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Association of vitamin D receptor gene polymorphisms with caries risk in children: a systematic review and meta-analysis

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Abstract

Background To investigate the association of vitamin D receptor (VDR) gene polymorphism with caries risk in children(< 18 years).

Methods The electronic databases PubMed, Cochrane, EMBASE, Web of Science, CNKI, Cqvip, and Wanfang were searched for observational studies on the relationship between VDR single nucleotide polymorphism(SNP) and caries, including cohort, case–control, and cross-sectional studies. Quality assessment of selected studies was conducted using the Newcastle Ottawa scale. Odds ratios (*OR*) with 95% confidence intervals (*CI*) values for associations of individual VDR SNP with dental caries were calculated based on four genetic models: allelic, recessive, dominant, and over-dominant.

Results Of 79 studies considered, 10 (nine case–control and one cross-sectional) were selected for analysis; the studies involved seven VDR SNPs: *ApaI(rs7975232)*,*BsmI(rs1544410)*,*FokI(rs2228570)*,*TaqI(rs731236)*, *TaqI/BglI(rs739837)*, *FokI(rs10735810)* and *Cdx-2(rs11568820)*. Alleles C and T of *FokI(rs10735810)* were significantly differently distributed in the caries and caries-free groups (*OR* = 1.33, 95% *CI*: 1.30–2.30, *P* = 0.03), with CC + CT genotypes at this locus associated with greater risk of developing caries than the TT genotype (*OR* = 1.87, 95%*CI*: 1.15–3.04, *P* = 0.01). Further, TT + CC genotype at *TaqI(rs731236)* was associated with a 1.33-fold higher risk of caries development than the TC genotype (*OR* = 1.33, 95%*CI*: 1.06–1.67, *P* = 0.02). On subgroup analysis, the association between *TaqI(rs731236)* and caries risk was affected by dentition type, and ethnicity (permanent dentition: *OR* = 1.48, 95%*CI*: 1.07–2.03, *P* = 0.02; Asian: *OR* = 1.38, 95%*CI*: 1.02–1.87, *P* = 0.03;). Genotype distributions at *BsmI(rs1544410)*, *TaqI/BglI(rs739837)*, *FokI(rs2228570)*, and *ApaI(rs7975232)* did not differ significantly between the caries and caries-free groups.

Conclusions Caries risk could be associated with *TaqI(rs731236)* and *FokI(rs10735810)* genotypes, and *TaqI(rs731236)* may be a risk factor for permanent teeth caries among Asian people.

Keywords Caries, Vitamin D receptor (VDR), Single nucleotide polymorphism (SNP), Caries risk

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Introduction

Globally, dental caries is still a major public health problem due to its high prevalence and negative impact on oral health related quality of life, especially in children. Dental caries is the most prevalent childhood disease, occurring five times more frequently than asthma, which ranks second in incidence [1–3]. Untreated caries in children can not only cause local pain, abscesses, loss of teeth, malocclusion, and digestive dysfunction but can also harm the subsequent eruption of permanent teeth, leading to speech difficulties, which can seriously affect the psychological and physical health of children [4–6].

Nevertheless, dental caries is a multifactorial infectious disease. Microbial, behavioral, and environmental influences have been widely studied [7, 8], but these factors are insufficient to explain susceptibility to dental caries, since some people are more likely to develop caries than others when exposed to similar environmental risks [9, 10], suggesting that heredity may also contribute to susceptibility [11]. Indeed, it is estimated that >40% of the risk of dental caries can be explained by genetic factors [12]. however, despite the potential importance of genetic influences, only a few genes associated with susceptibility to caries have been verified to date, and the molecules they encode may be involved in enamel formation, mineralization, immune response, taste, and saliva [13]. Vitamin D plays a crucial role in the mineralization and deposition of enamel [14]. Further, the vitamin D receptor (VDR) gene, which maps to human chromosome 12q13.1, is important in regulating calcium and phosphorus metabolism, as well as cell growth and differentiation [15, 16]. It has been proposed that the effects of vitamin D on dental caries may be meditated through serum $1,25(OH)_2D_3$ levels and VDR SNP since vitamin D levels are related to the occurrence of dental caries [17, 18], with insufficient vitamin D increasing the risk of their occurrence [19]; The VDR gene contains more than 200 polymorphic sites, among which the relationship with dental caries has been studied in seven SNPs: *ApaI(rs7975232)*, *BsmI(rs1544410)*, *FokI(rs2228570)*, *TaqI(rs731236)*, *TaqI/BglI(rs739837)*, *FokI(rs10735810)* and *Cdx-2(rs11568820)*. yet the conclusions of these publications were somehow inconsistent [20–22].

To clarify associations between these VDR SNPs and dental caries, this systematic review was designed to get a more credible conclusion by combing the results of all relevant publications, and to provide a theoretical basis for understanding the etiology of the condition and informing its primary prevention.

Materials and methods

Research question and study protocol

This study was registered in the PROSPERO database (Registration number: CRD42022384570) and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines [23]. The research question of this review was based on the PECOS framework, as follows: Population (P): subjects under the age of 18; Exposure (E): VDR SNPs; Comparator(C): with or without dental caries, confirmed by clinical examinations; Outcome (O): the association of VDR SNP with caries risk; and Study Design (S): observational studies on the relationship between VDR SNP and caries, including cohort, case–control, and cross-sectional studies.

Eligibility criteria

Inclusion of articles focusing on the association between VDR SNP and the risk of dental caries. Subjects > 18 years old were excluded. Reviews, abstracts, case reports and series, comments, letters to the editor, conference proceedings, in vitro investigations, and animal studies were also excluded.

Literature search strategy and selection of papers

The PubMed, Cochrane, EMBASE, Web of Science, CNKI, Cqvip, and Wanfang databases were searched for studies published in English or Chinese before August 31, 2022. The search strategies for each database are shown in Table 1. Search results were imported into EndNote software (v 20.0), and duplicates were removed. The titles and abstracts of identified reports were checked by two authors (XR Qin and Y Xu), and any disagreement was resolved by consensus with a third author (LL Wang). References in relevant published articles were also manually searched. Research publications from the same authors or institutions were scrutinized to eliminate any data redundancy. In cases of redundancy, only results from the most recent publications were included.

Data extraction

Relevant data were independently extracted from the included papers by two authors (XR Qin and Y Xu) in duplicate. Data extracted from the selected studies included study information (author, year, country, ethnicity, and study design), patient information (age, sample size, dentition type, and genotyping method), diagnostic information (diagnostic criteria for dental caries), and outcome information (VDR SNP loci and allele or genotype frequencies). To avoid the risk of retrieval bias, authors were not contacted about missing information

Table 1 Search strategy

Database	Key words	Results
PubMed	((vitamin D receptor gene polymorphism) and (dental caries)) or ((dental caries) AND (rs11568820)) or ((dental caries) AND (rs10735810)) or ((dental caries) AND (rs7975232)) or ((dental caries) AND (rs731236)) or ((dental caries) AND (rs1544410)) or ((dental caries) AND (CdX2)) or ((dental caries) AND (FokI)) or ((dental caries) AND (ApaI)) or ((dental caries) AND (TaqI)) or ((dental caries) AND (BsmI)) ((vitamin D receptor gene polymorphism) and (tooth decay)) or ((tooth decay) AND (rs11568820)) or ((tooth decay) AND (rs10735810)) or ((tooth decay) AND (rs7975232)) or ((tooth decay) AND (rs731236)) or ((tooth decay) AND (rs1544410)) or ((tooth decay) AND (CdX2)) or ((tooth decay) AND (FokI)) or ((tooth decay) AND (ApaI)) or ((tooth decay) AND (TaqI)) or ((tooth decay) AND (BsmI)) Last update posted on or before 08/31/2022	25
Web of Science	((vitamin D receptor gene polymorphism) and (dental caries)) or ((dental caries) AND (rs11568820)) or ((dental caries) AND (rs10735810)) or ((dental caries) AND (rs7975232)) or ((dental caries) AND (rs731236)) or ((dental caries) AND (rs1544410)) or ((dental caries) AND (CdX2)) or ((dental caries) AND (FokI)) or ((dental caries) AND (ApaI)) or ((dental caries) AND (TaqI)) or ((dental caries) AND (BsmI)) or ((vitamin D receptor gene polymorphism) and (tooth decay)) or ((tooth decay) AND (rs11568820)) or ((tooth decay) AND (rs731236)) or ((tooth decay) AND (rs7975232)) or ((tooth decay) AND (rs731236)) or ((tooth decay) AND (rs1544410)) or ((tooth decay) AND (CdX2)) or ((tooth decay) AND (FokI)) or ((tooth decay) AND (ApaI)) or ((tooth decay) AND (TaqI)) or ((tooth decay) AND (BsmI)) Last update posted on or before 08/31/2022	21
Cochrane Library	((vitamin D receptor gene polymorphism) and (dental caries)) or ((dental caries) AND (rs11568820)) or ((dental caries) AND (rs10735810)) or ((dental caries) AND (rs7975232)) or ((dental caries) AND (rs731236)) or ((dental caries) AND (rs1544410)) or ((dental caries) AND (CdX2)) or ((dental caries) AND (FokI)) or ((dental caries) AND (ApaI)) or ((dental caries) AND (TaqI)) or ((dental caries) AND (BsmI)) Last update posted on or before 08/31/2022	1
Embase	(vitamin D receptor gene polymorphism) and (dental caries) (dental caries) AND (rs11568820) (dental caries) AND (rs10735810) (dental caries) AND (rs7975232) (dental caries) AND (rs731236) (dental caries) AND (rs1544410) (dental caries) AND (CdX2) (dental caries) AND (FokI) (dental caries) AND (ApaI) (dental caries) AND (TaqI) (dental caries) AND (BsmI) Last update posted on or before 08/31/2022	23
CNKI	("龋齿"or"龋病") and (维生素D受体) and (多态性) ("龋齿"or"龋病") and ("TaqI"or"ApaI"or"FokI"or"BsmI"or"CdX2") ("龋齿"or"龋病") and ("rs10735810"or"rs731236"or"rs1544410" or"rs7975232"or"rs11568820") 截止日期: 2022年8月31日	3
Wanfang	(龋齿)(维生素D受体) (多态性) (龋)(TaqI) + (龋)(ApaI) + (龋)(FokI) + (龋)(BsmI) + (龋)(CdX2) (龋)(rs10735810) + (龋)(rs731236) + (龋)(rs1544410) + (龋)(rs7975232) + (龋)(rs11568820) 截止日期: 2022年8月31日	3
Cqvip	(龋齿)(维生素D受体) (多态性) (龋)(TaqI) + (龋)(ApaI) + (龋)(FokI) + (龋)(BsmI) + (龋)(CdX2) (龋)(rs10735810) + (龋)(rs731236) + (龋)(rs1544410) + (龋)(rs7975232) + (龋)(rs11568820) 截止日期: 2022年8月31日	2

required for the meta-analysis. To dichotomize the results of caries detection, the WHO 1997 [24], WHO 2013 [25], and ICDAS II [26] caries diagnostic criteria were combined to determine caries and caries-free classifications, where individuals classified as ICDAS = 0–2 and DMFT (dmft) = 0 in WHO 1997 and WHO 2013 were considered the caries-free group, and those defined as ICDAS = 3–6 and DMFT(dmft) > 0 in WHO 1997 and WHO 2013 considered the caries group. In the included articles, PCR-restriction fragment length polymorphism (RFLP) and real-time quantitative PCR were used to detect genotypes; SNP detected by PCR–RFLP were named according to restriction endonuclease binding sites, while those identified by real-time quantitative PCR were named according to alleles at the polymorphic site. For convenience, the one-to-one correspondence between genotypes named using the two methods with minor allele frequency was determined (Table 2) and variables are hereafter referred to using their unique reference SNP identification numbers.

Table 2 VDR SNP genotypes according to detection by the PCR-RFLP and real-time quantitative PCR detection methods

SNP	Restriction endonuclease/transcription factor binding site(s)	Allele	PCR-RFLP	Real-time quantitative PCR
TaqI(rs731236)	TaqI	T/C	TT	TT
			Tt	TC
			tt	CC
TaqI/BglI(rs739837)	TaqI/BglI	C/T		TT
				TG
				GG
FokI(rs10735810)	FokI	A/G	FF	CC
			Ff	CT
			ff	TT
FokI(rs2228570)	FokI	A/G		AA
		A>G		AG
				GG
ApaI(rs7975232)	ApaI	A/C	AA	AA
			Aa	AC
			Aa	CC
Cdx-2(rs11568820)	CDX2	A/G	AA	AA
			AG	AG
			GG	GG
BsmI(rs1544410)	BsmI	A/G	BB	AA
			Bb	AG
			bb	GG

Quality assessment

Quality assessment of included studies was carried out independently by two authors (XR Qin and Y Xu), and any disagreements were resolved by consensus. As included studies were all observational (nonrandomized), an accurate assessment of bias risk could not be conducted, and hence only quality was assessed. The Newcastle Ottawa scale (NOS), with minor modification, was used to assess the quality of the included case–control studies (https://www.ohri.ca//programs/clinical_epidemiology/oxford.asp), and added conformed to Hardy–Weinberg equilibrium. The NOS evaluates the methodological quality of each study, following a star system based on nine domains grouped into four main sets, namely, patient selection, comparability of study groups, exposure and Hardy–Weinberg equilibrium, and is scored by awarding a point for each answer. Studies were categorized as high quality, moderate quality, and low quality if they reached 7–9, 4–6, or 0–4 points, respectively (Table 3). The cross-sectional study was qualified by Appraisal tool for Cross Sectional Studies(AXIS) method(Table 4), and is measured as.The AXIS quality assessment tool has five components to assess the overall quality of studies, including introduction, methods, results, discussion and other. The presence of these components can be answered either with a yes, do not know or no comment. The total number of "yes" responses was counted for each study. A higher number of "yes" responses indicated a lower risk of bias.

Statistical analysis

SPSS 22.0 software (SPSS, Inc., Chicago, IL, USA) was used to apply the Kappa test to evaluate agreement among reviewers in article identification, screening, data extraction, and quality.

Meta-analysis was performed when warranted by the quality and quantity of included studies. Associations between VDR SNP and caries were assessed by calculating odds ratio (*OR*) with 95% confidence interval (*CI*) values, based on four genetic models: allelic, recessive, dominant, and over-dominant. Heterogeneity was assessed using the I^2 statistic and Cochrane's Q test, with $I^2 > 50\%$ or $P < 0.10$ on Cochrane's Q test, indicating substantial heterogeneity [27]. A random effects model when $I^2 > 50\%$ or $P < 0.10$ and a fixed effects model when $I^2 < 50\%$ or $P > 0.10$. $P < 0.05$ was considered statistically significant. Publication bias was evaluated by visual inspection of funnel plots [27], as well as by Egger's and Begg's tests. Sensitivity analyses (one study removed) were used to evaluate the stability of the results of

Table 3 Quality assessment according to the Newcastle Ottawa scale

	Item	Score criteria	Zhang(2006) [30]	Qin(2019) [28]	Yu(2017) [20]	Kong(2017) [29]	Holla(2017) [22]	Cogulu(2016) [21]	Aribam(2020) [32]	Barbosa(2020) [31]	Madalen(2020) [33]
1	Definition of caries	a. Yes, the definition and diagnosis of caries are correct, independent, and valid ☆ b. Yes, such as according to medical records or the doctor's own records ☆ c. No description		☆	☆	☆	☆	☆	☆	☆	☆
2	Disease representative	a. Are consecutive cases, or cases are well represented ☆ b. Presence of selectivity bias or no description		☆	☆	☆	☆			☆	☆
3	Definition of the caries-free group	a. No history of caries; patients to be studied☆ b. No description	☆	☆	☆	☆	☆	☆	☆	☆	☆
4	Selection of the caries-free group	a. Community control ☆ b. Hospital control c. No description		☆	☆	☆	☆			☆	☆
5	Comparability of cases and controls	a. Controls selected and analyzed based on presence or absence of caries ☆ b. Controls selected and analyzed based on other factors	☆	☆	☆	☆	☆	☆	☆	☆	☆
6	Exposure investigation and assessment methods	a. Reliable records ☆ b. Blind interview ☆ c. Unblinded interview self-report or medical record only d. No description	☆	☆	☆	☆	☆	☆	☆	☆	☆
7	Exposure The same investigation method	a. Yes ☆ b. No	☆	☆	☆	☆	☆	☆	☆	☆	☆

Table 3 (continued)

	Item	Score criteria	Zhang(2006) [30]	Qin(2019) [28]	Yu(2017) [20]	Kong(2017) [29]	Holla(2017) [22]	Cogulu(2016) [21]	Aribam(2020) [32]	Barbosa(2020) [31]	Madalen(2020) [33]
8	Exposure Nonresponse rate	a. The nonresponse rate was the same in both groups ☆ b. No nonresponse rate was described c. Nonresponse rate was different, but no reason was stated									
9	Conformed to Hardy–Weinberg equilibrium	a. Hardy–Weinberg equilibrium ☆ b. Hardy–Weinberg disequilibrium	☆	☆	☆	☆	☆	☆	☆	☆	☆
	Total		5	8	8	8	8	6	6	8	8

Table 4 Quality assessment according to the AXIS

Item	Score criteria	Fatturi (2020) [34] Do not know/ Yes/No comment
Introduction	1 Were the aims/objectives of the study clear?	Yes
Methods	2 Was the study design appropriate for the stated aim(s)?	Yes
	3 Was the sample size justified?	Yes
	4 Was the target/reference population clearly defined? (Is it clear who the research was about?)	Yes
	5 Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?	Yes
	6 Was the selection process likely to select subjects/participants that were representative?	Yes
	7 Were measures undertaken to address and categorise non-responders?	No comment
	8 Were the risk factor and outcome variables measured appropriate to the aims of the study?	Yes
	9 Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?	Yes
	10 Is it clear what was used to determined statistical significance and/or precision estimates? (eg,p values,CIs)	Yes
	11 Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	Yes
Results	12 Were the basic data adequately described?	Yes
	13 Does the response rate raise concerns about non-response bias?	Yes
	14 If appropriate, was information about non-responders described?	No comment
	15 Were the results internally consistent?	Yes
	16 Were the results for the analyses described in the methods, presented?	Yes
Discussion	17 Were the authors' discussions and conclusions justified by the results?	Yes
	18 Were the limitations of the study discussed?	Yes
Other	19 Were there any funding sources or conflicts of interest that may affect the authors'interpretation of the results?	No
	20 Was ethical approval or consent of participants attained?	Yes

analysis of data from included studies. Subgroup analyses, based on ethnicity, genotyping method, and tooth dentition, were conducted to determine the effects of subgroups on the overall results, if sufficient articles were included. Forest plots, subgroup analysis, and publication bias were conducted using Review manager 5 software (Revman5.4), while sensitivity analyses, Egger's test, and.

Begg's test were performed using Comprehensive Meta-Analysis version 3.0 (CMA 3.0) software.

Results

Systematic search

Study selection

A total of 78 studies were identified from databases, and one additional study was identified from an article reference list, bringing the total to 79, of which 14 satisfied the initial inclusion criteria. Reading of complete texts resulted in the inclusion of ten studies, of which nine were case–control studies [20–22, 28–33] and one was a cross-sectional investigation [34]; four studies were excluded because the subjects were older than 18 years [35–38] (Table S1). Details of the process for selection of research articles are presented as a flow diagram in Fig. 1.

Data extraction

Seven gene loci were involved in the selected studies: *ApaI(rs7975232)*, *BsmI(rs1544410)*,*FokI(rs2228570)*,*TaqI(rs731236)*, *TaqI/BglI(rs739837)*, *FokI(rs10735810)* and *Cdx-2(rs11568820)* (Tables 5 and 6). Six studies reported data on *TaqI(rs731236)* [20–22, 28, 29, 32], with 960 and 626 cases in the combined caries and control groups, respectively. Three studies reported data on *TaqI/BglI(rs739837)* [31, 33, 34], with 461 and 335 cases in the respective combined caries and control groups. The *FokI(rs10735810)* was included in three studies [20, 28, 29], with 753 and 576 cases in the combined caries and control groups, respectively, and there were three studies on *FokI(rs2228570)* [31, 33, 34], with 492 and 363 combined case and control group subjects, respectively. The *ApaI(rs7975232)* locus was included in three studies [20, 28, 29], with 752 cases in the combined caries group and 575 cases in the combined control group. There were four studies of *BsmI(rs1544410)* [20, 28–30], with 1065 and 676 cases in the combined caries and controls groups,

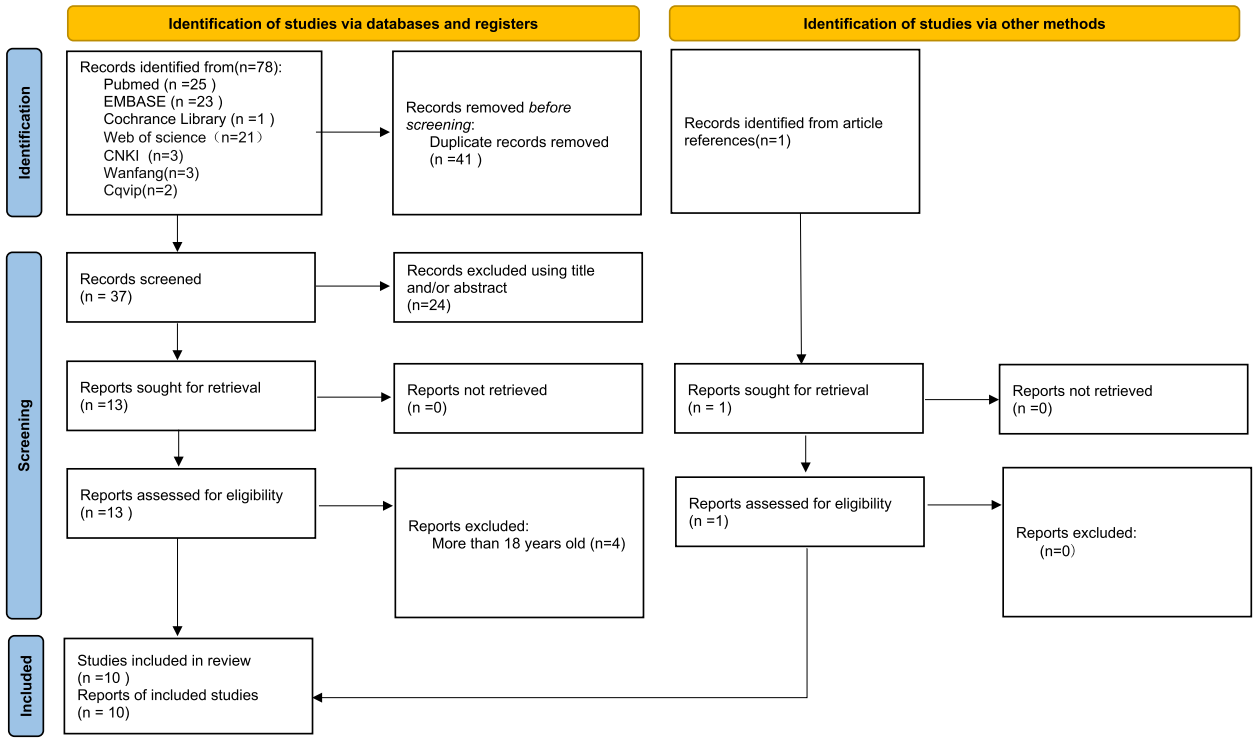

Fig. 1 PRISMA flow diagram

respectively. Finally, *Cdx-2(rs11568820)* was included in one study [28], with 303 cases in the caries group and 245 cases in the control group.

Quality assessment and Kappa test

Quality assessment of the included studies is shown in Tables 3 and 4. Overall, six studies were graded as having overall high.

quality [22, 28, 29, 31, 33, 34], and four were moderate quality [20, 21, 30, 32]; none was low quality (Tables 3 and 4).

The Kappa coefficients of the reviewers involved in article identification and screening, data extraction, and quality assessment were 0.892, 0.893, and 1.000 (Table S2); hence, all had values of > 0.800, indicating strong agreement among reviewers [39].

Meta-analysis

The *Cdx-2(rs11568820)* locus was only included in one article [28] and was, therefore, not subjected to meta-analysis. The other six loci included in this study, namely, *TaqI(rs731236)*, *TaqI/BglI(rs739837)*, *FokI(rs10735810)*, *FokI(rs2228570)*, *ApaI(rs7975232)*, and *BsmI(rs1544410)*, were analyzed by meta-analysis. Subgroup analyses of *TaqI(rs731236)* were also conducted, according to genotype detection method, ethnicity, and tooth dentition (primary, mixed, and permanent).

Meta-analysis of TaqI(rs731236) loci

The distribution of *TaqI(rs731236)* T and C alleles did not differ significantly between subjects with and without caries (*OR* = 1.01, 95% *CI*: 0.83–1.21, *P* = 0.96); however, analysis under the over-dominant genetic model showed that distribution of TT, TC, and CC genotypes differed significantly between subjects with and without caries, with the caries risk of the population with homozygous (TT or CC).

genotypes 1.33-fold higher than that of the population with the heterozygous (TC) genotype (*OR* = 1.33, 95% *CI*: 1.06–1.67, *P* = 0.02). Heterogeneity testing indicated no significant heterogeneity among the studies (I^2 = 0%, *P* = 0.51). Further, sensitivity analysis showed that the overall pooled estimate did not change significantly after removal of any study, indicating that the results were reliable (Fig S1). Further, funnel plot, Egger's test, and Begg's tests revealed no evidence of publication bias in the included literature (Table 7; Figs. 2 and 3a).

Subgroup analysis of *TaqI(rs731236)* demonstrated that caries risk was higher in subjects with homozygous (TT or CC) genotype, permanent dentition, and Asian ethnicity, genotyped by real-time quantitative PCR, than in those with heterozygous (TC) genotype, permanent dentition (*OR* = 1.48, 95% *CI*: 1.07–2.03, *P* = 0.02), and Asian ethnicity (*OR* = 1.38, 95% *CI*: 1.02–1.87, *P* = 0.03),

Table 5 Basic characteristics of included articles

Author	Country	Ethnicity	Study design	Age (years)	Dentition	Sample size	SNPs	Diagnostic criteria for caries	Findings
Zhang(2006) [30]	China	Asian	Case–control	6 ± 5.06 9 ± 3.12	Mixed	Case: 312 Control: 100	*BsmI(rs1544410)*	-	The risk of dental caries may be related to *BsmI(rs1544410)* gene polymorphisms
Qin(2019) [28]	China	Asian	Case–control	3–5	Primary	Case: 304 Control: 245	*BsmI(rs1544410)* *TaqI(rs731236)* *ApaI(rs7975232)* *FokI(rs10735810)* *Cdx-2(rs11568820)*	WHO1997	In multivariate analysis of genotypes and behavioral factors, *ApaI(rs7975232)*, *TaqI(rs731236)*,*BsmI(rs1544410)*, *Cdx-2(rs11568820)*,and *FokI(rs10735810)* were not associated with deciduous tooth decay
Yu(2017) [20]	China	Asian	Case–control	12	Permanent	Case: 200 Control: 200	*BsmI(rs1544410)* *TaqI(rs731236)* *ApaI(rs7975232)* *FokI(rs10735810)*	WHO1997	*Fok I(rs10735810)* gene polymorphisms may be associated with susceptibility to permanent tooth caries in Chinese adolescent
Kong(2017) [29]	China	Asian	Case–control	4–7	Primary	Case: 249 Control: 131	*BsmI(rs1544410)* *TaqI(rs731236)* *ApaI(rs7975232)* *FokI(rs10735810)*	WHO1997	*BsmI(rs1544410)* polymorphism was associated with the risk of deciduous tooth decay in Chinese children aged 4–7 years
Holla(2017) [22]	Czech	Caucasian	Case–control	13–15	Permanent	Case: 235 Control: 153	*TaqI(rs731236)*	WHO1997	The VDR *TaqI(rs731236)* gene variant cannot be used as a marker for identification of Czech children with increased dental caries risk
Cogulu(2016) [21]	Turkey	Caucasian	Case–control	6–12	Mixed	Case: 112 Control: 38	*ApaI(rs7975232)* *FokI(rs10735810)* *Cdx-2(rs11568820)* *TaqI(rs731236)*	WHO1997	There was statistically significant difference in the frequency of *TaqI(rs731236)* genotypes (tt) between caries-active and caries-free children
Fatturi (2020) [34]	Brazil	Mixed	cross-sectional	8	Mixed	Case: 208 Control:132	*TaqI/BglI(rs739837)* *FokI(rs2228570)*	WHO2013	No association was observed between dental caries, with *TaqI/BglI(rs739837)* and (*FokI(rs2228570)* polymorphisms

Table 5 (continued)

Author	Country	Ethnicity	Study design	Age (years)	Dentition	Sample size	SNPs	Diagnostic criteria for caries	Findings
Aribam(2020) [32]	India	Asian	Case–control	6–12	Mixed	Case: 235 Control: 153	*TaqI(rs731236)*	WHO1997	The *TaqI(rs731236)* SNP and its association with dental caries in children indicates a higher caries risk for a patient with 't' allele and 'tt' genotype
Barbosa(2020) [31]	Brazil	Mixed	Case–control	8–11	Mixed	Case: 203 Control: 150	*FokI(rs2228570)* *TaqI/ BglI(rs739837)*	ICDAS	The polymorphisms *FokI(rs2228570)* and BglI(rs739837) in VDR were not associated with dental caries or gingivitis
Madalen(2020) [33]	Brazil	Mixed	Case–control	6–13	Mixed	Case: 138 Control: 19	*FokI(rs2228570)* *TaqI/ BglI(rs739837)*	WHO	The genetic polymorphisms *FokI(rs2228570)* and *TaqI/ BglI(rs739837)* were not associated with dental caries in Brazilian children

genotyped by real-time quantitative PCR (*OR* = 1.52, 95% *CI*: 1.10–210, *P* = 0.01) (Tables 8, 9, 10).

Meta-analysis of FokI(rs10735810) loci

Funnel plot indicated that there was significant publication bias between the study by Yu et al. [16] and the other two included articles that analyzed *FokI(rs10735810)* data; however, Begg's ($Z = 1.04$, $P = 0.30$) and Egger's ($t = 1.83$, $P = 0.32$) tests indicated that there was no publication bias in these articles. A random effects model was used to merge the quantitative effects reported by the studies when the $I^2 > 50\%$ or $P < 0.10$ (Table 7; Figs. 3b and 4). The distribution of *FokI(rs10735810)* C and T alleles differed significantly between subjects with and without caries (*OR* = 1.33, 95% *CI*: 1.30–2.30, *P* = 0.03). Subjects with the CC + CT genotype had a significant 1.87-fold higher risk of caries than those with the TT genotype (*OR* = 1.87, 95% *CI*: 1.15–3.04, *P* = 0.01).

Meta-analysis of BsmI(rs1544410) loci

There was substantial heterogeneity among the included articles of *BsmI(rs1544410)*, a random effects model was used to merge the quantitative effects reported by the studies. The detection rate of the *BsmI(rs1544410)* AA genotype in the population was low. Analysis under the recessive and over-dominant models showed that there.

were no significant differences in the proportions of GG or GA genotypes between children with and without caries (recessive model:

OR = 0.86, 95% *CI*: 0.48–1.54, *P* = 0.61; over-dominant model: *OR* = 0.45, 95% *CI*: 0.48–1.49, *P* = 0.56); Moreover, sensitivity analysis demonstrated that the overall pooled estimate was significantly altered by excluding data from either of the articles, Qin [28] or Zhang [30] (Table 7; Figs. 3c and 5; Fig S3).

Meta-analysis of TaqI/BglI(rs739837), FokI(rs2228570), and ApaI(rs7975232) loci

Meta-analysis of the *TaqI/BglI(rs739837)*, *FokI(rs2228570)*, and *ApaI(rs7975232)* loci under recessive, dominant, and over-dominant models demonstrated no significant differences in genotype distribution between the caries and non-caries groups (Table 7; Fig.S4-S12).

Discussion

This meta-analysis evaluated the relationship between VDR SNPs, including *TaqI(rs731236)*, *TaqI/BglI(rs739837)*, *FokI(rs10735810)*, *FokI(rs2228570)*, *ApaI(rs7975232)*, *BsmI(rs1544410)*, and *Cdx-2(rs11568820)*, and risk of caries in subjects < 18 years old..

TaqI(rs731236) loci is located in exon 9 at the 3'end of VDR gene, which may affect mRNA splicing or impact VDR protein structure [15]. In this meta-analysis, homozygous (TT or CC) genotype at the

Table 6 Summary of VDR gene SNP allele and genotype data

SNP	Author(year)	Caries group (DMFT ≥ 1)					Caries-free group (DMFT = 0)				
TaqI(rs731236)		TT	TC	CC	T	C	TT	TC	CC	T	C
	Aribam(2020) [32]	22	25	13	69	51	26	23	11	75	45
	Qin(2019) [28]	274	29	1	577	31	206	37	1	449	39
	Kong(2017) [29]	230	19	0	479	19	120	11	0	251	11
	Yu(2017) [20]	0	29	171	29	371	0	42	158	42	358
	Holla(2017) [22]	95	110	30	300	170	51	85	17	187	119
	Cogulu(2016) [21]	35	46	31	116	108	15	14	9	44	32
TaqI/BglI(rs739837)		TT	TG	GG	T	G	TT	TG	GG	T	G
	Fatturi(2020) [34]	63	101	49	227	199	36	58	27	130	112
	Barbosa(2020) [31]	45	77	27	167	131	65	92	45	222	182
	Madalena(2020) [33]	34	52	13	120	78	5	6	1	16	8
FokI(rs10735810)		CC	CT	TT	C	T	CC	CT	TT	C	T
	Qin(2019) [28]	98	160	46	356	252	75	119	51	269	221
	Yu(2017) [20]	86	96	18	268	132	65	86	49	216	184
	Kong(2017) [29]	69	132	48	270	228	34	63	34	131	131
FokI(rs2228570)		AA	AG	GG	A	G	AA	AG	GG	A	G
	Fatturi(2020) [34]	22	85	97	129	279	13	63	56	89	175
	Barbosa(2020) [31]	19	56	75	94	206	27	88	88	142	264
	Madalena(2020) [33]	19	60	59	98	178	2	7	19	11	45
BsmI(rs1544410)		AA	AG	GG	A	G	AA	AG	GG	A	G
	Qin(2019) [28]	0	28	276	28	580	1	31	213	33	457
	Yu(2017) [20]	0	36	164	36	364	0	31	169	31	369
	Kong(2017) [29]	0	152	97	152	346	0	60	71	60	202
	Zhang(2006) [30]	19	106	187	144	48	1	8	91	10	190
ApaI(rs7975232)		CC	AC	AA	C	A	CC	AC	AA	C	A
	Qin(2019) [28]	157	129	17	443	163	123	100	21	346	142
	Yu(2017) [20]	82	85	33	249	151	97	79	24	273	127
	Kong(2017) [29]	118	87	44	323	175	70	43	18	183	79
Cdx-2(rs11568820)		AA	AG	GG	A	G	AA	AG	GG	A	G
	Qin(2019) [28]	37	124	84	198	292	59	145	99	263	343

TaqI(rs731236) locus was associated with a 1.33-fold higher risk of caries than the heterozygous (TC) genotype (*OR*=1.33, 95% *CI* 1.06–1.67, *P*=0.02), which differs from the findings of Lei et al. [40]. In Lei's study, *TaqI(rs731236)* SNP with dental caries in the allele contrast model (C vs. T) and in the recessive genetic model (CC vs. TT/CT). This may be because, in our study, the subjects included were 3-15 years old, and the oral environment, dietary habits, and microbial flora of children differ from those in middle-aged and older adults [41], who were also included in the study by Lei et al. Moreover, basal and induced VDR expression can be regulated by environmental, genetic, and epigenetic factors [42–44], which may account for the observed differences in research results. Sadeghi et al. [45] found no significant difference in *TaqI(rs731236)* between the two groups under an allelic model (T vs. C), similar to the findings of our study; however, under other genetic models, they also found no statistical difference between the two groups, which may be related to differences in meta-analysis effect models. Here, a fixed effect model was selected, according to the results of the Q test and the I^2 statistic, while Sadeghi et al. used random effect models to analyze all inheritance models.

Subgroup analysis of *TaqI(rs731236)* among different ethnic groups found that homozygous (TT or CC) genotype was associated with a higher risk of caries than heterozygous (TC) genotype (*OR*=1.38, 95% *CI*: 1.02–1.87, *P*=0.03) under the over-dominant genetic model in Asian populations, suggesting that homozygosity for this variant may be associated with caries risk in Asian populations, while no such correlation was found in the Caucasian population, consistent with the findings of Lei et al. [40]. These results may reflect regional and ethnic differences in the susceptibility to caries related to the *TaqI(rs731236)* SNP.

Table 7 Results of meta-analysis of VDR SNPs alleles under different genetic models

SNP		Effect model	OR (95%CI)	*Z*	*P*	I^2	*P*	Begg test	Egger test	Sensitivity test
TaqI (rs731236)	Allele(T VS.C)	fixed	1.01 (0.83–1.21)	0.05	0.96	41%	0.13	0.71	0.62	no
	Recessive (TT VS. TC + CC)	fixed	1.04 (0.98,1.11)	1.40	0.16	18%	0.30	0.46	0.12	no
	Dominant (TT + TC VS. CC)	fixed	0.75 (0.54,1.05)	1.68	0.09	0.0%	0.95	0.81	0.21	no
	Over-dominant (TT + CC VS. TC)	fixed	1.33 (1.06,1.67)	2.43	0.02	0.0%	0.51	0.26	0.07	no
TaqI/BglI (rs739837)	Allele(T VS.C)	fixed	1.00(0.81,1.23)	0.01	0.99	0.0%	0.81	0.29	0.24	no
	Recessive (TT VS. TG + GG)	fixed	0.93 (0.68,1.29)	0.43	0.67	0.0%	0.90	> 0.99	0.40	no
	Dominant (TT + TG VS. GG)	fixed	1.09 (0.76,1.58)	0.47	0.64	0.0%	0.63	> 0.99	0.60	no
	Over-dominant (TT + GG VS. TG)	fixed	0.89 (0.66,1.20)	0.78	0.44	0.0%	0.70	> 0.99	0.94	no
FokI (rs10735810)	Allele(C VS. T)	random	1.33 (1.30, 2.30)	2.21	0.03	60.0%	0.08	> 0.99	0.71	no
	Recessive (CC VS. CT + TT)	fixed	1.23 (1.04,2.35)	1.70	0.09	4.0%	0.35	> 0.99	0.97	no
	Dominant (CC + CT VS. TT)	random	1.87 (1.15,3.04)	2.53	0.01	64.0%	0.06	0.30	0.32	yes
	Over-dominant (CC + TT VS. CT)	fixed	0.83 (0.67,1.04)	1.64	0.10	0.0%	0.99	> 0.99	0.26	no
FokI (rs2228570)	Allele(A VS.G)	random	1.07 (0.70,1.64)	0.32	0.75	68%	0.04	0.30	0.04	no
	Recessive (AA VS. AG + GG)	fixed	1.09 (0.70,1.71)	0.40	0.69	0.0%	0.64	0.30	0.11	no
	Dominant (AA + AG VS. GG)	random	1.07 (0.59,1.96)	0.23	0.82	73%	0.03	0.30	0.01	no
	Over-dominant (AA + GG VS. AG)	random	1.04 (0.64,1.70)	0.15	0.88	58%	0.09	0.30	0.01	no
ApaI (rs7975232)	Allele (C VS. A)	random	0.89 (0.70,1.14)	0.94	0.35	53%	0.12	> 0.99	0.39	no
	Recessive (CC VS. CA + AA)	fixed	0.87 (0.70,1.09)	1.21	0.23	8%	0.34	> 0.99	0.28	no
	Dominant (CC + CA VS. AA)	random	0.91 (0.55,1.50)	0.37	0.71	50%	0.13	0.30	0.14	no
	Over-dominant (CC + AA VS. CA)	fixed	0.91 (0.73,1.14)	0.80	0.43	0.0%	0.98	> 0.99	0.57	no
BsmI (rs1544410)	Allele (G VS. A)	random	1.56 (0.76,3.24)	1.21	0.23	89%	< 0.01	> 0.99	0.66	yes
	Recessive (GG VS. GA + AA)	random	0.58 (0.26,1.30)	1.33	0.18	89%	< 0.01	> 0.99	0.55	yes
	Recessive (GG VS. GA + AA) [a]	random	0.86 (0.48,1.54)	0.51	0.61	76%	0.02	0.296	0.292	no
	Over-dominant (AA + GG VS. GA)	random	0.60 (0.28,1.25)	1.37	0.17	86%	< 0.01	> 0.99	0.56	yes
	Over-dominant (AA + GG VS. GA) [a]	random	0.85 (0.48,1.49)	0.58	0.56	74%	0.02	0.296	0.266	no

[a] Removed study of Zhang(2006) [30]

Bayram et al. [46] and Borilova et al. [47] showed that genetic factors can have different effects on enamel caries in primary and permanent teeth. An insertion/deletion polymorphism in the gene encoding angiotensin converting enzyme may be related to permanent tooth caries but not to primary tooth caries, especially in women in the Czech population [47]. This study found similar results, in that the homozygous (TT or CC) genotype of *TaqI(rs731236)* was associated with a higher risk of dental caries in permanent teeth than the heterozygous (TC) genotype under the over-dominant genetic model (*OR* = 1.48, 95% *CI*: 1.07–2.03, *P* = 0.02), similar to the findings of Lei et al. [40], suggesting that SNP at the *TaqI(rs731236)* locus is likely to affect the incidence of dental caries in permanent teeth but not in primary and mixed dentition.

Among the ten reports included in our analysis, five [20, 21, 29, 30, 32] used the PCR–RFLP genotyping method, and five [22, 28, 31, 33, 34] used real-time quantitative PCR. The publication years of the PCR–RFLP studies were one in 2006 [30], one in 2016 [21], two in 2017 [20, 29], and one in 2020 [32], while all literature reporting real-time quantitative PCR genotyping data was published since 2017, with three papers published in 2020 [31, 33, 34]. Hence, the studies using real-time quantitative PCR genotyping were conducted more recently. This study found that, when using real-time quantitative PCR genotyping, the homozygous (TT or CC) genotype was associated with a higher risk of caries than the heterozygous (TC) genotype (*OR* = 1.52, 95% *CI*: 1.10–2.10, *P* = 0.01) in the over-dominant genetic model, which may reflect the comparatively higher specificity of real-time quantitative PCR genotyping, which uses a closed tube mode to detect the target gene during amplification, with no requirement for further downstream steps, such as gel electrophoresis, which can increase the specificity of detection and reduce the possibility of cross-contamination, suggesting that the results of analysis of the *TaqI(rs731236)* polymorphism may be affected by different genotype detection methods. However, more studies should be conducted to confirm it.

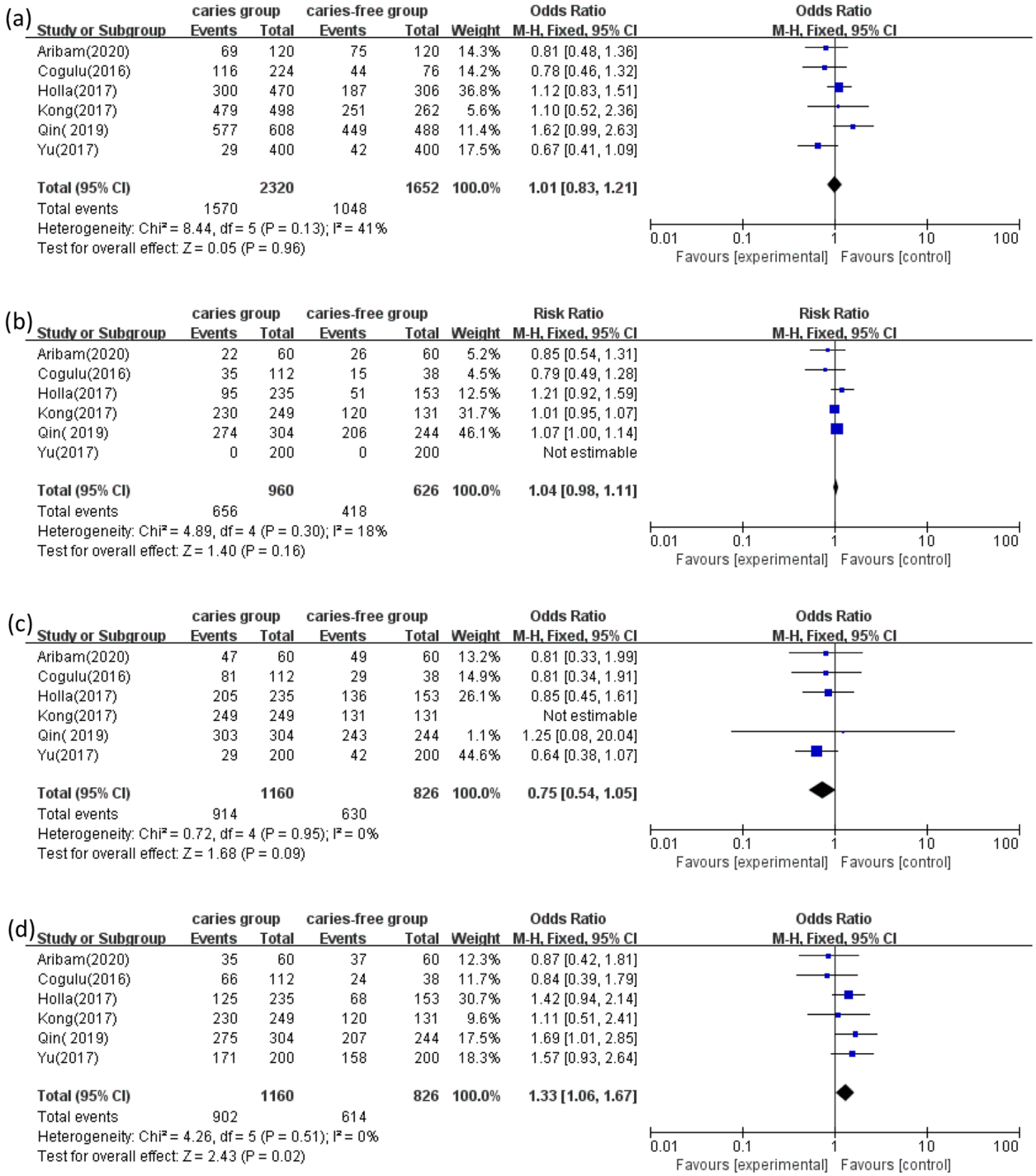

Fig. 2 The *TaqI(rs731236)* genetic polymorphism and caries risk (meta-analysis forest plot). **a** Allele(T VS. C); (**b**): Recessive(TT VS. TC + CC); (**c**): Dominant(TT + TC VS. CC); (**d**): Overdominant(TT + CC VS. TC)

Results of meta-analysis of *FokI(rs10735810)* allele and genotype data showed that C allele may be a risk factor for caries (*OR* = 1.33, 95% *CI*: 1.30–2.30, *P* = 0.03), with the risk of caries in subjects carrying the C allele 1.87-fold higher than that in subjects without the C allele (*OR* = 1.87, 95% *CI*: 1.15–3.04, *P* = 0.01). Sadeghi et al. [45] named genotypes at this locus based on restriction of endonuclease digestion sites. After one-to-one

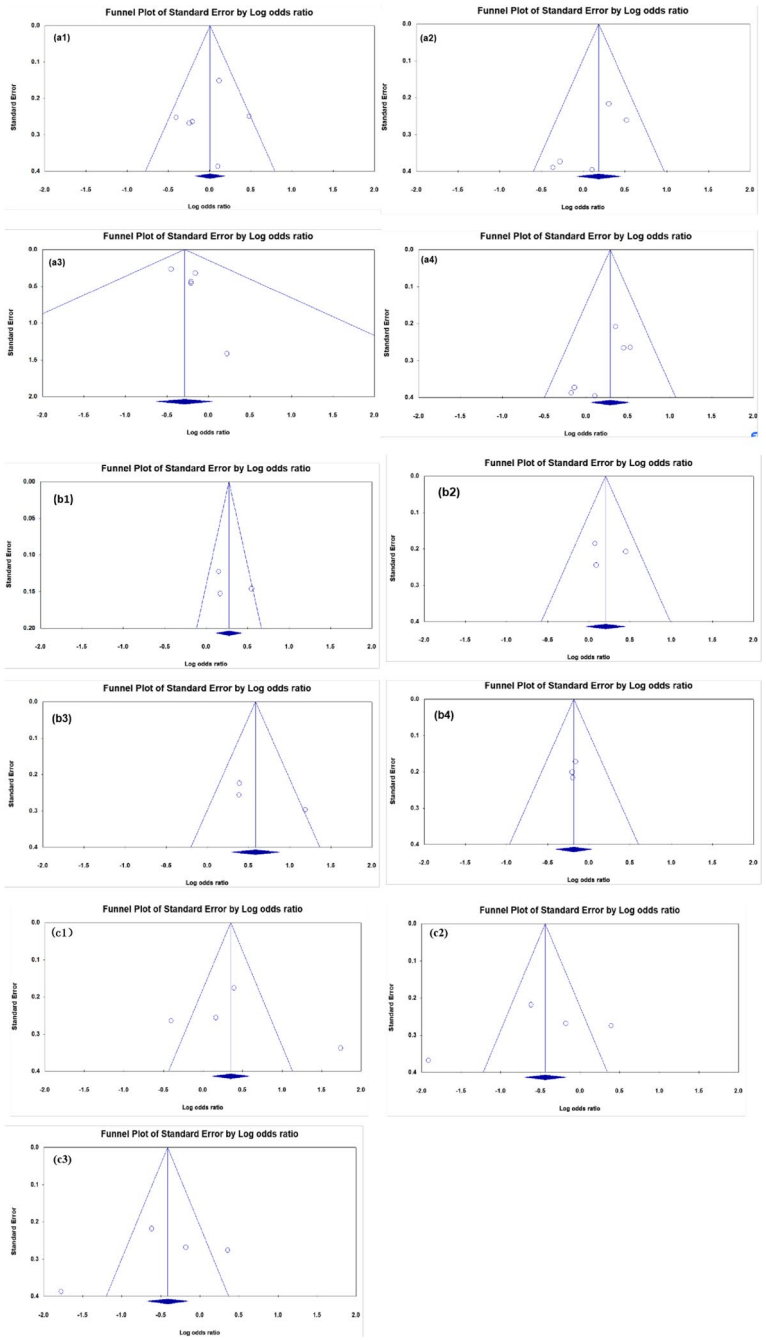

Fig. 3 Funnel plot of publication bias between *VDR* gene SNPs and caries risk: (**a**) *TaqI(rs731236)*, (**b**) *FokI(rs10735810)*, and (**c**) *BsmI(rs1544410).* (a1):*TaqI(rs731236)* Allele(T VS. C); (a2):*TaqI(rs731236)* Recessive(TT VS. TC + CC); (a3):*TaqI(rs731236)* Dominant(TT + TC VS. CC); (a4): *TaqI(rs731236)* Overdominant(TT + CC VS. TC). (b1):*FokI(rs10735810)* Allele(C VS. T); (b2): *FokI(rs10735810)* Recessive (CC VS. CT + TT); (b3):*FokI(rs10735810)* Dominant(CC + CT VS. TT); (b4): *FokI(rs10735810)* Overdominant(CC + TT VS. CT).(c1): *BsmI(rs1544410)* Allele(G VS. A); (c2):*BsmI(rs1544410)* Recessive(GG VS. GA + AA); (c3): *BsmI(rs1544410)* Overdominant(AA + GG VS. GA)

comparison, the results of this study were consistent with those of Sadeghi et al. [45]. The reason why rs10735810 is associated with susceptibility to caries may be related to the interaction of its cotranscription factors and its location in the gene structure [48]; *FokI(rs10735810)* is located near the 5'-untranslated region of the VDR gene, within the DNA binding domain [49–52], and the polymorphism changes the first potential start codon of the

Table 8 Subgroup meta-analysis of *TaqI(rs731236)* alleles under different genetic models, according to dentition type

	Dentition	Effect model	OR (95%*CI*)	*Z*	*P*	I^2	*P*
Allele (T VS.C)		random	0.98(0.76–1.27)	0.12	0.90	41%	0.13
	Primary		1.45(0.96–2.18)	1.76	0.08	0.0%	0.41
	Mixed		0.80(0.55–1.15)	1.21	0.23	0.0%	0.92
	Permanent		0.90(0.54–1.49)	0.41	0.68	68%	0.08
Recessive (TT VS. TC + CC)		fixed	1.21(0.93–1.56)	1.40	0.16	18%	0.30
	Primary		1.49(0.97–2.27)	1.83	0.07	0.0%	0.38
	Mixed		0.73(0.43–1.24)	1.18	0.24	0.0%	0.88
	Permanent		1.36(0.89–2.08)	1.41	0.16	-	-
Dominant (TT + TC VS. CC)		fixed	0.75 (0.54–1.05)	1.68	0.09	0.0%	0.95
	Primary		1.25(0.08–20.04)	0.16	0.88	-	-
	Mixed		0.81(0.44–1.51)	0.66	0.51	0.0%	1.00
	Permanent		0.72(0.48–1.07)	1.61	0.11	0.0%	0.49
Over-dominant (TT + CC VS. TC)		fixed	1.33 (1.06–1.67)	2.43	0.02	0.0%	0.51
	Primary		1.49(0.97–2.28)	1.82	0.07	0.0%	0.37
	Mixed		0.85(0.50–1.45)	0.59	0.56	0.0%	0.94
	Permanent		1.48(1.07–2.03)	2.37	0.02	0.0%	0.77

Table 9 Subgroup meta-analysis of *TaqI(rs731236)* alleles under different genetic models, according to ethnicity

	Ethnicity	Effect model	OR (95%*CI*)	*Z*	*P*	I^2	*P*
Allele (T VS.C)		random	0.98(0.76–1.27)	0.12	0.90	41%	0.13
	Asian		0.98(0.65–1.50)	0.07	0.94	57%	0.07
	Caucasian		1.00(0.72–1.39)	0.01	0.99	28%	0.24
Recessive (TT VS. TC + CC)		fixed	1.21(0.93–1.56)	1.41	0.16	27%	0.24
	Asian		1.16(0.85–1.60)	0.72	0.47	37%	0.20
	Caucasian		1.05(0.56–1.98)	0.16	0.88	55%	0.13
Dominant (TT + TC VS. CC)		fixed	0.75(0.54–1.05)	1.68	0.09	0.0%	0.95
	Asian		0.69(0.44–1.07)	1.65	0.10	0.0%	0.82
	Caucasian		0.84(0.50–1.39)	0.68	0.50	0.0%	0.92
Over-dominant (TT + CC VS. T)		fixed	1.33(1.06–1.67)	2.43	0.02	0.0%	0.51
	Asian		1.38(1.02–1.87)	2.11	0.03	0.0%	0.45
	Caucasian		1.26(0.88–1.80)	1.26	0.21	31%	0.23

VDR gene, from ATG to ACG, resulting in a VDR protein truncated by three amino acids, which is more effective in transactivation of vitamin D target genes [53]. Although funnel plot analysis showed that there was publication bias between the findings of Yu et al. [20] and those of the other two included articles, Begg's test ($Z=1.04$, $P=0.30$) and Egger's test ($t=1.83$, $P=0.32$) indicated that there was no publication bias in these reports; And our use of a random effects model to combine the effects can be expected to have mitigated the interference on the results of heterogeneity among the included studies to some extent.

The rate of detection of the AA genotype at *BsmI(rs1544410)* is low; three articles found no AA genotypes at this locus in the groups with caries [20, 28, 29] and there were also no individuals with this genotype in the group without caries in two studies [20, 29]. The results of analysis under recessive and over-dominant models showed that there were no significant differences in the proportions of GG or GA genotypes at *BsmI(rs1544410)* between subjects with and without caries ($OR=0.86$, 95% *CI*: 0.48–1.54, $P=0.61$; $OR=0.45$, 95% *CI*: 0.48–1.49, $P=0.56$), suggesting that this locus may not be related to the risk of caries; however, studies including *BsmI(rs1544410)* were highly heterogeneous($I^2>50\%$). Sensitivity analysis found that if either of the studies by Qin et al. [28] or Zhang et al. [30] were excluded, the magnitude of the combined effect changed

Table 10 Subgroup meta-analysis of *TaqI(rs731236)* alleles under different genetic models, according to genotype detection method

	Genotyping method	Effect model	OR (95%*CI*)	*Z*	*P*	I^2	*P*
Allele (T VS.C)		fixed	1.01(0.83-1.21)	0.05	0.96	41%	0.13
	PCR-RFLP		0.79(0.60-1.04)	1.71	0.09	0.0%	0.75
	Real-Time PCR		1.24(0.96-1.60)	1.67	0.10	36%	0.21
Recessive (TT VS. TC+CC)		fixed	1.21(0.93-1.56)	1.41	0.16	27%	0.24
	PCR-RFLP		1.49(0.97-2.27)	1.83	0.07	0.0%	0.38
	Real-Time PCR		0.83(0.54-1.29)	0.82	0.41	0.0%	0.67
Dominant (TT+TC VS. CC)		fixed	0.75 (0.54-1.05)	1.68	0.09	0.0%	0.95
	PCR-RFLP		0.70(0.47-1.05)	1.72	0.09	0.0%	0.84
	Real-Time PCR		0.87(0.47-1.61)	0.44	0.66	0.0%	0.79
Over-dominant (TT+CC VS. TC)		fixed	1.33(1.06-1.67)	2.43	0.02	0.0%	0.51
	PCR-RFLP		1.15(0.83-1.60)	0.84	0.40	0.0%	0.46
	Real-Time PCR		1.52(1.10-2.10)	2.56	0.01	0.0%	0.60

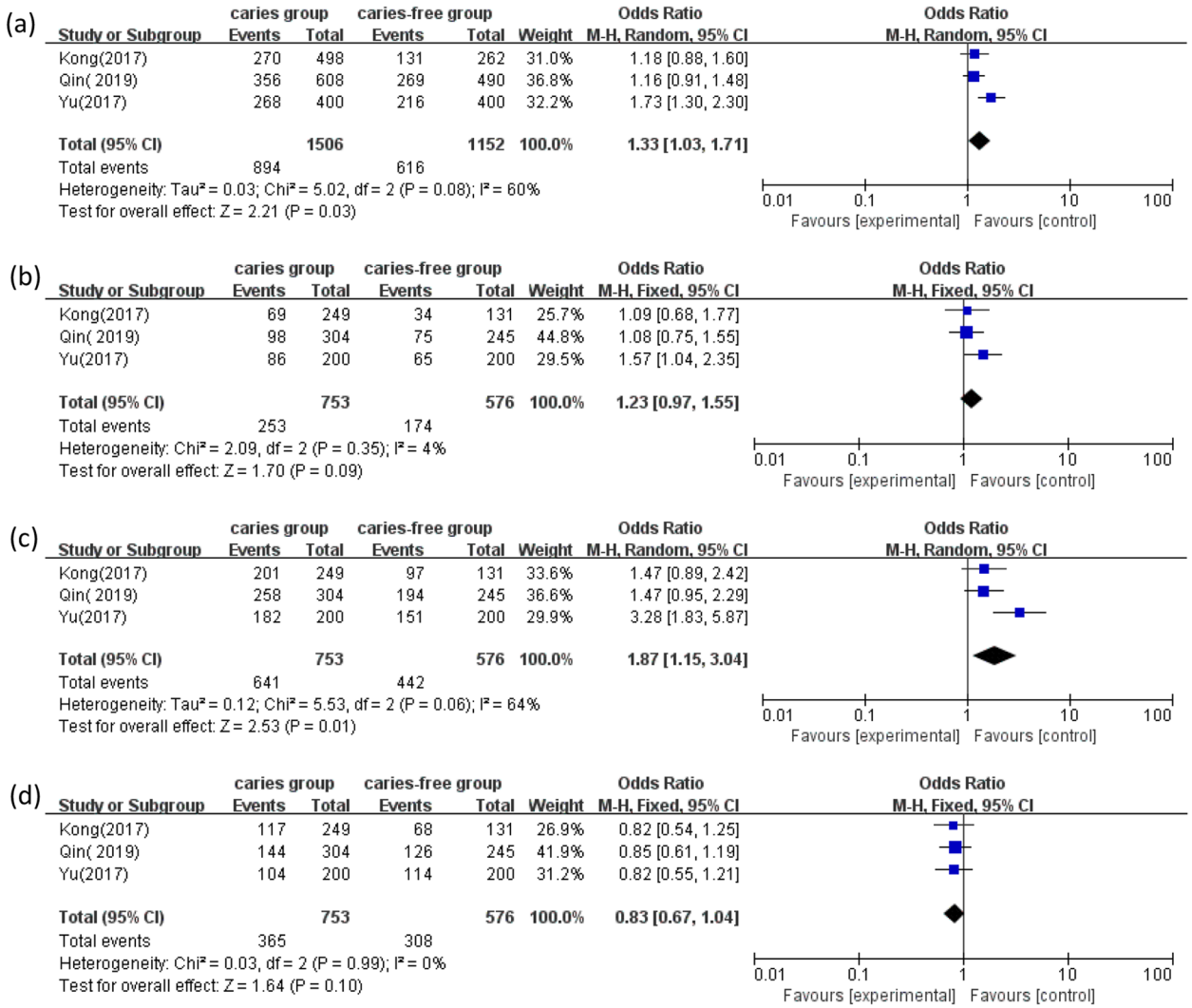

Fig. 4 The *FokI(rs10735810)* genetic polymorphism and caries risk (meta-analysis forest plot). **a** Allele(C VS. T); (**b**): Recessive(CC VS. CT + TT); (**c**): Dominant(CC + CT VS. TT); (d): Over-dominant(CC + TT VS. CT)

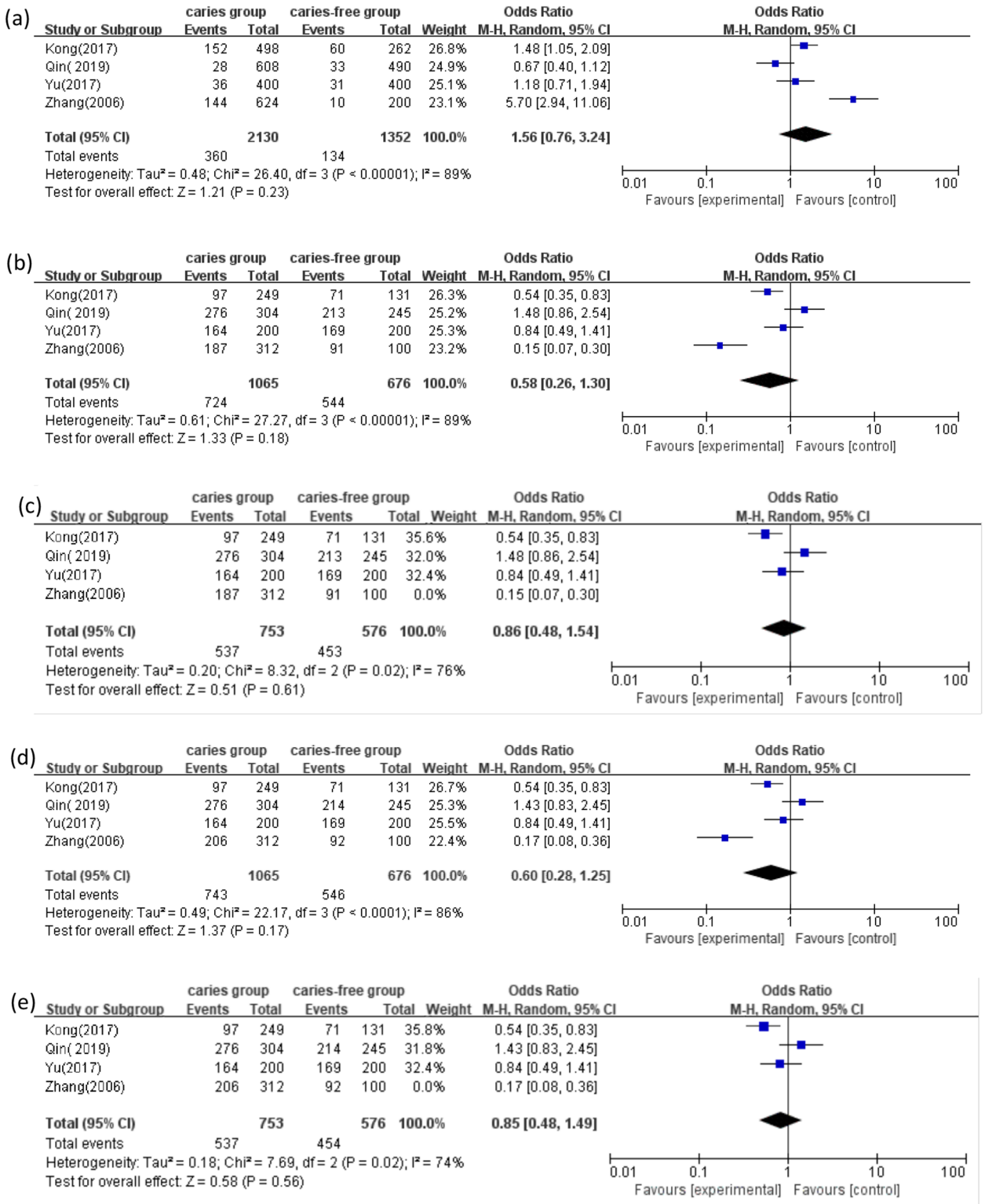

Fig. 5 The *Bsml(rs1544410)* genetic polymorphism and caries risk (meta-analysis forest plot). **a** Allele (G VS. A); (**b**): Recessive (GG vs. GA + AA); (**c**): Recessive (GG vs. GA + AA) Removed study of Zhang(2006) [30]; (**d**): Over-dominant (AA + GG VS. GA); (**e**): Over-dominant (AA + GG VS. GA) Removed study of Zhang(2006) [30]

significantly, but due to the limited number of articles included, more reliable results could not be obtained by eliminating articles. More new evidence is needed to further assess the correlation between the *BsmI(rs1544410)* variant and the risk of caries.

The results of meta-analysis of allelic, recessive, dominant, and over-dominant models at *TaqI/BglI(rs739837)*, *FokI(rs2228570)*, and *ApaI(rs7975232)* revealed no significant differences in genotype distributions between the caries and caries-free groups, consistent with the findings of Sadeghi et al. [45], suggesting that these SNPs are unlikely to be related to the risk of caries in children.

The meta-analysis had several limitations. Firstly, the studies included in this study are mainly case–control studies. Some studies showed mismatched sample sizes between case and control groups, and these bias risks may not be avoided; Secondly, data about the *Cdx-2(rs11568820)* loci was not subjected to meta-analysis because they were only reported in one article. Further research confirmation is needed from different races and regions. Thirdly, only one article studied linkage disequilibrium (LD) analysis [20]. In this article, four genetic loci SNP (*ApaI(rs7975232)*, *BsmI(rs1544410)*, *TaqI(rs731236)*, *FokI(rs10735810)* showed strong evidence of recombination except for *TaqI(rs731236)* and *BsmI(rs1544410)* in caries group data. But the linkage of *TaqI(rs731236)* and *BsmI(rs1544410)* in caries group still did not reach a strong LD level. Finally, the diagnostic criteria for dental caries(WHO 1997, WHO 2013, and ICDAS II) may influence the results, However, only one study used ICDAS. Despite the above limitations, this meta-analysis still has the following advantages: all study subjects met the Hardy-Weinbery equilibrium, the included studies involved a wide geographical distribution and different types of dentition, and all included studies had high quality scores. Therefore, this meta-analysis is a reasonable summary of the current published research findings and leads to more reliable conclusions.

Conclusion

The *FokI(rs10735810)* and *TaqI(rs731236)* variants could be related to caries risk, and the association of *TaqI(rs731236)* with caries risk may be affected by dentition type, ethnicity, and genotype detection method. These findings imply that *TaqI(rs731236)* has potential as an indicator of risk of caries in permanent dentition among Asian people, and that rs10735810 may also be an indicator of caries. The *TaqI/BglI(rs739837)*, *FokI(rs2228570)*, and *ApaI(rs7975232)* variants may not be associated with the risk of caries. Further, the evidence does not support an association of *BsmI(rs1544410)* with risk of caries, but this finding requires further confirmation.

Abbreviations

VDR	Vitamin D receptor
OR	Odds ratios
CI	Confidence intervals
SNP	Single nucleotide polymorphism
NOS	The Newcastle Ottawa scale
LD	Linkage disequilibrium

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

XR Qin, Y Xu and M Wang design this Study . XR Qin and M Wang performed Database searched, data extraction and data synthesis:. XR Qin, and M Wang wrote the Initial manuscript draft , XR Qin, Y Xu, LL Wang and SJ Xiong made critical revisions to the original manuscript . All authors read and approved the final version of the manuscript. XR Qin and M Wang contributed to the work equally.

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Availability of data and materials

Data is provided within the manuscript or supplementary information files. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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