

Supplementary table 1. Beta coefficients (95% CI) of relationship between log-sTfR and log-transformed values of variables related to MetS components		
	log-sTfR	
	Non-adjusted	Adjusted*
<i>Premenopausal women</i>		
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)
<i>Postmenopausal women</i>		
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)
<i>Men</i>		
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).

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	
<i>Women</i>						
	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).

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*
<i>Premenopausal women</i>		
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)
<i>Postmenopausal women</i>		
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)
<i>Men</i>		
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)
<p>*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).</p>		

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	
	log-HOMA-IR	log-insulin	log-HOMA-IR	log-insulin
<i>In</i>				
<i>Premenopausal women</i>	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)
<i>Postmenopausal women</i>	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)
<i>Men</i>	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).

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*
<i>Premenopausal women</i>	-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)
<i>Postmenopausal women</i>	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)
<i>Men</i>	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).

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)]
<i>In</i>						
<i>Premenopausal women(n=148)</i>	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)
<i>Postmenopausal women(n=270)</i>	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)
<i>Men (n=275)</i>	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)
<i>All**(n=693)</i>	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.

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*
<i>Premenopausal women</i>		
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)
<i>Postmenopausal women</i>		
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)

<i>Men</i>		
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)
<p>*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).</p>		

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)

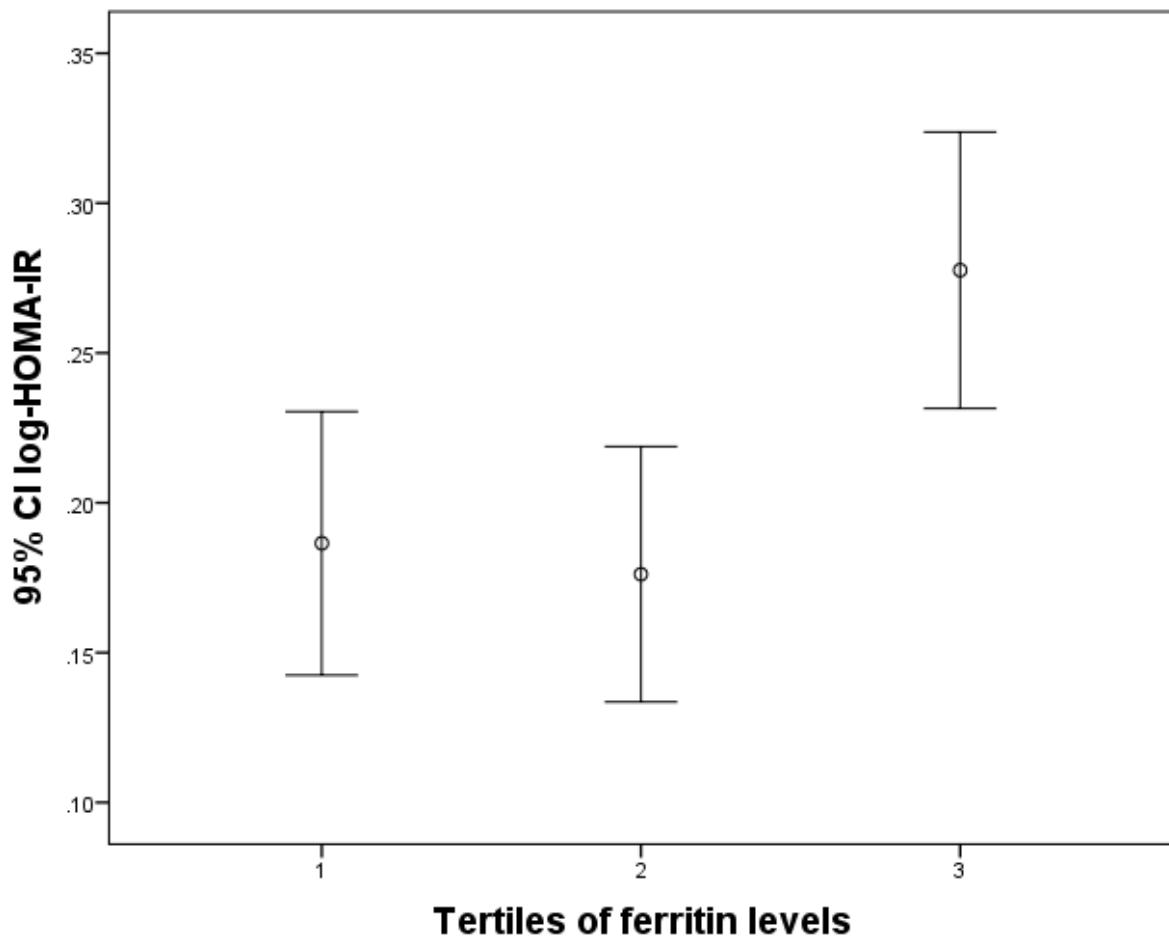
*Age, fibrinogen levels, smoking status (yes/no/ex-smoker), alcohol consumption (no/yes), BMI and sex/menopausal status (premenopausal women/ postmenopausal women/men). † Includes additionally individuals who reported current use of oral hypoglycemic medications or insulin regardless of fasting glucose 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).

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 /University	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	NP/2003-2004	52.1 ± 6.2 years (men) and	44.5	766	Metabolic syndrome(NCEP ATP-III) and its components (dichotomic variables)	Continuous : standardized means by categories of Metabolic	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

		Pieksamaki who were born in 1942,1947,1952,1957 or 1962		52.1 ± 6.2 years (women)				syndrome and its components			
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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.



Supplementary figure 1. Levels of HOMA-IR by sex/menopausal status-specific tertiles of ferritin in the whole group. Levels of HOMA-IR were significantly higher in the highest tertile of ferritin vs. tertiles 2 and 1 ($P=0.0019$ ANOVA / $P=0.0139$ ANCOVA). Covariates for ANCOVA were: age, fibrinogen levels, HbA1C, smoking status (yes/no/ex-smoker), alcohol consumption (no/yes), treatment with insulin and/or hypoglycemic drugs (yes/no), BMI and sex/menopausal status (premenopausal women [reference] / postmenopausal women/men). Analyses were performed with transformed values of skewed variables: square of age, square root of glycosylated hemoglobin, and logarithm of fibrinogen and body mass index. Further adjustment for cardiovascular disease, diabetes (excluding treatment with insulin and/or hypoglycemic drugs in the model), physical at work (sitting [reference], light, moderate, and hard), and physical activity at leisure (sitting [reference], light, moderate, and hard) did not affect the difference in log-HOMA-IR across tertiles of ferritin ($P=0.039$ ANCOVA).