Clinical Research Article

Causal Association Between Serum Thyrotropin and Obesity: A Bidirectional, Mendelian Randomization Study

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Abbreviations: BMI, body mass index; fT3, free 3,5,3′-triiodothyronine; fT4, free thyroxine; GIANT, Genetic Investigation of ANthropometric Traits consortium; GWAS, genome-wide association study; IV, instrument variable; IVW, inverse variance-weighted; MR, mendelian randomization; RCT, randomized controlled trial; SNV, single-nucleotide variation; TSH, thyrotropin.

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Abstract

Context: The association between serum thyrotropin (TSH) and obesity traits has been investigated previously in several epidemiological studies. However, the underlying causal association has not been established.

Objective: This work aimed to determine and analyze the causal association between serum TSH level and obesity-related traits (body mass index [BMI] and obesity).

Methods: The latest genome-wide association studies (GWASs) on TSH, BMI, and obesity were searched to obtain full statistics. Bidirectional 2-sample mendelian randomization (MR) was performed to explore the causal relationship between serum TSH and BMI and obesity. The inverse variance-weighted (IVW) and MR-Egger methods were used to combine the estimation for each single-nucleotide variation (formerly single-nucleotide polymorphism). Based on the preliminary MR results, free thyroxine (fT4) and free 3,5,3′-triiodothyronine (fT3) levels were also set as outcomes to further analyze the impact of BMI on them. BMI and obesity were treated as the outcomes to evaluate the effect of serum TSH on them, and TSH was set as the outcome to estimate the effect of BMI and obesity on it.

Results: IVW and MR-Egger results both indicated that genetically driven serum TSH did not causally lead to changes in BMI or obesity. Moreover, the IVW method showed that the TSH level could be significantly elevated by genetically predicted high BMI (β = .038, SE = 0.013, P = .004). In further MR analysis, the IVW method indicated that BMI could
causally increase the fT3 ($\beta = 10.123, SE = 2.523, P < .001$) while not significantly affecting the fT4 level.

**Conclusion:** Together with fT3, TSH can be significantly elevated by an increase in genetically driven BMI.

**Key Words:** mendelian randomization, TSH, obesity, BMI

Subclinical hypothyroidism is defined as a subclinical state of elevated serum thyrotropin (TSH) levels with a normal level of thyroxine (1). According to our recent cross-sectional study, the prevalence of subclinical hypothyroidism in mainland China increased from 3.22% in 1999 to 12.93% in 2016, nearly 20 years after the universal salt iodization policy (2). Based on the same study, the 97.5th percentile of the TSH level increased to 7.04 mU/L in the reference population (3), which is much higher than the upper limit provided by the manufacturer (4.20 mU/L).

A number of previous studies have demonstrated a positive association between supranormal TSH and cardiovascular risk, metabolic disorders, and mortality (4-6). Moreover, even for euthyroid individuals, the elevation of TSH levels within the reference interval might also correlate with adverse cardiovascular outcomes and various metabolic disorders (7, 8), including obesity (9). Therefore, with the increasing trend of subclinical hypothyroidism prevalence and TSH level, the aforementioned outcomes related to TSH cannot be ignored.

In addition to TSH elevation, obesity is also a major burden on public health. Obesity plays an important role in comorbidities such as cardiovascular diseases, diabetes, and cancers (10-12). According to data from the European Social Survey, the obesity prevalence has reached 15.9% in Europe in recent years, which is much higher than the 11% reported in 2000 (13). Another repeated cross-sectional study in mainland China confirmed that the median body mass index (BMI) increased by 2.30 from 1989 to 2011, with the obesity prevalence increasing from 1.97% to 14.79% (14). Obesity prevalence and BMI are now increasing yearly; thus, more potential targets that could control obesity traits are required to suppress the risks related to elevated BMI.

A number of previous cross-sectional studies have demonstrated a positive relationship between TSH and BMI or TSH and obesity phenotypes. Rahbar et al concluded that euthyroid individuals with relatively higher TSH levels tended to have higher BMI values and a higher risk of obesity (15). Based on data from the National Health and Nutrition Examination Survey, Kitahara et al found a positive association between TSH and BMI among euthyroid adults (16), which was similar to the findings from another Danish study (17). A community prospective study in the United States also verified the cross-sectional associations of baseline TSH and body weight, but the study found that baseline TSH levels were not associated with weight change during follow-up (18). Therefore, the causal association between TSH and obesity phenotype is debatable. Similar to these results, several cross-sectional studies found that TSH levels in individuals with obesity were significantly higher than those in controls with normal weight (19-21). However, related prospective studies have found different results from these prospective findings. Studies have found that TSH levels in obese patients could decrease after weight loss (22-24), while anorexic patients showed the opposite trend after weight gain (25). These studies suggested that the association between TSH and obesity traits might be more complicated than we thought.

Although there have been prospective studies that investigated the causal association between TSH and obesity traits to some extent (22-25), we could not guarantee that human intervention affects outcome merely through the method of exposure. For example, could the hypothalamus-pituitary-thyroid axis be directly affected by weight-loss drugs or surgical stress (26, 27)? Moreover, the role of confounding factors could not be ruled out by prospective studies, such as socioeconomic status and education.

Mendelian randomization (MR) is a powerful method for identifying causal inference using genetic variants as instrument variables (IVs) and has achieved great success in assessing causation between risk factors and diseases (28). It can minimize the impact of confounders on causal estimation since the genetic variants are randomly allocated at conception. In view of the fact that the previous epidemiological studies did not clearly establish a causal association between TSH and obesity phenotype, bidirectional 2-sample MR might help disentangle the complicated causal relationship between them. Here, we leveraged publicly available results from genome-wide association studies (GWASs) to investigate whether causation exists between TSH level and obesity and to evaluate and analyze the causal effect.

**Materials and Methods**

**Data Sources**

We searched for all TSH-related GWASs to date on the GWAS catalog website (https://www.ebi.ac.uk/gwas/), and a GWAS meta-analysis conducted by Zhou et al was found.
to have the largest sample size to date (29), including the HUNT study (N = 55 342), the MGI biobank (N = 10 085), and the ThyroidOmics consortium (N = 54 288), with more than 22 million single-nucleotide variations (SNVs; formerly single-nucleotide polymorphisms [SNPs]) tested. Individuals with a personal history of thyroid disorders were generally excluded.

GWAS summary statistics on BMI were downloaded from the Genetic Investigation of ANthropometric Traits consortium (GIANT), which is currently the largest GWAS on anthropometric phenotypes, consisting of data from the UK Biobank and GIANT Consortium (http://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files). The GWAS included up to 807 000 individuals and approximately 2.3 million SNVs (30).

The obesity-related GWAS database was also downloaded from the GWAS catalog website (https://www.ebi.ac.uk/gwas/), which is currently the only database on obesity phenotypes from public sources with full summary statistics (31). The GWAS meta-analysis consisted of 14 relevant studies, with 5530 cases (≥ 95th percentile of BMI) and 8318 controls (< 50th percentile of BMI). Approximately 2.54 million SNVs were thoroughly tested.

To minimize heterogeneity, all 3 GWASs were conducted on individuals of European ancestry.

Selection of Instrument Variables

We selected SNVs as IVs based on the fundamental principle of MR. As mentioned earlier, IVs had to be strongly associated with exposure (P < 5 × 10⁻⁶) and had to be solely associated with outcome of interest through the pathway of exposure (32). In addition, IVs should not be associated with any potential confounders. In this study, blood pressure, blood glucose, and blood lipids were identified as confounding factors when BMI or obesity was identified as the outcome, while thyroid antibodies, thyroxine, and 3,5,3′-triiodothyronine were identified as confounding factors when TSH was identified as the outcome. In addition, a crude model without exclusion of these confounding factors was also initially applied to assess the causal association between exposures and outcomes to ensure statistical power. We discarded all SNVs with a direct significant association (P < 1 × 10⁻⁵) with any confounding factor using a phenotype-wide association study method (https://gwas.mrcieu.ac.uk/). Furthermore, we selected IVs with further quality control based on minor allele frequency greater than or equal to 0.05. Qualified IVs were clustered based on their pairwise linkage disequilibrium (r² < 0.01). IVs that were significantly associated with the outcome after Bonferroni correction (P < .05/number of SNVs) were subsequently dropped. Finally, SNV harmonization was conducted to correct the orientation of the alleles.

Mendelian Randomization Estimation and Statistical Analysis

For each IV, we estimated the effect of exposure on the outcome using the Wald ratio estimation. All valid IV estimations were combined by the inverse variance-weighted (IVW) method, and the MR-Egger method was used as a supplement to IVW. MR-Egger regression and the Cochran Q test were applied to estimate pleiotropy and heterogeneity, respectively. We eliminated the possibility that the MR-Egger intercept had a P value of less than .05 with the exclusion of possible horizontal pleiotropy. If the P value of the Cochran Q test was less than .05, the final results of MR referred to a multiplicative random-effects model of IVW; otherwise, a fixed-effects model was used. To further assess the independent potency of each IV, leave-one-out sensitivity analysis was also performed. We considered a P value of less than .05 to indicate a statistically significant causal association between exposure and outcome.

Statistical analysis was performed with R version 3.4.3 (https://www.r-project.org/). The R package “TwoSampleMR” version 0.4.25 (https://github.com/MRCIEU/TwoSampleMR) was applied.

Results

Screen and Validation of Instrument Variables

SNVs that met the requirements were screened with the process mentioned earlier. The potency of each IV was assessed based on F statistics (F = β_exp²/SE_exp²). The F statistics ranged from 28.444 to 844.055, which indicated that all IVs were strongly associated with each exposure. We set up 2 models according to whether confounding factors of outcomes were considered. Sixty-five or 48 SNVs were considered IVs when MR between genetically predicted TSH and BMI was performed. Sixty or 40 SNVs were identified as IVs when we analyzed the causal relationship between genetically predicted TSH and the obesity phenotype. On the other hand, 918 or 903 IVs were enrolled in MR between genetically predicted BMI and the outcome TSH. Five or 4 IVs were enrolled when we conducted MR between genetically predicted obesity and TSH. Each set of regression analysis was performed under 2 models. Since model 1 did not exclude the influence of confounding factors, model 1 is only for reference, and the results of model 2 are obviously more credible.
Detailed information about the IVs included in model 1 (crude model) and model 2 (adjusted model) is listed in Supplementary Tables 1 and 2, respectively (listed in a digital research material repository) (33).

Bidirectional 2-Sample Mendelian Randomization Between Thyrotropin and Obesity Traits

The results of bidirectional 2-sample MR are displayed in Tables 1 to 4. As shown in Tables 1 and 2, serum TSH levels could not lead to changes in BMI or obesity risk. Regardless of whether the IVW or MR-Egger method was applied, model 1 and model 2 both showed similar nonsignificant results.

However, when we switched exposure and outcome to the other direction, different results were found. Owing to the high heterogeneity of 903 IVs in MR between genetically predicted BMI and the outcome TSH ($Q$ for Cochran $Q$ test = $3.938 \times 10^{-5}$), the results of the multiplicative random effects IVW method were preferred. As shown in Table 3, TSH showed a significant increasing tendency with increasing BMI ($\beta = .038$, SE = 0.013, $P = .004$) based on the results of multiplicative random effects IVW in model 2. In other words, for every SD (0.391) increase in BMI, TSH could significantly increase by 0.038 SDs. Therefore, a 0.391 increase in BMI leads to an increase in serum TSH of 0.039 mU/L. For the association between the genetically predicted obesity phenotype and TSH, we did not observe any significant result between them, which is shown in Table 4.

One-Directional 2-Sample Mendelian Randomization Between Body Mass Index and Free Thyroid Hormones

In view of the fact that genetically predicted BMI causally affects serum TSH concentration but not vice versa, the one-directional positive association has led us to further analysis. Driven by genetically increased BMI, it is still unknown whether the elevation of TSH is related to hypothyroidism or BMI simply promotes an increase in the set point of TSH. Therefore, we performed a further one-directional MR analysis between BMI and serum free thyroid hormone levels. We used the same GWAS BMI database as earlier (30), and the GWAS data regarding serum free thyroxine (fT4) and free 3,5,3′-triiodothyronine (fT3) were derived from the InCHIANTI study (Invecchiare in Chianti, aging in the Chianti area) (34). The summary data of the InCHIANTI study are publicly available and were downloaded from daGaP (https://www.ncbi.nlm.nih.gov/gap/advanced_search/?TERM=phs000215). The researchers selected 93 circulating indicators (including fT3 and fT4) and performed a GWAS analysis of an Italian population. In total, data from 1144 and 1149 individuals were included in the GWAS of fT3 and fT4, respectively.

Two and 4 SNVs were selected as the IVs when fT3 and fT4, respectively, were set as the outcome (detailed information on IVs is listed in Supplementary Table 3) (33). As shown in Table 5, the IVW method (random-effects model) indicated that an increase in BMI could causally elevate serum fT3 levels ($\beta = 10.123$, SE = 2.523, $P < .001$). However, the IVW and the MR-Egger method both showed nonsignificant causal associations between BMI and serum fT4.

Discussion

Based on the current largest GWAS on TSH and BMI, this bidirectional 2-sample MR study provides evidence of the causal relationship between them. We demonstrated for the first time that the TSH concentration could be significantly increased with genetically predicted high BMI, whereas genetically predicted high TSH may not significantly induce an increase in BMI. Because the GWAS on the obesity phenotype with a relatively small scale was

### Table 1. Results of mendelian randomization between genetically predicted thyrotropin (exposure) and body mass index (outcome)

| Analysis type | $N_{SNV}$ | $\beta$ | SE  | $P$     | $Q$       | $Q_P$     | Egger intercept | Intercept_P |
|---------------|-----------|---------|-----|---------|-----------|-----------|-----------------|-------------|
| IVW, fixed    |           |         |     |         |           |           |                 |             |
| Model 1       | 65        | .011    | 0.005 | .011    | 127.351   | $4.292 \times 10^{-6}$ | .001         | .231        |
| Model 2       | 48        | .008    | 0.005 | .144    | 79.911    | .002      | $3.859 \times 10^{-4}$ | .675        |
| IVW, random   |           |         |     |         |           |           |                 |             |
| Model 1       | 65        | .011    | 0.006 | .073    | 127.351   | $4.292 \times 10^{-6}$ | .001         | .231        |
| Model 2       | 48        | .008    | 0.007 | .263    | 79.911    | .002      | $3.859 \times 10^{-4}$ | .675        |
| MR-Egger      |           |         |     |         |           |           |                 |             |
| Model 1       | 65        | –.005   | 0.015 | .727    | 124.456   | $6.377 \times 10^{-6}$ | .001         | .231        |
| Model 2       | 48        | .001    | 0.016 | .935    | 79.602    | .002      | $3.859 \times 10^{-4}$ | .675        |

Model 1, crude; Model 2, SNVs associated with confounding factors (blood pressure, blood lipids, or blood glucose) were all excluded by the phenome-wide association study. $Q$ and $Q_P$ represent the Cochran $Q$ value and corresponding $P$ value for estimated heterogeneity; Egger intercept and intercept_P represent estimated pleiotropy effect and corresponding $P$ value.

Abbreviations: IVW, inverse variant-weighted; MR, mendelian randomization; SNV, single-nucleotide variation (formerly single-nucleotide polymorphism [SNP]).
selected, the number of IVs that meet the screening requirements is obviously smaller than that of the other 2 phenotypes. In addition, the GWAS we selected was based on the childhood obesity phenotype. Although an obesity-related genetic background can be carried during the lifetime, there are certain differences between childhood and lifelong obesity phenotypes. The discrepancy in age in different studies might also bias the final results. However, we can also explain this result from another side: Although genetically predicted BMI could significantly lead to increased TSH, childhood adiposity may not predict elevated TSH during the lifetime. In addition, to explore whether the hyperthyrotropinemia driven by increases in BMI was related to hypothyroidism, we conducted a subsequent one-directional MR analysis between genetically predicted BMI and serum fT3 and fT4 levels. The subsequent results indicated that BMI elevation also contributed to an increase in fT3.

Table 2. Results of mendelian randomization between genetically predicted thyrotropin (exposure) and obesity (outcome)

| Analysis type | N_{SNV} | OR (95% CI) | P | Q | Q_P | Egger intercept | Intercept_P |
|---------------|---------|-------------|---|---|-----|-----------------|-------------|
| IVW, fixed    | Model 1 | 60          | 1.162 (0.997-1.354) | .055 | 75.737 | .070 | 0.013 | .208 |
|               | Model 2 | 40          | 1.037 (0.872-1.232) | .682 | 45.395 | .223 | -0.009 | .478 |
| IVW, random   | Model 1 | 60          | 1.162 (0.988-1.336) | .090 | 75.737 | .070 | 0.013 | .208 |
|               | Model 2 | 40          | 1.037 (0.850-1.224) | .704 | 45.395 | .223 | -0.009 | .478 |
| MR-Egger      | Model 1 | 60          | 0.920 (0.520-1.319) | .683 | 73.678 | .080 | 0.013 | .208 |
|               | Model 2 | 40          | 1.190 (0.769-1.611) | .423 | 44.790 | .208 | -0.009 | .478 |

Model 1, crude; Model 2, SNVs associated with confounding factors (blood pressure, blood lipids, or blood glucose) were all excluded by the phenome-wide association study. Q and Q_P represent the Cochran Q value and corresponding P value for estimated heterogeneity; Egger intercept and intercept_P represent estimated pleiotropy effect and corresponding P value.

Abbreviations: IVW, inverse variant weighted; MR, mendelian randomization; OR, odds ratio; SNV, single-nucleotide variations (formerly single-nucleotide polymorphisms [SNPs]).

Table 3. Results of mendelian randomization between genetically predicted body mass index (exposure) and thyrotropin (outcome)

| Analysis type | N_{SNV} | \beta | SE  | P    | Q    | Q_P  | Egger intercept | Intercept_P |
|---------------|---------|-------|-----|------|------|------|-----------------|-------------|
| IVW, fixed    | Model 1 | 918   | .031| .012 | .010 | 1111.565 | 9.689 \times 10^{-6} | .191        |
|               | Model 2 | 903   | .038| .012 | .002 | 1079.502 | 4.062 \times 10^{-4} | .519        |
| IVW, random   | Model 1 | 918   | .031| .013 | .020 | 1111.565 | 9.689 \times 10^{-6} | .191        |
|               | Model 2 | 903   | .038| .013 | .004 | 1079.502 | 4.062 \times 10^{-4} | .519        |
| MR-Egger      | Model 1 | 918   | -.021| .042 | .612 | 1109.488 | 7.863 \times 10^{-4} | .191        |
|               | Model 2 | 903   | .011| .045 | .807 | 1079.004 | 4.062 \times 10^{-4} | .519        |

Model 1, crude; Model 2, SNVs associated with confounding factors (thyroid antibodies, thyroxine, or triiodothyronine) were all excluded by the phenome-wide association study. Q and Q_P represent the Cochran Q value and corresponding P value for estimated heterogeneity; Egger intercept and intercept_P represent estimated pleiotropy effect and corresponding P value.

Abbreviations: IVW, inverse variant weighted; MR, mendelian randomization; SNV, single-nucleotide variations (formerly single-nucleotide polymorphisms [SNPs]).

Table 4. Results of mendelian randomization between genetically predicted obesity (exposure) and thyrotropin (outcome)

| Analysis type | N_{SNV} | \beta  | SE   | P    | Q    | Q_P  | Egger intercept | Intercept_P |
|---------------|---------|--------|------|------|------|------|-----------------|-------------|
| IVW, fixed    | Model 1 | 5     | -.008| 0.012| .514 | 5.284 | .259 | 9.178 \times 10^{-4} | .970        |
|               | Model 2 | 4     | .003 | 0.009| .731 | 1.462 | .481 | -0.002 | .922        |
| IVW, random   | Model 1 | 5     | -.008| 0.013| .570 | 5.284 | .259 | 9.178 \times 10^{-4} | .970        |
|               | Model 2 | 4     | .003 | 0.013| .809 | 1.462 | .481 | -0.002 | .922        |
| MR-Egger      | Model 1 | 5     | -.012| 0.117| .923 | 5.281 | .152 | 9.178 \times 10^{-4} | .970        |
|               | Model 2 | 4     | .013 | 0.089| .899 | 1.474 | .688 | -0.002 | .922        |

Model 1, crude; Model 2, rs571312 associated with confounding factor (thyroxine level) was excluded by the phenome-wide association study. Q and Q_P represent the Cochran Q value and corresponding P value for estimated heterogeneity; Egger intercept and intercept_P represent estimated pleiotropy effect and corresponding P value.

Abbreviations: IVW, inverse variant weighted; MR, mendelian randomization; SNV, single-nucleotide variations (formerly single-nucleotide polymorphisms [SNPs]).
Although a number of observational studies have found a positive relationship between TSH and BMI, the underlying causality is currently unclear. Prospective studies have demonstrated that obese individuals generally had higher current or incident TSH (35, 36). On the other hand, individuals with higher baseline TSH levels also generally have higher BMI or tend to develop obesity during follow-up (37-39). However, several epidemiological studies did not reach the same conclusion. Lee et al considered that TSH within the reference range was significantly associated with BMI cross-sectionally rather than longitudinally (7). Another 10-year cohort study found that fT4 variation alone was negatively associated with follow-up BMI, whereas no significant association was found between TSH and BMI at follow-up (40). In addition, although we mentioned previously that weight loss or gain may be related to a decrease or increase in TSH, there are also studies that found no or even an opposite correlation between the variation in body weight and TSH (41-43). A 1-year prospective study conducted by Wolters et al found that a reduction in TSH during weight-loss intervention was related to weight rebound after intervention (44), which is worthy of further investigation. These studies indicate that the exact causal association between TSH and BMI or TSH and the obesity phenotype requires more evidence. Using the MR method, the present study found for the first time that the serum TSH level in Europeans could be increased as a result of genetically increased BMI, but not vice versa. In the future, the causal relation between BMI and TSH still needs to be verified among larger populations and different races.

Interestingly, in our further one-directional MR analysis, we found that genetically increased BMI could also induce an increase in serum fT3, indicating that the hyperthyrotropinemia caused by overweight is not due to hypothyroidism. Although only 2 SNVs were screened as the IVs and the validity of the results is not as stable as the relation shown by MR between BMI and TSH, such a causal association has also been confirmed by several previous studies. It has been demonstrated that in obese patients undergoing metabolic surgery or lifestyle intervention, serum fT3 could be significantly reduced along with TSH during follow-up, while the fT4 level showed nonsignificant variation (44, 45). Moreover, several cross-sectional studies also found similar associations (46-48). Based on the results of the present study and other relevant studies, we speculate that the causal association between BMI and TSH may be due to an increase in the TSH set point rather than thyroid damage.

In recent years, with the extensive development of GWAS, MR studies have also expanded. Traditional randomized controlled trial (RCT) research can confirm the causal relationship between different variables, although this research is also limited by various issues; thus, the implementation of RCTs faces many difficulties. Moreover, we cannot avoid the effects of various confounding factors or the direct influence of external intervention on outcome in RCT research, and the sample sizes of RCTs are generally not comparable to the thousands and millions that represent the sample sizes in GWAS. Therefore, MR is an ideal method when we need to explore the causal relationship between different indicators. A recently published MR study analyzed the causality between thyroid function and cardiovascular risk factors such as blood pressure, blood lipids, diabetes, and obesity traits (49). The authors found no significant evidence of causal associations between genetically predicted TSH and BMI, or vice versa. Although their research and our present research used the GIANT database on BMI, the GWAS database of TSH used in these 2 studies was not consistent (29, 50). In the aforementioned study, 72 167 individuals with TSH within the cohort-specific reference range were enrolled in the GWAS meta-analysis. On the other hand, the inclusion and exclusion criteria of the 3 studies are not consistent in the GWAS meta-analysis cited in the present study, although various
thyroid disorders were also ruled out. We speculated that the difference in inclusion/exclusion criteria and sample size might be the reason for the difference in results. At present, there are few MR studies on the relationship between thyroid dysfunction and metabolic abnormalities such as obesity. Therefore, the causality between TSH and BMI requires more MR studies to confirm.

The advantages and limitations of this study are as follows. First, we selected the largest GWAS databases on TSH and BMI, which ensures an authentic result. Second, we used MR to conclude for the first time that genetically predicted BMI leads to an increase in TSH and fT3, which also provides some explanation for some previous epidemiological investigations. However, the databases in this study are all derived from European populations. Whether these results are universal is still unknown. Moreover, the only GWAS database currently available on obesity is based on the childhood obesity phenotype, and the sample size and IVs that can be included are relatively small. Based on this database, we did not find a causal association between TSH and the obesity phenotype. In addition, we preliminarily confirmed that an increase in BMI can increase TSH based on 2 large-sample GWAS databases, and we then verified that fT3 could also be increased by genetically predicted BMI in another small-sample database; however, the data supporting these 2 outcomes were not from the same population. We believe that if the sequencing results for TSH and free thyroid hormones from the same population could be analyzed, the MR results might be more convincing.

In conclusion, the bidirectional 2-sample MR study provides evidence of a causal association between BMI and TSH, and the further 1-directional MR subsequently provides an explanation for the preliminary results. Together with TSH levels, serum fT3 levels can also be elevated by genetically increased BMI, whereas fT4 levels are not significantly affected by increases in BMI.

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Additional Information

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Data Availability: All data generated or analyzed in the present study are included in the data repositories listed in “References.”

References

1. Biondi B, Cappola AR, Cooper DS. Subclinical hypothyroidism: a review. JAMA. 2019;322(2):153-160.
2. Li Y, Teng D, Ba J, et al. Efficacy and safety of long-term universal salt iodization on thyroid disorders: epidemiological evidence from 31 provinces of Mainland China. Thyroid. 2020;30(4):568-579.
3. Zhao L, Teng D, Shi X, et al. The effect of increased iodine intake on serum thyrotropin: a cross-sectional, Chinese nationwide study. Thyroid. 2020;30(12):1810-1819.
4. Floriani C, Gencer B, Collet TH, Rodondi N. Subclinical thyroid dysfunction and cardiovascular diseases: 2016 update. Eur Heart J. 2018;39(7):503-507.
5. Kim JM, Kim BH, Lee H, et al. The relationship between thyroid function and different obesity phenotypes in Korean euthyroid adults. Diabetes Metab J. 2019;43(6):867-878.
6. Rodondi N, den Elzen WP, Bauer DC, et al; Thyroid Studies Collaboration. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. JAMA. 2010;304(12):1365-1374.
7. Lee JJ, Pedley A, Marqusee E, et al. Thyroid function and cardiovascular disease risk factors in euthyroid adults: a cross-sectional and longitudinal study. Clin Endocrinol (Oxf). 2016;85(6):932-941.
8. Ren R, Ma Y, Deng F, et al. Association between serum TSH levels and metabolic components in euthyroid subjects: a nationwide population-based study. Diabetes Metab Syndr Obes. 2019;12:1563-1569.
9. Zhang X, Li Y, Zhou X, Han X, Gao Y, Ji L. Association between serum thyrotropin within the euthyroid range and obesity. Endocr J. 2019;66(5):451-457.
10. Argéritos KI, Spyrou N, Mantzoros CS, Dalamaga M. Obesity and cancer risk: Emerging biological mechanisms and perspectives. Metabolism. 2019;92:121-135.
11. Csige I, Ujvárosy D, Szabó Z, et al. The impact of obesity on the cardiovascular system. J Diabetes Res. 2018;2018:3407306.
12. Polsky S, Ellis SL. Obesity, insulin resistance, and type 1 diabetes mellitus. Curr Opin Endocrinol Diabetes Obes. 2015;22(4):277-282.
13. Marques A, Peralta M, Naia A, Loureiro N, Gaspar de Matos M. Prevalence of adult overweight and obesity in 20 European countries, 2014. Eur J Public Health. 2018;28(2):295-300.
14. Chen Y, Peng Q, Yang Y, Zheng S, Wang Y, Lu W. The prevalence and increasing trends of overweight, general obesity, and abdominal obesity among Chinese adults: a repeated cross-sectional study. BMC Public Health. 2019;19(1):1293.
15. Rahbar AR, Kalantarhormozi M, Izadi F, et al. Relationship between body mass index, waist-to-hip ratio, and serum lipid concentrations and thyroid-stimulating hormone in the euthyroid adult population. Iran J Med Sci. 2017;42(3):301-305.
16. Kitahara CM, Platz EA, Ladenson PW, Mondul AM, Menke A, Berrington de Gonzalez A. Body fatness and markers of thyroid function among U.S. men and women. PLoS One. 2012;7(4):e34979.
17. Knudsen N, Laurberg P, Rasmussen LB, et al. Small differences in thyroid function may be important for body mass index and the occurrence of obesity in the population. J Clin Endocrinol Metab. 2005;90(7):4019-4024.

18. Fox CS, Pencina MJ, D’Agostino RB, et al. Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. Arch Intern Med. 2008;168(6):587-592.

19. Cho WK, Nam HK, Kim JH, et al. Thyroid function in Korean adolescents with obesity: results from the Korea National Health and Nutrition Examination Survey VI (2013-2015). Int J Endocrinol. 2018;2018:6874395.

20. Diniz MFHS, Belegoli AMR, Benseñor IM, Lotufo PA, Goulart AC, Barreto SM. Association between TSH levels within the reference range and adiposity markers at the baseline of the ELSA-Brasil study. PloS One. 2020;15(2):e0228801.

21. Santos Palacios S, Llaverio Valero M, Brugos-Larumbe A, Diez JJ, Guillén-Grima F, Galofré JC. Prevalence of thyroid dysfunction in a large southern European population. Analysis of modulatory factors. The APNA study. Clin Endocrinol (Oxf). 2018;89(3):367-375.

22. Chikunguwo S, Brethauer S, Nirujogi V, et al. Influence of obesity and surgical weight loss on thyroid hormone levels. Surg Obes Relat Dis. 2007;3(6):631-635.

23. Juiz-Valiña P, Outeiriño-Blanco E, Pértega S, et al. Effect of weight loss after bariatric surgery on thyroid-stimulating hormone levels in euthyroid patients with morbid obesity. Nutrients. 2019;11(5):1121.

24. Morteza Taghavi S, Rakni H, Fatemi S. Metformin decreases thyrotropin in overweight women with polycystic ovarian syndrome and hypothyroidism. Diab Vasc Dis Res. 2011;8(1):47-48.

25. Reinehr T, Isa A, de Sousa G, Dieffenbach R, Andler W. Thyroid hormones and their relation to weight status. Horm Res. 2008;70(1):51-57.

26. Michalaki M, Vagenakis AG, Argentou M, Myлонas P, Kalfarentzos F, Kyriazopoulou V. Dissociation of thyrotropin and leptin secretion in acute surgical stress in severely obese patients. Obes Surg. 2009;19(10):1424-1429.

27. Vázquez-Borrego MC, Fuentes-Fayos AC, Gaheite MD, Castaño JP, Kineman RD, Luque RM. The pituitary gland is a novel major site of action of metformin in non-human primates: a potential path to expand and integrate its metabolic actions. Cell Physiol Biochem. 2018;49(4):1444-1459.

28. Emdin CA, Khera AV, Kathiresan S. Mendelian randomization. JAMA. 2017;318(19):1925-1926.

29. Zhou W, Brumpton B, Kabil O, et al. GWAS of thyroid stimulating hormone highlights pleiotropic effects and inverse association with thyroid cancer. Nat Commun. 2020;11(1):3981.

30. Pulit SL, Stoneman C, Morris AP, et al; GIANT Consortium. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. Hum Mol Genet. 2019;28(1):166-174.

31. Bradford JP, Taal HR, Timpson NJ, et al; Early Growth Genetics Consortium. A genome-wide association meta-analysis identifies new childhood obesity loci. Nat Genet. 2012;44(5):526-531.

32. Zheng J, Baird D, Borges MC, et al. Recent developments in mendelian randomization studies. Curr Epidemiol Rep. 2017;4(4):330-345.

33. Wang X, Gao X, Han Y, et al. Supplementary data to the paper: Causal association between serum thyroid-stimulating hormone and obesity: a bidirectional mendelian randomization study. Dryad data set, Deposited March 29, 2021. https://doi.org/10.5061/dryad.0xwdbzrj

34. Wood AR, Perry JRB, Tanaka T, et al. Imputation of variants from the 1000 Genomes Project modestly improves known associations and can identify low-frequency variant-phenotype associations undetected by HapMap based imputation. PloS One. 2013;8(5):e64334.

35. Ghergherechi R, Hazhir N. Thyroid hormonal status among children with obesity. Ther Adv Endocrinol Metab. 2015;6(2):51-55.

36. Wang Y, Dong X, Fu C, et al. Thyroid stimulating hormone (TSH) is associated with general and abdominal obesity: a cohort study in school-aged girls during puberty in East China. Front Endocrinol (Lausanne). 2020;11:620.

37. Chen SY, Lin SJ, Lin SH, Chou YY. Early adiposity rebound and obesity in children with congenital hypothyroidism. Pediatr Neonatol. 2013;54(2):107-112.

38. Lee MK, Kim YM, Sohn SY, Lee JH, Won YJ, Kim SH. Evaluation of the relationship of subclinical hypothyroidism with metabolic syndrome and its components in adolescents: a population-based study. Endocrine. 2019;65(3):608-615.

39. Mehran L, Amouzegar A, Rahimabad PK, Tohidi M, Tahmasebinejad Z, Azizi F. Thyroid function and metabolic syndrome: a population-based thyroid study. Horm Metab Res. 2017;49(3):192-200.

40. Abdi H, Kazemian E, Gharibzadeh S, et al. Association between thyroid function and body mass index: a 10-year follow-up. Ann Nutr Metab. 2017;70(4):338-345.

41. Akasheh RT, Kroeger CM, Trepanowski JF, et al. Weight loss efficacy of alternate day fasting versus daily calorie restriction in subjects with subclinical hypothyroidism: a secondary analysis. Appl Physiol Nutr Metab. 2020;45(3):340-343.

42. Kouidrat Y, Diouf M, Desailloud R, Louhou R. Effects of a diet plus exercise program on thyroid function in patients with obesity. Metabol Open. 2019;2:100008.

43. Mwafy S, Yassin M, Mousa R. Thyroid hormones, lipid profile and anthropometric changes after programmed weight loss in Palestinian obese adult females. Diabetes Metab Syndr. 2018;12(3):269-273.

44. Wolters B, Lass N, Reinehr T. TSH and free triiodothyronine concentrations are associated with weight loss in a lifestyle intervention and weight regain afterwards in obese children. Eur J Endocrinol. 2013;168(3):323-329.

45. Karaman K, Mansıroglu K, Subasi O, et al. Thyroid hormone changes after sleeve gastrectomy with and without antral preservation. Obes Surg. 2021;31(1):224-231.

46. De Pergola G, Ciampolillo A, Paolotti S, Trerotoli P, Giorgino R. Free triiodothyronine and thyroid stimulating hormone are inversely associated with waist circumference, independently of insulin resistance, metabolic parameters and blood pressure in overweight and obese women. Clin Endocrinol (Oxf). 2007;67(2):265-269.

47. Nie X, Xu Y, Ma X, Xiao Y, Wang Y, Bao Y. Association between abdominal fat distribution and free triiodothyronine in a euthyroid population. Obes Facts. 2020;13(3):358-366.
48. Roef GL, Rietzschel ER, Van Daele CM, et al. Triiodothyronine and free thyroxine levels are differentially associated with metabolic profile and adiposity-related cardiovascular risk markers in euthyroid middle-aged subjects. *Thyroid*. 2014;24(2):223-231.

49. Kuś A, Marouli E, Del Greco MF, et al. Variation in normal range thyroid function affects serum cholesterol levels, blood pressure, and type 2 diabetes risk: a mendelian randomization study. *Thyroid*. 2021;31(5):721-731.

50. Teumer A, Chaker L, Groeneweg S, et al; Lifelines Cohort Study. Genome-wide analyses identify a role for SLC17A4 and AADAT in thyroid hormone regulation. *Nat Commun*. 2018;9(1):4455.