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# Subclinical thyroid dysfunction and incident diabetes: a systematic review and an individual participant data analysis of prospective cohort studies

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## Abstract

*Objective:* Few prospective studies have assessed whether individuals with subclinical thyroid dysfunction are more likely to develop diabetes, with conflicting results. In this study, we conducted a systematic review of the literature and an individual participant data analysis of multiple prospective cohorts to investigate the association between subclinical thyroid dysfunction and incident diabetes.

*Methods:* We performed a systematic review of the literature in Medline, Embase, and the Cochrane Library from inception to February 11, 2022. A two-stage individual participant data analysis was conducted to compare participants with subclinical hypothyroidism and subclinical hyperthyroidism vs euthyroidism at baseline and the adjusted risk of developing diabetes at follow-up.

*Results:* Among 61 178 adults from 18 studies, 49% were females, mean age was 58 years, and mean follow-up time was 8.2 years. At the last available follow-up, there was no association between subclinical hypothyroidism and incidence of diabetes (odds ratio (OR) = 1.02, 95% CI: 0.88–1.17, $I^2$ = 0%) or subclinical hyperthyroidism and incidence of diabetes

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(OR = 1.03, 95% CI: 0.82–1.30, $I^2$ = 0%), in age- and sex-adjusted analyses. Time-to-event analysis showed similar results (hazard ratio for subclinical hypothyroidism: 0.98, 95% CI: 0.87–1.11; hazard ratio for subclinical hyperthyroidism: 1.07, 95% CI: 0.88–1.29). The results were robust in all sub-group and sensitivity analyses.

*Conclusions:* This is the largest systematic review and individual participant data analysis to date investigating the prospective association between subclinical thyroid dysfunction and diabetes. We did not find an association between subclinical thyroid dysfunction and incident diabetes. Our results do not support screening patients with subclinical thyroid dysfunction for diabetes.

*Significance statement:* Evidence is conflicting regarding whether an association exists between subclinical thyroid dysfunction and incident diabetes. We therefore aimed to investigate whether individuals with subclinical thyroid dysfunction are more prone to develop diabetes in the long run as compared to euthyroid individuals. We included data from 18 international cohort studies with 61 178 adults and a mean follow-up time of 8.2 years. We did not find an association between subclinical hypothyroidism or subclinical hyperthyroidism at baseline and incident diabetes at follow-up. Our results have clinical implications as they neither support screening patients with subclinical thyroid dysfunction for diabetes nor treating them in the hope of preventing diabetes in the future.

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## Introduction

Thyroid dysfunction and diabetes are two of the most common endocrine diseases and studies have suggested that these two disorders tend to co-exist more frequently than expected by chance (1). Subclinical hypothyroidism (Shypo) is defined as an elevated serum thyroid-stimulating hormone (TSH) with serum free thyroxine (fT4) concentrations within the reference range (2). Shypo is a common disorder that affects up to 10% of the adult population (2) and has been associated with an increased risk of cardiovascular disease events and mortality (3). On the other hand, subclinical hyperthyroidism (Shyper) is diagnosed when serum TSH is low with fT4 and free triiodothyronine (fT3) concentrations within the reference range (2) and has also been associated with adverse events (4).

Results from cross-sectional studies on the association between diabetes and thyroid disease have been conflicting. A large cross-sectional study conducted in Norway among more than 30 000 individuals did not reveal an association between hypothyroidism and type 2 diabetes (5). Conversely, other cross-sectional studies have found an association between raised serum TSH levels and insulin resistance (6, 7). However, cross-sectional studies have several limitations including potential confounding by reverse causation. Moreover, it has been suggested that diabetes and thyroid disease have a bidirectional relationship (8, 9). Only a few longitudinal studies have investigated the association between thyroid dysfunction and incident diabetes with, again, conflicting results, and most studies only included individuals with overt thyroid disease. One prospective study conducted in the Netherlands found that higher TSH levels were associated with a higher risk of developing diabetes, particularly among individuals with pre-diabetes (10). Two other longitudinal studies did not find an association between Shypo and incidence of metabolic syndrome (11, 12). A recent meta-analysis of prospective studies found that there was no association between thyroid function and risk of type 2 diabetes when TSH was analyzed as a continuous variable (13). This study, however, did not specifically analyze subclinical thyroid dysfunction (SCTD) as a predictor of diabetes.

The conflicting results from the literature may be explained by a lack of power among studies, as well as differences in definitions of exposure and outcome and statistical methods. Individual participant data (IPD) analysis allows researchers to standardize definitions and methods across studies, as well as conduct sub-group analyses while also increasing statistical power (14). Therefore, we conducted a systematic review of the literature and an IPD analysis to explore whether individuals with SCTD are more prone to develop diabetes as compared to euthyroid individuals using data from prospective international cohort studies.

## Methods

This systematic review and IPD analysis were registered in the international Prospective Register of Systematic

Reviews PROSPERO (CRD 42021259695). We adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement for IPD systematic reviews (15).

## Search strategy and selection criteria

We performed a systematic literature search in Ovid Medline, Ovid Embase, and Cochrane Library from inception to February 11, 2022. We included publications from prospective studies that had data on baseline TSH in adults and that assessed incidence of diabetes during follow-up. The search strategy combined terms related to exposure (e.g. thyroid diseases, hyperthyroidism, hypothyroidism, thyroid hormones, triiodothyronine, thyroxine, thyrotropin, subclinical, mild) and outcome (e.g. diabetes, metabolic syndrome, insulin resistance, pre-diabetes). Details of the search strategy are presented in the Supplementary Appendix (see section on supplementary materials given at the end of this article). We excluded: (i) studies that only included participants with normal thyroid function at baseline, (ii) studies that only included participants with overt thyroid dysfunction at baseline, (iii) studies without a euthyroid control group, (iv) studies that only included participants who took thyroid-altering medications, and (v) studies that included only participants less than 18 years old or pregnant women. We only included studies published in English. Two authors (H.A. and F.V.) screened all references for eligibility and discrepancies were resolved by consensus with a third author (C.D.G.). Additional unpublished data were also identified from the Thyroid Studies Collaboration (TSC), a consortium of cohort studies that study the association between SCTD and various clinical outcomes (3).

## Data extraction and quality assessment

Studies that met the inclusion criteria were invited to collaborate in the present IPD analysis by sharing their data. We requested data on thyroid function at baseline (TSH, fT4, and when available, fT3), demographics, anthropometrics, medication use (levothyroxine, anti-thyroid medication, thyroid-altering medication, anti-diabetic medication), cardiovascular risk factors, and biochemical data to define diabetes. Thyroid medication was defined as levothyroxine or anti-thyroid medication use, and thyroid-altering medication was defined as levothyroxine, anti-thyroid medication, lithium, or amiodarone use. Each study was approved by its local ethics committee (Supplementary Table 1). The Newcastle–Ottawa Scale (NOS) was used to assess the quality of the included studies (16). The NOS contains eight items divided into three categories: selection, comparability, and outcome. Studies are given a score ranging from 0 to 9 stars with the highest score indicating the best methodological quality. Studies were classified into good, fair, and poor quality according to their star rating. The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool was also used to assess the certainty of the evidence (www.grade workinggroup.org) (17). To assess the study limitations (risk of bias) domain in the GRADE, we used the final NOS score. For example, if a study had a good NOS score, the study limitations domain in the GRADE would be considered as 'not serious'. Publication bias was explored with funnel plots and Egger's test.

## Exposures

The exposures in this study were Shypo and Shyper as compared to euthyroidism. As previously done in IPD analyses from the TSC (3, 18), we used uniform TSH cut-off levels and study-specific fT4 cut-off values to define thyroid status as fT4 assays show greater inter-method variation than third-generation TSH assays. Euthyroidism was defined as TSH from 0.45 to 4.49 mIU/L, subclinical hyperthyroidism as TSH < 0.45 mlU/L with fT4 in the reference range, and subclinical hypothyroidism as TSH ≥ 4.5 mlU/L with fT4 in the reference range. Participants with fT4 values out of the reference range were excluded from the analyses. Participants with missing fT4 values but with TSH levels below 0.45 mIU/L were considered to have subclinical rather than overt hyperthyroidism and participants who had missing fT4 values but TSH levels between 4.5 mIU/L and 19.9 mIU/L were considered to have subclinical rather than overt hypothyroidism. This strategy was adopted as individuals with TSH in these ranges are most likely to have subclinical rather than overt thyroid dysfunction (19, 20). We also used study-defined cut-offs to define the positivity of thyroid peroxidase antibodies (TPOAb).

## Outcomes

Our primary outcome was incident diabetes at the last available follow-up. Diabetes was defined according to the American Diabetic Association criteria as either: (i) fasting plasma glucose ≥ 7 mmol/L, (ii) 2-h glucose ≥ 11.1 mmol/L after an oral glucose tolerance test (OGTT), (iii) glycated hemoglobin (HbA1c) ≥ 6.5% (48 mmol/mol) (21) or use of blood glucose-lowering medication. Self-reported diabetes cases without ascertainment by biochemical data or medication use were not included in the primary analysis.

Although data on the type of diabetes (1 vs 2) were not available, we considered that most incident diabetes cases were type 2 diabetes. In the analysis of incident diabetes, we excluded participants with diabetes at baseline. We also excluded participants with missing data on thyroid status at baseline and diabetes status at baseline and follow-up. Secondary outcomes included incident diabetes at first available follow-up; incidence of pre-diabetes at first and last available follow-ups and time to diabetes. Pre-diabetes was defined according to the American Diabetic Association criteria as either: (i) fasting plasma glucose ≥ 5.6 mmol/L, (ii) 2-h glucose ≥ 7.8 mmol/L after an OGTT or a (iii) HbA1c ≥ 5.7% (39 mmol/mol) without meeting criteria for diabetes (21). Time to event of newly developed diabetes was measured from baseline TSH measurement to the date of the study visit when diabetes was ascertained (using biochemical data or self-report of anti-diabetic medication use), or, if available, date of diagnosis of diabetes.

### Statistical analysis

We conducted a two-stage IPD analysis. In the first stage, the effect size for each cohort was estimated, and in the second stage, they were pooled together using a random effects model. For the primary outcome, we assessed the association between Shypo and Shyper and incident diabetes at last available follow-up by calculating the odds ratio (OR) using a logistic regression model adjusted for age and sex. In line with previous studies investigating the association between thyroid function and diabetes (10, 22), we ran a multivariable model adjusting further for smoking, blood pressure, total cholesterol, BMI, and baseline fasting blood glucose as a secondary analysis. For the time-to-event outcome, we used a Cox-proportional hazards model and results were presented as hazard ratios (HR) as compared to the reference category (euthyroid individuals). Finally, for one cohort, where IPD was not available (22), aggregate data were added in the second stage of the IPD analysis to assess the association between Shypo and incident diabetes (data were not available for Shyper).

We also conducted pre-defined sub-group analyses on the primary outcome to identify possible sources of heterogeneity. We performed sub-group analyses by age (younger and older than 65 years), by sex, and by TSH levels (for Shypo: 4.50–6.99 mIU/L, 7.00–9.99 mIU/L, 10.0–19.9 mIU/L and for Shyper: 0.1–0.45 mIU/L, <0.1 mIU/L). We also stratified participants by TPOAb (positive vs negative). The latter sub-group analysis was not described in the PROSPERO protocol.

The following sensitivity analyses were performed: excluding participants with thyroid-altering drugs or thyroid hormone replacement at baseline; requiring fT3 (available in 6 cohorts) as well as fT4 to be within range to define Shyper; and limiting analyses to high-quality studies (i.e. studies that were classified as good quality using the NOS). The following sensitivity analyses were not originally described in the PROSPERO protocol but were subsequently added: limiting analyses to participants who have persistent Shypo and Shyper at follow-up, limiting analyses to studies with less than 20% missing data at follow-up, and for studies where additional data were available on diabetes status (i.e. self-reported diabetes or diabetes ascertainment using medical records), the definition of diabetes was extended to include this information as a sensitivity analysis.

We estimated heterogeneity using $I^2$ and the Q test. A *P*-value <0.05 was considered statistically significant. Stata 16.0 (StataCorp LP) was used to conduct all analyses.

## Results

Of the 2334 studies identified through the literature search, 4 studies met our inclusion criteria (10, 11, 12, 22) (Supplementary Fig. 1). We further identified 15 additional studies from other sources including from within the TSC (6, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36). We then invited the principal investigators of the identified studies ($n = 19$) to be included in the present IPD analysis. All but one study (22) which were identified through the literature search and from within the TSC accepted to participate. We received IPD from 18 studies from Europe, North America, Australia, and Asia. Study characteristics and baseline data of the 18 studies included in the IPD analysis are displayed in Table 1. After excluding individuals with confirmed diabetes at baseline, missing thyroid function or diabetes data at baseline, and individuals with overt hypothyroidism or hyperthyroidism at baseline, 61 178 participants were included in the analyses. Mean age was 58 years (range: 18–105) and 49% were women. Mean BMI was 26 kg/m$^2$ (range: 13–59). At baseline, 90% of participants were euthyroid, 7% of participants had Shypo, and 3% of participants had Shyper. Out of 39 742 individuals with available data at the last available follow-up (mean duration of 8.2 years), 2910 individuals (7.3%) developed diabetes. As none of the participants in the Shypo and Shyper groups developed diabetes in the Bari study, we were unable to include data from this study for further analyses.

**Table 1** Study characteristics at baseline measurement of thyroid function.

| Study, place | Participants, *n* | Age, mean (range), years | Women, *n* (%) | BMI, mean (range), kg/m² | Thyroid medication†, *n* (%) | Median TSH, mIU/L | Normal range FT4, pmol/L | Positive TPOAb, *n* (%) | Last available follow-up mean ± s.d., years |
|---|---|---|---|---|---|---|---|---|---|
| PROSPER Study, the Netherlands | 4774 | 75 (69–83) | 2316 (49) | 27 (15–50) | 159 (3) | 1.9 | 12–18 | N.A. | 3.2 ± 0.7 |
| ELSA-Brasil, Brazil | 10 839 | 51 (35–74) | 6004 (55) | 27 (15–58) | 675 (6) | 2.0 | 12–22 | 1198 (11) | 3.8 ± 0.4 |
| BARI Study, Italy | 170 | 61 (26–87) | 37 (22) | 28 (17–48) | 24 (14) | 2.2 | 9–23.2 | N.A. | 1.0 ± 0 |
| Leiden-85+ Study, the Netherlands | 232 | 85 (85–85) | 70 (30) | 27 (15–40) | 11 (5) | 1.6 | 13–23 | N.A. | 5.0 ± 0 |
| KLoSHA Study, South Korea | 560 | 77 (65–105) | 309 (55) | 23 (15–33) | 5 (0.9) | 2.6 | 11–23 | 31 (5) | 5.0 ± 0 |
| Rotterdam Study, the Netherlands | 8251 | 64 (45–101) | 4735 (57) | 27 (13–54) | 239 (3) | 1.9 | 11–25 | 1054 (13) | 8.3 ± 2.6 |
| Pizarra Study, Spain | 853 | 39 (18–66) | 525 (62) | 27 (16–47) | 3 (0.4) | 1.8 | 11–22 | 33 (4) | 6.7 ± 1.5 |
| MrOS, United States | 1237 | 74 (65–99) | 0 (0) | 27 (17–45) | 91 (8) | 2.0 | 9–24 | N.A. | 6.9 ± 0.4 |
| Di@bet.es Study, Spain | 3827 | 49 (18–93) | 2246 (59) | 28 (14–61) | 152 (4) | 2.1 | 11–22 | 320 (8) | 7.6 ± 0.5 |
| PREVEND Study, the Netherlands | 5692 | 52 (32–80) | 2864 (50) | 26 (17–58) | 123 (3) | 1.6 | 12–22 | 569 (10) | 7.7 ± 0.8 |
| HIMS, Australia | 740 | 75 (70–87) | 0 (0) | 26 (15–40) | 18 (2) | 2.0 | 10–23 | N.A. | 8.7 ± 0.9 |
| InChianti Study, Italy | 1044 | 68 (21–102) | 590 (57) | 27 (18–43) | 18 (2) | 1.4 | 10–27 | N.A. | 9.0 ± 0.2 |
| Health ABC Study, United States | 2178 | 75 (69–81) | 1138 (52) | 27 (15–51) | 218 (10) | 2.1 | 10–23 | N.A. | 9.2 ± 0.1 |
| EPIC-Norfolk Study, United Kingdom | 8386 | 58 (40–78) | 4596 (55) | 26 (15–59) | 5 (0.1) | 1.7 | 9–20 | N.A. | 9.2 ± 0.9 |
| Tehran Thyroid Study, Iran | 4586 | 39 (20–86) | 1895 (41) | 26 (15–52) | 81 (2) | 1.6 | 12–20 | 527 (11) | 9.8 ± 0.9 |
| CHS, United States | 3194 | 75 (64–98) | 1921 (60) | 26 (14–59) | 250 (8) | 2.2 | 9–22 | 413 (13) | 6.0 ± 0 |
| Busselton Health Study, Australia | 1966 | 49 (18–90) | 961 (49) | 25 (16–45) | 15 (0.8) | 1.5 | 9–23 | 223 (11) | 13 ± 0 |
| Whickham Survey, England | 2649 | 47 (18–93) | 1391 (53) | 25 (15–45) | 101 (4) | 2.1 | 3.6–13.6* | 179 (7)** | 21.9 ± 9.9 |
| Total | 61 178 | 58 (18–105) | 29 870 (49) | 26 (13–59) | 2188 (3) | 1.8 | N.A. | 4547 (10.7) | 8.2 ± 3.5 |

*Total T4 (μg/dL); **Antimicrosomal antibodies were used for the Whickham Survey as data on thyroid peroxidase antibodies were not available; †Thyroid medication was defined as levothyroxine or anti-thyroid medication use.

CHS, Cardiovascular Health Study; ELSA-Brasil, Brazilian Longitudinal Study of Adult Health; EPIC-Norfolk Study, European Prospective Investigation into Cancer – Norfolk Study; Health ABC Study, The Health, Aging, and Body Composition Study; HIMS, Health in Men Study; InChianti, Invecchiare in Chianti Study; KLoSHA, Korean Longitudinal Study on Health and Aging Study; Leiden 85+ Study, Leiden 85-plus Study; MrOS, Osteoporotic Fractures in Men Study; PREVEND, Prevention of Renal and Vascular End-stage Disease Study; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk Study; TPOAb, thyroid peroxidase antibodies.

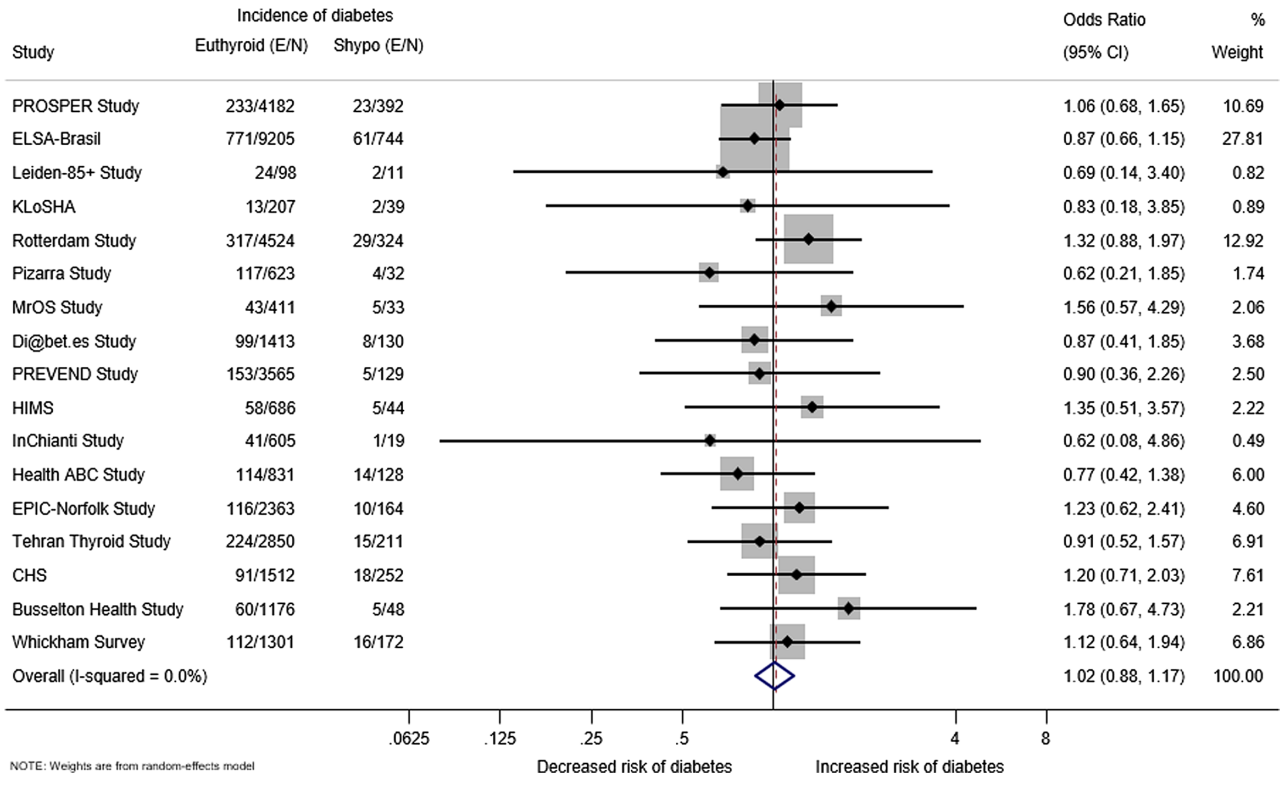


**Figure 1**

Age- and sex-adjusted logistic regression analysis of individual participant data of the association between subclinical hypothyroidism and incident diabetes at the last available follow-up.

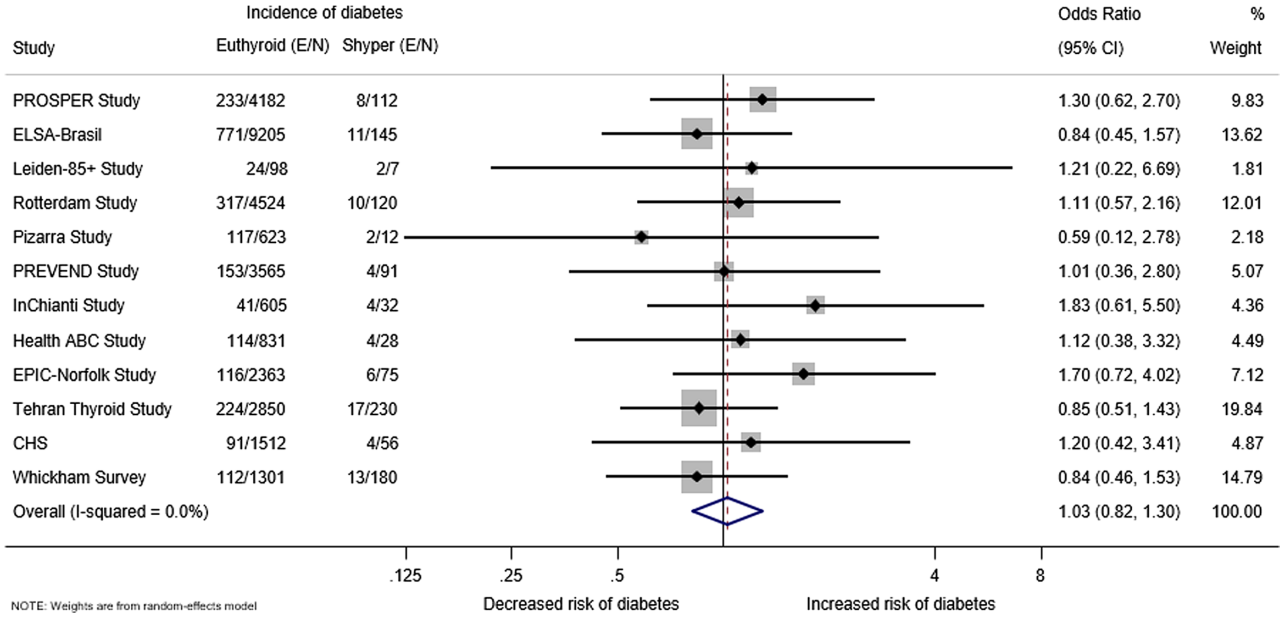


**Figure 2**

Age- and sex- adjusted logistic regression analysis of individual participant data of the association between subclinical hyperthyroidism and incident diabetes at the last available follow-up.

## Subclinical hypothyroidism

IPD age- and sex-adjusted analysis for the association between Shypo at baseline and incident diabetes at last available follow-up among 17 cohorts ($n = 36424$) is shown in Fig. 1. We found no association between Shypo at baseline and incident diabetes (OR = 1.02; 95% CI: 0.88–1.17). The $I^2$ statistic was 0%, indicating low heterogeneity among studies.

The associations between Shypo and various secondary outcomes are displayed in Table 2. There was no association between Shypo and incidence of pre-diabetes at last available follow-up (OR = 0.94; 95% CI: 0.84–1.05). Similarly, no association was found between Shypo and diabetes or pre-diabetes at first available follow-up (OR = 1.02; 95% CI: 0.88–1.17 for diabetes and OR = 0.96; 95%I CI: 0.85–1.09 for pre-diabetes). In the Cox regression model, the HR for developing diabetes was 0.98 (95% CI: 0.87–1.11). Multivariable analysis adjusted for age, sex, systolic and diastolic blood pressure, fasting blood glucose (or if not available, HbA1c or OGTT), smoking, total cholesterol, and BMI showed similar results to age-and sex-adjusted analyses for the association between Shypo and diabetes incidence at last available follow-up (OR = 0.97; 95% CI: 0.82–1.13). Including aggregate data from 54 333 euthyroid or Shypo participants of the study by Gronich *et al*. (22) (total $n = 90\,757$) did not change the results.

Sensitivity analyses for Shypo are shown in Table 3. When participants taking thyroid medication or who had missing thyroid medication data were excluded from the analyses ($n = 23\,992$ after exclusion), the results did not change. In addition, excluding participants who were taking thyroid-altering medication or who had missing thyroid-altering medication data ($n = 16\,971$ after exclusion) revealed similar results. When analyses were limited to participants who had repeat thyroid function testing to confirm the persistence of Shypo at follow-up ($n = 17\,441$), no significant association was found between Shypo and incident diabetes. Moreover, results from a sensitivity analysis where additional data when available (from medical records or self-reported diabetes status) were used to define incident diabetes ($n = 55\,652$) again revealed no association between Shypo and incident diabetes. Finally, limiting analyses to studies with less than 20% missing data at follow-up did not change our results.

Several sub-group analyses for Shypo are displayed in Fig. 3. Stratifying participants according to age (below and above 65 years of age), sex, TSH levels, and TPOAb status did not show different results as compared to the primary analysis.

## Subclinical hyperthyroidism

Data from 12 cohorts ($n = 32\,747$) showed the age- and sex-adjusted OR for the association between having Shyper at baseline and developing diabetes at last available follow-up was 1.03 (95% CI: 0.82–1.30, $I^2 = 0\%$) (Fig. 2). There was also no significant association between Shyper and incident diabetes at first available follow-up

**Table 2** Association between subclinical hypo- and hyper-thyroidism and secondary outcomes.

| Secondary outcome/analysis | Subclinical hypothyroidism | | | Subclinical hyperthyroidism | | |
|---|---|---|---|---|---|---|
| | Euthyroid (E/*n*) | Shypo (E/*n*) | OR (95% CI) | Euthyroid (E/*n*) | Shyper (E/*n*) | OR (95% CI) |
| Pre-diabetes at last available follow-up | 6539/22 423 | 527/1782 | 0.94 (0.84–1.05) | 6534/22 365 | 229/825 | 1.03 (0.85–1.25) |
| Diabetes at first available follow-up | 2097/36 485 | 166/2931 | 1.02 (0.88–1.17) | 1869/33 240 | 64/1182 | 1.07 (0.82–1.40) |
| Pre-diabetes at first available follow-up | 4358/22 707 | 374/1774 | 0.96 (0.85–1.09) | 4344/23 085 | 143/864 | 1.03 (0.89–1.19) |
| Multivariable analysis* | 2586/33 552 | 223/2872 | 0.97 (0.82–1.13) | 2313/31 659 | 85/1088 | 1.00 (0.78–1.28) |
| Incident diabetes including aggregate data from Gronich *et al*[22] | -/87693 | -/3064 | 1.12 (0.94–1.33)† | - | - | - |
| Time to diabetes (Cox regression) | 3240/42 562 | 283/3464 | 0.98 (0.87–1.11)‡ | 2959/38 572 | 117/1267 | 1.07 (0.88–1.29)‡ |

*Adjusted for age, sex, systolic blood pressure, diastolic blood pressure, fasting blood sugar, smoking, total cholesterol, and BMI. For the MrOS study, data on diastolic blood pressure were not available. For the EPIC-Norfolk study, data on fasting blood sugar at baseline were not available, the model was adjusted for HbA1c at baseline. For the Busselton study, data on fasting blood sugar at baseline were not available, the model was adjusted for oral glucose tolerance test result at baseline; †Incident diabetes analyzed as a risk ratio and data on number of events per category were not available for the study by Gronich *et al*.; ‡Value is HR (95% CI).

E/*n*, number of events/total number of participants at follow-up; HR, hazard ratio; OR, odds ratio; Shypo, subclinical hypothyroidism; Shyper, subclinical hyperthyroidism.

**Table 3** Sensitivity analysis on subclinical hypothyroidism and incident diabetes at last available follow-up.

| Sensitivity analysis | No. of participants | | No. of included studies | OR (95% CI) |
|---|---|---|---|---|
| | Euthyroid | Shypo | | |
| (1) Excluding participants with thyroid medication* | 22 215 | 1777 | 11 | 0.99 (0.82–1.21) |
| (2) Excluding participants with thyroid-altering medication** | 15 826 | 1145 | 6 | 0.96 (0.77–1.21) |
| (3) Limiting analyses to participants with repeated TFT at FU | 16 078 | 1333 | 6 | 0.96 (0.69–1.33) |
| (4) Using additional data to define diabetes† | 51 580 | 4072 | 17 | 1.05 (0.92–1.21) |
| (5) Limiting analyses to studies with <20% missing data at follow-up | 14 073 | 1180 | 3 | 0.94 (0.75–1.18) |
| (6) Limiting analyses to high-quality studies‡ | 37 577 | 3013 | 17 | 1.02 (0.88–1.17) |

*Thyroid medication was defined as levothyroxine or anti-thyroid medication use; **Thyroid-altering medication was defined as levothyroxine, anti-thyroid medication, lithium, or amiodarone use; †If available, self-reported diabetes and linkage to medical records were used to define diabetes; ‡All studies were classified as good quality according to the Newcastle–Ottawa quality assessment scale for cohort studies.
FU, follow-up; No. of participants, total number of participants at last available follow-up; OR, odds ratio; Shypo, subclinical hypothyroidism; TFT, thyroid function test.

(OR = 1.07; 95% CI: 0.82–1.40) or pre-diabetes at last and first available follow-up (OR = 1.03; 95% CI: 0.85–1.25 and OR = 1.03 (95% CI: 0.89–1.19, respectively) (Table 2). The HR for incidence of diabetes at last available follow-up for individuals with Shyper was 1.07 (95% CI: 0.88–1.29). The results were similar for several sensitivity and sub-group analyses (Fig. 4 and Table 4).

### Quality assessment

The quality of all studies included in the analyses was good according to the NOS (Supplementary Table 2). Based on the GRADE tool, certainty in the evidence for the primary outcome was low due to the observational nature of all studies (Supplementary Table 3). Funnel plots and Egger's test for the primary outcome did not suggest the presence of publication bias or a small study effect (Supplementary Figs 2 and 3).

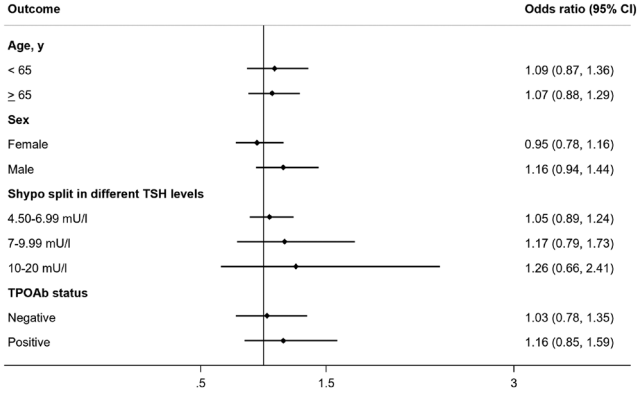


**Figure 3**
Association between subclinical hypothyroidism and incident diabetes at last available follow-up by sub-groups.

## Discussion

In this large IPD analysis of 61 178 participants, we did not find a prospective association between SCTD at baseline and incident diabetes or pre-diabetes at follow-up. Our results remained consistent in all sub-group and sensitivity analyses. To our knowledge, this is the first IPD to date investigating the association between SCTD and incident diabetes.

Our results are consistent with findings from a study conducted in Iran which did not find an association between TSH and fT4 in the subclinical thyroid range and fasting blood glucose during follow-up (11). In line with our findings, a large prospective study conducted in Taiwan found that high TSH was not associated with the incidence of diabetes (37). However, unlike the results from our study, the authors found that high TSH was associated with the incidence of pre-diabetes, although analyses were not restricted to individuals with subclinical thyroid

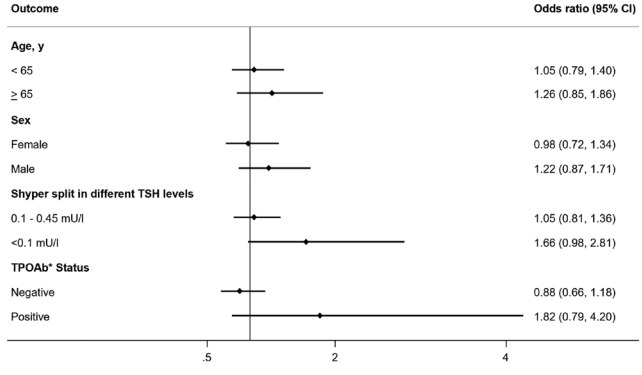


**Figure 4**
Association between subclinical hyperthyroidism and incident diabetes at last available follow-up by sub-groups.

**Table 4** Sensitivity analysis on subclinical hyperthyroidism and incident diabetes at last available follow-up.

| Sensitivity analysis | No. of participants | | No. of included studies | OR (95% CI) |
|---|---|---|---|---|
| | Euthyroid | Shyper | | |
| (1) Excluding participants with thyroid medication* | 19 765 | 470 | 9 | 0.91 (0.65–1.26) |
| (2) Excluding participants with thyroid-altering medication** | 14 080 | 230 | 5 | 0.83 (0.49–1.40) |
| (3) Limiting analyses to participants with repeated TFT at FU | 13 979 | 567 | 2 | 0.97 (0.36–2.60) |
| (4) Using additional data to define diabetes† | 44 928 | 1584 | 12 | 1.00 (0.81–1.22) |
| (5) Excluding participants without or with abnormal FT3 measurement | 15 397 | 467 | 6 | 0.94 (0.66–1.34) |
| (6) Limiting analyses to studies with <20% missing data at follow-up | 13 387 | 257 | 2 | 1.01 (0.63–1.62) |
| (7) Limiting analyses to high-quality studies‡ | 31 659 | 1088 | 12 | 1.03 (0.82–1.30) |

*Thyroid medication was defined as levothyroxine or anti-thyroid medication use; **Thyroid-altering medication was defined as levothyroxine, anti-thyroid medication, lithium, or amiodarone use; †If available, self-reported diabetes and linkage to medical records were used to define diabetes; ‡All studies were classified as good quality according to the Newcastle–Ottawa quality assessment scale for cohort studies.
FU, follow-up; OR, odds ratio; Shyper, subclinical hyperthyroidism; TFT, thyroid function test.

dysfunction (37). Results from the Rotterdam study were in contrast to our findings as they showed that higher TSH was associated with an increased risk of diabetes (HR = 1.13; 95% CI: 1.08–1.18 per 1 s.d. increase in log TSH) (10). However, it is noteworthy that the authors also included TSH within the reference range and overt thyroid disease which may explain the difference in results. Interestingly, a registry-based study in Israel found that Shypo was associated with incident diabetes only among statin users, and not among statin nonusers (22). The authors suggested that both Shypo and diabetes can be associated with mitochondrial dysfunction, which can be worsened by statin use (22).

It has been postulated that diabetes and thyroid dysfunction may have a bidirectional effect on each other (8, 9, 13). In theory, there are multiple underlying mechanisms that can explain how SCTD can contribute to the development of diabetes. First, hypothyroidism, both overt and subclinical, is associated with increased insulin resistance in part due to a decreased glucose uptake in muscle and adipose tissue (1). Moreover, TSH stimulates hepatic glucose production and reduces insulin secretion from pancreatic beta cells which in turn leads to higher serum glucose levels (1). Conversely, hyperglycemia can have an effect on thyroid hormones by controlling TSH secretion from the hypothalamus, influencing the conversion of fT4 to fT3 in peripheral tissues and affecting the TSH response to thyrotropin-releasing hormone (1). Moreover, it has been shown that raised serum insulin levels can lead to an increase in thyroid volume (9). In line with these mechanisms, a meta-analysis of cross-sectional studies by Han *et al*. in 2015 showed that diabetes was associated with a 1.93-fold increase in the risk of Shypo (38). Moreover, a study conducted in Australia among 420 women with diabetes found that 8.6% had Shypo (39). It is therefore possible that the diabetic state may contribute to the development of SCTD, which can explain the cross-sectional association between Shypo and diabetes that has been reported in the literature. Longitudinal studies assessing the prospective association between the presence of diabetes at baseline and SCTD at follow-up are thus warranted.

Our results have clinical implications as they neither support screening patients with SCTD for diabetes nor treating them in the hope of preventing diabetes in the future. This can therefore avoid performing unnecessary tests on patients and overtreating them which can lead to unwanted side effects.

Our study has several strengths, namely, it includes a large number of participants with a long mean follow-up time. As this study is an IPD analysis, we were able to standardize the definitions of SCTD and diabetes across studies and uniformly adjust for confounders to reduce heterogeneity across studies. We were also able to perform several sub-group analyses due to the large nature of this IPD. Moreover, we included unpublished data which increased the power of our study. However, our study also has limitations. Some studies included in our analysis were not designed to investigate the incident diabetes, and therefore, diabetes-related data were not collected for all participants at follow-up, which increased missing data during follow-up. However, we conducted a sensitivity analysis including only studies with less than 20% missing data during follow-up which showed that our results were robust. Moreover, SCTD was defined at a single time point (baseline) for the primary outcome. It is thus possible that

some individuals only present SCTD for a limited time period and then revert back to normal thyroid function, or may progress to overt thyroid disease. However, a sensitivity analysis that included only participants who had persistent SCTD at follow-up demonstrated that our results remained unchanged.

In conclusion, in this large IPD analysis, we did not find an association between SCTD and incident diabetes. Based on these findings, screening patients with Shypo for diabetes or treating them with levothyroxine with the aim of preventing diabetes would not be indicated.

**Supplementary materials**

This is linked to the online version of the paper at https://doi.org/10.1530/EJE-22-0523.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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**Data availability statement**

IPD are not publicly available due to confidentiality issues.

**Author contribution statement**

H A, C D G, and N R have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. H A, C D G, and N R had the final responsibility for the decision to submit for publication. Concept and design: H A, C D G, and N R. Systematic review of the literature: H A, F V. Acquisition, analysis, or interpretation of data: H A, C D G, and N R. Drafting of the manuscript: H A, C D G. Critical revision of the manuscript for important intellectual content: M F, F V, R P F D, S J L B, R P, M K, D B, A R C, B B Y, J P W, S J B, G C, L F, J G, S T, M I, J H M, S R, I M B, F A, A A, S V, N C, R G J W, N J W, W J, K W K, N R, C D G. Statistical analysis: H A, C D G, and N R. Obtained funding: N R. Supervision: N R, C D G. All authors read and approved the final manuscript.

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