Assessment of the simultaneous effect of hypothyroidism and thyroid autoimmunity with gestational diabetes on the incidence of type 2 diabetes

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Abstract

Introduction: Despite the evidence available on the adverse impact of gestational diabetes (GDM) and thyroid disorders on developing type 2 diabetes (T2DM), the concurrent influence of these disorders on the incidence of T2DM has not been reported yet. Methods: In this prospective study, 1894 non-diabetic women aged 20 to 60 years, with a history of at least one term delivery, without diagnosed hyperthyroidism were selected at the initiation of the Tehran Thyroid Study (TTS). Pooled logistic regression analyses were used to investigate the association of GDM, thyroid disorders i.e., hypothyroidism and/or thyroid peroxidase antibody (TPOAb) positivity and interaction between GDM and thyroid disorders with the risk of incident T2DM. Results: Of the 1894 participants of the present study, 346 (18.3%) had a history of GDM, and 832 (43.9%) had thyroid disorders. The total cumulative incidence rate of T2DM at the median follow-up time of ~ 12 years was overall 12/1000 person-years (95% confidence interval (CI): 10/1000–13/1000), with an incidence rate of 16/1000 (95%CI: 13/1000–20/1000) in women with GDM; and 11/100,000 (95%CI: 9/100,000–12/1000) among those without GDM. After adjustment for age, the risk of incident T2DM increased among individuals with previous GDM compared to women without a history of GDM (odds ratio (OR): 1.54, 95%CI: 1.06, 2.25). No significant associations were found between either thyroid disorders or the interaction between GDM and thyroid disorders with the development of T2DM; (OR: 1.14, 95%CI: 0.82, 1.58) and (OR: 1.27, 95%CI: 0.66, 2.43), respectively. Conclusion: GDM and thyroid disorders have no concurrent impacts on the incidence of T2DM.

Background

About 10% of pregnancies are affected by gestational diabetes mellitus (GDM) [1] which causes multiple adverse fetal and maternal health outcomes [2]. The risk of developing T2DM among women with a history of GDM is 2–10 fold greater compared to those with a healthy pregnancy [3, 4]. Similarly, thyroid disorders, the most common endocrine disorders in women of childbearing age [2], are more prevalent in pregnant women with GDM, compared to their healthy counterparts [5]. Also, a significant increase in incident thyroid autoimmunity has been reported among women with a history of GDM (31.6% vs. 9.7%) [1]. It has also been shown that clinical and subclinical hypothyroidism is more common among women with T2DM, compared to non-diabetic women [6, 7], e.g. in a population-based prospective cohort study with 7.9-year follow up of 8,452 individuals, hypothyroidism was reported as a risk factor for the incidence of T2DM, particularly among women with prediabetes [7]. Despite evidence on adverse effects of GDM or thyroid disorders i.e. hypothyroidism and thyroid autoimmunity, on the risk of developing T2DM, the concurrent effect of these disorders on incidence of T2DM has not been reported yet. This study was conducted to determine the effect of interaction between thyroid disorders, including hypothyroidism and/or thyroid autoimmunity, and GDM on the incidence of T2DM among participants of a population based cohort study, the Tehran Thyroid Study (TTS), over a median follow up of 12.5 years.

Materials And Methods

Study participants

The population of this study was selected from among participants of the Tehran Thyroid study (TTS), a prospective population-based cohort study, being conducted within the framework of the Tehran lipid and

glucose study (TLGS) [8]. Of TLGS participants, 5786(3407 women, and 2376 men) were randomly selected between March 1997-December 2004 to participate in the TTS in the iodine sufficient population of Tehran [9]. Cohort participants were physically examined every 3 years; follow-up assessments included a general physical examination and an interview during which the reproductive history including pregnancy outcomes was recorded and their overnight fasting blood samples were collected for future use. A part of this study has been dedicated to education for lifestyle modification, making the TLGS a pragmatic community trial [10]. Details of the study have been published elsewhere [9].

For the present study, women with at least one follow up visit and at least one term delivery who did not have known T2DM at the time of study recruitment were included (n = 2062). Participants with a diagnosis of hyperthyroidism (n = 152) and missing data (n = 16) were also excluded. Finally, data of 1894 eligible participants were used in the current analyses; the study flowchart is presented in Fig. 1.

The study proposal was approved by the medical ethics committee of the Research Institute for Endocrine Sciences (RIES) and written informed consent was obtained from all participants.

Clinical measurements

All participants invited to the TTS were referred to trained physicians after giving written informed consent. Details of examinations and procedures have been previously published [11, 12]. In brief, weight was measured with minimum clothing to the nearest 100 grams. Height was measured with a tape measure in a standing position, with shoulders in normal alignment. Body mass index (BMI) was calculated by dividing weight (kg) by height (m^2).Participants remained seated for 15 minutes; then a qualified physician measured blood pressure twice with a standard mercury sphygmomanometer, calibrated by the Iranian Institute of Standards and Industrial Researches.

Laboratory measurements

Blood samples were taken between 7:00 and 9:00 AM from all study participants, after a 12 to 14 hour overnight fast. The 75 g oral glucose tolerance test (OGTT) was also carried out on participants who were not taking glucose-lowering drugs. Fasting and 2-hour plasma glucose (2hPG), were determined using the enzymatic colorimetric method with glucose oxidase. Serum total cholesterol (TC) and triglycerides (TGs) were measured using the enzymatic calorimetric method with cholesterol esterase and cholesterol oxidase and glycerol phosphate oxidase, respectively. All these biochemical tests were performed on the day of sampling, using commercial kits (Pars Azmoon Inc., Tehran, Iran) by the Selectra 2 auto-analyzer (Vital Scientific, Spankeren, The Netherlands). All samples were analyzed only when quality control met the acceptable criteria. Both inter- and intra-assay coefficients of variation were < 2.3% for glucose, < 2.1% for TGs and < 2% for TC.

Baseline and follow-up free thyroxine (FT4) and thyroid-stimulating hormone (TSH) were determined in -70ºC stored serum samples by the electrochemiluminescence immunoassay method, using Roche Diagnostics kits and a Roche/Hitachi Cobas e-411 analyzer (GmbH, Mannheim, Germany). Lyophilized quality control material (Lyphochek Immunoassay plus Control, Bio-Rad Laboratories) was used to monitor the accuracy of assay; intra- and inter-assay coefficients of variation (CVs) were 1.3% and 3.7% for FT4 and 1.5% and 4.5% for TSH determinations, respectively. Thyroid peroxidase antibody (TPOAb) was assayed by immunoenzymometric assay (IEMA) using the related kit (Monobind, Costa Mesa, CA, USA) and the Sunrise ELISA reader (Tecan Co.,

Salzburg, Austria); intra- and inter-assay CVs were 3.9% and 4.7%, respectively. All measurements were simultaneously performed at the research laboratory of the Research Institute for Endocrine Sciences (RIES) in 2012.

Definition of variables and outcomes

At the time of data collection, women were asked about their history of GDM based on a self-reporting questionnaire and medical records if needed [13]. Based on the Iranian national screening program, the World Health Organization (WHO) criteria for universal screening of GDM [12]were used.

The American Diabetes Association criteria were used to define T2DM [14]as using anti-diabetic drugs or having FBS ≥ 7 mmol/l (measured twice) or 2 h plasma glucose (OGTT) ≥ 11.1 mmol/l. A family history of diabetes is defined as having a history of T2DM in the 1st-degree family members. Subclinical- and overt hypothyroidism were defined as serum TSH level > 5.06 mU/L with normal FT4 level and serum TSH level > 5.06 mU/L and FT4 < 0.91 ng/dl respectively. Subclinical and overt hyperthyroidism was defined as serum TSH level < 0.34 mU/L and normal FT4 level and as TSH concentrations < 0.34 mU/L with serum FT4 concentration > 1.55 ng/dl respectively [15].TPOAb positivity was defined as having values > 35.04 IU/mL in females [16]. In the present study, we defined thyroid disorders as the presence of hypothyroidism (clinical or subclinical) or TPOAb positivity or using Levothyroxine. We excluded all those with clinical or subclinical hyperthyroidism as well as those using anti-thyroid drugs.

Statistical analyses:

Continuous variables were checked for normality using the one-sample Kolmogorov–Smirnov test, and reported as mean (standard deviation) if they had a normal distribution or median with inter-quartile range (IQR25-75) for variables with skewed distribution. Categorical variables are presented as numbers and percentages. Characteristics of women were compared between groups, applying the ANOVA or test for continuous and categorical variables, respectively. The Kruskal-Wallis test was applied to compare variables with skewed distribution. As data was interval censored and time to T2DM was not known, pooled logistic regression was used to assess the effects of GDM, thyroid disorders, free T4, TSH, thyroid autoimmunity and the interaction between GDM and thyroid disorders on developing T2DM as well as to calculate odds ratios (OR). This model treats every interval as a mini follow-up study, pools the observations of all intervals together into one pooled sample, and does a logistic regression on the pooled dataset [17].

All analyses were adjusted for age (model 1); age, BMI, educational status, smoking, family history of DM (model 2) and intermediate covariates, including serum TG and TC concentration, systolic blood pressure (SBP), diastolic blood pressure (DBP), and FBS (model 3). Statistical analysis was performed using the software package STATA (version 14; STATA Inc., College Station, TX, USA); significance level was set at $P < 0.05$, and confidence interval (CI) as 95%.

Results

Of 1894 eligible women, 346 (18.3%) had GDM and 493 (26%) had thyroid disorders, including hypothyroidism and/or thyroid autoimmunity; of those with thyroid disorders, 77 (15.6%) had a history of GDM, as well. The median and IQR for follow-up years were 12.5 (IQR: 11.8–13.4).

Subjects were divided into four groups based on having a history of GDM and thyroid disorders as follows: 1) not having a history of GDM and thyroid disorders; 2) having a history of GDM and thyroid disorders; 3) having a history of GDM without thyroid disorders and 4) having thyroid disorders without a history of GDM.

Baseline characteristics of study participants based on their history of GDM and thyroid disorders are presented in Table 1. Individuals without a history of GDM and thyroid disorders had lower BMI compared to other groups. We found significant differences in FT4, TSH, and TPOAb levels between groups.

The results of pooled logistic regression analyses on the association of thyroid disorders, GDM, and interaction terms of thyroid disorders and GDM for developing T2DM are presented in Table 2. Compared to women without a history of GDM, OR for the T2DM incident was significantly higher among individuals with GDM in an unadjusted model (OR: 1.54; 95%CI: 1.06, 2.25); the association observed remained statistically significant even after adjusting for age (OR: 1.67; 95%CI: (1.14, 2.45). Our study found no significant association between either thyroid disorders (OR: 1.14, 95%CI: 0.82, 1.58) or the interaction between GDM and thyroid disorders (OR: 1.27, 95%CI: 0.66, 2.43) on development of T2DM.

Results of pooled logistic regression analyses on the effect of GDM, serum FT4 levels, and the interaction between GDM and serum FT4 concentration on the development of T2DM are shown in Table 3. There was no significant association of the interaction between GDM and FT4 with the progression of T2DM; neither was any relation found between serumFT4, TSH, and TPOAb levels and the incidence of T2DM in pooled logistic regression analyses before and after adjustment for potential confounders (Table 3 and supplementary tables 1, and 2).

The total cumulative incidence rate of T2DM diagnosed at the median follow-up time of 12.5 years was overall 12/1000 person-years (95%CI: 10/1000–13/1000), with an incidence rate of 16/1000 (95%CI: 13/1000–20/1000) in women with GDM; it was 11/100,000 (95%CI: 9/100,000–12/1000) among those without GDM. The cumulative incidence rate of T2DM for women with and without thyroid disorders was 13/1000 (95%CI: 10/1000–16/1000) and 11/1000 (95%CI: 10/1000–13/1000) respectively.

Discussion

The present study indicated no synergistic effect between GDM and thyroid disorders on the incidence of T2DM. Despite the higher risk of incident T2DM among women with a history of GDM, women with thyroid dysfunction had similar risk for development of T2DM, compared to their counterparts with normal thyroid function.

To the best of our knowledge, no previous studies have investigated the synergistic effect of GDM with thyroid disorders on the development of T2DM, although several have investigated the associations of GDM and thyroid disorders per se with the risk of incident T2DM [18- 19- 20- 21- 22].The findings of our study showed a higher risk of developing T2DM in patients with a history of GDM, compared to those without a history of GDM, an observation consistent with findings of previous studies [18- 19- 20–21]. A systematic review and meta-analysis of cohort studies conducted by Bellamy et al revealed that the risk of incident T2DM in women with a history of GDM was 7.43 (95%CI:4.79–11.51) times higher than those without any history [20]. The adverse effects of GDM on developing T2DM may be attributable to epigenetic changes induced by maternal

hyperglycemia in target tissues, such as skeletal muscle and subcutaneous adipose tissue [23]. Moreover, increase in circulating levels of leptin, inflammatory biomarkers e.g. TNF-α and C-reactive protein (CRP) and the fat content in liver and muscle, as well as the decreased adiponectin concentration reported in women with prior GDM, may partly explain woman's predisposition to T2DM following GDM [24].

There is no consensus about the adverse effects of thyroid dysfunction with further development of T2DM. The present study showed no statistically significant increase in the development of T2DM following thyroid disorders. In agreement with the results of our study, Sadatamini et al. showed that the incidence of thyroid dysfunction in T2DM patients was not higher than non-diabetic participants during 12 years of follow up [22]. However, a longitudinal cohort study conducted among 25,575 adults aged > 18 years by Chen et al. in Taiwan with follow up of > 10 years reported that the incidence of T2DM was greater among individuals with either hypo- or hyperthyroidism, with most incident cases of T2DM occurring the first five years of thyroid disorders [25].In another prospective cohort of 8,452 participants with a 7.9 year follow up, hypothyroidism was identified as a risk factor for increased risk of incident T2DM, more so in pre-diabetic patients [7], findings contrary to those of our investigation; their findings however also indicated that the risk for developing T2DM drops from 35–15% when FT4 reached to normal levels[7].

No significant associations of serum FT4, TSH, and TPOAb levels with incidence of T2DM were observed in our data, using either simple or pooled logistic regression analyses. In contrast of our findings, Yeqing et al. in a cross-sectional study (n = 15,296), performed in China, demonstrated that decreased FT3, FT3/FT4 ratios, and increased FT4 levels are independently related to a higher prevalence of T2DM in both males and females, and TSH is inversely related to T2DM in males only[26]; however the results of the Mohammed et al. study of 2797 type 2 diabetic patients, revealed no significant differences in serum thyroid levels between T2DM patients and their healthy counterparts ($P < 0.05$); their results also indicated that the frequency of thyroid autoimmunity was not significantly higher in type 2 diabetic patients than in the non-diabetic control group[27].

According to the results of the current study, the incidence of T2DM increased significantly with time and age, a finding in agreement with the results of previous studies [28- 29- 30]. Evidence suggests that senescent cells, implicated in the generation of insulin resistance, accumulate in various tissues with aging [31].

Regarding study strengths, this is the first study with a longitudinal design, long term follow-up, and large sample size investigating the possible interaction between the history of GDM and thyroid disorders in the incidence of T2DM. Also, using pooled logistic approaches helped us to further adjust our results for assumed confounders that were precisely measured in this study including age, familial history of diabetes, smoking, anthropometric indices, and physical activity and lipid profiles. However, the present analyses do have some limitations, which should be addressed. First, GDM was determined based on a self-reporting questionnaire and medical records, although the universal screening strategy of GDM in Iran and subsequent monitoring and treatment of GDM may restrict this bias. Last but not least, serum FT3 levels, as biologically active hormones involved in glucose metabolism [32], were not assessed in the current study.

Conclusion

In conclusion, no synergistic effect was found between GDM and thyroid disorders on the incidence of T2DM. However, women with a history of GDM were at higher risk of developing T2DM later in their life. As women age, the risk of T2DM incidence is also increasing. Given the significant prevalence of T2DM, targeted healthcare systems, and lifestyle modification are recommended.

Abbreviations

GDM: Gestational diabetes, T2DM: Type 2 diabetes, TTS: Tehran Thyroid Study, TLGS: Tehran lipid and glucose study, FT4: Free thyroxin, TSH: thyroid stimulating hormone, TPOAb: Thyroid peroxidase antibody, RIES: Research Institute for Endocrine Sciences, OGTT: Oral glucose tolerance test, 2hPG: 2-hour plasma glucose, TC: Serum total cholesterol, TGs: serum triglycerides, SBP: Systolic blood pressure, DBP: diastolic blood pressure.

Declarations

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Conflict of Interests

The authors declare that they have no conflict of interest.

Ethics

The study protocol was approved by the ethics committee of the Research Institute for Endocrine Sciences and all patients gave written informed consent.

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Tables

Table 1. characteristics of the study participants at recruitment

Group	Without GDM & without thyroid disorders(N=1132)	With GDM & with thyroid disorders(N=77)	With GDM & without thyroid disorders(N=269)	Without GDM & with thyroid disorder(N=416)	P-value
Variables					
Age(Years)[a]	39.06±10.06	36.06±8.20	38.33±7.71	40.31±10.22	0.07
Weight(Kg)[a]	67.22±10.76	73.52±12.28	71.44±11.27	69.71±11.75	<0.001
Height(m)[a]	1.56±0.0538	1.57±0.05	1.57±0.05	1.57±0.05	0.05
BMI(kg/)[a]	27.34±4.34	29.74±5.18	28.62±4.33	28.20±4.57	<0.001
FBS(mg/dL)[a]	88.46±8.70	87.74±10.11	89.73±10.09	87.67±8.69	0.03
BS-2hpp(mg/dL)[a]	106.62±25.82	107.76±24.80	109.07±22.89	104.12±24.60	0.08
Smoking status	39(3.4%)	2(2.6%)	14(5.2%)	20(4.8%)	0.37
Family history of diabetes	316(27.9%)	21(27.3%)	80(29.7%)	101(24.3%)	0.44
Educational status					0.02
<6 years	384(33.9%)	32(41.5%)	69(26.6%)	122(29.3%)	
6-12 years	632(55.8%)	41(53.2%)	178(66.2%)	256(61.5%)	
>12 years	116(10.2%)	4(5.2%)	22(8.2%)	38(9.1%)	
Triglycerides (mg/dL) [b]	126 (87-181)	121(85-176)	128(92-201)	131(90-189)	0.24
Total Cholesterol(mg/dL)[a]	205.14±46.14	200.18±37.10	205.21±38.00	209.60±47.56	0.22
Systolic-BP(mmHg)[a]	114.06±16.87	111.66±13.49	113.04±13.93	115.14±16.35	0.21
Diastolic-BP(mmHg)[a]	76.08±10.42	74.93±8.30	76.53±9.75	75.93±10.18	0.66
Free-T4(ng/dL)[b]	1.16(1.06-1.26)	1.02(0.86-1.20)	1.13(1.06-1.24)	1.05(0.89-1.18)	<0.001
TSH(mIU/L)[b]	1.72(1.09-2.60)	3.59(1.87-6.33)	1.61(1.08-2.31)	3.90(1.98-6.37)	<0.001
TPOAb level(IU/mL)[b]	5.05(3.17-8.39)	44.49(4.94-264.77)	4.33(3.15-9.52)	71.58(12.49-245.28)	<0.001
Hypothyroidism n(%)[c]	0	10(13%)	0	54(13%)	<0.001
Subclinical Hypothyroidism n(%)[c]	0	17(22.1%)	0	113(27.2%)	<0.001
TPOAb positivity n(%)[c]	0	47(61%)	0	274(65.8%)	<0.001
Hypothyroxinemia n(%)[c]	0	15(19.5%)	0	59(14.2%)	<0.001

[a] Variables with normal distribution are reported as Mean ± SD and compared using ANOVA test.

[b] Variables with non-normal distribution are reported as median (Q1, Q3) compared using Kruskal Wallis Test.

[c] Categorical variables are presented as number (%) and compared using the chi-square test

FBS: Fasting blood sugar, Bs-2hpp: Blood sugar 2 hours postprandial, Systolic BP: Systolic blood pressure, Diastolic BP: Diastolic blood pressure, Free-T4: Free thyroxine, TSH: Thyroid-stimulating hormone, TPOAb: Thyroid peroxidase antibody.

Table 2. Associations of GDM, thyroid disorders, and interaction between GDM and thyroid disorders on development of T2DM using a pooled logistic analysis.

Variables	Unadjusted model		Model 1		Model 2		Model 3	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Thyroid disorder	1.14(0.82, 1.58)	0.44	1.13(0.81, 1.57)	0.46	1.08(0.77, 1.51)	0.64	1.24(0.87, 1.75)	0.22
GDM	1.54(1.06, 2.25)	0.02	1.67(1.14, 2.45)	0.01	1.40(0.94, 2.07)	0.09	1.42(0.95, 2.12)	0.08
GDM* Thyroid disorder	1.27(0.66, 2.43)	0.47	1.32(0.69, 2.54)	0.40	1.16(0.58, 2.31)	0.67	1.41(0.71, 2.80)	0.33

Model 1: adjusted for age,
Model 2: adjusted for age, BMI, educational status, smoking and family history of DM,
Model 3: adjusted for serum triglycerides, serum total-cholesterol, serum HDL-cholesterol, systolic blood pressure, diastolic blood pressure, and fasting plasma glucose

Thyroid disorders: Clinical, subclinical hypothyroidism, and thyroid autoimmunity, GDM: gestational diabetes, T2DM: type 2 diabetes mellitus,
OR: odds ratio, CI: confidence interval.

Table 3. Associations of GDM, serum FT4 levels, and interaction between GDM and serum FT4 on the development of T2DM using pooled logistic regression analyses

Variables	Unadjusted model		Model 1		Model 2		Model 3	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
FT4(ng/dL)	1.02(0.94, 1.10)	0.70	1.02(0.94, 1.11)	0.63	1.01(0.93, 1.10)	0.76	1.0.6(0.97 , 1.15)	0.23
GDM	1.05(0.15, 7.10)	0.96	0.95(0.13, 6.67)	0.96	0.42(0.06, 3.07)	0.39	0.58(0.08, 4.35)	0.60
GDM * FT4	0.95(0.81, 1.13)	0.60	0.94(0.79, 1.11)	0.48	0.89(0.75, 1.06)	0.19	0.91(0.77, 1.09)	0.31

Model 1: adjusted for age,
Model 2: adjusted for age, BMI, educational status, smoking and family history of DM,
Model 3: adjusted for serum triglycerides, total and HDL-cholesterol levels, systolic blood pressure, diastolic blood pressure, and FBS.

GDM: gestational diabetes, T2DM: type 2 diabetes mellitus, FT4: free thyroxin

Figures

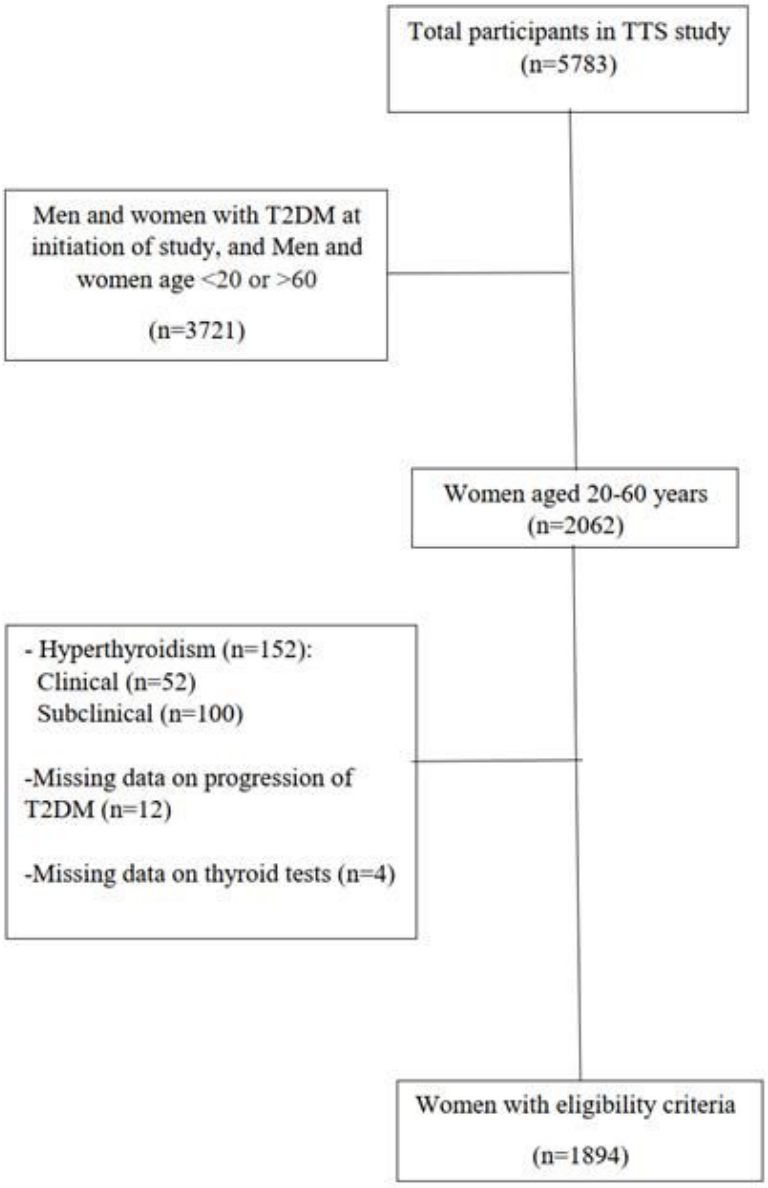

Figure 1

Overview of the study population