# Subclinical hypothyroidism and clinical outcomes after cardiac surgery: A systematic review and meta-analysis



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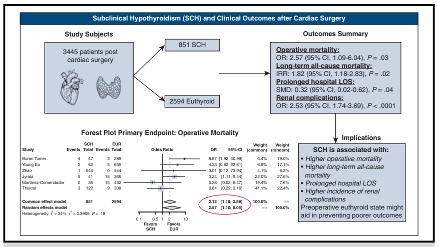
## ABSTRACT

**Background:** Subclinical hypothyroidism (SCH) is associated with major adverse cardiovascular events. Despite the recognized negative impact of SCH on cardiovascular health, research on cardiac postoperative outcomes with SCH has yielded conflicting results, and patients are not currently treated for SCH before cardiac surgery procedures.

**Methods:** We performed a study-level meta-analysis on the impact of SCH on patients undergoing nonurgent cardiac surgery, including coronary artery bypass grafting and valve and aortic surgery. The primary outcome was operative mortality. Secondary outcomes were hospital length of stay (LOS), intensive care unit (ICU) stay, postoperative atrial fibrillation (POAF), intra-aortic balloon pump (IABP) use, renal complications, and long-term all-cause mortality.

**Results:** Seven observational studies, with a total of 3445 patients, including 851 [24.7%] diagnosed with SCH and 2594 [75.3%] euthyroid patients) were identified. Compared to euthyroid patients, the patients with SCH had higher rates of operative mortality (odds ratio [OR], 2.57; 95% confidence interval [CI], 1.09-6.04; $P = .03$), prolonged hospital LOS (standardized mean difference, 0.32; 95% CI, 0.02-0.62; $P = .04$), a higher rate of renal complications (OR, 2.53; 95% CI, 1.74-3.69; $P < .0001$), but no significant differences in ICU stay, POAF, or IABP use. At mean follow-up of 49.3 months, the presence of SCH was associated with a higher rate of all-cause mortality (incidence rate ratio, 1.82; 95% CI, 1.18-2.83; $P = .02$).

**Conclusions:** Patients with SCH have higher operative mortality, prolonged hospital LOS, and increased renal complications after cardiac surgery. Achieving and maintaining a euthyroid state prior to and after cardiac surgery procedures might improve outcomes in these patients. (JTCVS Open 2024;18:64-79)




**Study population, outcomes summary, and forest plot for primary outcome and implications.**

### CENTRAL MESSAGE

Subclinical hypothyroidism was associated with higher rates of operative mortality, renal complications, and long-term mortality and longer hospital length of stay compared with a euthyroid state.

### PERSPECTIVE

Patients with subclinical hypothyroidism have higher operative mortality, prolonged hospital length of stay, and a higher rate of renal complications after cardiac surgery. The gradual initiation of thyroid replacement therapy could be considered in an attempt to decrease the incidence of postoperative major adverse cardiovascular events, although further and more robust evidence is needed.

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Dell'Aquila and Dr Rossi contributed equally to this work.

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**Abbreviations and Acronyms**

| | |
|---|---|
| BMI | = body mass index |
| CABG | = coronary artery bypass grafting |
| CHD | = coronary heart disease |
| CI | = confidence interval |
| CVA | = cerebrovascular accident |
| IABP | = intra-aortic balloon pump |
| ICU | = intensive care unit |
| IRR | = incidence rate ratio |
| LOS | = length of stay |
| MACE | = major adverse cardiovascular events |
| OR | = odds ratio |
| POAF | = postoperative atrial fibrillation |
| SCH | = subclinical hypothyroidism |
| SMD | = standardized mean difference |
| TSH | = thyroid-stimulating hormone |

Subclinical hypothyroidism (SCH) is defined as serum free thyroxine and 3,5,3′-triiodothyronine within reference ranges in the presence of an elevated serum thyroid-stimulating hormone (TSH) level. SCH can be classified as grade 1 (TSH >4.0 or 4.5 mIU/L, but <10 mIU/L) or grade 2 (TSH >10 mIU/L). Patients with SCH typically do not exhibit overt clinical symptoms, making it a subtle but significant health concern. The prevalence of SCH in the population varies from 4% to 20%, occurring more frequently in adults age >65 years.[1,2] The approach to treating SCH has remained a contentious issue, with different recommendations provided by medical guidelines in the United States and Europe.[3-5] This divergence underscores the complexity of managing this condition and its complications.

SCH is associated with an increased risk of congestive heart failure, fatal stroke, and postoperative atrial fibrillation (POAF).[6-8] Furthermore, it is considered an independent predictor of coronary heart disease (CHD).[9,10]

The increased cardiovascular risk seen in SCH patients is theorized to be related to increased cholesterol and homocysteine levels and decreased low-density lipoprotein receptors. This association also has been noted in patients with overt hypothyroidism.[11,12] In addition, patients with SCH have decreased nitric oxide-mediated vascular relaxation, impaired endothelial function, higher prevalences of aortic calcification and myocardial infarction, decreased left ventricular global longitudinal strain, and accelerated cardiac pathologic remodeling.[13-15] SCH also might increase peripheral insulin resistance and activate prothrombotic pathways and hypercoagulability.[14,16]

Given the risk of adverse cardiovascular outcomes after coronary artery bypass grafting (CABG), preoperative diagnosis and treatment of SCH may reduce major adverse cardiovascular events (MACE) and mortality.[17] Despite the recognized negative impact of SCH on cardiovascular health, research on postoperative outcomes for cardiac surgery patients with SCH has yielded conflicting results.[18,19] Determining the optimal approach for patients diagnosed with SCH before nonurgent cardiac surgery remains unclear.[20-22] This study aimed to evaluate whether subclinical thyroid dysfunction significantly impacts clinical outcomes after cardiac surgery.

## METHODS

Institutional Review Board approval of this analysis was not required, because no human or animal subjects were involved. This review was registered with the National Institute for Health Research International Registry of Systematic Reviews (PROSPERO; CRD 471397) and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

### Search Strategy

A medical librarian (M.D.) performed a comprehensive literature search to identify contemporary studies reporting clinical outcomes in patients diagnosed with SCH and euthyroid patients. Searches were performed in August 2023 and included 3 databases: Ovid MEDLINE (all; 1946 to present), Ovid Embase (1974 to present), and the Cochrane Library. The complete search strategy for Ovid MEDLINE is shown in Table E1.

### Study Selection and Data Extraction

After de-duplication, studies were screened by 2 independent reviewers (M.D.A. and C.S.R.); any discrepancies were resolved by the senior author (M.G.). A first round of screening based on title and abstract content was performed, and studies were considered for inclusion if they were written in English and compared outcomes between patients diagnosed with SCH and euthyroid patients. Animal studies, abstracts, case reports, commentaries, editorials, expert opinions, conference presentations, studies with pediatric populations, and studies not reporting the outcomes of interest were excluded. For the selected studies, the full text was pulled for a second round of eligibility screening. References for articles selected also were reviewed for relevant studies not captured by the original search.

Two investigators (M.D.A. and C.S.R.) independently performed data extraction, and the integrity of the data was verified by the corresponding author (M.G.). The extracted variables included study characteristics (publication year, country, sample size, study design, mean follow-up, and population adjustments), as well as patient demographics (age, sex, body mass index [BMI], smoking status, diabetes, chronic obstructive pulmonary disease, TSH baseline, prior cerebrovascular accident [CVA]). The risk of bias of the included studies was assessed using the Newcastle–Ottawa risk of bias assessment scale (Table E2).

### Outcomes

The primary outcome was operative mortality (defined as 30-day/in-hospital). Secondary outcomes were hospital length of stay (LOS), intensive care unit (ICU) stay, POAF, intra-aortic balloon pump (IABP) use, renal complications (defined as acute kidney injury or need of dialysis), and long-term all-cause mortality.

### Statistical Analysis

Meta-analysis was performed on outcomes for which ≥3 studies presented comparable data. Short-term categorical variables were analyzed using odds ratio (OR) and 95% confidence interval (95% CI). An OR

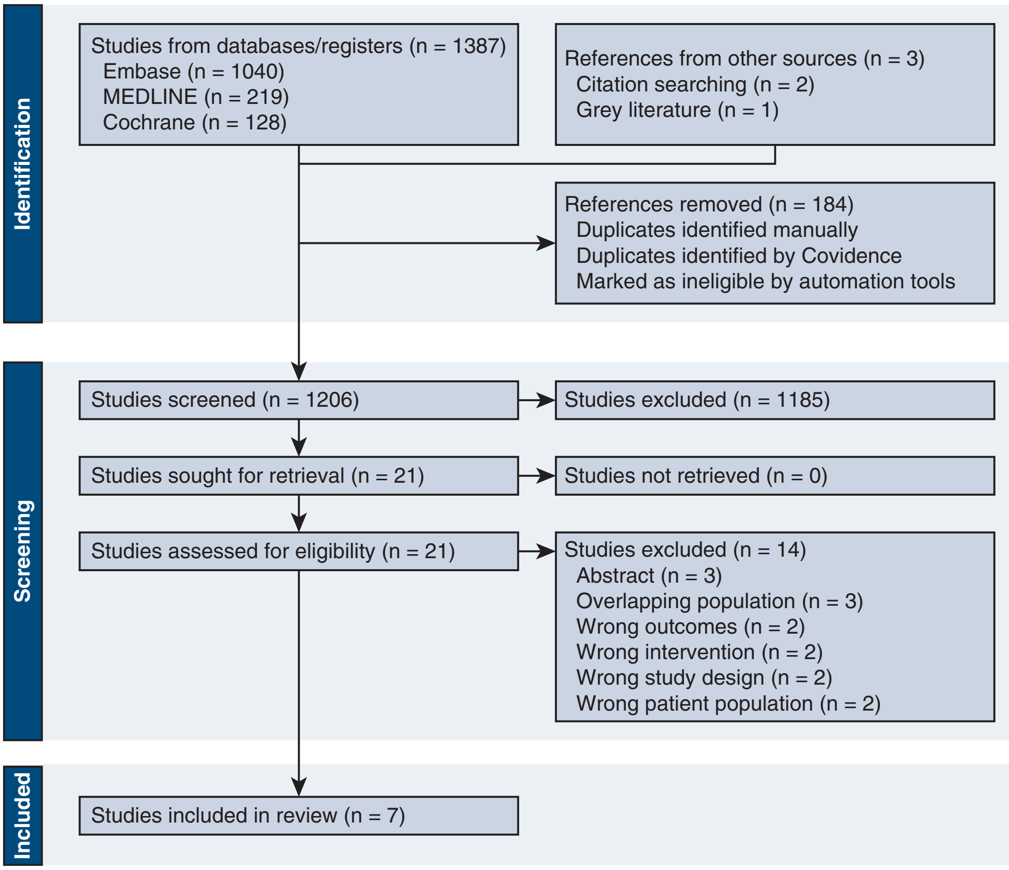


**FIGURE 1.** PRISMA flow diagram.

>1 indicated that the outcome was more frequently present in the SCH group. Long-term categorical variables were analyzed based on the time-to-event data using incidence rate ratio (IRR) and 95% CI. An IRR >1 indicated that the outcome was more frequently present in the SCH group. Continuous variables were analyzed using the standardized mean difference (SMD) and 95% CI. An SMD >0 corresponded to longer stay in the SCH group.

Random effects models were used as primary models. Results were displayed in forest plots. Between-study statistical heterogeneity was assessed with the Cochran Q statistic and by estimating $I^2$. High heterogeneity was defined as a significance level of $P < .10$ and an $I^2$ of $\geq 50\%$.

### Sensitivity Analyses

All the meta-analytic comparisons were repeated using fixed models as sensitivity analyses. A leave-one-out analysis for the primary outcome was performed to assess the robustness of the estimate. A funnel plot was created to evaluate publication bias. A subgroup analysis of the studies that involved isolated CABG patients was performed. Finally, a meta-regression was used to explore the associations of age, sex, BMI, smoking status, hypertension, diabetes, chronic obstructive pulmonary disease, TSH baseline level, and prior CVA with the pooled estimate for the primary outcome. All statistical analyses were performed using R version 4.1.1 (R Project for Statistical Computing) within RStudio.

## RESULTS

### Study Characteristics

A total of 1206 studies were screened, of which 7 met the criteria for inclusion in our final analysis. Figure 1 shows the PRISMA flowchart for study selection. Included studies were published between 2012 and 2023 and originated from Turkey, China, South Korea, United States, Spain, and India. Six studies were based on risk-adjusted populations.

We identified a total of 3445 patients, including 2594 (75.3%) euthyroid patients and 851 (24.7%) diagnosed with SCH. The number of patients in each study ranged from 336 to 1088, with a median sample size of 467 (interquartile range, 406-717). Table 1 shows the details of the included studies.

The studies reported by Park and colleague[1] and Kong and colleagues[2] were excluded because of overlapping population with the study reported by Kim and colleagues[24] The study conducted by Wang and colleagues[27] on SCH and postoperative mortality in acute type A aortic dissection (ATAAD) was also excluded. In addition, Zhao and colleagues published 2 studies, in 2021[28] and 2023,[17] with the same propensity-matched cohort but considering different outcomes. Baseline characteristics were extracted from the 2021 study, and outcomes were extracted from the 2023 study.

### Patient Characteristics

The mean patient age ranged from 58.9 to 70.6 years, and the proportion of females ranged from 21.0% to

**TABLE 1. Summary of included studies**

| Study | Year of publication | Country | Patients | Study design | Follow-up, mean | Extracted outcomes |
|---|---|---|---|---|---|---|
| Boran Tumer et al[23] | 2020 | Turkey | 336 | Retrospective cohort study | 30 d | • Operative mortality<br>• Hospital LOS<br>• Renal complications<br>• ICU stay<br>• IABP use |
| Kim et al[24] | 2020 | South Korea | 565 | Retrospective cohort study | 8 y | • Postoperative AF<br>• Long-term all-cause mortality |
| Joe et al[19] | 2022 | South Korea | 717 | Retrospective cohort study | 2.5 y | • Operative mortality<br>• Hospital LOS<br>• Renal complications<br>• ICU stay<br>• Long-term all-cause mortality |
| Zhao et al[17] | 2023 | China | 1088 | Retrospective cohort study | 3 y | • Operative mortality<br>• Hospital LOS<br>• Renal complications<br>• ICU stay<br>• IABP use<br>• Long-term all-cause mortality |
| Jyrala et al[25] | 2012 | United States | 406 | Retrospective cohort study | 3 y | • Operative mortality<br>• Hospital LOS<br>• Renal complications<br>• ICU stay<br>• Postoperative AF<br>• IABP use |
| Martínez-Comendador et al[18] | 2016 | Spain | 467 | Retrospective cohort study | 3 y | • Operative mortality<br>• Hospital LOS<br>• Renal complications<br>• ICU stay<br>• Postoperative AF |
| Thukral et al[26] | 2022 | India | 449 | Retrospective cohort study | 30 d | • Operative mortality<br>• ICU stay<br>• Postoperative AF<br>• IABP use |

*LOS*, Length of stay; *ICU*, intensive care unit; *IABP*, intra-aortic balloon pump; *AF*, atrial fibrillation.

54.8%. BMI ranged from 23.0 to 27.8 kg/m$^2$, the percentage of smokers ranged from 23.0% to 42.61%, the prevalence of diabetes ranged from 10.6% to 53.44%, the prevalence of hypertension ranged from 30.8% to 75.1%, the TSH baseline values ranged from 2.01 to 3.26 mIU/L, and the incidence of prior CVA ranged from 7.0% to 19.1%. Baseline characteristics were summarized in Table E3.

### Meta-Analysis: Primary Outcome

Compared to euthyroid patients, the patients with SCH had a higher incidence of operative mortality (OR, 2.57; 95% CI, 1.09-6.04; $P = .03$). Figures 2 and 3 shows a forest plot for operative mortality. The leave-one-out analysis was consistent with the main analysis (Figure E1); Figure E2 shows the funnel plot.

In the subgroup analysis, the association between SCH and operative mortality was stronger in the isolated CABG cohort compared with the general cardiac surgery cohort, although the interaction was not significant (isolated CABG: OR, 3.00; 95% CI, 0.86-10.41; general cardiac surgery: OR, 1.80; 95% CI, 0.32-10.36; $P$ for interaction = .64) (Figure E3). In meta-regression analyses, the proportion of female patients was inversely associated with the OR for the primary outcome (beta $= -0.0825 \pm 0.0397$; $P = .04$) (Table E4).

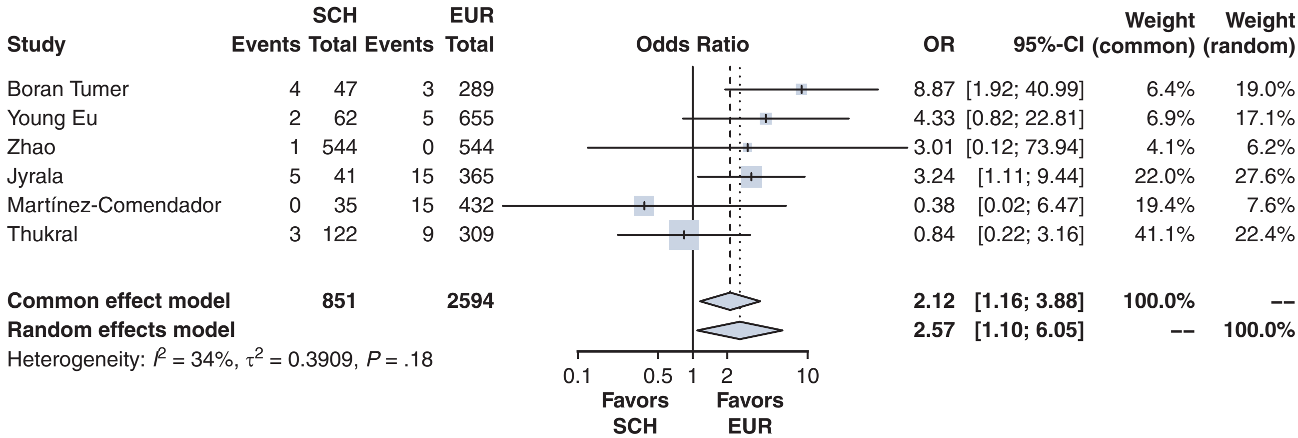


**FIGURE 2.** Forest plot for the primary endpoint, operative mortality. *SCH*, Subclinical hypothyroidism; *EUR*, euthyroid; *OR*, odds ratio; *CI*, confidence interval.

## Secondary Outcomes

Table 2 provide results of the meta-analysis. Compared to euthyroid patients, those with SCH had prolonged hospital LOS (SMD, 0.32; 95% CI, 0.02-0.62; $P = .04$; Figure 4) and a higher incidence of renal complications (OR, 2.53; 95% CI, 1.74-3.69; $P < .0001$; Figure 5). There was no significant difference between euthyroid patients and those with SCH in terms of ICU stay (SMD, 0.30; 95% CI, −0.08 to 0.68; $P = .12$), incidence of POAF (OR, 1.25; 95% CI, 0.57-2.75; $P = .57$), or IABP use (OR, 1.49; 95% CI, 0.57-2.86; $P = .41$) (Figures E4-E6).

At a mean follow-up of 49.3 months, SCH was associated with higher all-cause mortality (IRR, 1.82; 95% CI, 1.18-2.83; $P = .02$) (Figure 6).

## DISCUSSION

In the present study, we found worse postoperative outcomes in patients diagnosed with SCH prior to cardiac surgery compared to euthyroid patients. SCH was associated with higher rates of operative mortality, renal complications, and long-term all-cause mortality, as well as prolonged hospital LOS. There were no significant differences between the 2 patient groups in terms of ICU stay, POAF, and IABP use.

Our study is the first meta-analysis to evaluate the association between SCH and postoperative and long-term outcomes following cardiac surgery. The primary outcome was reported by 6 of the 7 retrospective studies that we analyzed,[18,19,23,25,26,28] and based on our analysis, SCH patients had a greater risk of operative mortality compared to their euthyroid counterparts. Although not surgery-related, other meta-analytic studies have been conducted focusing on cardiovascular outcomes, showing that SCH is associated with increased CHD and mortality.[29-31]

Different factors may contribute to our finding of increased operative mortality after cardiac surgery in patients with SCH. Due to the effect of thyroid hormones on the myocardium and vascular endothelium, patients affected by SCH and hypothyroidism undergo changes in cardiovascular function, namely, decreased heart rate

**TABLE 2. Outcomes summary**

| Outcome | Studies | Patients | Effect estimate (95% CI) | *P* value |
|---|---|---|---|---|
| Operative mortality | 6 | 3445 | OR: 2.57, (1.09-6.04) | .03 |
| Hospital length of stay | 5 | 3014 | SMD: 0.32 (0.02-0.62) | .04 |
| Renal complications | 5 | 3014 | OR: 2.53 (1.74-3.69) | .0001 |
| Intensive care unit stay | 6 | 3445 | SMD: 0.30 (−0.08 to 0.68) | .12 |
| Postoperative atrial fibrillation | 4 | 2392 | OR: 1.25 (0.57-2.75) | .57 |
| Intra-aortic balloon pump use | 4 | 2261 | OR: 1.49 (0.57-2.86) | .41 |
| Long-term all-cause mortality | 3 | 2370 | IRR: 1.82 (1.18-2.83) | .02 |

*CI*, Confidence interval; *OR*, odds ratio; *SMD*, standardized mean difference; *IRR*, incidence rate ratio.

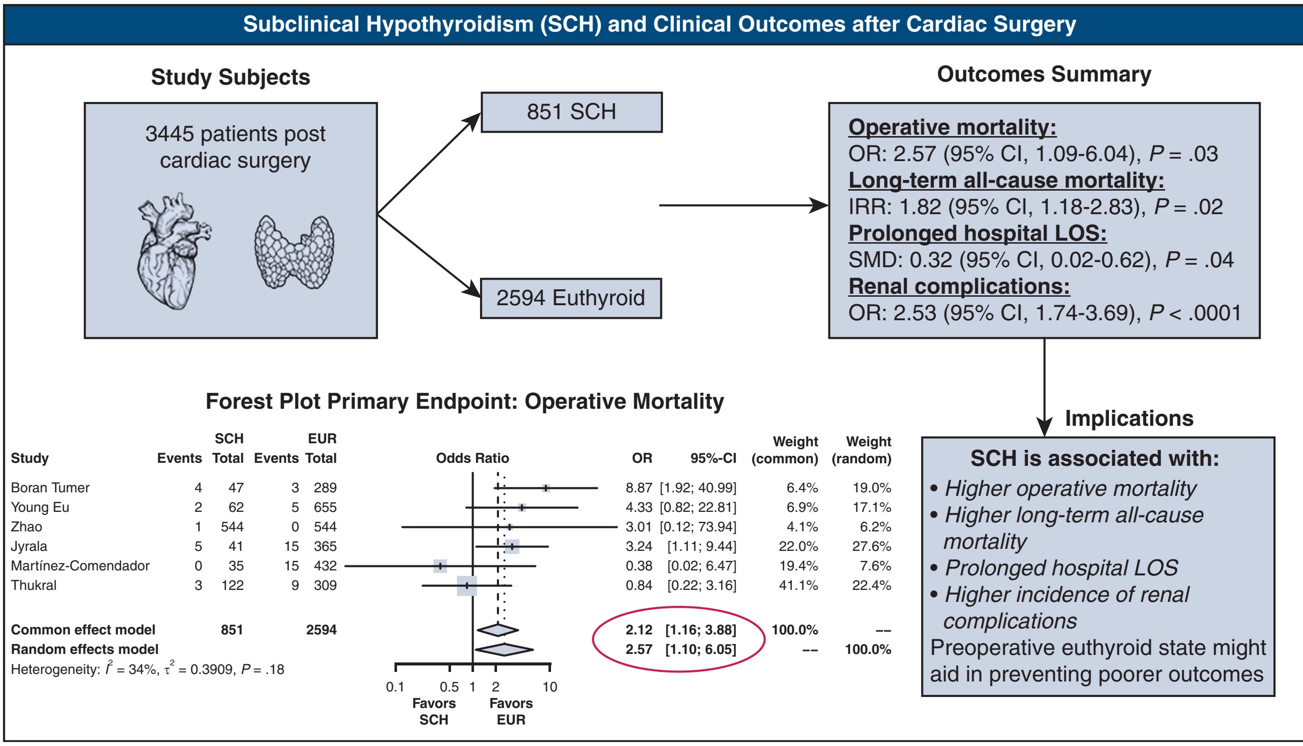


**FIGURE 3.** Forest plot for hospital length of stay. *SCH*, Subclinical hypothyroidism; *EUR*, euthyroid; *OR*, odds ratio; *CI*, confidence interval.

and myocardial contractility and increased peripheral vascular resistance.[32] SCH may also increase low-density lipoprotein levels and decrease high-density lipoprotein levels, enhancing the risk of atherosclerosis and CHD.[32]

Postoperative secondary outcomes were compared to the results from existing literature. However, there is a significant heterogeneity in the results in relation to POAF. Park and colleagues[1] reported that POAF was 2.5 times more common in the hypothyroid group while Zhao and colleagues[17] found no significant difference between the 2 groups. According to Baumgartner and colleagues,[33] free serum thyroxine levels within the high-normal range were associated with increased risk of AF, but AF events did not increase across TSH categories within the euthyroid range or in SCH. In a study including clinical hypothyroid patients, Komatsu and colleagues[34] even considered hypothyroidism a protective factor against POAF. In our study, the difference in the incidence of POAF was not significant, possibly due to the multifactorial nature of POAF.

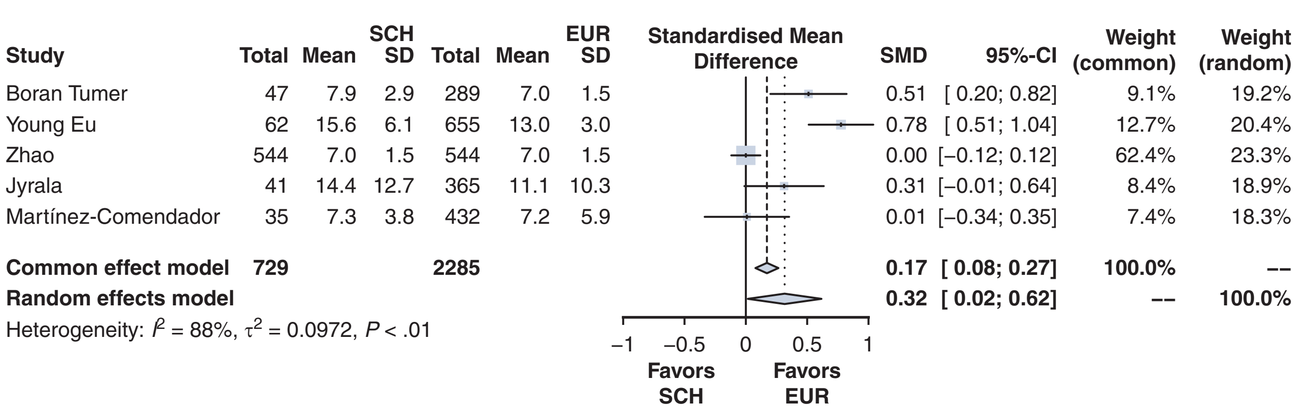


**FIGURE 4.** Forest plot for renal complications. *SCH*, Subclinical hypothyroidism; *EUR*, euthyroid; *OR*, odds ratio; *CI*, confidence interval.

| Study | SCH Events | SCH Total | EUR Events | EUR Total | OR | 95%-CI | Weight (common) | Weight (random) |
|---|---|---|---|---|---|---|---|---|
| Boran Tumer | 15 | 47 | 42 | 289 | 2.76 | [1.38; 5.52] | 23.6% | 25.3% |
| Young Eu | 24 | 62 | 97 | 655 | 3.63 | [2.09; 6.33] | 30.3% | 36.7% |
| Zhao | 0 | 544 | 1 | 544 | 0.33 | [0.01; 8.19] | 4.4% | 1.4% |
| Jyrala | 8 | 41 | 46 | 365 | 1.68 | [0.73; 3.86] | 22.0% | 18.4% |
| Martínez-Comendador | 8 | 35 | 58 | 432 | 1.91 | [0.83; 4.41] | 19.7% | 18.3% |
| **Common effect model** | | **729** | | **2285** | **2.51** | **[1.78; 3.54]** | **100.0%** | **--** |
| **Random effects model** | | | | | **2.53** | **[1.74; 3.69]** | **--** | **100.0%** |

Heterogeneity: $I^2 = 13\%$, $\tau^2 = 0.0208$, $P = .33$

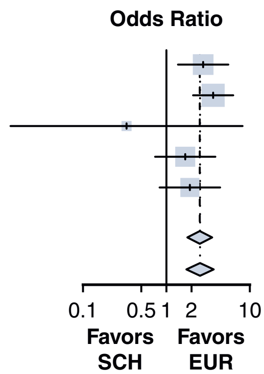


**FIGURE 5.** Forest plot for long-term all-cause mortality. *CI*, Confidence interval; *SCH*, subclinical hypothyroidism; *EUR*, euthyroid.

Our results, along with findings from the scientific literature, suggest that SCH is significantly associated with renal complications. According to Chonchol and colleagues[35] and Chang and colleagues,[36] SCH was independently associated with progressively lower estimated glomerular filtration rate and represents a risk factor for reduced renal function.[35,36] Although it is often ignored preoperatively, SCH can be treated, and Shin and colleagues[37] demonstrated that thyroid hormone therapy preserved renal function in compliant patients, and also found that thyroid hormone therapy is also an independent predictor of renal complications in chronic kidney disease patients with SCH.

Although the long-term data was reported in 3 of the 7 studies, SCH was associated with higher all-cause mortality. This finding also can be identified in the interventional scenario, as prior literature has indicated that SCH affects long-term outcomes in patients undergoing percutaneous coronary intervention.[38] In the long-term, sustained high levels of TSH may hinder patients' stress response after cardiac surgery, potentially leading to worse clinical outcomes.

Initiation of thyroid replacement therapy could be considered in an attempt to decrease the incidence on postoperative MACE even if evidence of clear benefit is currently lacking. Given the retrospective nature of the studies included and the potential influence of confounders it is possible that SCH is a risk indicator, rather than an independent risk factor, for postoperative MACE.

More robust evidence is needed to understand the impact of SCH and, consequently, thyroid replacement therapy on postoperative outcomes in patients with SCH undergoing cardiac surgery. A randomized clinical trial should be designed to assess whether preoperative thyroid replacement therapy reduces to the incidence of MACE in patients with SCH.

This work has the intrinsic limitations of study-level meta-analyses based on retrospective observational series, such as the risk of methodologic heterogeneity of the included studies, residual confounders, ecologic fallacy of meta-regression, and a possible treatment allocation bias, where surgeons can change their surgical decision based on patients' laboratory data.

| Study | Treatment effect | Standard error | Weight (fixed) | Weight (random) | Incidence Rate Ratio |
|---|---|---|---|---|---|
| Kim-CABG | 0.5306 | 0.2224 | 68.0% | 68.0% | 1.70 [1.10; 2.63] |
| Kim-Valve | 0.2927 | 0.5580 | 10.8% | 10.8% | 1.34 [0.45; 4.00] |
| Young Eu | 1.5686 | 1.0298 | 3.2% | 3.2% | 4.80 [0.64; 36.13] |
| Zhao | 0.8755 | 0.4310 | 18.1% | 18.1% | 2.40 [1.03; 5.59] |
| **Total (common effect, 95% CI)** | | | **100.0%** | **--** | **1.82 [1.27; 2.61]** |
| **Total (random effect, 95% CI)** | | | **--** | **100.0%** | **1.82 [1.18; 2.83]** |

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.69$, df = 3 ($P = .638$); $I^2 = 0\%$

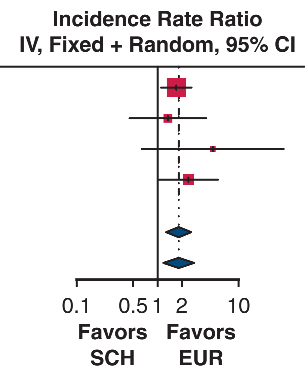


**FIGURE 6.** Graphical abstract. *OR*, Odds ratio; *SMD*, standardized mean difference; *IRR*, incidence rate ratio.

## CONCLUSIONS

The analysis showed that patients with SCH have higher operative mortality, prolonged hospital LOS, and increased renal complications after cardiac surgery. Further studies are needed to determine whether preoperative initiation of thyroid replacement therapy might aid in preventing poor outcomes.

### Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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**Key Words:** subclinical hypothyroidism, thyroid dysfunction, cardiac surgery

| Study | OR | 95%-CI | *P*-value | Tau2 | Tau | I2 |
|---|---|---|---|---|---|---|
| Omitting Boran Tumer | 1.97 | [0.85; 4.57] | .12 | 0.2017 | 0.4491 | 14% |
| Omitting Jyrala | 2.32 | [0.73; 7.43] | .15 | 0.7743 | 0.8800 | 46% |
| Omitting Martínez-Comendador | 3.01 | [1.26; 7.16] | .01 | 0.3465 | 0.5886 | 30% |
| Omitting Thukral | 3.72 | [1.80; 7.71] | < .01 | < 0.0001 | 0.0006 | 0% |
| Omitting Young Eu | 2.27 | [0.80; 6.47] | .13 | 0.6232 | 0.7894 | 44% |
| Omitting Zhao | 2.53 | [0.99; 6.43] | .05 | 0.5001 | 0.7072 | 47% |
| **Random effects model** | **2.57** | **[1.10; 6.05]** | **.03** | **0.3909** | **0.6252** | **34%** |

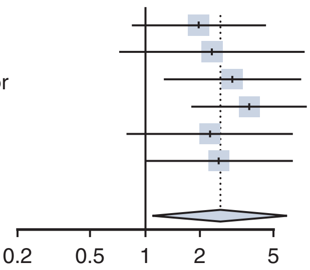



**FIGURE E1.** Leave-one-out analysis for the primary endpoint (operative mortality). *CI*, Confidence interval.

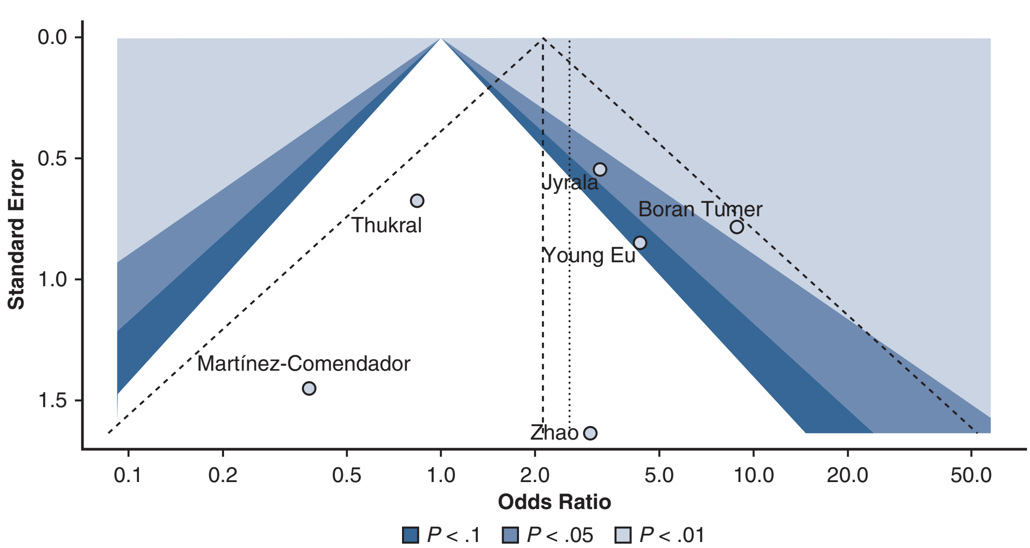
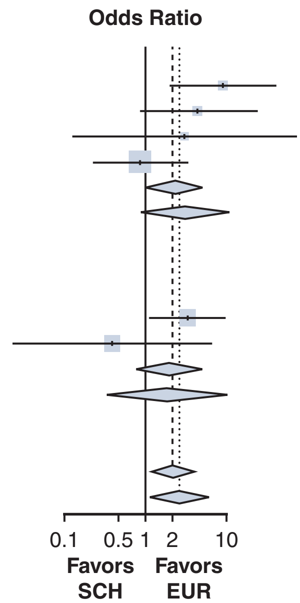



**FIGURE E2.** Funnel for the primary endpoint (operative mortality).

| Study | SCH Events | SCH Total | EUR Events | EUR Total | OR | 95%-CI | Weight (common) | Weight (random) |
|---|---|---|---|---|---|---|---|---|
| **isolated_cabg = 1** | | | | | | | | |
| Boran Tumer | 4 | 47 | 3 | 289 | 8.87 | [1.92; 40.99] | 6.4% | 19.0% |
| Young Eu | 2 | 62 | 5 | 655 | 4.33 | [0.82; 22.81] | 6.9% | 17.1% |
| Zhao | 1 | 544 | 0 | 544 | 3.01 | [0.12; 73.94] | 4.1% | 6.2% |
| Thukral | 3 | 122 | 9 | 309 | 0.84 | [0.22; 3.16] | 41.1% | 22.4% |
| **Common effect model** | | **775** | | **1797** | **2.28** | **[1.04; 5.01]** | **58.6%** | **––** |
| **Random effects model** | | | | | **3.00** | **[0.86; 10.41]** | **––** | **64.7%** |
| Heterogeneity: $I^2 = 47\%$, $\tau^2 = 0.7853$, $P = .13$ | | | | | | | | |
| **isolated_cabg = 0** | | | | | | | | |
| Jyrala | 5 | 41 | 15 | 365 | 3.24 | [1.11; 9.44] | 22.0% | 27.6% |
| Martínez-Comendador | 0 | 35 | 15 | 432 | 0.38 | [0.02; 6.47] | 19.4% | 7.6% |
| **Common effect model** | | **76** | | **797** | **1.90** | **[0.74; 4.89]** | **41.4%** | **––** |
| **Random effects model** | | | | | **1.80** | **[0.32; 10.26]** | **––** | **35.3%** |
| Heterogeneity: $I^2 = 48\%$, $\tau^2 = 0.7853$, $P = .17$ | | | | | | | | |
| **Common effect model** | | **851** | | **2594** | **2.12** | **[1.16; 3.88]** | **100.0%** | **––** |
| **Random effects model** | | | | | **2.57** | **[1.10; 6.05]** | **––** | **100.0%** |




Heterogeneity: $I^2 = 34\%$, $\tau^2 = 0.3909$, $P = .18$
Residual heterogeneity: $I^2 = 47\%$, $\tau^2 = 0.7853$, $P = .11$
Test for subgroup differences (common effect): $\chi^2_1 = 0.08$, df = 1 ($P = .77$)
Test for subgroup differences (random effects): $\chi^2_1 = 0.22$, df = 1 ($P = .64$)

**FIGURE E3.** Subgroup analysis addressing isolated coronary artery bypass grafting (CABG) cohorts. *SCH*, Subclinical hypothyroidism; *EUR*, euthyroid; *CI*, confidence interval.

| Study | SCH Total | SCH Mean | SCH SD | EUR Total | EUR Mean | EUR SD | SMD | 95%-CI | Weight (common) | Weight (random) |
|---|---|---|---|---|---|---|---|---|---|---|
| Boran Tumer | 47 | 2.6 | 1.5 | 289 | 2.1 | 1.1 | 0.37 | [0.06; 0.68] | 7.7% | 16.2% |
| Young Eu | 62 | 3.7 | 1.5 | 655 | 2.7 | 0.7 | 1.20 | [0.93; 1.47] | 10.3% | 16.7% |
| Zhao | 544 | 2.3 | 2.2 | 544 | 2.3 | 2.2 | 0.00 | [–0.12; 0.12] | 52.1% | 17.9% |
| Jyrala | 41 | 5.1 | 10.3 | 365 | 3.2 | 6.5 | 0.27 | [–0.05; 0.60] | 7.0% | 16.1% |
| Martínez-Comendador | 35 | 1.8 | 1.1 | 432 | 1.8 | 1.7 | –0.01 | [–0.35; 0.34] | 6.2% | 15.8% |
| Thukral | 122 | 3.1 | 3.3 | 309 | 3.1 | 5.3 | –0.01 | [–0.22; 0.20] | 16.7% | 17.3% |
| **Common effect model** | **851** | | | **2594** | | | **0.17** | **[0.08; 0.25]** | **100.0%** | **––** |
| **Random effects model** | | | | | | | **0.30** | **[–0.08; 0.68]** | **––** | **100.0%** |

Heterogeneity: $I^2 = 93\%$, $\tau^2 = 0.2029$, $P < .01$

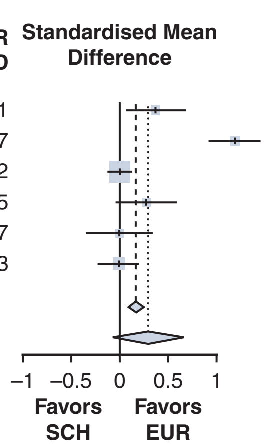



**FIGURE E4.** Forest plot for intensive care unit stay. *SCH*, Subclinical hypothyroidism; *EUR*, euthyroid; *CI*, confidence interval.

| Study | SCH Events | SCH Total | EUR Events | EUR Total | OR | 95%-CI | Weight (common) | Weight (random) |
|---|---|---|---|---|---|---|---|---|
| Zhao | 111 | 544 | 112 | 544 | 0.99 | [0.74; 1.33] | 81.8% | 36.7% |
| Jyrala | 3 | 41 | 50 | 365 | 0.50 | [0.15; 1.67] | 8.6% | 20.1% |
| Martínez-Comendador | 20 | 35 | 129 | 432 | 3.13 | [1.55; 6.31] | 7.6% | 29.6% |
| Thukral | 2 | 122 | 4 | 309 | 1.27 | [0.23; 7.03] | 2.0% | 13.6% |
| **Common effect model** | | **742** | | **1650** | **1.12** | **[0.86; 1.44]** | **100.0%** | **--** |
| **Random effects model** | | | | | **1.25** | **[0.57; 2.75]** | **--** | **100.0%** |

Heterogeneity: $I^2 = 72\%$, $\tau^2 = 0.4154$, $P = .01$

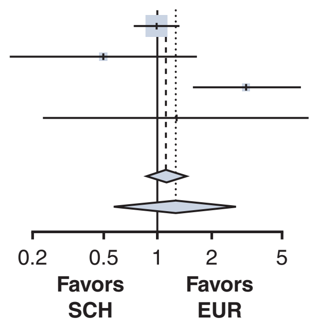



**FIGURE E5.** Forest plot for postoperative atrial fibrillation. *SCH*, Subclinical hypothyroidism; *EUR*, euthyroid; *CI*, confidence interval.

| Study | SCH Events | SCH Total | EUR Events | EUR Total | OR | 95%-CI | Weight (common) | Weight (random) |
|---|---|---|---|---|---|---|---|---|
| Boran Tumer | 5 | 47 | 8 | 289 | 4.18 | [1.31; 13.38] | 12.5% | 28.5% |
| Zhao | 3 | 544 | 3 | 544 | 1.00 | [0.20; 4.98] | 18.6% | 20.6% |
| Jyrala | 2 | 41 | 9 | 365 | 2.03 | [0.42; 9.73] | 10.8% | 21.2% |
| Thukral | 4 | 122 | 17 | 309 | 0.58 | [0.19; 1.77] | 58.1% | 29.7% |
| **Common effect model** | | **754** | | **1507** | **1.27** | **[0.67; 2.39]** | **100.0%** | **--** |
| **Random effects model** | | | | | **1.49** | **[0.57; 3.86]** | **--** | **100.0%** |

Heterogeneity: $I^2 = 51\%$, $\tau^2 = 0.4750$, $P = .10$

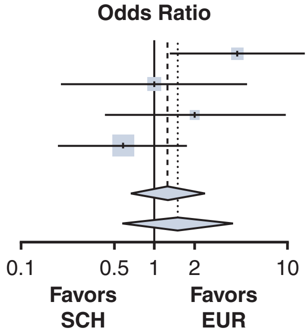



**FIGURE E6.** Forest plot for intra-aortic balloon pump use. *SCH*, Subclinical hypothyroidism; *EUR*, euthyroid; *CI*, confidence interval.

**TABLE E1. Search strategy for Ovid MEDLINE**

| Line number | Search | Number of results |
|---|---|---|
| DB | Ovid MEDLINE (all–1946 to present)<br>Searched on August 29, 2023<br>No language, article type, or publication date limits | |
| 1 | Hypothyroidism/ | 29,370 |
| 2 | (hypothyroidism* or hypothyreoidism* or hypothyreosis or hypothyroidea or hypothyroidosis or hypothyrosis or thyroid-stimulating hormone deficien* or TSH deficien* or thyroid dysfunction* or elevated TSH or high TSH or elevated thyroid-stimulating hormone or high thyroid-stimulating hormone or thyroid failure or SCH or SCHT).tw. | 48,952 |
| 3 | 1 or 2 | 59,019 |
| 4 | Sternotomy/or Sternum/su [Surgery] | 7302 |
| 5 | (sternotomy or sternotomies).tw. | 11,398 |
| 6 | Cardiac Surgical Procedures/or (cardiac surg*or heart surg* or heart valve surgery or cardiac operation* or heart operation* or cardiosurgery or myocardial resection or cardiothoracic surg* or cardiothoracic operation*).tw. | 67,496 |
| 7 | Mitral Valve Annuloplasty/ | 1933 |
| 8 | ((bicuspid cardiac valve or bicuspid cardiac valvular or bicuspid heart valve or bicuspid heart valvular or bicuspid or bicuspid valve or bicuspid valvular or left atrioventricular cardiac valve or left atrioventricular heart valve or left atrioventricular valvular or mitral cardiac valve or mitral cardiac valvular or mitral heart valve or mitral heart valvular or mitral or mitral valvular) adj2 (annuloplast* or repair or replacement)).tw. | 15,425 |
| 9 | Coronary Artery Bypass/or Coronary Artery Bypass, Off-Pump/ | 55,371 |
| 10 | (coronary adj2 (bypass* or graft* or surger*)).tw. | 57,397 |
| 11 | (CABG or aorticocoronary anastomosis or total arterial revasculari*ation* or multiple arterial revasculari*ation*).tw. | 20,936 |
| 12 | Heart Transplantation/or (heart transplantation* or heart transplant or heart grafting* or cardiac transplantation* or cardiac transplant).tw. | 48,563 |
| 13 | Cardiomyoplasty/or (cardiomyoplasty or cardiomyoplasties).tw. | 997 |
| 14 | Heart Valve Prosthesis Implantation/or (heart valve prosthesis implantation or heart valve prosthesis implant).tw. | 27,500 |
| 15 | Myocardial Revascularization/or (cardiac muscle revascularisation or cardiac muscle revascularization or coronary revascularisation or coronary revascularization or heart muscle revascularisation or heart myocardium revascularisation or heart revascularisation or heart revascularization or internal mammary arterial anastomosis or internal mammary arterial implantation or internal mammary artery anastomosis or internal mammary artery graft or internal mammary artery implant or internal mammary artery implantation or internal mammary-coronary artery anastomosis or Coronary Internal Mammary Artery Anastomosis or myocardial revascularisation or myocardial revascularization or myocardium revascularisation or myocardium revascularization or transmyocardial laser revascularisation or transmyocardial laser revascularization or vineberg operation).tw. | 22,462 |
| 16 | Cardiac Valve Annuloplasty/or (Cardiac Valve Annuloplasty or Cardiac Valve Annuloplasties or Valvular Annuloplasties or Valvular Annuloplasty or Heart Valve Annuloplasty or Heart Valve Annuloplasties or Cardiac Valve Annulus Repair or Heart Valve Annulus Repair or Cardiac Valve Annular Repair or Heart Valve Annular Repair or Cardiac Valve Annular Reduction or Cardiac Valve Annulus Shortening or Cardiac Valve Annulus Reduction).tw. | 1001 |
| 17 | (Aortic Valve Repair or Aortic Valve Replacement or aorta valve replacement or aorta valve transplantation or aortic valve transplantation or aortic valve xenotransplantation or aorta surg* or aortic surg* or aortic dissection or aorta dissection).tw. | 42,868 |
| 18 | (tricuspid valve repair or tricuspid valve replacement or tricuspid valve transplantation).tw. | 2093 |
| 19 | Heart-Assist Devices/or (heart assist device* or heart assist pump* or vascular assist device* or artificial ventricle* or ventricle assist device* or artificial heart ventricle*).tw. | 18,098 |
| 20 | Transmyocardial Laser Revascularization/or (transmyocardial laser revascularization or trans-myocardial laser revascularization or transmyocardial laser revascularisation or trans-myocardial laser revascularisation).tw. | 500 |
| 21 | or/4-20 | 282,651 |
| 22 | 3 and 21 | 219 |
| DB | Ovid Embase (1974 to present)<br>Searched on August 29, 2023<br>No language, article type, or publication date limits | |
| 1 | Hypothyroidism/or subclinical hypothyroidism/ | 77,999 |
| 2 | (hypothyroidism* or hypothyreoidism* or hypothyreosis or hypothyroidea or hypothyroidosis or hypothyrosis or thyroid-stimulating hormone deficien* or TSH deficien* or thyroid dysfunction* or elevated TSH or high TSH or elevated thyroid-stimulating hormone or high thyroid-stimulating hormone or thyroid failure or SCH or SCHT).tw. | 78,845 |
| 3 | 1 or 2 | 112,374 |

*(Continued)*

**TABLE E1. Continued**

| Line number | Search | Number of results |
|---|---|---|
| 4 | Sternotomy/or sternum/su [Surgery] | 25,788 |
| 5 | (sternotomy or sternotomies).tw. | 16,711 |
| 6 | Heart surgery/or (cardiac surg*or heart surg* or heart valve surgery or cardiac operation* or heart operation* or cardiosurgery or myocardial resection or cardiothoracic surg* or cardiothoracic operation*).tw. | 107,274 |
| 7 | Mitral annuloplasty/ | 2758 |
| 8 | ((bicuspid cardiac valve or bicuspid cardiac valvular or bicuspid heart valve or bicuspid heart valvular or bicuspid or bicuspid valve or bicuspid valvular or left atrioventricular cardiac valve or left atrioventricular heart valve or left atrioventricular valvular or mitral cardiac valve or mitral cardiac valvular or mitral heart valve or mitral heart valvular or mitral or mitral valvular) adj2 (annuloplast* or repair or replacement)).tw. | 21,768 |
| 9 | Coronary artery bypass graft/ | 87,238 |
| 10 | (coronary adj2 (bypass* or graft* or surger*)).tw. | 77,290 |
| 11 | (CABG or aorticocoronary anastomosis or total arterial revasculari*ation* or multiple arterial revasculari*ation*).tw. | 38,388 |
| 12 | Heart transplantation/or (heart transplantation* or heart transplant or heart grafting* or cardiac transplantation* or cardiac transplant).tw. | 78,717 |
| 13 | Cardiomyoplasty/or (cardiomyoplasty or cardiomyoplasties).tw. | 1358 |
| 14 | Heart valve replacement/or (heart valve prosthesis implantation or heart valve prosthesis implant).tw. | 15,730 |
| 15 | Heart muscle revascularization/or (cardiac muscle revascularisation or cardiac muscle revascularization or coronary revascularisation or coronary revascularization or heart muscle revascularisation or heart myocardium revascularisation or heart revascularisation or heart revascularization or internal mammary arterial anastomosis or internal mammary arterial implantation or internal mammary artery anastomosis or internal mammary artery graft or internal mammary artery implant or internal mammary artery implantation or internal mammary-coronary artery anastomosis or Coronary Internal Mammary Artery Anastomosis or myocardial revascularisation or myocardial revascularization or myocardium revascularisation or myocardium revascularization or transmyocardial laser revascularisation or transmyocardial laser revascularization or vineberg operation).tw. | 44,698 |
| 16 | Annuloplasty/or (Cardiac Valve Annuloplasty or Cardiac Valve Annuloplasties or Valvular Annuloplasties or Valvular Annuloplasty or Heart Valve Annuloplasty or Heart Valve Annuloplasties or Cardiac Valve Annulus Repair or Heart Valve Annulus Repair or Cardiac Valve Annular Repair or Heart Valve Annular Repair or Cardiac Valve Annular Reduction or Cardiac Valve Annulus Shortening or Cardiac Valve Annulus Reduction).tw. | 3519 |
| 17 | (Aortic Valve Repair or Aortic Valve Replacement or aorta valve replacement or aorta valve transplantation or aortic valve transplantation or aortic valve xenotransplantation).tw. | 35,419 |
| 18 | (tricuspid valve repair or tricuspid valve replacement or tricuspid valve transplantation).tw. | 3136 |
| 19 | Heart assist device/or (heart assist device* or heart assist pump* or vascular assist device* or artificial ventricle* or ventricle assist device* or artificial heart ventricle*).tw. | 8619 |
| 20 | Heart muscle revascularization/or (transmyocardial laser revascularization or trans-myocardial laser revascularization or transmyocardial laser revascularisation or trans-myocardial laser revascularisation).tw. | 38,081 |
| 21 | or/4-20 | 397,962 |
| 22 | 3 and 21 | 1040 |
| DB | Cochrane Library (Wiley)<br>Searched on August 29, 2023<br>No language, article type, or publication date limits | |
| 1 | (hypothyroidism* or hypothyreoidism* or hypothyreosis or hypothyroidea or hypothyroidosis or hypothyrosis or thyroid-stimulating hormone deficien* or TSH deficien* or thyroid dysfunction* or elevated TSH or high TSH or elevated thyroid-stimulating hormone or high thyroid-stimulating hormone or thyroid failure or SCH or SCHT):ti,ab | 5443 |
| 2 | (sternotomy or sternotomies):ti,ab | 1268 |
| 3 | (cardiac surg*or heart surg* or heart valve surgery or cardiac operation* or heart operation* or cardiosurgery or myocardial resection or cardiothoracic surg* or cardiothoracic operation*):ti,ab | 9334 |
| 4 | ((bicuspid cardiac valve or bicuspid cardiac valvular or bicuspid heart valve or bicuspid heart valvular or bicuspid or bicuspid valve or bicuspid valvular or left atrioventricular cardiac valve or left atrioventricular heart valve or left atrioventricular valvular or mitral cardiac valve or mitral cardiac valvular or mitral heart valve or mitral heart valvular or mitral or mitral valvular) NEAR/2 (annuloplast* or repair or replacement)):ti,ab | 3512 |

*(Continued)*

**TABLE E1. Continued**

| Line number | Search | Number of results |
|---|---|---|
| 5 | (coronary NEAR/2 (bypass* or graft* or surger*)):ti,ab | 11,906 |
| 6 | (CABG or aorticocoronary anastomosis or total arterial revascularization* or multiple arterial revascularization*):ti,ab | 6690 |
| 7 | (heart transplantation* or heart transplant or heart grafting* or cardiac transplantation* or cardiac transplant or cardiomyoplasty or cardiomyoplasties or heart valve prosthesis implantation or heart valve prosthesis implant):ti,ab | 5773 |
| 8 | (cardiac muscle revascularisation or cardiac muscle revascularization or coronary revascularisation or coronary revascularization or heart muscle revascularisation or heart myocardium revascularisation or heart revascularisation or heart revascularization or internal mammary arterial anastomosis or internal mammary arterial implantation or internal mammary artery anastomosis or internal mammary artery graft or internal mammary artery implant or internal mammary artery implantation or internal mammary-coronary artery anastomosis or Coronary Internal Mammary Artery Anastomosis or myocardial revascularisation or myocardial revascularization or myocardium revascularisation or myocardium revascularization or transmyocardial laser revascularisation or transmyocardial laser revascularization or vineberg operation):ti,ab | 11,005 |
| 9 | (Cardiac Valve Annuloplasty or Cardiac Valve Annuloplasties or Valvular Annuloplasties or Valvular Annuloplasty or Heart Valve Annuloplasty or Heart Valve Annuloplasties or Cardiac Valve Annulus Repair or Heart Valve Annulus Repair or Cardiac Valve Annular Repair or Heart Valve Annular Repair or Cardiac Valve Annular Reduction or Cardiac Valve Annulus Shortening or Cardiac Valve Annulus Reduction or Aortic Valve Repair or Aortic Valve Replacement or aorta valve replacement or aorta valve transplantation or aortic valve transplantation or aortic valve xenotransplantation):ti,ab | 2116 |
| 10 | (tricuspid valve repair or tricuspid valve replacement or tricuspid valve transplantation or heart assist device* or heart assist pump* or vascular assist device* or artificial ventricle* or ventricle assist device* or artificial heart ventricle* or transmyocardial laser revascularization or trans-myocardial laser revascularization or transmyocardial laser revascularisation or trans-myocardial laser revascularisation):ti,ab | 931 |
| 11 | #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 | 36,205 |
| 12 | #1 AND #11 | 128 |

*DB*, Database.

**TABLE E2. Newcastle–Ottawa risk of bias assessment scale**

| Study | Selection | Comparability | Outcome/ Exposure |
|---|---|---|---|
| Boran Tumer et al, 2020[23] | **** | ** | ** |
| Kim et al, 2020[24] | **** | ** | *** |
| Joe et al, 2022[19] | **** | ** | *** |
| Zhao et al, 2023[17] | **** | ** | *** |
| Jyrala et al, 2012[25] | *** | ** | *** |
| Martínez-Comendador et al, 2016[18] | **** | ** | *** |
| Thukral et al, 2022[26] | **** | ** | ** |

**TABLE E3. Demographics of included patients from the selected studies**

| Study | Age, y, mean ± SD | | Female sex, % | | BMI, mean ± SD | | Smoking, % | | Hypertension, % | | DM, % | | TSH level, % | | Prior CVA, % | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | EUR | SCH | EUR | SCH | EUR | SCH | EUR | SCH | EUR | SCH | EUR | SCH | EUR | SCH | EUR | SCH |
| Boran Tumer et al[23] | 60.9 ± 10.1 | 64.9 ± 12.1 | 21.8 | 44.7 | 30.1 | 51.1 | NR | NR | 63.7 | 61.7 | 33.2 | 46.8 | 1.7 ± 1.0 | 5.1 ± 1.2 | NR | NR |
| Kim et al – CABG[24] | 65.8 ± 9.8 | 66.4 ± 10.4 | 27.1 | 37.9 | 24.7 ± 3.0 | 24.7 ± 3.0 | 24.6 | 19.7 | 74.2 | 80.3 | 51.9 | 57.6 | 1.9 ± 0.9 | 5.7 ± 2.3 | 18.8 | 21.2 |
| Kim et al – valve[24] | 60.7 ± 12.3 | 60.7 ± 12.8 | 50.6 | 76.5 | 23.9 ± 3.6 | 24.1 ± 3.2 | 46.0 | 17.6 | 33.3 | 17.6 | 10.3 | 11.8 | 2.1 ± 0.9 | 5.3 ± 1.0 | 16.1 | 5.9 |
| Joe et al[19] | 65.4 ± 9.4 | 67.4 ± 8.3 | 20.9 | 21.0 | 24.6 ± 3.0 | 24.2 ± 2.3 | NR | NR | 70.5 | 74.2 | 53.0 | 58.1 | 1.6 ± 1.0 | 6.0 ± 2.0 | 13.4 | 17.7 |
| Zhao et al[17] | 64.3 ± 8.2 | 64.7 ± 8.2 | 37.1 | 36.6 | 25.7 ± 3.0 | 25.8 ± 3.0 | 40.8 | 41.4 | 68.6 | 69.3 | 35.7 | 35.8 | 1.9 ± 1.0 | 6.4 ± 1.9 | 18.9 | 17.3 |
| Jyrala et al[25] | 67.5 ± 11.0 | 66.8 ± 13.1 | 36.7 | 53.7 | 27.3 ± 5.6 | 28.0 ± 6.5 | NR | NR | NR | NR | 40.3 | 48.8 | NR | NR | 7.4 | 2.4 |
| Martínez-Comendador et al[18] | 70.5 ± 11.1 | 71.5 ± 10.2 | 41.7 | 28.6 | 27.8 ± 4.3 | 27.2 ± 3.8 | 41.9 | 51.4 | 63.4 | 51.4 | 22.5 | 22.9 | 1.8 ± 0.9 | 5.0 ± 1 .4 | 6.7 | 11.4 |
| Thukral et al[26] | 59.28 ± 9.5 | 58.27 ± 9.9 | 15.9 | 23.8 | 24.7 ± 4.4 | 25.2 ± 4.2 | 2.9 | 1.6 | NR | NR | 43.0 | 36.9 | 2.3 ± 0.9 | 5.8 ± 1.7 | NR | NR |

*BMI*, Body mass index; *DM*, diabetes; *TSH*, thyroid-stimulating hormone; *CVA*, cerebrovascular accident; *EUR*, euthyroid; *SCH*, subclinical hypothyroidism; *NR*, not reported.

**TABLE E4. Meta regression for the primary endpoint of operative mortality**

| Variable | Beta ± SE | *P* value |
|---|---|---|
| Age, mean | −0.0138 ± 0.1360 | .91 |
| Female sex, % | −0.0825 ± 0.0397 | .04 |
| BMI, mean | −0.0465 ± 0.4014 | .90 |
| Smoking, % | 0.0022 ± 0.0324 | .94 |
| Hypertension, % | −0.0660 ± 0.1513 | .66 |
| Diabetes, % | 0.0411 ± 0.0600 | .49 |
| COPD, % | 0.0251 ± 0.1176 | .83 |
| TSH level, mean | −0.4722 ± 0.8022 | .55 |
| Prior CVA, % | 0.0496 ± 0.1127 | .66 |

*BMI*, Body mass index; *COPD*, chronic obstructive pulmonary disease; *TSH*, thyroid-stimulating hormone; *CVA*, cerebrovascular accident.