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Corresponding author:

Yongping Yuan

yuanyongping125@126.com

Author Affiliation:

Department of Stomatology, Ningbo College of Health Sciences.

Li, YQ¹; Zhang, L²; Cen, W³; Yuan, YP⁴.**ADMINISTRATIVE INFORMATION****Support** - None.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY202380014**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 August 2023 and was last updated on 02 August 2023.**INTRODUCTION**

Review question / Objective To investigate the association between Kallikrein-related peptidase-4 (KLK4) rs2235091 polymorphism and susceptibility to dental caries (DC) by a method of systematic review and meta-analysis.

Condition being studied Dental caries (DC) is a plaque-mediated disease in which chronic progressive destruction of dental hard tissue is triggered by various factors, mainly bacteria. Early childhood caries is defined as the presence of one or more decayed, missing, or filled teeth in children under 71 months of age. DC has been listed by the World Health Organization (WHO) as one of the three major human-focused diseases. Deciduous DC is the most common oral disease in children clinically and a serious social public health problem in developing countries. Its prevalence in children in some developed countries is at a low level but is relatively high and dramatically on the rise in underdeveloped countries.

METHODS

Participant or population Individuals diagnosed with DC or those without DC, general good health, without age restrictions.

Intervention Frequency of individuals with DC in the population with KLK4 rs2235091 polymorphism.

Comparator Frequency of individuals with DC in the population without KLK4 rs2235091 polymorphism.

Study designs to be included Cross-sectional, case-control, or cohort studies on KLK4 rs2235091 polymorphism associated with deciduous tooth caries or permanent dental caries.

Eligibility criteria 2.2.1 Inclusion criteria: (1) Study design: Cross-sectional, case-control, or cohort studies on KLK4 rs2235091 polymorphism associated with deciduous tooth caries or permanent dental caries; (2) Populations:

Individuals diagnosed with DC or those without DC, general good health, without age restrictions; (3) Comparison: Frequency of individuals with DC in the population without KLK4 rs2235091 polymorphism; (4) Exposure: Frequency of individuals with DC in the population with KLK4 rs2235091 polymorphism; (5) Outcomes: The rate of allele or genotype frequency according to caries incidence. The caries phenotype involved incipient or white spot lesions, and cavitated lesions. 2.2.2 Exclusion criteria included: (1) Letters, conference abstracts, animal or cell experiments; (2) Articles without access to obtain full text or original data; (3) Inadequate data provided to extract the data of each genotype and calculate the pooled odds ratio (OR) of each genetic model, or literature directly not reporting the corresponding OR value in the genetic model.

Information sources The PubMed, Web of Science, Cochrane Library, and Embase databases were searched for relevant English literature published from inception to April 1, 2023. Literature on the association of susceptibility to DC with KLK4 rs2235091 polymorphism was collected, and reference lists of the retrieved literature were further searched to expand our search results. The main search strategy was as follows: ("KLK4" OR "kallikrein-related peptidase-4") AND ("dental caries" OR "caries" OR "decay") AND ("Single nucleotide polymorphism" OR "polymorphism" OR "variant"). The search language was limited to English. In addition, we traced the relevant records through reviews and searched them manually to improve the search.

Main outcome(s) The rate of allele or genotype frequency according to caries incidence. The caries phenotype involved incipient or white spot lesions, and cavitated lesions.

Quality assessment / Risk of bias analysis The methodological qualities of the cohort and case-control studies were assessed using the NOS score. The overall scores were 9. Scores of 7–9, 4–6, and < 4 indicated high, moderate, and low methodological quality, respectively.

The cross-sectional study was assessed by the evaluation criteria recommended by the Agency for Healthcare Research and Quality (AHRQ). The AHRQ criteria contained 11 items in total, and each item had 3 options; "Yes" counted 1 score, while "No" or "Unclear" counted 0 scores. According to the total scores, the papers were rated as low-quality research (0 ~ 3 scores), medium-quality research (4 ~ 7 scores), or high-quality research (8 ~ 11 scores).

Strategy of data synthesis Stata 15.0 statistical software was applied for this meta-analysis. ORs and 95% confidence intervals (CIs) served as effect sizes. We calculated the Hardy-Weinberg Equilibrium in the controls. Heterogeneity across the included studies was assessed using the χ^2 test and I² statistics. $P > 0.05$ and $I^2 < 50\%$ pointed to no significant heterogeneity, and a fixed-effects model (FEM) was utilized; otherwise, a random-effects model (REM) was employed. We adopted Egger's test to inspect publication bias.

Subgroup analysis Subgroup analysis was performed according to whether the caries were primary or permanent dentition.

Sensitivity analysis Sensitivity analyses was performed to verify the stability of the results obtained.

Country(ies) involved China.

Keywords KLK4; polymorphism; meta-analysis; dental caries; caries susceptibility.

Contributions of each author

Author 1 - Youqin Li.

Email: zjnbjanlee@126.com

Author 2 - Lei Zhang.

Email: 15624142@qq.com

Author 3 - Wen Cen.

Email: 598700093@qq.com

Author 4 - Yongping Yuan.

Email: yuanyongping125@126.com