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| **Supplementary table 1. Beta coefficients (95% CI) of relationship between log-sTfR and log-transformed values of variables related to MetS components** | | |
|  | log-sTfR | |
| *Premenopausal*  *women* | Non-adjusted | Adjusted\* |
| log-glucose | 0.03 (-0.07 to 0.15) | 0.01 (-0.09 to 0.12) |
| log- HDL-C | -0.006 (-0.15 to 0.14) | 0.008 (-0.14 to 0.16) |
| log-TG | **0.32 (0.01 to 0.63)** | 0.26 (-0.04 to 0.56) |
| log-SBP | 0.07 (-0.01 to 0.17) | 0.04 (-0.04 to 0.12) |
| log-DBP | 0.01 (-0.07 to 0.11) | -0.002 (-0.08 to 0.08) |
| log- WC | 0.06 (-0.02 to 0.15) | 0.007 (-0.03 to 0.05) |
| *Postmenopausal*  *women* |  |  |
| log-glucose | 0.06 (-0.12 to 0.24) | -0.04 (-0.22 to 0.14) |
| log- HDL-C | 0.04 (-0.08 to 0.17) | 0.07 (-0.06 to 0.21) |
| log-TG | 0.01 (-0.37 to 0.40) | -0.14 (-0.53 to 0.23) |
| log-SBP | 0.10 (-0.03 to 0.25) | -0.007 (-0.13 to 0.12) |
| log-DBP | -0.01 (-0.12 to 0.09) | -0.06 (-0.17 to 0.04) |
| log- WC | **0.15 (0.05 to 0.25)** | 0.05 (-0.004 to 0.10) |
| *Men* |  |  |
| log-glucose | **0.18 (0.002 to 0.37)** | 0.09 (-0.09 to 0.27) |
| log- HDL-C | -0.03 (-0.18 to 0.11) | -0.02 (-0.18 to 0.12) |
| log-TG | 0.33 (-0.14 to 0.81) | 0.34 (-0.13 to 0.82) |
| log-SBP | 0.10 (-0.03 to 0.25) | -0.01 (-0.14 to 0.11) |
| log-DBP | 0.05 (-0.07 to 0.18) | 0.01 (-0.11 to 0.14) |
| log- WC | **0.12 (0.02 to 0.22)** | 0.01 (-0.02 to 0.06) |
| \*Age, fibrinogen levels, smoking status (yes/no/ex-smoker), alcohol consumption (no/yes), and BMI. Multivariable adjusted analyses were performed on transformed values of skewed variables: logarithm of sTfR , ferritin , body mass index and fibrinogen values; square of age. . TG, triglycerides. SBP, systolic blood pressure. DBP, diastolic blood pressure. WC, waist circumference. HDL-C, HDL cholesterol. Significant associations are shown in bold (P<0.05). | | |

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| **Supplementary table 2. Odds ratios(95% CI) for metabolic syndrome and its components per SD of iron markers in women of the study** | | | | | | |
|  | Z score log-sTfR | | Z score log-ferritin | | Z score log-sTfR/ferritin ratio | |
| *Women* |  |  |  |  |  |  |
|  | Non-adjusted | Adjusted\* | Non-adjusted | Adjusted\* | Non-adjusted | Adjusted\* |
| High glucose † | 1.09 (0.90-1.33) | 1.07 (0.85-1.36) | **1.53 (1.24-1.88)** | 1.12 (0.88-1.43) | **0.72 (0.59-0.89**) | 0.93 (0.73-1.18) |
| Low HDL-C | 1.17 (0.81-1.69) | 1.16 (0.84-1.61) | 1.05 (0.71-1.55) | 0.83 (0.52-1.31) | 1.00 (0.68-1.49) | 1.23 (0.79-1.91) |
| High TG | 1.05 (0.86-1.28) | 1.02 (0.80-1.30) | **1.66 (1.32-2.08)** | **1.41 (1.08-1.83)** | **0.67 (0.53-0.84)** | **0.76 (0.59-0.99)** |
| High BP¶ | 1.10 (0.90-1.34) | 1.10 (0.85-1.42) | **1.74 (1.41-2.14)** | 1.03 (0.77-1.36) | **0.66 (0.54-0.81)** | 1.01 (0.77-1.32) |
| High WC | 1.01 (0.78-1.31) | 0.90 (0.67-1.20) | **1.53 (1.18-1.95)** | 0.90 (0.57-1.42) | **0.72 (0.56-0.91)** | 0.99 (0.67-1.47) |
| MetS | 1.06 (0.86-1.30) | 1.02 (0.78-1.30) | **2.22 (1.77-2.80)** | **1.55 (1.13-2.13)** | **0.55 (0.44-0.68)** | **0.73 (0.54-0.99)** |
| \*Age, fibrinogen levels, smoking status (yes/no/ex-smoker), alcohol consumption (no/yes), BMI and menopause. † Includes additionally individuals who reported current use of oral hypoglycaemic medications or insulin regardless of fasting glucose values .¶ Includes additionally individuals who reported current use of antihypertensive medications regardless of blood pressure values. TG, triglycerides. BP, blood pressure.. WC, waist circumference. HDL-C, HDL cholesterol. MetS, metabolic syndrome. Significant associations are shown in bold (P<0.05). | | | | | | |

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| **Supplementary table 3. Odds ratios(95% CI) for metabolic syndrome and its components per SD of the sTfR/ferritin ratio in the study subjects categorised by sex and menopausal status** | | |
|  | Z score log-sTfR/ferritin ratio | |
|  | Non-adjusted | Adjusted\* |
| *Premenopausal*  *women* |  |  |
| High glucose † | 1.20 (0.79-1.80) | 1.06 (0.68-1.63) |
| Low HDL-C | 1.11 (0.63-1.96) | 1.12 (0.59-2.10) |
| High TG | 0.83 (0.53-1.29) | 0.79 (0.49-1.27) |
| High BP¶ | 1.15 (0.81-1.63) | 1.08 (0.74-1.59) |
| High WC | 1.21 (0.86-1.70) | 1.02 (0.64-1.61) |
| MetS | 1.01 (0.72-1.41) | 0.86 (0.58-1.27) |
| *Postmenopausal*  *women* |  |  |
| High glucose † | 0.86 (0.68-1.08) | 0.86 (0.67-1.10) |
| Low HDL-C | 1.34 (0.70-2.56) | 1.38 (0.72-2.67) |
| High TG | 0.82 (0.64-1.04) | 0.79 (0.61-1.03) |
| High BP¶ | 0.92 (0.69-1.24) | 0.92 (0.64-1.30) |
| High WC | 0.94 (0.53-1.65) | 0.90 (0.39-2.03) |
| MetS | **0.67 (0.48-0.92)** | **0.59 (0.39-0.89)** |
| *Men* |  |  |
| High glucose † | 0.80 (0.63-1.02) | 0.79 (0.61-1.02) |
| Low HDL-C | **0.64 (0.48-0.85)** | **0.66 (0.49-0.89)** |
| High TG | **0.64 (0.49-0.83)** | **0.68 (0.51-0.89)** |
| High BP¶ | 0.91 (0.71-1.17) | 0.94 (0.70-1.26) |
| High WC | **0.75 (0.58-0.96)** | 0.83 (0.56-1.24) |
| MetS | **0.59 (0.45-0.77)** | **0.58 (0.43-0.79)** |
| \*Age, fibrinogen levels, smoking status (yes/no/ex-smoker), alcohol consumption (no/yes), and BMI. † Includes additionally individuals who reported current use of oral hypoglycaemic medications or insulin regardless of fasting glucose values .¶ Includes additionally individuals who reported current use of antihypertensive medications regardless of blood pressure values. TG, triglycerides. BP, blood pressure.. WC, waist circumference. HDL-C, HDL cholesterol. MetS, metabolic syndrome. Significant associations are shown in bold (P<0.05). | | |

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| **Supplementary table 4. Adjusted\* Beta coefficients (95% CI) for values of log-HOMA-IR and log-insulin by levels of iron markers in the study subjects** | | | | |
| Independent variable | log-sTfR | | log-ferritin | |
| Dependant variable | log-HOMA-IR | log-insulin | log-HOMA-IR | log-insulin |
| *In* |  |  |  |  |
| *Premenopausal women* | 0.07 (-0.12 to 0.27) | 0.15 (-0.27 to 0.58) | 0.05 (-0.05 to 0.16) | 0.09 (-0.14 to 0.33) |
| *Postmenopausal women* | **0.34 (0.05 to 0.63)** | **0.83 (0.23 to 1.43)** | 0.01 (-0.09 to 0.11) | 0.01 (-0.19 to 0.23) |
| *Men* | **0.44 (0.14 to 0.75)** | **0.98 (0.34 to 1.63)** | 0.01 (-0.09 to 0.11) | -0.03 (-0.26 to 0.18) |
| All\*\* | **0.24 (0.09 to 0.39)** | **0.54 (0.23 to 0.86)** | 0.04 (-0.01 to 0.10) | 0.06 (-0.06 to 0.19) |
| \*Age, fibrinogen levels, smoking status (yes/no/ex-smoker), alcohol consumption (no/yes), treatment with insulin and/or hypoglycaemic drugs (yes/no), and BMI. \*\* Additionally adjusted for sex/menopausal status (premenopausal women [reference] / postmenopausal women/men). Multivariable adjusted analyses were performed on transformed values of skewed variables: logarithm of sTfR , ferritin , HOMA-IR values, body mass index and fibrinogen values; square of age. Significant associations are shown in bold (P<0.05). | | | | |

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| **Supplementary table 5. Beta coefficients (95% CI) for values of glycosylated haemoglobin (HbA1C) by levels of iron markers in the study subjects** | | | | |
|  | log-sTfR | | log-ferritin | |
|  | Non-adjusted | Adjusted\* | Non-adjusted | Adjusted\* |
| *Premenopausal women* | -0.06 (-0.14 to 0.01) | -0.06 (-0.14 to 0.01) | 0.02 (-0.01 to 0.07) | 0.02 (-0.01 to 0.07) |
| *Postmenopausal women* | 0.02 (-0.13 to 0.17) | -0.04 (-0.17 to 0.08) | -0.007 (-0.06 to 0.04) | -0.009 (-0.05 to 0.03) |
| *Men* | **0.18 (0.03 to 0.33)** | 0.03 (-0.09 to 0.16) | 0.02 (-0.02 to 0.07) | 0.001 (-0.04 to 0.04) |
| All\*\* | 0.01 (-0.05 to 0.09) | -0.03 (-0.10 to 0.02) | **0.05 (0.01 to 0.08)** | 0.005 (-0.02 to 0.03) |
| \*Age, fibrinogen levels, smoking status (yes/no/ex-smoker), alcohol consumption (no/yes), treatment with insulin and/or hypoglycaemic drugs (yes/no), and BMI. \* Additionally adjusted for sex/menopausal status (premenopausal women [reference] / postmenopausal women/men). Multivariable adjusted analyses were performed on transformed values of skewed variables: logarithm of sTfR , ferritin , body mass index and fibrinogen values; square of age and square root(sqrt) of glycosylated haemoglobin. Significant associations are shown in bold (P<0.05). | | | | |

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| **Supplementary table 6. Associations\* between iron markers and metabolic syndrome, insulin resistance, and glycosylated hemoglobin additionally adjusted for physical activity, diabetes and cardiovascular disease** | | | | | | |
| Independent variable | Z score log-sTfR | log-sTfR | log-sTfR | Z score log-ferritin | log-ferritin | log-ferritin |
| Dependent  variable | MetS  [OR(95%CI)] | log-HOMA-IR  [Beta(95%CI)] | Sqrt-HbA1C  [Beta(95%CI)] | MetS  [OR(95%CI)] | log-HOMA-IR  [Beta(95%CI)] | Sqrt-HbA1C  [Beta(95%CI)] |
| *In* |  |  |  |  |  |  |
| *Premenopausal women(n=148)* | 1.21 (0.79 to 1.87) | 0.07 (-0.12 to 0.28) | -0.07 (-0.16 to 0.04) | 1.45 (0.93 to 2.26) | 0.03 (-0.08 to 0.14) | 0.02 (-0.01 to 0.07) |
| *Postmenopausal women(n=270)* | 0.70 (0.43 to 1.14) † | **0.44 (0.13 to 0.75)** | 0.01 (-0.14 to 0.15) | **2.01 (1.25 to 3.23)**† | -0.02 (-0.13 to 0.08) | -0.01 (-0.06 to 0.03) |
| *Men (n=275)* | 0.82 (0.59 to 1.10) | **0.36 (0.05 to 0.67)** | -0.02 (-0.15 to 0.10) | **2.06 (1.46 to 2.92)** | 0.03 (-0.07 to 0.13) | -0.001 (-0.04 to 0.04) |
| All\*\*(n=693) | 0.95 (0.78 to 1.16) | **0.24 (0.08 to 0.39)** | -0.03 (-0.10 to 0.03) | **2.00 (1.52 to 2.63)** | 0.03 (-0.03 to 0.09) | 0.004 (-0.02 to 0.03) |
| \*Adjusted for age, fibrinogen levels, smoking status (yes/no/ex-smoker), alcohol consumption (no/yes), diabetes (yes/no), cardiovascular disease(yes/no), physical at work (sitting [reference], light, moderate, and hard), physical activity at leisure (sitting [reference], light, moderate, and hard), and BMI. \*\* Additionally adjusted for sex/menopausal status (premenopausal women [reference] / postmenopausal women/men). Multivariable adjusted analyses were performed on transformed values of skewed variables: logarithm of sTfR , ferritin , body mass index and fibrinogen values; square of age and square root (sqrt) of glycosylated haemoglobin. Significant associations are shown in bold (P<0.05). † In postmenopausal women all the cases with diabetes had MetS and therefore diabetes was omitted in the model. | | | | | | |

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| **Supplementary table 7. Odds ratios(95% CI) for metabolic syndrome and its components per SD of the iron markers in the study subjects categorised by sex and menopausal status with additional adjustment for BMI** | | |
|  | Z score log-sTfR | Z score log-ferritin |
|  | Adjusted\* | Adjusted\* |
| *Premenopausal*  *women* |  |  |
| High glucose † | 1.23 (0.77-1.99) | 1.02 (0.65-1.59) |
| Low HDL-C | 1.14 (0.69-1.94) | 0.94 (0.50-1.77) |
| High TG | 1.30 (0.80-2.10) | 1.56 (0.97-2.53) |
| High BP¶ | 1.28 (0.84-1.95) | 1.00 (0.68-1.46) |
| High WC | 0.89 (0.60-1.32) | 0.87 (0.54-1.42) |
| MetS | 1.19 (0.78-1.80) | 1.35 (0.90-2.02) |
| *Postmenopausal*  *women* |  |  |
| High glucose † | 0.96 (0.74-1.24) | 1.17 (0.91-1.50) |
| Low HDL-C | 1.39 (0.70-2.72) | 0.76 (0.41-1.41) |
| High TG | 0.89 (0.68-1.15) | 1.26 (0.97-1.63) |
| High BP¶ | 0.89 (0.62-1.29) | 1.06 (0.74-1.50) |
| High WC | 0.61 (0.27-1.39) | 0.93 (0.37-2.33)Ψ |
| MetS | 0.73 (0.47-1.15) | **1.71 (1.12-2.62)** |
| *Men* |  |  |
| High glucose † | 1.08 (0.83-1.40) | **1.34 (1.03-1.75)** |
| Low HDL-C | 0.93 (0.70-1.22) | **1.56 (1.16-2.11)** |
| High TG | 1.04 (0.80-1.36) | **1.60 (1.20-2.12)** |
| High BP¶ | 0.91 (0.67-1.24) | 1.04 (0.77-1.39) |
| High WC | 1.11 (0.70-1.75) | 1.27 (0.84-1.86) |
| MetS | 0.87 (0.66-1.17) | **1.78 (1.31-2.42)** |
| \*Age, fibrinogen levels, smoking status (yes/no/ex-smoker), alcohol consumption (no/yes), and BMI. † Includes additionally individuals who reported current use of oral hypoglycemic medications or insulin regardless of fasting glucose values.¶ Includes additionally individuals who reported current use of antihypertensive medications regardless of blood pressure values. TG, triglycerides. BP, blood pressure.. WC, waist circumference. Ψ 59 cases were omitted because in the category of ex-smoker all of the subjects had high WC. HDL-C, HDL cholesterol. MetS, metabolic syndrome. Significant associations are show in bold (P<0.05). | | |

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| **Supplementary table 8. Odds ratios(95% CI) for metabolic syndrome and its components per SD of iron markers in the whole sample with additional adjustment for BMI** | | | |
|  | Z score log-sTfR | Z score log-ferritin | Z score log-sTfR/ferritin ratio |
|  | Adjusted\* | Adjusted\* | Adjusted\* |
| High glucose † | 1.08(0.90-1.28) | **1.27 (1.03-1.56)** | 0.85 (0.69-1.04) |
| Low HDL-C | 0.96 (0.74-1.23) | **1.34 (1.01-1.78)** | 0.77 (0.58-1.01) |
| High TG | 1.01 (0.85-1.21) | **1.62 (1.30-2.03)** | **0.68 (0.55-0.84)** |
| High BP¶ | 1.02 (0.84-1.23) | 1.09 (0.85-1.38) | 0.94 (0.75-1.18) |
| High WC | 0.90 (0.71-1.15) | 1.11 (0.80-1.56) | 0.88 (0.64-1.19) |
| MetS | 0.91 (0.75-1.09) | **1.93 (1.49-2.49)** | **0.58 (0.46-0.74)** |
| \*Age, fibrinogen levels, smoking status (yes/no/ex-smoker), alcohol consumption (no/yes), BMI and sex/menopausal status (premenopausal women/ postmenopausal women/men). † Includes additionally individuals who reported current use of oral hypoglycemic medications or insulin regardless of fasting glucose values .¶ Includes additionally individuals who reported current use of antihypertensive medications regardless of blood pressure values. TG, triglycerides. BP, blood pressure.. WC, waist circumference. HDL-C, HDL cholesterol. MetS, metabolic syndrome. Significant associations are show in bold (P<0.05). | | | |

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| **Supplementary table 9. Studies in general population on sTfR and Metabolic syndrome found in PUBMED and EMBASE by applying the searching “metabolic syndrome OR blood pressure OR fasting glucose OR waist circumference OR triglycerides OR HDL cholesterol” AND “transferrin receptor” (until July/2015). [Only studies in adults were included and in vitro studies, genetic studies and those conducted in specific populations (pregnant women, and patients with diseases) were not included]”** | | | | | | | | | | | |
| Authors, year of publication  (reference) | Study | Location/Universe | Study/  Year of survey | Age range  (years) | Male (%) | Total sample | Cardiovascular risk markers (outcomes and analysis-effect estimate) | sTfR :  Continuous /categorical-ordinal | Association | | Adjustments |
|  |  |  |  |  |  |  |  |  | Yes | No |  |
| Montonen et al., 2012  (13) | Cross-sectional | Germany/ Potsdam population | Epic -Potsdam | 35-65 | 37.9 | 1969 | WC, HDL-C and TG (continuous). Partial Pearson Correlations | Continuous | With WC (r=0.13), (p<0.001). | With HDL-C and TG | Age and gender |
| Aderibigbe et al., 2011  (14) | Cross-sectional | South Africa/ Population from North West province | PURE/2005 | ≥35 | 0 | 1262 | WC, LDL-C, HDL-C, TG, DBP, SBP and FG. Levels (mean and 95%CI) across categories of iron markers. | Categorical. Quartiles. | With TG: Higher levels in quartiles 3 and 4 vs quartile 1.  With DBP: Higher in quartile 4 vs quartiles 1 and 2. | With LDL-C, HDL-C, WC, SBP and FG. | Age, BMI, smoking, alcohol consumption and CRP. |
| Leiva et al., 2013  (20) | Cross-sectional | Chile/Population from Talca. | Research Program of Risk  Factors for Cardiovascular Disease of Talca, (PIFRECV) | 45-  65 | 30.9 | 155 | Metabolic syndrome(NCEP ATP-III) (dichotomic variable) | Continuous : means by Metabolic syndrome (yes/no) | Lower levels of sTfR in subjects with MetS | --------------------- | Sex |
| Hamalainen et al.,2012  (12) | Cross-sectional | Finland/Middle –aged subjects from Pieksamaki who were born in 1942,1947,1952,1957 or 1962 | NP/2003-2004 | 52.1 ± 6.2 years(men) and 52.1 ± 6.2 years (women) | 44.5 | 766 | Metabolic syndrome(NCEP ATP-III) and its components (dichotomic variables) | Continuous : standardized means by categories of Metabolic syndrome and its components | Higher sTfR in subjects with increased WC | Metabolic syndrome, and high blood pressure, FG, TG and low HDL-C | Age, sex, hs-CRP,  smoking and physical activity |
| sTfR, soluble transferrin receptor. WC, waist circumference. LDL-C, LDL cholesterol. HDL-C, HDL cholesterol. TG, triglycerides. DBP, diastolic blood pressure. SBP, systolic blood pressure. FG, fasting glucose. | | | | | | | | | | | |