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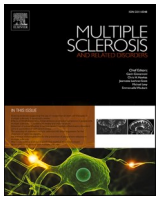

Original article

Vitamin D and cardiovascular outcomes in multiple sclerosis

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ABSTRACT

Background: Vitamin D (25(OH)D) deficiency is linked to increased cardiovascular disease (CVD) risk in the general population, but its implications for people with multiple sclerosis (pwMS) remain unexplored. This study aimed to evaluate the association of 25(OH)D with long-term CVD outcomes in pwMS and the impact of vitamin D supplementation.

Methods: This observational cohort study analysed anonymised medical records from 70 healthcare organisations following pwMS for 5-years (2019–2024). PwMS and deficient or inadequate 25(OH)D levels were 1:1 propensity-score matched with pwMS and adequate 25(OH)D levels, for demographics, comorbidities, and cardiovascular care. Cox proportional hazard models analysed the incidence of all-cause mortality, stroke, acute myocardial infarction, heart failure, angina, atrial fibrillation/flutter, and a composite measure of major adverse cardiovascular events (MACE). Propensity-matched pwMS who had deficient or inadequate 25(OH)D levels taking cholecalciferol were compared to pwMS and adequate 25(OH)D levels (not taking supplementation).

Results: Amongst 74,372 pwMS, 9 % had deficient 25(OH)D levels, 18 % inadequate, and 73 % adequate. Deficient, or inadequate 25(OH)D levels were associated with an increased rate of MACE (HR, 1.32 [95 % CI: 1.19, 1.46], HR, 1.29 [95 % CI: 1.20, 1.40], respectively) compared to those with adequate levels. Cholecalciferol supplementation in pwMS and deficient or inadequate 25(OH)D levels did not alleviate the higher CVD rate (HR, 1.39 [95 % CI: 1.21,1.60], HR, 1.31 [95 % CI: 1.17, 1.47], respectively) in comparison to those with adequate 25 (OH)D levels taking no vitamin D supplementation.

Conclusions: Deficient or inadequate 25(OH)D levels in pwMS were associated with an increased rate of MACE, which may not be mitigated by vitamin D supplementation.

Introduction

Affecting an estimated 2.8 million people globally (Walton et al., 2020), multiple sclerosis (MS) is a chronic inflammatory disease characterised by progressive demyelination in the central nervous system. People diagnosed with MS exhibit an elevated risk of cardiovascular disease (CVD) compared to their demographically matched counterparts without MS (Hong et al., 2019; Rapp et al., 2021; Persson et al., 2020; Palladino et al., 2020; Marrie et al., 2015). A Mendelian randomisation study suggested a genetic link between the risk of MS and CVD (Yang

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et al., 2022). Additionally, the chronic recurrent episodes of MS are hypothesised to contribute to the long-term development of cardiovascular dysfunction (Mincu et al., 2015).

Emerging research suggests that vitamin D deficiency is a growing public health concern on a global scale (Holick and Chen, 2008). Vitamin D deficiency may be a potential contributor to the pathogenesis of CVDs in the general population (Janjusevic et al., 2022; Izzo et al., 2021). Moreover, research in people with MS (pwMS) has revealed that they possess significantly lower serum levels of vitamin D, measured using 25-hydroxyvitamin D (25(OH)D), in comparison to control subjects without MS (Correale et al., 2008; van der Mei et al., 2007). The prevalence of MS varies across the globe, with the greatest incidence typically observed at extreme latitudes in both northern and southern hemispheres. This observation may imply a correlation with sunlight exposure and, subsequently, vitamin D levels (Hassan-Smith and Douglas, 2011). Despite a potential association between low vitamin D and both MS risk and progression (Moosazadeh et al., 2021; Sintzel et al., 2018), the impact of 25(OH)D levels on the rate of CVD within pwMS remains unexplored.

While a consistent association between vitamin D deficiency and increased risk of cardiovascular outcomes has been documented in the general population, research on the potential mitigating effect of vitamin D supplementation remains inconclusive (Janjusevic et al., 2022; Izzo et al., 2021; Burgess and Gill, 2021). One study in 20,025 patients with no prior history of myocardial infarction, found that vitamin D supplementation in those with 25(OH)D levels >20ng/mL and >30ng/mL were associated with a significantly lower risk of all-cause mortality (Acharya et al., 2021). Whilst another study in 176 patients with suspected coronary atherosclerosis found that vitamin D supplementation was associated with better coronary atherosclerosis profiles, independent of cardiovascular risk factors (Feuchtner et al., 2021). Despite these promising results, many other studies have failed to show a meaningful effect of vitamin D supplementation on cardiovascular disease (Scragg et al., 2017; Manson et al., 2019; Thompson et al., 2023; Barbarawi et al., 2019). Vitamin D supplementation did not improve recognised cardiovascular risk factors such as biomarkers of glycaemia, inflammation, neurohormonal action and lipids in the DAYLIGHT trial (Miao et al., 2021). Additionally, research investigating the impact of vitamin D supplementation in other neurological conditions, Parkinson's disease (Zhou et al., 2019) and Alzheimer's disease (Landel et al., 2016), have not shown beneficial results. Furthermore, despite a cross-sectional study in >2,000 pwMS finding that 81.8 % of participants took vitamin D supplementation (Jelinek et al., 2015), the relationship between vitamin D supplementation and cardiovascular outcomes has not been previously investigated in pwMS.

Therefore, the aims of this study were 1) to assess the prevalence of vitamin D levels in pwMS, 2) to examine the association of vitamin D deficiency on the incidence of cardiovascular outcomes in pwMS within a 5-year follow-up period, and 3) to investigate the association of vitamin D supplementation on cardiovascular outcomes in pwMS and vitamin D deficiency.

Methods

Study design

This observational cohort study utilised anonymised data within TriNetX®, a global federated health research network that accesses electronic medical records (EMR) from various academic medical centres, specialty physician practices, and community hospitals, primarily in the USA (Palchuk et al., 2023). When institutions submit data to the network, it undergoes mapping to standardised clinical terminologies. TriNetX® conducts regular internal evaluations and thorough data quality assessments during each update, focusing on conformance, completeness, and plausibility (Kahn et al., 2016). As a federated network, research conducted via TriNetX® does not require ethical approval or informed consent, as no personally identifiable information is obtained. Access to TriNetX® data can be requested via the platform's interface (https://live.trinetx.com); however, this may involve associated expenses, necessitate a data-sharing agreement, and does not permit access of identifiable participant information.

The TriNetX® network was searched on June 10, 2024, and deidentified datasets with a minimum follow-up of 5 years from the index event (MS and vitamin D measurement recorded in database) were examined. The EMR data comprised de-identified details concerning participant demographics, diagnoses, procedures, medications, and laboratory measurements. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, as outlined in the Supplementary material, Table S1. At the time of the search, 70 (primarily USA-based) participating healthcare organisations had data available for individuals who met the study inclusion criteria in the Global Collaborative Network.

Cohort

PwMS identified with at least 5-years of follow-up data from 2019 to 2024 were included using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code G35 (MS). PwMS were included with a measurement of 25-hydroxyvitamin D2 (25(OH)D) that occurred within 6 months before or 6 months after record of MS in the database, using the Logical Observation Identifiers Names and Codes (LOINC) 1989–3.

Exposure

To assess the association between deficient and inadequate 25(OH)D levels compared to adequate 25(OH)D levels in pwMS on long-term cardiovascular outcomes, pwMS were first disaggregated by categories of 25(OH)D levels. Categories were defined as deficient (<12ng/mL), inadequate (13–20ng/mL), a composite of deficient/inadequate (<20ng/mL), or adequate (24–150ng/mL) (National Institutes of Health Office of Dietary Supplements 2024). Participants taking vitamin D supplementation within 6 months before or 1 year after record of MS in the database were identified using the RxNorm code 2418 (cholecalciferol), whilst those taking no vitamin D supplementation within 6 months before or 1 year after record of MS in the database were identified using the RxNorm codes 2418 (cholecalciferol), 1894 (calcitriol), 12062 (alfacalcidol), and 11253 (vitamin D).

Statistical analysis

All statistical analyses were completed within the TriNetX online platform. Forest plots for all analyses were created in R-Studio (2024.04.1 + 748). Baseline characteristics were compared using χ^2 tests or independent-sample *t* tests. Participants were propensity score matched for age, sex, race, kidney function (eGFR: MDRD), body mass index (BMI), cardiovascular comorbidities (including ischemic heart diseases, heart failure, diabetes mellitus), autoimmune conditions, mental health disorders (including anxiety and depression), nicotine dependence, socioeconomic status, cardiovascular procedures (including electrocardiography, echocardiography, catheterisation, cardiac devices, and electrophysiological procedures), analgesics, antidepressants, cardiovascular medications (including β-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, and angiotensin-converting-enzyme inhibitors), and vitamin D supplement use. Covariate balance between groups was assessed using standardised mean differences (SMDs). Baseline characteristics with a SMD between cohorts score lower than 0.1 was considered well matched (Haukoos and Lewis, 2015). Results are reported as hazard ratio (HR) with 95 % confidence intervals (CIs) and Kaplan-Meier survival curves with log-rank tests. No imputations were made for missing data. Censoring was applied, and a patient was removed (censored) from the

analysis after the last event in their electronic record. Models produced HRs with 95 % CIs for 1-day to 5-year incidence of all-cause mortality, ischemic stroke (cerebrovascular infarction, ICD-10-CM:I63), acute myocardial infarction (ICD-10-CM:I21), heart failure (ICD-10-CM:I50), angina (ICD-10-CM:I20), atrial fibrillation/flutter (ICD-10-CM:I48), as well as a composite measure of major adverse cardiovascular events (MACE) that comprised of all 6 aforementioned outcomes, comparing pwMS with deficient or inadequate 25(OH)D levels versus propensity-matched pwMS with adequate 25(OH)D levels. To comprehensively assess calcium regulation, both 25(OH)D and parathyroid hormone (PTH) levels were assessed. Accordingly, the current study reports the likelihood of vitamin D levels being associated with abnormal PTH levels (exceeding the upper limit of normal, >65 pg/mL). Lastly, to examine the impact of vitamin D supplementation (cholecalciferol) on long-term cardiovascular outcomes, cohorts were stratified by 25(OH)D. Using logistic regression, participants taking cholecalciferol, recorded within 1 month before and up to 1 year after recording of MS in the database, with either deficient, inadequate, or

Table 1
PwMS and deficient 25(OH)D levels vs PwMS and adequate 25(OH)D levels before and after propensity score matching.

	Initial Populations			Propensity Score Matching		
	People with multiple sclerosis and deficient vitamin D levels (n = 6878); % (n)	People with multiple sclerosis and adequate vitamin D levels (n = 54,621); % (n)	Std diff.	People with multiple sclerosis and deficient vitamin D levels (n = 6870); % (n)	People with multiple sclerosis and adequate vitamin D levels (n = 6870); % (n)	Std diff.
Age at Index; mean (SD)	44.3 (13.9)	48.4 (14.2)	0.291	44.3 (13.9)	44.5 (14.0)	0.017
Female	43.6 (2996)	67.8 (37,041)	0.017	72.3 (4969)	72.7 (4996)	0.009
Male	26.6 (1826)	23.3 (12,712)	0.076	26.6 (1825)	26.3 (1810)	0.005
Black or African American	22.4 (1539)	8.4 (4564)	0.396	22.3 (1533)	21.9 (1506)	0.009
White	43.6 (2996)	67.8 (37,041)	0.503	43.6 (2996)	43.2 (2966)	0.009
Asian	1 (70)	0.8 (427)	0.025	1 (70)	1 (66)	0.006
Other Race	3.5 (240)	3.5 (1896)	0.001	3.5 (240)	3.3 (228)	0.01
Comorbidities						
Hypertensive diseases	24.1 (1660)	21.3 (11,657)	0.067	24.1 (1654)	23 (1578)	0.026
Other forms of heart disease	12.2 (836)	10.7 (5843)	0.046	12.1 (834)	11 (753)	0.037
Diseases of arteries, arterioles and capillaries	4.2 (290)	5.3 (2881)	0.05	4.2 (290)	3.9 (267)	0.017
Cerebrovascular diseases	7.1 (489)	5.4 (2925)	0.073	5.1 (347)	4.7 (324)	0.016
Ischemic heart diseases	5.1 (349)	4.6 (2487)	0.024	2.3 (156)	2.2 (154)	0.002
Pulmonary heart disease and diseases of pulmonary circulation	2.3 (157)	1.9 (1048)	0.025	14.3 (983)	13.3 (915)	0.029
Nicotine dependence	14.4 (987)	8.6 (4683)	0.182	24.4 (1676)	22.5 (1544)	0.045
Mood [affective] disorders	24.4 (1680)	23.5 (12,853)	0.021	20.9 (1433)	20 (1377)	0.02
Anxiety	20.9 (1435)	21.2 (11,600)	0.009	0.1 (10)	0.1 (10)	<0.001
Extreme Poverty	0.1 (10)	0 (17)	0.038	0.3 (19)	0.2 (15)	0.012
Unemployment, unspecified	0.3 (19)	0.1 (73)	0.032	0.1 (10)	0.2 (13)	0.011
Problems related to living alone	0.2 (12)	0.1 (41)	0.028	11.3 (773)	10.5 (718)	0.026
Rheumatoid arthritis	1.2 (83)	1.4 (749)	0.015	1.2 (82)	1.1 (77)	0.007
Other specific noninfective gastroenteritis and colitis	4.1 (279)	2.6 (1435)	0.08	4 (277)	4 (274)	0.002
Crohn's disease	0.9 (62)	0.6 (352)	0.029	0.9 (61)	0.9 (62)	0.002
Ulcerative collitis	0.5 (35)	0.6 (349)	0.017	0.5 (35)	0.5 (37)	0.004
Guillain-Barre syndrome	0.2 (15)	0.2 (99)	0.008	0.2 (15)	0.1 (10)	0.017
Chronic inflammatory demyelinating polyneuritis	0.3 (18)	0.3 (153)	0.004	0.3 (18)	0.2 (13)	0.015
Psoriasis	0.9 (63)	1.2 (669)	0.03	0.9 (63)	0.9 (64)	0.002
Type 1 diabetes mellitus	2.1 (146)	1.1 (594)	0.082	2.1 (142)	2 (135)	0.007
Type 2 diabetes mellitus	10.3 (711)	7.4 (4022)	0.105	10.3 (705)	10.1 (691)	0.007
Thyrotoxicosis with diffuse goiter without thyrotoxic crisis or storm	0.5 (36)	0.5 (297)	0.003	0.5 (36)	0.5 (37)	0.002
Autoimmune thyroiditis	0.5 (34)	1.2 (655)	0.077	0.5 (34)	0.5 (34)	<0.001
Myasthenia gravis	0.3 (24)	0.3 (191)	<0.001	0.3 (24)	0.3 (21)	0.008
Systemic sclerosis [scleroderma]	0.2 (14)	0.2 (109)	0.001	0.2 (14)	0.2 (16)	0.006
Arteritis, unspecified	0.3 (18)	0.4 (200)	0.019	0.3 (18)	0.3 (19)	0.003
Systemic lupus erythematosus	1.2 (85)	0.9 (477)	0.036	1.2 (85)	1.2 (82)	0.004
Cardiovascular Care						
Cardiovascular procedures	27.4 (1883)	25.9 (14,154)	0.033	27.3 (1878)	25.7 (1767)	0.037
Cardiovascular medications	45.9 (3157)	44.5 (24,302)	0.028	45.9 (3151)	44.4 (3053)	0.029
Analgesics	55.6 (3822)	49.9 (27,247)	0.114	1.2 (85)	1.2 (82)	0.004
Antidepressants	34.2 (2355)	35.8 (19,540)	0.032	34.2 (2350)	32.6 (2243)	0.033
Ergocalciferol	17.7 (1216)	11.3 (6170)	0.182	17.7 (1213)	18 (1240)	0.01
Calcitriol	0.5 (33)	0.4 (198)	0.018	0.5 (33)	0.6 (41)	0.016
Calcifediol	0.1 (10)	0 (13)	0.042	0.1 (10)	0.1 (10)	<0.001
Cholecalciferol	15.1 (1035)	22.8 (12,436)	0.198	15.1 (1035)	14.4 (990)	0.018
Laboratory Measurements						
eGFR; mean (SD)	94.6 (32.8)	89.2 (25.1)	0.185	94.6 (32.8)	91.7 (26.6)	0.096
BMI; mean (SD)	30.8 (8.6)	28.3 (7.2)	0.31	30.8 (8.6)	29.1 (7.5)	0.213

25(OH)D; 25-hydroxyvitamin D, BMI; body mass index, CVD; cardiovascular disease, eGFR; glomerular filtration rate, PwMS; people with multiple sclerosis, SD; standard deviation.

deficient/inadequate 25(OH)D levels were 1:1 propensity score matched to participants with adequate 25(OH)D levels not taking any vitamin D supplementation for the same aforementioned variables minus vitamin D supplementation. Cox proportional hazards regression models produced HRs with 95 % CIs for 1-day to 5-year incidence of MACE from 2019 to 2024, comparing pwMS and deficient, or inadequate 25(OH)D levels taking cholecalciferol versus propensity-matched pwMS and adequate 25(OH)D levels taking no vitamin D supplementation. Sensitivity analyses were conducted to examine the incidence of MACE and the association of supplementation at least 1 year after and within 5 years of recording of MS in the database. Statistical significance was defined as $P < 0.01$ to account for multiple testing.

Results

In total 74,372 people with a record of MS and at least 5 years of follow-up data from 2019 to 2024, with a 25(OH)D measurement occurring within 6 months prior and 6 months after recording of MS in

Table 2
PwMS and inadequate 25(OH)D levels vs PwMS and adequate 25(OH)D levels before and after propensity score matching.

	Initial Populations			Propensity Score Matching		
	People with multiple sclerosis and deficient vitamin D levels (n = 13,233); % (n)	People with multiple sclerosis and adequate vitamin D levels (n = 54,621); % (n)	Std diff.	People with multiple sclerosis and deficient vitamin D levels (n = 13,219); % (n)	People with multiple sclerosis and adequate vitamin D levels (n = 13,219); % (n)	Std diff.
Age at Index; mean (SD)	43.4 (13.9)	48.4 (14.2)	0.352	43.4 (13.9)	43.1 (13.7)	0.023
Female	53.8 (7115)	67.8 (37,041)	0.038	71.4 (9440)	71.3 (9430)	0.002
Male	26.8 (3550)	23.3 (12,712)	0.082	26.8 (3545)	27.1 (3578)	0.006
Black or African American	14.8 (1962)	8.4 (4564)	0.203	14.8 (1956)	14.2 (1873)	0.018
White	53.8 (7115)	67.8 (37,041)	0.29	53.8 (7114)	53.2 (7037)	0.012
Asian	0.9 (118)	0.8 (427)	0.012	0.9 (118)	0.9 (116)	0.002
Other Race	5 (664)	3.5 (1896)	0.077	5 (664)	5.1 (680)	0.006
Comorbidities						
Hypertensive diseases	21.4 (2834)	21.3 (11,657)	0.002	21.4 (2829)	19.6 (2595)	0.044
Other forms of heart disease	11.3 (1499)	10.7 (5843)	0.02	11.3 (1495)	10.4 (1377)	0.029
Diseases of arteries, arterioles and capillaries	4.6 (614)	5.3 (2881)	0.029	4.6 (611)	4.1 (536)	0.028
Cerebrovascular diseases	6.2 (821)	5.4 (2925)	0.036	6.2 (816)	5.6 (734)	0.026
Ischemic heart diseases	4.8 (632)	4.6 (2487)	0.011	4.8 (629)	4.4 (579)	0.018
Pulmonary heart disease and diseases of pulmonary circulation	2.2 (289)	1.9 (1048)	0.019	2.2 (287)	1.9 (256)	0.017
Nicotine dependence	12.5 (1647)	8.6 (4683)	0.127	12.4 (1639)	10.9 (1447)	0.045
Mood [affective] disorders	25.2 (3333)	23.5 (12,853)	0.039	25.2 (3326)	23.5 (3109)	0.038
Anxiety	22.4 (2968)	21.2 (11,600)	0.029	22.4 (2962)	21.2 (2797)	0.03
Extreme Poverty	0.1 (11)	0 (17)	0.022	0.1 (11)	0.1 (10)	0.003
Unemployment, unspecified	0.3 (34)	0.1 (73)	0.028	0.2 (32)	0.2 (26)	0.01
Problems related to living alone	0.1 (12)	0.1 (41)	0.005	0.1 (12)	0.1 (12)	<0.001
Rheumatoid arthritis	1.3 (167)	1.4 (749)	0.01	11.6 (1540)	10.7 (1410)	0.031
Other specific noninfective gastroenteritis and colitis	3.5 (457)	2.6 (1435)	0.048	1.3 (166)	1.1 (148)	0.013
Crohn's disease	0.8 (110)	0.6 (352)	0.022	3.4 (453)	3.1 (405)	0.02
Ulcerative collitis	0.6 (75)	0.6 (349)	0.009	0.8 (108)	0.8 (102)	0.005
Guillain-Barre syndrome	0.3 (42)	0.2 (99)	0.027	0.6 (75)	0.5 (71)	0.004
Chronic inflammatory demyelinating polyneuritis	0.4 (50)	0.3 (153)	0.017	0.3 (42)	0.2 (32)	0.014
Psoriasis	1.1 (144)	1.2 (669)	0.013	0.4 (50)	0.3 (40)	0.013
Type 1 diabetes mellitus	1.7 (221)	1.1 (594)	0.05	1.1 (143)	1 (126)	0.013
Type 2 diabetes mellitus	8.8 (1170)	7.4 (4022)	0.054	1.7 (219)	1.4 (187)	0.02
Thyrotoxicosis with diffuse goiter without thyrotoxic crisis or storm	0.5 (65)	0.5 (297)	0.007	8.8 (1166)	7.9 (1050)	0.032
Autoimmune thyroiditis	0.8 (102)	1.2 (655)	0.043	0.5 (65)	0.5 (70)	0.005
Myasthenia gravis	0.4 (58)	0.3 (191)	0.014	0.8 (102)	0.8 (108)	0.005
Systemic sclerosis [scleroderma]	0.2 (27)	0.2 (109)	0.001	0.4 (58)	0.5 (61)	0.003
Arteritis, unspecified	0.5 (64)	0.4 (200)	0.018	0.2 (27)	0.2 (23)	0.007
Systemic lupus erythematosus	1.1 (146)	0.9 (477)	0.023	0.5 (63)	0.4 (48)	0.018
Cardiovascular Care						
Cardiovascular procedures	28.7 (3794)	25.9 (14,154)	0.062	28.6 (3786)	26.4 (3496)	0.049
Cardiovascular medications	43.3 (5728)	44.5 (24,302)	0.024	43.3 (5721)	40.6 (5364)	0.055
Analgesics	53.6 (7088)	49.9 (27,247)	0.074	53.6 (7081)	51.7 (6831)	0.038
Antidepressants	34.7 (4593)	35.8 (19,540)	0.022	34.7 (4586)	33.2 (4393)	0.031
Ergocalciferol	15.5 (2049)	11.3 (6170)	0.123	15.5 (2046)	15.1 (2001)	0.009
Calcitriol	0.3 (44)	0.4 (198)	0.005	0.3 (44)	0.4 (48)	0.005
Calcifediol	0.1 (10)	0 (13)	0.023	0.1 (10)	0.1 (10)	<0.001
Cholecalciferol	17 (2252)	22.8 (12,436)	0.144	17 (2251)	16.2 (2141)	0.022
Laboratory Measurements						
eGFR; mean (SD)	93.8 (27.4)	89.2 (25.1)	0.176	93.8 (27.4)	92.8 (25.3)	0.039
BMI; mean (SD)	30.3 (8.2)	28.3 (7.2)	0.261	30.3 (8.2)	28.8 (7.5)	0.201

25(OH)D; 25-hydroxyvitamin D, BMI; body mass index, CVD; cardiovascular disease, eGFR; glomerular filtration rate, PwMS; people with multiple sclerosis, SD; standard deviation.

the database, were identified. Of these, 9 % were categorised as deficient 25(OH)D levels ($n = 6,878$), 18 % as inadequate ($n = 13,233$), and 73 % as adequate ($n = 54,261$).

Vitamin D levels and cardiovascular outcomes

In all analyses, propensity-score matched cohorts were well balanced on all included characteristics (Tables 1-2, supplementary table S2). Those with deficient levels of 25(OH)D ($n = 6,870$ each cohort) were significantly more likely to experience incident MACE (HR, 1.32 [95 % CI 1.19, 1.46]), as well as individual outcomes of all-cause mortality (HR, 1.49 [95 % CI 1.25, 1.77]), heart failure (HR, 1.35 [95 % CI 1.13, 1.60]), and atrial fibrillation/flutter (HR, 1.35 [95 % CI 1.11, 1.66]) in the 5-year follow-up period, in comparison to propensity-matched pwMS and adequate 25(OH) levels (Fig. 1). No difference was found between cohorts for rates of stroke, acute myocardial infarction, and angina.

Those with inadequate levels of 25(OH)D ($n = 13,219$ each cohort) were significantly more likely to experience incident MACE (HR, 1.29 [95 % CI 1.20, 1.40]), as well as individual outcomes of all-cause mortality (HR, 1.39 [95 % CI 1.22, 1.60]), stroke (HR, 1.35 [95 % CI 1.15, 1.57]), heart failure (HR, 1.42 [95 % CI 1.24, 1.63]), and atrial fibrillation/flutter (HR, 1.33 [95 % CI 1.13, 1.56]) in the 5-year follow-up period, in comparison to propensity-matched pwMS and adequate 25 (OH) levels. No significant difference was found between cohorts for rates of acute myocardial and angina. The composite group of those with deficient/inadequate 25(OH)D levels showed similar findings as individual groups in comparison to those with adequate 25(OH)D levels (Fig. 1). Sensitivity analyses examining 5-year MACE incidence at least 1 year after recording of MS in the database showed similar findings (supplemental figure S1).

Elevated PTH levels were observed in pwMS and deficient, deficient/inadequate, or inadequate 25(OH)D levels compared to pwMS and adequate 25(OH)D levels (HRs, 1.54, 1.41, 1.23, respectively).

Vitamin D supplementation and cardiovascular outcomes

In all analyses, propensity-score matched cohorts were well balanced on all included characteristics (supplementary tables S3–5). There was a significantly greater rate of incident MACE (HR, 1.39 [95 % CI 1.21,

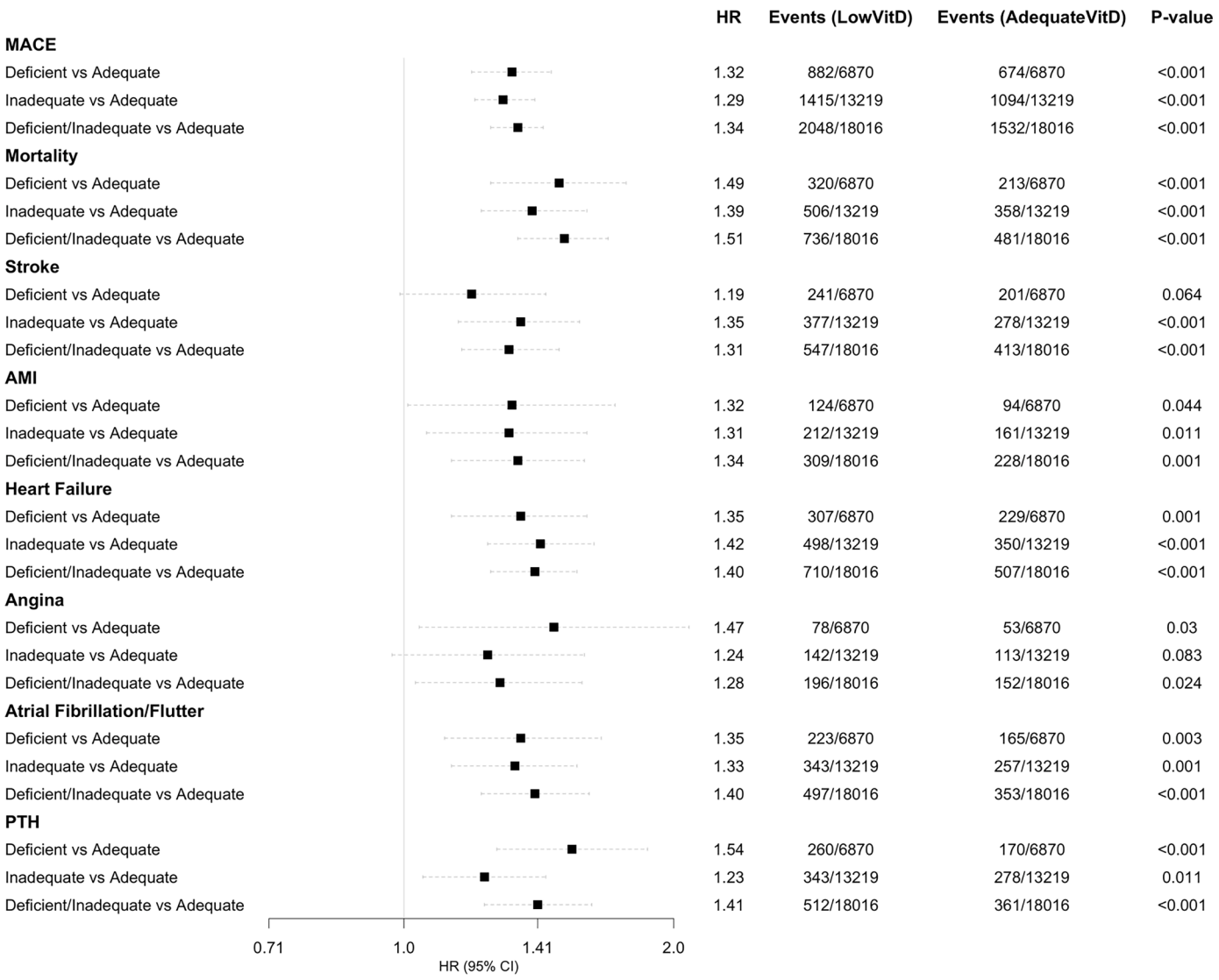

Fig. 1. Forest plot presenting hazard ratios for 5-year incidence of MACE, all-cause mortality, stroke, acute myocardial infarction, heart failure, angina, and atrial fibrillation/flutter comparing people with multiple sclerosis and low vitamin D (deficient, inadequate, and deficient/inadequate) levels to propensity-score matched people with multiple sclerosis with adequate vitamin D levels. *AMI; acute myocardial infarction, CI; confidence intervals, HR; hazard ratio, MACE; major adverse cardiovascular events, PTH; parathyroid hormone, VitD; 25-hydroxyvitamin D.*

1.60]), all-cause mortality (HR, 1.33 [95 % CI 1.05, 2.16]), stroke (HR, 1.53 [95 % CI 1.16, 2.00]), acute myocardial infarction (HR, 1.63 [95 % CI 1.13, 2.35]), and atrial fibrillation/flutter (HR, 1.85 [95 % CI 1.40, 2.44]) within the 5-year follow-up period, in pwMS with deficient 25 (OH)D levels taking cholecalciferol compared to propensity-matched pwMS and adequate 25(OH)D levels (not taking vitamin D supplementation) ($n = 2,783$ in each cohort). There was no significant difference in incidence of angina and heart failure (Fig. 2).

In pwMS and inadequate 25(OH)D levels taking cholecalciferol compared to propensity-matched pwMS and adequate 25(OH)D levels taking no vitamin D supplementation ($n = 4,596$ in each cohort), there was a significantly greater rate of incident MACE (HR, 1.31 [95 % CI 1.17, 1.47]), all-cause mortality (HR, 1.27 [95 % CI 1.05, 1.54]), heart failure (HR, 1.54 [95 % CI 1.26, 1.87]), and atrial fibrillation/flutter (HR, 1.43 [95 % CI 1.15, 1.79]) in the 5-year follow-up period, in pwMS and inadequate 25(OH)D levels taking cholecalciferol. There was no significant difference in incidence of stroke, acute myocardial infarction, or angina. The composite group of those with deficient/inadequate 25 (OH)D levels taking cholecalciferol showed similar findings as individual groups in comparison to those with adequate 25(OH)D levels not taking vitamin D supplementation (Fig. 2). Sensitivity analyses examining 5-year MACE incidence at least 1 year after a record of MS on the database also showed similar findings (supplemental figure S2).

Elevated PTH levels were observed in pwMS and deficient, deficient/inadequate, or inadequate 25(OH)D levels taking cholecalciferol compared to pwMS and adequate 25(OH)D levels not taking vitamin D supplementation (HRs, 1.53, 1.54, 1.42, respectively).

Discussion

Given established evidence linking low 25(OH)D levels to increased cardiovascular risk in the general population, and the inconclusive findings regarding the impact of vitamin D supplementation on cardiovascular outcomes (Janjusevic et al., 2022; Izzo et al., 2021), this observational cohort study aimed to address significant gaps in our understanding within the context of MS. First, amongst 74,372 pwMS, 9 % were categorised as having deficient 25(OH)D levels ($n = 6,878$), 18 % as inadequate ($n = 13,233$), and 73 % as adequate ($n = 54,261$). Analysis revealed that pwMS and deficient or inadequate 25(OH)D levels exhibited a significantly higher rate of MACE (HR, 1.32, 1.29, respectively) compared to those with adequate 25(OH)D levels. Furthermore, cholecalciferol supplementation in those with deficient or inadequate 25(OH)D levels was not associated with a lower rate of CVD (HR, 1.39, 1.31, respectively) in comparison to those with adequate 25 (OH)D levels taking no vitamin D supplementation.

The literature consistently demonstrates an association between vitamin D deficiency and CVD within the general population (Janjusevic et al., 2022; Izzo et al., 2021). Insufficient 25(OH)D levels have been linked to an increased likelihood of recurrent complications and poorer outcomes (Cosentino et al., 2021). Furthermore, research in the general population has observed a gradual escalation in CVD risk corresponding to decreasing levels of 25(OH)D (Brøndum-Jacobsen et al., 2012). A

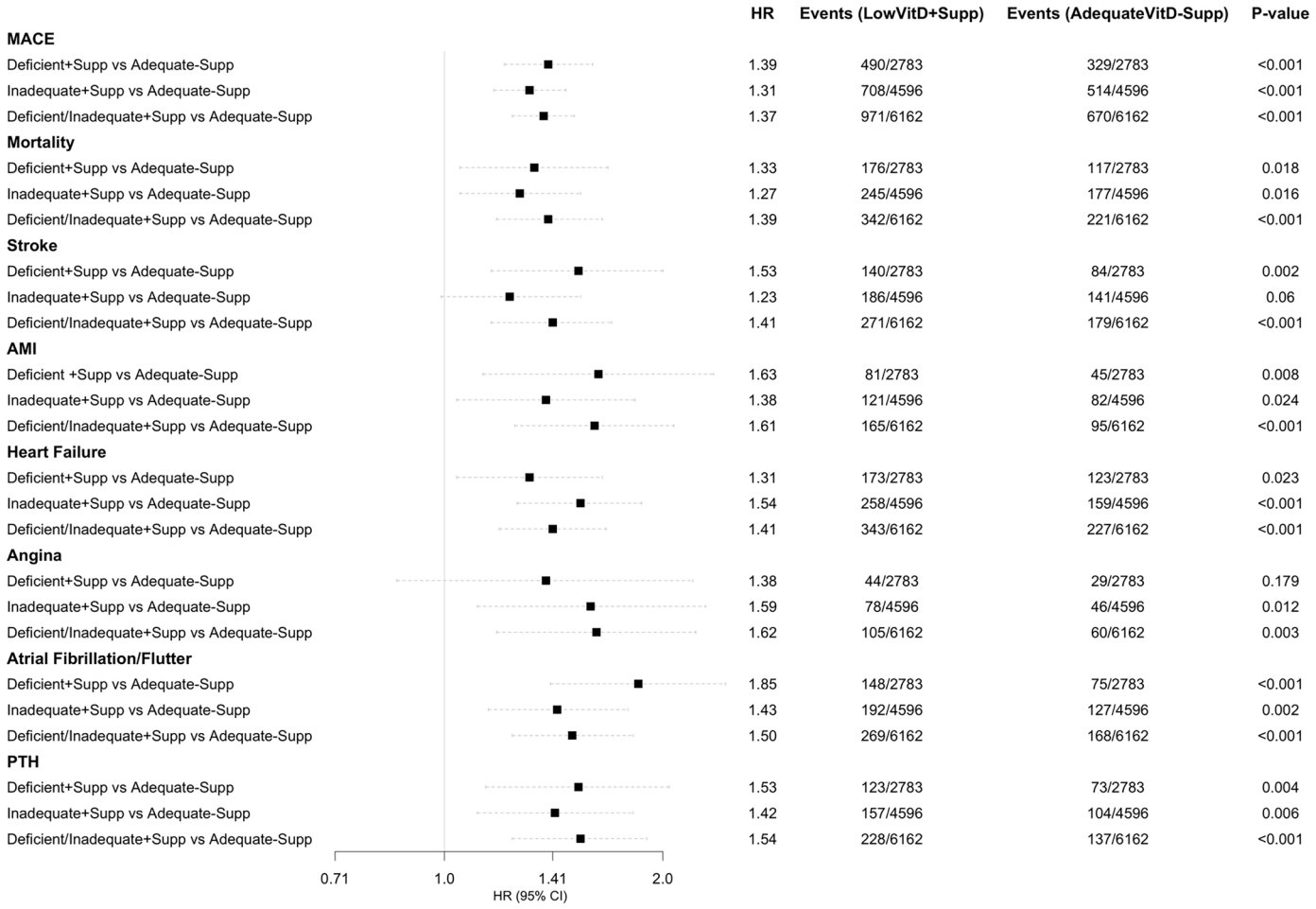

Fig. 2. Forest plot presenting hazard ratios for 5-year incidence of MACE, all-cause mortality, stroke, acute myocardial infarction, heart failure, angina, and atrial fibrillation/flutter comparing people with multiple sclerosis and low vitamin D levels (deficient, inadequate, and deficient/inadequate) taking cholecalciferol to propensity-score matched people with multiple sclerosis and adequate 25(OH)D levels not taking vitamin D supplementation. *AMI; acute myocardial infarction, CI; confidence intervals, HR; hazard ratio, MACE; major adverse cardiovascular events, PTH; parathyroid hormone, Supp; Vitamin D supplementation, VitD; 25-hydroxyvitamin D.*

meta-analysis conducted in the general population demonstrated an adjusted relative risk of 1.52 for CVD when comparing the lowest to the highest categories of 25(OH)D levels (Wang et al., 2012). Moreover, the increase in CVD risk with decreasing 25(OH)D levels appeared to be linear within the range of 8–24 ng/mL. The current study results mirrored these findings, with the rate of MACE progressively increasing as 25(OH)D levels declined (29 % and 32 % increased rate in pwMS with inadequate and deficient 25(OH)D levels, respectively, compared to those with adequate levels). The present findings align with previous research in the general population, which has linked vitamin D deficiency to increased mortality (Sutherland et al., 2022), stroke (Yarlagadda et al., 2020), heart failure (Jiang et al., 2016), myocardial infarction (Wang et al., 2012), and atrial fibrillation (Liu et al., 2019). There is an established link between low 25(OH)D levels and increased inflammation, a critical factor in the pathogenesis of CVD (Henein et al., 2022; Lawler et al., 2021). Notably, elevated C-reactive protein (CRP), an inflammatory marker, have been suggested to be caused by vitamin D deficiency (Zhou and Hyppönen, 2023). The increased inflammation in pwMS coupled with vitamin D deficiency may augment the likelihood of MACE when contrasted to pwMS and adequate 25(OH)D levels. Consequently, targeting both vitamin D deficiency and inflammation appears to be a potential focal point for interventions aimed at reducing cardiovascular risk in this population.

Despite the link between low vitamin D and increased CVD risk, the impact of vitamin D supplementation on CVD outcomes in pwMS remains unclear. While monthly vitamin D supplementation has been demonstrated to increase serum 25(OH)D levels (Khaw et al., 2017) and some studies have suggested potential benefits in preventing CVD development and associated mortality (Acharya et al., 2021; Feuchtner et al., 2021), many investigations are yet to show conclusive beneficial effects for preventing or improving cardiovascular outcomes in the general population (Janjusevic et al., 2022; Izzo et al., 2021; Scragg et al., 2017; Manson et al., 2019; Thompson et al., 2023; Barbarawi et al., 2019; Cosentino et al., 2021). A placebo-controlled supplementation trial in generally healthy men and women in Finland ($n = 2,495$) found that high-dose (1,600–3,200 IU/d) vitamin D_3 supplementation may reduce the incidence of atrial fibrillation (Virtanen et al., 2023). Yet, a meta-analysis including a broad population ($n = 83,291$), found that vitamin D supplementation (predominantly cholecalciferol) was not associated with reduced risks of MACE, myocardial infarction, stroke, or all-cause mortality compared with placebo (Barbarawi et al., 2019). The current study similarly found that the increased rate of MACE, myocardial infarction, stroke, and all-cause mortality remained in pwMS with deficient, or inadequate 25(OH)D levels compared to those with adequate 25(OH)D levels despite receiving cholecalciferol (HRs for MACE of 1.39, 1.31, respectively). A randomised controlled trial (RCT) in 41 people with relapsing-remitting MS or clinically isolated syndrome found no difference in disability progression between low dose cholecalciferol (400 IU per day) vs high dose cholecalciferol (20,400 IU per day) groups (Dörr et al., 2020). However, another RCT in 45 pwMS found that a high dosage regimen of vitamin D supplementation (4,370 IU per day of cholecalciferol) was more effective in achieving serum 25(OH)D levels of >30 ng/mL in comparison to a low dose (800 IU per day) supplementation (100 % vs 25 %, respectively) (Golan et al., 2013), suggesting that the type and dosage of vitamin D supplementation may be an important factor to elicit changes in serum 25(OH)D levels and subsequently CVD outcomes. Accordingly, drawing comparisons between studies on vitamin D supplementation and CVD outcomes is challenging due to substantial heterogeneity in methodologies, other variations in factors such as baseline 25(OH)D levels, participant age, and presence of comorbidities may also influence results. Future, robust clinical trials are necessary to further explore the influence of vitamin D supplementation on the rate of CVD in pwMS. These trials should account for potential confounding factors such as lifestyle influences and seasonal variations in 25(OH)D levels.

Notably, the present study found a significantly increased likelihood of elevated PTH levels (over 65pg/mL) in pwMS with deficient (54 %) and inadequate (23 %) 25(OH)D levels compared to those with adequate 25(OH)D. This highlights a potential disruption in calcium homeostasis. While the body attempts to compensate for low 25(OH)D by raising PTH, chronically elevated PTH levels can have unfavourable consequences, such as an impairment of bone health (Tageldin and Martin, 2020), mitochondrial function and oxidative stress (National Institutes of Health Office of Dietary Supplements 2021). These findings underscore the importance of maintaining adequate 25(OH)D levels to regulate PTH secretion for overall health. The likelihood of PTH values >65pg/mL slightly decreased by 1 % in those with deficient and decreased by 19 % in those with inadequate 25(OH)D levels taking cholecalciferol, however remained magnified compared to propensity-matched pwMS and adequate 25(OH)D levels not taking vitamin D supplementation. Previous research in people with relapsing-remitting MS ($n = 83$) has reported a decrease in PTH levels after 12 months of vitamin D supplements (Walawska-Hrycek et al., 2021). Additionally, a significant decrease in PTH levels was reported after 3 months of high dose vitamin D supplementation (4,370 IU per day of cholecalciferol, change from 30.4 ± 13.5 pg/mL to 25.0 ± 10.0 pg/mL, $p = 0.04$), whilst no significant change occurred after 3 months of a low dose (800 IU per day) supplementation (Golan et al., 2013). These results suggest that vitamin D supplementation may decrease the rate of augmented PTH concentration associated with insufficient 25(OH)D levels. Though, results may vary with a higher dose and extended duration, particularly for individuals with low baseline 25(OH)D levels. Additionally, other factors such as calcium intake, method of PTH measurement, and baseline PTH levels can influence PTH response (Sai et al., 2011). Some previous studies have demonstrated an increased cardiovascular risk associated with vitamin D and calcium supplementation. For instance, a meta-analysis found that supplementation of >20 mcg vitamin D_3 per day, when taken with calcium supplements significantly increased blood pressure in participants with overweight and obesity, which may be linked to extraosseous deposition and calcification (Golzarand et al., 2016). Further research including robust clinical trials should be conducted to determine the underlying mechanisms and consider various factors that could influence findings, such as supplementation practices and individual participant characteristics.

Limitations

The current study benefits from its large sample size and propensity score matching which controls for potential confounding variables such as age, sex, ethnicity, comorbidities, and medication use. However, several limitations should be considered when interpreting the findings. Confounding factors, such as MS subtype, lifestyle behaviours (e.g. diet, smoking, physical activity), genetic influences, over-the-counter vitamin D supplementation, or medication dosage and frequency could potentially impact the study results. Furthermore, certain variables included in the PSM process, such as cardiovascular medications and procedures, are likely markers of incident CVD. Their inclusion was necessary to ensure balance between the cohorts, though this approach could introduce bias in the estimated rates of incident MACE. The data were sourced from EMR databases of healthcare organisations, and there may be underreporting or misclassification of certain health conditions. Additionally, outcomes that occurred outside the TriNetX network are likely to be underrepresented. Diagnoses relied solely on ICD codes, which can vary in accuracy and details across healthcare organisations (Chong et al., 2011). Finally, the study's predominantly US-based population may limit the generalisability of the results to broader populations, and further research is needed with broader geographical representation to ascertain the applicability of these findings beyond this specific cohort. Future research should aim to address these limitations by incorporating data on MS subtypes, lifestyle factors, and detailed medication use.

Conclusion

In conclusion, this observational cohort study found that pwMS and low 25(OH)D levels exhibited a significantly higher rate of incident MACE compared to pwMS with adequate 25(OH)D levels within a 5-year follow-up period. Vitamin D supplementation did not seem to impact the higher rate of MACE. Therefore, vitamin D deficiency may be a contributing factor to worsened cardiovascular health in pwMS, and supplementation alone may be insufficient to fully mitigate this risk.

CRediT authorship contribution statement

Madeleine France-Ratcliffe: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Stephanie L. Harrison:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing, Methodology. **Leona A. Verma:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing. **Azmil H. Abdul-Rahim:** Conceptualization, Funding acquisition, Methodology, Project administration, Writing – review & editing. **Linsay McCallum:** Conceptualization, Funding acquisition, Methodology, Project administration, Writing – review & editing. **Carolyn A. Young:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Garry McDowell:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Benjamin JR Buckley:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no competing interests.

Data Availability

A request can be made to TriNetX (https://live.trinetx.com) to access data in the research network but may require costs and necessitate a data sharing agreement. No patient identifiable information can be provided.

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Author contributions

BJRB, MFR, GMcD, SLH, LAR, AHAR, LMcC, and CAY were involved in conceptualisation and design of the study. MFR conducted the analyses with support from BJRB and GMcD. All authors were involved in the interpretation of the results. MFR drafted the manuscript and prepared tables and figures. All authors reviewed the results, revised it critically, approved the final version of the manuscript and agreed to be accountable for all aspects of this work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2024.106155.

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