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Association between vitamin D receptor polymorphisms and acute pancreatitis
A protocol for systematic review and meta analysis

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Abstract

Background: Several studies have been performed to investigate the association between *vitamin D receptor* (*VDR*) gene polymorphism and acute pancreatitis, but the results are inconclusive. We conducted this meta-analysis for a precise estimation of the association between BsmI (rs1544410), ApaI (rs7975232), TaqI (rs731236), and FokI (rs2228570) polymorphisms and acute pancreatitis.

Methods: Appropriate studies were retrieved by searching Web of Science, PubMed, Scopus, and Google scholar databases, until January 31, 2021. Two reviewers independently conducted data extraction and literature quality evaluation. Odds ratios and 95% confidence intervals were calculated to evaluate the strength of the association.

All of the data were analyzed with Stata 16.0.

Results: The results of this meta-analysis will be submitted to a peer-reviewed journal for publication.

Conclusions: This meta-analysis will summarize the association between BsmI, ApaI, TaqI, and FokI polymorphisms and the risk of acute pancreatitis.

Ethics and dissemination: Ethical approval was not required for this study. The systematic review will be published in a peer-reviewed journal, presented at conferences, and shared on social media platforms.

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Abbreviations: AP = acute pancreatitis, HWE = Hardy–Weinberg equilibrium, OR = odds ratio, VD = vitamin D.

Keywords: acute pancreatitis, polymorphism, protocol, meta-analysis, vitamin D receptor

1. Introduction

Acute pancreatitis (AP) is a common acute abdomen characterized by acute abdominal pain, abdominal distension, nausea, vomiting, abdominal tenderness, and rebound pain.[1,2] A large number of studies have revealed that AP is related to a variety of factors, including excessive drinking, high blood lipids, metabolic disorders, pancreatic duct obstruction, virus or bacterial infection, and so on.[3–7] However, not all individuals who are exposed to similar risk factors will develop AP, indicating that genetic factors play an important role in the occurrence and development of AP.

Vitamin D (VD) dysregulation was proposed to be associated with the production of AP.[8] The imbalance of active VD level is a major cause of hypercalcemia that is a risk element for AP. Due to polymorphisms in the *VDR* gene, the impairment of *VDR* can lead to a significant effect on the equilibrium of VD levels in the circulation and on its activity in the body. Moreover, Serum 25-hydroxyvitamin D3(25-(OH) D3) level was inversely related to the severity of AP and inflammatory markers such as C-reactive protein. VD also affects the innate and adaptive immune responses and reduces oxidative stress, which could initiate AP.[9]

In recent years, there are more and more studies on the relationship between *VDR* polymorphism and the risk of AP, but the results of these studies are not consistent.[10,11] In this study, we performed a systematic review and a meta-analysis to evaluate the association between different genetic variants of *VDR* gene and AP, and to evaluate the association of BsmI, ApaI, TaqI, and FokI polymorphisms within different ethnic subgroups. The results were pooled together to obtain reliable conclusions.

2. Methods

2.1. Study registration

The protocol of this review was registered in OSF (OSF registration number: DOI 10.17605/OSF.IO/83W7R). It was

reported to follow the statement guidelines of preferred reporting items for systematic reviews and meta-analyses protocol.[12]

2.2. Inclusion criteria

Qualified studies have to meet the following criteria:

(1) Predefined diagnosis criteria for AP;
(2) Case-control studies evaluated the association between BsmI, ApaI, TaqI, and FokI polymorphism and AP risk;
(3) Provided detailed genotype frequencies;
(4) If multiple reports based on the same study population were available, the most recent or largest study will be selected.

2.3. Exclusion criteria

The main exclusion criteria are as follows:

(1) Insufficient data offered to calculate Odds ratio (OR) estimate;
(2) Non-case-control studies;
(3) Duplicate data from a same cohort.

2.4. Search strategy

Two investigators independently performed a systematically computerized search for English studies through Web of Science, PubMed, Scopus, and Google Scholar databases up to January 31, 2021. The keywords for searching included the combination of "*vitamin D receptor, VDR*, polymorphism, BsmI, rs1544410, ApaI, rs7975232, TaqI, rs731236, FokI, rs2228570, pancreatitis, acute pancreatitis." Furthermore, studies were identified through manual searches on reviews and retrieved studies. The search strategy for PubMed is displayed in Table 1, and the corresponding keywords would be applied in other databases.

2.5. Data collection and analysis
2.5.1. Selection of studies. Two reviewers complete the screening process independently, and any differences are decided by a third reviewer. The screening process of the article includes reading the title, the abstract, and the full text, so as to determine whether it meets the inclusion criteria. The researchers record the reasons to exclude each study in light of the preferred reporting items for systematic reviews and meta-analysis guidelines and report the screening results as well. The flowchart is exhibited in Figure 1.

2.5.2. Data extraction. The collected information from each article are as follows: The first author and year, country, region, race, gene frequency of case group and control group, source of control group, *P* value for Hardy–Weinberg equilibrium (HWE) of controls, single nucleotide polymorphism detection method and so on. If the extracted data are inconsistent, discussion should be made to solve it.

2.5.3. Methodology quality assessment. Two authors independently assessed the quality of the included studies based on Newcastle Ottawa Scale.[13] This scale uses a star rating system to judge the methodological quality and consists of three parts, namely selection, comparability, and ascertainment of exposure. The full score is 9 stars, and the score of 5 or more is regarded as "high quality." Otherwise, the study is regarded as "low quality."[14] Any disagreements on the Newcastle-Ottawa scale

Table 1

Search strategy in PubMed database.

Number	Search terms
#1	Pancreatitis[MeSH]
#2	Pancreatitides[Title/Abstract]
#3	or/1–2
#4	Receptors, Calcitriol[MeSH]
#5	Calcitriol Receptors[Title/Abstract]
#6	Cholecalciferol Receptors[Title/Abstract]
#7	Receptors, Vitamin D[Title/Abstract]
#8	Vitamin D 3 Receptors[Title/Abstract]
#9	Vitamin D Receptors[Title/Abstract]
#10	1,25-Dihydroxycholecalciferol Receptor[Title/Abstract]
#11	1,25-Dihydroxycholecalciferol Receptors[Title/Abstract]
#12	1,25-Dihydroxyvitamin D 3 Receptor[Title/Abstract]
#13	1,25-Dihydroxyvitamin D3 Receptor[Title/Abstract]
#14	1,25-Dihydroxyvitamin D3 Receptors[Title/Abstract]
#15	Calcitriol Receptor[Title/Abstract]
#16	Receptors, 1,25-Dihydroxyvitamin D 3[Title/Abstract]
#17	Receptors, Cholecalciferol[Title/Abstract]
#18	Receptors, Vitamin D 3[Title/Abstract]
#19	Receptors, Vitamin D3[Title/Abstract]
#20	Vitamin D 3 Receptor[Title/Abstract]
#21	Vitamin D Receptor[Title/Abstract]
#22	Vitamin D3 Receptor[Title/Abstract]
#23	Vitamin D3 Receptors[Title/Abstract]
#24	1,25 Dihydroxycholecalciferol Receptor[Title/Abstract]
#25	1,25 Dihydroxycholecalciferol Receptors[Title/Abstract]
#26	1,25 Dihydroxyvitamin D 3 Receptor[Title/Abstract]
#27	1,25 Dihydroxyvitamin D3 Receptor[Title/Abstract]
#28	1,25 Dihydroxyvitamin D3 Receptors[Title/Abstract]
#29	D Receptor, Vitamin[Title/Abstract]
#30	D Receptors, Vitamin[Title/Abstract]
#31	D3 Receptor, 1,25-Dihydroxyvitamin[Title/Abstract]
#32	D3 Receptor, Vitamin[Title/Abstract]
#33	D3 Receptors, 1,25-Dihydroxyvitamin[Title/Abstract]
#34	D3 Receptors, Vitamin[Title/Abstract]
#35	Receptor, 1,25-Dihydroxycholecalciferol[Title/Abstract]
#36	Receptor, 1,25-Dihydroxyvitamin D3[Title/Abstract]
#37	Receptor, Calcitriol[Title/Abstract]
#38	Receptor, Vitamin D[Title/Abstract]
#39	Receptor, Vitamin D3[Title/Abstract]
#40	Receptors, 1,25-Dihydroxycholecalciferol[Title/Abstract]
#41	Receptors, 1,25-Dihydroxyvitamin D3[Title/Abstract]
#42	or/4–41
#43	polymorph*[Title/Abstract]
#44	susceptibility[Title/Abstract]
#45	or/43–44
#46	#3 and #42 and #45

score of the studies were resolved through a comprehensive reassessment by other authors.

2.5.4. Dealing with missing data. The reason for the loss of data in the period of data screening and extraction is identified here. If the data of potential studies are insufficient, missing, or vague, we would attempt to contact the authors. These studies would be excluded only if the data are not available through the method described above.

2.5.5. Statistical analysis. Crude Odds ratio (ORs) with corresponding 95% confidence intervals were used to estimate the strength of the association between the BsmI, ApaI, TaqI, and FokI polymorphism and AP risk. The statistical significance of the pooled ORs was examined by performing Z test and $P < .05$ was
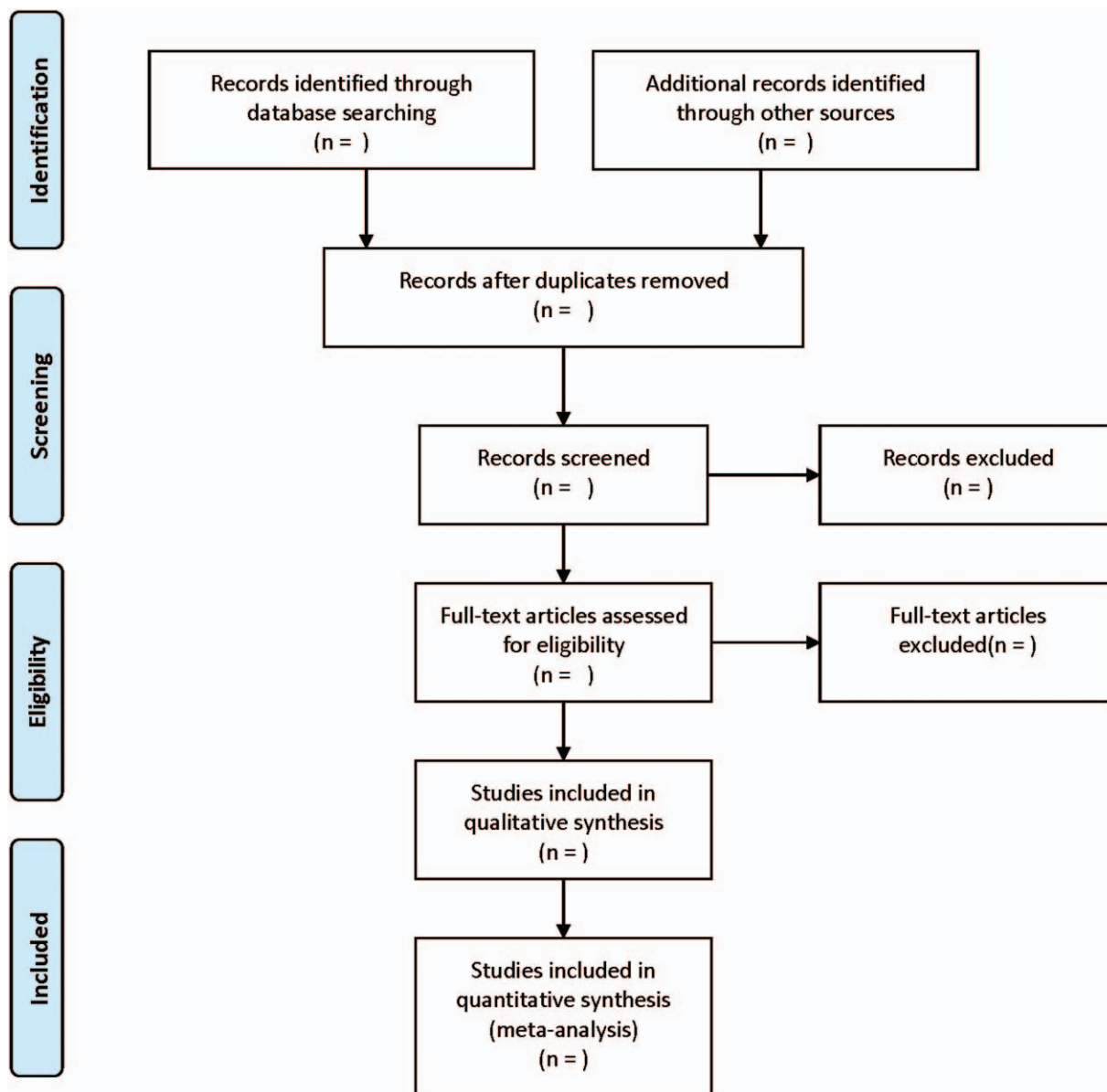
Figure 1. Flow diagram of study selection process.

considered as statistically significant. In the meta-analysis, the overall pooled ORs were calculated for four models, including the allelic, dominant, recessive, and homozygous models. Deviation from HWE was examined by carrying out Chi-square test and P value $< .05$ indicated a departure from HWE. The between-study heterogeneity was assessed by the I^2 statistic, which was calculated from the Q statistic. If the heterogeneity was statistically significant ($P < .05$ for Q-test or $I^2 > 50\%$), the random-effects model (based on DerSimonian-Laird method) was adopted to get the pooled estimates. Otherwise, the fixed-effects model (based on Mantel–Haenszel method) was adopted. All of the statistical analyses were conducted by STATA 16.0 (StataCorp, College Station, TX), and the P values were 2-sided.

2.5.6. Subgroup analysis. We will conduct subgroup analyses based on age, ethnicity, and disease severity

2.5.7. Sensitivity analysis. The eligible study was sequentially removed to perform the sensitivity analysis.

2.5.8. Assessment of publication biases. Publication bias was assessed by Begg rank correlation and Egger linear regression. The publication bias was regarded as statistically difference when $P < .05$.[15,16]

2.5.9. Ethics and dissemination. The content of this article does not involve moral approval or ethical review and would be presented in print or at relevant conferences.

3. Discussion

In recent years, studies on the relationship between inflammatory mediators and the risk of AP have proved that the severe systemic inflammatory response triggered by AP is not mediated by a single vector, but has complex pathophysiological pathways.

Among these pathways, oxidative stress and cytokines are particularly important.[17]

The 25-(OH) D3 participates in human immune and inflammatory response.[18] Kim et al discovered that the concentration of 25-(OH) D3 in AP dogs was significantly lower than that in healthy dogs.[19] Active VD metabolite, and 1,25-dihydroxyvitamin D selectively bind to specific *VDR*.[20] Afterward, the *VDR* regulates the transcription of genes that are involved in calcium metabolism, cell proliferation and differentiation, senescence, and *t*-cell-mediated immune response.[21–28] *VDR* is also expressed in pancreatic β cells and may play an important role in maintaining normal insulin levels consistent with glucose concentration and glucose tolerance.[29–31] The polymorphism of *VDR* may have key effects on the balance of circulating VD concentrations and the activity of final metabolites throughout the body, because VD works through *VDR*.

So far, although many researchers have focused on the relationship between *VDR* polymorphism and AP susceptibility, the cumulative evidence of this association has not been systematically evaluated. In this study, we will conduct a systematic review and meta-analysis to combine the results of numerous studies and generate more reliable risk association estimation to guide the prevention and treatment of AP. The advantages of this study are as follows:

(1) Large data sets from all eligible latest studies will be merged;
(2) In order to explore heterogeneity, we will try to avoid post-subgroup analysis;
(3) Sensitivity analysis will be conducted on each genetic model for the improvement of the reliability of the results. Therefore, the release protocol will avoid potential biases related to data mining as much as possible and help to obtain convincing evidence.

Author contributions

Conceptualization: Mengqin Li.
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Resources: Junzuo Gong.
Software: Junzuo Gong, Hua Zhou.
Supervision: Mengqin Li.
Validation: Tianyi Mou, Hua Zhou, Xiaofeng Li.
Visualization: Xiaofeng Li, Hua Zhou.
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