

INPLASY PROTOCOL

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**Review Stage at time of this
submission:** The review has
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Conflicts of interest:
No conflict of interest.

Cardiovascular Risk Factors in Children and Adolescents with Subclinical Hypothyroidism: A protocol for meta-analysis and systematic review

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Review question / Objective: Do children and adolescents with subclinical hypothyroidism have higher cardiovascular risk?

Condition being studied: Subclinical hypothyroidism (SH) is a biochemical disease, which thyrotropin (TSH) serum levels are above the upper limit of the reference range for the assay, whereas serum free T4 level that is within the population reference range. In adults, SH is a frequent occurrence, with an incidence rate of between 4% and 20%, and it has a high chance of developing overt hypothyroidism. Due to the lack of research data, the prevalence of children seems to be relatively low, less than 2%. At the same time, there are many studies proving that SH does increase cardiovascular risk in adults. However, for children and adolescents, there are few studies in this area, but it's necessary, because if there's a cardiovascular risk factor in childhood, there's a greater cardiovascular risk in adulthood.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 April 2020 and was last updated on 26 April 2020 (registration number INPLASY202040182).

INTRODUCTION

Review question / Objective: Do children and adolescents with subclinical hypothyroidism have higher cardiovascular risk?

Rationale: As we all know, thyroid hormone has anti-atherosclerotic effects. A large

and growing body of research has confirmed that hypothyroidism accelerates the atherosclerotic process in several ways. At the same time, there are many studies proving that SH does increase cardiovascular risk in adults. However, there are few studies in children and adolescents. According to some studies.

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METHODS

Search strategy: The following electronic databases will be searched from the inception through the present to find studies that live up to our standard: PubMed, EMBASE, Web of Science, Cochrane Library, CNKI, Wanfang and VIP. And we will screen reference lists of identifying studies. Two experienced researchers (HD and QW) worked out the research strategy independently. We will use the following keywords to search for literature: children, adolescents, subclinical hypothyroidism, cardiovascular, lipids, insulin resistance and intima-media thickness.

Participant or population: The study will include Children and adolescents participants under the age of 18. Patients who receive L-T4 replacement therapy will be excluded.

Intervention: The exposed group will be participants who have been diagnosed with Subclinical hypothyroidism.

Comparator: The control group will be healthy children with normal thyroid functions.

Study designs to be included: Case-control, cohort and cross-sectional studies.

Eligibility criteria: The study includes children and adolescent participants under the age of 18. To control the potential bias and have a comparison, only those with the control group can be included in this review. Lipid profile will be the primary outcome. We will include case-control studies, cohort studies and cross-sectional studies.

Information sources: The following electronic databases will be searched from the inception through the present to find studies that live up to our standard: PubMed, EMBASE, Web of Science, Cochrane Library, CNKI, Wanfang and VIP. And we will screen reference lists of identifying studies.

Main outcome(s): Lipid profile will be the primary outcome, including Serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C).

Additional outcome(s): The secondary outcomes (if documented) will include other cardiovascular risk factors, like intima-media thickness (IMT), insulin resistance, and tissue Doppler imaging.

Data management: If one standard research is not available online, we will send an email to the author to get the full text or the required data. Finally, we will import all research articles that are compliant with inclusion criteria into Endnote X9 and remove duplicate research. Also, in this meta-analysis, the same research published in multiple publications will be regarded as one. We will consensus with a third researcher (XLQ) to resolve the differences.

Quality assessment / Risk of bias analysis: We will use the Newcastle-Ottawa Scale for cohort studies to assess the quality of included studies, which is evaluated from three aspects, including object selection, comparability, outcome and exposure. By

comparing this scale, the studies will be divided into three levels: high quality (7–9 stars), moderate quality (4–6 stars) or low quality (0–3 stars).

Strategy of data synthesis: We analyzed our data using RevMan, version 5.3 Windows (Cochrane Collaboration, Oxford, UK). We assessed heterogeneity using I^2 statistics. When I^2 statistic exceeded 50%, we will use random effect model to pool across studies, if it is not more than 50%, we will use the fixed effect model. We will use standardized mean difference (SMD) and 95% confidence interval, which is for continuous results, and for dichotomy results, we will use relative risk (RR) and 95% confidence interval.

Subgroup analysis: The potential heterogeneity (i.e., $I^2 \geq 50\%$) will be explored using subgroup analyses based on participants, and exposure characteristics mentioned above. like sex, obesity (yes/no), TSH levels (level 1: 4.5 -10 mIU/L, level 2: TSH ≥ 10 mIU/L), If there is enough data, we will consider more subgroup analysis.

Sensibility analysis: We conduct the sensitivity analysis by excluding literature successively.

Language: English only or a language that can be translated into English.

Country(ies) involved: China.

Other relevant information: No.

Keywords: Children, adolescents, subclinical hypothyroidism, cardiovascular, lipid.

Dissemination plans: This study is helpful to enhance our understanding of Subclinical hypothyroidism in children and provide a reference for the treatment of children with SH. This study will be submitted to a high-impact clinical journal.

Contributions of each author:

Author 1 - Huan Deng - Conceived the idea, designed the study, literature retrieval and drafted the initial manuscript.

Author 2 - Xian Wang - Conceived the idea, drafted the initial manuscript and methodology support.

Author 3 - Xianliang Qiu - Literature retrieval and the revision of the manuscript.

Author 4 - Qin Wen - Literature retrieval and the revision of the manuscript.

Author 5 - Shiyu Liu - The revision of the manuscript.

Author 6 - Qiu Chen - Review guarantor and participated in the revision of the manuscript.