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Association of subclinical thyroid dysfunction with chronic kidney disease in adults: A systematic review and meta-analysis

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ABSTRACT

Objective: To summarize the evidence regarding the association between subclinical thyroid dysfunctions and chronic kidney disease (CKD) in adults. *Methods:* The literature was searched for English-published studies from inception till the 16th of December 2022. The search included MEDLINE/PubMed, Academic Search Complete (EBSCOhost) and Web of Science using the terms ('subclinical hypothyroidism and thyroid dysfunction') AND ("chronic kidney disease or chronic renal failure or ckd or esrd'). *Results:* Eleven studies were included. Subclinical hypothyroidism was significantly associated with a higher risk of CKD compared to euthyroid individuals (Odds ratio (OR): 1.43, (95% CI: 1.23–1.65), P<0.001, n=11). Subgroup analyses by adjusting for confounders or diabetes mellitus did not alter the results significantly. However, the ORs were significantly lower with longitudinal studies compared to cross-sectional studies (OR: 1.17 vs. 1.68, respectively, p<0.001). Subclinical hyperthyroidism was associated with a higher risk of CKD than euthyroid individuals, but the association was not significant (OR: 1.19, (95% CI: 0.92–1.53), P=0.18, n=3). *Conclusions:* Subclinical hypothyroidism is significantly associated with an increased risk of CKD. However, more longitudinal studies are required to confirm the effect of subclinical hypothyroidism as an exposure on the outcome of newly diagnosed CKD. The association between subclinical hyperthyroidism and CKD is understudied and warrants more research to ascertain its effect on the risk of CKD.

Keywords: Chronic kidney disease, subclinical hypothyroidism, subclinical hyperthyroidism, meta-analysis

1. INTRODUCTION

Chronic kidney disease (CKD) is a condition which is defined as "abnormalities of kidney structure or function, present for >3 months, with implications for health" (Stevens and Levin, 2013). The rate of CKD is increasing globally, representing a public health problem worldwide. The global estimated prevalence of CKD is 13.4%, with 4.902 to 7.083 million patients requiring renal replacement therapy (Lv and Zhang, 2019).

Research has identified several risk factors that are associated with the development and progression of CKD, such as diabetes mellitus and hypertension (Hamrahian and Falkner, 2017; Boer et al., 2022). However, other factors seem to be affecting renal function as control of the well-identified risk factors did not hinder further deterioration of renal function (Schultheiss et al., 2017).

Several studies have suggested that thyroid dysfunctions can influence renal functions both through direct effects on the kidney and indirectly through an effect on the cardiovascular and regulating systems of thyroid hormone release, metabolism and excretion (Iglesias et al., 2017). Overt hypothyroidism has been studied extensively and thyroxin replacement provided beneficial effects by increasing the estimated glomerular filtration rate (eGFR) in hypothyroid patients (Bulur et al., 2017; Eşme et al., 2021).

Meanwhile, the effect of subclinical thyroid dysfunctions on renal function is controversial. Subclinical thyroid dysfunctions are conditions in which a disease exists, but no symptoms appear. The diagnosis of subclinical thyroid dysfunctions depends on laboratory assessment of TSH as well as the thyroid hormones (T4 and T3). Subclinical hypothyroidism is detected if serum TSH concentrations are above the normal range while serum T3 and T4 concentrations are within the normal range. Likewise, subclinical hyperthyroidism is diagnosed when serum TSH concentrations are below the reference range while serum T3 and T4 concentrations are within normal (Cooper and Biondi, 2012).

Studies that were conducted on a population of CKD patients reported a high prevalence of subclinical hypothyroidism (Naseem et al., 2018; Anum et al., 2022; Reque-Santivañez et al., 2022). There is a need to evaluate the evidence regarding the role of subclinical hypo and hyperthyroidism in deteriorating renal function or contributing to CKD development. If such an association is established, control of thyroid status may prevent or delay the deterioration of kidney functions in susceptible individuals, thus reducing the resultant morbidity and mortality. Therefore, this meta-analysis was carried out to summarize the evidence regarding the relationship between subclinical thyroid dysfunctions and CKD in adults.

2. MATERIALS AND METHODS

Methodology

The conduction and reporting of this systematic review and meta-analysis was following the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (Stroup et al., 2000).

The research questions

Are subclinical thyroid dysfunctions (i.e., subclinical hypo or hyperthyroidism) associated with a higher risk of suffering CKD in an adult population?

Research aims and objectives

This meta-analysis aims at assessing the relationship between subclinical thyroid dysfunctions and CKD in adults, with the following objectives:

To assess the risk of CKD in adults with subclinical hypothyroidism compared to euthyroid individuals.

To assess the risk of CKD in adults with subclinical hyperthyroidism compared to euthyroid individuals.

Eligibility criteria for studies

Types of studies

Only observational cohorts, case-control and cross-sectional studies published in English were included in this systematic review and meta-analysis.

Participants

Eligible studies included adult individuals in whom thyroid and renal functions were assessed.

Exposure and outcome

Eligible studies assessed the outcome of CKD in relation to subclinical thyroid dysfunction as an exposure variable.

Exclusion criteria

The following forms of publications were excluded: Conference abstracts/posters, case reports, reviews, editorials, commentaries and clinical guidelines. Moreover, studies were excluded if: a) conducted on animal models and pediatric patients; b) included only a population of CKD patients without control; c) assessed overt thyroid dysfunction only; or d) did not report CKD as a binary outcome.

Search strategy

Electronic searches

We conducted a search of the electronic databases of MEDLINE/PubMed, Academic Search Complete (EBSCOhost) and Web of Science (WOS) for studies published in the English language from inception to the 16th of December 2022. The search terms used for MEDLINE/PubMed were ("Thyroid Diseases"(Mesh)) AND "Renal Insufficiency, Chronic"(Mesh)). The search terms for EBSCO host were (subclinical hypothyroidism and thyroid dysfunction) AND (chronic kidney disease or chronic renal failure or ckd or esrd), with the filter for article publications. For the WOS, we used (chronic kidney disease) AND (subclinical thyroid dysfunction). In the three databases, the search was limited to articles published in the English language.

Other resources

We examined the lists of reference in the retrieved relevant studies from the search of electronic databases to find other eligible studies.

Selection of studies

Literature search and screening the titles and abstracts of the studies yielded by the search were performed. For potentially relevant studies, the full text article was retrieved and assessed for eligibility using the aforementioned criteria (under the heading "Eligibility criteria for studies"). The search results, the titles and abstracts as well as the full text articles were revised.

Data extraction

A standardized sheet for extraction of data from the included studies was used, including (a) the study characteristics (country, study design, time span of recruitment, the sample size and the study's inclusion and exclusion criteria); (b) patients' characteristics (age and sex); (c) the cut-off levels for diagnosing subclinical thyroid dysfunctions; (d) the numbers of patients with CKD in each group of thyroid function status; and e) the odds or hazard ratio with their 95% confidence intervals (CI) of CKD in each group of thyroid dysfunction relative to the euthyroid group. The extracted data were checked to ensure consistency and clarity.

Assessment of the risk of bias in included studies

The risk of bias was assessed using the National Heart, Lung and Blood Institute (NHLBI) study quality assessment tool for observational cohort and cross-sectional studies (National Heart, 2021).

Data synthesis

Review Manager (Rev Man Version 5.4. The Cochrane Collaboration, 2020) was used for conducting the meta-analysis and creating forest plots. Publication bias was assessed by inspecting the generated funnel plots. The categorical dichotomous outcome of CKD was summarized as an odds ratio (OR) with 95% CI. An OR > 1 indicated a higher risk in the subclinical thyroid dysfunction group, while an OR< 1 indicated a higher risk in the euthyroid group. An OR of 1 indicated the same risk in both groups. The pooling of data was done using the inverse variance method in the case of raw data and the method of generic inverse variance in the case of pre calculated OR (by entering the natural logarithms of OR and their standard errors).

The data were tested for heterogeneity using the Cochrane Chi-square heterogeneity test and I^2 index. Significant heterogeneity across the studies was detected if the Cochrane chi-square test had a p-value < 0.1 and the I^2 index was above 50%. If heterogeneity was non-significant, pooling of the data was performed using the fixed-effect model, but the random-effects model was used if there was significant heterogeneity. A p-value < 0.05 was considered significant to interpret the comparisons between groups. Subgroup analysis was conducted for potential confounders.

3. RESULTS

Results of literature search and study selection

The results of the search and selection process are illustrated in Figure 1. The search of electronic databases showed 952 records, out of which 79 duplicates were removed. The titles and abstracts of the remaining 873 records were screened, resulting in the removal of 842 records (107 ineligible publication types, 591 non-relevant articles, 136 studies in CKD patients and 8 studies with overt thyroid dysfunction only). The full text of the remaining 31 articles was sought, with the successful retrieval of 30 articles. Assessment of the full-text articles lead to the exclusion of 19 studies in which CKD was not reported as a binary outcome. Screening of the reference lists of the retrieved articles identified six studies out of which five were duplicates to the electronic search and one included CKD patients only. Finally, eleven studies were found eligible and were incorporated in this review (Asvold et al., 2011; Gopinath et al., 2013; Ye et al., 2013; Jia et al., 2015; Chaker et al., 2016; Chuang et al., 2016; Miranda É et al., 2017; Schultheiss et al., 2017; Zhou et al., 2017; Chang et al., 2018; Zhang et al., 2018).

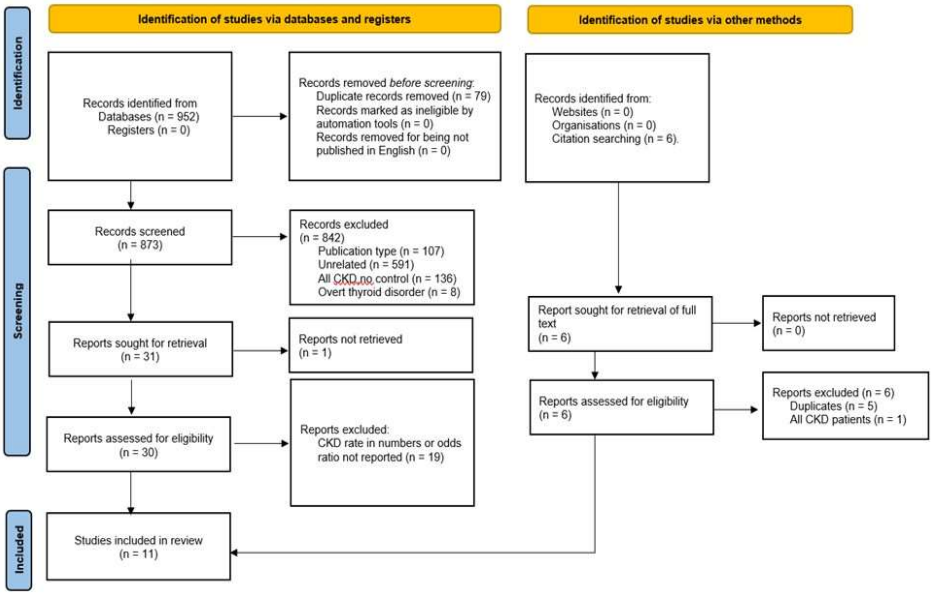

Figure 1 The PRISMA flow chart diagram for the results of the literature search and study selection

Basic characteristics and risk of bias assessment of the included studies

The basic characteristics of the included studies

Seven studies were cross-sectional in design (Asvold et al., 2011; Gopinath et al., 2013; Ye et al., 2013; Jia et al., 2015; Miranda et al., 2017; Chang et al., 2018; Zhang et al., 2018), while the remaining four were longitudinal: two prospective cohorts (Chaker et al., 2016; Schultheiss et al., 2017), one retrospective cohort (Chuang et al., 2016) and one case control study (Zhou et al., 2017). Four studies were conducted on a Chinese population (Ye et al., 2013; Jia et al., 2015; Zhou et al., 2017; Zhang et al., 2018), while two studies were in Taiwan (Chuang et al., 2016; Chang et al., 2018). The sample size widely varied across the studies from 933 to 29,480. The age also varied widely with some studies including mainly or solely elderly people (Gopinath et al., 2013; Jia et al., 2015; Chaker et al., 2016; Chuang et al., 2016; Zhang et al., 2018). The prevalence of the male sex also varied among the studies, with one study including only men (Ye et al., 2013). In the other studies, men generally accounted for less than half the sample (Table 1).

The calculation of the estimated glomerular filtration rate was done using the four variable Modification of Diet in Renal Disease (MDRD) formula in five studies (Asvold et al., 2011; Gopinath et al., 2013; Jia et al., 2015; Chuang et al., 2016; Zhou et al., 2017). The other six studies used the CKD Epidemiology Collaboration (CKD-EPI) formula (Ye et al., 2013; Chaker et al., 2016; Miranda et al., 2017; Schultheiss et al., 2017; Chang et al., 2018; Zhang et al., 2018). The definition of CKD was unified in nearly all studies (eGFR <60ml/ min/ 1.73 m^2), but one study included, besides eGFR, the presence of proteinuria ≥ 1+ (Chuang et al., 2016). Another study diagnosed CKD as eGFR GFR <60 ml/ min/ 1.73 m^2 or a urine albumin creatinine ratio (UACR) > 2.5 mg/mmol in men and > 3.5 mg/mmol in women. The cut-off values of thyroid stimulating hormone (TSH) slightly varied among the studies. Also, some studies adjusted the regression models to age and sex only (Gopinath et al., 2013; Chang et al., 2018) while a widely varied range of confounders was used by the other studies (Table 2).

Table 1 The settings and characteristics of the included studies (n = 11)

Study	Country	Time span	Study design	Follow-up (years)	Sample size	Age	Male Sex
Asvold 2011	Norway	1995 to 1997	Cross-sectional	-	29,480	Median (range) 57 (41–98)	33.1%
Chaker 2016	Netherlands	1997 to 2008	Prospective cohort study	8.1	5,103	63.6 ± 9.4	43.6%
Chang 2018	Taiwan	1996 to 2006	Cross-sectional	-	74,356	Euthyroid: 41.7 ± 13.4 Hypo: 46.76 ± 14.1	49.8%
Chuang 2016	Taiwan	2005 to 2010	Retrospective cohort	3	41,454	Euthyroid: 75.8 ± 6.4 Schypo: 76.6 ± 6.8	Euthyroid: 52.2% Schypo: 47.5%
Gopinath 2013	Australia	2002 to 2004	Cross-sectional	-	1,571	73.6	40.8%
Jia 2015	China	2012 to 2013	Cross-sectional	-	933	Euthyroid: 61.5 ± 12.3 Schypo: 63.7 ± 11.1	Euthyroid 49.2% Schypo 31.7%
Miranda 2017	Brazil	Aug 2008 to Dec 2010	Cross-sectional	-	13,193	Median (IQR) 51 (45–58)	48.2%
Schultheiss 2017	USA	1987 to 1998 & 2011 to 2013	Prospective cohort	19.6	11,872	57.4 ± 5.7	43.5%
Ye 2013	China	Jan 2009 to Dec 2011	Cross-sectional	-	8,126	44.99 ± 12.05	100.0%
Zhang 2018	China	Jan 2012 to Dec 2017	Cross-sectional	-	5,936	62 ± 11	49%
Zhou 2017	China	Jan 2011 to Dec 2015	Case-control	-	3,815	Euthyroid: 56.4±11.6 Schypo: 56.1±11.5	Euthyroid: 42.4% Schypo 42.4%

The rate of CKD in groups of thyroid dysfunctions is presented in Table 3. The rates of CKD differed across the studies, with the highest rates in the study by Jia et al., (2015) and the lowest rate in the study by Ye et al., (2013). In general, the rate was highest in the group of subclinical hypothyroidisms and lowest in the euthyroid group. However, one study reported a higher rate of CKD in the subclinical hyperthyroidism group (Ye et al., 2013). The association of CKD with subclinical hyperthyroidism was direct in three studies only (Asvold et al., 2011; Ye et al., 2013; Zhang et al., 2018), while the other studies either excluded those patients or merged them with the overt hyperthyroidism group due to the low number of cases.

Table 2 The calculation of eGFR and diagnosis of subclinical hypothyroidism and chronic kidney disease in the included studies (n = 11)

Study	Calculation of egfr	Definition of SC hypothyroidism	Definition of SC hyperthyroidism	Definition of CKD	Adjusting models for
Asvold 2011	4-variable MDRD formula	TSH 3.6–4.0 mU/l or TSH >4.0 mU/l & FT4 =>8.0 pmol/l	TSH 0.20–0.49 mU/l; or TSH <0.20 mU/l with FT4 & total T3 within reference range	eGFR <60ml/min/1.73 m^2	Age, sex, smoking
Chaker 2016	CKD-EPI Study equation	TSH >4.0 IU/L & FT4 values = 11–25 pmol/L	TSH <0.4 IU/L & FT4 values within normal range (11–25 pmol/L).	eGFR <60ml/min/1.73 m^2	Age, sex, SBP, DBP, antihypertensive medication, smoking,

					total cholesterol, HDL, DM, history of coronary heart disease and BMI
Chang 2018	CKD-EPI Study equation	4.5 < T4 < 12 μg/dL and TSH > 5 mIU/L	not done	eGFR <60ml/min/1.73 m^2	Age, sex
Chuang 2016	4-variable MDRD formula	one or more TSH value of 5–10 mIU/L	TSH value of 0.1 mIU/L	< 60 mL/min per 1.73 m^2 or ≥60 mL/min per 1.73 m^2 with proteinuria ≥ 1+	Sex, age, hypertension, DM, dyslipidemia (low HDL-C, high LDL-C, hypertriglyceridemia), hyperuricemia, abnormal liver function, anemia, obesity, smoking, and alcohol drinking
Gopinath 2013	4-variable MDRD formula	TSH > 4.0 mIU/L with normal FT4	TSH < 0.1 mIU/L with normal FT4	eGFR <60ml/min/1.73 m^2	Age and sex
Jia 2015	4-variable MDRD formula	normal levels of FT3 & FT4, but TSH > 5 mU/l	not done	GFR < 60 ml/min/1.73 m^2 or a UACR > 2.5 mg/mmol in men & > 3.5 mg/mmol in women	Age, gender, diabetes duration, hypertension, smoking and drinking status, BMI and hba1c.
Miranda 2017	CKD-EPI Study equation	TSH >4 mIU/L, normal FT4 levels, and no use of medication to treat hypothyroidism.	Low serum TSH, normal levels of FT4, and no use of thyroid drugs	eGFR <60ml/min/1.73 m^2	Adjusted for sex and race
Schultheiss 2017	CKD-EPI Study equation	TSH >5.1 mIU/L & FT4 within the reference range of 10.9–18.0 pmol/L	TSH below the reference range & FT4 within the reference range	eGFR <60ml/min/1.73 m^2	Age, gender, race, serum albumin, BMI, hs-CRP, smoking status, SBP, DM, LDL and HDL cholesterol, triglycerides, hypertension and medication Use for cholesterol and/or DM.
Ye 2013	CKD-EPI Study equation	TSH >4.00 mIU/l, normal FT4	TSH <0.40 mIU/L, normal FT4	eGFR <60ml/min/1.73 m^2	Age, BMI, hypertension, & diabetes
Zhang 2018	CKD-EPI Study equation	TSH level > 4.78 mIU/l with a FT4 level within normal range	TSH level < 0.55 mIU/l with a FT4 level within normal range.	eGFR <60ml/min/1.73 m^2	-
Zhou 2017	4-variable MDRD formula	19.9mIU/L>TSH > 4.78 mIU/L with normal FT4.		eGFR <60ml/min/1.73 m^2	Age, duration of diabetes, glycosylated hemoglobin (A1C), BMI, blood

					pressure, and LDL cholesterol,

CKD-EPI: CKD Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; UACR: Urinary albumin creatinine ratio.

Table 3 The prevalence/incidence rate of chronic kidney disease in the included studies (n = 11)

Study	Euthyroidism	SC hypothyroidism	SC hyperthyroidism
Asvold 2011	5.13%	12.30%	7.24%
Chaker 2016	NR	NR	-
Chang 2018	4.76%	9.22%	-
Chuang 2016	24.09%	28.53%	-
Gopinath 2013	18%	33.9%	-
Jia 2015	39.65%	46.03%	-
Miranda 2017	5.67%	10.81%	-
Schultheiss 2017	NR	NR	-
Ye 2013	0.53%	0.81%	2.08%
Zhang 2018	10.10%	16.02%	13.31%
Zhou 2017	5.50%	15.60%	-

NR: not recorded and cannot be calculated from published data

Risk of bias assessment in the included studies

Table 4 summarizes the risk of bias assessment using the NHLBI tool. All studies had a low ROB concerning the clarity of the research question, clear specification and definition of the study population, sufficiency of the participation rate and recruiting groups from the same population using uniform criteria. The domains with the highest ROB were sample size justification and blinding of outcome assessors which were observed in all studies; though non-blinding is unlikely to bias the results as they are defined by laboratory measurements and not subjective assessment. In addition, all studies did not perform repeated exposure assessments (as most were cross-sectional) except for one study (Chaker et al., 2016).

Table 4 The assessment of the risk of bias using the NHLBI tools for quality assessment (n = 11)

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Asvold 2011	Yes	Yes	Yes	Yes	No	No	No	NA	Yes	No	Yes	No	No	Yes
Chaker 2016	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	Yes
Chang 2018	Yes	Yes	Yes	Yes	No	No	No	NA	Yes	No	Yes	No	No	Yes
Chuang 2016	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	No	No	Yes	No	Yes	Yes
Gopinath 2013	Yes	Yes	Yes	Yes	No	Yes	No	NA	Yes	No	Yes	No	No	Yes
Jia 2015	Yes	Yes	Yes	Yes	No	Yes	No	NA	Yes	No	Yes	No	No	Yes
Miranda 2017	Yes	Yes	Yes	Yes	No	Yes	No	NA	Yes	No	Yes	No	No	Yes
Schultheiss 2017	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	No	Yes	No	Yes	Yes
Ye 2013	Yes	Yes	Yes	Yes	No	Yes	No	NA	Yes	No	Yes	No	No	Yes
Zhang 2018	Yes	Yes	Yes	Yes	No	Yes	No	NA	Yes	No	Yes	No	No	No
Zhou 2017	Yes	Yes	Yes	Yes	No	No	-	-	-	No	Yes	No	-	Yes

Q1 Research question; Q2 Was the study population clearly specified and defined?; Q3 Was the participation rate of eligible persons at least 50%?; Q4 Groups recruited from the same population and uniform eligibility criteria; Q5 Sample size justification; Q6 Exposure assessed prior to outcome measurement; Q7 Sufficient timeframe to see an effect; Q8 Different levels of the exposure of interest; Q9 Exposure measures and assessment; Q10 Repeated exposure assessment; Q11 Outcome measures; Q12 Blinding of outcome assessors; Q13 Follow-up rate; Q14 Statistical analyses; NA: non-applicable.

Results of meta-analysis

The association of subclinical hypothyroidism with CKD

Using the counts of CKD cases and the total number in each group from 8 studies (Asvold et al., 2011; Ye et al., 2013; Jia et al., 2015; Chuang et al., 2016; Miranda et al., 2017; Zhou et al., 2017; Chang et al., 2018; Zhang et al., 2018), the results of the meta-analysis showed that subclinical hypothyroidism carried a significantly higher risk of CKD compared to the euthyroid group (OR: 1.90, (95% CI: 1.44–2.52), P<0.001, n=8) (Figure 2). However, there was considerable heterogeneity among the studies (Chi p-value<0.001, I2= 92%). Cohen's d effect size was medium (Cohen's d = 0.354).

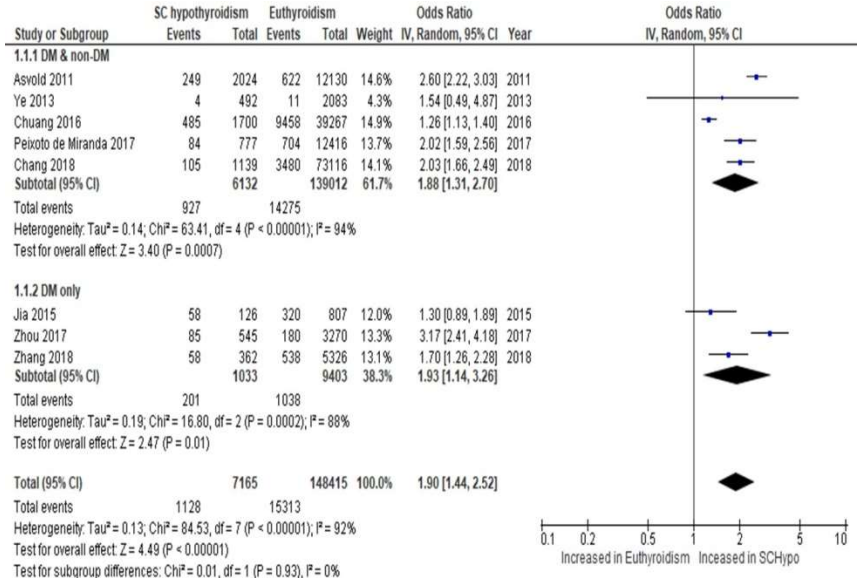

Figure 2 Forest plot showing the pooled rate of CKD in patients with subclinical hypothyroidism compared to euthyroid patients using raw data from the included studies. The studies were sub grouped according to including diabetics only or not (n = 8)

The same outcome was assessed by pooling the ORs that were reported from multivariate analyses by ten of the included studies (Asvold et al., 2011; Gopinath et al., 2013; Ye et al., 2013; Jia et al., 2015; Chaker et al., 2016; Chuang et al., 2016; Miranda et al., 2017; Schultheiss et al., 2017; Zhou et al., 2017; Chang et al., 2018). The analysis showed also a significantly higher risk of CKD in the subclinical hypothyroidism group (OR: 1.40, (95% CI: 1.20–1.63), P<0.001, n=10) (Figure 3), with considerable heterogeneity among the studies (Chi p-value<0.001, I2= 76%). Cohen's effect size was 0.186, indicating a small effect size. We calculated the OR and CI for the raw data of the study by Zhang et al., (2018) and added them to the analysis, causing a slight increase in the OR. The risk seems to become lower when potential confounders are adjusted for. However, the considerable heterogeneity may be partially attributed to the inclusion of different confounders in the computation of the OR by each study.

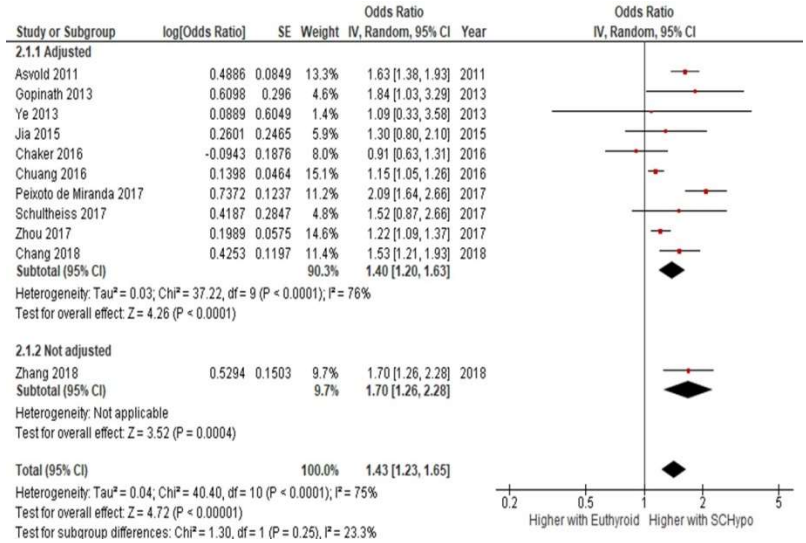

Figure 3 Forest plot showing the pooled rate of CKD in patients with subclinical hypothyroidism compared to euthyroid patients using the reported odds ratio from the included studies plus calculated odds ratio from raw data of the study by Zhang et al., (2018) the studies were sub grouped according to adjusted odds ratio or not (n = 11)

The association of subclinical hyperthyroidism with CKD

Using the reported OR of CKD from two studies (Asvold et al., 2011; Ye et al., 2013), the results of the meta-analysis showed a non-significant association of subclinical hyperthyroidism with CKD (OR: 1.06, (95% CI: 0.76–1.49), P=0.73, n=2) (Figure 4), with minimal heterogeneity between the two studies (Chi p-value=0.45, I2= 0%). The Cohen's d effect size was small (Cohen's d = 0.032). Adding the calculated OR from the raw data of the study by Zhang et al., (2018), no significant change occurred in the results.

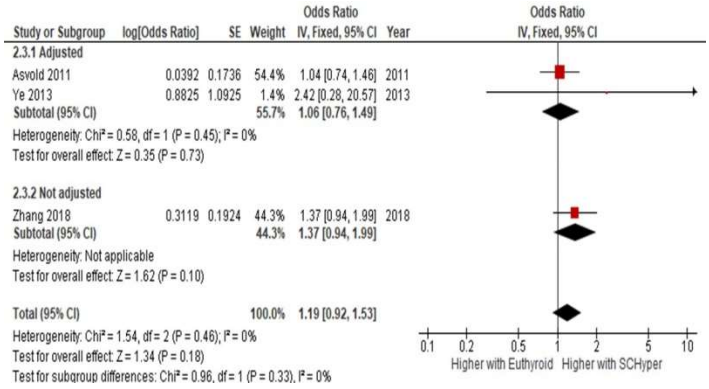

Figure 4 Forest plot showing the pooled rate of CKD in patients with subclinical hyperthyroidism compared to euthyroid patients using the reported odds ratio from the included studies plus calculated odds ratio from raw data of the study by Zhang et al., (2018) the studies were sub grouped according to adjusted odds ratio or not (n = 3)

Subgroup analysis

Subgroup analysis was done only for the relationship between subclinical hypothyroidism and CKD, as the number of studies for subclinical hyperthyroidism was low. The first subgroup analysis was based on the inclusion of diabetics only in the study or a mixture of diabetics and non-diabetics. The subgroup differences were not significant (p = 0.69). Interestingly, considerable heterogeneity was observed within each subgroup (Chi p-valu<0.001, I^2 > 70%), but not between the two subgroups, suggesting the effect of other confounders within each group (Figure 5).

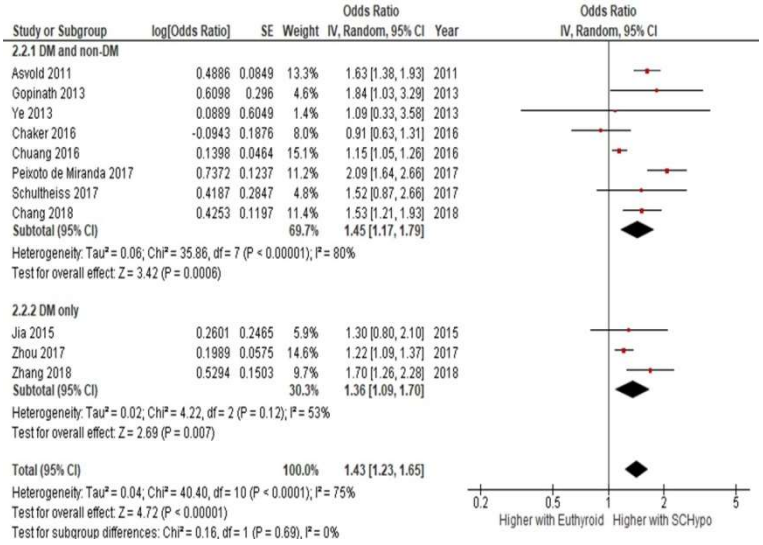

Figure 5 Forest plot showing the pooled rate of CKD in patients with subclinical hypothyroidism compared to euthyroid patients using the reported odds ratio from the included studies plus calculated odds ratio from raw data of the study by Zhang et al., (2018) the studies were sub grouped according to including diabetics only or not (n = 11)

The second subgroup analysis was based on the study design. The risk of CKD with subclinical hypothyroidism was significantly lower with longitudinal studies compared to cross-sectional studies (OR: 1.17 vs. 1.68, respectively, p for subgroup difference <0.001). The two subgroups showed considerable heterogeneity between each other (Chi p-value<0.001, I^2 = 96.8%), but not within each subgroup (Chi p-value= 0.35 and 0.47, I^2 = 9% and 0%) (Figure 6).

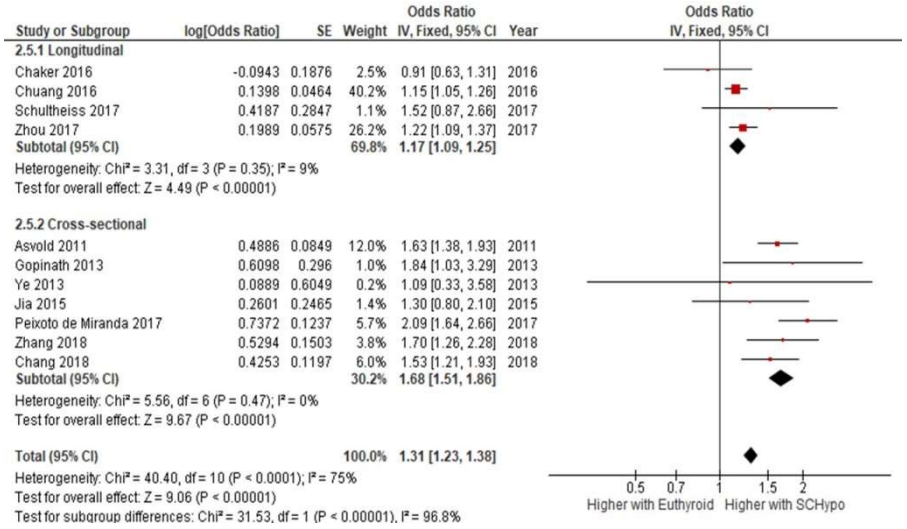

Figure 6 Forest plot showing the pooled rate of CKD in patients with subclinical hypothyroidism compared to euthyroid patients using the reported odds ratio from the included studies plus calculated odds ratio from raw data of the study by Zhang et al., (2018) the studies were sub grouped according to the study design (n = 11)

4. DISCUSSION

Summary of the main findings

The results of this meta-analysis suggest that the risk of CKD increases by 1.4 folds in the presence of subclinical hypothyroidism. This association was significant whether the pooling involved the unadjusted (OR: 1.90, (95% CI: 1.44–2.52), P<0.001, n=8) or adjusted ORs group (OR: 1.40, (95% CI: 1.20–1.63), P<0.001, n=10). In either case, there was considerable heterogeneity among the included studies. Probable reasons for this heterogeneity may include the age of the patients, the study design (longitudinal versus cross-sectional), the high prevalence of other diseases associated with CKD and variations of the confounders that were entered into the multivariate analysis.

The age of the patients varied among the studies, with some studies including exclusively elderly individuals or a high proportion of elderly (Gopinath et al., 2013; Jia et al., 2015; Chaker et al., 2016; Chuang et al., 2016; Zhang et al., 2018). However, we were unable to perform subgroup analysis according to age as the results of most studies that included both middle-aged and elderly subjects were not presented for the different age groups. It is crucial to assess the potential effect of age on the development of CKD. Moreover, some studies suggest that the incidence of subclinical hypothyroidism increases with advanced age (Asvold et al., 2011; Biondi et al., 2019). Older age is associated with several comorbidities which may predispose to the development of CKD. In addition, the metabolism of thyroid hormones declines with increased age, resulting in an increase in the TSH level (Bremner et al., 2012; Waring et al., 2012). The effect of reduced metabolism with age on thyroid hormones could lead to the exaggeration of the reported rates of subclinical hypothyroidism in this age group (Biondi et al., 2019).

Subgroup analysis was done for the study type and the inclusion of diabetics only. We found an increased risk for CKD with subclinical hypothyroidism in studies that included diabetics only and those containing a mixture of diabetics and non-diabetics, with no significant difference between the subgroups (p = 0.69). However, the assessment of the risk in diabetics requires studies that include non-diabetic patients only, which was not available for this meta-analysis. We conducted a subgroup analysis according to the design of the included studies. The pooled OR from the longitudinal studies was significantly lower than that pooled from the cross-sectional studies (OR: 1.17 vs. 1.68, respectively, p<0.001).

Longitudinal studies provide some evidence regarding the causality between the dependent and independent variables, which cannot be concluded from cross-sectional studies. This is particularly true in assessing the association between thyroid dysfunction and CKD, as a bidirectional relationship seems to exist. Animal studies showed that thyroid hormones can affect kidney function through both direct and indirect mechanisms. These mechanisms include reducing cardiac output, vasoconstriction of intra-renal blood vessels, decreased production and activity of renin-angiotensin-aldosterone and increased tubuloglomerular feedback (Iglesias et al., 2017). Some clinical studies also have revealed that thyroid hormone administration in patients with subclinical hypothyroidism may preserve eGFR and delay the progression of CKD (Shin et al., 2012; Shin et al., 2013; Hennessey et al., 2021). On the other hand, CKD can affect thyroid hormones through alterations of their regulation by the hypothalamic-pituitary-thyroid axis as well as changes in their metabolism, degradation and excretion (Rhee et al., 2015; Rhee, 2016; Dubczak et al., 2019).

There was a paucity of observational studies that reported on the prevalence of CKD in subclinical hyperthyroidism. This is presumably due to the lower prevalence of subclinical hyperthyroidism compared to subclinical hypothyroidism (Al-Eidan et al., 2018; Jukić et al., 2022). Only three studies reported data for CKD risk in subjects with subclinical hyperthyroidism. The pooling of the findings of these results gave marginally non-significant results CKD (OR: 1.19, (95% CI: 0.92–1.53), P=0.18, n=3). Subgroup analysis was not done for subclinical hyperthyroidism due to the low number of studies besides minimal heterogeneity across the studies. Interestingly, some studies have reported that subclinical hyperthyroidism increases eGFR (Iglesias et al., 2017), but it seems that it leads to declining renal functions in the long run as inferred from the pooled ORs in this meta-analysis. The same observation was reported by another previous meta-analysis (Wang et al., 2020).

Overall completeness, applicability and quality of the evidence

The increased likelihood of CKD in subjects with subclinical hypothyroidism, relative to euthyroid subjects, was small to moderate in this meta-analysis (Cohen's d = 0.186 to 0.354). The larger effect size was obtained when using calculating the unadjusted ORs from the studies' raw data. The effect size was reduced by pooling the pre-calculated adjusted ORs, which is logical since the multivariate analyses adjusted for several factors that could on their own influence the occurrence of CKD such as age and diabetes. The included studies showed a high ROB in some domains, particularly sample size calculation and blinding of outcome assessors. Furthermore, most studies did not perform repeated exposure assessments, being cross-sectional in design. However, we considered that the non-blinding of outcome assessors is unlikely to introduce bias into the studies' results as the diagnosis of CKD was based on laboratory measurements. The results of the ROB assessment indicate the need for longitudinal studies to assess the effect of subclinical thyroid dysfunctions on the development of CKD, taking into consideration the calculation of sample size as well as performing repeated assessments of thyroid hormones and renal functions.

The studies of this meta-analysis may be limited by the considerable heterogeneity among the included studies. Several differences existed considering the study design, the basic characteristics of the participants (e.g., age, sex, race, comorbidities and receiving thyroxin treatment), as well as the cut-off values used to determine the states of euthyroidism and subclinical thyroid dysfunctions. In addition, our results were inconclusive regarding the effect of subclinical hyperthyroidism due to the low number of studies. We could not carry out subgroup analysis based on the age or administration of thyroxine as the data were not reported separately for these subsets.

Agreements and disagreements with other studies or reviews

Two previous meta-analyses addressed the relationship between subclinical thyroid dysfunctions and renal function. The first was an individual patient meta-analysis that was published in 2019 (Meuwese et al., 2019) and included 16 cohorts. The meta-analysis pooled the eGFR but did not give details on the binary outcome of CKD. They found that subjects with subclinical hypothyroidism had a lower eGFR than the euthyroid subjects. However, there was no further deterioration in eGFR was found on follow-up. The authors concluded that subclinical hypothyroidism was not linked to a worsening of renal function. They suggested that the reported association by cross-sectional studies may reflect the effect of reduced renal function on thyroid hormone, not the reverse. The other meta-analysis was published in 2020 and included eight studies (Wang et al., 2020). Their results showed that subclinical hypothyroidism was significantly associated with a higher risk of CKD 1.37 (95% CI: 1.13–1.67, P <0.001). Similarly, they found that subclinical hyperthyroidism was not significantly associated with alterations in the likelihood of CKD (OR: 1.16 (95%CI: 0.97–1.39), P = 0.115).

5. CONCLUSIONS

Implications for practice, policy and future research

The results of this meta-analysis suggest that subclinical hypothyroidism has a significant association with increased risk of CKD. However, the evidence was inconclusive regarding the effect of subclinical hyperthyroidism. There is a need for longitudinal studies to confirm the effect of subclinical thyroid dysfunction as an exposure on the outcome of newly diagnosed CKD, with particular attention to reporting the association between subclinical hyperthyroidism and CKD which is under studied. Future studies should adopt sample size calculations to avoid the non-detection of an existent association or the recording of a non-existent one. In addition, future studies should report on subsets of patients to explore the effects of potential confounders such as age, sex and comorbidities.

Authors' contributions

All authors contributed to the study conception and design. Literature search and data collection were performed by Laila Abdullah S Alanazi, Atheer Mansour E Alatawi, Dhuha Abdullah H Al Qasir, Shaden Akram A Alanazi and Raghad Abdulrahman A Aljohani Data extraction, risk of bias assessment and analysis were performed by Waad Ali M Alkaabneh, Tariq Alrasheed, Hadeel Ahmed A Albalawi and Anwar Saad E Alrashidi. The first draft of the manuscript was written by Nada Saleem S Alhawiti and Maryam Awad H Albalawi. The final draft of the manuscript was written by Tariq Alrasheed and Waad Ali M Alkaabneh.

Ethical approval

Not applicable.

Informed consent

Not applicable.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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