INPLASY PROTOCOL

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Review Stage at time of this submission: **The review has not yet started.**

Conflicts of interest: **There are no conflicts of interest.**

Blood DNA methylation and Type 2 Diabetes Mellitus: a protocol for systematic review and meta-analysis

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Review question / Objective: **This systematic review aims to assess and summarize the studies which examine the relationship between blood DNA methylation and T2D, including global DNA methylation, candidate-gene methylation, and GWAS studies. Indeed, this study will explore the possibility of blood DNA methylation as a biomarker and intervention targets for T2D.**
Condition being studied: **Type 2 diabetes (T2D) is the most common type of diabetes, accounting for around 90% of all diabetes over the world. The characteristics of T2D include increased hyperinsulinemia, insulin resistance, and pancreatic β-cell failure with up to 50% cell loss at diagnosis. Epidemiology of T2D is affected by genetic and environmental factors. Genome-wide association studies have led to the identification of common variants of glycemic genetic traits for T2D, however, these only accounts for 10% of total trait variance.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 April 2020 and was last updated on 22 April 2020 (registration number INPLASY202040136).

INTRODUCTION

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METHODS

Search strategy: The following electronic bibliographic databases will be searched from inception: EMBASE, MEDLINE, Web of Science, Cochrane Central, CNKI, Wanfang and VIP. Meanwhile, Clinical Trials (ClinicalTrials.gov) will also be searched.

Participant or population: Adults with Type 2 diabetes and non-diabetic donors.

Intervention: Examines for blood DNA methylation including global DNA methylation, candidate-gene methylation, and genome-wide association.

Comparator: Blood DNA methylation from non-diabetic donors.

Study designs to be included: Any randomized controlled, longitudinal, cross-sectional, and case-control studies with sufficient information will be included.

Eligibility criteria: This systematic review and meta-analysis will identify and summarize the studies which examine blood DNA methylation in T2D and controlled human subjects. The studies published in Chinese, English and other languages that can be translated through Google Translate will be considered. In addition, the review will include global DNA methylation studies, candidate-gene methylation studies, as well as genome-wide association studies (GWAS). Any randomized controlled, longitudinal, cross-sectional, and case-control studies with sufficient information will be included.

Information sources: The following electronic bibliographic databases will be searched from inception: EMBASE, MEDLINE, Web of Science, Cochrane Central, CNKI, Wanfang and VIP. Meanwhile, Clinical Trials (ClinicalTrials.gov) will also be searched. The included studies will also be hand-searched to identify other potentially eligible studies. In addition, it is essential for contacting the authors if there is incomplete or misunderstanding information.

Main outcome(s): The difference in the expression of blood DNA methylation (including global DNA methylation, specific genes, and GWAS) between T2D patients and non-T2D subjects.

Additional outcome(s): The systematic review will evaluate characteristics of reported studies such as the blood cell types used, methods of quantifying DNA methylation and the participants' demographics (age, gender, race, and adiposity).

Quality assessment / Risk of bias analysis: The Cochrane Risk of Bias Assessment Tool will be used to assess the bias of randomized controlled studies, and the Newcastle-Ottawa Scale (NOS) for non-randomized controlled studies. All the assessment will be investigated by two independent reviewers The overall quality of extracted data will be assessed by using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment tool. Disagreements and conflicts will be resolved by discussing it with a third reviewer. Funnel plots will be performed to assess the publication bias if more than ten studies. The systematic review and meta-analysis will be reported in accordance with PRISMA guidelines.

Strategy of data synthesis: The Cochrane Risk of Bias Assessment Tool will be used to assess the bias of randomized controlled studies, and the Newcastle-Ottawa Scale (NOS) for non-randomized controlled studies. All the assessment will be investigated by two independent reviewers The overall quality of extracted data will be assessed by using the Grading of Recommendations, Assessment,

Development and Evaluation (GRADE) assessment tool. Disagreements and conflicts will be resolved by discussing it with a third reviewer. Funnel plots will be performed to assess the publication bias if more than ten studies. The systematic review and meta-analysis will be reported in accordance with PRISMA guidelines.

Subgroup analysis: The different cell types for DNA methylation, different methods for isolating DNA and measuring DNA methylation.

Sensibility analysis: Odds ratio and 95% CIs will be calculated to assess the association between blood DNA methylation and T2D. Rate ratios (RR) or hazard risks (HR) will be extracted in cohort studies.

Language: There are no restrictions on language.

Country(ies) involved: All countries can be involved.

Keywords: Peripheral blood, Global DNA methylation, Candidate-gene DNA methylation, Genome-wide DNA methylation, type 2 diabetes, epigenetics.