Supplementary Table 1. Association of sex and iron biomarkers with NT-proBNP, in model 3 and 4

|  |  |  |
| --- | --- | --- |
|  | Model 3\* | Model 4† |
| Beta (95% CI) § | Beta (95% CI) § |
| Sex (ref=m) | 0.41 (0.38, 0.44) | 0.34 (0.31, 0.38) |
| Ferritin, µg/L‡ | -0.04 (-0.07, -0.01) | 0.004 (-0.03, 0.04) |
| Hepcidin, nmol/l | -0.03 (-0.06, 0.002) | -0.20 (-0.03, 0.03) |
| sTfR, mg/l | -0.08 (-0.15, -0.01) | -0.12 (-0.20, -0.05) |
| TSAT, % | 0.11 (0.05, 0.17) | 0.23 (0.16, 0.29) |

\*Model 3 was adjusted for age, BMI, smoking, alcohol use, total cholesterol, hs-CRP, eGFR, SBP, lipid-lowering drugs, antihypertensive drugs and T2D

†Model 4 was adjusted for age, BMI, smoking, alcohol use, total cholesterol, hs-CRP, eGFR, SBP, lipid-lowering drugs, antihypertensive drugs, T2D, and hemoglobin.

‡Analyses of iron biomarker were additionally adjusted for sex.

§Statistical test: multiple linear regression. All iron biomarkers and NT-proBNP were log transformed.

CI indicates confidence interval; sTfR, soluble transferrin receptor; TSAT, transferrin saturation; BMI, body mass index; hs-CRP, high-sensitivity c-reactive protein; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; and T2D, type 2 diabetes mellitus.

Supplementary Table 2. Association of sex with iron biomarkers

|  |  |  |
| --- | --- | --- |
| Iron biomarkers | Model 3\* | Model 4† |
| Beta (95% CI) ‡ | Beta (95% CI) ‡ |
| Ferritin, µg/L | -0.39 (-0.42, -0.36) | -0.24 (-0.27, -0.20) |
| Hepcidin, nmol/l | -0.21 (-0.24, -0.18) | -0.12 (-0.15, -0.08) |
| sTfR, mg/l | 0.02 (0.01, 0.03) | -0.01 (-0.03, 0.002) |
| TSAT, % | -0.07 (-0.08, -0.06) | 0.01 (-0.003, 0.03) |

\*Model 3 was adjusted for age, BMI, smoking, alcohol use, total cholesterol, hs-CRP, eGFR, SBP, lipid-lowering drugs, antihypertensive drugs and T2D

†Model 4 was adjusted for age, BMI, smoking, alcohol use, total cholesterol, hs-CRP, eGFR, SBP, lipid-lowering drugs, antihypertensive drugs, T2D, and hemoglobin.

‡Statistical test: multiple linear regression. All iron biomarkers were log transformed.

CI indicates confidence interval; sTfR, soluble transferrin receptor; TSAT, transferrin saturation; BMI, body mass index; hs-CRP, high-sensitivity c-reactive protein; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; and T2D, type 2 diabetes mellitus.

Reference category for sex is men.

Supplementary Table 3. Mediation analyses of iron biomarkers on the association between sex and NT-proBNP

|  |  |  |  |
| --- | --- | --- | --- |
| Iron biomarkers | Model 3\* | | |
| Effects|| | Coefficient  (95% CI) | Mediated proportion  (%)† |
| Ferritin, µg/L | Indirect  Total | 0.015 (0.003, 0.03)  0.40 (0.38, 0.43) | 4% ‡ |
| TSAT, % | Indirect  Total | -0.008 (-0.01, -0.003)  0.40 (0.38, 0.43) | 2% § |

In mediation analysis, only the iron biomarkers that were both associated with sex and NT-proBNP were evaluated.

\*Model 3 was adjusted for age, BMI, smoking, alcohol use, total cholesterol, hs-CRP, eGFR, SBP, lipid-lowering drugs, antihypertensive drugs and T2D.

†Mediated proportion is calculated as the ratio of indirect effect to the total effect and is expressed in percentage.

‡Positive mediator effect; §Negative mediator effect

||Statistical test: mediation analysis. All iron biomarkers and NT-proBNP were log transformed.

CI indicates confidence interval; TSAT, transferrin saturation; and BMI, body mass index; hs-CRP, high-sensitivity c-reactive protein; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; and T2D, type 2 diabetes mellitus.

Supplementary Table 4. Association of iron status with NT-proBNP

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Iron status  (ref= Normal group) | Model 1\* | Model 2† | Model 3‡ | Model 4§ |
| Beta (95% CI) || | | | |
| Absolute iron deficiency | 0.03 (-0.02, 0.07) | 0.02 (-0.02, 0.06) | 0.006 (-0.04, 0.05) | -0.05 (-0.10, -0.007) |
| Iron overload | 0.01 (-0.03, 0.05) | 0.02 (-0.02, 0.06) | 0.02 (-0.03, 0.06) | 0.02 (-0.02, 0.06) |

\*Model 1 was adjusted for age and sex.

†Model 2 was adjusted for age, sex, BMI, smoking, and alcohol use.

‡Model 3 was adjusted for age, sex, BMI, smoking, alcohol use, total cholesterol, hs-CRP, eGFR, SBP, lipid-lowering drugs, antihypertensive drugs and T2D.

§Model 4 was adjusted for age, sex, BMI, smoking, alcohol use, total cholesterol, hs-CRP, eGFR, SBP, lipid-lowering drugs, antihypertensive drugs, T2D, and hemoglobin.

||Statistical test: multiple linear regression

CI indicates confidence interval; sTfR, soluble transferrin receptor; TSAT, transferrin saturation; BMI, body mass index; hs-CRP, high-sensitivity c-reactive protein; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; and T2D, type 2 diabetes mellitus.

Supplementary Table 5. Association of sex with iron status

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Iron status  (ref= Normal group) | Model 1\* | Model 2† | Model 3‡ | Model 4§ |
| Odds Ratio (95% CI) || | | | |
| Absolute iron deficiency | 2.78 (2.17, 3.56) | 2.5 (1.95, 3.23) | 2.48 (1.65, 3.73) | 0.52 (0.33, 0.82) |
| Iron overload | 0.20 (0.16, 0.30) | 0.20 (0.16, 0.26) | 0.22 (0.16, 0.30) | 0.28 (0.20, 0.41) |

\*Model 1 was adjusted for age and sex.

†Model 2 was adjusted for age, sex, BMI, smoking, and alcohol use.

‡Model 3 was adjusted for age, sex, BMI, smoking, alcohol use, total cholesterol, hs-CRP, eGFR, SBP, lipid-lowering drugs, antihypertensive drugs and T2D.

§Model 4 was adjusted for age, sex, BMI, smoking, alcohol use, total cholesterol, hs-CRP, eGFR, SBP, lipid-lowering drugs, antihypertensive drugs, T2D, and hemoglobin.

||Statistical test: multiple logistic regression

CI indicates confidence interval; sTfR, soluble transferrin receptor; TSAT, transferrin saturation; BMI, body mass index; hs-CRP, high-sensitivity c-reactive protein; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; and T2D, type 2 diabetes mellitus.

Reference category for sex is men.

Supplementary Table 6. Association of sex and iron biomarkers with NT-proBNP, after exclusion of participants who reported use of anti-hypertensive medications, lipid-lowering drugs or having diabetes

|  |  |
| --- | --- |
|  | Model 2\* |
| Beta (95% CI) ‡ |
| Sex (ref=m) | 0.36 (0.33, 0.38) |
| Ferritin, µg/L† | -0.04 (-0.07, -0.007) |
| Hepcidin, nmol/l | -0.03 (-0.06, 0.007) |
| sTfR, mg/l | -0.10 (-0.17, -0.02) |
| TSAT, % | 0.08 (0.02, 0.15) |

\*Model 2 was adjusted for age, BMI, smoking, and alcohol use.

†Analyses of iron biomarker were additionally adjusted for sex.

‡Statistical test: multiple linear regression. All iron biomarkers and NT-proBNP were log transformed.

CI indicates confidence interval; sTfR, soluble transferrin receptor; TSAT, transferrin saturation; and BMI, body mass index.

Supplementary Table 7. Association of sex with iron biomarkers; after exclusion of participants who reported use of anti-hypertensive medications, lipid-lowering drugs or having diabetes

|  |  |
| --- | --- |
|  | Model 2\* |
| Beta (95% CI) † |
| Ferritin, µg/L | -0.40 (-0.43, -0.38) |
| Hepcidin, nmol/l | -0.24 (-0.26, -0.22) |
| sTfR, mg/l | -0.002 (-0.01, 0.008) |
| TSAT, % | -0.08 (-0.09, -0.07) |

\*Model 2 was adjusted for age, BMI, smoking, and alcohol use.

†Statistical test: multiple linear regression. All iron biomarkers were log transformed.

CI indicates confidence interval; sTfR, soluble transferrin receptor; TSAT, transferrin saturation; and BMI, body mass index.

Reference category for sex is men.

Supplementary Table 8. Mediation analyses of iron biomarkers on the association between sex and NT-proBNP, after exclusion of participants who reported use of anti-hypertensive medications, lipid-lowering drugs or having diabetes

|  |  |  |  |
| --- | --- | --- | --- |
|  | Model 2\* | | |
| Iron biomarkers | Effects|| | Coefficient  (95% CI) | Mediated proportion  (%)† |
| Ferritin, µg/L | Indirect  Total | 0.02 (0.002, 0.03)  0.36 (0.33, 0.38) | 5.5% ‡ |
| sTfR, mg/l | Indirect  Total | 0.0002 (-0.0008, 0.0013)  0.36 (0.33, 0.38) |  |
| TSAT, % | Indirect  Total | -0.007 (-0.01, -0.002)  0.36 (0.33, 0.38 | 1.9% § |

In mediation analysis, only the iron biomarkers that were both associated with sex and NT-proBNP were evaluated.

\*Model 2 was adjusted for age, BMI, smoking, and alcohol use.

†Mediated proportion is calculated as the ratio of indirect effect to the total effect and is expressed in percentage.

‡Positive mediator effect; §Negative mediator effect

||Statistical test: mediation analysis. All iron biomarkers and NT-proBNP were log transformed.

CI indicates confidence interval; sTfR, soluble transferrin receptor; TSAT, transferrin saturation; and BMI, body mass index.

Supplementary Table 9. Association of sex and iron biomarkers with NT-proBNP, based on median age, 51 years

|  |  |  |
| --- | --- | --- |
| Model 2\* | Age group ≤51 years (n=2681) | Age group >51 years (n=2662) |
| Beta (95% CI) ‡ | Beta (95% CI) |
| Sex (ref=m) | 0.45 (0.41, 0.48) | 0.25 (0.21, 0.28) |
| Ferritin, µg/L† | 0.02 (-0.05, 0.08) | -0.02 (-0.06, 0.02) |
| Hepcidin, nmol/l | -0.004 (-0.07, 0.06) | -0.004 (-0.05, 0.04) |
| sTfR, mg/l | -0.12 (-0.26, 0.02) | -0.12 (-0.22, 0.03) |
| TSAT, % | 0.12 (0.004, 0.23) | 0.07 (-0.01, 0.15) |

\*Model 2 was adjusted for age, BMI, smoking, and alcohol use.

†Analyses of iron biomarker were additionally adjusted for sex.

‡ Statistical test: multiple linear regression. All iron biomarkers and NT-proBNP were log transformed.

CI indicates confidence interval; sTfR, soluble transferrin receptor; TSAT, transferrin saturation; and BMI, body mass index.

Supplementary Table 10. Association of sex with iron biomarkers, based on median age, 51 years

|  |  |  |
| --- | --- | --- |
| Model 2\* | Age group ≤51 years (n=2681) | Age group >51 years (n=2662) |
| Beta (95% CI) † | Beta (95% CI) |
| Ferritin, µg/L | -0.56 (-0.60, -0.52) | -0.40 (-0.42, -0.36) |
| Hepcidin, nmol/l | -0.41 (-0.45, -0.36) | -0.23 (-0.26, -0.20) |
| sTfR, mg/l | 0.000 (-0.02, 0.02) | -0.004 (-0.01, 0.008) |
| TSAT, % | -0.10 (-0.12, -0.07) | -0.07 (-0.08, -0.06) |

\*Model 2 was adjusted for age, BMI, smoking, and alcohol use.

† Statistical test: multiple linear regression. All iron biomarkers were log transformed.

CI indicates confidence interval; sTfR, soluble transferrin receptor; TSAT, transferrin saturation; and BMI, body mass index.

Supplementary Table 11. Mediation analyses of iron biomarkers on the association between sex and NT-proBNP, based on median age, 51 years

|  |  |  |  |
| --- | --- | --- | --- |
| Model 2\* | Age group ≤51 years (n=2681) | | |
| Iron biomarkers | Effects§ | Coefficient  (95% CI) | Mediated proportion  (%)† |
| TSAT, % | Indirect  Total | -0.01 (-0.02, -0.007)  0.47 (0.42, 0.51) | 2.1% ‡ |

In mediation analysis, only the iron biomarkers that were both associated with sex and NT-proBNP were evaluated.

\*Model 2 was adjusted for age, BMI, smoking, and alcohol use.

†Mediated proportion is calculated as the ratio of indirect effect to the total effect and is expressed in percentage.

‡Negative mediator effect

§Statistical test: mediation analysis. All iron biomarkers and NT-proBNP were log transformed.

CI indicates confidence interval; TSAT, transferrin saturation; and BMI, body mass index.