**Additional Material**

**Association of impaired sensitivity to thyroid hormones with hyperuricemia through obesity in the euthyroid population**

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**Table S1** Basic characteristics of the participants according to obesity or not

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Overall** | **Non-obesity** | **Obesity** f | ***P* value** |
| Participants, No. | 28153 | 22497 | 5656 |  |
| Age, mean (SD), y | 47.4 (13.4) | 47.3 (13.5) | 48.0 (13.0) | **<0.001** |
| Sex |  |  |  | **<0.001** |
| Female | 10548 (37.5) | 9424 (41.9) | 1124 (19.9) |  |
| Male | 17065 (62.5) | 13073 (58.1) | 4532 (80.1) |  |
| Educational level |  |  |  | **<0.001** |
| Primary | 2570 (9.1) | 1984 (8.8) | 586 (10.4) |  |
| Secondary | 19956 (70.9) | 15942 (70.9) | 4014 (71.0) |  |
| Tertiary | 5627 (20.0) | 4571 (20.3) | 1056 (18.7) |  |
| Active physical activity a | 11373 (40.4) | 9157 (40.7) | 2216 (39.2) | **0.038** |
| Current smoking | 7278 (25.9) | 5517 (24.5) | 1761 (31.1) | **<0.001** |
| Current drinking | 14610 (51.9) | 11418 (50.8) | 3192 (56.4) | **<0.001** |
| BMI, mean (SD), kg/m2 b | 25.3 (3.5) | 24.0 (2.5) | 30.4 (2.3) | **<0.001** |
| Hypertension c  Diabetes d | 6071 (21.6)  2864 (10.2) | 3946 (17.5)  1935 (8.6) | 2125 (37.6)  929 (16.4) | **<0.001**  **<0.001** |
| TSH, median [IQR], mIU/L | 1.9 [1.4, 2.7] | 1.9 [1.4, 2.7] | 2.0 [1.4, 2.7] | **0.004** |
| FT4, median [IQR], pmol/L | 15.8 [14.3, 17.4] | 15.8 [14.2, 17.4] | 15.9 [14.3, 17.4] | **0.040** |
| UA, mean (SD), μmol/L | 341.0 (89.4) | 329.4 (85.6) | 386.9 (89.3) | **<0.001** |
| Hyperuricemia e | 5968 (21.2) | 3889 (17.3) | 2079 (36.8) | **<0.001** |

Abbreviations: SD, standard deviation; IQR, interquartile range; BMI, body mass index; TSH, thyrotropin; FT4, free thyroxine; UA, uric acid.

SI conversion factors: To convert FT4 to ng/dL, divided by 12.871.

a Active physical activity refers to having moderate or intense exercise ≥80 minutes a weak.

b BMI is calculated as weight in kilograms divided by height in meters squared. Data of BMI were available among 28153 participants.

c Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or self-reported diagnosis history of hypertension or use of any anti-hypertensive medication.

d Diabetes was defined as fasting glucose ≥7.0 mmol/L or self-reported diagnosis history of diabetes or using any glucose-lowering medication.

e Hyperuricemia was defined as serum uric acid ≥360 μmol/L in female and ≥420 μmol/L in male or using uric acid lowering medications.

f Obesity was defined using BMI ≥ 28.0 kg/m2 for the Chinese population.

**Table S2** Logistic regression analysis for the association of thyroid hormone sensitivity and hyperuricemia among 28153 participants with available BMI data

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Model 1** | |  | **Model 2** | |
| **OR (95% CI)** | **P value** |  | **OR (95% CI)** | ***P* value** |
| TFQI |  |  |  |  |  |
| Group 1 | 1 [Ref] |  |  | 1 [Ref] |  |
| Group 2 | 1.048 (0.981-1.120) | 0.166 |  | 1.020 (0.952-1.092) | 0.579 |
| Group 3 | 1.119 (1.033-1.212) | **0.006** |  | 1.023 (0.942-1.111) | 0.592 |
| Group 4 | 1.354 (1.184-1.549) | **<0.001** |  | 1.141 (0.994-1.127) | 0.061 |
| PTFQI |  |  |  |  |  |
| Group 1 | 1 [Ref] |  |  | 1 [Ref] |  |
| Group 2 | 1.052 (0.984-1.124) | 0.138 |  | 1.024 (0.956-1.097) | 0.495 |
| Group 3 | 1.114 (1.029-1.205) | **0.008** |  | 1.017 (0.938-1.104) | 0.680 |
| Group 4 | 1.379 (1.209-1.573) | **<0.001** |  | 1.151 (1.005-1.318) | **0.042** |
| TSHI |  |  |  |  |  |
| Quartile 1 | 1 [Ref] |  |  | 1 [Ref] |  |
| Quartile 2 | 0.996 (0.917-1.081) | 0.916 |  | 1.018 (0.936-1.108) | 0.677 |
| Quartile 3 | 1.056 (0.973-1.145) | 0.191 |  | 1.075 (0.989-1.169) | 0.088 |
| Quartile 4 | 1.136 (1.048-1.231) | **0.002** |  | 1.108 (1.020-1.204) | **0.015** |
| TT4RI |  |  |  |  |  |
| Quartile 1 | 1 [Ref] |  |  | 1 [Ref] |  |
| Quartile 2 | 0.993 (0.916-1.078) | 0.876 |  | 1.015 (0.934-1.104) | 0.721 |
| Quartile 3 | 1.042 (0.961-1.131) | 0.315 |  | 1.094 (1.006-1.189) | **0.036** |
| Quartile 4 | 1.086 (1.002-1.177) | **0.044** |  | 1.164 (1.071-1.265) | **<0.001** |

Abbreviations: OR, odds ratio; CI, confidence interval; TFQI, thyroid feedback quantile-based index; PTFQI, parametric thyroid feedback quantile-based index; TT4RI, thyrotrophic thyroxine resistance index; TSHI, thyroid-stimulating hormone index.

Model 1: crude model; model 2: adjusted for sex, age (continuous), education level (categorical), current smoking (categorical), current drinking (categorical), active physical activity (categorical), hypertension (categorical) and diabetes (categorical).

**Table S3** Mediation analyses of the association of continuous thyroid hormones sensitivity indices and hyperuricemia

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **β (95% CI)** | | | **Mediated**  **Proportion** |
|  | **Total Effect** | **Direct Effect** | **Indirect Effect** |
| TFQI | 0.0090 (0.0043 to 0.0138) | 0.0061 (0.0020 to 0.0112) | 0.0029 (0.0017 to 0.0040) | **32.35% a** |
| PTFQI | 0.0090 (0.0043 to 0.0139) | 0.0061 (0.0020 to 0.0112) | 0.0029 (0.0017 to 0.0040) | **32.29% a** |
| TT4RI | 0.0045 (-0.0001 to 0.0093) | 0.0028 (-0.0012 to 0.0078) | 0.0018 (0.0006 to 0.0029) | **39.63% b** |
| TSHI | 0.0065 (0.0018 to 0.0113) | 0.0042 (0.0001 to 0.0093) | 0.0024 (0.0012 to 0.0035) | **37.68% a** |

Abbreviations: CI, confidence interval; TFQI, thyroid feedback quantile-based index; PTFQI, parametric thyroid feedback quantile-based index; TT4RI, thyrotrophic thyroxine resistance index; TSHI, thyroid-stimulating hormone index.

a P value <0.001.

b P value <0.05.

**Table S4** Estimated direct and indirect effect of thyroid hormones sensitivity indices (categorical) on hyperuricemia

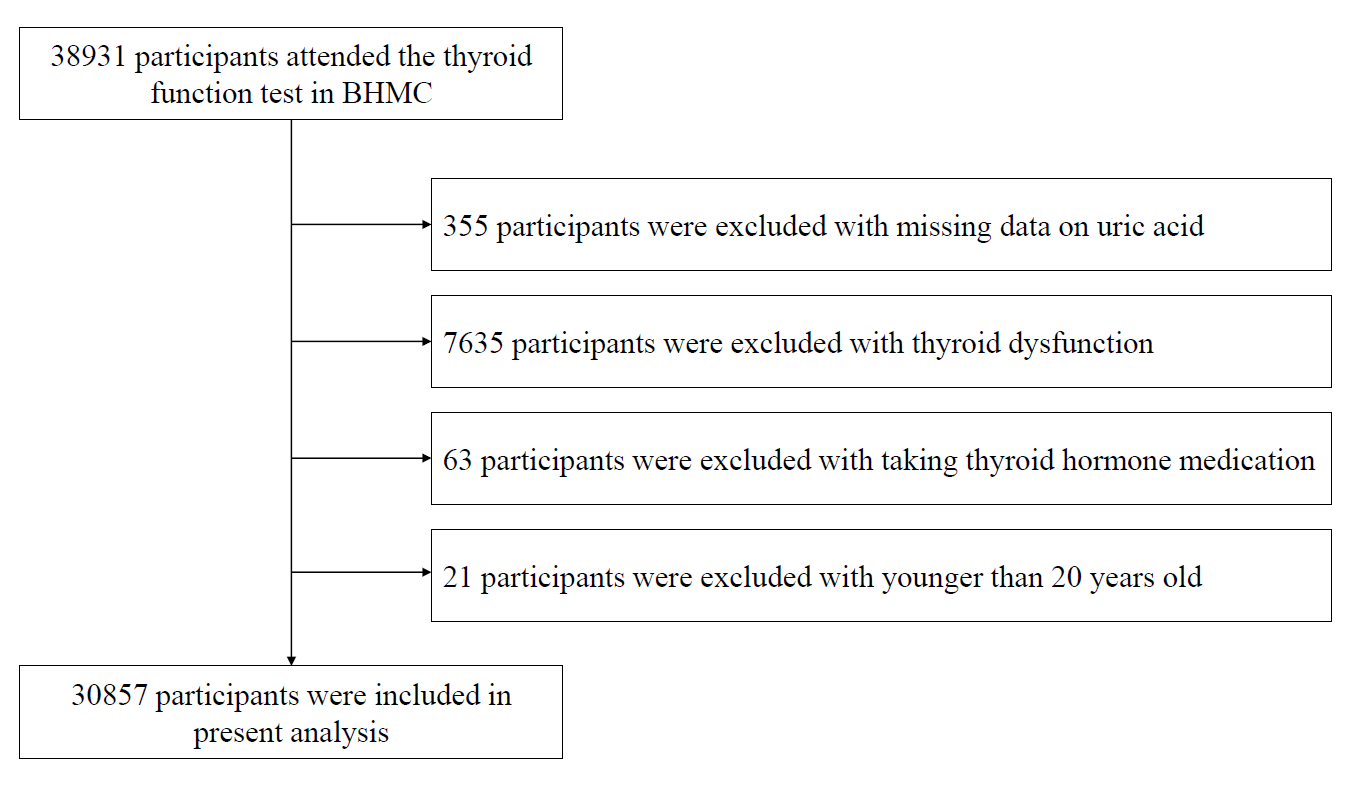
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **HUA, No./**  **Total No.** | **β (95% CI) a** | | | **% Mediated** |
| **Total Effect** | **Direct Effect** | **Indirect Effect** |
| TFQI |  |  |  |  |  |
| Group 1 | 2738 / 13420 | [Ref] | [Ref] | [Ref] |  |
| Group 2 | 1843 / 8704 | 0.0074 (-0.0035 to 0.0201) | 0.0035 (-0.0070 to 0.0157) | 0.0039 (0.0014 to 0.0060) | 53.10 |
| Group 3 | 1069 / 4795 | 0.0187 (0.0040 to 0.0332) | 0.0126 (-0.0015 to 0.0225) | 0.0061 (0.0020 to 0.0093) | 32.54 b |
| Group 4 | 318 / 1234 | 0.0520 (0.0299 to 0.0785) | 0.0430 (0.0228 to 0.0692) | 0.0090 (0.0025 to 0.0161) | 17.31 b |
| PTFQI |  |  |  |  |  |
| Group 1 | 2711 / 13310 | [Ref] | [Ref] | [Ref] |  |
| Group 2 | 1825 / 8609 | 0.0080 (-0.0018 to 0.0214) | 0.0039 (-0.0057 to 0.0170) | 0.0041 (0.0017 to 0.0065) | 51.06 |
| Group 3 | 1098 / 4953 | 0.0177 (0.0039 to 0.0313) | 0.0117 (-0.0013 to 0.0245) | 0.0059 (0.0022 to 0.0092) | 33.62 b |
| Group 4 | 334 / 1281 | 0.0558 (0.0329 to 0.0822) | 0.0457 (0.0224 to 0.0719) | 0.0101 (0.0035 to 0.0170) | 18.06 b |
| TT4RI |  |  |  |  |  |
| Quartile 1 | 1453 / 7018 | [Ref] | [Ref] | [Ref] |  |
| Quartile 2 | 1449 / 7035 | -0.0010 (-0.0127 to 0.0141) | -0.0008 (-0.0120 to 0.0120) | -0.0002 (-0.0036 to 0.0034) | 20.49 |
| Quartile 3 | 1509 / 7053 | 0.0060 (-0.0056 to 0.0185) | 0.0032 (-0.0077 to 0.0152) | 0.0027 (-0.0006 to 0.0066) | 45.96 |
| Quartile 4 | 1557 / 7047 | 0.0128 (0.0023 to 0.0255) | 0.0075 (-0.0031 to 0.0201) | 0.0053 (0.0021 to 0.0091) | 41.29 b |
| TSHI |  |  |  |  |  |
| Quartile 1 | 1435 / 7016 | [Ref] | [Ref] | [Ref] |  |
| Quartile 2 | 1431 / 7021 | -0.0010 (-0.0116 to 0.0144) | -0.0023 (-0.0117 to 0.0115) | 0.0013 (-0.0018 to 0.0047) | -129.42 |
| Quartile 3 | 1509 / 7068 | 0.0083 (-0.0049 to 0.0229) | 0.0033 (-0.0088 to 0.0182) | 0.0049 (0.0012 to 0.0087) | 59.51 |
| Quartile 4 | 1593 / 7048 | 0.0207 (0.0093 to 0.0330) | 0.0142 (0.0027 to 0.0263) | 0.0065 (0.0031 to 0.0100) | 31.30 b |

Abbreviations: HUA, hyperuricemia; CI, confidence interval; TFQI, thyroid feedback quantile-based index; PTFQI, parametric thyroid feedback quantile-based index; TT4RI, thyrotrophic thyroxine resistance index; TSHI, thyroid-stimulating hormone index.

a Refers to the pairwise comparison with group1 or quartile 1 as the reference group.

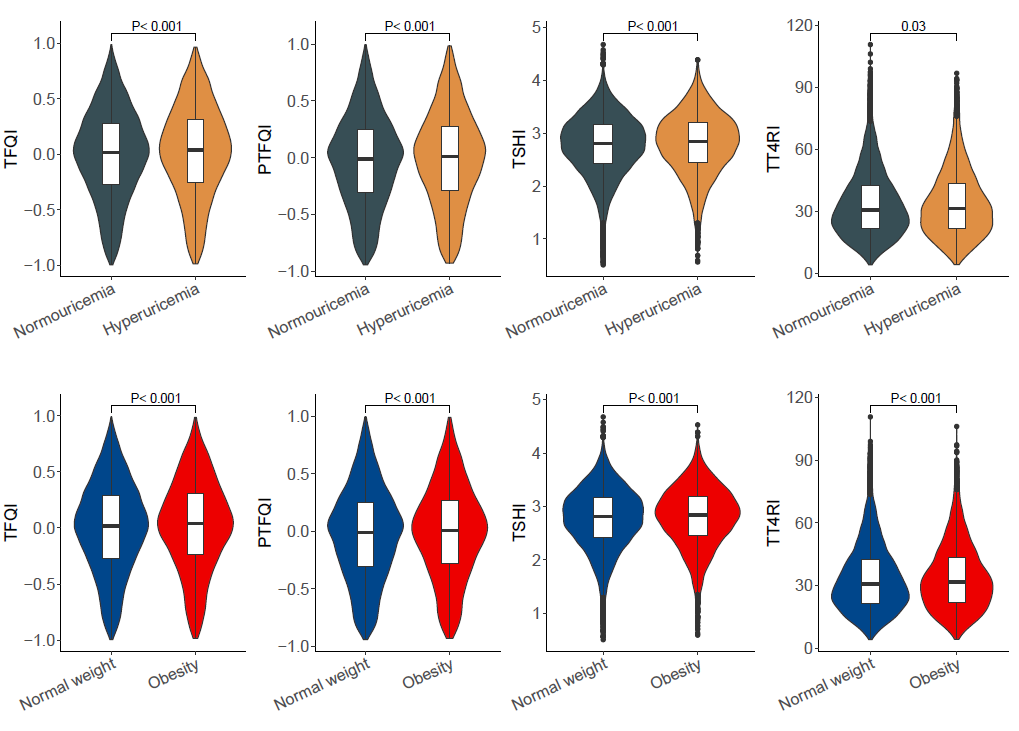
b P value < 0.05.

**Supplemental Figures**



**Figure S1** Flow chart of this current study

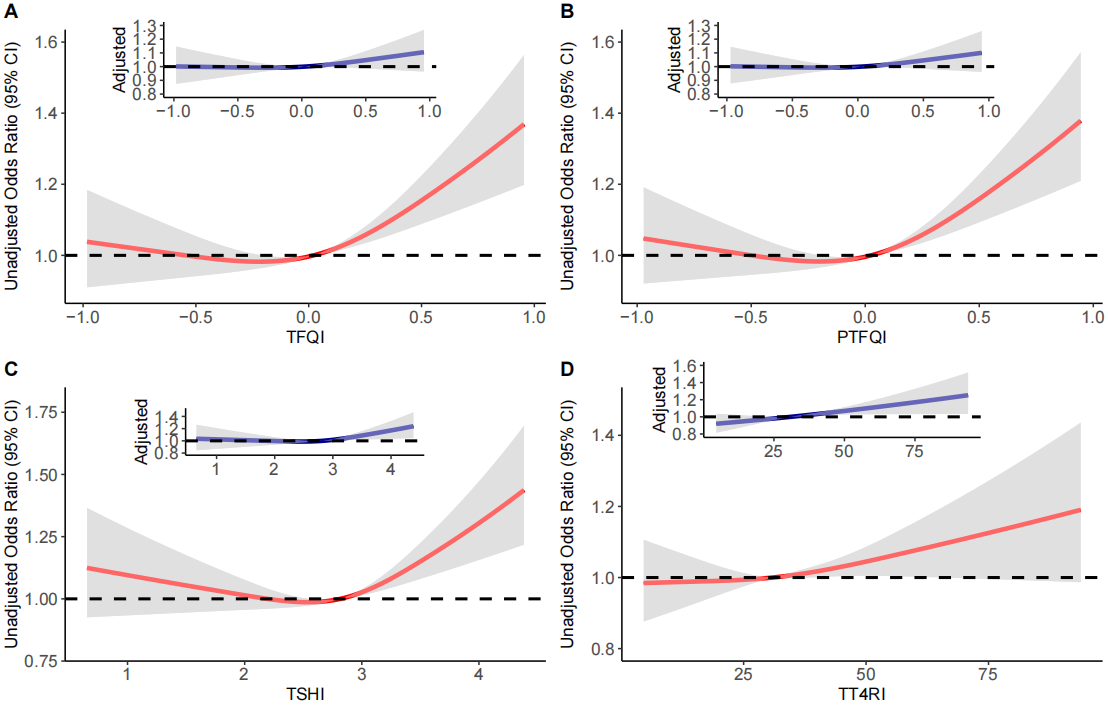
Abbreviations: BHMC, Beijing health management cohort.



**Figure S2** The violin plot and boxplot in distribution of thyroid hormone sensitivity indices between two groups

Abbreviations: TFQI, thyroid feedback quantile-based index; PTFQI, parametric thyroid feedback quantile-based index; TT4RI, thyrotrophic thyroxine resistance index; TSHI, thyroid-stimulating hormone index.

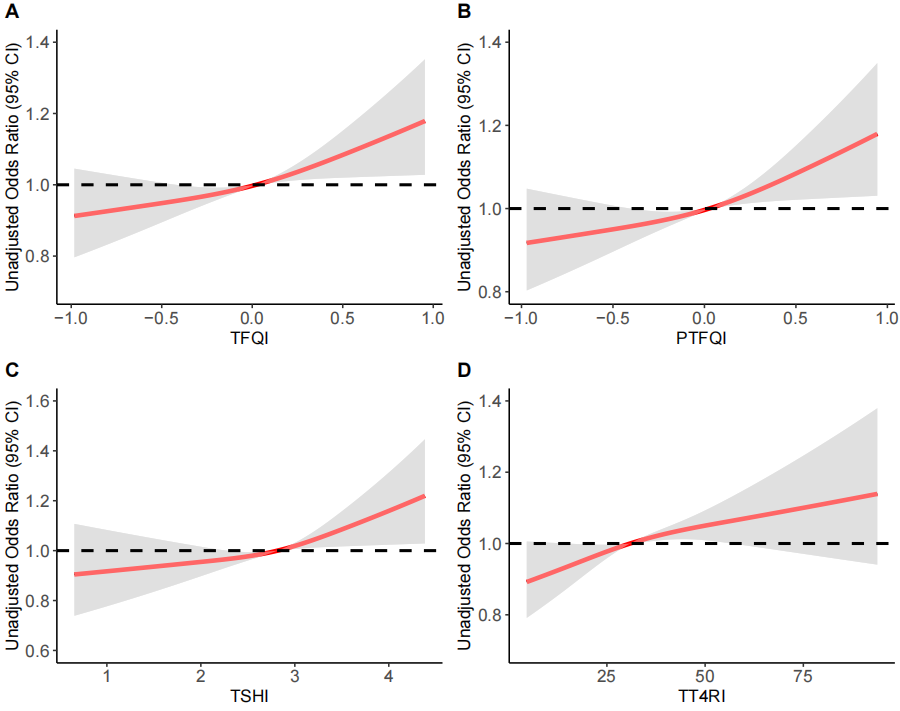
Obesity was defined using BMI ≥ 28.0 kg/m2.



**Figure S3** Unadjusted and adjusted dose-response relationship between thyroid hormone sensitivity indices and hyperuricemia using restricted cubic spline method among 28153 participants with available BMI data

Restricted cubic spline regression model was conducted using 3 knots at the 10th, 50th, and 90th percentiles; results were adjusted for sex, age (continuous), education level (categorical), current smoking (categorical), current drinking (categorical), active physical activity (categorical), hypertension (categorical) and diabetes (categorical).

Abbreviations: BMI, body mass index; TFQI, thyroid feedback quantile-based index; PTFQI, parametric thyroid feedback quantile-based index; TT4RI, thyrotrophic thyroxine resistance index; TSHI, thyroid-stimulating hormone index.



**Figure S4** Dose-response relationship between thyroid hormone sensitivity indices and obesity using restricted cubic spline method among 28153 participants with available BMI data

Abbreviations: BMI, body mass index; TFQI, thyroid feedback quantile-based index; PTFQI, parametric thyroid feedback quantile-based index; TT4RI, thyrotrophic thyroxine resistance index; TSHI, thyroid-stimulating hormone index.

Obesity was defined using BMI ≥ 28.0 kg/m2.