Cardiovascular Risk Factors in Children and Adolescents with Subclinical Hypothyroidism: A Meta-analysis and Systematic Review

Huan DENG (✉ dengh1027@163.com)

Hospital of Chengdu University of Traditional Chinese Medicine

Research

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Abstract

Introduction: Subclinical hypothyroidism (SCH) is serum thyrotropin slightly increased, while serum free thyroxine level in the normal range, many studies are proving that SCH does increase cardiovascular risk in adults. However, current studies on cardiovascular risk in children and adolescents with SCH have not been conclusive. Therefore, we did a meta-analysis and systematic review of the included case-control and cross-sectional studies to make up for the lack of data in this direction.

Methods: We searched the following databases from its inception until May 9, 2020: PubMed, EMBASE, Web of Science, Cochrane Library, CNKI, Wanfang, and VIP. The Newcastle-Ottawa Scale was used to check on the quality of these studies. I^2 statistics and subgroups were used to analyze heterogeneity. The sensitivity analysis assessed the stability of the results against the overall effect by "leave-one-out". When the systematic review contains more than 10 articles, funnel plots and Egger regression test was made to evaluate publication bias.

Result: Twelve observational studies were enrolled in our meta-analysis. TC was significantly higher in SCH patients than in normal thyroid subjects (WMD=6.01, 95% CI: 3.70-8.31, $P<0.00001$), TG (WMD=9.86, 95% CI: 5.72-14.01, $P<0.00001$), LDL (WMD=4.33, 95% CI: 1.78-6.87, $P=0.0009$), and IVRT (WMD=7.85, 95% CI: 3.99-11.72, $P<0.0001$). At the same time, we found no significant differences in HDL, IMT, and HOMA-IR between the two groups.

Conclusions: Our study confirmed that SCH changes lipid profile and heart function in children and adolescents.

Register: The protocol of this systematic review and meta-analysis was registered on the NPLASY (No. 202040182). The protocol has been published, it can be found in <https://pubmed.ncbi.nlm.nih.gov/32756074/>.

Introduction

Subclinical hypothyroidism (SCH) is serum thyrotropin (TSH) slightly increased, while serum free thyroxine (FT4) level in normal range^{1,2}. In some respects, SCH can be regarded as a mild loss of thyroid, which is brought about by various reasons. Including congenital and acquired primary thyroid diseases^{3,4}, one of the most important causes is autoimmune thyroid disease.

The upper limit of normal TSH levels is different from different age groups^{5,6}. The normal upper limits to the thyroid-stimulating hormone in adults and children are usually set at about 4.0-5.0 mIU/L⁷. According to the level of TSH, SCH can be divided into two categories: When TSH value is less than 10 mIU/L, it is defined as mild SCH, Conversely, it is severe SCH⁸. In children, the incidence rate of SCH is less than 2%⁹. The probability of SCH progressing to overt hypothyroidism is approximately 2% to 6% per year¹⁰.

As we all know, the thyroid hormone has anti-atherosclerotic effects¹¹. A large and growing body of research¹²⁻¹⁶ has confirmed that hypothyroidism accelerates the atherosclerotic in several ways, such as lipid profile¹²⁻¹⁴, blood pressure¹⁵, and endothelial function¹⁶, it also has a direct impact on cardiovascular function¹⁷. At the same time, many studies¹⁸⁻²⁰ are proving that SCH does increase cardiovascular risk in adults. It comprises the following aspects: left ventricular diastolic function¹⁸, arterial function¹⁹, lipid profile²⁰, and more. However, because of the small sample size and various confounding factors, current studies on cardiovascular risk in children and adolescents with SCH have not been conclusive. Therefore, we did a meta-analysis and systematic review of the included case-control and cross-sectional studies to make up for the lack of data in this direction, objective to compare the differences in cardiovascular risk causes between children and adolescents with and without SCH, including lipid profile parameters, intima-media thickness (IMT), insulin resistance, and isovolumic relaxation time (IVRT).

Methods

A meta-analysis of Observational Studies in Epidemiology (MOOSE)²¹ was strictly implemented in our study. The protocol for this study has been published. The article can be found in <https://pubmed.ncbi.nlm.nih.gov/32756074/>.

2.1 Search strategy

We searched the following databases from its inception until May 9, 2020: PubMed, EMBASE, Web of Science, Cochrane Library, CNKI, Wanfang, and VIP. At the same time, we also looked up by reading the references. A search strategy was developed using a combination of medical subheadings (MeSH) words and keywords related to Subclinical hypothyroidism, children and adolescents, cardiovascular. Mesh words include 'child', 'Adolescent', 'pediatric', 'Subclinical hypothyroidism', 'cardiovascular', 'lipids', 'Insulin Resistance', 'intima-media thickness' and 'Atherosclerosis'.

Two investigators (HD, PPH) reviewed the article separately, and discuss it with the third member (XLQ) in case of a dispute. For articles in incomplete data, we contacted the author by email to obtain the full text or required data. If there are 2 or more articles from the same group of participants, we will choose studies with more complete data and a larger sample size. Only articles published in English were included.

2.2 eligibility criteria

The meta-analysis included cross-sectional studies and case-control studies. The subjects included in the meta-analysis were people under 18 years old, which compared the cardiovascular risk factors of patients with SCH (case group) and people with normal thyroid function (control group) including at least one cardiovascular risk factor, including any of the four lipid profile parameters, intima-media thickness (IMT), insulin resistance, and isovolumic relaxation time (IVRT).

2.3 Quality assessment and data extraction

Our study mainly includes case-control studies and cross-sectional studies. The Newcastle-Ottawa Scale (NOS)²² used to be used to evaluate biases in studies included in this meta-analysis. This scale is evaluated from three aspects, including object selection, comparability, outcome, and exposure. By comparing this scale, all studies were be divided into three quality grades based on scores: high, medium, and low, and high-quality articles score 7-9 stars, medium quality is 4-6 stars, and the lowest is 0-3 stars. See Table 2 for details.

The data were extracted by two investigators (HD, PPH) and reviewed by a third (XLQ). The following information was be extracted: author, study design, year of publication, TSH cutoff value to define SCH, FT4 measurement, characteristics of study populations (sample size, area, and mean age), mean value, and standard deviation of results in both SH and EU groups.

2.4 Data synthesis

We standardized the units of all the results: the units of cholesterol (TC, LDL-C, and HDL-C) and triglyceride (TG) were multiplied by 38.67 and 88.57 respectively to convert from mmol/L to mg/dL. We assessed heterogeneity using the I^2 statistics. When the I^2 value is 0, there is no heterogeneity; low heterogeneity occurs when I^2 is less than 25%, high heterogeneity occurs when I^2 is greater than 50%, and moderate heterogeneity occurs between the two. If the I^2 statistic exceeded 50%, the random effect model will be utilized to summarize the study, and if it is not more than 50%, the fixed effects model will be applied. Weighted mean difference (WMD) and 95% confidence interval (CI) for continuous variables served to represent the differences between the case group and the control group. When moderate or higher heterogeneity is present, subgroup analysis was adopted to explain the causes of heterogeneity. We conducted a subgroup analysis of study type, study country, NOS score, TSH cutoff, obesity, and SCH degree. The sensitivity analysis assessed the stability of the results against the overall effect by "leave-one-out". When the system review contains more than 10 articles, funnel plots and egger regression test was be made to evaluate publication bias. In this study, the statistically significant value was $p < 0.05$ for two tails. RevMan, version 5.3 Windows (Cochrane Collaboration, Oxford, UK). was be used to analyze the statistical data.

Results

3.1 Study selection: After eliminating repeated citations, 270 articles were found. First, 209 articles unrelated to SCH and cardiovascular risk factors were excluded from the reading summary, then, the next step is by reading the full text to filter: 14 studies were excluded because there were no relevant outcomes, 14 studies were excluded because there was no control between the euthyroid group and the SCH patients group, 1 study did not meet the requirements of observational study and 19 studies were excluded because they did not meet inclusion criteria or lacked data. As for the uniform data articles, we only take the research with more complete data and a larger sample size, so there are 2 articles excluded. Finally, 11 studies were included in our analysis (Figure 1). A total of 3995 participants were included, of whom 817 children and adolescents had SCH, and 3,178 were euthyroid.

9 studies²³⁻³¹ compared TC levels in 753 SCH patients and 3097 controls. 8 studies^{23-29,32} (540 cases and 1923 controls) evaluated TG, 6 studies^{23-27,29} reported LDL (453 cases and 1832 controls), 8^{23-27,29,31,32} reported HDL (715 cases and 3107 controls), 5^{24-27,29} reported insulin resistance (312 cases and 1160 controls), and 3 studies^{24,28,29} (112 cases and 83 controls) assessed CIMT, isovolumic relaxation time (IVRT) was evaluated in 3 studies^{29,32,33} (91 cases and 110 controls).

3.2 Study characteristics: The main characteristics of the studies are shown in Table 1. 7 studies are case-control studies, and the remaining four were cross-sectional studies. 4 studies included only people with mild SCH as case groups. According to the NOS, 6 studies are of high quality.

3.3 Lipid profile: Serum cholesterol was assessed in 9 studies involving a total of 3850 participants. Meta-analysis results showed that the TC level of SCH patients was significantly increased compared with the control group (Figure 2A, WMD=6.39, 95% CI: 4.02-8.76, $P < 0.00001$). There was low heterogeneity between studies ($I^2 = 10\%$; $P = 0.35$). Because the number of articles is less than 10, the publication bias is not considered. Subgroup analysis was not performed because of the low heterogeneity of the literature. The results were robust by comparing and analyzing the sensitivity of the articles.

Serum triglycerides were evaluated in 8 studies involving 2465 participants. It turns out that the TG level of patients with SCH was significantly higher than that of the control group (Figure 2B, WMD=9.92, 95% CI: 5.59-14.24, $P < 0.00001$) without heterogeneity among studies ($I^2 = 0\%$; $P = 0.86$). Through sensitivity analysis, the results are robust.

Seven studies, evaluating a total of 2285 participants, showed a significant increase in serum LDL in SCH patients than in control subjects (Figure 2C, WMD=4.10, 95% CI: 1.45-6.75, $P = 0.002$), and the heterogeneity between studies was moderate ($I^2 = 44\%$; $P = 0.11$). Through sensitivity analysis, the results are robust. To keep the results free from confounding factors, subgroup analysis was performed. By subgroup analysis of the diagnostic thresholds for SCH, we found that when the cut-off value of TSH used in the study was less than 5mIU/L ($n = 4$), a larger WMD value was reported (WMD= 4.52, 95% CI: 1.59-7.45, $P = 0.003$) and there was no heterogeneity between studies ($I^2 = 0\%$; $P = 0.51$).

Serum HDL was assessed in 8 studies, involving a total of 3822 individuals, indicated that there was no significant difference between the SCH group and the control group (Figure 2D, WMD=-1.81, 95% CI: -4.44-0.81, $P = 0.18$) with significant heterogeneity among studies ($I^2 = 85\%$; $P < 0.00001$). Subgroup analysis of study type, study country, NOS, TSH cutoff, obesity, and SCH degree did not reveal the source of heterogeneity. Through sensitivity analysis, the results are robust.

3.4 Intima-media thickness: The data of IMT came from 3 studies, involving 195 participants. The difference between the two groups was not statistically significant (Figure 2E, WMD=0.02, 95% CI: -0.01-0.06, P=0.23) with high heterogeneity among studies ($I^2 = 77\%$; P =0.01). After excluding Isik 2016²⁸ through sensitivity analysis, the results of meta-analysis showed that there was no heterogeneity in the remaining articles(WMD= 0.00, 95% CI: -0.03-0.03, P=0.85, $I^2 = 0\%$; P =0.79).

3.5 Insulin resistance: IR was calculated using the homeostasis model assessment (HOMA-IR) equation formula³⁴. 5 studies supplied this data, including 1,472 participants. The results revealed that the differences between the SCH group and the control group were not statistically significant (Figure 2F, WMD=0.34, 95% CI: -0.07-0.75, P=0.11) and were accompanied by high heterogeneity ($I^2 = 75\%$; P =0.003). Subgroup analysis of article types revealed that case-control trials reported higher WMD value (WMD=0.46, 95% CI: 0.06-0.87, P=0.02) and less heterogeneity ($I^2 = 48\%$; P =0.17). Sensitivity analysis showed that the results were unstable.

3.6 Isovolumic relaxation time: 3 studies with a total of 201 participants indicated higher IVRT values in the SCH group compared to the control group (Figure 2G, WMD=7.85, 95% CI: 3.99-11.72, P<0.0001) with significant heterogeneity among studies ($I^2 = 58\%$; P =0.09). After excluding Yadav 2017²⁹ through sensitivity analysis, the results of meta-analysis showed that there was no heterogeneity in the remaining articles(WMD= 9.32, 95% CI: 6.86-11.79, P<0.00001, $I^2 = 0\%$; P =0.50).

Discussion

In this meta-analysis, we included 11 articles that provided data on 817 cases of subclinical hypothyroidism and 3178 cases of children with normal thyroid function. All the included articles were in English, including 6 articles of high quality and 5 articles of medium quality. By analyzing these data, it was found that children and adolescents with SCH had higher TC, TG, and LDL than normal subjects, while the HDL was no significant difference between the SCH group and the control group. In the analysis, it was also concluded that there was no significant difference in insulin resistance and intima-media thickness between SCH patients and normal children, but the isovolumic relaxation time of SCH patients was significantly increased compared with that of normal children. However, due to the small number of literature and unstable results, it requires further discussion.

In the case of lipids, several studies have demonstrated that changes in the lipid profile are associated with cardiovascular risk³⁵. As high levels of TC, LDL, and TG, as well as low levels of HDL, are risk factors for cardiovascular disease³⁶. Since the thyroid hormone regulates many enzymes in the transport of lipoproteins, the lipid profile of SCH patients is more likely to change³⁷. The thyroid hormone also increases hepatic cholesterol synthesis by inducing hydroxymethylglutaryl coenzyme A (HMG CoA) reductase and decreases intestinal cholesterol absorption³⁸⁻⁴⁰. Thyroid hormone can also affect the expression of LDL receptor^{40,41}. Besides, it has been reported that TSH can increase TC level independently⁴². At the same time, the thyroid hormone can increase the activity of lipoprotein lipase and reduce the level of triglyceride⁴³. Due to the interaction of multiple mechanisms, the overall effect of SCH on blood lipids is still controversial. Our study showed that SCH patients had higher TC, TG, and LDL than normal subjects. No publication bias was found by funnel plot. This result was per the majority of conclusions of previous studies. A meta-analysis of lipid changes in adult patients with SCH has come to the same conclusion²⁰. For HDL, our study did not find significant differences between the two groups, and this result has high and unexplained heterogeneity, which requires careful interpretation and more studies in the future.

The pathological basis of cardiovascular disease is the diffuse thickening and hardening of the large and medium arteries. Endothelial dysfunction in SCH patients may be caused by the decrease of nitric oxide utilization¹⁶, or indirectly by hypercholesterolemia and hypertension in SCH patients⁴⁴. Various clinical studies have demonstrated that IMT is an independent predictor of cardiovascular disease⁴⁵. In a previous meta-analysis of cardiovascular risk in adult SCH patients, they found significant differences in IMT between the case group and the control group, albeit with considerable heterogeneity⁴⁶. However, no significant difference was seen in our study. The reasons may be as follows: First, our study found little literature on this indicator, and the results were heterogeneous and unstable. In the sensitivity analysis, we found that the Isik-Balci's²⁸ article was the primary source of heterogeneity. Reviewing this article again, we noted that this may be due to the higher age of the SCH patient group compared to the control group, although there was no statistically significant difference. Secondly, IMT is also bound up with obesity, smoking, age, and other factors, and the huge difference between adults and children in these aspects may also be the reason for the difference in results. More evidence is needed to make sure of intimal injury in SCH children in the future.

Insulin resistance has been suggested as an independent risk factor of atherosclerosis⁴⁷. Since thyroid hormones can be involved in the regulation of blood sugar and blood lipids, patients with thyroid dysfunction are more likely to suffer from a series of metabolic disorders. A retrospective pediatric study found that within the reference range, TSH levels increase with increased insulin and HOMA levels⁴⁸. However, in our study, no significant difference was found between the HOMA value of patients with SCH and that of the control group, which may be due to the feeble control of potential confounders in the included study.

It has long been reported that subclinical hypothyroidism may lead to diastolic dysfunction. Previous studies have shown that SCH affects the left ventricular function of patients, showing increased isovolumic relaxation time and decreased mean aortic acceleration (a reliable indicator of left ventricular systolic function), and returning to normal after levothyroxine treatment⁴⁹. This may lead to poor physical exercise ability⁵⁰. Its mechanism is not clear, now there are mainly the following kinds: On the one hand, SCH leads to endothelial dysfunction and arterial stiffness by affecting the production of NO and other pathways⁵¹. On the other hand, the pathogenesis of diastolic dysfunction might be influenced by TSH stimuli for apoptotic-derived microparticles⁵². Also, other studies have shown that it may also be related to systemic inflammation⁵³. Due to the lack of data on children, our analysis included only three

articles. Even though significant differences were found between the two groups, the results were not robust. The article²⁹ that caused the heterogeneity may be due to the high cut-off value of TSH.

There are many limitations to our study. First, some of the observational studies included in our analysis did not control potential confounding factors, so more experimental data are needed to explain this result; secondly, as the cut-off value of TSH for diagnostic SCH has not been determined at present, the cut-off value of included literature is also different, which may lead to some heterogeneity, it needs to be determined by more studies in the future; third, we cannot determine the duration of hypothyroidism, because it has been reported that SCH in children is a self-limiting disease. In a large pediatric cohort comprising 121052 cases, children with a slightly higher TSH may return to normal within 5 years⁵⁴. Besides, the time and degree of hypothyroidism can significantly affect blood lipid levels. Finally, we cannot give a reasonable explanation for the heterogeneity of HDL in our study, which may be related to other potential confounding factors in the included studies, more clinical studies are needed for further discussion.

Conclusion

Our analysis indicates that children and adolescents with subclinical hypothyroidism have higher serum TC, TG, LDL levels, which may increase cardiovascular risk. At the same time, IVRT of children and adolescents with SCH is longer than that of normal people, which also shows that SCH can damage their cardiac function. Therefore, the cardiovascular function of children with SCH should be closely monitored. For HDL, insulin resistance, and IMT, The difference between the two groups was not statistically significant, and further research is necessary. Since our study only involves observational experiments, the results need to be more cautious. In the future, large-scale, long-term clinical studies will be needed to further confirm the risk of cardiovascular events in children with SCH, whether treatment is needed, and whether treatment will reduce the risk.

Abbreviations

SCH= subclinical hypothyroidism, TSH= thyrotropin, FT4= free thyroxine, TC= total cholesterol, HDL-C= high-density lipoprotein cholesterol, TG= triglycerides, LDL-C= low-density lipoprotein cholesterol, IMT= intima-media thickness, CNKI= China National Knowledge Infrastructure, VIP= China Science and Technology Journal Database, NOS= the Newcastle-Ottawa Scale, EU= euthyroid, PRISMA =Preferred Reporting Items for Systematic Reviews and Meta-Analyses, MOOSE =Meta-analysis of Observational Studies in Epidemiology, MeSH =medical subheadings, WMD=weighted mean difference, IVRT=Isovolumic relaxation time, IR=insulin resistance, HMG CoA= hydroxymethylglutaryl coenzyme A.

Declarations

1.Acknowledgments

Not applicable

2. Funding

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3. Contributions

Idea conception: HD, XW. Literature retrieval: HD, QW, XLQ. Methodology: HD, XW. Writing-initial manuscript: HD, PPH. Review guarantor: QC. All authors participated in the revision of the manuscript and agreed to publish it.

4. Ethical approval

Not required- there is only for the data in the published literature, and does not collect personal primary data.

5. Consent for publication

Not required.

6. Competing interests

None declared.

7. Availability of data and materials

All data generated or analyzed during this meta-analysis can be found in the references.

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Tables

Table1. Characteristics of included studies.

Author	Year	Country	Study design	Participants (SCH/EU)	Age (SCH/EU)	TSH cutoff value	T4 measured?	Measure outcomes	NOS score
Dahl2018	2018	USA	Cross-sectional study	228/1215	13.3±4.2/13.4±3.9	>5mIU/L	Y	TC, c-HDL	7
Isik 2016	2016	Turkey	Case-control study	53/31	9.25±4.2/7.19±5.15	>5mIU/L	Y	triglyceride, TC, CIMT	8
Jin 2018	2018	South Korea	Cross-sectional study	154/950	14.4±3/14.7±2.8	≥ 4.5mIU/L	Y	triglyceride, c-LDL, TC, c-HDL, HOMA-IR	8
Kara 2020	2020	Turkey	Cross-sectional study	77/138	12.32±2.81/12.33±2.83	>5mIU/L	Y	triglyceride, c-LDL, TC, c-HDL, HOMA-IR	7
Radetti 2017	2017	Italy	Cross-sectional study	125/645	13.8±2.7/14.5±2.5	>4.5mIU/L	Y	triglyceride, c-LDL, TC, c-HDL, HOMA-IR, hsCRP	6
Unal 2017	2017	Turkey	Case-control study	38/38	8.1±3.6/8.9±2.4	>4.2mIU/L	Y	triglyceride, c-LDL, TC, c-HDL, CIMT	6
Yadav 2017	2017	India	Case-control study	27/20	10.98±2.36/10.85±2.44	>7.5mIU/L	Y	triglyceride, c-LDL, TC, c-HDL, HOMA-IR, hsCRP, CIMT, IVRT	7
Farghaly2019	2019	Egypt	Case-control study	32/32	13.6±2.5/13.2±2.1	>4mIU/L	Y	triglyceride, c-LDL, TC, c-HDL, HOMA-IR, hsCRP, CIMT	7
Atabek 2003	2003	Turkey	Case-control study	19/19	15±1.8/14.9±1.9	>4mIU/L	Y	TC	6
Brienza 2013	2013	Italy	Case-control study	34/60	9.7±2.7/10.4±2.6	>4.2mIU/L	Y	triglyceride, c-HDL, IVRT	6
Irdem 2016	2016	Turkey	Case-control study	30/30	7.8±3.2/8.4±3.6	>4.2mIU/L	Y	IVRT	6

Table 2: Newcastle-Ottawa Scale

Study ID	01. Is the case definition adequate? (0-1 star)	02. Representativeness of the cases (0-1 star)	03. Selection of Controls (0-1 star)	04. Definition of Controls (0-1 star)	05. Comparability of cases and controls on the basis (0-2 stars)	06. Ascertainment of exposure (0-1 star)	07. Same method of ascertainment for cases and controls (0-1 star)	08. Non-Response rate (0-1 star)	Total (0-9 stars)
Dahl 2018	□	□		□	□□		□	□	7
Isik 2016	□	□		□	□□	□	□	□	8
Jin 2018	□	□	□	□	□□		□	□	8
Kara 2020	□	□		□	□□		□	□	7
Radetti 2017		□	□	□	□		□	□	6
Unal 2017		□		□	□	□	□	□	6
Yadav 2017		□		□	□□	□	□	□	7
Farghaly 2019	□			□	□□	□	□	□	7
Atabek 2003	□			□	□	□	□	□	6
Brienza 2013				□	□□	□	□	□	6
Irdem 2016				□	□□	□	□	□	6

Figures

Figure 1

flow diagram.

Figure 2

Forest plots for the effect of SCH patients on cardiovascular risk markers including Serum cholesterol(A), triglycerides(B), LDL(C), HDL(D), IMT(E), Insulin resistance(F), Isovolumic relaxation time(G).