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Review article

Association between vitamin D receptor polymorphism and breast cancer in women: An umbrella review of meta-analyses of observational investigations

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ABSTRACT

This study aimed to conduct an umbrella review of meta-analyses to synthesize the existing evidence regarding the relationship between vitamin D receptor (VDR) polymorphism and breast cancer (BC) risk. A comprehensive search was performed across multiple databases, including Embase, PubMed, Scopus, the Cochrane Database of Systematic Reviews, and the Web of Science. The investigation included 17 meta-analyses for the *Bsm*I polymorphism, 6 for the Cdx2 polymorphism, and 6 for the Poly (A) polymorphism. Among the 119 datasets analyzed, only 6 (5 %) reported statistically significant outcomes ($p < 0.05$), comprising 2 comparisons for VDR *Bsm*I polymorphism (3 %), 1 for VDR Cdx-2 polymorphism (4 %), and 3 for VDR Poly (A) polymorphism (14 %), across various genetic models. Notably, significant heterogeneity was observed in 82 comparisons, and publication bias was detected in 16 comparisons. Furthermore, a substantial proportion (86 %) of the included studies exhibited critically low methodological quality. In conclusion, our findings suggest that VDR polymorphism (*Bsm*I, Cdx-2, and Poly (A)) is not strongly associated with BC risk in the general population.

1. Introduction

Breast cancer (BC) stands as the most prevalent form of cancer among women, presenting a significant global health concern (Harbeck et al., 2019). Recent data from the World Health Organization (WHO) underscores the gravity of the issue, with approximately 2.3 million women diagnosed with BC and nearly 670,000 subjects died from the disease worldwide in 2022 alone (https://www.who.int/news-room/fact-sheets/detail/breast-cancer). Breast cancer manifests across all nations, affecting women post-puberty and exhibiting elevated rates with advancing age (https://www.who.int/news-room/fact-sheets/detail/breast-cancer). A comprehensive report spanning from 1990 to 2017 reveals a notable surge in both the incidence and mortality rates of BC globally, albeit with regional disparities (Lima et al., 2021). It is widely acknowledged that genetic predisposition and environmental factors play pivotal roles in BC susceptibility and progression (Rudolph et al., 2016). Among the myriad genetic elements implicated in BC risk, the Vitamin D receptor (VDR) gene emerges as a noteworthy candidate. Positioned on the 12th chromosome (q13.1), the VDR gene spans 75 kp of DNA across 11 exons (Miyamoto et al., 1997). Operating through binding with its ligand vitamin D, the VDR promotes a spectrum of signaling pathways, influencing the activation of downstream genes and contributing to BC prevention (Welsh, 2012; Krishnan and Feldman, 2011). The VDR gene harbors numerous polymorphic variations that disrupt its expression and function, thereby influencing susceptibility to various diseases such as tuberculosis, osteoporosis, diabetes, and various cancers, including BC (Iqbal and Khan, 2017). To date, only a few single nucleotide polymorphisms (SNPs) within the VDR gene have been scrutinized regarding their association with BC risk with contradictory results including Bsm1, Cdx2, and Poly (A) (Iqbal et al., 2015; Rashid et al., 2015; Colagar et al., 2015; Guo et al., 2015; Mishra et al., 2013; Shahbazi et al., 2013). Recent findings have shed light on the diminished

Abbreviations: BC, breast cancer; WHO, World Health Organization; VDR, vitamin D receptor; SNPs, single nucleotide polymorphisms; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ORs, odds ratios; CIs, confidence intervals; NOS, Newcastle Ottawa Scale; STREGA, Strengthening the Reporting of Genetic Association Studies; HWE, Hardy–Weinberg equilibrium.

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expression of VDR in invasive BC tissues compared to normal counterparts (Lopes et al., 2010). Consequently, genetic monitoring of *Bsm*I, Cdx-2, and Poly (A) polymorphisms could be utilized to predict and identify individuals at the highest risk of BC incidence. Meta-analyses exploring the link between VDR *Bsm*I, Cdx-2, and Poly (A) polymorphisms and BC incidence have yielded inconclusive results. While some studies suggest no association between these polymorphisms and BC risk (Huang et al., 2014; Du et al., 2014; Lee and Song, 2014), others indicate a significant increase in BC risk associated with VDR Bsm1, Cdx-2, and Poly (A) gene polymorphisms (Iqbal et al., 2015; Bakhshaiesh et al., 2022; Li et al., 2018). To address this discrepancy comprehensively, we conducted a systematic review of relevant meta-analyses to elucidate the associations between VDR *Bsm*I, Cdx-2, and Poly (A) polymorphisms and BC incidence. Through this study, we aim to provide a comprehensive overview and clarify the current understanding of these genetic variants in BC susceptibility.

2. Materials and methods

An umbrella review was conducted to analyze meta-analyses investigating the relationships between VDR *Bsm*I, Cdx-2, and Poly (A) polymorphisms and the risk of BC. The research protocol was pre-registered in PROSPERO (registration number: CRD42024533344) prior to commencing the umbrella review. This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015).

2.1. Literature search

In January 2024, a comprehensive literature search was conducted using various online databases, including Embase, PubMed, Scopus, the Cochrane Database of Systematic Reviews, and the Web of Science. The search encompassed meta-analyses of case-control studies with no restriction on publication date. Two researchers independently conducted the literature search (JZ and FT). Only articles written in English were considered. The search strategy was developed utilizing the following MeSH terms and keywords: ((("Vitamin D" [Mesh] OR "Ergocalciferols" [Mesh] OR "Vitamin D Deficiency" [Mesh] OR "Cholecalciferol" [Mesh]) OR ((((Vitamin D [Title/Abstract]) OR (Ergocalciferols [Title/Abstract])) OR (Cholecalciferol [Title/Abstract])) OR (""25-hydroxycholecalciferol"" [Title/Abstract]))) AND (("Breast Neoplasms" [Mesh]) OR ((("breast neoplasm" [Title/Abstract]) OR ("breast cancer" [Title/Abstract])) OR ("breast tumor" [Title/Abstract]))))) AND ((meta-analysis [Publication Type]) OR (meta-analysis [Title/Abstract]))","(("Vitamin D" [MeSH Terms] OR "Ergocalciferols" [MeSH Terms] OR "Vitamin D Deficiency" [MeSH Terms] OR "Cholecalciferol" [MeSH Terms] OR (""Vitamin D"[Title/Abstract] OR "Ergocalciferols"[Title/Abstract] OR "Cholecalciferol" [Title/Abstract] OR ""25-hydroxycholecalciferol" [Title/Abstract])) AND ("Breast Neoplasms" [MeSH Terms] OR ("breast neoplasm" [Title/Abstract] OR "breast cancer" [Title/Abstract] OR "breast tumor" [Title/Abstract])) AND ("meta-analysis" [Publication Type] OR "meta-analysis" [Title/Abstract]). Each retrieved article underwent detailed review, including evaluation of title, abstract, and full text. Inclusion and exclusion criteria were then applied to determine article eligibility, with any discrepancies resolved through consensus.

2.2. Eligibility criteria and exclusion criteria

Meta-analyses were considered eligible for inclusion if they met the following criteria: (Harbeck et al., 2019) Included observational studies; (Lima et al., 2021) Reported on the association between VDR Bsm1, Cdx-2, and Poly (A) gene polymorphisms and BC incidence; and (Rudolph et al., 2016) Presented pooled summary effects data, such as odds ratios (ORs) and their corresponding 95 % confidence intervals (CIs). Protocols, conference abstracts, and letters to editors were excluded from consideration. In cases where multiple meta-analyses reported the same health outcome concurrently, preference was given to the meta-analysis with the largest number of included studies.

2.3. Data extraction

Two researchers (JZ and FT) independently conducted data extraction from the selected articles. Extracted information included the first author, publication year, number of included studies, study design, total numbers of cases and controls, source of control, participant ethnicity, and genotyping method used. Additionally, ORs and their corresponding 95 % CIs for each genetic model in each eligible meta-analysis were extracted. Other extracted values included p-values for total pooled effects, Cochran's Q statistic, Egger's test, and I^2 statistic. Furthermore, documentation was made regarding whether the selected meta-analyses applied any criteria to assess the quality of the included studies.

2.4. Assessment of methodological quality

The methodological quality of each included published meta-analysis of case-control studies was evaluated using the validated AMSTAR 2 tool. This tool has demonstrated effectiveness and reliability in assessing the quality of systematic review methodologies. The AMSTAR tool comprises 16 items focusing on the conduct of a meta-analysis. High methodological quality is indicated by either no or only one non-critical weakness, while moderate methodological quality is characterized by more than one non-critical weakness. A single serious flaw, with or without non-critical defects, denotes low methodological quality, whereas more than one critical weakness, with or without non-serious defects, suggests critically low methodological quality. Any discrepancies in AMSTAR 2 scores were resolved through discussion.

2.5. Data analysis

From each of the published studies, the outcome data of the available meta-analyses was extracted along with the estimated summary effect at the corresponding 95 % CI. The total impacts of the pooled meta-analysis were considered significant when the p-value was <0.05. Heterogeneity was assessed using the I^2 test and Q test, with significance set at $p < 0.1$. Publication bias was evaluated using Egger's test, also considered significant at $p < 0.1$. Instead of conducting a search for primary studies within the meta-analysis and reanalyzing the summary estimates with 95 % CI, existing effect sizes and 95 % CI for each variable were directly extracted.

3. Results

3.1. Search results

The flowchart depicting the article selection process is presented in Fig. 1. Initially, 217 articles were identified, with duplicates removed. Following the screening of titles and abstracts against our inclusion criteria, 185 publications (85 %) were excluded. Upon full-text review of the remaining 32 articles, one was found not to report a meta-analysis, nine were excluded due to outcomes not related to VDR polymorphisms, and one did not report BC incidence (Fig. 1). After thorough evaluation, 21 original meta-analyses were identified (Iqbal and Khan, 2017; Huang et al., 2014; Du et al., 2014; Lee and Song, 2014; Bakhshaiesh et al., 2022; Li et al., 2018; Dai et al., 2015; Huang et al., 2013; Li et al., 2014; Lu et al., 2016; Mun et al., 2015; Raimondi et al., 2009; Raimondi et al., 2014; Tang et al., 2009; Wang et al., 2013a; Xu et al., 2014a; Xu et al., 2014b; Yang et al., 2014; Zhang and Song, 2014; Zhao et al., 2023; Zhou et al., 2013), investigating the associations between VDR *Bsm*I, Cdx-2, and Poly (A) polymorphisms and BC incidence. All meta-analyses included in the study design comprised case-control studies. These 21 eligible papers encompassed data from 119 meta-analyses

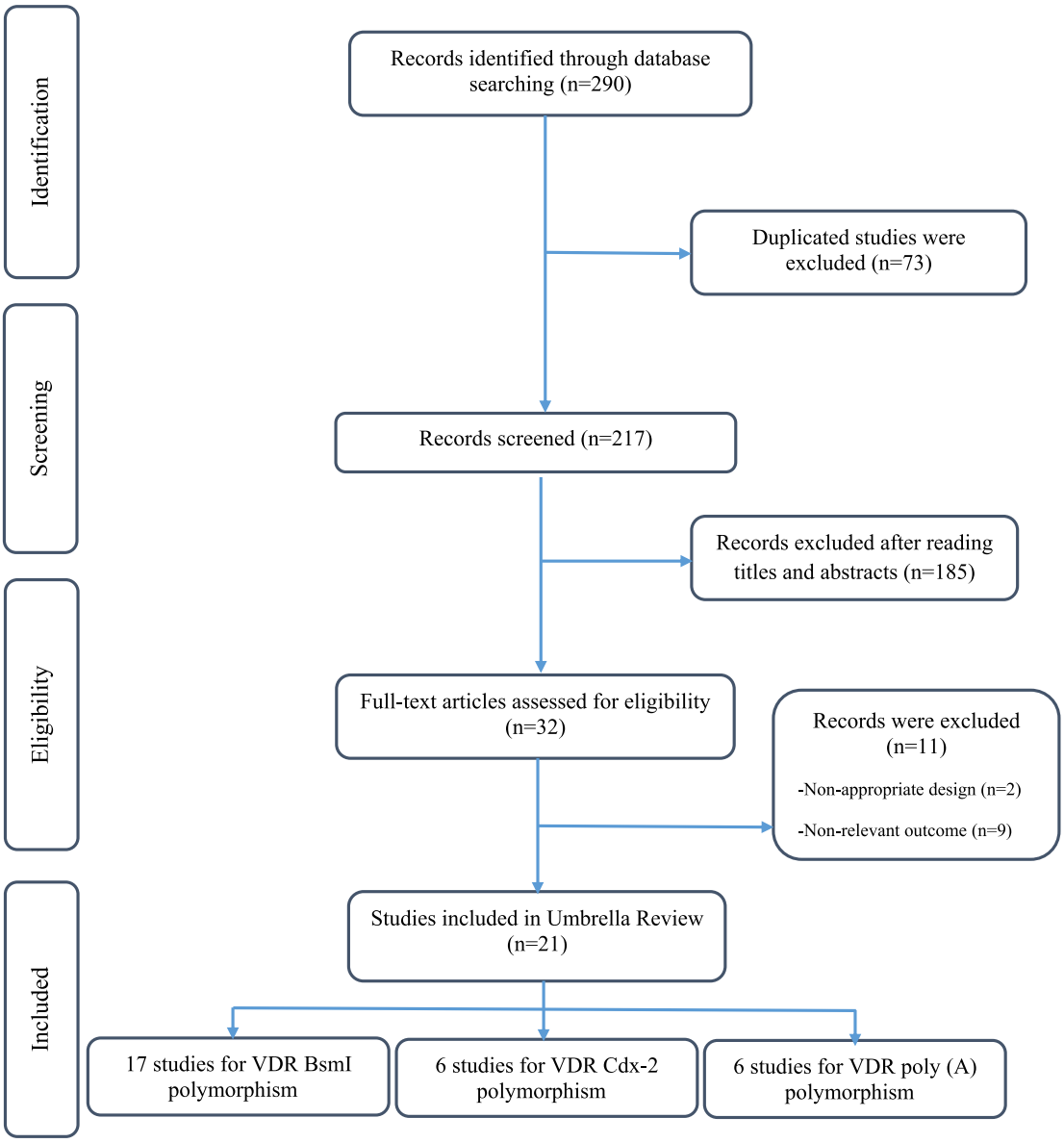

Fig. 1. Flowchart of the selection procedure.

(comparisons) across three broad areas: VDR BsmI polymorphism (n = 71 comparisons), VDR Cdx-2 polymorphism (n = 26 comparisons), and VDR Poly (A) polymorphism (n = 22 comparisons). Each meta-analysis comprised between 2 and 26 studies, with a median of 12 studies. The publication dates of the eligible articles ranged from 2009 to 2022. The median number of case and control subjects in each meta-analysis was 7759 and 9652, respectively. Fifteen studies were performed in China, two in Italy, two in Korea, one in Iran, and one in Pakistan (see Tables 1, 2, and 3). Among the included papers, 24 % utilized the Newcastle Ottawa Scale (NOS) for qualitative assessment of the primary studies, 5 % employed traditional epidemiological considerations and cancer genetic issues, and another 5 % utilized the Strengthening the Reporting of Genetic Association Studies (STREGA) criteria as quality assessment tools. Notably, 66 % of the papers did not conduct any quality assessment. Most meta-analyses incorporated high-quality trials, and the genotype distribution of the control population was predominantly consistent with Hardy–Weinberg equilibrium (HWE) across the included primary studies. Detailed characteristics of the eligible studies are provided in Tables 1, 2, and 3.

3.2. Summary effect size

The investigation into associations between VDR *Bsm*I, Cdx-2, and Poly (A) polymorphisms and BC incidence involved the assessment of homozygote, heterozygote, dominant, recessive, and allele contrast genetic models. All meta-analyses included in this study utilized pooled ORs and corresponding 95 % CIs to evaluate the strength of association between VDR polymorphisms and BC risk. Among the 119 data sets analyzed, 6 (5 %) reported statistically significant summary outcomes, with ORs ranging from 1.18 to 2.24 ($p < 0.05$). These significant associations were observed across various genetic models, encompassing 2 comparisons in VDR *Bsm*I polymorphism (3 %, 2/71), 1 in VDR Cdx-2 polymorphism (4 %, 1/26), and 3 in VDR Poly (A) polymorphism (14 %, 3/22). Consequently, our findings suggest that while VDR BsmI, Cdx-2, and Poly (A) polymorphisms may not be strongly associated with susceptibility to BC overall, a more notable association was observed between VDR Poly (A) polymorphism and BC risk.

Table 1
Summary of Odds Ratios (OR) with 95 % Confidence Intervals (95 % CI) for each meta-analysis on breast cancer risk associated with Vitamin D receptor *Bsm*I polymorphism across various genetic models: Homozygote (bb vs. BB), Heterozygote (Bb vs. BB), Dominant (bb/Bb vs. BB), Recessive (bb vs. Bb/BB), and allele b vs. allele B.

Citation (first author et al., year)	Location	Number of studies in meta-analysis	Cases	Controls	Source of control	Genetic Model	OR (95 % CI)/ I^2, P-heterogeneity	Ethnicity	Genotyping method	Quality assessment scale and outcome
Du et al., 2014	China	17	10,212	12,808	HB & PB	Homozygote	0.84 (0.69, 1.02)/ 75.50 %, P < 0.001	Caucasian, African-American, Asian, Hispanic	TaqMan, QIAamp, PCR-RFLP	Yes (traditional epidemiological considerations and cancer genetic issues) 14/17 high
						Heterozygote	0.93 (0.81, 1.06)/ 73.10 %, P < 0.001			
						Dominant	0.89 (0.78, 1.02)/ 61.00 %, P < 0.001			
						Recessive	0.90 (0.78, 1.04)/ 78.70 %, P < 0.001			
						Allele b vs allele B	0.92 (0.83, 1.01)/ 80.00 %, P < 0.001			
Huang et al., 2014	China	12	16,122	20,645	HB & PB	Homozygote	0.91 (0.82, 1.01)/ ND	Iranian, African-American, Hispanic, Non-Hispanic White, Caucasian, Han Chinese, Japanese-American, Polish	PCR-RFLP, TaqMan, MassArray, Allele-specific PCR, MicroArray	Yes (NOS)
						Dominant	1.04 (0.98, 1.11)/ ND			
						Recessive	0.94 (0.86, 1.02)/ ND			
						Allele b vs allele B	0.97 (0.93, 1.02)/ ND			
Iqbal and Khan, 2017	Pakistan	20	20,555	25,794	ND	Homozygote	1.18 (1.05, 1.32)/ 57.40 %, P = 0.001	Caucasian, African, American, Hispanic, Asian, African-American, Japanese, Hawaiian, Polish, French Canadian, Turkish	PCR-RFLP, TaqMan, QIAamp, MassArray iPLEX	Yes (NOS) 20/20 high
						Dominant	1.09 (1.00, 1.18)/ 46.60 %, P = 0.01			
						Recessive	0.93 (0.85, 1.01)/ 64.50 %, P < 0.001			
						Allele b vs allele B	1.06 (0.99, 1.12)/ 66.90 %, P < 0.001			
Lee and Song, 2014	Korea	15	8839	10,310	ND	Homozygote	0.96 (0.81, 1.14)/ 55.10 %, P = 0.005	Hispanic, African-American, Asian, European, Arab	ND	No
						Dominant	0.95 (0.86, 1.04)/ 25.70 %, P = 0.170			
						Recessive	1.01 (0.95, 1.08)/ 69.20 %, P < 0.001			
						Allele b vs allele B	0.99 (0.96, 1.09)/ 68.80 %, P < 0.001			
Li et al., 2018	China	26	ND	ND	ND	Homozygote	1.05 (0.99, 1.12)/ 61.00 %, P < 0.001	African-American, Caucasian	PCR-RFLP, TaqMan	Yes (NOS) 26/26 high

(*continued on next page*)

Table 1 (*continued*)

Citation (first author et al., year)	Location	Number of studies in meta-analysis	Cases	Controls	Source of control	Genetic Model	OR (95 % CI)/ I^2, P-heterogeneity	Ethnicity	Genotyping method	Quality assessment scale and outcome
						Heterozygote	1.04 (0.98, 1.10)/ 23.70 %, P = 0.137			
						Dominant	1.04 (0.99, 1.10)/ 45.60 %, P = 0.007			
						Recessive	1.02 (0.97, 1.06)/ 69.00 %, P < 0.001			
						Allele b vs allele B	1.02 (0.99, 1.05)/ 70.80 %, P < 0.001			
Li et al., 2014	China	19	15,275	20,029	HB & PB	Homozygote	0.97 (0.91, 1.03)/ P = 0.316	Caucasian, African-American, Asian	PCR–RFLP, Allele–specific PCR, ABI, RL-PCR, TaqMan	No
						Heterozygote	1.00 (0.96, 1.04)/ P = 0.782			
						Dominant	0.96 (0.91, 1.02)/ P = 0.497			
						Recessive	1.00 (0.96, 1.03)/ P = 0.755			
						Allele b vs allele B	0.99 (0.96, 1.02)/ P = 0.191			
Lu et al., 2016	China	2	6839	8994	ND	Homozygote	1.01 (0.91, 1.12)/ 0.00 %, P = 0.435	Caucasian	TaqMan, MGB Eclipse assays	No
						Dominant	1.00 (0.92, 1.10)/ 6.90 %, P = 0.372			
						Recessive	0.96 (0.81, 1.14)/ 58.70 %, P = 0.033			
						Allele b vs allele B	1.00 (0.87, 1.15)/ 66.70 %, P = 0.01			
Mun et al., 2015	Republic of Korea	24	16,293	21,555	ND	Homozygote	0.91 (0.80–1.03)/ 56.00 %, P = 0.002	Caucasian, Asian, African-American	PCR-RFLP, TaqMan	No
						Heterozygote	0.96 (0.87–1.06)/ 62.00 %, P < 0.001			
						Dominant	0.94 (0.86–1.04)/ 66.00 %, P < 0.001			
						Recessive	0.93 (0.85–1.03)/ 39.00 %, P = 0.050			
Bakhshaiesh et al., 2022	Iran	5	668	669	ND	Homozygote	1.91 (0.90, 4.04)/ 72.00 %, P = 0.005	Iranian	PCR-RFLP	No
						Heterozygote	0.89 (0.51, 1.53)/ 68.00 %, P = 0.012			
						Dominant	2.24 (1.35, 3.72)/			

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Table 1 (*continued*)

Citation (first author et al., year)	Location	Number of studies in meta-analysis	Cases	Controls	Source of control	Genetic Model	OR (95 % CI)/ I^2, P-heterogeneity	Ethnicity	Genotyping method	Quality assessment scale and outcome
							59.00 %, P = 0.042			
						Recessive	1.09 (0.57, 2.08)/ 80.00 %			
						Allele b vs allele B	1.31 (0.84, 2.03)/ 84.00 %, P < 0.001			
Raimondi et al., 2014	Italy	16	16,059	20,713	HB & PB	Homozygote	0.98 (0.91, 1.05)/ 23.00 %	Caucasian, Asian, Hispanic, Hawaiian, African-American	PCR-RFLP, TaqMan, iPLEX	No
						Heterozygote	0.99 (0.93, 1.05)/ 28.00 %			
						Recessive	0.97 (0.89, 1.05)/ 40.00 %			
Raimondi et al., 2009	Italy	15	12,201	15,982	HB & PB	Homozygote	0.95 (0.88, 1.03)/ 7.00 %, P = 0.370	Caucasian, African-American, Asian, Hispanic, Hawaiian	ND	No
						Heterozygote	0.97 (0.91, 1.02)/ 22.00 %, P = 0.170			
Tang et al., 2009	China	14	5498	7943	ND	Heterozygote	1.02 (0.87, 1.20)/ P = 0.03	European, Asian, African	PCR-RFLP, MicroArray, TaqMan, Allele-specific PCR	No
						Dominant	0.97 (0.83, 1.13)/ P = 0.01			
						Recessive	1.03 (0.87, 1.23)/ P < 0.001			
						Allele b vs allele B	1.00 (0.92, 1.08)/ P < 0.001			
Wang et al., 2013a	China	23	11,129	14,169	ND	Homozygote	1.07 (0.94, 1.22)/ P = 0.001	Caucasian, Asian, mixed	ND	No
						Dominant	1.03 (0.93, 1.16)/ P = 0.008			
						Recessive	1.06 (0.94, 1.19)/ P < 0.001			
						Allele b vs allele B	1.04 (0.96, 1.12)/ P < 0.001			
Xu et al., 2014b	China	24	19,311	23,977	HB & PB	Homozygote	1.04 (0.90, 1.20)/ 74.80 %, P < 0.001	African-American, Caucasian, Asian, Mixed	PCR-RFLP, TaqMan	No
						Heterozygote	0.94 (0.81, 1.09)/ 78.50 %, P < 0.001			
						Dominant	0.98 (0.85, 1.13)/ 78.40 %, P < 0.001			
						Recessive	1.06 (0.97, 1.17)/ 70.60 %, P < 0.001			
						Allele b vs allele B	1.02 (0.95, 1.10)/ 76.80 %, P < 0.001			
Yang et al., 2014	China	13	14,755	18,633	HB & PB	Homozygote	1.00 (0.90, 1.11)/ P = 0.010	Caucasian, European	PCR–RFLP, MicroArray, TaqMan, PCR,	No

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Table 1 (*continued*)

Citation (first author et al., year)	Location	Number of studies in meta-analysis	Cases	Controls	Source of control	Genetic Model	OR (95 % CI)/ I^2, P-heterogeneity	Ethnicity	Genotyping method	Quality assessment scale and outcome
						Heterozygote	1.02 (0.90, 1.22)/ P = 0.060		Allele–specific PCR, MassArray	
						Dominant	1.01 (0.95, 1.03)/ P = 0.040			
						Recessive	1.01 (0.91, 1.13)/ P = 0.020			
Zhang and Song, 2014	China	25	16,160	21,023	ND	Homozygote	1.07 (0.97, 1.17)/ 44.00 %, P = 0.010	European, Asian, Mixed	PCR-RFLP, TaqMan	Yes (STREGA) 12/25 high
						Dominant	1.03 (0.94, 1.13)/ 54.00 %, P < 0.001			
						Recessive	1.05 (0.97, 1.14)/ 66.00 %, P < 0.001			
						Allele b vs allele B	1.04 (0.98, 1.09)/ 56.00 %, P = 0.003			
Zhao et al., 2023	China	25	8194	11,902	ND	Homozygote	1.26 (0.83, 1.93)/ ND	ND	PCR-RFLP, PCR	Yes (NOS)
						Heterozygote	1.12 (0.89, 1.40)/ ND			
						Dominant	1.16 (0.87, 1.55)/ ND			
						Recessive	1.18 (0.89, 1.57)/ ND			
						Allele b vs allele B	1.10 (0.89, 1.36)/ ND			

OR, odds ratio; CI, confidence interval; HB, hospital based; PB, population based; NOS, Newcastle Ottawa Scale; STREGA, strengthening the reporting of genetic association studies; TaqMan, TaqManSNP; PCR-RFLP, polymerase chain reaction and restriction fragment length polymorphism; *ABI, Applied Biosystems*; *RL-PCR*, reverse ligation-mediated and polymerase chain reaction; ND, not defined.

3.3. Heterogeneity and publication bias

Out of the 119 meta-analyses conducted, 19 data sets revealed no significant heterogeneity among studies ($p \geq 0.1$ of Q test), while 82 exhibited substantial heterogeneity ($p < 0.1$ of Q test). However, information on heterogeneity between studies was not reported in 18 results across three articles. Concerning publication bias, 103 outcomes showed no statistical evidence of publication bias ($p \geq 0.1$ of Egger's test), whereas 16 outcomes indicated the presence of publication bias ($p < 0.1$ of Egger's test).

3.4. Quality assessment of included meta-analyses

The methodological quality assessment results of the 21 included articles are presented in Table 4. Among these, only 3 (14 %) studies were categorized as low quality, while the remaining 18 (86 %) were deemed critically low. According to the AMSTAR 2 criteria, none of the investigations were rated as moderate or high quality.

4. Discussion

The etiology of BC remains elusive, encompassing a complex interplay of environmental factors, molecular signaling pathways, and host genetic elements (Lu et al., 2016). Notably, compelling epidemiological evidence suggests a correlation between increased vitamin D intake and a diminished risk of colorectal (Ma et al., 2011; Wu et al., 2007) and breast cancers (Wang et al., 2013b; Van Der Rhee et al., 2013). This protective effect of vitamin D is thought to be mediated by its regulation of cellular proliferation, differentiation, and apoptosis (Lee and Song, 2014). Vitamin D exerts its effects by binding with the VDR (Lu et al., 2016). The VDR gene, situated on the 12th chromosome (q13.1), harbors several SNPs that may influence mRNA stability, Vitamin D uptake, metabolism, and serum levels of biologically active Vitamin D, thereby affecting cancer susceptibility (Raimondi et al., 2009; Tang et al., 2009). Despite numerous large-scale population studies conducted over the past two decades to explore the link between VDR gene variants and BC risk, findings have yielded conflicting results. In our present umbrella review, we systematically identified 21 meta-analyses of observational studies to assess the existing evidence concerning the association between VDR *Bsm*I, Cdx-2, and Poly (A) polymorphisms and BC incidence. Furthermore, we offer a comprehensive synthesis of the available evidence and meticulously evaluate the methodological rigor of the included meta-analyses. Our findings indicate that VDR BsmI, Cdx-2, and Poly (A) polymorphisms did not exhibit a significant association with BC susceptibility in the majority of studies reviewed (Huang et al., 2014; Du et al., 2014; Lee and Song, 2014; Dai et al., 2015; Huang et al.,

Table 2
Summary of Odds Ratios (OR) with 95 % Confidence Intervals (95 % CI) for each meta-analysis on breast cancer risk associated with Vitamin D receptor Cdx-2 polymorphism across various genetic models: Homozygote (AA vs. GG), Heterozygote (GA vs. GG), Dominant (AA/GA vs. GG), Recessive (AA vs. GA/GG), and allele L vs. allele S.

Citation (first author et al., year)	Location	Number of studies in meta-analysis	Cases	Controls	Source of control	Genetic model	OR (95 % CI)/ I^2, P-heterogeneity	Ethnicity	Genotyping method	Quality assessment scale and outcome
Dai et al., 2015	China	5	3938	5100	HB & PB	Homozygote	1.69 (0.97, 3.94)/ 92.00 %, P < 0.001	Caucasian, African-American, Asian	PCR-RFLP, Illumina Golden Gate assay, TARMS-PCR, Pyrosequencing	Yes (NOS) 5/5 high
						Heterozygote	0.98 (0.81, 1.20)/ 61.00 %, P = 0.040			
						Dominant	1.00 (0.78, 1.28)/ 80.00 %, P = 0.001			
						Recessive	1.69 (0.82, 3.10)/ 91.00 %, P < 0.001			
						Allele A vs allele G	1.06 (0.87, 1.29)/ 82.00 %, P < 0.001			
Huang et al., 2014	China	4	3841	5039	PB	Homozygote	1.22 (0.98, 1.50)/ ND	Caucasian, African-American	PCR-RFLP, Illumina Golden Gate assay, MassArray iPLEX, Pyrosequencing	Yes (NOS)
						Dominant	1.03 (0.87, 1.21)/ ND			
						Recessive	0.83 (0.63, 1.08)/ ND			
						Allele A vs allele G	0.95 (0.86, 1.06)/ ND			
Iqbal and Khan, 2017	Pakistan	4	4216	5455	HB & PB	Homozygote	0.54 (0.25, 1.16)/ 91.60 %, P < 0.001	Caucasian, African-American, Asian, European, American, German	PCR-RFLP, TARMS-PCR, Sequencing, MassArray iPLEX	Yes (NOS) 4/4 high
						Dominant	1.05 (0.86, 1.28)/ 75.30 %, P = 0.007			
						Recessive	0.58 (0.23, 1.46)/ 94.80 %, P < 0.001			
						Allele A vs allele G	0.75 (0.42, 1.34)/ 98.00 %, P < 0.001			
Li et al., 2018	China	7	ND	ND	ND	Homozygote	1.18 (0.96, 1.44)/ 32.40 %, P = 0.181	Caucasian, African-American	PCR-RFLP, TaqMan	Yes (NOS) 7/7 high
						Heterozygote	1.01 (0.93, 1.11)/ 55.40 %, P = 0.047			
						Dominant	1.01 (0.93, 1.09)/ 50.70 %, P = 0.057			
						Recessive	1.23 (1.05, 1.46)/ 38.60 %, P = 0.135			
						Allele A vs allele	1.03 (0.96, 1.11)/ 57.80 %, P = 0.027			

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Table 2 (*continued*)

Citation (first author et al., year)	Location	Number of studies in meta-analysis	Cases	Controls	Source of control	Genetic model	OR (95 % CI)/ I^2, P-heterogeneity	Ethnicity	Genotyping method	Quality assessment scale and outcome
Mun et al., 2015	Republic of Korea	4	3841	5039	ND	Homozygote	1.24 (0.89–1.73)/ 51.00 %, P = 0.100	Caucasian, African-American	PCR-RFLP, Illumina Golden Gate assay	No
						Heterozygote	1.00 (0.82–1.23)/ 66.00 %, P = 0.030			
						Dominant	0.98 (0.80–1.21)/ 72.00 %, P = 0.010			
						Recessive	1.18 (0.89–1.56)/ 59.00 %, P = 0.060			
Zhou et al., 2013	China	4	3841	5039	ND	Homozygote	0.97 (0.64, 1.45)/ 67.30 %, P = 0.027	Caucasian, African	ND	No
						Dominant	0.94 (0.80, 1.10)/ 62.10 %, P = 0.048			
						Recessive	0.99 (0.65, 1.51)/ 70.70 %, P = 0.017			
						Allele A vs allele G	0.96 (0.84, 1.09)/ 57.70 %, P = 0.069			

OR, odds ratio; CI, confidence interval; HB, hospital based; PB, NOS, Newcastle Ottawa Scale; population based; PCR-RFLP, polymerase chain reaction and restriction fragment length polymorphism; TARMS-PCR, tetraprimer amplification refractory mutation system-polymerase chain reaction; TaqMan, TaqManSNP; ND, not defined.

2013; Li et al., 2014; Lu et al., 2016; Mun et al., 2015; Raimondi et al., 2009; Raimondi et al., 2014; Tang et al., 2009; Wang et al., 2013a; Xu et al., 2014a; Xu et al., 2014b; Yang et al., 2014; Zhang and Song, 2014; Zhao et al., 2023; Zhou et al., 2013). Nonetheless, some contradictory findings have been documented. Iqbal et al. (Iqbal and Khan, 2017) evaluated VDR gene polymorphisms and their associations with BC risk. They found that the *Bsm*I polymorphism in the homozygote genetic model and the Poly (A) polymorphism in the homozygote, dominant, and allele L vs. allele S genetic models were associated with an increased risk of BC. Conversely, the Cdx-2 polymorphism was not associated with BC risk. However, despite a large sample size, heterogeneity among patients might have skewed the results of this meta-analysis. Additionally, Oghabi Bakhshaiesh et al. (Bakhshaiesh et al., 2022) analyzed the association between the BsmI polymorphism and BC risk in Iranian patients across 5 studies (668 cases and 669 controls), suggesting that the dominant model of the BsmI polymorphism increased the risk of BC. Considering that VDR genotypes differ significantly among various ethnic groups, including only Iranian women in this meta-analysis may account for these contradictory results. Moreover, the low number of included studies, small sample sizes, lack of quality assessment of the included studies, and deviation from HWE in some of the original studies are significant limitations that could affect the findings. Li et al. (Li et al., 2018) reported that only the recessive model of the Cdx-2 polymorphism increased BC risk, while the other two polymorphisms showed no association.

A key contributing factor to these discrepancies is the substantial heterogeneity observed among the original studies. Among the 119 comparisons analyzed, 82 exhibited significant heterogeneity. Variations in adjusted factors of ORs across studies, such as age, age at menarche, menopausal status, body mass index, hormone replacement therapy usage, family history, race, and smoking, could introduce bias and heterogeneity into our analysis. This considerable heterogeneity undermines the reliability of the results obtained. Furthermore, out of the 119 comparisons, 16 displayed notable publication bias, indicating that certain negative findings may not have been reported. Publication bias can arise due to researchers' tendency to favor positive results for publication, resulting in an overrepresentation of positive outcomes in the literature. Additionally, according to the AMSTAR 2 criteria, 86 % of the studies included in our umbrella analysis exhibited “critically low” methodological quality. Critical flaws, such as the absence of a registered protocol, lack of duplicate study selection and data extraction in the meta-analyses considered, were prevalent. Moreover, none of the meta-analyses provided detailed information regarding their funding sources. Given that VDR genotypes vary considerably across ethnicities (Uitterlinden et al., 2004), differences in participant backgrounds and ethnicity may also contribute to the observed contradictory results. Finally, usage of different genotypic methods could also have influenced the results.

An umbrella review offers distinct advantages over traditional systematic reviews or meta-analyses as it provides a comprehensive overview of findings pertaining to specific phenomena or research questions (Aromataris et al., 2015). To the best of our knowledge, our study represents the first utilization of this method to conduct a thorough critical appraisal of published associations between VDR *Bsm*I, Cdx-2, and Poly (A) polymorphisms and BC incidence. Our research team systematically searched five reputable scientific databases using a robust search strategy, accompanied by clearly defined eligibility criteria and data extraction parameters. Furthermore, the methodological quality of the included meta-analyses was rigorously evaluated using the AMSTAR 2 tool, a widely recognized benchmark for assessing the quality of meta-

Table 3
Summary of Odds Ratios (OR) with 95 % Confidence Intervals (95 % CI) for each meta-analysis on breast cancer risk associated with Vitamin D receptor poly (A) polymorphism across various genetic models: Homozygote (LL vs. SS), Heterozygote (SL vs. SS), Dominant (LL/SL vs. SS), Recessive (LL vs. SL/SS), and allele L vs. allele S.

Citation (first author et al., year)	Location	Number of studies in meta-analysis	Cases	Controls	Source of control	Genetic model	OR (95 % CI)/ I^2, P-heterogeneity	Ethnicity	Genotyping method	Quality assessment scale and outcome
Huang et al., 2014	China	5	5456	5653	HB & PB	Homozygote	0.95 (0.73, 1.25)/ ND	Hispanic, Non-Hispanic White, Hindus and Muslims, African-American, Caucasian	PCR-RFLP	Yes (NOS)
						Dominant	0.98 (0.88, 1.09)/ ND			
						Recessive	0.95 (0.78, 1.17)/ ND			
						Allele L vs allele S	0.99 (0.87, 1.13)/ ND			
Huang et al., 2013	China	6	4892	4854		Recessive	0.97 (0.81, 1.17)/ ND	Caucasian, African-American, Asian, Latinas	ND	No
Iqbal and Khan, 2017	Pakistan	8	7325	7343	HB & PB	Homozygote	1.41 (1.06, 1.88)/ 75.60 %, P < 0.001	Caucasian, African, American, Hispanic, Asian, Swedish	PCR-RFLP, PCR-SSCP, TaqMan	Yes (NOS) 8/8 high
						Dominant	1.19 (1.00, 1.43)/ 56.80 %, P = 0.023			
						Recessive	0.81 (0.67, 0.98)/ 75.30 %, P < 0.001			
						Allele L vs allele S	1.18 (1.03, 1.35)/ 77.40 %, P < 0.001			
Li et al., 2018	China	8	ND	ND	ND	Homozygote	1.07 (0.94, 1.23)/ 78.40 %, P < 0.001	African-American, Caucasian	PCR-RFLP, TaqMan	Yes (NOS) 8/8 high
						Heterozygote	1.06 (0.93, 1.20)/ 34.40 %, P = 0.154			
						Dominant	1.07 (0.95, 1.21)/ 61.80 %, P = 0.011			
						Recessive	0.98 (0.90, 1.07)/ 79.70 %, P < 0.001			
						Allele L vs allele S	1.02 (0.96, 1.09)/ 81.80 %, P < 0.001			
Xu et al., 2014a	China	11	6631	6718	ND	Homozygote	0.96 (0.79, 1.18)/ 66.00 %, P = 0.001	Caucasians, Asians, Africans, and Latinas	ND	No
						Dominant	1.00 (0.91, 1.10)/ 37.00 %			
						Recessive	0.96 (0.83, 1.12)/ 74.00 %, P < 0.001			
						Allele L vs allele S	0.99 (0.90, 1.09)/ 69.00 %			
Zhang and Song, 2014	China	7	5493	5566	ND	Homozygote	0.99 (0.77, 1.29)/ 74.00 %, P < 0.001	European, Asian	PCR-RFLP, TaqMan	Yes (STREGA) 4/7 high

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Table 3 (*continued*)

Citation (first author et al., year)	Location	Number of studies in meta-analysis	Cases	Controls	Source of control	Genetic model	OR (95 % CI)/ I^2, P-heterogeneity	Ethnicity	Genotyping method	Quality assessment scale and outcome
						Dominant	1.04 (0.88, 1.27)/ 49.00 %, P = 0.070			
						Recessive	0.99 (0.83, 1.20)/ 76.00 %, P < 0.001			
						Allele L vs allele S	1.00 (0.85, 1.18)/ 77.00 %, P < 0.001			

OR, odds ratio; CI, confidence interval; HB, hospital based; PB, population based; NOS, Newcastle Ottawa Scale; STREGA, strengthening the reporting of genetic association studies; PCR-RFLP, polymerase chain reaction and restriction fragment length polymorphism; PCR-SSCP, polymerase chain reaction and single-strand conformation polymorphism; TaqMan, TaqManSNP; ND, not defined.

Table 4
Results of assess the methodological quality of meta-analysis.

First author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Overall
Dai et al., 2015	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Du et al., 2014	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Huang et al., 2014	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Huang et al., 2013	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Iqbal and Khan, 2017	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Lee and Song, 2014	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Li et al., 2018	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Li et al., 2014	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Lu et al., 2016	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Mun et al., 2015	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Bakhshaiesh et al., 2022	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Raimondi et al., 2014	Yes	No	Yes	Yes	No	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Raimondi et al., 2009	Yes	No	Yes	Yes	No	No	No	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Tang et al., 2009	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Wang et al., 2013a	Yes	No	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Xu et al., 2014a	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low
Xu et al., 2014b	Yes	No	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Critically low
Yang et al., 2014	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Critically low
Zhang and Song, 2014	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Zhao et al., 2023	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low
Zhou et al., 2013	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Critically low

The result of assess the methodological quality using AMSTAR 2: Q1- Did the research questions and inclusion criteria for the review include the components of PICO? Q2- Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review, and did the report justify any significant deviations from the protocol? Q3- Did the review authors explain their selection of the study designs for inclusion in the review? Q4- Did the review authors use a comprehensive literature search strategy? Q5- Did the review authors perform study selection in duplicate? Q6- Did the review authors perform data extraction in duplicate? Q7- Did the review authors provide a list of excluded studies and justify the exclusions? Q8- Did the review authors describe the included studies in adequate detail? Q9- Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? 10- Did the review authors report on the sources of funding for the studies included in the review? Q11- If meta-analysis was performed, did the review authors use appropriate methods for the statistical combination of results? Q12- If a meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? Q13- Did the review authors account for RoB in individual studies when interpreting/discussing the review results? Q14- Did the review authors provide a satisfactory explanation for and discussion of any heterogeneity observed in the review results? Q15- If they performed quantitative synthesis, did the review authors conduct an adequate investigation of publication bias (small-study bias) and discuss its likely impact on the review results? Q16- Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

analysis methods. Moreover, the sample sizes of the primary studies included in our umbrella review were notably large, which reduces the likelihood of bias compared to smaller studies. Additionally, it is worth noting that the genotype distributions of most control SNPs were consistent with HWE, further enhancing the robustness of our findings.

Our umbrella review is subject to several limitations. Firstly, the inclusion of only English-published meta-analyses may have resulted in the omission of relevant information published in other languages, potentially impacting the assessment outcomes. Secondly, a significant proportion of the meta-analyses exhibited heterogeneity, which may stem from selection bias among other factors. Variations in participant backgrounds and adjusted factors of controls could contribute to this heterogeneity. Thirdly, the majority of studies included in our umbrella analysis were characterized by "critically low" methodological quality, which undermines confidence in the results obtained.

In conclusion, our study provides evidence suggesting that VDR polymorphisms (*Bsm*I, Cdx-2, and Poly (A)) are not significantly associated with the risk of BC in the general population. However, further research is warranted to elucidate and validate these findings.

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Consent for publication

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CRediT authorship contribution statement

Yaxing Li: Writing – original draft, Visualization, Validation, Supervision, Formal analysis, Data curation, Conceptualization. **Junqin Zhang:** Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation. **Fei Tian:** Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Methodology, Conceptualization. **Paniz Anvarifard:** Writing – review & editing, Supervision, Project administration. **Na Li:** Writing – review & editing, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no “competing interests” in this study.

Data availability

Data will be made available on request.

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