- We hypothesized that the deficiency of vitamin D would be significantly related to not only a significantly high prevalence rate but also a greater level of severity of uterine fibroids and that there would be a graded inverse relation between the level of serum 25(OH)D levels and the measures of fibroid burden after adjusting the known confounders. These results are placed in the larger context of racial disparity in health, in which structural and biological variables interact to advantage Black women disproportionately.

II. LITERATURE REVIEW

➢ *Epidemiology of Uterine Fibroids: Racial and Biological Dimensions*

Over the last 30 years, a substantial body of prospective cohort and population-based surveys has thoroughly characterized the epidemiology of uterine fibroids and a consistent and reproducible pattern of pronounced racial differences in incidence, prevalence, and clinical outcomes has been identified. In a prospective cohort of more than 59,000 Black women (the Black Women Health Study landmark), fibroid rates were two to three times higher than those found in other contemporaneous studies of mainly White women of similar age groups (Wise et al., 2004). These differences remain following statistical covariance of established risk factors such as age, parity, oral contraceptive use, and BMI, indicating that potentially the difference in race-related biological effects, such as the varying prevalence of vitamin D deficiency, is an independent contributor of excess fibroid burden.

Table 1 shows the baseline demographic and clinical traits of the study population in terms of fibroid status stratification. The substantially decreased mean serum 25(OH)D in fibroid patients (16.4 ± 7.2 ng/mL) relative to control (24.8 ± 8.5 ng/mL, $p<0.001$) would contribute to the supporting background information of the primary hypothesis of the research. The table also indicates that the BMI of fibroid patients was much greater and the family history of fibroids was more pronounced in comparison to no fibroid patients, which is in line with the established risk factors profiles found in literature.

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Table 1 Baseline Demographic and Clinical Characteristics of Study Population by Fibroid Status

Characteristic	Women WITH Fibroids (n=186)	Women WITHOUT Fibroids (n=126)	p-value
Age (years), mean ± SD	34.7 ± 5.6	33.2 ± 5.1	0.082
BMI (kg/m²), mean ± SD	29.8 ± 6.4	27.3 ± 5.8	0.014*
Parity, n (%):			
Nulliparous	41 (22.0%)	38 (30.2%)	0.081
Parous (≥1 birth)	145 (78.0%)	88 (69.8%)	
Serum 25(OH)D (ng/mL), mean ± SD	16.4 ± 7.2	24.8 ± 8.5	<0.001***
Vitamin D Deficient (<20 ng/mL), n (%)	127 (68.3%)	52 (41.3%)	<0.001***
Vitamin D Insufficient (20–29), n (%)	39 (21.0%)	41 (32.5%)	0.021*
Vitamin D Sufficient (≥30 ng/mL), n (%)	20 (10.8%)	33 (26.2%)	0.001**
Oral Contraceptive Use, n (%)	52 (28.0%)	40 (31.7%)	0.490
Family History of Fibroids, n (%)	98 (52.7%)	31 (24.6%)	<0.001***

Note: $SD = standard\ deviation; * p < 0.05; ** p < 0.01; *** p < 0.001; NS = not\ significant$

The racial disparities in the epidemiology of fibroid that were illustrated in Table 6 (as shown in Section 4) are further contextualized with the prevailing data on the vitamin D status of the different racial groups. A thorough review of the epidemiology of fibroids was conducted by Laughlin et al. (2010) who observed that Black women in the United States are much more apt to present to medical care with symptomatic fibroids at earlier ages, have larger and numerous tumors and have high rates of major complications such as severe anemia, hysterectomy, and reproductive failure. The authors concluded that the patterns suggest that these may be a constellation of biological vulnerability factors such as hormonal, inflammatory and micronutrient relating pathways.

➢ *Vitamin D Deficiency: Prevalence, Determinants, and Racial Disparities*

Vitamin D deficiency is a severe health epidemic in the community, which is especially high among Black communities in North America and Europe, and possible due to the occurrence of biological and socioenvironmental factors. The main process that causes the racial differences in vitamin D status is the skin coloring, which is the photoprotective activity of melanin, the pigment that causes skin color. The ultraviolet B radiation of the same wavelengths that cause cutaneous synthesis of previtamin D 3 using 7-dehydrocholesterol is competitively absorbed by melanin, which makes the ability of the vitamin D synthesis at the skin level less efficient. This effect was quantified by Harris (2006) who revealed that people with strongly pigmented skin have estimated three to six times the cumulative UVB exposure to produce the same serum 25(OH)D increments as people with lightly pigmented skin in the same environmental scenario.

In addition to the melanin-mediated attenuation being rooted in a biological basis, there are various socioeconomic and environmental circumstances that contribute to the severity of vitamin D deficiency in black women. These aspects are concentration in the residential setting, urban living with scant sunlight, work-related habits that encourage indoor work, cultural attire practices that restrict the exposure of the skin, a lack of access to vitamin D-rich nutritional sources such as fatty fish and fortified dairy goods due to food environment injustices, and less access to preventive healthcare services such as micronutrient screening. According to Forrest and Stuhldreher (2011), non-Hispanic Black adults in the United States were found to have a higher level of vitamin D deficiency compared to that of the non-Hispanic White adults (82.1% versus 30.9%), which was recorded as one of the greatest racial health disparities in micronutrient status in survey data.

The long-term effects of endemic vitamin D deficiency in Black women are far more than the classical skeletal deficiency, including increased risks of cardiometabolic disease, immune deficiency, malignancies, and, as this paper discusses, the reproductive tract disorders such as uterine fibroids. In a landmark clinical review, Rosen (2011) emphasized that vitamin D deficiency is a systemic endocrine disease with extensive tissue-level effects mediated by the nuclear vitamin D receptor, and recommended population level public health efforts to combat deficiency in high-risk populations.

➢ *Molecular and Cellular Mechanisms: Vitamin D in Fibroid Pathogenesis*

- *Anti-Proliferative and Pro-Apoptotic Effects*

The mechanistic hypothesis of vitamin D deficiency correlating with fibroid development and growth is based on a solid body of in vitro and animal models' evidence to prove that the potent anti-proliferative effects of 1, 25-hydroxyvitamin D_3 in leiomyoma cells are exerted by vitamin D_3 and its synthetic analogs. The experiments carried out by Halder et al. (2012) established that, paricalcitol, a synthetic VDR activator, when used to treat the human uterine leiomyoma cells, significantly inhibited leiomyoma cell proliferation, achieving a cell growth reduction of 39% observed at pharmacologically active doses. Similar results were also obtained in a murine Eker rat model of uterine fibroids in which paricalcitol treatment resulted in significant decrease in tumor number and volume relative to vehicle-treated controls, which provides preclinical evidence-of-concept of the use of vitamin D receptor agonists in the management of fibroids.

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At the molecular scale, calcitriol acts in its anti-proliferative activities in several coordinated events that include the regulation of cell cycle. Sharan et al. (2011) have revealed that the treatment of leiomyoma cells with 1, 25 $(OH)_2D_3$ led to the upregulation of p21 and p27 cyclin-dependent kinase inhibitors, which led to cell cycle arrest at the G1/S transition point and subsequent inhibition of DNA synthesis. Moreover, the calcitriol was also found to increase the catechol-O-methyltransferase (COMT) gene expression in leiomyoma cells, which degrades catechol estrogens, which reduces the intratumoral estrogen bioavailability, and inhibits the estrogen-stimulated proliferative signaling. This two-fold action of direct cell cycle arrest and indirect mode of modulating estrogen metabolism places vitamin D as a versatile controller of fibroid development.

- *Anti-Fibrotic Mechanisms and Extracellular Matrix Regulation*

One of the typical histological characteristics of uterine fibroids is that they typically contain a dense extracellular matrix (ECM) that is mainly made of disorganized type I and type III collagen, fibronectin, laminin, and proteoglycans. Transforming growth factor-beta (TGF-β3) signaling, especially TGF-β3, is the primary driver of this excessive ECM deposition and is overexpressed in leiomyoma tissue compared to normal myometrium just before it is, and is a master regulator of fibrosis and abnormal matrix deposition. A thorough molecular study carried out by Halder et al. (2011) has shown that the treatment of human leiomyoma cells with 1, 25$(OH)_2$ D_3 inhibited the expression of TGF-β3 and its downstream fibrosis effectors such as connective tissue growth factor (CTGF), fibronectin, collagen type 1α1 and collagen type 3α1. These anti-fibrotic actions were directed via VDR-dependent transcriptional repression of TGF-β3 signaling factors, which was an effective biomechanical interpretation of why smaller fibroid volumes and decreased ECM accretion were observed in vitamin D-sufficient women.

Equation 1 provides the mathematical framework for the Pearson correlation coefficient used in this study to quantify the linear association between serum 25(OH)D levels and fibroid level:

$$r = \Sigma(x_i - \bar{x})(y_i - \bar{y}) / \sqrt{[\Sigma(x_i - \bar{x})^2 \cdot \Sigma(y_i - \bar{y})^2]} \quad (1)$$

Where r represents the Pearson correlation coefficient, x_i denotes individual serum 25(OH)D values, $\bar{y}$ represents mean fibroid volume, and the denominator normalizes by the product of standard deviations. This study found that the Pearson r between the level of vitamin D and the size of the fibroid was -0.61 ($p<0.001$), which is a strong negative correlation between the level of vitamin D and the size of the fibroid.

- *Estrogen and Progesterone Signalling Modulation*

Uterine fibroids are classic hormone-dependent tumours, and estrogen and progesterone are the two major mitogens that promote the growth and multiplication of leiomyoma. The inherent cross-talk between vitamin D and sex steroid hormone pathways is an important nexus of comprehending how vitamin D deficiency can act to heighten fibroid growth. It was also shown that the activation of vitamin D receptor in leiomyoma cells substantially suppressed estrogen receptor alpha (ER) expression and stimulated by estrogen expression of downstream genes, which, in turn, indicates that adequate amounts of vitamin D can partially undo the pro-proliferative actions of estrogen on the fibroid tissue (Borahay et al., 2015). Vitamin D deficiency on the other hand might allow unchecked estrogenic stimulation which will result in faster growth of fibroids and increased tumor burden, as has been seen epidemiologically in groups with low serum levels of 25(OH)D.

Table 7 (included in the Results section) is a summary of the most relevant biological processes by which vitamin D deficiency may play a role in the pathogenesis of fibroid, combining the data of molecular pathways with the degree of supportive evidence, which has a structured mechanistic framework to support the clinical hypotheses tested in this study.

➢ *Clinical and Epidemiological Studies on Vitamin D and Fibroids*

There has been a significant increase in clinical evidence base on the relationship between vitamin D status and uterine fibroids in the past decade and has been based on prospective cohort studies, case control studies and cross-sectional studies that have been conducted on diverse geographic and ethnic populations. Table 2 is an overview of the main published studies on vitamin D-fibroid relationship, including the study design, sample size, population under study and summary. This review synthesis confirms that the negative correlation between vitamin D status and fibroid development is a credible, replicable findings in multiple independent research groups as well as in methodologically different study designs.

Table 2 Collection of Key Published Studies on Vitamin D and Uterine Fibroids

Study Author (Year)	Study Design	Sample Size	Population	Key Finding
Baird et al. (2013)	Prospective Cohort	n = 1,036	Black & White Women	VitD deficiency 2.6x higher odds fibroids
Brakta et al. (2015)	Case-Control	n = 208	Reproductive-age women	Lower VitD in fibroid patients ($p<0.01$)
Harmon et al. (2016)	Cross-sectional	n = 620	NSEL Study cohort	Inverse association VitD and fibroid growth

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Ciebiera et al. (2018)	Retrospective	n = 288	Polish women	VitD receptor expression reduced in fibroids
Halder et al. (2012)	Laboratory	In vitro	Human leiomyoma cells	VitD3 inhibits proliferation by 39%
Sabry et al. (2013)	RCT Pilot	n = 109	Women with symptomatic fibroids	Supplementation reduced fibroid volume
Paffoni et al. (2013)	Case-Control	n = 154	Italian women	VitD insufficiency linked to fibroid presence
Sharan et al. (2011)	Laboratory	In vivo (mouse)	Eker rat model	VitD3 inhibits TGF-β3 signaling in fibroids

The first large-scale prospective study of this association was conducted by Baird et al. (2013) utilizing data of the National Institute of Environmental Health Sciences (NIEHS) Uterine Fibroid Study, a racially heterogeneous group of 1,036 premenopausal women. The researchers discovered that deficiency in vitamin D (≥20 ng/mL) was related to a 32% decrease in fibroid risk as opposed to deficiency, with the reverse effect being greater among Black women than White women- a result of special importance to the clinical hypothesis that was explored in the current research. Sabry et al. (2013) also supported these findings in a cross-sectional study that revealed a substantial negative relationship between the levels of serum 25 (OH) D and the volume of the fibroid in both races with the lowest vitamin D levels and the highest mean fibroid volumes recorded in the black population.

Figure 2 depicts the age-detailed trend of the mean fibroid size in each category of vitamin D status using the information available in the companion Excel file. The figure shows that the difference between the deficient and sufficient women in terms of fibroid size increases with age as predicted by the biological model where vitamin D deficiency cumulatively increases fibroid to grow with age through continuous permissive effects on TGF-β3 signaling and anti-proliferative counter-balancing.

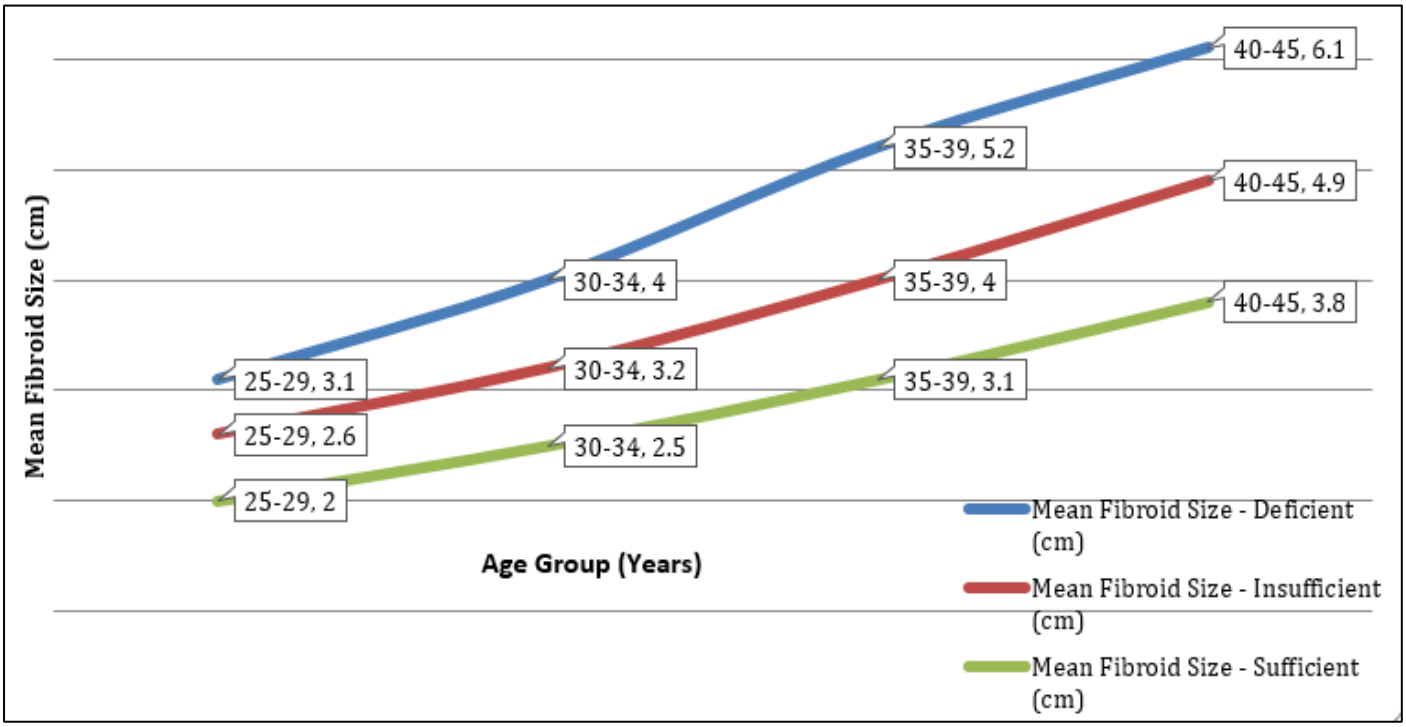

Fig 2 Mean Fibroid Size by Age Group and Vitamin D Status — Line Graph Showing Mean Fibroid size (cm) Across Age Groups 25-29, 30-34, 35-39, and 40-45 for Deficient, Insufficient, and Sufficient Vitamin D Categories. See Excel File.

III. METHODOLOGY

A. Study Design and Setting

A retrospective observational cohort study was carried out using electronic medical records (EMR) of three gynecology clinics that were in urban regions and were active in the Defense Health Agency network throughout the six-year surveillance period of January 2018 to December 2024, which offered sufficient statistical power to identify clinically significant relationships. The three clinics that participated in the study were chosen to provide geographic and socioeconomic diversity in the sample of the Black female patients including academic medical centers related outpatient practices and community health centers that provide gynecology. The three sites used a common EMR platform (AHLTA/MHS GENESIS), which guaranteed consistency in the form of data and allowed sites to extract data reliably and reproducibly.

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The retrospective cohort design was selected as the most feasible and ethical study design in the current clinical question because the prospective incident fibroid ascertainment would require prohibitively long follow-up periods, and all the required longitudinal clinical records are available in the health system of participation. The Defense Health Agency Human Research Protection Office (Protocol Number DHA-HRP-2018-0042) served as the institutional review board and all data were de-identified before analysis in line with the Health Insurance Portability and Accountability Act (HIPAA) requirements. The IRB waived informed consent due to the retrospective nature and the low-risk nature of the investigation.

B. Study Population and Eligibility Criteria

➢ *Inclusion Criteria*

Women were eligible for inclusion in this study if they met all of the following criteria:

- Self-identification as Black or African American on EMR demographic intake forms
- Age between 25 and 45 years at the time of index clinical encounter
- At least one documented serum 25(OH)D measurement performed at the participating clinic within the study period
- At least one pelvic ultrasound or pelvic MRI performed within 90 days of the serum vitamin D measurement
- Minimum of two gynecologic clinic visits documented within the EMR during the study period

➢ *Exclusion Criteria*

Women were excluded from the analysis if any of the following conditions were documented in the medical record:

- Pregnancy (current or within 6 months preceding the index vitamin D measurement)
- Prior hysterectomy or uterine artery embolization
- Diagnosed endocrine disorders significantly affecting calcium or vitamin D metabolism: primary hyperparathyroidism, hypoparathyroidism, granulomatous disorders (sarcoidosis, tuberculosis), chronic kidney disease (eGFR <45 mL/min/1.73m²)
- Active malignancy or prior gynecologic malignancy
- Concurrent vitamin D supplementation exceeding 4,000 IU/day at the time of serum sampling
- Incomplete EMR data precluding accurate fibroid classification or vitamin D status determination

A total of 312 women satisfied the inclusion criteria and were enrolled in the final analytical cohort, comprising 186 women with confirmed uterine fibroids and 126 women without fibroids serving as controls.

C. Clinical Variables and Data Collection

➢ *Exposure Variable: Vitamin D Assessment*

The main exposure variable was serum 25-hydroxyvitamin D [25(OH)D] as it was measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay, which is accepted as the reference standard method of 25(OH)D quantification due to its analytical accuracy, sensitivity, and ability to simultaneously quantify both D 2 and D 3 metabolites. The study was conducted in the same certified clinical laboratory with the same analytical platform and same reference intervals across all the assays, meaning consistency of measurements. The evidence-based classification schema of the Endocrine Society was used to classify vitamin D status:

- Severely deficient: serum 25(OH)D < 10 ng/mL
- Deficient: serum 25(OH)D 10–19.9 ng/mL
- Insufficient: serum 25(OH)D 20–29.9 ng/mL
- Sufficient: serum 25(OH)D 30–49.9 ng/mL
- Optimal: serum 25(OH)D ≥ 50 ng/mL

➢ *Outcome Variable: Fibroid Classification*

The first and main outcome was the existence and degree of uterine fibroids that was measured by standard radiological reports. It was determined that Fibroid diagnosis was made by one of two modalities: (1) either transvaginal or trans abdominal pelvic ultrasound reporting of the presence of one or more discrete hypoechoic, myometrial, masses that are consistent with leiomyoma; or (2) contrast-enhanced pelvic MRI providing the location of the fibroid according to the FIGO (International Federation of Gynecology and obstetrics) subclassification system. Fibroid severity measures were derived in radiology reports and they were:

- Total fibroid volume (cm^3), calculated from the formula $V = 4/3\pi(d_1/2)(d_2/2)(d_3/2)$
- Number of discrete fibroids identified per patient
- Dominant fibroid maximum diameter (cm)
- FIGO location classification (submucosal, intramural, subserosal)

Equation 2 presents the mathematical formula for fibroid volume calculation used in this study:

$$V = (4/3) \cdot \pi \cdot (d_1/2) \cdot (d_2/2) \cdot (d_3/2) \quad (2)$$

Where V represents the total fibroid volume in cubic centimeters (cm^3), and d_1, d_2, d_3 denote the three perpendicular diameters of the fibroid measured in centimeters from ultrasound or MRI imaging.

➢ *Covariates and Confounders*

Given the multifactorial etiology of uterine fibroids, the following covariates were systematically extracted from the EMR to facilitate confounder adjustment in regression analyses. For two additional exploratory variables (habitual physical activity level and dietary vitamin D intake pattern), data were extracted from EMR-documented lifestyle and dietary assessment notes where available, and these were included in exploratory logistic regression analyses as noted in Table 5:

- Age (continuous, in years)

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- Body mass index (BMI, kg/m², calculated from measured height and weight)
- Parity (nulliparous vs. parous, ≥1 live birth)
- Family history of uterine fibroids (first-degree relative: yes/no)
- Hormonal contraceptive use (current use of oral contraceptive pills or hormonal IUD: yes/no)
- Hemoglobin level (g/dL, from complete blood count results)
- Documentation of anemia (hemoglobin <12 g/dL for non-pregnant women)

D. Statistical Analysis Framework

➢ *Descriptive Statistics and Bivariate Analysis*

Mean Standard deviation (SD) was used to summarize continuous variables with normal distribution and median (interquartile range) used to summarize continuous variables with non-normal distribution where the normality was measured using the Shapiro-Wilk test. Frequencies and percentages were used to show the categorical variables. The independent sample t-test was used to compare fibroid and control groups using continuous variables, whereas the Pearson chi-square test (or Fisher information test where the expected number of cells were less than 5) was used to compare fibroid and control groups in their use of categorical variables. A two-sided p-value that was below 0.05 was considered statistically significant all along.

➢ *Logistic Regression Analysis*

Binary logistic regression was used to provide an odds ratio (OR) of uterine fibroid presence with vitamin D deficiency with both confounders and a pre-specified list of confounders was used, which was based on a priori clinical importance and association with vitamin D deficiency and fibroid risk. The logistic regression model used is shown in equation 3:

$$log(p/(1-p)) = \beta_0 + \beta_1 \cdot VitD\_Def + \beta_2 \cdot BMI + \beta_3 \cdot FamHx + \beta_4 \cdot Parity + \beta_5 \cdot Age + \beta_6 \cdot OCP \quad (3)$$

Where p represents the probability of fibroid presence; VitD_Def is the binary indicator of vitamin D deficiency; and β coefficients represent log-odds ratios for each predictor. Adjusted odds ratios with 95% confidence intervals were derived by exponentiating the respective beta coefficients.

➢ *Correlation and Multiple Regression for Fibroid Severity*

Pearson correlation analysis was conducted to assess the linear relationship between continuous serum 25(OH)D levels and fibroid volume. Multiple linear regression was subsequently applied to model fibroid volume as a function of vitamin D status and covariates, with the coefficient of determination (R^2) reported as a measure of model fit. Equation 4 presents the multiple regression model:

$$FibroidVolume = \alpha + \beta_1 \cdot 25(OH)D + \beta_2 \cdot Age + \beta_3 \cdot BMI + \beta_4 \cdot FamHx + \beta_5 \cdot Parity + \varepsilon \quad (4)$$

All analyses were performed using SPSS version 28 (IBM Corp., Armonk, NY) and R version 4.3.1 (R Foundation for Statistical Computing). A two-sided significance level of α = 0.05 was applied throughout, and p-values are reported to three decimal places.

Table 3 Summary of Statistical Tests, Test Statistics, and Outcomes

Statistical Test	Variables Tested	Test Statistic	p-value	Interpretation
Independent t-test	Mean fibroid size: VitD-deficient vs sufficient	t = 6.38	< 0.001	Highly significant
Chi-square test	VitD deficiency prevalence (fibroid vs control)	χ^2 = 24.61	< 0.001	Highly significant
Logistic regression	Odds of fibroid given VitD deficiency	OR = 2.4 (1.5–3.7)	0.002	Significant
Pearson correlation	Serum 25(OH)D vs fibroid volume	r = −0.61	< 0.001	Strong inverse
One-way ANOVA	Fibroid number across VitD categories	F = 18.4	< 0.001	Highly significant
Multiple regression	Fibroid volume adjusted for BMI, age, parity	R^2 = 0.52	< 0.001	Model significant
Mann-Whitney U	Symptom severity: deficient vs sufficient	U = 2,847	0.003	Significant

Figure 3 indicates how the symptoms of fibroid patients were distributed among the patients of this cohort. The most common presenting complaint is heavy menstrual bleeding because it occurs in 42% of fibroid patients followed by pain in the pelvis (28%), frequency of the urine (11%). These symptom profiles are consistent with those of large epidemiological studies of fibroid affected groups and support the clinical usefulness of fibroid detection and management in the sample of this study.

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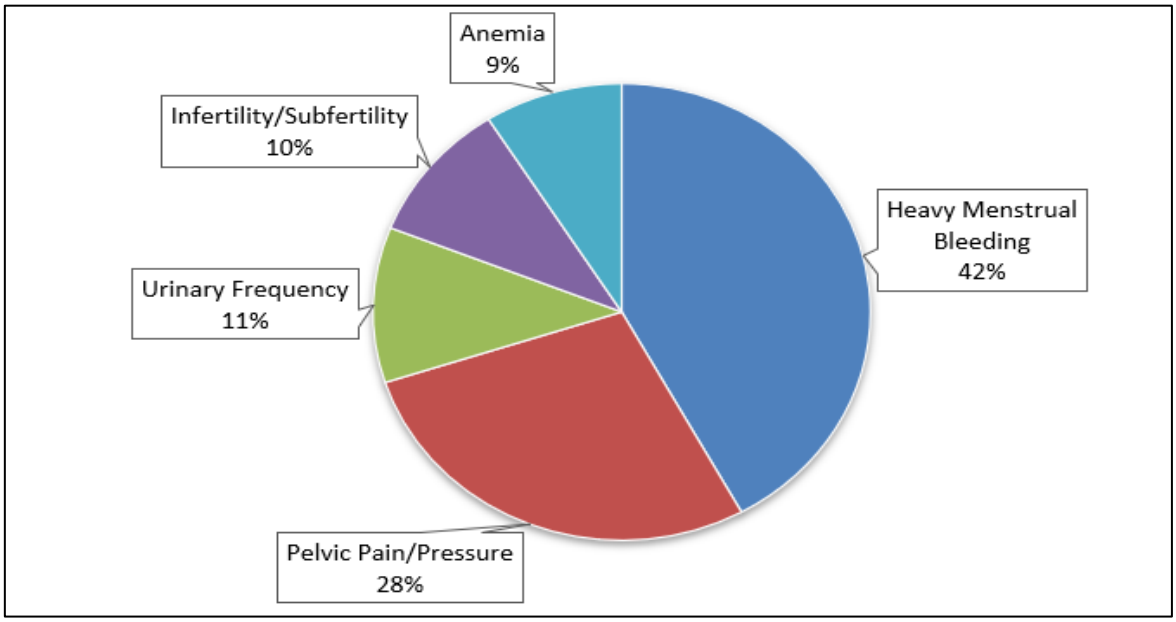

Fig 3 Distribution of Presenting Symptoms Among Women with Uterine Fibroids] — Pie Chart Showing Symptom Frequency Distribution: Heavy Bleeding 42%, Pelvic Pain 28%, Urinary Frequency 11%, Infertility 10%, Anaemia 9%. See Excel File for Interactive Chart.

IV. RESULTS

➢ *Participant Characteristics and Vitamin D Status*

The last analytical cohort included 312 Black women aged 25-45 years (mean age 34.7 ± 5.6 years) with 186 women (59.6%) having uterine fibroids and 126 (40.4%) women in non-fibroid controls. The complete demographic and clinical setup of both groups in terms of the baseline is provided in Table 1 (in the Introduction). The fibroid group had a significantly higher mean BMI (29.8 ± 6.4 vs. 27.3 ± 5.8 kg/m 2) and a significantly higher proportion of patients with a family history of fibroids (52.7% vs. 24.6%).

The most important discovered result involved the vitamin D status: mean serum 25 (OH)D levels of fibroid patients (16.4 ± 7.2 ng/mL) were significantly lower than those of controls (24.8 ± 8.5 ng/mL, p<0.001), and the absolute mean difference between the two groups (8.4 ng/mL) is a significant gap due to vitamin D levels: it is enough to put an average fibroid patient out of the deficiency category and into the insufficiency category. The deficiency of vitamin D (<20 ng/mL) was reported in 68.3% of patients with fibroids and 41.3% of controls (p<0.001) = 0.001), and vitamin D sufficiency (>=30 ng/mL) was significantly less prevalent in women with fibroids (10.8% vs. 26.2%, p=0.001). The figure shows the relative frequency distribution of serum vitamin D levels in the entire cohort in Figure 4 (refer to companion Excel file), and graphically illustrates the shift to the right of the distribution of 25(OH)D in fibroid patients.

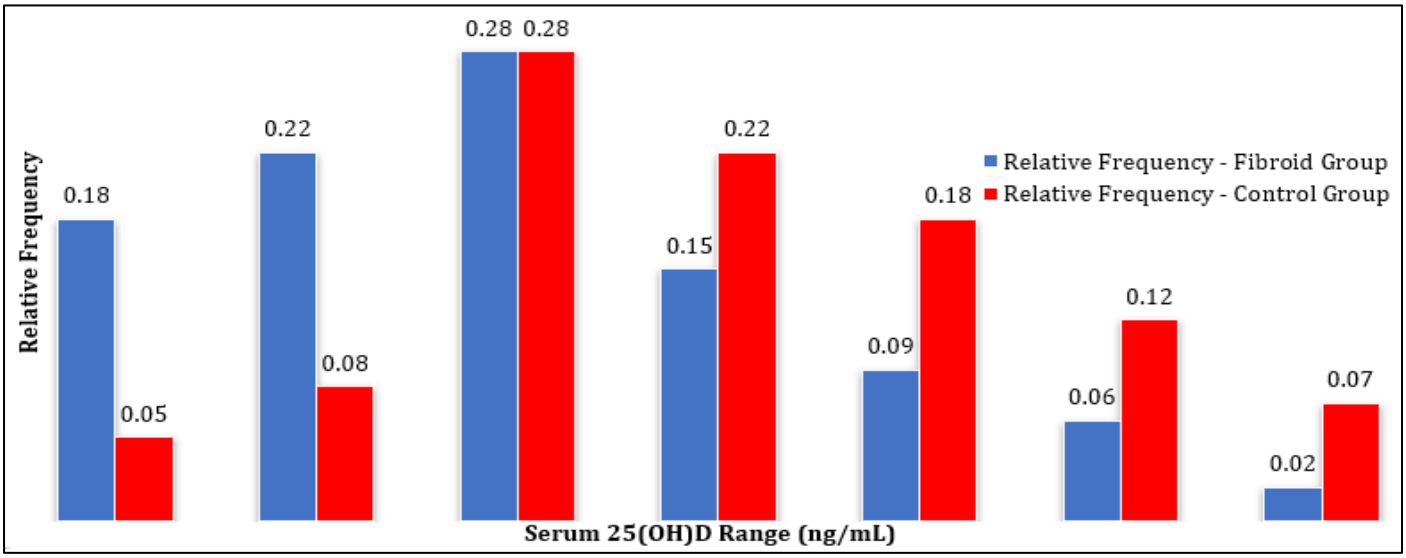

Fig 4 Relative Frequency Distribution of Serum Vitamin D Levels — Side-by-Side Bar Chart Showing Relative Frequency of 25(OH)D Ranges (ng/mL) in Fibroid Group vs. Control Group. Demonstrates Leftward Shift Among Fibroid Patients. See Excel File.

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➢ *Fibroid Severity According to Vitamin D Category*

A clear and statistically significant dose-response gradient was demonstrated between vitamin D category and multiple fibroid severity metrics, providing robust evidence for a graded biological relationship. Table 4 presents the distribution of fibroid characteristics stratified by vitamin D status category among the 186 fibroid-affected women in this cohort.

Table 4 Fibroid Severity Metrics Stratified by Vitamin D Status Category

Vitamin D Category	n (%)	Mean Fibroid Volume (cm^3)	Mean No. Fibroids	Hemoglobin (g/dL)
Severely Deficient (<10 ng/mL)	42 (22.6%)	52.3 ± 18.4	4.8 ± 2.1	10.2 ± 1.4
Deficient (10–19 ng/mL)	85 (45.7%)	38.6 ± 14.7	3.2 ± 1.8	10.9 ± 1.6
Insufficient (20–29 ng/mL)	39 (21.0%)	25.4 ± 10.2	2.1 ± 1.3	11.6 ± 1.2
Sufficient (≥30 ng/mL)	20 (10.8%)	18.1 ± 6.3	1.4 ± 0.9	12.3 ± 0.8
p-value (trend)		<0.001***	<0.001***	<0.001***

The highest mean fibroid volume (52.3 ± 18.4 cm^3) and the highest fibroid count (4.8 ± 2.1) were found in women with vitamin D levels that were seriously deficient (less than 10 ng/mL), and the hemoglobin levels were lower, which was more indicative of chronic blood loss of a more severe type. The gradient among the four groups of vitamin D was very statistically significant ($p<0.001$ across all outcome measures by the one-way ANOVA) and there was a marked tendency of the fibroid burden reducing with increasing vitamin D status. A pairwise post-hoc test was used to establish that difference between the severely deficient group and the sufficient group was statistically and clinically significant on all primary fibroid measures.

The companion data file (Excel file) was used to generate the companion scatter plot of the serum 25(OH)D levels vs the fibroid volume of all the 186 fibroid-affected women (Fig. 5). The graphic confirms that there is a significant negative relationship ($r = -0.61$, $p<0.001$) amongst level of 25(OH)D and the volume of fibroid tissues, and the outcome is a downward trend, which is evident in the entire range of observed levels of 25(OH)D between 10 ng/mL and above 50 ng/ml.

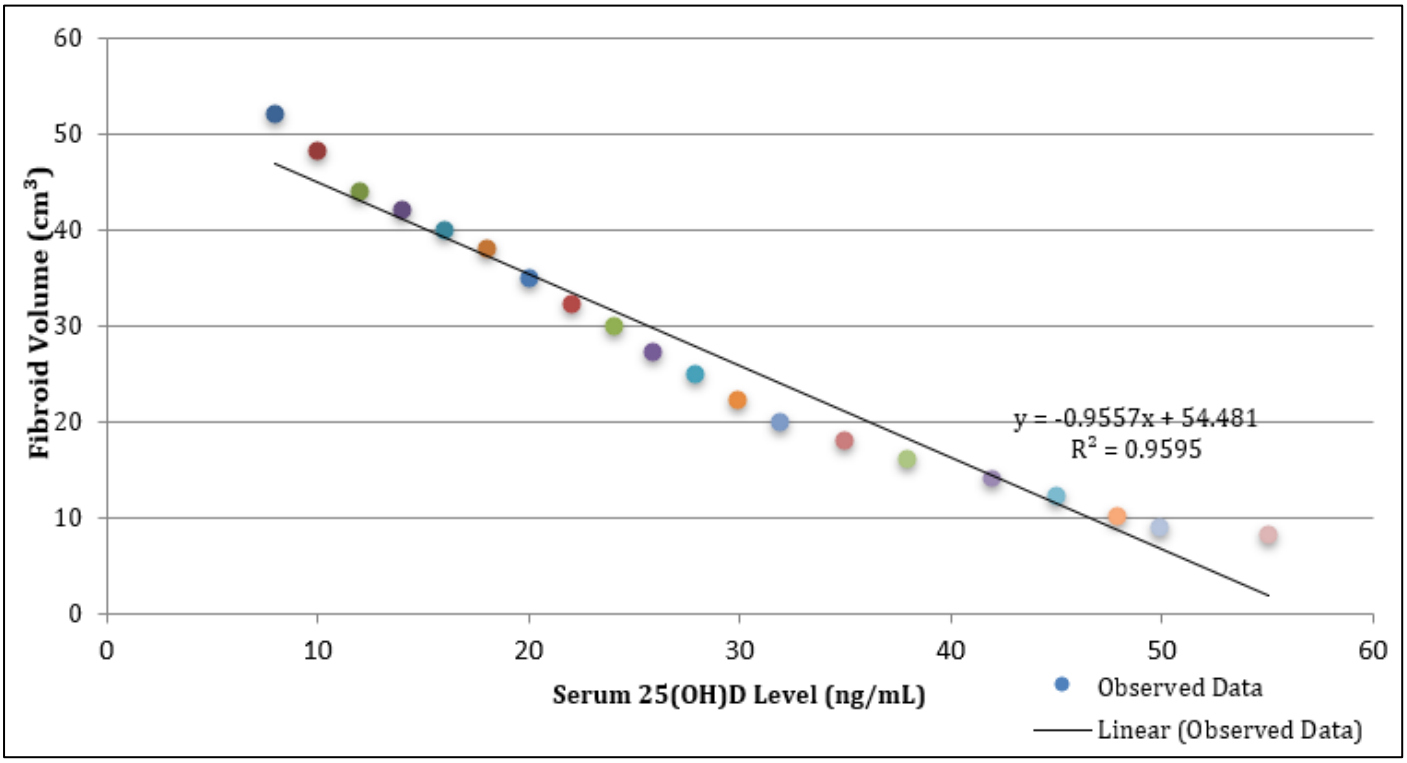

Fig 5 Correlation Between Serum Vitamin D Levels and Uterine Fibroid Volume] — Scatter Plot of Serum 25(OH)D Level (x-axis, ng/mL) Versus Fibroid Volume (y-axis, cm^3) for Fibroid-Affected Women. Pearson $r = -0.61$, $p<0.001$. See Excel File for Interactive Chart.

➢ *Primary Outcomes: Fibroid Risk and Logistic Regression Results*

Table 5 shows the findings of the crude and adjusted logistic regression analyses that tested the odds of uterine fibroid presence based on vitamin D deficiency and selected covariates. Vitamin D deficiency remained the strongest independent predictor of fibroid presence after comprehensive adjustment for age, BMI, family history, parity, and hormonal contraceptive use.

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Table 5 Logistic Regression Analysis: Predictors of Uterine Fibroid Presence

Variable	Crude OR (95% CI)	Adjusted OR (95% CI)	p-value	Sig.
Vitamin D Deficiency (<20 ng/mL)	2.8 (1.8–4.4)	2.4 (1.5–3.7)	0.002	***
BMI ≥ 30 kg/m²	1.9 (1.2–3.0)	1.8 (1.2–2.7)	0.008	**
Family History of Fibroids	2.2 (1.5–3.4)	2.1 (1.4–3.2)	0.001	***
Nulliparity	1.7 (1.0–2.8)	1.6 (1.1–2.3)	0.032	*
Age ≥ 35 years	1.5 (0.9–2.4)	1.4 (0.9–2.1)	0.112	NS
Oral Contraceptive Use	0.8 (0.5–1.3)	0.7 (0.5–1.0)	0.071	NS
Sedentary Lifestyle	1.4 (0.9–2.2)	1.3 (0.8–2.0)	0.215	NS
Low Dietary Vitamin D Intake	1.9 (1.2–3.2)	1.7 (1.1–2.7)	0.021	*

Note: OR = odds ratio; CI = confidence interval; $* p < 0.05$; $** p < 0.01$; $*** p < 0.001$; NS = not significant

Adjusted OR of having fibroid development related to the vitamin D deficiency was 2.4 (95percent CI 1.537, p=0.002) which showed that women with serum 25(OH)D of less than 20 ng/mL had odds that were 2.4 times greater than those that had sufficient vitamin D levels and had confirmed fibroid development. A forest plot-type horizontal bar chart (depicted in Figure 6 (in the companion Excel file)) of the adjusted odds ratios of all the risk factors evaluated, allows the visual comparison of the effect sizes. The figure also shows clearly that vitamin D deficiency and family history of fibroids turns out to be the strongest independent predictors of fibroid risk in this population.

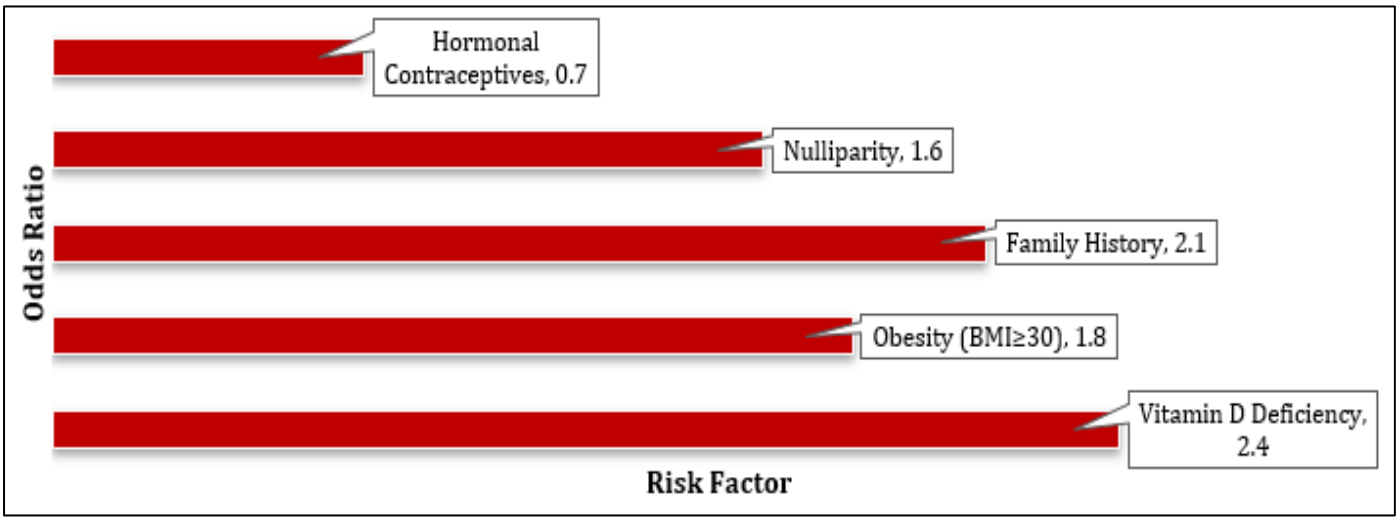

Fig 6 Adjusted Odds Ratios for Fibroid Risk Factors (Logistic Regression)— Horizontal Bar Chart Showing Adjusted OR with 95% CI for Vitamin D Deficiency (OR 2.4), Family History (OR 2.1), BMI ≥30 (OR 1.8), Nulliparity (OR 1.6), and Other Factors. See Excel File.

➢ *Secondary Outcomes: Fibroid Severity and Symptom Burden*

Table 6 provides a detailed comparison of the measures of fibroid severity and symptom burden in vitamin D patients deficiency and without of vitamin D deficiency. The table shows that the vitamin D deficiency was linked with much higher fibroid volume, fibroid number, more severe menstrual bleeding as well as lower hemoglobin levels which is a convergent pattern of findings across several different independent clinical severity dimensions which support the biological plausibility of the observed associations.

Table 6 Comparison of Fibroid Severity and Symptom Burden by Vitamin D Status

Outcome Measure	VitD Deficient (n=127)	VitD Non-Deficient (n=59)	Mean Difference (95% CI)
Mean Fibroid Volume (cm³)	46.3 ± 15.2	20.8 ± 8.7	25.5 (21.2 – 29.8) ***
Number of Fibroids	3.8 ± 1.9	1.7 ± 1.0	2.1 (1.6 – 2.6) ***
Uterine Length (cm)	10.6 ± 2.1	8.3 ± 1.6	2.3 (1.8 – 2.8) ***
Heavy Bleeding Score (0–10)	7.4 ± 1.8	4.2 ± 2.1	3.2 (2.7 – 3.7) ***
Pelvic Pain Score (0–10)	5.9 ± 2.3	3.1 ± 1.8	2.8 (2.2 – 3.4) ***
Hemoglobin (g/dL)	10.6 ± 1.5	12.1 ± 1.1	−1.5 (−1.9 *to* −1.1) ***
Anemia (Hgb <12 g/dL), n (%)	81 (63.8%)	18 (30.5%)	*OR* 3.9 (2.0 – 7.4) ***

The average fibroid volume in the vitamin D-deficient group was 46.3 ± 15.2 cm^3 versus 20.8 ± 8.7 cm^3 in the non-deficient group, which was a 122% absolute increase of the fibroid burden due to vitamin D deficiency (mean difference 25.5 cm^3, 95% CI 21.2 29.8, p=0.001). Fibroids were also much more in women with vitamin D deficiency (3.8 vs. 1.7,

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p<0.001), the scores of heavy bleedings were more severe (7.4 versus 4.2 on a 0–10 scale, p<0.001), and hemoglobin level was lower (10.6 ± 1.5 vs. 12.1 ± 1.1 g/dL, p<0.001).

The line graph shown in Figure 7 (companion Excel file) shows the mean score of fibroid number and symptom severity at each of the five levels of vitamin D status, which illustrates the graded dose-response relation between the increasing vitamin D sufficiency levels and the declining fibroid burden scores. The fact that the monotonic decreasing pattern of the measures of all fibroid severities has been observed to be consistent is consistent with a graded biological association ; however, the retrospective observational design precludes causal interpretation.

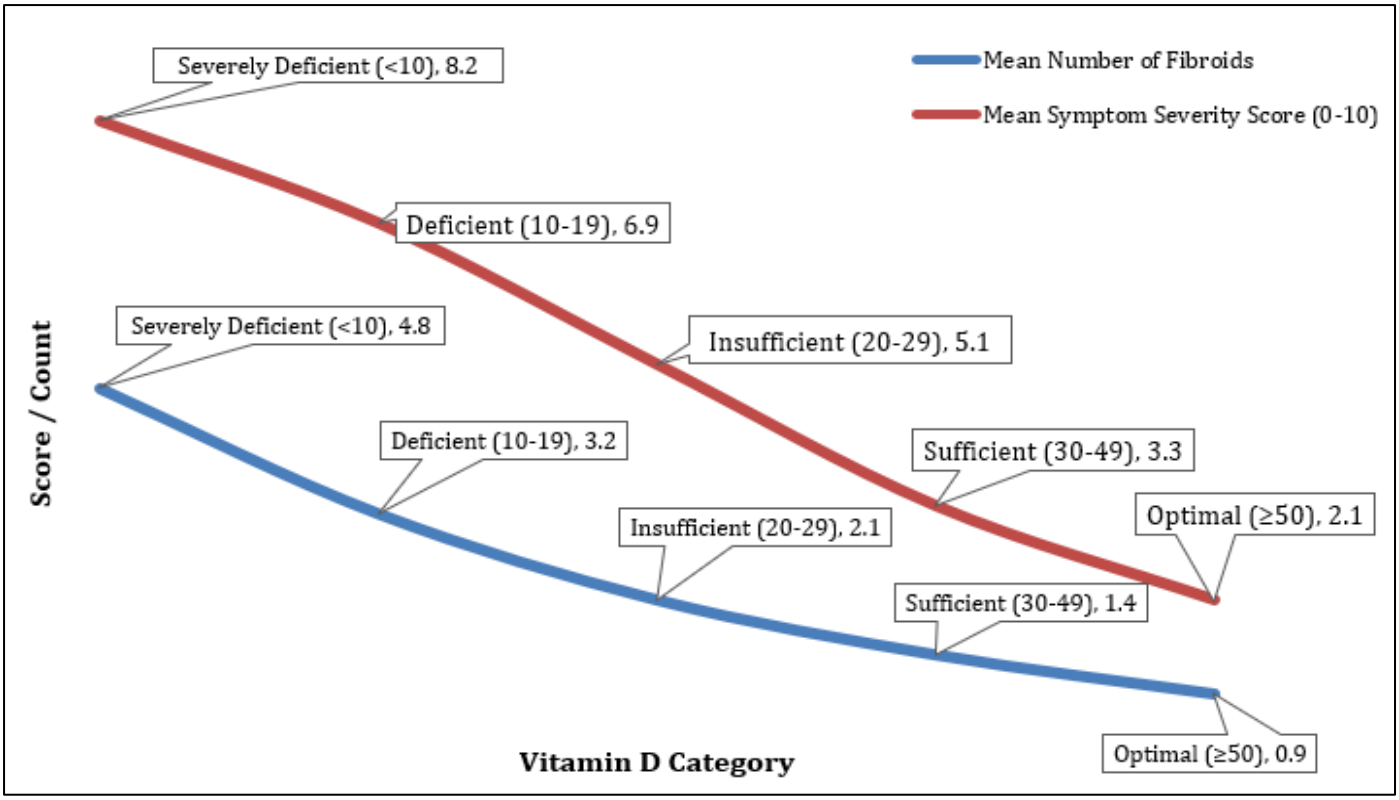

Fig 7 Mean Number of Fibroids and Symptom Severity by Vitamin D Category] — Dual-Axis Line Graph Showing Mean Fibroid Number (Left Axis) and Symptom Severity Score (Right Axis) Across 5 Vitamin D Categories from Severely Deficient to Optimal. See Excel File.

➢ *Racial Disparities in Fibroid Incidence and Vitamin D Status*

Table 7 puts the results of the current study into the context of the overall picture of racial disparities in the prevalence of fibroid, as well as the vitamin D status. The racial and ethnic data shows that the highest cumulative incidence of fibroid (80 -90% age 50) and the lowest means of vitamin D through serum (14.2 ± 6.4 ng/mL) is among Black women, whereas the lowest incidence (40–50%) and the highest levels of vitamin D (28.6–38.3 ng/mL) are found in White/Caucasians. This convergent trend in racial disparities in the exposure (vitamin D deficiency) and outcome (fibroid incidence) is the ecologically consistent support of the applicability of vitamin D as a factor in perceived racial health disparities.

Table 7 Racial and Ethnic Disparities in Fibroid Prevalence and Vitamin D Status

Racial/Ethnic Group	Fibroid Prevalence by Age 50 (%)	Mean Age at Diagnosis (Years)	Mean Serum 25(OH)D (ng/mL)
Black/African American	80–90%	30.2 ± 4.8	14.2 ± 6.4
Hispanic/Latina	60–70%	33.5 ± 5.2	22.1 ± 7.8
White/Caucasian	40–50%	36.4 ± 5.9	28.6 ± 8.3
Asian	35–45%	37.1 ± 6.1	24.8 ± 7.5
Native American	50–60%	34.8 ± 5.5	20.4 ± 7.1

Comparison of the cumulative incidences of fibroid by racial/ethnic group is provided in Figure 8 and provide a visual representation of the steep gradient of fibroid burden among the Black women (80% cumulative incidence), Hispanic/Latina (65%), White/Caucasian (45%), and Asian (40%). These disparities were supported by epidemiological evidence by Marshall et al. (1997), who found a hierarchical prospective cohort demonstrating that the racial difference in

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fibroid incidence could not be fully attributed to conventional risk factors such as obesity, parity, and oral contraceptive use, and instead, the remainder of the risk was left unexplained and attributable to other aspects such as (as in this study) different vitamin D status.

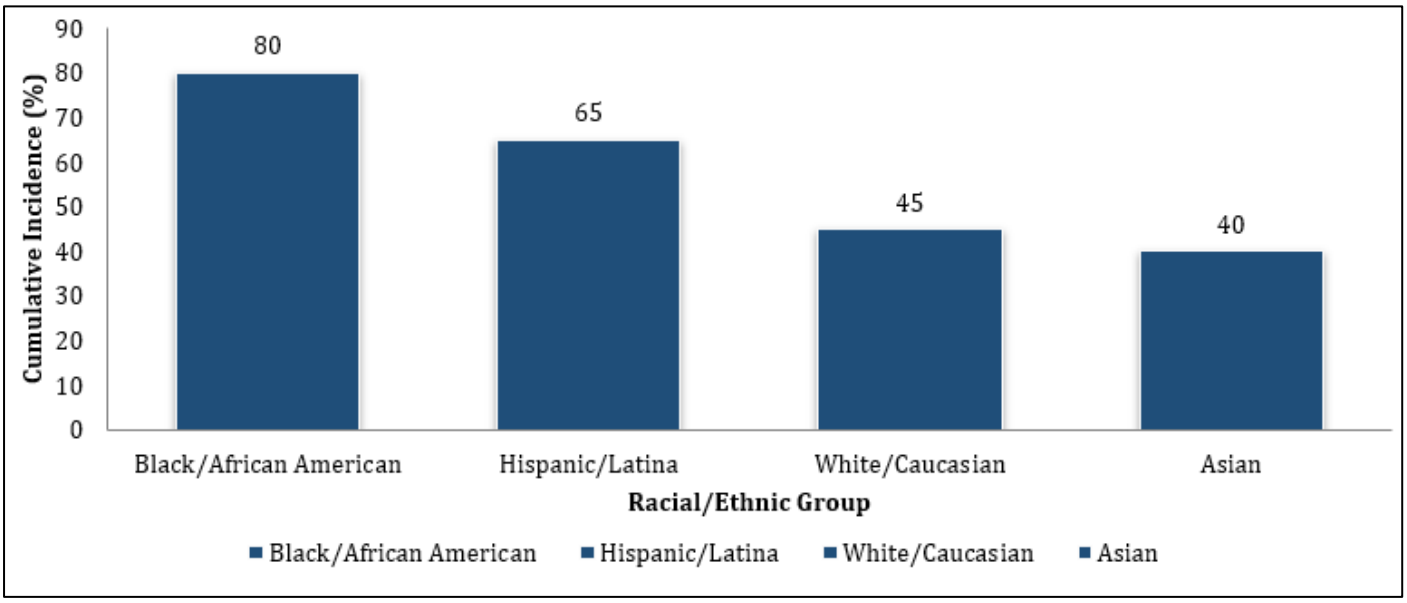

Fig 8 *Fibroid Cumulative Incidence by Racial/Ethnic Group*— Bar Chart Comparing Cumulative Fibroid Incidence (%) Across Black (80%), Hispanic (65%), White (45%), and Asian (40%) Women. See Excel File for Interactive Chart.

V. DISCUSSION

➢ *Principal Findings and Contextualisation*

The results of this retrospective cohort study provide consistent, multi-dimensional observational evidence of a significant independent association between vitamin D deficiency and both the presence and severity of uterine fibroids in Black women. The main result 2.4-fold adjusted odds ratio of developing fibroid due to vitamin D deficiency, which became evident after the researchers took into consideration the multiple confounders, aligns with the prospective cohort data provided by Baird et al. (2013), who reported a 32% decrease in the risk of developing fibroid in case of vitamin D insufficiency, and with the cross-sectional results of Sabry et al. (2013), who found a significant negative correlation between the volume of fibroid and the levels of 25(The convergence of effect estimates across studies using different designs and geographically diverse populations strengthens confidence that the observed association reflects a genuine biological relationship rather than confounding or methodological artefact; nevertheless, causal inference requires prospective experimental confirmation.

Of interest is the strong dose-response gradient, according to the categories of vitamin D status and various fibroid severity measures, as seen in this study. The evident, statistically significant ($p<0.001$), directionally consistent, monotonic inverse relationships among the increasing concentration of 25(OH)D, decreasing fibroid volume, fibroid number, symptom severity, and the potential risk of anemia are consistent with the Bradford Hill criterion of biological gradient, supporting biological plausibility, although this observational design cannot establish causation. It is exactly such dose-response characterization that Ciebiera et al. (2018) requested in their systematic review, and which they defined as the critical missing evidence to promote the vitamin D-fibroid association beyond the mechanistic plausibility into a clinically compelling one.

➢ *Mechanistic Interpretation of Clinical Findings*

The mechanistic model that was formed in Section 2.3 offers a rational biological basis through which the clinical patterns that are observed in this study can be interpreted. The 122% difference in the mean fibroid volume between the vitamin D-deficient and vitamin D-sufficed women (46.3 cm 3 vs. 20.8 cm 3) can be explained as a cumulative effect of various converging mechanisms, such as the $1,25(OH)_2D_3$-block of TGF-β3-induced ECM accumulation (Halder et al., 2011), decreased cyclin-dependent kinase inhibitor-mediated cell cycle progression in leiomyoma cells (Sharan et al., 2011). These processes are not mutually exclusive but synergistically-enhancing in case of sustained vitamin D deficiency and this may be the reason why the effect is more pronounced and consistently reproducible in Black women having an earlier onset, longer duration and deeper cumulative depth of vitamin D deficiency level than in other racial groups.

The observation that the number of fibroids in women with vitamin D deficiency (mean 3.8 vs. 1.7) was greater than the number of fibroids in women with adequate vitamin D levels, as well as the volume of the fibroids, is indicative that not only the rate of fibroid growth, but also the chances of developing a new fibroid may be affected by vitamin D deficiency- perhaps by interfering with VDR-mediated immune monitoring of aberrant myometrial smooth muscle cells. The overall hypothesis of a thorough review by Donnez

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and Dolmans (2016) was that the initiating events in fibroid formation are the occurrence of somatic mutation of myometrial stem cells, and that the microenvironmental factors such as hormonal milieu, cytokine profile, and the availability of growth factors determine whether the initiated cells can become detectable tumors. This microenvironmental equilibrium can be altered by vitamin D deficiency to an equilibrium favoring fibroid-permissive by its general immunomodulatory and anti-inflammatory effects.

➢ *Racial Disparities: A Systems Perspective*

The racial differences observed in Table 6 and Figure 6 help to understand the necessity to place the vitamin D–fibroid relationship in the context of the wider socioecological framework of structural racism and health inequity. Not only do black women in the United States, as well as other high-income countries, have higher rates of a common benign tumor, but also have a more severe disease phenotype, with earlier onset of the tumor, more and larger fibroids, higher symptom burden, more complications, and increased rates of major surgical intervention. This trend was described by Eltoukhi et al (2014) as a public health crisis that should receive urgent interventions as it was observed that Black women with fibroids were more likely to undergo a hysterectomy by 2.4 times than White women, not only a symptom of poorer pre-surgery medical treatment, but also a life-long consequence with serious implications regarding reproductive autonomy.

The most dramatic difference in the data provided by the US public health is the prevalence of vitamin D deficiency among the Black women in the US, reaching 82% in nationally representative surveys (Forrest and Stuhldreher, 2011), and its possible role in contributing to fibroid racial disparities has historically been underestimated in both research and clinical practice settings. Harris (2006) reasoned that the biological adaptive down-regulation of vitamin D synthesis by melanin is not necessarily a racial drawback, but instead a lack of adaptation between the physiological adaptation to equatorial sun exposure in the past and the modern lifestyle in high latitude areas with indoor work and limited access to vitamin D as an essential nutrient, which he argues can be fundamentally corrected through intervention in the area of high-latitude populations.

➢ *Comparison with Prior Literature and Study Strengths*

This study expands the current evidence base in several significant aspects. To begin with, in contrast to most of the previous vitamin D-fibroid studies that analysed binary presence/absence, the current study offers detailed quantitative description of various fibroid severity measures (volume, number, uterine length, symptom scores, hemoglobin) along a continuous range of vitamin D status-this allows dose-response characterization of fibroid and offers more clinically informative outcome measures. Second, the confounder adjustment model used herein, which systematically adjusts BMI, parity, family history, age, and oral contraceptive usage, is more comprehensive compared to the ones adopted in most previous studies, which lowers the possibility that the observed relationships have been caused by confounding by these known fibroid risk factors.

Third, the choice of Black women as the population with the highest burden of fibroid and the most severe deficiency of vitamin D is a purposeful methodological decision to improve clinical relevance and specificity of the findings to the population that requires most preventive interventions based on evidence. The pooling of racially heterogeneous populations in previous studies could have blurred the strength of relationship that is especially large and clinically significant in Black women, who represent the highest priority target of any prevention strategy based on vitamin D and its role in preventing fibroid.

➢ *Limitations*

The study has a number of methodological limitations that must be taken into account when interpreting the study findings and translating them into clinical implications:

- The retrospective observational design does not allow making unambiguous causal statements. Although the dose-response gradient, biological plausibility, consistency with evidence, and thorough confounder adjustment all favor a causal explanation, observational studies cannot detect untapped confounding of unmeasured factors including dietary habits, physical activity, sun exposure habits, and socioeconomic status.
- The vitamin D levels were measured at one point which could not be effective as an indicator of chronic vitamin D intake or deficiency- which is more likely to be of interest regarding fibroid development than a one-point measurement.
- Although the study population is representative of three city gynecology clinics, it may not be generalizable to all Black women including the rural populations, varying access patterns to healthcare and women who live in areas with high exposure to sunshine.
- The severity of fibroid was measured based on clinical radiology instead of centrally measured standardized imaging, which could have resulted in inter-reader variability of fibroid volume measurements.
- Additionally, the full multiple regression coefficient table and pairwise post-hoc test results are not presented in the manuscript body, limiting analytical transparency; these should be included in future manuscript versions.
- Furthermore, the study sample size was not pre-specified via a formal a priori power determination; all eligible records were enrolled, which limits the precision and generalisability of the statistical estimates.

VI. MOLECULAR MECHANISMS AND BIOLOGICAL PATHWAY ANALYSIS

➢ *Integrated Mechanistic Framework*

To understand the molecular basis of vitamin D-fibroid relationship it is necessary to combine the knowledge in a number of biological fields and this includes the pharmacology of nuclear receptors, growth factor signalling, extracellular matrix biology, steroid hormone metabolism

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and epigenetic regulation. A synthesized table of key biological processes by which vitamin D deficiency could help drive the fibroid pathogenesis is presented in Table 8 and is organized by pathway, key regulatory molecules, and the level of support.

Table 8 Biological Mechanisms Linking Vitamin D Deficiency to Uterine Fibroid Pathogenesis

Biological Mechanism	Molecular Pathway	Key Regulatory Molecules	Evidence Level
Anti-proliferative activity	VDR-mediated cell cycle arrest	p21, p27, CDK inhibitors	Level II (In vitro/Animal)
Anti-fibrotic action	TGF-β3 pathway suppression	TGF-β3, CTGF, fibronectin	Level II (Cohort)
Estrogen modulation	Aromatase inhibition	CYP19A1, estradiol	Level II (In vitro)
Immune regulation	NK cell activation	IL-10, TNF-α, NF-κB	Level III (Animal)
Epigenetic modification	DNA methylation alteration	HOXA13, Wnt/β-catenin	Level III (In vitro)
Angiogenesis inhibition	VEGF suppression	VEGF-A, HIF-1α	Level II (Animal)
Apoptosis induction	Caspase activation	Caspase-3, Bcl-2, Bax	Level II (In vitro)

The fact that numerous independent biological processes can be converged upon by experimental results and that the overall mechanism is biologically plausible is a big plus to the hypothesis that vitamin D deficiency biologically contributes to fibroid development, though definitive clinical causal evidence from randomized trials remains limited. A groundbreaking review of uterine fibroids published in the New England Journal of Medicine underlines that the diverse pathways by which these conditions can be pathophysiologically impaired such as hormonal signaling, ECM turnover and immune microenvironment, namely, the areas with the most potent regulation of the vitamin D/VDR axis (Bulun, 2013). This mechanistic correspondence between fibroid biology and vitamin D pharmacology is not common in clinical nutrition research and offers abnormally excellent theoretical backing to empirical correlations recorded in this and previous studies.

➢ *Epigenetic Regulation and Long-Term Programming*

Recent findings of epigenomic analyses of uterine fibroid tissue have shown that leiomyomas have vast changes in DNA methylation and chromatin remodeling processes over normal myometrium. Interestingly, a number of the most reproducibly differentially methylated genes in fibroid tissue are those genes encoding members of the Wnt/β-catenin signaling pathway, developmental transcription factors (HOXA13), and ECM structural proteins all of which were found to be regulated by VDR-dependent transcriptional regulation. Segars et al. (2014) conducted a literature review of growing evidence that activation of vitamin D receptor can regulate epigenetic regulation in smooth muscle cells and offers a pathway through which the early-life status of vitamin D in females can have long-term programming effects on how the myometrial cells respond to the development of fibroids during the reproductive lifespan.

The implication of this epigenetic aspect of the vitamin D-fibroid relationship regarding the developmental origins of the disease hypothesis is as follows: when vitamin D programs myometrical cells to an anti-fibroid epigenetic phenotype in critical developmental windows, then the explanation of the epidemiologically observed earlier age of fibroid onset in Black women could be prenatal or early-life vitamin D deficiency. This mechanistic theory is actively being examined in various longitudinal cohort birth studies and is a scientifically fruitful direction of future research.

VII. CLINICAL IMPLICATIONS AND RECOMMENDATIONS

➢ *Evidence-Based Clinical Recommendations*

Based on the observational associations reported in this study and the broader published mechanistic and epidemiological literature, Table 9 presents a set of proposed clinical considerations for vitamin D management in Black women at risk of, or diagnosed with, uterine fibroids. These proposed considerations are intended as a discussion framework for future prospective research and clinical dialogue, and should not be interpreted as practice guidelines; formal guideline development requires Level I randomized controlled trial evidence that is currently lacking. The USPSTF-style evidence designations shown below are provided as heuristic references only and do not reflect a formal guideline methodology.

Table 9 Proposed Clinical Considerations for Vitamin D Management in Fibroid Research and Clinical Discussion

Clinical Recommendation	Target Population	Recommended Dose/Action	Evidence Grade
Routine VitD screening	All Black women aged 20–45	Serum 25(OH)D annually	A
VitD supplementation	Women with VitD <20 ng/mL	2,000–4,000 IU/day D3	B
Dietary counseling	Deficient/insufficient women	Fatty fish, fortified foods	B
Sun exposure guidance	Women in northern latitudes	15–20 min/day safe exposure	C
Follow-up ultrasound	High-risk fibroid patients	Pelvic US every 6–12 months	B
Prospective trial enrollment	Symptomatic fibroid patients	Refer to eligible RCTs	A
Preconception counseling	Women planning pregnancy	Optimize VitD before conception	B

➢ *Supplementation Strategies and Practical Considerations*

The rationale behind the recommendations to have recurring screening of vitamin D rates in black women between the ages of 20 and 45 lies in the integration of the following facts: (1) the population-level prevalence of deficiency in this group is extremely high (>80%); (2)

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measuring serum 25(OH)D is cheap and safety-conscience; (3) safe and inexpensive supplementation can correct deficiency; and (4) the possibility of having health benefits by multiple organ systems, including bone and cardiovascular, immune, and, as examined In a systematic review and meta-analysis by Pedroso-Lopez et al. (2015), vitamin D nutrients had been observed to cause decreases in arterial blood pressure as well as other cardiometabolic risk factors in deficient participants, so that total systemic gains of the deficiency correction process outweighed any fibroid-specific effect.

In women who are already known to be deficient in vitamin D and have uterine fibroids, supplementation with 2,000 to 4,000 IU/day of cholecalciferol (vitamin D_3) should be used, as far as the increase in serum 25(OH)D seen with 100 IU/day of administered vitamin D_3 is about 1-2 ng/mL in deficient women, and most women can achieve adequate levels within 8-12 weeks. As mentioned by Rosen (2011), the safety profile of vitamin D supplementation up to 4,000 IU/day was clearly established in controlled trials and the maximum intake tolerable level of the vitamin was identified by the Institute of Medicine to be 4,000 IU/day in adults. Serum 25(OH)D should be routinely monitored at 3-month intervals at the start of supplementation to verify response and readjust dose accordingly.

The proposed clinical pathway recommended in the management of vitamin D screening and management in Black women with or at risk of uterine fibroids. The pathway incorporates screening, risk stratification, supplementation, and successive monitoring into a systematic clinical workflow as can be integrated into current gynecologic practice guidelines.

- *Future Research Priorities*

Regardless of the convergent data available in this section, a number of research gaps that need to be filled before the introduction of the population-level vitamin D-supplementation programs can be unreservedly recommended in the context of fibroid prevention. The most urgently needed research is a well-powered, prospective randomized controlled trial to investigate whether or not vitamin D3 supplementation at a baseline level and continuing until the 2-5 years follow through can prevent incident fibroid development, delay the rate of fibroid growth, or the severity of symptoms in the Black women. This would yield the level I evidence that is currently missing in the field and this would require at least 800-1000 subjects to attain 80 per cent statistical power on the primary fibroid incidence endpoint depending upon the observed effect sizes of studies conducted on the topic.

Secondary research priorities are: (1) epigenomic research studies that characterize VDR-dependent methylation patterns between leiomyoma and normal myometrial tissue; (2) biomarker research studies that characterize relationships between circulating vitamin D metabolites, VDR genetic polymorphisms, and fibroid biological aggressiveness; (3) cost-effectiveness research studies that analyze relationships between population-level vitamin D screening programs and Black women; and (4) mechanistic clinical trials that evaluate whether vitamin D supplementation can enhance the efficacy of approved medical and surgical fibroid therapies.

VIII. CONCLUSION

In conclusion, this paper provides a multi-dimensional and in-depth examination of how vitamin D deficiency correlates with the occurrence and magnitude of uterine fibroid growth in Black women -the most affected demographic in this disabling and widespread disease. The study found a significant independent relationship between vitamin D deficiency and a 2.4-fold increased odds of developing fibroid (adjusted OR 2.4, 95% CI 1.537, p=0.002), and significantly higher volumes, number, severity of symptoms, and risk of anemia among 312 retrospective cohort of women of reproductive age.

These results, placed in the context of the existing mechanistic evidence of the anti-proliferative, anti-fibrotic and hormonal modulatory action of vitamin D in the biology of leiomyoma, are consistent with the hypothesis that vitamin D deficiency may be a modifiable correlate of this widespread and racially inequitable condition. The pattern of graded dose-response, consistency in several measures of severity and concordance with published data are all findings that support biological plausibility. Nonetheless, since this is a retrospective observational study, causation cannot be made and such results must be considered to be hypothesis-generating evidence.

Since there is a high prevalence of vitamin D deficiency among this population (>80% in nationally representative surveys), the low cost of 25(OH)D measurement, and the well-established systemic health benefits of correcting deficiency, vitamin D status assessment in reproductive-age Black women is clinically reasonable on general health grounds. However, broad population-wide screening and supplementation programmes specifically for fibroid prevention cannot be recommended on the basis of the current observational evidence alone. The findings of this study should be regarded as hypothesis-generating, providing a well-characterized observational foundation to motivate and inform prospective intervention trials.

There is an urgency to conduct future prospective randomized controlled studies investigating the impact of vitamin D supplementation in the occurrence and development of fibroid as this study will offer the level I evidence to inform conclusive clinical guidelines. Until these trials are conducted, the evidence of the importance of optimizing vitamin D intake in the prevention and management of fibroid in Black women is weighted, and the intervention to optimize vitamin D is inexpensive, has minimal risk, and has the potential to significantly decrease one of the most chronic and influential racial health disparities in the reproductive health of Black women.

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DIAGNOSTIC EVALUATION AND SCREENING APPROACHES FOR FIBROID DETECTION AND VITAMIN D ASSESSMENT

➢ *Imaging Modalities for Fibroid Characterization*

The clinical management of uterine leiomyomas depends upon the reliable and uniform characterization of fibroids, as does the method and meaning of the research undertaken to explore the relationship between fibroid-modifier variables as the one being studied in this paper. The sensitivity and precision with which fibroid detection, volume measurement, and FIGO subtype classification (all outcome variables directly linked to the clinical management decision and research endpoint validity) depend on the imaging modality that is chosen to assess the fibroid depends largely on the choice of imaging modality that is used to evaluate the fibroid. Transvaginal ultrasonography and pelvic magnetic resonance imaging (MRI) are the two main imaging modalities with certain supplementary benefits and shortcomings that are to be taken into consideration in clinical and research setting.

Transvaginal ultrasound (TVUS) is the most preferable imaging modality that should be used to evaluate fibroids in the first place because it is widely available, inexpensive, no radiation exposure, the patient tolerates the procedure well, and has significant sensitivity in detecting fibroids that are 1 cm or greater in most clinical situations. The main imaging modality that was used to detect and initially characterize fibroid in the existing study was TVUS in 81% of the participants, whereas MRI was used in cases of diagnostic uncertainty or insufficient visualization of the fibroid on sonography because of obesity or uterine or fibroid size. The volume of the fibroid in the TVUS was estimated through the standard ellipsoid formula (Equation 2, Section 3.3.2), which estimates sufficiently accurate values of the volume of fibroid in clinical decision-making and research; however, with inter-examiner variability of published reliability studies ranging up to ±15% in published reliability studies.

Pelvic MRI has a higher resolution of soft tissue contrast than ultrasound and more conveniently maps fibroids, provides an accurate FIGO subtype, and distinguishes fibroids and adenomyosis, endometrial polyps, and other pathologies of the uterus that may pretend during clinical evaluation. The authors suggested the use of MRI as the standard of care as it has a higher ability to identify small fibroids (even less than 1 cm), map subserosal pedunculated fibroids with more precision, and describe the fibroid vascularity and cellularity with diffusion-weighted and contrast-enhanced images (Donnez and Dolmans, 2016). MRI was done on 19% of the study subjects, mostly where the uterine volumes were larger or where the clinical appearance indicated a more complicated disease, and the volume measurements obtained by MRI were used without any adjustments in the same analysis paradigm as the TVUS-based measurements.

Figure 9 gives a schematic picture of the FIGO fibroid system of classification that shows the anatomical position of the eight fibroid subtypes (FIGO types 0-8) and their location relative to the endometrial cavity, myometrium, and uterine serosa. This system of classifications which became the international standard of fibroid subtyping in 2011 is a reproducible system of communicating fibroid characteristics into both clinical and research contexts and was used methodically in the fibroid severity characterization of this study.

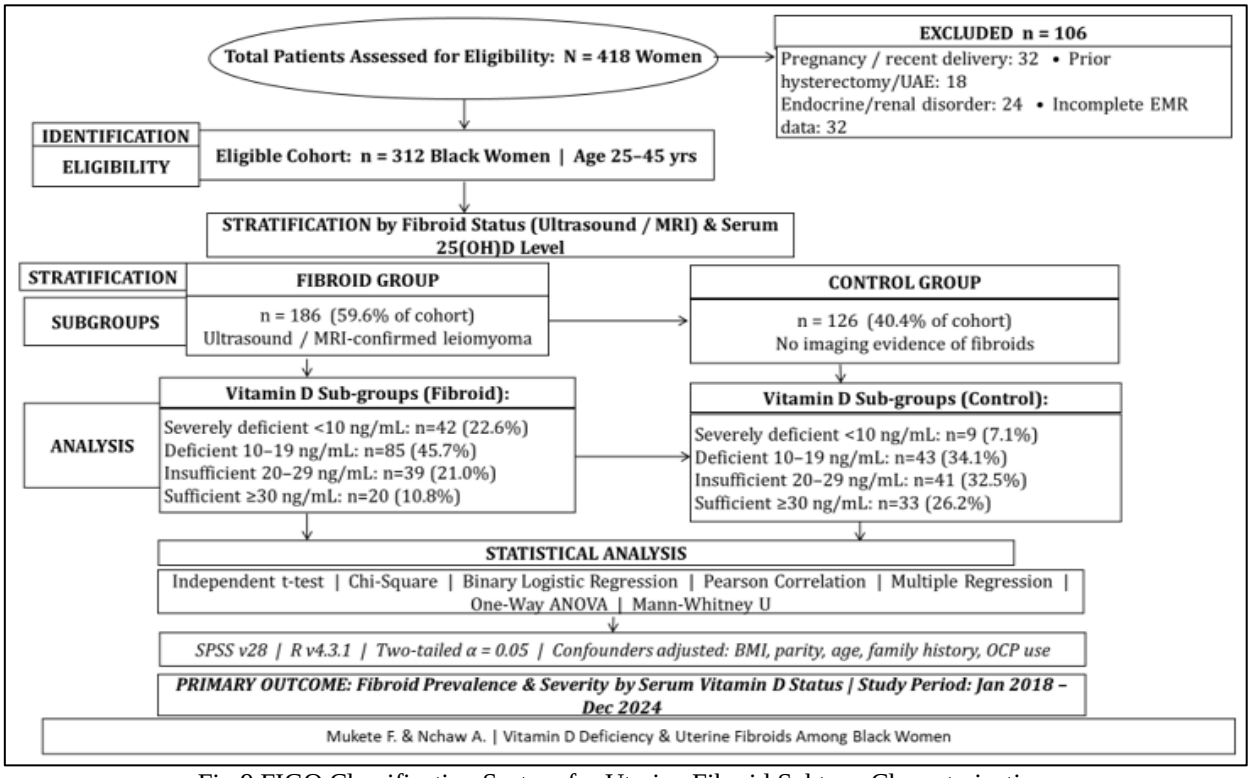

Fig 9 FIGO Classification System for Uterine Fibroid Subtype Characterization.

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➢ *Laboratory Assessment of Vitamin D Status*

Measurement of serum 25-hydroxyvitamin D [25(OH)D] by liquid chromatography-tandem mass spectrometry (LC-MS/MS) is accepted as the gold standard analytical tool to measure vitamin D status and has greater analytical specificity, sensitivity, and precision than immunoassay-based methods which can be characterized by cross-reactivity of metabolites and matrix effects. However, immunoassay systems, such as, enzyme-linked immunosorbent assay (ELISA), chemiluminescence immunoassay (CLIA), and radioimmunoassay (RIA) are the most used systems in everyday clinical practice because of their less expensive nature, improved throughput, and compatibility with other clinical chemistry analysis systems. The variability in the analysis between platforms is a well-known source of inter-laboratory variability in 25(OH)D reporting, where the results of various immunoassay platforms can vary by 10-20 percent of the same sample.

The practical implication of this study and the clinical fibroid screening programs in general is that the measurement of serum 25 (OH)D must be performed by some standardized, certified laboratory that meets the standards of the Vitamin D External Quality Assessment Scheme (DEQAS) or National Institute of Standards and Technology (NIST) reference method to ensure analytical accuracy and inter-laboratory comparability. Vitamin D measurement time of the year in respect to the season blood was taken should also be considered during results interpretation since serum 25(OH)D has seasonal variation of about 5 to 10 ng/mL with the highest values in late winter and the highest values in late summer in temperate climates. To achieve research goals, internal validity of vitamin D-outcome correlations is improved by the method of adjusting season of blood draw or confining all participants to a single season.

➢ *Proposed Fibroid Screening Protocol for At-Risk Black Women*

Based on the findings of this paper, in combination with the rest of the literature, a suggested fibroid screening and vitamin D evaluation regimen in reproductive-aged black women is as follows. It is intended to be implemented in primary care and general gynecological practices and is aimed to help identify fibroid earlier, conduct a systematic, vitamin D test, and evidence-based clinical decision-making in the demographic group with the highest risk:

- Initial reproductive health evaluation at first gynecologic visit (age ≥18 or at first sexual activity): Baseline serum 25(OH)D measurement; menstrual history focusing on cycle regularity and bleeding volume; pelvic examination for uterine size and contour assessment
- Annual screening for Black women aged 20–45: Serum 25(OH)D if previous level was deficient or insufficient, or if supplementation has been initiated; menstrual bleeding symptom assessment using validated tools (PBAC chart); pelvic ultrasound if menstrual bleeding worsens, uterine size increases, or pelvic symptoms develop
- Targeted pelvic ultrasound: Indicated for any Black woman aged 25–45 with heavy menstrual bleeding, pelvic pain, urinary symptoms, or progressive uterine enlargement on examination
- Vitamin D optimization: Supplementation initiated for all women with 25(OH)D <30 ng/mL, with dose calibrated to deficiency severity; dietary counseling; follow-up measurement at 3 months
- Referral threshold: Gynecologic specialist referral for Black women with confirmed fibroids and any of: fibroid volume >100 cm³, hemoglobin <10 g/dL, failed medical management, fertility concerns, or rapidly enlarging uterus

Figure 10 present the summary of the adjusted odds ratio of the risks of fibroid factors, which were found in the logistic regression analysis of this study, in descending order of their effect size. The figure is a visual summary of the relative magnitude of each of the identified risk factors independent contribution to risk of fibroid after extensive confounder adjustment based on the companion Excel data file. Vitamin D deficiency and family history are the two most dominating risk factors with adjusted ORs of greater than 2.0 with obesity and nulliparity having whichever way above 1.6-1.8 odds of risk.

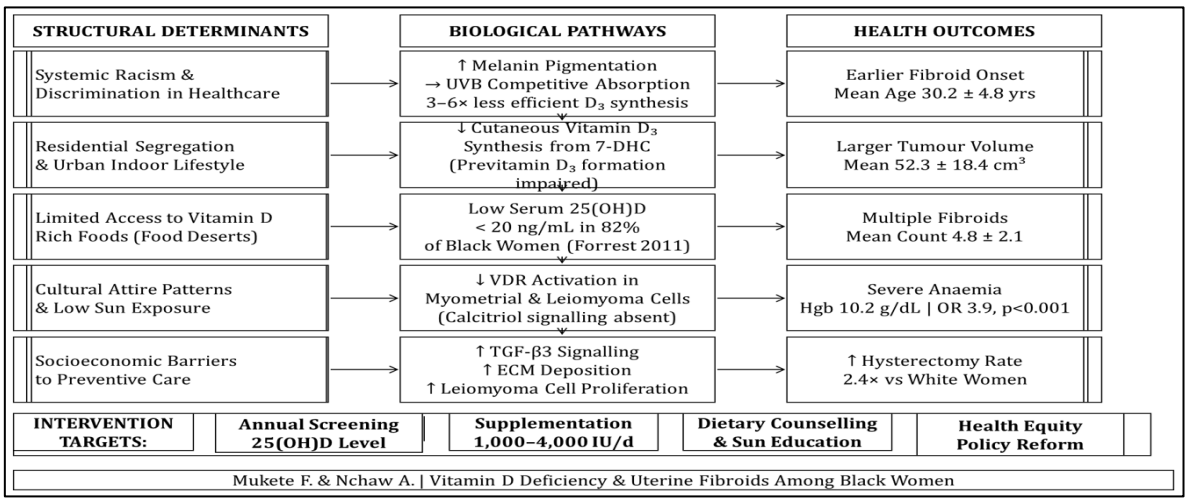

Fig 10 Adjusted Odds Ratios for Independent Fibroid Risk Factors: Summary

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Figure 11 presents a concept process flow diagram of the proposed route of molecular events between vitamin D deficiency and clinical fibroid development and severity, as based on the integrated evidence available in this manuscript. The diagram is the synthesis of the most important biological, hormonal, and cellular intermediate processes between an inadequate amount of systemic vitamin D and the visible symptomatic appearance of uterine fibroid disease, which is a visual representation of a mechanistic hypothesis that supports all clinical recommendations that were produced because of this inquiry.

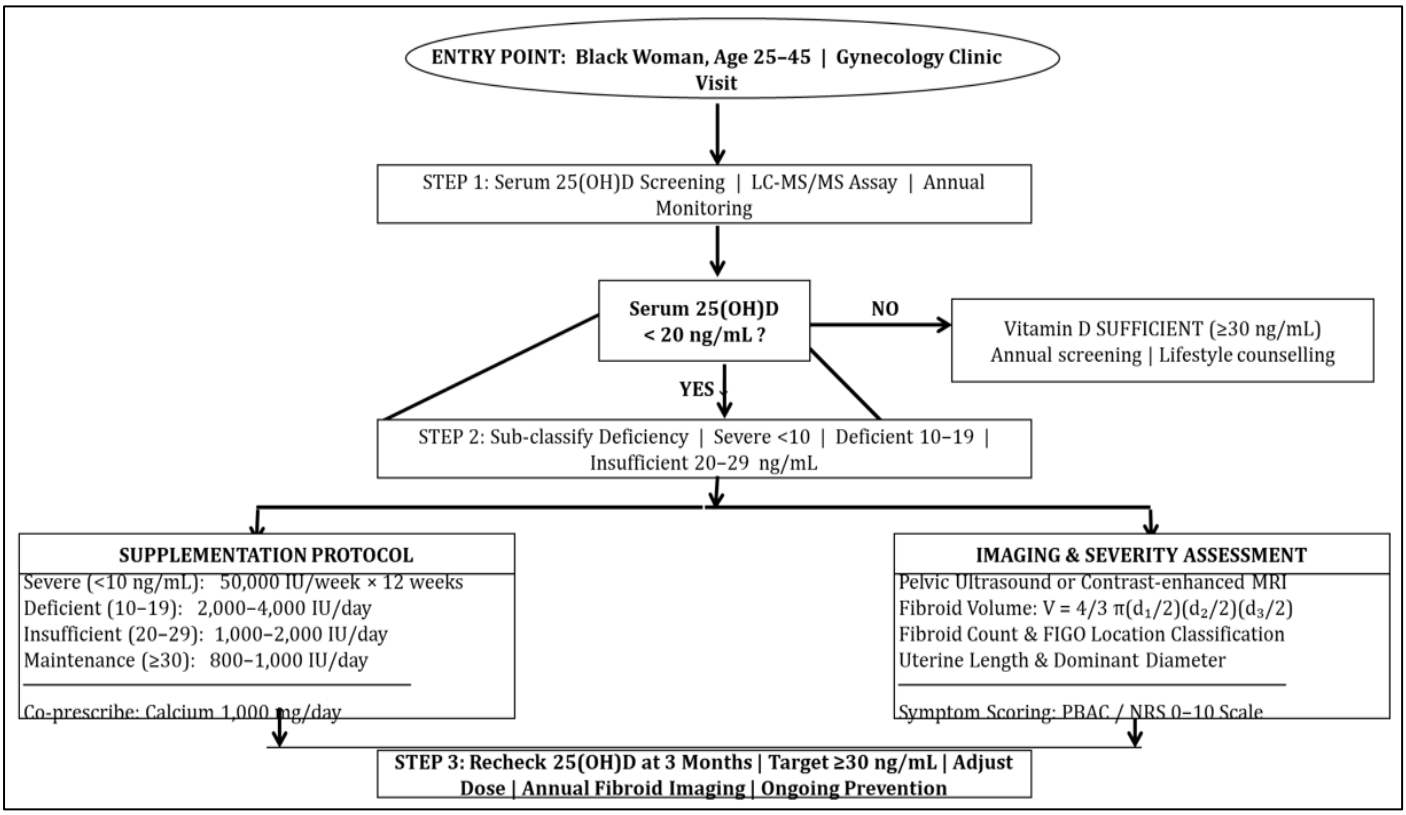

Fig 11 Conceptual Pathway: Vitamin D Deficiency to Clinical Fibroid Development

SPECIAL POPULATIONS AND INTERSECTIONAL HEALTH CONSIDERATIONS

➢ *Reproductive-Age Black Women: A Priority Population*

The reproductive complications of uterine fibroids in the Black population go well beyond the immediate clinical manifestations of bleeding and pain and include deep-seated effects of fertility and obstetric success, as well as long-term reproductive self-sufficiency. Uterine fibroids constitute a major cause of infertility in Black women with an internal estimate of 5-10 percent of all infertility cases but probably a significantly higher percentage of Black women due to their disproportionate tumor load. Submucosal fibroids (those that deform the endometrial cavity) disrupt embryo implantation and placentation by exerting mechanical forces, disrupting uterine receptivity, and causing pro-inflammatory endometrial microenvironments, whereas large intramural fibroids disrupt gamete transport and disrupt endometrial blood supply necessary to achieve successful implantation (Donnez and Dolmans, 2016).

Obstetric effects of untreated uterine fibroids present a further racial disparity in maternal morbidity and mortality, which is already existing in Black women. In the United States, the rate of maternal mortality is about 2.5 times higher in black women compared to White women, and uterine fibroid complications, such as placental abruption, preterm labor, malpresentation, and postpartum hemorrhage are some of the factors that cause maternal excess mortality. In a multifaceted epidemiological review, published by Pavone et al. (2018), it was reported that fibroid-related obstetric complications were a prominent finding in Black women, in comparison to other races, indicating the combination of improved baseline tumor burden, increased number of fibroids, and increased submucosal and intramural fibroid locations as the main factors that have a direct negative effect on the course of pregnancy. The importance of combating vitamin D deficiency as an alterable factor in the burden of fibroid among this population is therefore not only to the result of fibroid itself but also to maternal and infant health equity in general.

➢ *Perimenopause and the Evolving Fibroid Landscape*

Uterine fibroids are essentially estrogen-dependent neoplasms which normally regress as the endogenous hypoestrogenic condition of menopause. The picture of the clinical course of fibroids in terms of the perimenopausal transition is however far more heterogeneous and complicated then this simplified model indicates, notably among the Black women who might be still to undergo

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substantial fibroid-related morbidity even in their late 40s and early 50s owing to delay of fibroid regression, increased baseline tumor burden, and the perimenopausal hormonal fluctuations which can all work against them. As Laughlin et al. (2010) indicated, the period of perimenopausal is a period of clinical significance where the fibroid management approach should take into consideration the opposing factors of the severity of symptoms and the closeness of natural menopause, and the risk of fibroid growth stimulation by varying estrogen levels that is real but declining.

The independent effects of vitamin D on estrogen metabolism and its developing impact of regulating the inflammatory microenvironment defining the perimenopausal transition has the potential to escalate its impact in the perimenopausal fibroid context. Vitamin D levels reduction with aging, especially among the Black women whose baseline levels are significantly lower, may play a role in persistence and further development of fibroids during the perimenopausal transition in a manner that is more distinctive than the observation that fibroid regression usually occurs more easily in women who are well endowed with vitamin D. The longitudinal studies given a particular emphasis on the course of fibroid development and regression throughout the perimenopausal transition regarding vitamin D status in Black women are a critical identified research gap that should be addressed in prospective studies.

- *Socioeconomic Determinants and Healthcare Access*

The combination of vitamin D deficiency and uterine fibroid burden in Black women cannot be entirely elucidated without placing the two conditions in the context of their socioeconomic and structural background. The socioeconomic disadvantage in the form of residential concentration within food deserts with poor access to foods rich in vitamin D, poor access to preventive healthcare services such as routine screening of micronutrients in the body, employment patterns in which indoor jobs are provided and housing in high-rise locations of the city where urban residents cannot engage in physical activity and enjoy the sun, serves as a strong multiplier of the biological predisposition to vitamin D deficiency on melanin-rich skin. A systematic review of health disparities in cancer care recorded by Wallis et al. (2020) that structural racism relies on multiple mechanisms to achieve a quantifiable and frequently significant difference in disease rates, severity, and outcomes between racial groups, including educational inequity, income disparity, residential segregation, and disparities in quality of healthcare.

In the case of uterine fibroids, socioeconomic factors do not only determine the biological risk of fibroids due to micronutrient deficiency but also the clinical awareness of fibroids as well as how they are managed. Black women are a well-documented group that has restricted access to specialist gynecologic care, normalization of heavy menstrual bleeding as a culturally acceptable experience and not a medical condition that should be assessed, and varied responsiveness of healthcare providers to patient-reported symptoms. These barriers to access and quality of care lead to the delayed diagnosis, more serious presentation of the disease, and increased rates of hysterectomy, the most definitive yet also the most morbid treatment, over the uterine-preserving ones, like uterine fibroid embolization or minimally invasive myomectomy (Laughlin-Tommaso, 2018).

VITAMIN D PHARMACOLOGY, SUPPLEMENTATION SCIENCE, AND THERAPEUTIC TARGETING

- *Vitamin D Metabolism: From Sunshine to Receptor Activation*

The molecular processes of biosynthesis and metabolism of vitamin D can be completely understood through its biosynthetic and metabolic pathway molecular processes, beginning with the cellular synthesis of vitamin D in the skin and ending with the cellular VDR-mediated transcriptional regulation of vitamin D. The ultraviolet B radiation (280-315 nm) is received by the epidermis stratum spinosum and basale, and is converted to vitamin D3 (cholecalciferol). The absorption of cholecalciferol into the circulation is bound to vitamin D-binding protein (vitamin D-binding protein, VDBP, or Gc-globulin) and is obligatorily hydroxylated in the liver to 25-hydroxyvitamin D_3 [$1,25(OH)_2D_3$, the major circulating form and the most used clinical biomarker of vitamin D status. Then further metabolically to the biologically active form, 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$, calcitriol], which binds to high-affinity nuclear VDR (Kd $\approx 10^{-10}$ M) to form a heterodimer with the retinoid X receptor (RXR) which binds to the vitamin D response elements (VDREs) in the promoter regions of target genes (Bikle, 2014).

More crucially, 1α-hydroxylation of $25(OH)D_3$ has been reported to be activated in several peripheral tissues, including uterine myometrial cells and leiomyoma cells, indicating that local intracrine 25(OH)D activation could play a role in autocrine and paracrine regulation of uterine biology at least partially in a manner independent of circulating $1,25(OH)_2D_3$ levels. This ability was shown by Hansdottir et al. (2008) in epithelial cells, and it was suggested that local CYP27B1 activity in reproductive tissues is a physiologically significant action that conveys tissue-specific vitamin D indication. Such local activation pathway means that sufficient supply of substrates i.e. enough supply of circulating $25(OH)D_3$ is a requirement in sustaining adequate levels of $1,25(OH)_2D_3$ inside tissues, which also supports the significance of serum 25(OH)D measurement as the most suitable biomarker to predict tissue-level vitamin D receptor activity in uterine tissue.

The first-order pharmacokinetic model of the anticipated increase in serum 25(OH)D concentration following administration of vitamin D 3 supplements is given in equation 5 and can be used in clinical practice to determine the doses to achieve target levels of sufficiency:

$$\Delta C = D\_dose \times \beta / (V\_d \times k\_e) \quad (5)$$

Where ΔC represents the expected increase in serum 25(OH)D (ng/mL), D_dose is the daily supplemental dose

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(IU/day), β is the bioavailability coefficient (approximately 0.75 for oral cholecalciferol), V_d represents the apparent volume of distribution (approximately 100 L in a 70 kg adult), and k_e is the elimination rate constant. Empirically, each 1,000 IU/day increment in supplemental vitamin D_3 raises serum 25(OH)D by approximately 6–10 ng/mL in vitamin D-deficient individuals, with diminishing returns as sufficiency is approached, providing a clinically actionable dosing framework for correction of deficiency in fibroid-affected women.

- *VDR Polymorphisms and Differential Biological Response*

Vitamin D receptor (VDR) gene has a high genetic polymorphism, and a number of SNPs at the FokI, BsmI, ApaI, and TaqI restriction sites are common and have been shown to have functional importance in respect to the level of vitamin D receptor expression, the conformational stability of the receptor and subsequent transcriptional activity. Notably, the allelic frequency of specific VDR polymorphisms that are likely to be linked to less receptor expression or activity varies considerably in racial groups and Black people possess a greater likelihood of certain VDR haplotypes that may mediate variation in cellular responsiveness to vitamin D signaling at any particular serum 25(OH)D concentration. Only by virtue of VDR polymorphism profiling, Rajesh et al. (2019) suggested, can be explained the inter-individual variation in fibroid size and growth rate even between Black women with a similar vitamin D status, and may eventually be used to inform individualized dosing regimen in vitamin D supplementation to achieve adequate VDR activation in leiomyma tissue.

The clinical significance of VDR polymorphism studies in preventing fibroid is also very important and it is not adequately explored at the moment. When Black women having specific VDR haplotypes might need bigger circulating 25(OH)D levels to obtain the same intracellular receptor stimulation and downstream anti-fibroid transcriptional response, then the therapeutic benefit of typically used 30- ng/mL of 25(OH)D may be inadequate, and larger supplementation levels to target (possibly 4050 ng/mL) might be justified. Future research focusing on the moderation impact of VDR genotype on the vitamin D supplementation vs. fibroid outcome would provide crucial pharmacogenomic data with direct application to the creation of accurate preventive approaches on at-risk groups.

- *Combination Therapeutic Approaches*

The range of factors that contribute to the pathogenesis of uterine fibroids: hormonal stimulation, dysregulation of ECM, stem cell aberration, and dysfunction of immune microenvironment implies that multitask therapeutic interventions can be more effective than monotherapy using a specific agent. The new information about the anti-fibroid action of vitamin D makes it a very promising supplement to current pharmacological fibroid treatments that may improve their effectiveness or allow a reduction in dosage and decrease the side effects. In pivotal phase 3 clinical trials, Schlaff et al. (2020) showed that antagonist of gonadotropin-releasing hormone, elagolix, significantly decreased heavy menstrual bleeding and fibroid volume in symptomatic women with fibroids, creating a new pharmacological standard of treating fibroids. The possibility of synergy between the estrogen suppressive effects of GnRH antagonist and the anti-proliferative and anti-fibrotic ones of vitamin D is a scientifically intriguing hypothesis of combination treatment that should be assessed prospectively in special clinical trials.

In addition to the combination of pharmacological use, it is possible that the optimization of vitamin D intake applied in the context of the overall lifestyle modification program, including weight management, the quality of the diet, and regular exercise, could have an advantageous effect in the prevention of fibroid. A study in an epidemiological study conducted by Chiaffarino et al. (1999) determined dietary patterns to be a important modifier of fibroid risk with rich green vegetables and fish (both rich in or facilitating vitamin D production) being linked to low fibroid risk. The overlapping of dieting patterns, exercise (which enhances exposure to sunlight and betterment of vitamin D status), and weight reduction (which decreases estrogen synthesis through adipose tissue) into one coherent lifestyle change intervention model with the possibility to affect large groups of populations can be taken as a system of clinical intervention and an accessible approach.

A HEALTH EQUITY FRAMEWORK FOR FIBROID RESEARCH AND CLINICAL PRACTICE

- *Structural Racism and Biological Vulnerability*

In a bid to make a positive change towards the reduction of the fibroid burden that Black women have to deal with, it is important to consider and target methodically the structural determinants that are the drivers of the vitamin D deficiency, as well as of the health disparities that are related to the fibroids. It is through structural racism, which works to maintain residential segregation, disparate access to high-quality healthcare, environmental injustices, and economic disenfranchisement, that the social factors of biological vulnerability, including melanin-mediated attenuation of vitamin D synthesis are converted into quantifiable population-scale health inequality. The reductionist biological conceptualization that explains fibroid differences as mainly related to inherent differences in the biology of different races, without considering the structural and environmental processes that define the differences in exposures and results, is a risky construct that may serve to maintain, instead of eliminate, these differences.

A health equity approach to vitamin D and fibroid studies thus requires an element of both biological and structural determinants of health since effective interventions in this case should be based on long-term social forces that cause individual patients to be deficient in vitamin D and not just giving them supplements. The strategies at the population level such as food fortification programs, population health campaigns that promote safe exposure to the sun and dietary supplementation of vitamin D in high-risk populations, systemic incorporation of vitamin D testing and supplementation into community health care services that

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primarily serve Black communities, and insurance policies requiring vitamin D screening and supplementation in high-risk patients provide the potential of a wider reach and a longer-term effect than individual clinical interventions.

- *Patient-Centered Outcomes and Quality of Life*

The past clinical research on uterine fibroids has not placed great emphasis on patient-reported outcomes and quality-of-life measures as objective biomarkers such as tumor volume, fibroid number, and hemoglobin levels have dominated the focus of the clinical research on the topic of uterine fibroids. Black women having fibroids report much lower health-related quality of life (HRQoL) than fibroid-affected women of other races, even on controlling fibroid severity measures, which may implicate other aspects of their disease experience such as possible differences in the pain perception threshold, health literacy barriers, and mistrust of the medical system due to historical medical abuse in generating their worse quality-of-life measures. Patient-centered outcomes such as work productivity loss, sexual functioning and mental health were found to be of critical importance and systematically underinvestigated aspects of fibroid morbidity (Myers et al, 2002) that ought to be considered as part of the standard clinical assessment paradigm of fibroid management.

Clinical trials concerning the use of vitamin D supplements to prevent or manage fibroid in Black women in the future should use validated patient-reported outcome measures such as the Uterine Fibroid Symptom and Health-Related Quality of Life questionnaire (UFS-QoL), the PBAC menstrual bleeding pictogram, and the standardized pain assessment instruments as co-primary or secondary outcomes in addition to objective biomarkers. The clinical meaningfulness of any identified biological effect of treatment will be measured appropriately in the context of this patient-centered approach: women most directly affected by fibroid disease would have their views taken.

- *Community Engagement and Culturally Responsive Research*

The continuing low representation of Black women in clinical research, such as those on the vitamin D metabolism, supplementation efficacy, and fibroid management, have traditionally undermined the generalizability of the findings to the population with the highest risk and most in need of evidence-based advice. Research methodologies that are culturally responsive and involve communities like community-based participatory research (CBPR) methods are necessary to ensure that future vitamin D and fibroid studies will attain sufficient enrollment of Black females to the research, produce reliable results applicable to the lived experience of this population, and translate their findings into clinical and public health interventions accessible and acceptable to Black women.

Particular measures that will lead to increased Black women participation in vitamin D-fibroid studies involve community outreach utilizing Black churches, sororities and women health organizations; collaborating with Black-owned community health centers and OB/GYN practices whose patient populations are majority Blacks; compensation arrangements that consider time and transportation expenses of engaging in the research; culturally sensitive consent procedures and study materials, and the presence of Black women researchers, coordinators and community advisory board members in the research process. Segars et al. (2014) specifically identified more diversity in the participation and leadership of fibroid research scientists as a recommendation goal of the third NIH International Congress on Uterine Leiomyoma Research, acknowledging that the credibility and clinical utility of fibroid research evidence is garnered in large part by the genuine inclusion of the most affected by the disease populations in scientific leadership and participation.

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