

Macro TSH and the Misdiagnosis of Hypothyroidism: Evidence from a Cross-Sectional Study

Davoud Amirkashani

Iran University of Medical Sciences

Mostafa Abdollahi Sarvi

abdollahisarvi.m@gmail.com

Iran University of Medical Sciences

Mostafa Masoumi

Iran University of Medical Sciences

Mona Nourbakhsh

Iran University of Medical Sciences

Research Article

Keywords: Macro TSH, Hypothyroidism, Subclinical Hypothyroidism, Thyrotropin, Thyroid Function Tests

Posted Date: October 11th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11058799/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Thyroid-stimulating hormone (TSH) is the primary marker for diagnosing hypothyroidism. However, macro TSH, a biologically inactive TSH-immunoglobulin complex that can falsely elevate serum TSH, leading to misdiagnosis and unnecessary treatment. This diagnostic pitfall is particularly critical in asymptomatic individuals and pregnant women.

Methods

This cross-sectional study evaluated 171 adult patients (50 men, 50 non-pregnant women, and 71 pregnant women) presenting with elevated total TSH but minimal or no hypothyroid symptoms between January 2024 and March 2025. Macro TSH was identified using polyethylene glycol (PEG) precipitation, and free TSH was calculated by subtracting macro TSH from total TSH. Diagnostic reclassifications were evaluated using chi-square and correlation analyses.

Results

Significant diagnostic discordance was observed after macro TSH screening. Among non-pregnant adults, 69% of patients initially diagnosed with hypothyroidism based on total TSH were reclassified as euthyroid when free TSH was utilized ($p < 0.001$). Similarly, 54 of 71 pregnant women (76%) initially labeled with clinical or subclinical hypothyroidism were reclassified as euthyroid ($p < 0.001$). Total TSH strongly correlated with macro TSH levels, whereas free TSH showed no such association.

Conclusion

the only reliance on total TSH values causes substantial overdiagnosis of hypothyroidism due to macro TSH interference. Screening for macro TSH in discordant or asymptomatic cases improves diagnostic accuracy and prevents unnecessary levothyroxine therapy, especially during pregnancy. These findings support further investigation into integrating macro TSH evaluation into diagnostic algorithms for discordant thyroid test cases.

1 Introduction

Thyroid disorders, particularly hypothyroidism, are among the most prevalent endocrine disorders globally and are diagnosed primarily through the evaluation of serum thyroid-stimulating hormone (TSH) levels and free thyroxine (T4) concentrations (1). General guidelines typically place the upper limit of normal TSH levels at approximately 4–5 mIU/L. An elevation in TSH, coupled with reduced free T4 levels,

commonly establishes the diagnosis of hypothyroidism; however, in some situations, laboratory results may contrast with clinical presentation (2).

Recent studies have highlighted a critical nuance in this diagnostic approach. Macro TSH forms when TSH binds primarily to immunoglobulin G (IgG) (1). This complex remains biologically inactive and can misleadingly elevate serum TSH levels when detected via conventional immunoassays (3). As a result, the measured TSH values reported by laboratories do not accurately reflect the true bioactive TSH levels in patients with macro TSH (4). Due to the slow clearance of macro TSH by the kidneys, its accumulation in serum can cause false elevations in TSH levels (5), potentially leading to an erroneous diagnosis of hypothyroidism, even in patients with normal free T4 and free TSH levels (6).

With such diagnostic errors, patients misdiagnosed with hypothyroidism often undergo unnecessary treatments, typically levothyroxine therapy (7). While this treatment is intended to normalize thyroid hormone levels and alleviate symptoms, inappropriate use of levothyroxine can lead to overtreatment, resulting in symptoms of thyrotoxicosis such as palpitations, anxiety, weight loss, and osteoporosis (1, 3). These unnecessary treatments not only expose patients to potential adverse effects but also contribute to increased healthcare costs. The economic impact of misdiagnosis extends beyond individual patients: unneeded prescriptions, follow-up appointments, and routine thyroid function tests impose an additional financial burden on healthcare systems. Moreover, the psychological distress associated with a misdiagnosis of a chronic condition especially in pregnant women and can degrade patients' quality of life, causing anxiety and unnecessary lifestyle adjustments. (8–11)

The objective of this study is to evaluate the prevalence of macro TSH in patients presenting with elevated total TSH values. We utilized polyethylene glycol (PEG) precipitation methods to distinguish macro TSH from free TSH, thereby identifying cases of false elevations that contribute to the misdiagnosis of hypothyroidism. Ultimately, this study aims to establish the prevalence of macro TSH interference and inform future research, contributing to improved patient care in endocrinology.

2 Materials and methods

2.1 Study Design and Population

This cross-sectional observational study was conducted at Ali Asghar Hospital between January 2024 and March 2025. The study population initially comprised 171 adult participants: 50 adult men, 50 non-pregnant adult women, and 71 pregnant adult women. All participants had been referred to the specialized endocrinology outpatient clinic following an incidental laboratory finding of abnormal thyroid function tests showing elevated total TSH levels, suggestive of hypothyroidism. (figure – 1)

- **Inclusion Criteria:** Age 18 years; documented total serum TSH level > 4.5 mIU/L on initial screening; and an asymptomatic or minimally symptomatic clinical presentation.

- **Exclusion Criteria:** A known history of thyroid disease or prior thyroidectomy; current or past treatment with levothyroxine, anti-thyroid medications, or amiodarone; known autoimmune conditions; clinical evidence of severe systemic illness; or renal impairment (defined as an estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m²)

Methodological Note on Selection Bias

Because all subjects were recruited from a tertiary endocrinology referral clinic rather than via unselected community screening, a degree of selection bias is acknowledged. This cohort specifically represents patients with a higher likelihood of biochemical discordance.

2.2 Sample Size Justification

The sample size was calculated based on an expected prevalence of macro TSH of approximately 10–12% among patients with isolated, unexplained TSH elevations, as reported in historical literature. Using a single-proportion sample size formula:

$$n = (z^2 \cdot p(1 - p)) / d^2$$

Where:

- Z = 1.96 (for a 95% confidence interval)
- p = 0.11 (estimated prevalence of 11%)
- d = 0.05 (margin of error of 5%)

The minimum required sample size was determined to be approximately 150 patients. Our final enrollment of 171 participants provides sufficient statistical power to determine macro TSH prevalence and diagnostic reclassification rates accurately.

2.3 Laboratory Assays and Methodological Details

2.3.1 Primary Immunoassays

Venous blood samples were collected from all fast-fasting participants at the initial clinical visit. Serum was separated within 30 minutes of collection by centrifugation at 3000 times $\times$ g for 10 minutes. Serum total TSH and free thyroxine (FT4) levels were measured using a commercial Electrochemiluminescence Immunoassay (ECLIA) on an automated analyzer.

- **Total TSH Reference Range:** 0.4 to 4.5 mIU/L (Intra-assay coefficient of variation [CV] < 3.2% Inter-assay CV < 4.5%).
- **FreeT4 Reference Range:** 0.7 to 1.8 ng/dL (Intra-assay CV < 2.8%; Inter-assay CV < 3.9%).

2.3.2 Polyethylene Glycol (PEG) Precipitation for Macro TSH

To investigate macro TSH interference, all samples demonstrating a total TSH value greater than 10 mIU/L underwent PEG precipitation using a protocol optimized from macroprolactin screening:

1. Aliquots of 50 μ L of patient serum were thoroughly mixed with 50 μ L of a 25% aqueous PEG 6000 solution, yielding a final reactant PEG concentration of 12.5%.
2. The mixture was incubated at room temperature (22–24 deg C) for 15 minutes to facilitate macromolecular protein precipitation.
3. The sample was centrifuged at 4000 $\times$ g for 20 minutes at 4 deg C.
4. The supernatant was clear-fractionated and re-assayed for TSH via ECLIA to yield the uncorrected supernatant TSH value.

Because the serum-to-PEG volume ratio introduces a 1:2 dilution factor, the true bioactive Free TSH concentration was calculated by multiplying the supernatant TSH value by 2:

$$\text{Free TSH (mIU/L)} = \text{Supernatant TSH} \times 2$$

The percentage of TSH precipitated by PEG, representing the fraction of macro TSH complexes present was calculated using the following formula:

$$\text{PEG Precipitation \%} = \left(1 - \frac{\text{Supernatant TSH} \times 2}{\text{Total TSH}} \right) \times 100$$

A PEG Precipitation value > 90% was established as the diagnostic threshold confirming the presence of significant macro TSH interference.

2.3.3 validation and Interference Control

- Gel Filtration Chromatography (GFC): To validate the diagnostic accuracy of the PEG screening method, size-exclusion gel filtration chromatography using a Sephacryl S-300 column was performed as a confirmatory reference method on a subset of highly positive samples (n = 15).
- Heterophilic Antibody Exclusion: To ensure that false-positive elevations or precipitation artifacts were not driven by heterophilic antibodies, all discrepant samples exhibiting high total TSH but an indeterminate PEG precipitation profile were pre-treated with commercial Heterophilic Blocking Tubes (HBT) prior to re-assaying. No significant analytical shifts were observed following HBT treatment, confirming that macro TSH complexes were the primary source of analytical interference.

2.4 Simplified Clinical Classification Scheme

To optimize presentation clarity, participants were categorized into exactly three distinct diagnostic groups based on their FT4, baseline total TSH, and recalculated post-PEG bioactive Free TSH thresholds:

Diagnostic Group	Free Thyroxine (FT4) Status	Free TSH (Post-PEG Bioactive Fraction) Status
1. Euthyroid (Normal)	Normal range 0.7–1.8 ng/dL)	Normal range (< 4.5mIU/L)
2. Subclinical Hypothyroidism	Normal range (0.7–1.8 ng/dL)	Elevated (> 4.5 mIU/L)
3. Overt (Clinical) Hypothyroidism	Decreased (< 0.7 ng/d)	Elevated (> 4.5mIU/L)

This uniform classification system was applied twice to each patient: first using the raw total TSH value (traditional method), and second using the corrected Free TSH value, allowing a direct evaluation of diagnostic reclassification.

2.5 Ethical Considerations and Data Handling

The study protocol was approved by the Institutional Review Board (IRB) of the Iran University of Medical Sciences (Approval Number: 05-2024-815). Written informed consent was obtained from all participants prior to enrollment. To protect patient privacy, all clinical, demographic, and laboratory data were completely anonymized at the point of collection using alphanumeric master codes. Laboratory records were stored in an encrypted database accessible only to the primary investigator. All handling, processing, and archiving of patient specimens conformed strictly to the ethical principles outlined in the Declaration of Helsinki.

2.6 Statistical Analysis

Quantitative variables are expressed as mean $\pm$ standard deviation (SD), and categorical variables are reported as frequencies and percentages. Within-subject comparisons between baseline mean Total TSH values and corresponding post-PEG Free TSH values were performed using the paired Wilcoxon signed-rank test (due to non-normal distribution of raw TSH scores). Cross-tabulations demonstrating diagnostic group shifting (traditional vs. corrected methods) were analyzed using the Chi-square test or McNemar's test where appropriate. Bivariate correlations between continuous indices (Total TSH, Free TSH, Macro TSH fraction, and Age) were evaluated using Pearson or Spearman rank correlation coefficients based on distribution profiles. Statistical analyses were executed using Python libraries, including NumPy v2.0.1 and SciPy v1.14.0. A two-tailed $p < 0.05$ was considered statistically significant (12, 13).

3 Results

3.1 Characteristics of patients

The demographic and biochemical characteristics of the study participants are detailed in Tables-1 and 2, stratified by pregnancy status. A total of 100 adult participants (50 men and 50 non-pregnant women)

were included in this group. The mean age was 33.03 ± 10.71 years (range: 18–61). Total TSH, Macro TSH and recalculated free TSH Noted in Table.1. Free T4 levels were categorized into lower or upper normal range, with most patients clustering in the lower-normal category. On the other hand, A total of 71 pregnant women was analyzed separately due to differing physiological and hormonal baselines. The mean age was 28.89 ± 3.54 years (range: 19–36). Total TSH ranged Total TSH, Macro TSH and the corresponding free TSH Noted in Table-2. As with the non-pregnant group, T4 values were qualitatively reported and primarily fell within the lower normal range.

These baseline findings informed further subgroup analysis and diagnostic reclassification based on the contribution of macro TSH.

Table 1
Characteristics of non-pregnant adults (n = 100). This table Summarizes Subjects demographic data including; age, Total TSH, Macro TSH, and free TSH. Most participants had normal-range T4 values.

PARAMETERS	Min	Max	Mean	Median	Standard Deviation
Age (year)	18	61	33.03	30.5	10.71
Total TSH (mIU/L)	8	18	10.77	10.0	1.71
Macro TSH (mIU/L)	2	15	6.89	7.0	2.35
Free TSH (mIU/L)	1	8	3.81	4.0	1.75

Table 2
Characteristics of pregnant women (n = 71).

PARAMETERS	Min	Max	Mean	Median	Standard Deviation
Age (year)	19	36	28.88	29.0	3.54
Total TSH (mIU/L)	7	15	10.15	10.0	1.76
Macro TSH (mIU/L)	2	13	6.71	7.0	2.23
Free TSH (mIU/L)	1	8	3.45	3.0	1.55

Includes age, total TSH, macro TSH, and free TSH. T4 values were within the normal range as noted in the section.

3.2 Prevalence of Hypothyroidism by Diagnostic Method

The classification of hypothyroidism showed marked variation depending on whether total TSH or free TSH (corrected for macro TSH) was used as the diagnostic basis. Table-3 summarizes the diagnostic outcomes for the 100 non-pregnant adults, while Table 4 presents corresponding data for the 71 pregnant participants.

Table 3
Diagnostic classification by total TSH vs. free TSH in non-pregnant adults (n = 100).

Diagnosed by Free TSH					
		Normal	Subclinical	Clinical	total
Diagnosed by total TSH	Subclinical	42	22	0	64
	Clinical	27	0	9	36
	Total	69	22	9	100

Shows cross-tabulation of hypothyroidism categories based on two methods; notable discordance observed.

Among the non-pregnant adults (Table-3), total TSH-based classification diagnosed a statistically significant (Chi-square p-value < 0.001) higher number of individuals with subclinical or clinical hypothyroidism compared to the free TSH-based approach (Figure-2).

Similarly, in pregnant women (Table-4), the prevalence of hypothyroidism was significantly lower (Chi-square p-value < 0.001) when assessed using free TSH. Of the 49 pregnant women initially categorized as having subclinical hypothyroidism by total TSH, 39 were reclassified as normal after macro TSH exclusion. Among 22 women labeled as clinically hypothyroid, 15 were later identified as euthyroid by the free TSH method (Figure-3).

Table 4
Diagnostic classification by total TSH vs. free TSH in pregnant women (n = 71).

Diagnosed by Free TSH					
		Normal	Subclinical	Clinical	Total
Diagnosed by total TSH	Subclinical hypothyroidism	39	10	0	49
	Clinical Hypothyroidism	15	0	7	22
	Total	54	10	7	71

Presents category agreement; results highlight misclassification risk when relying on total TSH alone.

Visualizes diagnostic shifts when using free TSH versus total TSH in pregnancy; highlights increased false positives with total TSH. (Difference are significant with p-value of 0.001)

3.3 Correlation Between Thyroid indices

According to the correlation analysis of non-pregnant and pregnant adults illustrated in *Figure-4* and *Figure-5* respectively, there was no significant correlation observed between **total TSH** and **free TSH**

levels in adults, suggesting a weak relationship between these two commonly used thyroid markers ($p > 0.05$). This finding was similarly replicated among pregnant participants.

Additionally, no significant correlation was found between either total TSH or free TSH with age or gender, indicating that these demographic factors did not meaningfully influence the TSH values in our population.

In contrast, a strong and statistically significant correlation was observed between total TSH and macro TSH levels, while free TSH did not show a similar relationship with macro TSH. These findings further emphasize the divergence between total and free TSH metrics in the assessment of thyroid function.

4 Discussion

This study aimed to investigate the clinical implications of macro TSH in the diagnosis of hypothyroidism. Our findings reveal that macro TSH may significantly affect thyroid function tests, potentially leading to misdiagnosis and unnecessary treatment (8, 9, 14). This discussion contextualizes the key findings and their implications, addresses limitations, and proposes future research directions.

The main objective of this study was to evaluate the prevalence of macro TSH and its role in the misdiagnosis of hypothyroidism. We found that when macro TSH was excluded from total TSH measurements, the diagnosis of hypothyroidism was significantly altered (9, 14). In both non-pregnant and pregnant adults, total TSH-based classifications identified a higher prevalence of subclinical and clinical hypothyroidism compared to the free TSH method. This discrepancy suggests that the presence of macro TSH may contribute to the overdiagnosis of hypothyroidism, particularly when total TSH is used as the sole diagnostic marker. Notably, our confirmed high prevalence of macro TSH (71.9% overall) persisted even after making strict methodological adjustments to our inclusion criteria and final reacting PEG concentration. This rate is higher than general population screenings because our cohort consisted entirely of referred outpatients with pre-existing biochemical discrepancies, introducing a referral bias that enriches the sample for macro TSH. This trend is supported by a recent systematic review by Piticchio et al. (2025) (DOI: 10.1111/cen.15179), which highlights how literature trends and cohort selection criteria heavily influence macro TSH detection rates globally.

These results align with previous studies that have reported macro TSH as a cause of misdiagnosis in hypothyroidism. For instance, research by J. Jin et al. (8) has demonstrated that macro TSH can artificially elevate TSH levels, leading to the false diagnosis of hypothyroidism in patients with normal free T4 levels. Our study further substantiates this finding by showing that when macro TSH is taken into account, the diagnostic reclassification rate is high, especially in pregnant women where hormonal fluctuations may exacerbate the effect of macro TSH. From a mechanistic standpoint, macro TSH forms when standard monomeric TSH binds to circulating autoantibodies—primarily of the immunoglobulin G (IgG) class—creating a high-molecular-weight complex. This structure hinders renal clearance, causing serum accumulation, yet it remains biologically inactive because it cannot properly bind thyroid receptors. Interestingly, while general autoimmune thyroid conditions show a clear female

predominance, our study did not find a significant association with gender. This lack of female predominance may stem from sampling bias within our highly specific referral population or platform-specific assay variability in capturing low-affinity antibody complexes.

An interesting and unexpected finding was the lack of a significant correlation between total TSH and free TSH levels in both non-pregnant and pregnant adults. This suggests that these two markers, often used interchangeably in clinical settings, may not be as closely related as traditionally believed. While total TSH and macro TSH levels were strongly correlated, the absence of a similar relationship between total TSH and free TSH underscores the importance of distinguishing between these metrics in thyroid function assessment.

While the findings of this study are compelling, several limitations must be acknowledged. First, the study is cross-sectional in nature, which limits the ability to infer causality. Longitudinal studies would provide more insight into the long-term consequences of macro TSH-related misdiagnosis. Additionally, the use of PEG precipitation and gel filtration chromatography for macro TSH detection, while effective, may not be universally available in all clinical settings, thus limiting the generalizability of the findings (6). Moreover, our study focused primarily on adult patients, with pregnant women analyzed as a separate subgroup. Further research is needed to explore the role of macro TSH in pediatric and elderly populations, where thyroid dysfunction may manifest differently.

Given the significant findings in this study, further investigation into improved diagnostic protocols is warranted. Future studies should aim to develop more accessible and accurate methods for detecting macro TSH in routine clinical practice. Additionally, exploring the impact of macro TSH on treatment outcomes, particularly with levothyroxine therapy, could provide valuable insights into the broader therapeutic consequences of misdiagnosis. Furthermore, exploring the role of other thyroid markers in conjunction with total and free TSH may yield more reliable diagnostic tools.

The implications of this research are far-reaching, particularly in clinical endocrinology. By improving the accuracy of hypothyroidism diagnosis, we can prevent unnecessary treatments and reduce healthcare costs. The findings highlight the importance of considering macro TSH in diagnostic protocols and encourage the incorporation of free TSH testing, especially in patients with discordant thyroid function tests (15). Specifically, our results show that specific patient groups would benefit immensely from macro TSH evaluation, namely individuals with persistently elevated TSH but entirely normal Free T4, or asymptomatic patients with discordant thyroid function results. Clinicians should be mindful of the potential for overdiagnosis, particularly in populations like pregnant women, where hormonal changes may confound results. Ultimately, this study underscores the need for greater diagnostic precision to enhance patient care and reduce the risks associated with inappropriate treatment (14, 16). Addressing this clinical misclassification directly protects patients from the consequences of unnecessary levothyroxine management such as drug-induced thyrotoxicosis, bone loss, or cardiac risks, while lowering the economic burden of lifelong prescriptions and repetitive laboratory follow-ups on the healthcare system.

In conclusion, this study demonstrates that macro TSH is a highly prevalent confounding factor in patients referred for elevated total TSH, leading to substantial overdiagnosis of hypothyroidism. Correcting for macro TSH via PEG precipitation reveals that a majority of these individuals are actually euthyroid. Implementing targeted macro TSH screening for asymptomatic patients with discordant thyroid profiles holds significant clinical and economic value, though further multi-center research is needed to fully standardize these screening protocols internationally.

Declarations

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

DA: Project administration- Conceptualization - Data curation – Investigation- Methodology - review & editing

MM: Writing – original draft - Visualization

MAS: Formal analysis – Software- Visualization - Writing – original draft

MN: Formal analysis – Writing – original draft

All authors read and revised the manuscript.

Funding

No funding was received for conducting this study.

Acknowledgments

We sincerely thank the personnel of Ali Asghar Hospital for their invaluable assistance in facilitating patient visits and creating a conducive environment for this research

Data Availability Statement

The datasets gathered and Analyzed for this study are available upon a reasonable request from the author.

Code availability

The underlying code used for model development, training, and evaluation in this study is not publicly available but may be made available to qualified researchers upon reasonable request from the corresponding author.

Ethics approval and consent to participate

Not applicable – (The study approved by the ethics committee as mentioned in the text)

Consent for publication

Not applicable

Clinical trial number

not applicable

Acknowledgment

Not applicable

References

1. Hattori N, Ishihara T, Matsuoka N, Saito T, Shimatsu A. Anti-Thyrotropin Autoantibodies in Patients with Macro-Thyrotropin and Long-Term Changes in Macro-Thyrotropin and Serum Thyrotropin Levels. *Thyroid*. 2017;27(2):138–46.
2. Gurnell M, Halsall DJ, Chatterjee VK. What should be done when thyroid function tests do not make sense? *Clin Endocrinol (Oxf)*. 2011;74(6):673–8.
3. Kirac CO, Abusoglu S, Paydas Hataysal E, Kebapcilar A, Ipekci SH, Ünlü A, et al. A rare cause of subclinical hypothyroidism: macro-thyroid-stimulating hormone. *Diagnosis (Berl)*. 2020;7(1):75–7.
4. Donadio-Andrei S, Hubert N, Raverot V, Plantin-Carrenard E, Kuczewski E, Charrié A, et al. A challenging case: highly variable TSH in a mother and her two children. *Clin Chem Lab Med*. 2019;57(6):e114–7.
5. Hattori N, Aisaka K, Yamada A, Matsuda T, Shimatsu A. Prevalence and Pathogenesis of Macro-Thyrotropin in Neonates: Analysis of Umbilical Cord Blood from 939 Neonates and Their Mothers. *Thyroid*. 2023;33(1):45–52.
6. Mills F, Jeffery J, Mackenzie P, Cranfield A, Ayling RM. An immunoglobulin G complexed form of thyroid-stimulating hormone (macro thyroid-stimulating hormone) is a cause of elevated serum thyroid-stimulating hormone concentration. *Ann Clin Biochem*. 2013;50(Pt 5):416–20.
7. Favresse J, Burlacu MC, Maiter D, Gruson D. Interferences With Thyroid Function Immunoassays: Clinical Implications and Detection Algorithm. *Endocr Rev*. 2018;39(5):830–50.

8. Jin J, Zhang X, Wang S, Shan Z, Teng W, Teng X. Falsely Elevated Thyroid-Stimulating Hormone Level Due to Macro-TSH Interference: A Case Report. *Ann Lab Med*. 2025;45(4):459–62.
9. Larsson A, Gåfvels M, Karlsson T. Falsely Elevated Thyroid-Stimulating Hormone Results due to Interference by M-Component of IgG-Lambda Type. *Case Rep Oncol*. 2020;13(2):680–2.
10. Chiardi I, Rotondi M, Cantù M, Keller F, Trimboli P. Macro-TSH: An Uncommon Explanation for Persistent TSH Elevation That Thyroidologists Have to Keep in Mind. *J Pers Med*. 2023;13(10).
11. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. *Thyroid*. 2014;24(12):1670–751.
12. Harris CR, Millman KJ, van der Walt SJ, Gommers R, Virtanen P, Cournapeau D, et al. Array programming with NumPy. *Nature*. 2020;585(7825):357–62.
13. Virtanen P, Gommers R, Oliphant TE, Haberland M, Reddy T, Cournapeau D, et al. SciPy 1.0: fundamental algorithms for scientific computing in Python. *Nat Methods*. 2020;17(3):261–72.
14. Sakai H, Fukuda G, Suzuki N, Watanabe C, Odawara M. Falsely elevated thyroid-stimulating hormone (TSH) level due to macro-TSH. *Endocr J*. 2009;56(3):435–40.
15. Mendoza H, Connacher A, Srivastava R. Unexplained high thyroid stimulating hormone: a BIG problem. *BMJ Case Rep*. 2009;2009.
16. Halsall DJ, Fahie-Wilson MN, Hall SK, Barker P, Anderson J, Gama R et al. Macro thyrotropin-IgG complex causes factitious increases in thyroid-stimulating hormone screening tests in a neonate and mother. *Clin Chem*. 2006;52(10):1968-9; author reply 9–70.

Figures

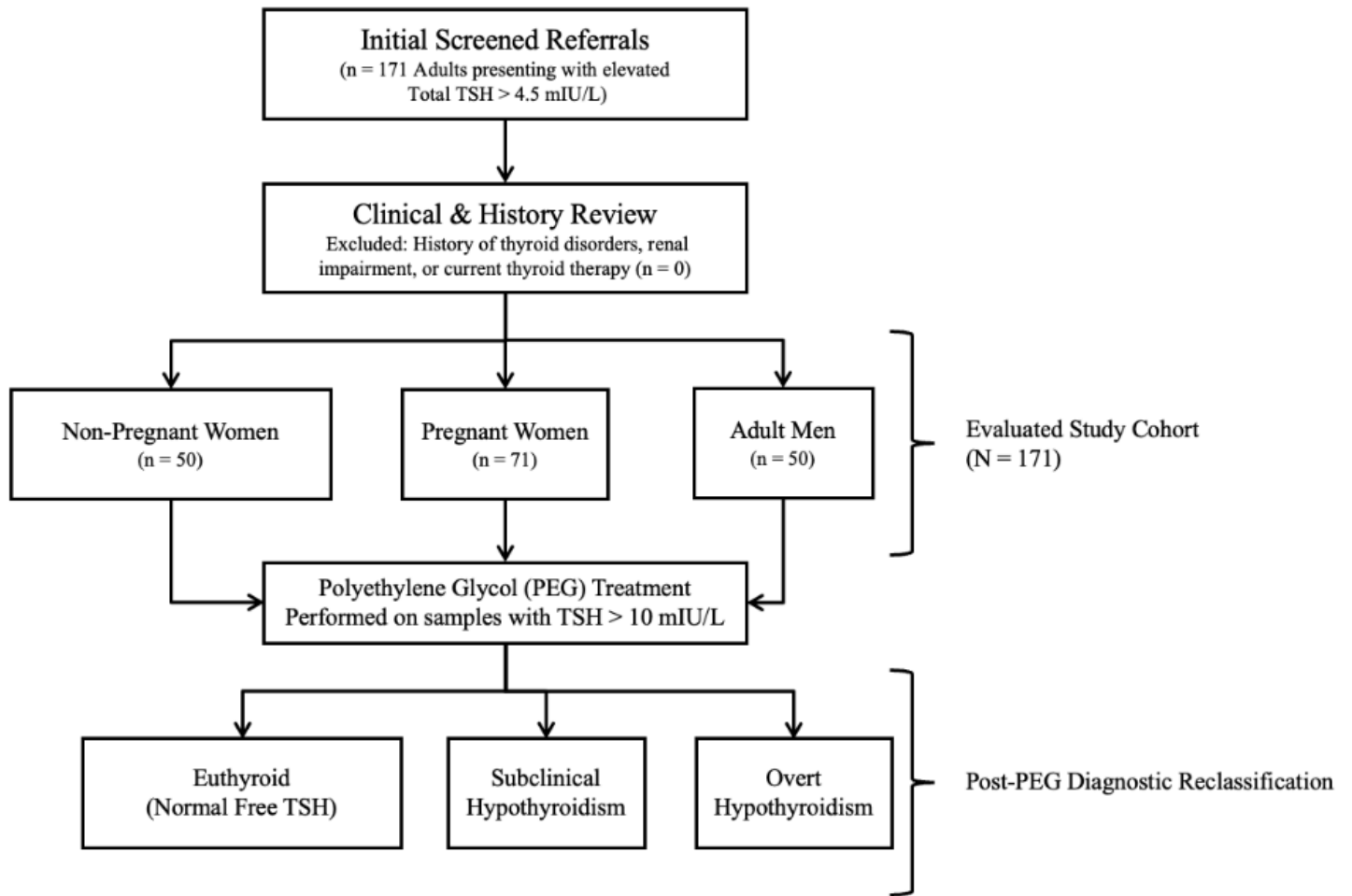


Figure 1

the Study design Diagram

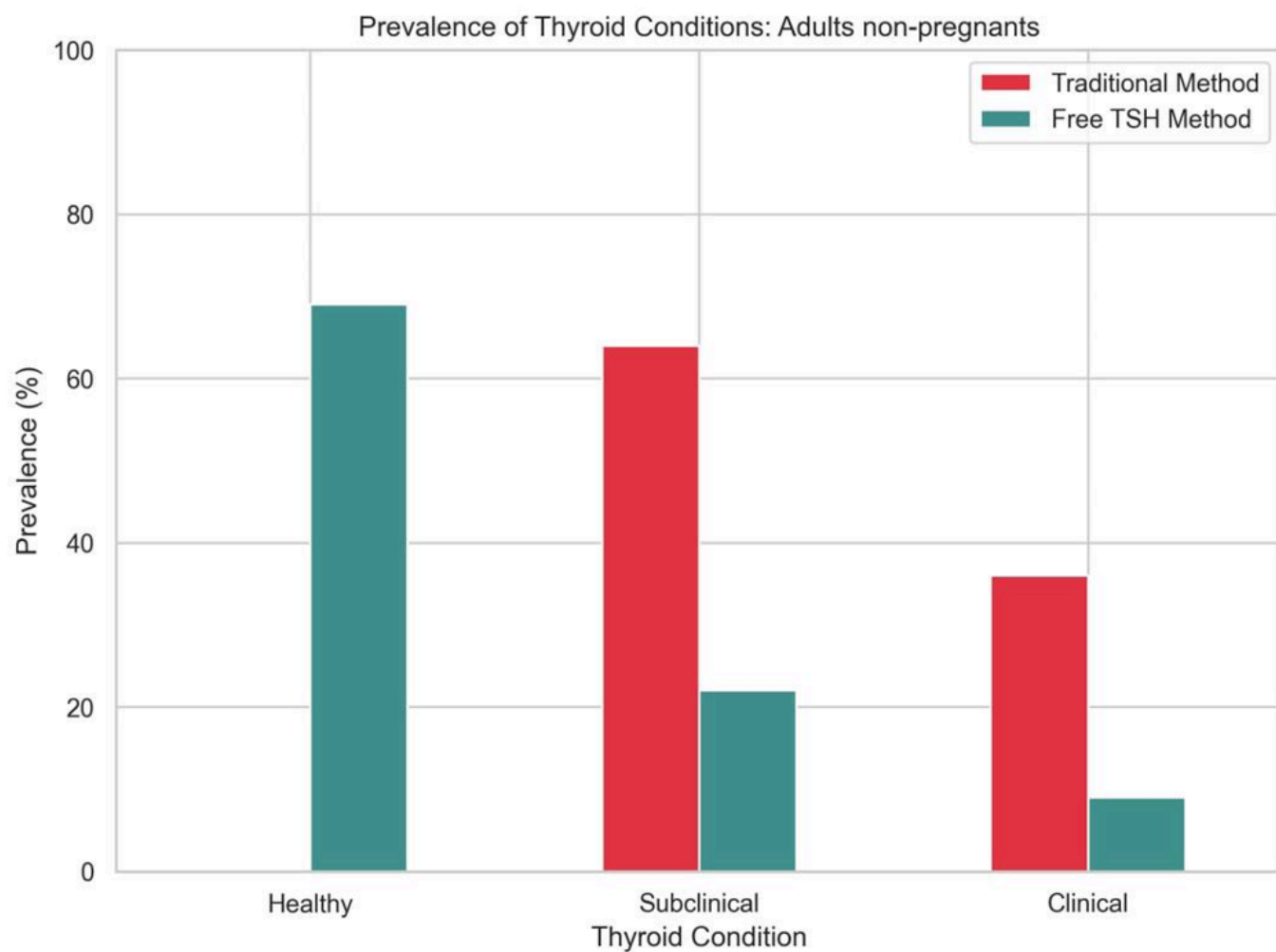


Figure 2

Comparison of diagnostic classification percentages using total TSH vs. free TSH in non-pregnant adults. Bar plot showing the proportion of patients categorized as normal, subclinical, and clinical hypothyroidism by each method. (Difference are significant with p-value of 0.001)

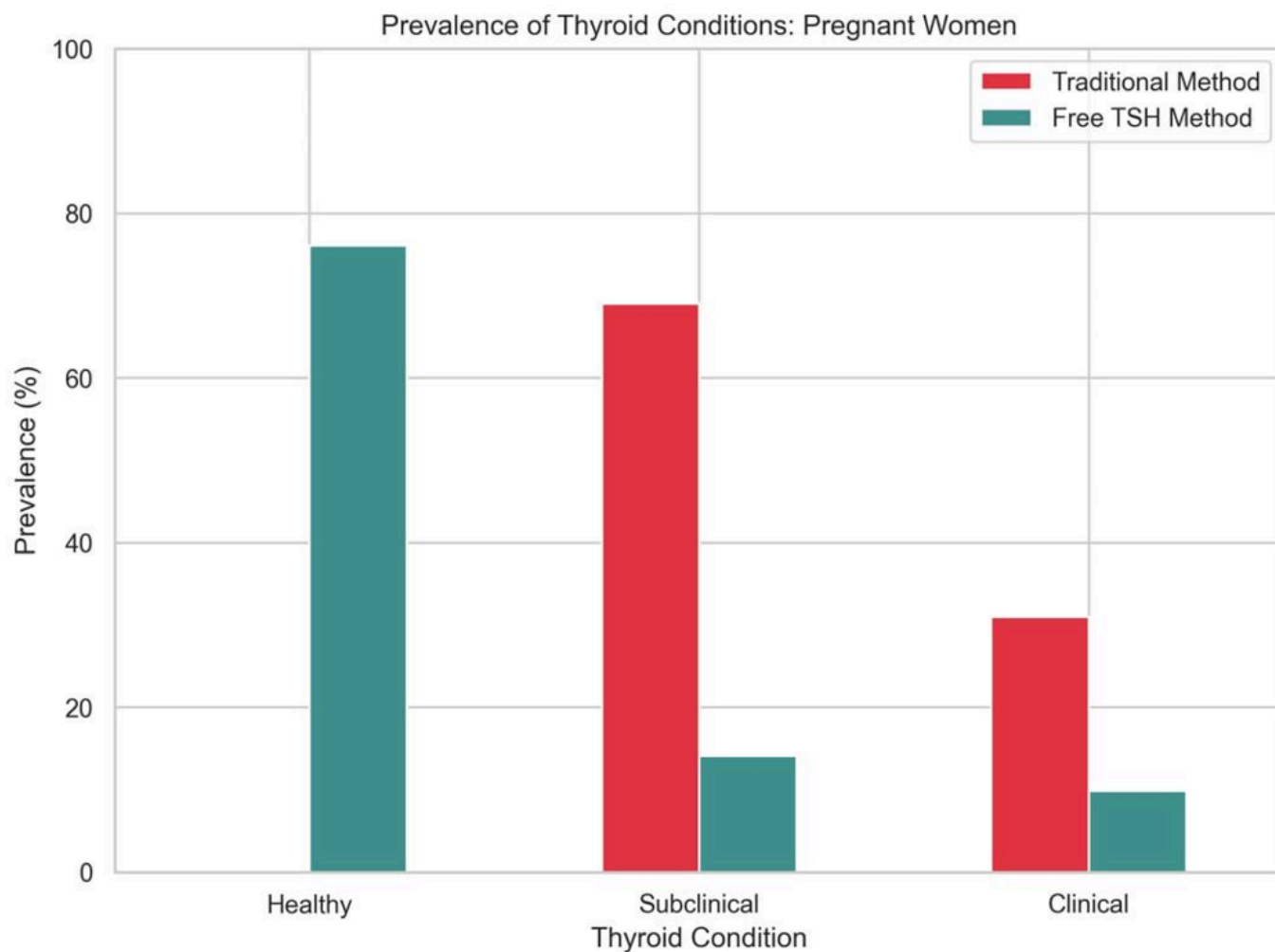


Figure 3

Comparison of diagnostic classification percentages in pregnant women.

Visualizes diagnostic shifts when using free TSH versus total TSH in pregnancy; highlights increased false positives with total TSH. (*Difference are significant with p-value of 0.001*)

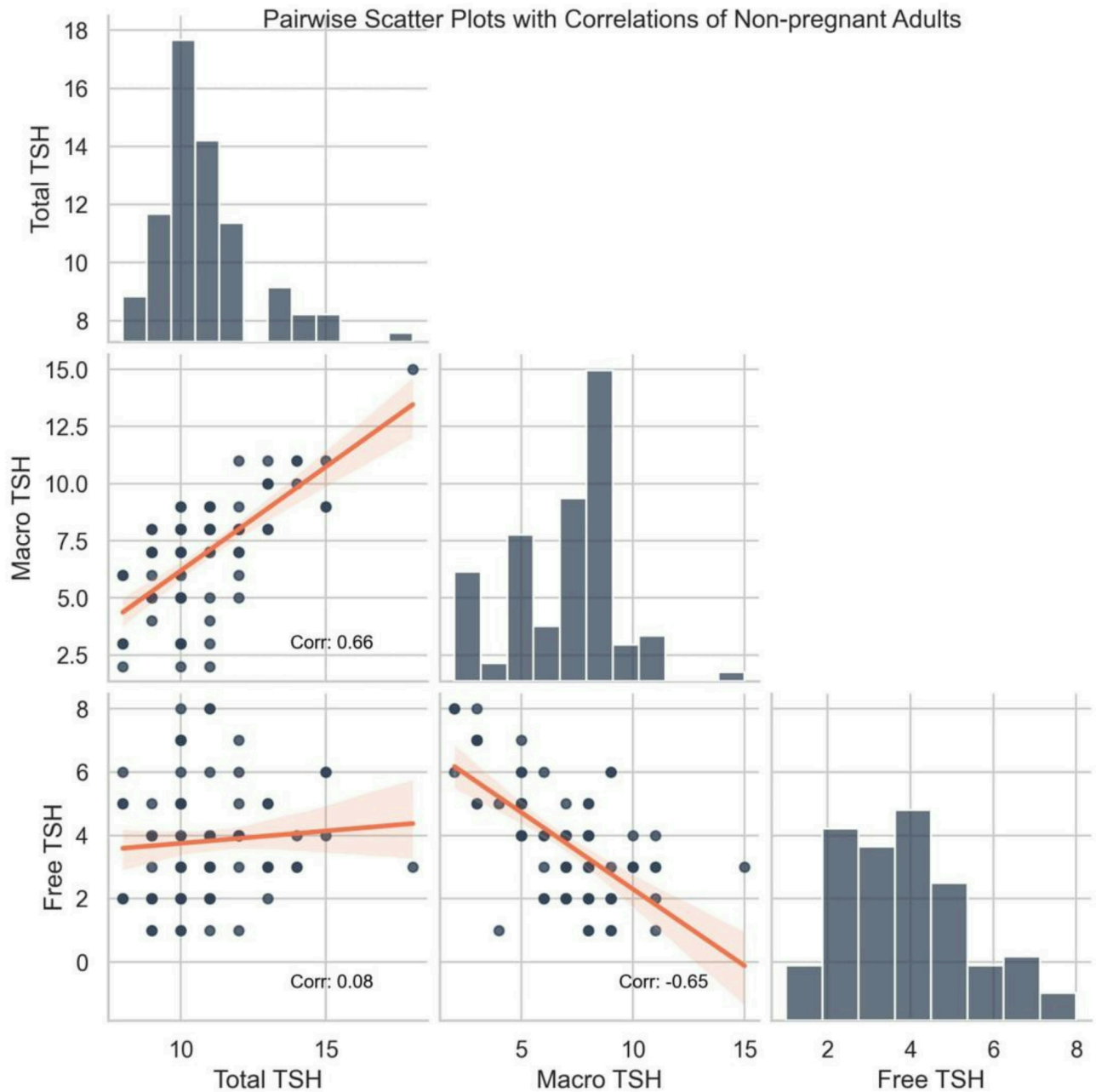


Figure 4

Pairwise scatter plots and correlation analysis among thyroid indices in non-pregnant adults. A strong and significant correlation was observed between Total TSH and Macro TSH levels. However, Free TSH showed weak or no correlation with either Total or Macro TSH. This suggests a potential discrepancy in using Total TSH alone for diagnostic purposes in this group.

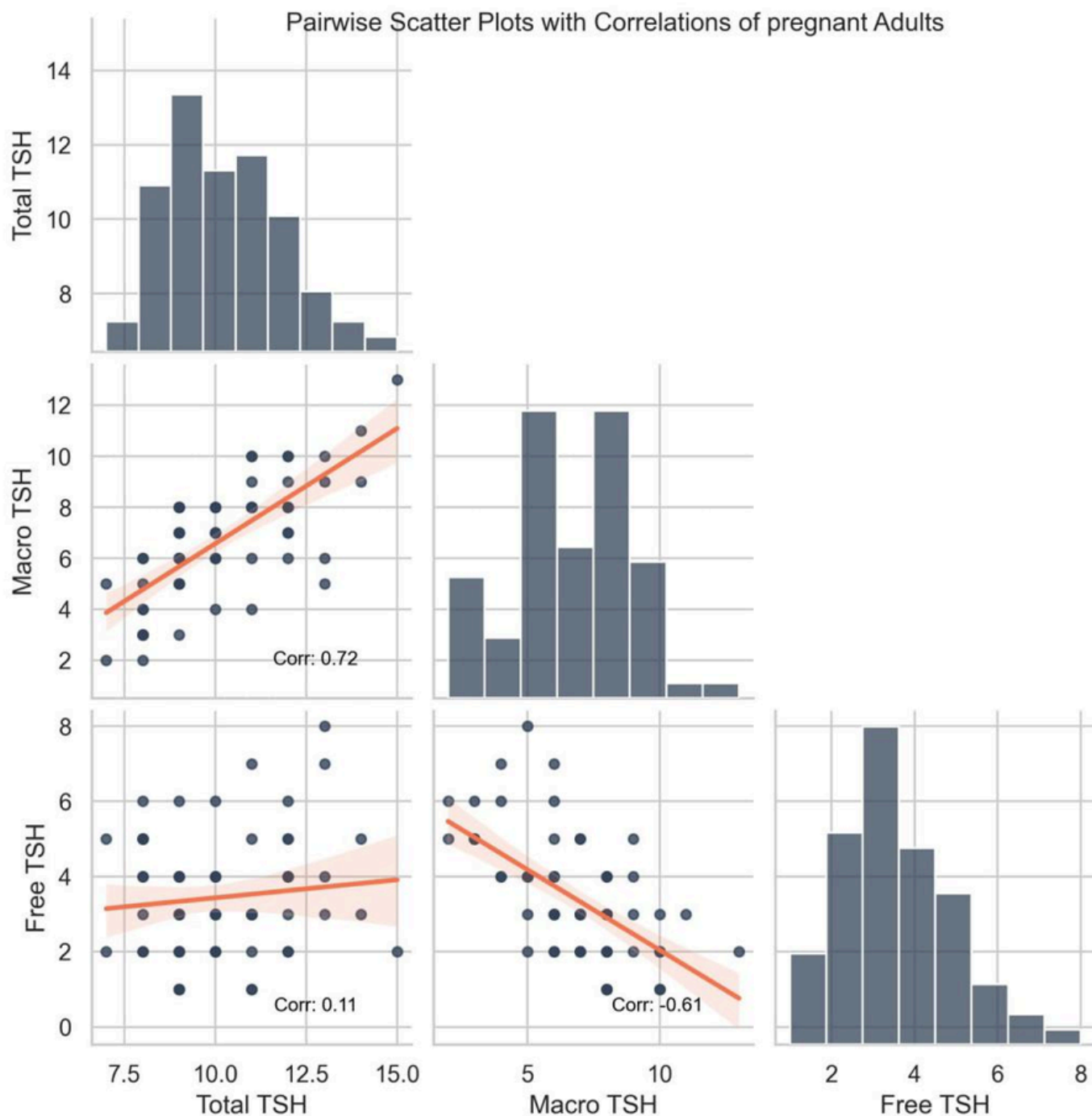


Figure 5

Pairwise scatter plots and correlation analysis among thyroid indices in pregnant women. The plot demonstrates a strong and statistically significant correlation between Total TSH and Macro TSH. In contrast, Free TSH exhibited weak or no correlation with either Total TSH or Macro TSH. These findings highlight the limited predictive relationship between Total and Free TSH in this population.