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Vitamin D deficiency and risk of incident atrial fibrillation/flutter

A multicenter longitudinal cohort study

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Abstract

The association between vitamin D deficiency (VDD) and incident atrial fibrillation/flutter (AF) remains controversial due to conflicting evidence from cross-sectional studies. This study assessed the association between VDD and incident AF using a large-scale, multi-institutional cohort with propensity score matching. This longitudinal cohort study utilized the TriNetX platform, analyzing individuals aged ≥40 years with 2 serum 25-hydroxyvitamin D measurements between 2010 and 2023. Patients with sustained VDD (<20 ng/mL) were compared to controls (≥30 ng/mL) using 1:1 propensity score matching. The primary outcome was incident AF within 3 years. Dose–response analysis across vitamin D categories and subgroup analyses were performed. After matching, 137,407 patients were analyzed in each group. VDD was significantly associated with higher AF risk (hazard ratio [HR]: 1.83, 95% confidence interval: 1.68–1.99, $P < .001$). A clear dose–response relationship emerged, with HRs of 1.90 for severe deficiency (<10 ng/mL), 1.94 for moderate deficiency (10–20 ng/mL), and 1.60 for insufficiency (20–30 ng/mL). The association persisted during 3 to 6 year follow-up and was consistent across all AF subtypes. VDD was also associated with increased ischemic stroke and pneumonia risk. Subgroup analyses revealed that dyslipidemia significantly modified the VDD–AF association (HR: 1.84 vs 1.50 without dyslipidemia, $P = .017$). VDD was significantly associated with increased incident AF risk in a dose-dependent manner. These findings support VDD as a potentially modifiable risk factor and highlight the importance of vitamin D status in comprehensive cardiovascular risk assessment. Further prospective and interventional studies are warranted to validate these associations and clarify the underlying mechanisms.

Abbreviations: 25(OH)D = 25-hydroxyvitamin D, AF = atrial fibrillation/flutter, Af = atrial fibrillation, CI = confidence interval, HR = hazard ratio, SMD = standardized mean difference, VDD = vitamin D deficiency.

Keywords: atrial fibrillation, pneumonia, stroke, vitamin d deficiency, vitamin D status

1. Introduction

Atrial fibrillation/flutter (AF) represents the most prevalent sustained cardiac arrhythmia globally, affecting approximately 33.5 million individuals worldwide, with its prevalence projected to increase substantially due to population aging and rising cardiovascular comorbidities.[1–3] AF is associated with increased risks of heart failure, stroke, and mortality risk, imposing significant clinical and economic burdens on healthcare systems.[4–6] Beyond its well-recognized association with cardiovascular complications and increased risk of stroke, AF has been linked to a broad spectrum of adverse outcomes, including diminished physical performance, reduced quality of life, functional disability, and cognitive decline progressing to dementia.[7–12] Given the substantial morbidity and healthcare costs associated with AF management, preventive approaches targeting modifiable risk factors have emerged as essential components of contemporary cardiovascular care.

The association of vitamin D deficiency (VDD) with new-onset AF remains controversial, with existing evidence presenting

C-CK and K-CH contributed equally to this work.

Informed consent was not required for this retrospective study, as it involved secondary analysis of preexisting data without any interventions or direct participant interaction.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

The study protocol was approved by the Institutional Review Board of Chi Mei Medical Center, which granted a waiver of informed consent in compliance with its observational research regulations (IRB number: 11310-E04).

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conflicting findings.[13–18] Although several observational studies have suggested an association between low vitamin D levels and increased AF risk,[16,19,20] the causal relationship remains unclear owing to significant methodological limitations in the current literature. Most previous investigations have employed cross-sectional designs that cannot establish temporal relationships between vitamin D status and AF development.[16,19,20] Furthermore, many studies have failed to adequately control for important confounding variables, including cardiovascular comorbidities, medications, and non-cardiovascular factors, which may independently influence both vitamin D levels and arrhythmia risk. The lack of propensity score matching and insufficient follow-up periods in the existing research have further limited the ability to draw definitive conclusions regarding this potential association.

Therefore, we hypothesized that VDD is independently associated with an increased risk of incident AF. Using the extensive, multicenter TriNetX Research Network enabled robust propensity score matching and long-term follow-up across diverse populations, thereby enhancing the generalizability of our findings. Furthermore, the inclusion of a dose–response design allowed us to assess whether the risk of AF increased progressively with greater degrees of VDD, providing stronger evidence for a potential biological gradient.

2. Methods

2.1. Data source

This retrospective, multicenter cohort study was conducted using the TriNetX platform, which provides access to a broad spectrum of structured clinical data, including diagnostic codes, laboratory values, medical procedures, prescribed medications, and clinical outcomes, making it suitable for large-scale, real-world evidence analyses. TriNetX adheres to the Health Insurance Portability and Accountability Act Privacy Rule by ensuring that all personal identifiers are removed, thereby safeguarding patient confidentiality while enabling comprehensive research. The platform has been widely utilized in clinical investigations across fields such as surgery, chronic disease research, and population health.[21–23] As the data were de-identified and analyzed retrospectively, informed consent was not required. Ethical approval for the study was obtained from the Institutional Review Board of Chi Mei Medical Center (Institutional Review Board number: 11310-E04).

2.2. Study population

Individuals aged ≥40 years who had at least 2 serum 25-hydroxyvitamin D [25(OH)D] measurements between January 1, 2010, and December 31, 2023, were screened for eligibility. Participants were categorized based on their vitamin D status. Those who had 2 vitamin D measurements within a 3- to 12-month interval, both showing serum 25(OH)D levels below 20 ng/mL, were included in the VDD group. Conversely, patients whose 2 measurements within the same time interval exceeded 30 ng/mL were assigned to the control group, representing individuals with sustained vitamin D sufficiency. The index date was defined as the date of the 1st of the 2 qualifying 25(OH)D tests that met the inclusion criteria within the 3- to 12-month window. This approach ensured stable categorization of vitamin D status and minimized misclassification due to transient fluctuations.

Information regarding the standardization or harmonization of vitamin D assays across participating healthcare organizations was not available within the TriNetX platform. Each contributing institution performs laboratory testing according to its own certified local standards and quality-control procedures, which may involve different assay methods or reference ranges. As all data were de-identified and aggregated at the institutional level, assay harmonization could not be further verified.

2.3. Exclusion criteria

To ensure accurate identification of incident arrhythmia cases, individuals with any documented diagnosis of AF (International Classification of Diseases, 10th Revision: I48) prior to the index date were excluded. Patients with a history of stage 4 or 5 chronic kidney disease or end-stage renal disease were also excluded because of impaired vitamin D metabolism, commonly seen in advanced renal dysfunction. Other exclusion criteria included documented diagnoses of Crohn, liver cirrhosis, or prior use of antiarrhythmic medications, which could confound the relationship between vitamin D status and arrhythmia risk. Patients who had undergone heart transplantation at any time before the index date or who had received cardiac surgery within 3 months preceding the index date were likewise excluded.

To eliminate the influence of acute physiological stressors, individuals were excluded if they experienced any of the following conditions within 1 month prior to the index date: acute kidney injury, sepsis, coronavirus disease 2019 infection, intensive care unit admission, acute myocardial infarction, pericarditis, or myocarditis. Lastly, patients with electrocardiographic findings indicating corrected QT intervals >500 ms or <300 ms were excluded, given the known association between abnormal QT intervals and arrhythmia risk, independent of vitamin D status.

2.4. Data collection and propensity score matching

Patient demographics and clinical information were extracted from medical records covering the 3-year period preceding each individual's index date. To ensure comparability between groups and mitigate potential confounding, we applied 1:1 propensity score matching using a greedy nearest-neighbor algorithm without replacement. The matching algorithm incorporated demographic factors, such as age, sex, race, and body mass index, along with major comorbidities and pertinent laboratory results.

Given the well-established clinical predictors of AF, the propensity model also accounted for cardiovascular conditions commonly associated with elevated AF risk, including ischemic heart disease, heart failure, mitral valve abnormalities, and chronic obstructive pulmonary disease.[18,24–26] In addition, we adjusted for the use of medications that may influence AF risk, including glucagon-like peptide-1 receptor agonists, sodium–glucose co-transporter 2 inhibitors, and systemic corticosteroids.[27,28] Recognizing that nutritional status may act as a potential confounder, we further matched patients based on documented vitamin D supplementation to reduce residual bias.

2.5. Outcome definitions

We defined the primary outcome of interest as the occurrence of a 1st-time diagnosis of AF within 3 years after the index date. Given that atrial fibrillation (Af) is more prevalent than atrial flutter, we further evaluated the relationship between VDD and distinct AF subtypes, including paroxysmal, persistent, and permanent Af. To minimize the inclusion of undetected preexisting cases, a 30-day post-index exclusion window was applied. Secondary outcomes included ischemic stroke and pneumonia, with pneumonia serving as a positive control, given its established association with VDD.[29,30] Extended follow-up analysis examined outcomes occurring between years 3 and 6 post-index to assess the persistence of associations. All outcomes were identified using the appropriate International Classification of Diseases, 10th Revision diagnostic codes from the electronic medical records.

2.6. Dose–response relationship

To further explore a potential dose–response relationship and reinforce causal interpretation, we categorized patients with suboptimal vitamin D levels into 3 groups based on serum 25(OH)D concentrations: severe deficiency (<10 ng/mL), moderate deficiency (10–20 ng/mL), and insufficiency (20–30 ng/mL). Each group was independently compared with a shared reference cohort (≥30 ng/mL). This stratified approach enabled us to examine whether the risk of AF increased progressively with greater degrees of vitamin D inadequacy, thereby providing evidence of a biological gradient in the observed association.

2.7. Statistical analysis

Missing data for baseline covariates and laboratory variables were addressed using complete-case analysis. Because TriNetX provides de-identified, harmonized data aggregated from institutional electronic medical records, additional imputation was not feasible. Each participating organization contributes internally validated data that meet quality-control standards, minimizing the proportion of missing values in the analytic dataset. Baseline demographic and clinical characteristics were summarized using descriptive statistics. Continuous variables were reported as means with standard deviations, while categorical variables were expressed as counts and proportions. To assess the quality of matching, we examined standardized mean differences (SMDs), with values <0.1 considered indicative of adequate covariate balance. The distribution of propensity scores across groups was also reviewed graphically to ensure sufficient overlap.

Time-to-event analyses were conducted using Kaplan–Meier survival curves, with statistical differences between groups assessed using the log-rank test. Cox proportional hazards models were used to estimate hazard ratios (HRs) and the corresponding 95% confidence intervals (CI). To explore potential effect modification, pre-specified subgroup analyses were performed based on age (45–65 vs >65 years), sex, and common cardiovascular risk factors, including hypertension, diabetes mellitus, obesity, dyslipidemia, and ischemic heart disease. Statistical analyses were conducted using the TriNetX Analytics Platform. A 2-tailed *P*-value of <.05 was regarded as indicative of statistical significance.

3. Results

3.1. Patient selection and baseline characteristics

A total of 103,281,109 adult patients were initially identified from the TriNetX database between 2010 and 2023 (Fig. 1). Of these, 299,298 patients were diagnosed with VDD, and 1253,569 patients had vitamin D sufficiency. After applying the exclusion criteria, the cohort was reduced to 145,179 patients in the VDD group and 498,563 patients in the control group. Before propensity score matching, significant imbalances were observed in various baseline characteristics between the VDD and control groups (Table 1). The control group was notably older (60.5 ± 13.5 years vs 54.6 ± 14.1 years), had a higher proportion of females (71.4% vs 66.0%), and a higher percentage of White individuals (66.7% vs 41.0%). Disparities were also evident across several comorbidities, including dyslipidemia, neoplasms, and nicotine dependence. Laboratory data and medication use also showed significant imbalances, with the control group having a higher percentage of patients on antilipemic agents and vitamin D supplements.

After matching, 137,407 patients remained in each group, demonstrating excellent covariate balance with all SMDs falling below the 0.1 threshold, indicating adequate balance (Table 1). For instance, age at index was 55.2 ± 14.1 years in the VDD group and 55.6 ± 13.8 years in the control group (SMD = 0.029). Similarly, the proportion of females was 66.2% in the VDD group and 65.4% in the control group (SMD = 0.019). The improved overlap and balance of the propensity score distributions post-matching are visually represented in Figure 2.

3.2. Association between VDD and 3-year AF risk before matching

Within the early stage (3 years) follow-up, the incidence of AF was 1.10% in the VDD group versus 0.60% in the control group (HR: 1.27, 95% CI: 1.20–1.35, $P < .001$) (Table 2). Paroxysmal Af also showed a higher incidence in the VDD group (HR: 1.13, $P = .017$), as did permanent Af (HR: 1.20, $P = .038$). Persistent Af, however, did not show a statistically significant difference (HR: 0.91, 95% CI: 0.73–1.13, $P = .374$). Similarly, the VDD group had an increased risk of ischemic stroke (HR: 1.20, 95% CI: 1.15–1.26, $P < .001$) and pneumonia (HR: 1.22, 95% CI: 1.17–1.26, $P < .001$) in the early stages. During the late stage (3–6 years) follow-up, the elevated risks persisted. The risk of AF was higher in the VDD group than in the control group (HR: 1.24, 95% CI: 1.19–1.30, $P < .001$). Paroxysmal Af (HR: 1.17, $P < .001$) and permanent Af (HR: 1.32, $P < .001$) remained significantly higher in the VDD group. Ischemic stroke (HR: 1.26, $P < .001$) and pneumonia (HR: 1.15, $P < .001$) also continued to show an increased risk in the VDD group.

3.3. Association between VDD and 3-year AF risk after matching

After matching, the association between VDD and the risk of incident AF, ischemic stroke, and pneumonia became more pronounced (Table 3). During the 3-year follow-up period, individuals in the VDD group were associated with a significantly higher risk of incident AF compared to the control group (HR: 1.83, 95% CI: 1.68–1.99, $P < .001$). All subtypes of AF also showed increased risks: paroxysmal Af (HR: 1.70, $P = .017$), persistent Af (HR: 1.60, $P = .003$), and permanent Af (HR: 1.48, $P = .001$). Consistent with the pre-matched analysis, ischemic stroke (HR: 1.39, $P < .001$) and pneumonia (HR: 1.37, $P < .001$) also showed significantly elevated risks in the VDD group. The sustained risk was further confirmed in the 3 to 6 year follow-up period after matching (Table 3). The VDD group continued to exhibit a significantly higher risk of AF (HR: 1.74, 95% CI: 1.63–1.86, $P < .001$). Similar trends were observed for paroxysmal Af (HR: 1.76, $P < .001$), persistent Af (HR: 1.51, $P < .001$), and permanent Af (HR: 1.92, $P < .001$). The risks of ischemic stroke (HR: 1.51, $P < .001$) and pneumonia (HR: 1.33, $P < .001$) also remained significantly elevated in the VDD group.

3.4. Dose–response relationship

At the 3-year follow-up, analysis of the dose–response relationship demonstrated a stepwise increase in the risks of AF, ischemic stroke, and pneumonia corresponding to the severity of VDD (Table 4). Compared to the control group (≥30 ng/mL), patients with severe VDD (<10 ng/mL) had the highest risk of AF (HR: 1.90, 95% CI: 1.60–2.27, $P < .001$). This risk slightly decreased in the moderate deficiency group (10–20 ng/mL) (HR: 1.94, 95% CI: 1.75–2.14, $P < .001$), and further in the insufficiency group (20–30 ng/mL) (HR: 1.60, 95% CI: 1.50–1.71, $P < .001$). A similar dose–response pattern was observed for ischemic stroke, with HRs of 1.47 ($P < .001$) for severe deficiency, 1.36 ($P < .001$) for moderate deficiency, and 1.16 ($P < .001$) for insufficiency. Pneumonia also demonstrated a dose-dependent relationship with HRs of 1.42 ($P < .001$) for severe deficiency, 1.32 ($P < .001$) for moderate deficiency, and 1.18 ($P < .001$) for insufficiency.

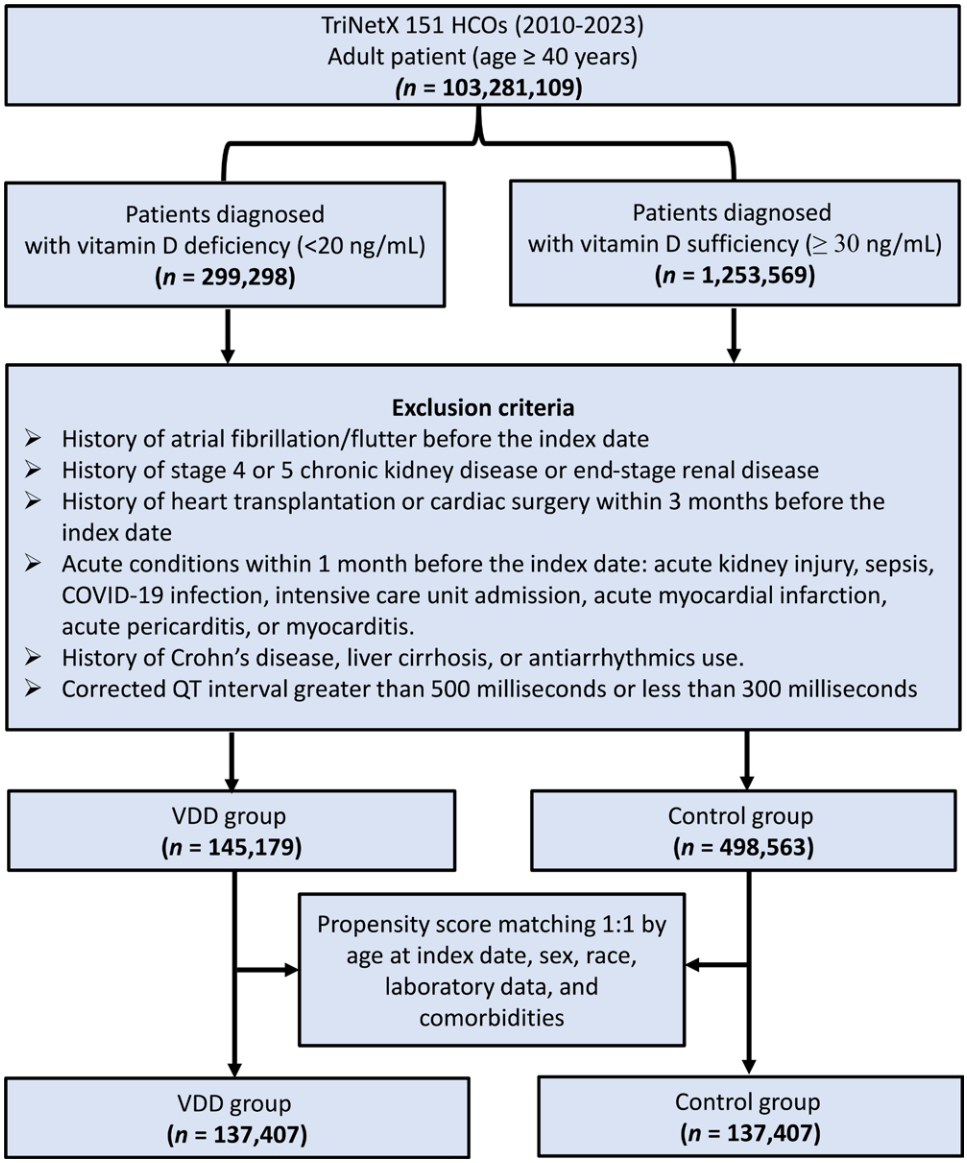


Figure 1. Patient selection flowchart from the TriNetX database. The flowchart illustrates the systematic exclusion process applied to identify eligible patients with vitamin D deficiency (VDD) and vitamin D sufficiency (control group). HCOs = healthcare organizations.

3.5. Subgroup analysis

Subgroup analyses were conducted to explore potential effect modification by various demographic and clinical factors on the association between VDD and the risk of AF at the 3-year follow-up (Table 5). The increased risk of AF associated with VDD was consistently observed across all pre-specified subgroups, including sex, age categories (40–65 years and >65 years), hypertension status, diabetes mellitus status, obesity status, and ischemic heart disease status. However, dyslipidemia emerged as a significant modifier of the association between VDD and AF risk (*P* for interaction = .017). Patients with dyslipidemia showed a stronger association between VDD and AF risk (HR: 1.84) than those without dyslipidemia (HR: 1.50).

3.6. Multivariable Cox regression analysis of independent predictors

Multivariable Cox proportional hazards regression analysis was performed to identify independent risk factors for incident AF (Table 6). After adjusting for male sex, age at index, diabetes mellitus, chronic kidney disease, and other cardiovascular disease, VDD remained a significant and independent risk factor for incident AF, with an adjusted HR of 1.80 (95% CI: 1.70–1.91, $P < .001$).

4. Discussion

Our analysis of 274,814 propensity-matched patients revealed that VDD was associated with the risk of developing AF (HR: 1.83) over a 3-year follow-up period. This association demonstrates several important characteristics that strengthen the evidence for a potential causal relationship. First, we observed a clear dose–response relationship, with the highest risk among patients with moderate-to-severe VDD (HR: 1.90 for severe, and HR:1.94 for moderate) compared to those with insufficiency (HR: 1.60). Second, the association persisted across all major subtypes of AF, including the paroxysmal, persistent, and permanent forms. Third, the elevated risk remained significant during extended follow-up (3–6 years), suggesting that VDD may have lasting effects on arrhythmogenic processes. Additionally, our findings were validated by parallel increases in pneumonia risk, a well-established consequence of VDD, and were consistent across diverse patient subgroups, indicating broad clinical relevance.

Table 1

Baseline characteristics of patients before and after propensity score matching.

Variables	Before matching			After matching		
	VDD group (n = 145,179)	Control group (n = 498,563)	SMD*	VDD group (n = 137,407)	Control group (n = 137,407)	SMD*
Patient characteristics						
Age at index (yr)	54.6 ± 14.1	60.5 ± 13.5	0.424	55.2 ± 14.1	55.6 ± 13.8	0.029
Female	95,748 (66.0%)	356,094 (71.4%)	0.118	91,019 (66.2%)	89,809 (65.4%)	0.019
BMI ≥ 30 kg/m^2	32,494 (22.4%)	89,506 (18.0%)	0.111	28,917 (21.0%)	29,787 (21.7%)	0.015
White	59,529 (41.0%)	332,531 (66.7%)	0.533	59,279 (43.1%)	56,689 (41.3%)	0.038
Black or African American	27,135 (18.7%)	36,996 (7.4%)	0.339	21,851 (15.9%)	21,883 (15.9%)	0.001
Asian	6887 (4.7%)	22,213 (4.5%)	0.014	6814 (5.0%)	6560 (4.8%)	0.009
Comorbidities						
Essential (primary) hypertension	34,479 (23.7%)	136,496 (27.4%)	0.083	31,879 (23.2%)	32,341 (23.5%)	0.008
Dyslipidemia	30,598 (21.1%)	151,778 (30.4%)	0.215	29,312 (21.3%)	29,750 (21.7%)	0.008
Diabetes mellitus	19,389 (13.4%)	59,013 (11.8%)	0.046	17,471 (12.7%)	17,612 (12.8%)	0.003
Neoplasms	16,226 (11.2%)	72,367 (14.5%)	0.100	15,494 (11.3%)	15,335 (11.2%)	0.004
Overweight and obesity	17,081 (11.8%)	45,198 (9.1%)	0.088	14,969 (10.9%)	15,447 (11.2%)	0.011
Nicotine dependence	6987 (4.8%)	14,173 (2.8%)	0.103	5700 (4.1%)	5572 (4.1%)	0.005
Other anemias	6330 (4.4%)	20,052 (4.0%)	0.017	5614 (4.1%)	5545 (4.0%)	0.003
Ischemic heart diseases	4464 (3.1%)	18,499 (3.7%)	0.035	4189 (3.0%)	4154 (3.0%)	0.001
Obstructive sleep apnea	4579 (3.2%)	16,120 (3.2%)	0.005	4172 (3.0%)	4131 (3.0%)	0.002
Chronic kidney disease	4416 (3.0%)	20,478 (4.1%)	0.057	4131 (3.0%)	4148 (3.0%)	0.001
Diseases of liver	3892 (2.7%)	11,963 (2.4%)	0.018	3510 (2.6%)	3359 (2.4%)	0.007
COPD	2831 (2.0%)	9304 (1.9%)	0.006	2555 (1.9%)	2467 (1.8%)	0.005
Alcohol related disorders	1913 (1.3%)	3306 (0.7%)	0.066	1432 (1.0%)	1437 (1.0%)	<0.001
Heart failure	1659 (1.1%)	4331 (0.9%)	0.027	1421 (1.0%)	1392 (1.0%)	0.002
COVID-19	1326 (0.9%)	5542 (1.1%)	0.020	1278 (0.9%)	1286 (0.9%)	0.001
Nonrheumatic mitral valve disorders	844 (0.6%)	5396 (1.1%)	0.055	809 (0.6%)	805 (0.6%)	<0.001
Venous embolism and thrombosis	888 (0.6%)	2794 (0.6%)	0.007	801 (0.6%)	748 (0.5%)	0.005
Long-term (current) use of steroids	695 (0.5%)	2878 (0.6%)	0.014	645 (0.5%)	628 (0.5%)	0.002
Rheumatic mitral valve diseases	136 (0.1%)	763 (0.2%)	0.017	124 (0.1%)	129 (0.1%)	0.001
Laboratory data						
Hemoglobin ≥ 12 mg/dL	77,724 (53.5%)	259,344 (52.0%)	0.030	73,588 (53.6%)	75,375 (54.9%)	0.026
Hemoglobin A1c > 7%	13,734 (9.5%)	32,461 (6.5%)	0.109	12,005 (8.7%)	12,211 (8.9%)	0.005
Albumin g/dL (≥3.5 g/dL)	69,638 (48.0%)	245,363 (49.2%)	0.025	65,331 (47.5%)	67,359 (49.0%)	0.030
eGFR > 60 mL/min/1.73 m^2	83,129 (57.3%)	267,447 (53.6%)	0.073	77,639 (56.5%)	79,101 (57.6%)	0.021
Medications						
Antilipemic agents	20,307 (14.0%)	94,456 (18.9%)	0.134	19,090 (13.9%)	19,062 (13.9%)	0.001
Vitamin D supplements	11,176 (7.7%)	92,720 (18.6%)	0.327	11,108 (8.1%)	12,305 (9.0%)	0.031
Beta blockers	12,172 (8.4%)	46,220 (9.3%)	0.031	11,065 (8.1%)	11,114 (8.1%)	0.001
Calcium channel blockers	11,660 (8.0%)	39,110 (7.8%)	0.007	10,347 (7.5%)	10,364 (7.5%)	<0.001
Insulin	7352 (5.1%)	16,189 (3.2%)	0.091	6149 (4.5%)	6160 (4.5%)	<0.001
GLP-1	1937 (1.3%)	8499 (1.7%)	0.030	1830 (1.3%)	1901 (1.4%)	0.004
Antianginals	1820 (1.3%)	5984 (1.2%)	0.005	1611 (1.2%)	1589 (1.2%)	0.001
SGLT2 inhibitors	1218 (0.8%)	5600 (1.1%)	0.029	1158 (0.8%)	1191 (0.9%)	0.003

BMI = body mass index, COPD = chronic obstructive pulmonary disease, eGFR = estimated glomerular filtration rate, GLP-1 = glucagon-like peptide-1, SGLT2 = sodium–glucose co-transporter 2, SMD = standardized mean differences, VDD = vitamin D deficiency.

*SMD values <0.1 indicate adequate balance between groups.

The biological mechanisms underlying the association between VDD and AF involve multiple interconnected pathways that affect cardiac electrophysiology and structural remodeling. Vitamin D receptors are widely distributed throughout cardiac tissue, including cardiomyocytes, fibroblasts, and vascular smooth muscle cells, enabling the direct modulation of cardiac function.[31,32] VDD promotes cardiac fibrosis through the activation of the renin–angiotensin–aldosterone system, leading to increased collagen deposition and atrial structural remodeling, which creates a substrate for arrhythmia maintenance.[33,34] Additionally, VDD impairs calcium homeostasis by reducing calcium-binding protein expression and altering intracellular calcium handling,[35] which disrupts normal cardiac conduction. The deficiency also triggers inflammatory processes, elevating cytokines such as interleukin-6 and tumor necrosis factor-alpha,[36] which contribute to atrial electrical remodeling.

Our pre-matching analysis revealed only a modest association between VDD and AF risk (HR, 1.27). This weak association likely reflects the substantial baseline differences between patient groups, including age, comorbidity burden, and medication use patterns, which independently influence both vitamin D status and arrhythmia risk. However, after implementing propensity score matching to balance these confounders, we observed a dramatically stronger association (HR: 1.83), suggesting that previous studies may have significantly underestimated the true relationship owing to the inadequate control of confounding factors. The dose–response relationship we identified provides additional evidence supporting a causal interpretation of our findings. The clear threshold effect observed between vitamin D insufficiency (HR: 1.60) and deficiency categories (HR: 1.90–1.94) demonstrates a biological gradient that is characteristic of causal associations. Notably, individuals with vitamin D insufficiency (25(OH)D 20–30 ng/mL) also exhibited a significantly increased risk compared to those with sufficient vitamin D levels, suggesting that the threshold for cardiovascular protection may be higher than that traditionally recognized for bone health.

Previous studies investigating VDD and AF have typically treated AF as a single entity without distinguishing between its clinical subtypes. Our study addresses this important gap by demonstrating that VDD increases the risk across all major

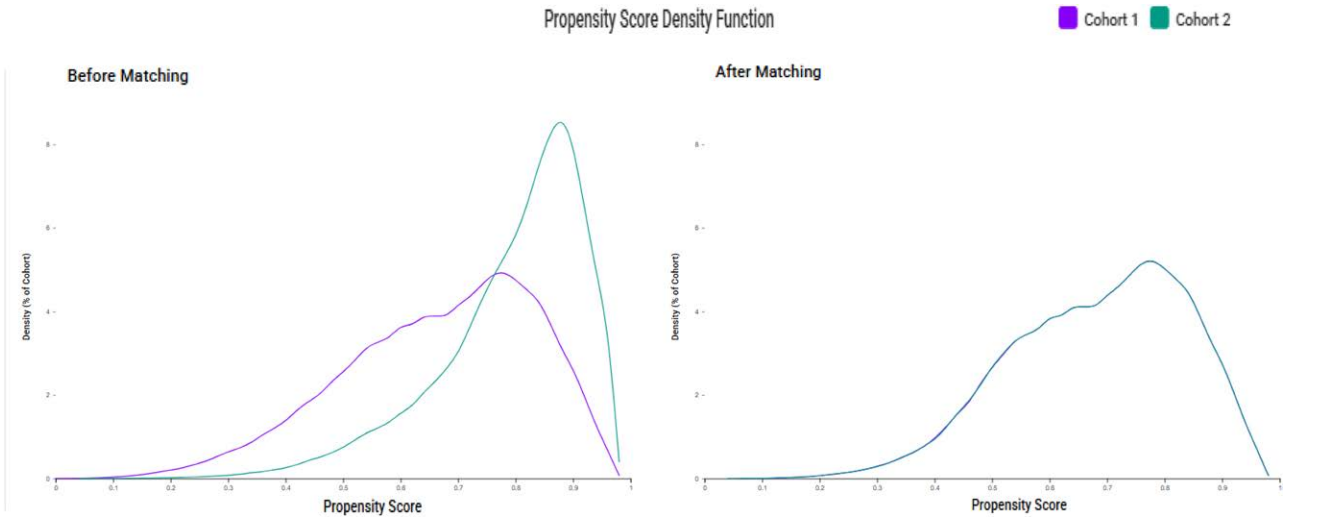


Figure 2. The propensity score distributions for the vitamin D deficiency (VDD) group (Cohort 1, purple) and the matched control group (Cohort 2, green). In the left panel, the pre-matching distribution reveals clear divergence between cohorts, suggesting a baseline imbalance. In contrast, the right panel displays the post-matching distribution following 1:1 propensity score matching based on demographics (age, sex, and race), laboratory values, and comorbidities. The improved overlap demonstrates the successful balancing of covariates and enhanced comparability between groups.

Table 2

Association between vitamin D deficiency and risk of atrial fibrillation/flutter before matching.

Outcomes	VDD group (n = 145,179)	Control group (n = 498,563)		
	Events (%)	Events (%)	HR (95% CI)	*P*-value
Early stage (3 yr)				
AF	1509 (1.10%)	817 (0.60%)	1.27 (1.20–1.35)	<.001
Paroxysmal Af	534 (0.37%)	1617 (0.32%)	1.13 (1.02–1.24)	.017
Persistent Af	104 (0.07%)	391 (0.08%)	0.91 (0.73–1.13)	.374
Permanent Af	174 (0.12%)	495 (0.10%)	1.20 (1.01–1.43))	.038
Ischemic stroke	2400 (1.65%)	6855 (1.37%)	1.20 (1.15–1.26)	<.001
Pneumonia	4493 (3.08%)	12,682 (2.54%)	1.22 (1.17–1.26)	<.001
Late stage (3–6 yr)				
AF	2492 (1.71%)	6326 (1.27%)	1.24 (1.19–1.30)	<.001
Paroxysmal Af	1147 (0.79%)	3081 (0.62%)	1.17 (1.09–1.25)	<.001
Persistent Af	264 (0.18%)	838 (0.17%)	0.98 (0.85–1.12)	.760
Permanent Af	418 (0.29%)	988 (0.20%)	1.32 (1.18–1.48)	<.001
Ischemic stroke	2206 (1.51%)	5530 (1.11%)	1.26 (1.20–1.32)	<.001
Pneumonia	3857 (2.65%)	10,513 (2.11%)	1.15 (1.11–1.19)	<.001

Af = atrial fibrillation, AF = atrial fibrillation/flutter, CI = confidence interval, HR = hazard ratio, VDD = vitamin D deficiency.

AF subtypes, including paroxysmal, persistent, and permanent forms. Interestingly, the finding that permanent AF showed progressively increasing risk ratios from the early (HR: 1.48) to late follow-up periods (HR: 1.92) suggests that VDD may not only trigger initial arrhythmia episodes but also promote progression to more sustained forms of AF. This pattern is consistent with the known effects of VDD on atrial structural remodeling,[37] which is expected to facilitate the transition from paroxysmal to persistent and ultimately permanent AF. These subtype-specific findings have important clinical implications, as they suggest that VDD may influence both the initiation and progression of atrial arrhythmias.

The parallel increase in pneumonia risk among vitamin D-deficient patients serves as an important biological validation of our findings, given the well-established association between VDD and increased susceptibility to respiratory infections.[29,30] The dose–response relationship for pneumonia (HR ranging from 1.18 for insufficiency to 1.42 for severe deficiency) closely paralleled our AF findings, providing confidence that our observed associations reflect true biological effects rather than residual confounding or methodological artifacts. Our observation of increased ischemic stroke risk, particularly during the late stage follow-up period (HR: 1.51), provides additional clinical information for understanding the broader cardiovascular consequences of VDD. The temporal pattern of stroke risk increase aligns with the expected natural history of AF progression, as patients who develop AF subsequently face an elevated thromboembolic risk. The finding that stroke risk showed the most pronounced increase during the 3 to 6 year follow-up period (compared to 1–3 years) is consistent with the concept that stroke risk accumulates as AF burden increases over time. This delayed stroke risk elevation supports the hypothesis that VDD initiates a cascade of cardiovascular complications, beginning with arrhythmia development and subsequently leading to thromboembolic events.

Our subgroup analyses revealed an important finding regarding effect modification by dyslipidemia status. The significantly stronger relationship between VDD and AF risk in individuals with dyslipidemia (HR: 1.84) than in those without dyslipidemia (HR: 1.50, *P* for interaction = .017) suggests that dyslipidemia may act as a synergistic risk factor. This finding has important clinical implications, as it indicates that patients

Table 3

Association between VDD and risk of atrial fibrillation/flutter after matching.

Outcomes	VDD group (n = 137,407)	Control group (n = 137,407)		
	Events (%)	Events (%)	HR (95% CI)	*P*-value
Early stage (3 yr)				
AF	1509 (1.10%)	817 (0.60%)	1.83 (1.68–1.99)	<.001
Paroxysmal Af	516 (0.38%)	300 (0.22%)	1.70 (1.47–1.96)	.017
Persistent Af	101 (0.07%)	62 (0.05%)	1.60 (1.17–2.20)	.003
Permanent Af	170 (0.12%)	113 (0.08%)	1.48 (1.17–1.88)	.001
Ischemic stroke	2245 (1.63%)	1607 (1.17%)	1.39 (1.30–1.48)	<.001
Pneumonia	4177 (3.04%)	3020 (2.20%)	1.37 (1.31–1.44)	<.001
Late stage (3–6 yr)				
AF	2402 (1.75%)	1265 (0.92%)	1.74 (1.63–1.86)	<.001
Paroxysmal Af	1096 (0.80%)	568 (0.41%)	1.76 (1.59–1.95)	<.001
Persistent Af	251 (0.18%)	150 (0.11%)	1.51 (1.23–1.85)	<.001
Permanent Af	403 (0.29%)	190 (0.14%)	1.92 (1.62–2.28)	<.001
Ischemic stroke	2069 (1.51%)	1260 (0.92%)	1.51 (1.41–1.62)	<.001
Pneumonia	3655 (2.66%)	2505 (1.82%)	1.33 (1.26–1.40)	<.001

Af = atrial fibrillation, AF = atrial fibrillation/flutter, CI = confidence interval, HR = hazard ratio, VDD = vitamin D deficiency.

Table 4

Dose–response relationship across different levels of 25(OH)D at 3-year follow-up.

	Severe VDD vs control group*		Moderate VDD vs control group†		VDI vs control group‡	
Outcomes	HR (95% CI)	*P*-values	HR (95% CI)	*P*-values	HR (95% CI)	*P*-values
AF	1.90 (1.60–2.27)	<.001	1.94 (1.75–2.14)	<.001	1.60 (1.50–1.71)	<.001
Ischemic stroke	1.47 (1.27–1.69)	<.001	1.36 (1.26–1.46)	<.001	1.16 (1.10–1.22)	<.001
Pneumonia	1.42 (1.29–1.58)	<.001	1.32 (1.25–1.39)	<.001	1.18 (1.14–1.22)	<.001

AF = atrial fibrillation/flutter, CI = confidence interval, HR = hazard ratio, VDI = vitamin D insufficiency (25(OH)D 20–30 ng/mL), moderate VDD = vitamin D deficiency (25(OH)D 10–20 ng/mL), severe VDD = 25(OH)D < 10 ng/mL, 25(OH)D = 25-hydroxyvitamin D.

*n = 23993 for each group.

†n = 101,903 for each group.

‡n = 241,977 for each group.

Table 5

Subgroup analyses of association between vitamin D deficiency and risk of atrial fibrillation/flutter at 3-year follow-up.

Subgroup analysis	N for each group	HR (95% CI)	*P*-value	*P* for interaction
Sex				
Male	43,283	1.72 (1.50–1.96)	<.001	Reference
Female	90,913	1.82 (1.62–2.05)	<.001	.534
Age				
40–65 yr	76,919	1.85 (1.47–2.32)	<.001	Reference
>65 yr	59,777	1.65 (1.51–1.80)	<.001	.383
Dyslipidemia				
Yes	55,526	1.84 (1.63–2.08)	<.001	Reference
No	81,402	1.50 (1.35–1.68)	<.001	.017
Hypertension				
Yes	52,717	1.68 (1.50–1.88)	<.001	Reference
No	84,180	1.75 (1.54–1.98)	<.001	.637
Diabetes mellitus				
Yes	30,057	1.74 (1.49–2.03)	<.001	Reference
No	106,674	1.74 (1.57–1.92)	<.001	1.000
Obesity				
Yes	31,155	2.06 (1.69–2.51)	<.001	Reference
No	105,722	1.68 (1.53–1.85)	<.001	.091
Ischemic heart disease				
Yes	10,042	1.75 (1.44–2.12)	.001	Reference
No	127,318	1.75 (1.59–1.92)	<.001	1.000

CI = confidence interval, HR = hazard ratio

with both VDD and dyslipidemia may represent a particularly high-risk subgroup for developing AF. The biological mechanism underlying this interaction may involve the convergent effects of VDD and dyslipidemia on endothelial dysfunction, oxidative stress, and inflammatory pathways that contribute to atrial remodeling. This observation supports a more targeted approach to vitamin D assessment and potential supplementation, particularly in patients with dyslipidemia.

These results have important implications for clinical decision-making and the development of targeted preventive strategies

Table 6

Multivariable Cox regression analysis of independent predictors for new-onset atrial fibrillation/flutter.

Variable	HR (95% CI)	*P*-value
VDD group vs control group	1.80 (1.70–1.91)	<.001
Male	1.58 (1.49–1.67)	<.001
Age at index	1.09 (1.09–1.09)	<.001
Diabetes mellitus	1.18 (1.10–1.27)	<.001
Chronic kidney disease (CKD)	1.21 (1.10–1.32)	<.001
Heart failure	2.04 (1.80–2.31)	<.001
Ischemic heart diseases	1.47 (1.34–1.60)	<.001
Nonrheumatic mitral valve disorders	1.42 (1.20–1.67)	<.001
Essential (primary) hypertension	1.22 (1.15–1.29)	<.001

CI = confidence interval, HR = hazard ratio.

in cardiology. The substantial increase in AF risk associated with VDD, combined with the dose–response relationship and persistence of effects over extended follow-up, suggests that vitamin D status assessment should be considered as part of comprehensive cardiovascular risk evaluation. Given the high prevalence of VDD in many populations and the potentially modifiable nature of this risk factor, screening and supplementation programs may represent cost-effective approaches to AF prevention.

Several limitations of our study must be acknowledged. First, we cannot definitively establish causality despite the strong associations and dose–response relationships observed. Residual confounding may persist despite our comprehensive propensity matching approach, particularly from unmeasured variables such as dietary patterns, sun exposure, and socioeconomic factors that influence both vitamin D status and cardiovascular health. Second, our reliance on diagnostic coding for outcome identification may have resulted in some misclassification, although the use of multiple healthcare institutions and consistent coding practices across the TriNetX network likely minimized systematic bias. Third, we lacked information about vitamin D supplementation compliance and dosing regimens, which could have influenced the relationship between the measured vitamin D levels and clinical outcomes. Fourth, our study population was predominantly derived from healthcare systems in specific geographic regions, which may limit the generalizability to other populations with different demographic characteristics, healthcare practices, or environmental vitamin D exposure patterns. Finally, the observational nature of our study design prevents the assessment of whether vitamin D supplementation might modify AF risk in deficient patients, which remains an important question for future randomized controlled trials.

5. Conclusion

This large-scale, multi-institutional cohort study provides evidence that VDD is significantly associated with the risk of incident AF in a dose-dependent manner. This association persists across all major AF subtypes, remains significant during extended follow-up, and is consistent across diverse patient subgroups. Importantly, dyslipidemia emerged as a significant effect modifier, with patients having both VDD and dyslipidemia showing particularly elevated AF risk (HR: 1.84 vs 1.50 in those without dyslipidemia). Although randomized controlled trials are needed to establish causality and optimal intervention strategies, these findings suggest that vitamin D status assessment should be considered as part of comprehensive cardiovascular risk evaluation, with particular attention paid to patients with concurrent dyslipidemia.

Author contributions

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