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The prevalence of thyroid dysfunction and autoimmunity in women with history of miscarriage or subfertility

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Abstract:	Objective To describe the prevalence of, and factors associated with different thyroid dysfunction phenotypes, in asymptomatic preconception women. Design Observational cohort study. Setting 49 hospitals across the UK between 2011-2016. Participants Women aged 16-41years with history of miscarriage or subfertility trying for a pregnancy. Methods Prevalences and 95%CI's were estimated using the binomial exact method. Multivariate logistic regression analyses were conducted to identify risk factors for thyroid disease. Intervention None. Main outcome measure Rates of thyroid dysfunction. Results Thyroid function and thyroid peroxidase antibody (TPOAb) data were available for 19,213 and 19,237 women respectively. The prevalence of abnormal thyroid function was 4.8% (95%CI 4.5-5.1); euthyroidism defined as thyroid stimulating hormone (TSH) 0.44-4.50mIU/L and free-thyroxine (fT4) 10-21pmol/L. Overt hypothyroidism (TSH>4.50mIU/L, fT4<10pmol/L) was present in 0.2% (95%CI 0.1-0.3) and overt hyperthyroidism (TSH<0.44mIU/L, fT4>21pmol/L) in 0.3% (95%CI 0.2-0.3). The prevalence of subclinical hypothyroidism (SCH) using an upper TSH concentration of 4.50mIU/L was 2.4% (95%CI 2.1-2.6). Lowering the upper TSH to 2.50mIU/L resulted in higher rates of SCH, 19.9% (95%CI 19.3-20.5). Multiple regression analyses showed increased odds of SCH (TSH>4.50mIU/L) with BMI ≥35.0kg/m2 (aOR1.71 95%CI 1.13-2.57;p=0.01) and Asian ethnicity (aOR1.76 95%CI 1.31-2.37;p<0.001), and increased odds of SCH (TSH≥2.50mIU/L) with subfertility (aOR1.16 1.04-1.29;p=0.008). TPOAb positivity was prevalent in 9.5% (95%CI 9.1-9.9). Conclusions The prevalence of undiagnosed overt thyroid disease is low. Subclinical hypothyroidism and TPOAb are common, particularly in women with higher BMI or Asian ethnicity. A TSH cut-off of 2.50mIU/L to define SCH results in a significant proportion of women potentially requiring levothyroxine treatment.
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Please select the statement below that describes the availability of the data generated or analyzed in your manuscript.	
SPECIAL REQUESTS: In place of a cover letter, enter specific comments or requests to the editors here	We would like to thank you for the continued opportunity to publish our paper in your journal. We very much wish for our study to be published in JCEM as we believe this is the best platform through which to publish this work. We wanted to write to you directly to address the ongoing concerns raised by reviewer 2. We would be most grateful if you could consider our response within your editorial team without sending on for reviewer comments, as we believe there is a misunderstanding of the nature and conduct of this study. We have uploaded our formal letter to yourselves in place of the point-by-point rebuttal. We have addressed the concerns raised by reviewer 2 in this letter. Should you decide a formal separate response to reviewer 2 is still required we will provide one. Many thanks.

UNIVERSITY OF BIRMINGHAM

Institute of Metabolism and Systems Research

Tommys National Miscarriage Centre

Centre for Women's and Newborn Health, Birmingham Women's and Children's Foundation Trust

11th May 2020

Dear JCEM editorial team,

We would like to thank you for the continued opportunity to publish our paper ***"The prevalence of thyroid dysfunction and autoimmunity in women with history of miscarriage or subfertility"*** in your journal. We very much wish for our study to be published in JCEM as we believe this is the best platform through which to publish this work. We wanted to write to you directly to address the ongoing concerns raised by reviewer 2. We would be most grateful if you could consider our response within your editorial team without sending on for reviewer comments as we believe there is a misunderstanding of the nature and conduct of this study. However, should you decide a formal separate response to reviewer 2 is still required we will provide one.

Reviewer 1:
My initial comments have been thoughtfully addressed and I have no additional concerns.

Reviewer 2:
The authors performed a survey which demonstrated that none of the 49 sites had a local policy to perform thyroid function tests in women who had one miscarriage. Nevertheless, the international guidelines are quite clear on this. The lack of a local policy does not mean that the practioners did not follow evidence based international guidelines. In regards to the population of subfertile women, the authors note in their response that, "The principal investigators at each site, where women were recruited with subfertility, have confirmed that where possible all new patients were offered thyroid function and TPO testing… ". Furthermore, women who presented to their local practioners with symptoms of either overt hypothyroidism or overt hyperthyroidism, would have been tested and if found to have thyroid disease, would not have been referred for inclusion in the TABLET study. For all of this reason, the study cannot be construed as a true prevalence study. As the study is not a true prevalence study it is not accurate to state that "our study approach has adopted the most pragmatic method…" and then present the data as true prevalence data. What can be stated is that within the population of women referred to participate in the TABLET study, the prevalence of thyroid disease was found to be the following. These data cannot be construed as a true prevalence study as it is unknown what percentage of women were tested for thyroid disease, found to have thyroid disease and therefore never referred for participation in the TABLET trial.

Our response

We understand the reviewers concern regarding our study not representing a true prevalence study, however we have detailed our reasons below to contest this notion.

With regards to the issue of testing and prior diagnosis of thyroid disease in women seen in primary care, this would relate only to women who were symptomatic of thyroid disease. Primary care practitioners in the UK would not be offering thyroid function testing to asymptomatic women. The key important point of note in our prevalence study is that all women approached for screening were asymptomatic. We completely agree that symptomatic women are likely to have already been tested and treated prior to any secondary care contact. We are not making any objection to this statement. Our study presents the rates of thyroid disease in the asymptomatic, ordinarily unscreened, population.

As the reviewer correctly states, international guidance (in particular the Endocrine Society Clinical Practice guideline (ESCPG) by De Groot et al in 2012) does state that women with a prior history of miscarriage should be offered thyroid function testing. However, this is not currently, and never has been, standard practice in the UK amongst primary or secondary care providers. We have confirmed through our principal investigator survey that no woman with a history of 1 or 2 miscarriages would have been offered routine thyroid function testing outside of our study at any of the recruiting hospitals. This UK practice is also verified by Professor Boelaert, who led the UK NICE guidance on management of thyroid diseases and is a member of the Society for Endocrinology Clinical Committee. Therefore, our reported disease prevalence in asymptomatic women with history of 1 or 2 miscarriages is as accurate as possible.

Regarding the prevalence of disease in the population of women with history of recurrent miscarriages, we believe this is also accurate. UK guidance recommends all women with recurrent pregnancy losses are cared for by professionals with the necessary expertise and should be seen in specifically designated recurrent miscarriage clinics. Through our principal investigator survey, we confirmed that all new referrals to the recurrent miscarriage clinics (defined as women with 3 or more pregnancy losses) were offered thyroid function testing within the scope of our study. This, therefore, represents as close to a true prevalence as possible in this population.

The only population where we accept there may be an underestimate of the true prevalence is the subfertility population. This is due to the inconsistent practice across the recruiting sites. Some hospitals had a local policy to offer routine thyroid function testing to all women presenting with subfertility. As not all women were screened at their first fertility appointment, we accept that a proportion of women may have been already diagnosed and treated for thyroid dysfunction. This is reflected in the conclusion of our manuscript.

Overall, we strongly believe that our study has adopted the most pragmatic approach to determine an accurate measurement of thyroid disease prevalence in asymptomatic women with history of miscarriage or subfertility. Consequently, we are anxious to not lose the overall message in our study, which would be the case if we were to make the changes as requested by reviewer 2. We also note that reviewer 1 has not raised the issue of inaccurate prevalence.

We hope that you and your editorial team can review our response independently and we look forward to hearing from you.

Yours sincerely,

Rima Dhillon-Smith, Kristien Boelaert and Arri Coomarasamy

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The prevalence of thyroid dysfunction and autoimmunity in women with history of miscarriage or subfertility

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Abstract

Objective

To describe the prevalence of, and factors associated with different thyroid dysfunction phenotypes, in asymptomatic preconception women.

Design

Observational cohort study.

Setting

49 hospitals across the UK between 2011-2016.

Participants

Women aged 16-41years with history of miscarriage or subfertility trying for a pregnancy.

Methods

Prevalences and 95%CI's were estimated using the binomial exact method. Multivariate logistic regression analyses were conducted to identify risk factors for thyroid disease.

Intervention

None.

Main outcome measure

Rates of thyroid dysfunction.

Results

Thyroid function and thyroid peroxidase antibody (TPOAb) data were available for 19,213 and 19,237 women respectively. The prevalence of abnormal thyroid function was 4.8% (95%CI 4.5-5.1); euthyroidism defined as thyroid stimulating hormone (TSH) 0.44-4.50mIU/L and free-thyroxine (fT4) 10-21pmol/L. Overt hypothyroidism (TSH>4.50mIU/L, fT4<10pmol/L) was present in 0.2% (95%CI 0.1-0.3) and overt hyperthyroidism (TSH<0.44mIU/L, fT4>21pmol/L) in 0.3% (95%CI 0.2-0.3). The prevalence of subclinical hypothyroidism (SCH) using an upper TSH concentration of 4.50mIU/L was 2.4% (95%CI 2.1-2.6). Lowering the upper TSH to 2.50mIU/L resulted in higher rates of SCH, 19.9% (95%CI 19.3-20.5). Multiple regression analyses showed increased odds of SCH (TSH>4.50mIU/L) with BMI $\geq$35.0kg/m^2 (aOR1.71 95%CI 1.13-2.57;p=0.01) and Asian ethnicity (aOR1.76 95%CI 1.31-2.37;p<0.001), and increased odds of SCH (TSH$\geq$2.50mIU/L) with subfertility (aOR1.16 1.04-1.29;p=0.008). TPOAb positivity was prevalent in 9.5% (95%CI 9.1-9.9).

Conclusions

The prevalence of undiagnosed overt thyroid disease is low. Subclinical hypothyroidism and TPOAb are common, particularly in women with higher BMI or Asian ethnicity. A TSH cut-off of 2.50mIU/L to define SCH results in a significant proportion of women potentially requiring levothyroxine treatment.

Keywords

Thyroid disease, thyroid autoimmunity, prevalence, preconception, miscarriage, subfertility

Precis

This study of over 19,000 women with history of miscarriage or subfertility found undiagnosed overt thyroid disease in preconception women is low. Subclinical hypothyroidism is common, particularly in higher BMI or Asian women.

INTRODUCTION

Thyroid disorders are amongst the most prevalent medical conditions in women of reproductive age. The prevalence of thyroid disorders in pregnancy are well documented in those with known disease, however, there is little known of the unscreened asymptomatic preconception population.

Detection of thyroid disorders preconception is essential due to the adverse effects thyroid abnormalities have on conception and pregnancy. It is well established that both uncontrolled thyrotoxicosis and overt hypothyroidism are associated with adverse pregnancy outcomes such as reduced fertility, miscarriage, pre-eclampsia and pre-term birth[1–3]. Subclinical hyperthyroidism and subclinical hypothyroidism (SCH) are biochemical diagnoses defined by an abnormal serum thyroid stimulating hormone (TSH) with normal concentrations of free thyroxine. They may represent the earliest stages of thyroid dysfunction and can progress to overt disease[4]. SCH has been linked to subfertility, miscarriage, pre-term birth, pre-eclampsia, and perinatal mortality[5]. Thyroid peroxidase antibodies (TPOAb) have also been associated with adverse pregnancy outcomes such as subfertility, recurrent miscarriages and pre-term birth[6,7]. The presence of TPOAb increases the risk of progression to subclinical and overt thyroid disease in pregnancy[8,9].

There is international agreement on the treatment of overt thyroid disease. However, the treatment strategies for SCH or TPOAb pre-conception and antenatally are debated. The European Thyroid Association (ETA) and American Thyroid Association (ATA) recommend levothyroxine (LT4) replacement in pregnant women with SCH[10,11]. The ATA guideline specifically refers to using internal or transferable pregnancy-specific TSH reference ranges and if these are not available, an upper reference limit of 4.0mU/L may be used[11]. The same guideline recommends a lower threshold for treatment in TPOAb positive women, using a cut off TSH of >2.5mIU/L[11]. These recommendations are based on the notion that any possible benefits of treatment with LT4 are thought to outweigh any potential risks. However, a retrospective cohort study of 5405 women with SCH in pregnancy contests this notion[12]. This study found that women who received LT4 treatment had lower adjusted odds of pregnancy loss (OR 0.62, 95% CI 0.48 to 0.82) but higher odds of preterm delivery (1.60, 1.14 to 2.24), gestational diabetes (1.37, 1.05 to 1.79), and pre-eclampsia (1.61, 1.10 to 2.37) compared to untreated women. The cohort was subgrouped into women with pre-treatment TSH values of 2.5-4.0mIU/L and those with TSH values 4.1-10mIU/L. The adjusted odds of pregnancy loss were lower in treated women than in untreated women if their pre-treatment TSH concentration was 4.1-10mIU/L (OR 0.45, 0.30 to 0.65) but not if it was 2.5-4.0mIU/L (0.91, 0.65 to 1.23)

(p<0.01). This study not only shows no benefit from treating the mildly elevated TSH subgroup but also suggests harm in doing so[12].

The definition of SCH and recommendations of when to initiate LT4 treatment differs between population subgroups. The Endocrine Society Clinical Practice Guideline (ESCPG) recommends a preconception TSH of <2.5mIU/L for all subfertile women and women with history of miscarriage or pre-term birth[13]. The 2017 ATA guideline recommends "*subclinically hypothyroid women undergoing IVF should be treated with LT4…to achieve a TSH concentration <2.5mU/L*"[11]. The American Society for Reproductive Medicine (ASRM) guideline on subclinical hypothyroidism in the infertile female adopts a similar guidance which is that TSH concentrations over the non-pregnant lab reference range (typically >4.0mIU/L) should be treated with levothyroxine to maintain levels below 2.5mIU/L. It also maintains that there is insufficient evidence that LT4 therapy in women with TSH levels between 2.5 and 4.0mIU/L is associated with improvement in pregnancy and miscarriage rates. In spite of this, they recommend that it is advisable to treat when the TSH is >2.5mIU/L in the first trimester of pregnancy[14].

Regarding screening for thyroid disease, the ATA and ASRM recommends TSH testing for all women seeking care for infertility[11,14], this is supported by the ESCPG who also recommend screening women with any history of miscarriage[13]. However, National Institute of Health and Care Excellence (NICE) does not recommend routine screening for women with subfertility[15]. The ESHRE guideline recommends TSH and TPOAb testing for all women with recurrent pregnancy losses[16].

In order to determine if screening programmes are cost-effective and to understand the impact of varying cut-off levels for diagnosing subclinical thyroid disease, the prevalence of the disease must first be established. To our knowledge, the prevalence of varying degrees of thyroid dysfunction and associated risk factors has not been assessed systematically in women with history of miscarriage or subfertility.

Our study objective was to describe the prevalence of, and factors associated with, different thyroid dysfunction phenotypes, in preconception asymptomatic women with history of miscarriage or subfertility.

METHODS

This was a multi-centre prospective observational cohort study conducted across 49 hospitals in the UK between November 2011 and January 2016. This study directly linked to a large multi-centre randomised controlled trial (The TABLET trial; ISRCTN15948785).

Eligibility criteria and recruitment setting

The eligibility criteria were as follows: history of miscarriage or subfertility, aged between 16-41 years, actively trying for a pregnancy in the subsequent 12 months, not known to have current thyroid illness, not known to have cardiac problems, and not taking amiodarone or lithium.

History of miscarriage was defined as any pregnancy which was confirmed by a positive pregnancy test (both biochemical and clinical pregnancies included). For women with subfertility, this was defined as any woman seen in a secondary care setting for subfertility.

Participants were recruited from the following clinical settings: early pregnancy units (EPU) screening women with recent miscarriage; recurrent miscarriage clinics; infertility clinics or women who had contacted the trial team as self-referrals via the trial website or via social media. All new referrals to recurrent miscarriage services and infertility clinics were approached to participate. Participants who had consented for screening, but for whom no result was available (either due to insufficient sample taken or laboratory processing errors), were contacted and offered a repeat blood test.

Thyroid function tests

Serum samples were analysed for TSH and Free T4 using any one of the study-approved analysers. These were: Roche Modular E170, Roche Elecsys® 1010 or 2010, Roche Cobas®, Abbott architect and Siemens Advia Centaur. All laboratories participated in the UK national external quality assurance scheme (NEQAS) to ensure consistency in testing and these analysers specifically were deemed to produce comparable results.

Rather than applying specific reference ranges dependent on the laboratory assay used, we adopted a pragmatic approach when defining euthyroidism and used a commonly accepted reference range in the UK of 0.44-4.50mIU/L for TSH and 10-21pmol/L for fT4. Values below and above these ranges were considered abnormal. The euthyroid group was further sub-divided into TSH 0.44-2.49mIU/L and 2.50-4.50mIU/L, as the latter is commonly regarded as subclinical hypothyroidism by many fertility and early pregnancy specialists. Subclinical hypothyroidism was also analysed in two further groups; moderate (TSH 4.51-10mIU/L) and severe (>10mIU/L). Most guidelines adopt different

management approaches depending on the degree of TSH abnormality based on these different cut-offs both in the preconception period[10,11] and outside pregnancy[17–19].

TPO antibody evaluation

A range of anti-TPO antibody assays were utilised each with different detection limits and thresholds for test positivity pre-determined by the manufacturer (supplementary table S1[20]). These variations are an accepted part of normal UK practice. Quality assurance for assays in the laboratories of all participating centres was provided by UK Immunology, Immunochemistry and Allergy National External Quality Assurance Service (NEQAS IIA),[21] which showed over 99% concordance in the classification of samples as either positive or negative for TPO antibodies across all assays. Therefore, we did not define a threshold for TPO positivity but instead accepted the categorical classification provided by the laboratories servicing the participating centres (supplementary table S1[20]).

Participant characteristics

The following participant characteristics were recorded and categorised for each screened patient: age, body-mass index (BMI), ethnicity and originating clinical population.

Age (in years) was grouped into 5 year blocks: 17-21; 22-26; 27-31; 32-36; 37-41. BMI (kg/m2) was categorised according to WHO recommendations: underweight <18.5; normal weight 18.5-24.9; overweight 25.0-29.9; obese class I 30.0-34.9; obese class II and III ≥35.0[22]. Ethnicity was selected from a list of 17 options, as per the NHS ethnic category codes and grouped as: “White”; “Asian” (Indian/Pakistani/Bangladeshi/Other South Asian); “Black” (African/Caribbean/Other Black); “Mixed” (mixed White/Asian, mixed White/Black African, mixed White/Black Caribbean, other mixed background); “Chinese” and “Other” ethnic group. Originating clinical population referred to the clinical setting where patients were screened: women with history of one or two miscarriages (i.e. EPU setting), women with history of recurrent miscarriage, women seen in the fertility setting or other.

Screening process

Every eligible participant was approached in the relevant clinical areas and all women were required to give written consent to have their blood taken for thyroid function and TPOAb. For each participant screened, they were assigned an individual screening number. Their baseline characteristics and corresponding thyroid function and thyroid antibody results were all inputted onto an electronic data collection page. Participants with normal thyroid function and positive for TPOAb were then offered to enter the full trial.

Statistical analyses

An overall description of the study population was presented using the patient characteristic subgroups as categorical variables. Prevalences, with their 95% confidence intervals, were estimated for each thyroid dysfunction group and for TPOAb using the binomial exact method. TPOAb positivity was further explored in thyroid dysfunction subgroups.

Five clinically important thyroid dysfunction groups, which are not mutually exclusive, were explored: overt hypothyroidism, overt hyperthyroidism, SCH with TSH >4.50mIU/L (combining moderate and severe SCH), SCH with TSH ≥2.50mIU/L, and SCH with TSH ≥2.50mIU/L *and* TPOAb positive. Multiple logistic regression analyses were performed to assess the relationship between the relevant thyroid function group and the following variables: age, BMI, ethnicity, population and TPOAb positivity. The reference group for each patient characteristic variable was selected on the basis of which was deemed the "lowest risk" or the largest group. Finally, an analysis was performed to determine the relationship between TPOAb positivity and TSH concentrations.

All analyses were done using Stata statistical software, release 14 (Stata Corp, College Station, TX, 2015).

RESULTS

A total of 19,350 women gave written consent to have testing for thyroid function and TPOAb. Thyroid function results were available for 19,213 women and TPOAb results for 19,237 women. The list of the 49 recruitment centres and the numbers of women recruited at each site is presented in supplementary table S2[20].

The pre-screening logs did not show any obvious disparities in age, BMI or ethnicity between those who gave consent and those who did not. The most common reason for declining consent was that women preferred not to know their thyroid status; this contributed to less than 0.5% of all women approached; thus, the cohort was deemed representative of women with no known thyroid dysfunction seen in the miscarriage care and subfertility clinical settings.

Prevalence of thyroid dysfunction

The overall prevalence of thyroid dysfunction is shown in Figure 1. The overall prevalence of thyroid dysfunction (euthyroidism defined as TSH 0.44-4.5mIU/L, free T4 10-21pmol/L) is 4.8% (95% CI 4.5-5.1). Overt hypothyroidism (defined as TSH >4.50mIU/L and fT4

<10pmol/L) was present in 0.2% (95% CI 0.1-0.3) and overt hyperthyroidism (defined as TSH <0.44mIU/L and fT4 >21pmol/L) in 0.3% (95% CI 0.2-0.3). The prevalence of subclinical hypothyroidism (SCH) using an upper TSH concentration of 4.50mIU/L was 2.4% (95% CI 2.1-2.6). Lowering the upper TSH limit to 2.50mIU/L resulted in a higher rate of SCH of 19.9% (95% CI 19.3-20.5).

Applying an upper limit of TSH to 2.50mIU/L to only those with subfertility or ≥3 miscarriages i.e. the "highest risk populations" showed the prevalence to be 20.1% and 16.1% respectively (supplementary table S3[20]). The prevalence of thyroid dysfunction in various patient characteristic subgroups is shown in supplementary table S3[20].

Risk factors for thyroid dysfunction

TPOAb positivity was the factor associated most significantly with any degree of thyroid dysfunction, after adjustment for confounders (Table 1). The relationship between patient characteristics and thyroid function are presented in Table 1. Multiple regression analyses found increased odds of SCH (TSH >4.50mIU/L) with body-mass index (BMI) ≥35.0kg/m^2 (aOR 1.71 (95% CI 1.13-2.57, p=0.01) and Asian ethnicity (aOR 1.76 (95% CI 1.31-2.37) p<0.001), as well as increased odds of SCH (TSH ≥2.50mIU/L) with subfertility (aOR 1.16 (1.04-1.29) p=0.008).

Prevalence of and risk factors for TPO antibody positivity

The overall prevalence of TPOAb was 9.5% (9.1-9.9%) (Table 2). The prevalence of TPOAb positivity by patient characteristic subgroups is shown in supplementary table S3[20]. The association of patient characteristic subgroups with TPOAb positivity, following adjustment for confounders, is shown in Table 3. There was a dose-response relationship observed between TPOAb positivity and BMI, Class III obese women (BMI ≥35.0 kg/m^2) were statistically significantly more likely to be TPOAb positive compared with women of normal weight. Black women were less likely to be TPOAb positive than White women. There were no significant differences in TPOAb positivity between the originating population groups.

Association between TPOAb positivity and thyroid dysfunction

The prevalence of TPOAb by individual thyroid dysfunction group is shown in Table 3. Women with overt thyroid dysfunction had higher prevalences of TPOAb positivity and this was most pronounced in those with overt hypothyroidism. In those with subclinical hypothyroidism, higher rates of TPOAb positivity were observed in the categories with higher serum TSH concentrations. Of those with isolated hypothyroxinaemia (IH), 87% were TPOAb positive, however on closer inspection of the free T4 data the mean was

8.9pmol/L and median 9.6pmol/L. Therefore, this group was unlikely to represent the true IH population and instead were categorised as IH due to the strict reference range used. Using a lower free T4 cut off of 8.0pmol/L resulted in only 4 cases of IH with a mean value of 2.1pmol/L and none of these were TPOAb positive.

Finally, we determined the relationship between categories of TSH concentration and the prevalence of TPOAb positivity as shown in Figure 2. The probability of TPOAb positivity was lowest in women with TSH 0.44-2.5mIU/L and increased gradually with increasing TSH concentrations. TPOAb positivity was associated with both raised and suppressed TSH concentrations, and more pronounced effects were seen with higher concentrations.

DISCUSSION

Main findings

To our knowledge, this is the first systematic evaluation, adopting the most pragmatic approach, to assess thyroid function and TPOAb status in asymptomatic preconception women with history of miscarriage or subfertility. Using current accepted reference ranges, we classified 95.2% of women as euthyroid, with undiagnosed disorders of overt hypothyroidism in 0.2%, overt hyperthyroidism in 0.3%, severe subclinical hypothyroidism ((TSH >10mIU/L) in 0.2% and SCH (TSH>4.50mU/L) in 2.4%. Lowering the upper limit of TSH to 2.50mU/L, as is the recommendation by international societies for “high risk” women (i.e. those with history of RPL or undergoing ART), would class 16-20% of women as subclinically hypothyroid.

We identified higher body-mass index, Asian ethnicity, subfertility and TPOAb positivity as independent factors associated with higher TSH concentrations. 9.5% of women expressed TPOAb. Women with a history of ≥3 miscarriages or subfertility were not more likely to be TPOAb positive than those with one or two previous miscarriages. Raised BMI (≥35.0 kg/m^2) was associated with higher rates, while Black ethnicity was linked to lower rates of TPOAb positivity.

Strengths and limitations

The main strengths of this study were the large sample size and the widespread geographical representation across the UK, allowing precise determination of the prevalence of and risk factors for different forms of thyroid dysfunction.

One of the limitations is that our population belonged to a “selected population”, with miscarriage or infertility. There is no control group in our study as the eligibility criteria for screening had to match with that of the TABLET trial. Therefore, thyroid function in these

women may not represent that of true unselected “low risk” women with no gynaecological or obstetric risk factors. On the other hand, this study includes women who have engaged in the health system and therefore those who are most likely to benefit from a screening programme. Many “low risk” women have no contact with health professionals in the preconception period or have unplanned pregnancies, thus would not have the chance to be screened.

The variables collected within our cohort study were limited for pragmatic reasons and we have therefore been unable to perform detailed exploratory analyses. For example, we have not been able to comment on the rates of thyroid dysfunction in women with different causes of subfertility or analyse the data separately for those who underwent IVF treatment and those who did not. However, we present an overall prevalence of thyroid dysfunction in women within a “high risk” population.

Another limitation is that our exploration of risk factors did not adjust for multiplicity; hence we cannot rule out increased chance of false positive findings.

Finally, we did not assess iodine status. Previous studies in the UK have suggested that UK is a mildly iodine deficient population and this could have increased the prevalence of thyroid disease[23].

Underestimation of true prevalence?

It could be speculated that our reported prevalence’s are an underestimation of the true rates. The reason for this is that it is unknown how many women with miscarriage or subfertility may have been screened for thyroid dysfunction and treated by their Gynaecologist or primary care provider and therefore never referred to participate in our study.

For women with history of 1 or 2 miscarriages it is not routine practice in the UK to offer thyroid function or TPOAb testing in primary or secondary care. The clinicians recruiting at each site in our study have verified that these women would not have been tested prior to or outside of our study. Therefore, these women were opportunistically screened within our study and so the results reflect as close to as possible the true disease prevalence.

For women with 3 or more miscarriages, routine practice in the UK is for referral to a secondary care provider with a recurrent miscarriage service for further investigations. All clinicians recruiting in this setting verified that, where possible, all new patients were offered TFT and TPOAb testing at initial contact within the remit of our study. Therefore, the findings in this population also represent the best possible true prevalence rates.

With regards to the subfertile population, TPOAb testing was not routinely performed at any of our recruiting sites outside of the study. Therefore, we can be reassured that our reported TPOAb prevalence in subfertile women is as close as possible to the true prevalence. However, testing for thyroid dysfunction in the subfertile population is an important potential confounder which may have resulted in underestimation of the true prevalence and the results should therefore be interpreted with some caution. Although the UK leading clinical guidance provider, NICE, do not recommend routine thyroid function testing in subfertile women this is common practice across secondary care providers. Despite the fact we urged all sites to approach women on their initial contact in secondary care, this was not consistent as some women were recruited from clinics in the outpatient setting while others were only approached at the point of starting IVF treatment. In addition, some subfertile women may have already had their thyroid function tested (and treated) by their primary care provider prior to referral. This means that there will be an unknown proportion of women who were offered TFT testing outside of the remit of our study and may have already been diagnosed and treated and therefore excluded from our prevalence figures. It would be very difficult to quantify the number of women potentially missed and we believe our study approach has adopted the most pragmatic method of capturing the women presenting to secondary care for subfertility. However, we accept that the reported disease prevalence for thyroid dysfunction in the asymptomatic subfertile population is likely to be higher than we have found.

Interpretation

Our data are consistent with studies reporting that women with subfertility are more likely to have subclinical hypothyroidism[5,24,25]. Our observation of higher TSH concentrations in Asian and lower concentrations in Black women, may reflect normal inter-ethnic variation, consistent with previous documentation of lower TSH levels in people from Black or Hispanic origin compared with White Caucasian populations[26]. A large Dutch study of 3944 women found significant ethnic differences in serum TSH, T4, and TPO-antibody positivity and important diagnostic discrepancies were identified when population and ethnicity-specific reference ranges were applied resulting in a change of diagnosis for 18% of women[27]. Further work is required to prevent misdiagnosing and subsequent mistreatment for women from certain ethnic backgrounds.

Higher prevalence of TPOAb have been reported in women with subfertility (10-31%) and recurrent pregnancy loss (17-33%) compared with the general population (6-20%)[28]. Our data did not identify a significant association between TPOAb positivity and a history of recurrent miscarriage or infertility. The recently published TABLET (Thyroid Antibodies and LEvoThyroxine) trial, to which this study was linked, found no improvement in live birth or any secondary pregnancy or neonatal outcomes in euthyroid TPOAb positive women taking 50mcg LT4 compared with placebo[29]. However, around 8% of women in

each group did go on to develop thyroid dysfunction and detection of this would not have been possible without knowing TPOAb status and performing the appropriate thyroid monitoring in pregnancy. Further evidence is required to determine the need to screen these specific populations.

Implications for clinical practice

We have shown the prevalence of differing thyroid abnormalities when universally screening otherwise healthy women with history of miscarriage or subfertility. Using this strategy, 0.5% were found to have overt thyroid dysfunction. In pregnancy, severe SCH would be considered overt hypothyroidism and so a further 0.2% would need definitive treatment. Screening for SCH, using a TSH cut off of 2.5mIU/L as recommended for women with subfertility or recurrent miscarriage, will result in up to 20% of women diagnosed as having thyroid dysfunction and potentially requiring levothyroxine treatment, with 4% having SCH *and* TPOAb. Not forgetting that these figures are likely to represent an underestimate of the true prevalence. This could constitute a significant burden to healthcare systems, and may generate unnecessary patient anxiety. In the absence of evidence of benefit with LT4 treatment and possible suggestion of harm, for mild SCH or TPOAb positivity we pose the question of whether screening should be performed at all in asymptomatic individuals. Although knowing TPOAb status will identify those women who require antenatal monitoring of thyroid function, there is no proven treatment to modify pregnancy outcome. Case finding in the subfertile and recurrent miscarriage populations, by identifying risk factors such as ethnicity and BMI, may be a better strategy.

Future work

Many clinicians screen for and treat subclinical hypothyroidism (TSH ≥2.50mIU/L and normal fT4) in women with subfertility or history of miscarriage, despite ongoing uncertainty over the benefits and cost implications of this management strategy. Further studies, including health economic analyses, are needed to determine if treating 0.7% of such women, who have undiagnosed severe SCH or overt thyroid disease and are at risk of pregnancy complications, outweighs the costs of universal screening. It is well established that screening should not be implemented if treatment does not have any effect on the natural progression of the disease. Large randomised trials are needed to establish if preconception LT4 treatment of mild SCH with or without TPOAb positivity is beneficial. If treatment is found to be beneficial, this study presents the prevalence of thyroid disorders that can be expected and explored which factors are associated with thyroid dysfunction and TPOAb positivity that could guide the development of suitable cost-effective screening strategies and aid clinical decision making in primary and secondary care.

Ethical approval

Ethical approval was obtained from Berkshire B Research Ethics Committee (REC reference 13/SC/0642).

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Author disclosure statement

No competing financial interests exist.

Authors contributions

The study was designed by R. Dhillon-Smith (RDS), A. Coomarasamy (AC), K. Boelaert (KB), A. Tobias (AT), P.P. Smith (PPS), S. Chan (SC), S. Thangaratinam (ST), J. Daniels (JD) and L.J. Middleton (LJM). Data gathering was carried out by RDS, J.J. Chu (JJC), K. Sunner (KS), K. Baker (KB) and S. Farrell-Carver (SFC). Data analysis was performed by AT, PPS and LJM. The data and analyses are vouched for by RDS, AC, AT, and PPS. RDS, AC, KB and SC wrote the paper and made the decision to publish. RDS wrote the first draft of the manuscript. R. Bender-Atik, R. Agrawal, K. Bhatia, E. Edi-Osagie, A. Ewies, T. Ghobara, P. Gupta, D. Jurkovic, Y. Khalaf, K. Mulbagal, N. Nunes, C. Overton, S. Quenby, R. Rai, N. Raine-Fenning, L. Robinson, J. Ross, A. Sizer, R. Small, M. Underwood and M.D. Kilby provided critical input in to the conduct of the trial and drafting of the manuscript.

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References:

1. Zimmerman D. Fetal and neonatal hyperthyroidism. Thyroid Off J Am Thyroid Assoc. 1999 Jul;9(7):727–33.

2. Earl R, Crowther CA, Middleton P. Interventions for preventing and treating hyperthyroidism in pregnancy. Cochrane Database Syst Rev. 2010;(9):CD008633.

3. Nazarpour S, Ramezani Tehrani F, Simbar M, Azizi F. Thyroid dysfunction and pregnancy outcomes. Iran J Reprod Med. 2015 Jul;13(7):387–96.

4. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA. 2004 Jan 14;291(2):228–38.

5. van den Boogaard E, Vissenberg R, Land JA, van Wely M, van der Post JAM, Goddijn M, et al. Significance of (sub)clinical thyroid dysfunction and thyroid autoimmunity before conception and in early pregnancy: a systematic review. Hum Reprod Update. 2011 Oct;17(5):605–19.

6. Glinoer D, Soto MF, Bourdoux P, Lejeune B, Delange F, Lemone M, et al. Pregnancy in patients with mild thyroid abnormalities: maternal and neonatal repercussions. J Clin Endocrinol Metab. 1991 Aug;73(2):421–7.

7. Glinoer D, Delange F. The potential repercussions of maternal, fetal, and neonatal hypothyroxinemia on the progeny. Thyroid Off J Am Thyroid Assoc. 2000 Oct;10(10):871–87.

8. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab. 2006 Jul;91(7):2587–91.

9. Negro R, Formoso G, Coppola L, Presicce G, Mangieri T, Pezzarossa A, et al. Euthyroid women with autoimmune disease undergoing assisted reproduction technologies: the role of autoimmunity and thyroid function. J Endocrinol Invest. 2007 Jan;30(1):3–8.

10. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. Eur Thyroid J. 2014 Jun;3(2):76–94.

11. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. Thyroid Off J Am Thyroid Assoc. 2017 Mar;27(3):315–89.

12. Maraka S, Mwangi R, McCoy RG, Yao X, Sangaralingham LR, Singh Ospina NM, et al. Thyroid hormone treatment among pregnant women with subclinical hypothyroidism: US national assessment. BMJ. 2017 Jan 25;356:i6865.

13. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012 Aug;97(8):2543–65.

14. Practice Committee of the American Society for Reproductive Medicine. Subclinical hypothyroidism in the infertile female population: a guideline. Fertil Steril. 2015 Sep;104(3):545–53.

15. Fertility problems: assessment and treatment | Guidance and guidelines | NICE [Internet]. [cited 2018 May 20]. Available from: https://www.nice.org.uk/guidance/cg156/chapter/Recommendations#initial-advice-to-people-concerned-about-delays-in-conception

16. Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, et al. ESHRE guideline: recurrent pregnancy loss. Hum Reprod Open [Internet]. 2018

Feb 1 [cited 2018 Apr 30];2018(2). Available from: https://academic.oup.com/hropen/article/2018/2/hoy004/4963604

17. Pearce SHS, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, et al. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. Eur Thyroid J. 2013 Dec;2(4):215–28.

18. Okosieme O, Gilbert J, Abraham P, Boelaert K, Dayan C, Gurnell M, et al. Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. Clin Endocrinol (Oxf). 2016 Jun;84(6):799–808.

19. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol. 2012 Dec;18(6):988–1028.

20. R.K. Dhillon-Smith, A. Tobias, P.P. Smith, L.J. Middleton, K.K. Sunner, K. Baker, S. Farrell-Carver, R. Bender-Atik, R. Agrawal, K. Bhatia, J.J. Chu, E. Edi-Osagie, A. Ewies, T. Ghobara, P. Gupta, D. Jurkovic, Y. Khalaf, K. Mulbagal, N. Nunes, C. Overton, S. Quenby, R. Rai, N. Raine-Fenning, L. Robinson, J. Ross, A. Sizer, R. Small, M. Underwood, M.D. Kilby, J. Daniels, S. Thangaratinam, S. Chan, K. Boelaert, A. Coomarasamy. Data from: The prevalence of thyroid dysfunction and autoimmunity in women with history of miscarriage or subfertility across the United Kingdom. Figshare. Deposited 28 February 2020. **https://doi.org/10.6084/m9.figshare.11913558.v1**

21. Allergy Test UK, Assay Finder, Immunology Lab, quality assessment oncology immunodeficiency [Internet]. [cited 2018 Aug 4]. Available from: https://www.immqas.org.uk/Default.asp?S=675627643&C=1252&CID=1

22. http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi.

23. Bath SC, Rayman MP. A review of the iodine status of UK pregnant women and its implications for the offspring. Environ Geochem Health. 2015 Aug;37(4):619–29.

24. Abalovich M, Mitelberg L, Allami C, Gutierrez S, Alcaraz G, Otero P, et al. Subclinical hypothyroidism and thyroid autoimmunity in women with infertility. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2007 May;23(5):279–83.

25. Feldthusen A-D, Pedersen PL, Larsen J, Toft Kristensen T, Ellervik C, Kvetny J. Impaired Fertility Associated with Subclinical Hypothyroidism and Thyroid Autoimmunity: The Danish General Suburban Population Study. J Pregnancy. 2015;2015:132718.

26. Surks MI, Boucai L. Age- and race-based serum thyrotropin reference limits. J Clin Endocrinol Metab. 2010 Feb;95(2):496–502.

27. Korevaar TIM, Medici M, de Rijke YB, Visser W, de Muinck Keizer-Schrama SMPF, Jaddoe VWV, et al. Ethnic differences in maternal thyroid parameters during pregnancy: the Generation R study. J Clin Endocrinol Metab. 2013 Sep;98(9):3678–86.

28. Thangaratinam S, Tan A, Knox E, Kilby MD, Franklyn J, Coomarasamy A. Association between thyroid autoantibodies and miscarriage and preterm birth: meta-analysis of evidence. BMJ. 2011;342:d2616.

29. Dhillon-Smith RK, Middleton LJ, Sunner KK, Cheed V, Baker K, Farrell-Carver S, et al. Levothyroxine in Women with Thyroid Peroxidase Antibodies before Conception. N Engl J Med. 2019 04;380(14):1316–25.

Figure Legend

Figure 1. Overall prevalence of thyroid dysfunction

(Free T4 measured in pmol/L and TSH in mIU/L)

Figure 2. Probability of TPO antibody positivity vs. TSH concentration

Table legend

Table 1. Risk factors for clinically important thyroid dysfunction groups

	Overt Hypothyroid (n=36)		**Overt Hyperthyroid** (n=49)		**SCH** (TSH >4.50, fT4 10-21) (n=451)		**SCH** (TSH ≥2.50, fT4 10-21) (n=3825)		**SCH** (TSH ≥2.50, fT4 10-21) and TPOAb positive (n=784)	
	aOR[1]	(95% CI)	aOR	(95% CI)	aOR	(95% CI)	aOR	(95% CI)	aOR	(95% CI)
Age (years)										
17-21	1.79	(0.18, 18.11)	2.45	(0.46, 13.05)	0.94	(0.39, 2.30)	1	(0.71, 1.40)	1.2	(0.50-2.90)
22-26	Ref		Ref		Ref		Ref		Ref	
27-31	0.8	(0.20, 3.28)	0.78	(0.26, 2.36)	0.67	(0.44, 1.03)	1.04	(0.89, 1.22)	1.38	(0.92-2.07)
32-36	0.75	(0.19, 2.96)	0.57	(0.18, 1.78)	0.99	(0.7, 1.46)	1.07	(0.92, 1.25)	1.28	(0.87-1.90)
37-41	0.56	(0.11, 2.82)	0.54	(0.14, 2.05)	0.86	(0.56, 1.35)	1.01	(0.85, 1.20)	1.29	(0.84-1.99)
BMI										
<18.5	-	-	4.35*	(1.21, 15.56)	0.37	(0.09, 1.50)	0.79	(0.56, 1.12)	0.94	(0.38-2.31)
18.5-24.9	Ref		Ref		Ref		Ref		Ref	
25.0-29.9	3.92*	(1.34, 11.42)	0.74	(0.30, 1.84)	1.06	(0.78, 1.45)	1.07	(0.95, 1.20)	0.95	(0.71-1.27)
30.0-34.9	1.37	(0.26, 7.14)	0.46	(0.10, 2.01)	1.23	(0.84, 1.81)	1.06*	(1.00, 1.42)	1.51*	(1.04-2.18)
≥35.0	1.84	(0.35, 9.65)	0.33	(0.04, 2.50)	1.71*	(1.13, 2.57)	1.38**	(1.16, 1.64)	1.73**	(1.16-2.58)
Ethnicity										
White	Ref		Ref		Ref		Ref		Ref	
Black	0.88	(0.11, 6.94)	4.63*	(1.48, 14.50)	0.68	(0.34, 1.36)	0.68**	(0.55, 0.85)	0.49	(0.23-1.04)
Asian	1.29	(0.45, 3.68)	1.79	(0.72, 4.46)	1.76**	(1.31, 2.37)	1.38**	(1.22, 1.55)	1.06	(0.78-1.43)
Chinese	-	-	-	-	0.82	(0.20, 3.42)	1.17	(0.76, 1.80)	0.48	(0.13-1.79)
Mixed	-	-	-	-	0.43	(0.11, 1.77)	0.65*	(0.44, 0.96)	0.55	(0.19-1.57)
Other	-	-	4.38	(0.97, 19.64)	0.94	(0.38, 2.35)	1.08	(0.78, 1.48)	0.81	(0.38-1.73)

Population												
1 or 2 miscarriages	Ref			Ref			Ref			Ref			Ref	
Recurrent miscarriage	1.46	(0.48, 4.43)		0.87	(0.26, 2.84)		0.96	(0.66, 1.39)		0.89	(0.77, 1.02)		1.01	(0.72-1.42)
Infertility	0.76	(0.26, 2.20)		1.27	(0.54, 2.99)		1.04	(0.77, 1.39)		1.16*	(1.04, 1.29)		1.09	(0.82-1.44)
Other	-	-		2.89	(0.35, 23.53)		0.69	(0.21, 2.25)		0.95	(0.65, 1.39)		0.7	(0.25-1.91)
TPO positive												
No	Ref			Ref			Ref			Ref				
Yes	21.97**	(8.36, 57.72)		8.09**	(3.75, 17.42)		8.43**	(6.50, 10.92)		3.55**	(3.12, 4.04)			

*p value <0.05

**p value <0.001

[1]Adjusted odds ratios were produced for each thyroid dysfunction subgroup using the demographic variables age, BMI, ethnicity, originating clinical population and TPOAb positivity.

Table 2. Prevalence of TPOAb across different thyroid dysfunction groups

Thyroid function	TPOAb +ve n = 1827 (9.5%) 95% CI 9.1-9.9	TPOAb –ve n = 17410 (90.5%) 95% CI 91-99
	% (95% CI)	*Number; % (95% CI)*
Euthyroid:		
Euthyroid (TSH 0.44-4.50)	8.5% (8.1-8.9)	91.5% (91.1-92.0)
Euthyroid (TSH 0.44-2.49)	6.5% (6.1-6.9)	93.5% (93.1-93.9)
Euthyroid (TSH 2.50-4.50)	17.0% (15.8-18.3)	83.0% (81.7-84.2)
Overt thyroid disease	53.0% (41.8-63.9)	47.0% (36.1-58.2)
Hypothyroid	69.4% (51.9-83.7)	30.6% (16.4-48.1)
Hyperthyroid	40.8% (27.0-55.8)	59.2% (44.2-73.0)
Subclinical hypothyroid:		
Severe SCH (TSH >10.0)	80.0% (61.4-92.2)	20.0% (7.7-38.6)
Mod. SCH (TSH 4.51-10.0)	40.3% (35.6-45.2)	59.7% (54.8-64.4)
TSH >4.50	43.0% (38.4-47.7)	57.0% (52.3-61.7)
TSH ≥2.50	20.5% (19.2-21.8)	79.5% (78.1-80.8)
Subclinical hyperthyroid	12.9% (8.9-17.8)	87.1% (82.2-91.1)
Isolated hypothyroxinaemia	87.0% (73.7-95.1)	13% (4.9-26.2)

Table 3. Risk factors for TPOAb positivity

	Adjusted odds ratio (95% CI)	P value
Age (years)[a]		
17-21	0.89 (0.57, 1.38)	0.599
22-26	Reference group	
27-31	0.97 (0.79, 1.19)	0.788
32-36	1.10 (0.90, 1.34)	0.368
37-41	1.12 (0.90, 1.40)	0.299
BMI (kg/m^2) [b]		
<18.5	0.77 (0.49, 1.22)	0.272
18.5-24.9	Reference group	
25.0-29.9	0.99 (0.85, 1.14)	0.846
30.0-34.9	1.09 (0.90, 1.32)	0.391
≥35.0	1.54 (1.25, 1.91)	<0.001
Ethnicity [c]		
White	Reference group	
Black	0.43 (0.30, 0.60)	<0.001
Asian	1.13 (0.96, 1.32)	0.136
Chinese	0.91 (0.50, 1.66)	0.761
Mixed	0.69 (0.43, 1.11)	0.127
Other	1.19 (0.80, 1.75)	0.390
Population [d]		
1 or 2 miscarriages	Reference group	
Recurrent miscarriage	0.84 (0.51, 1.38)	0.496
Infertility	0.95 (0.83, 1.10)	0.502
Other	1.04 (0.88, 1.24)	0.638

[a] Adjusted for BMI, ethnicity and population
[b] Adjusted for age, ethnicity and population
[c] Adjusted for age, BMI and population
[d] Adjusted for age, BMI and ethnicity

Figure

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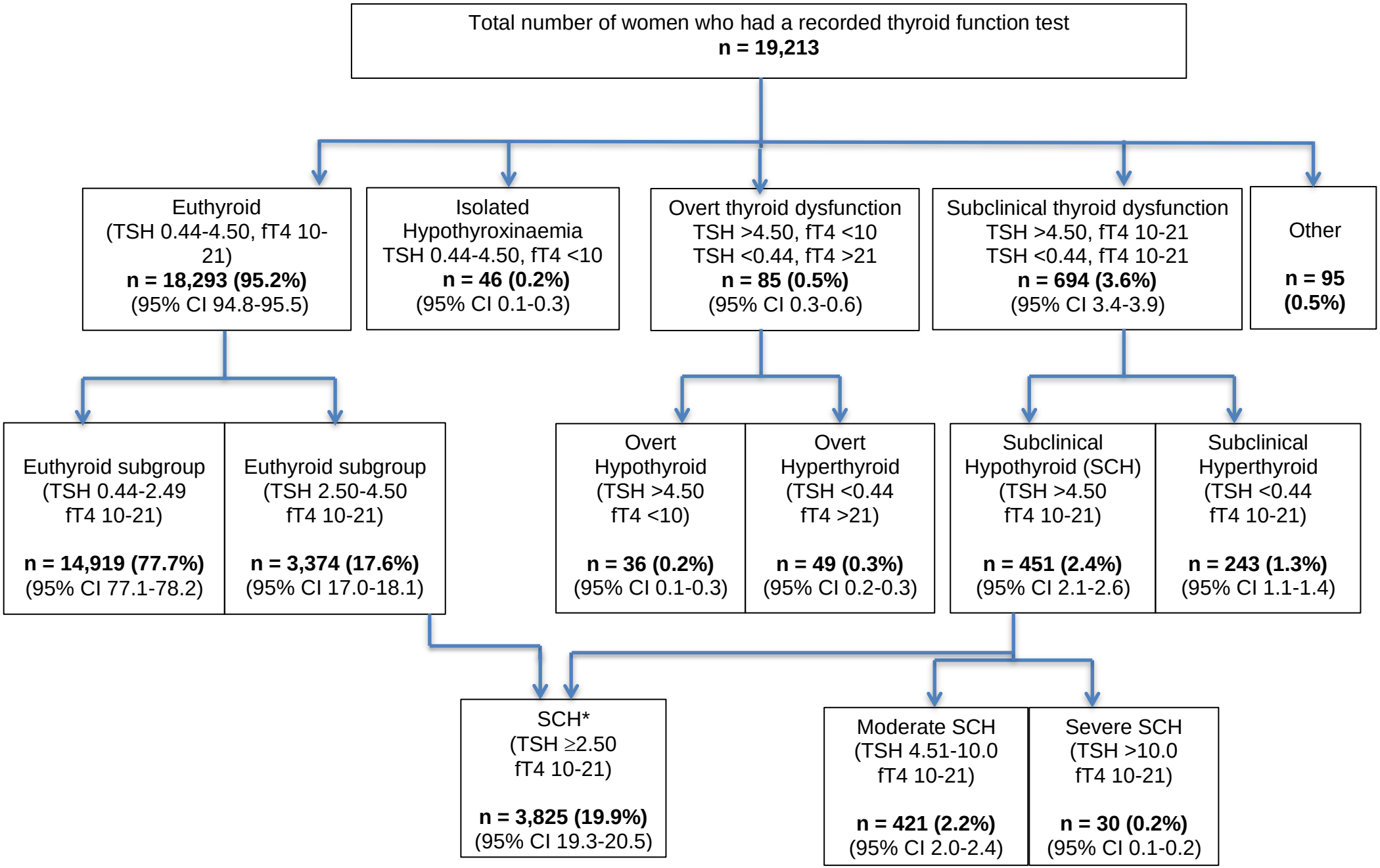

Figure

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