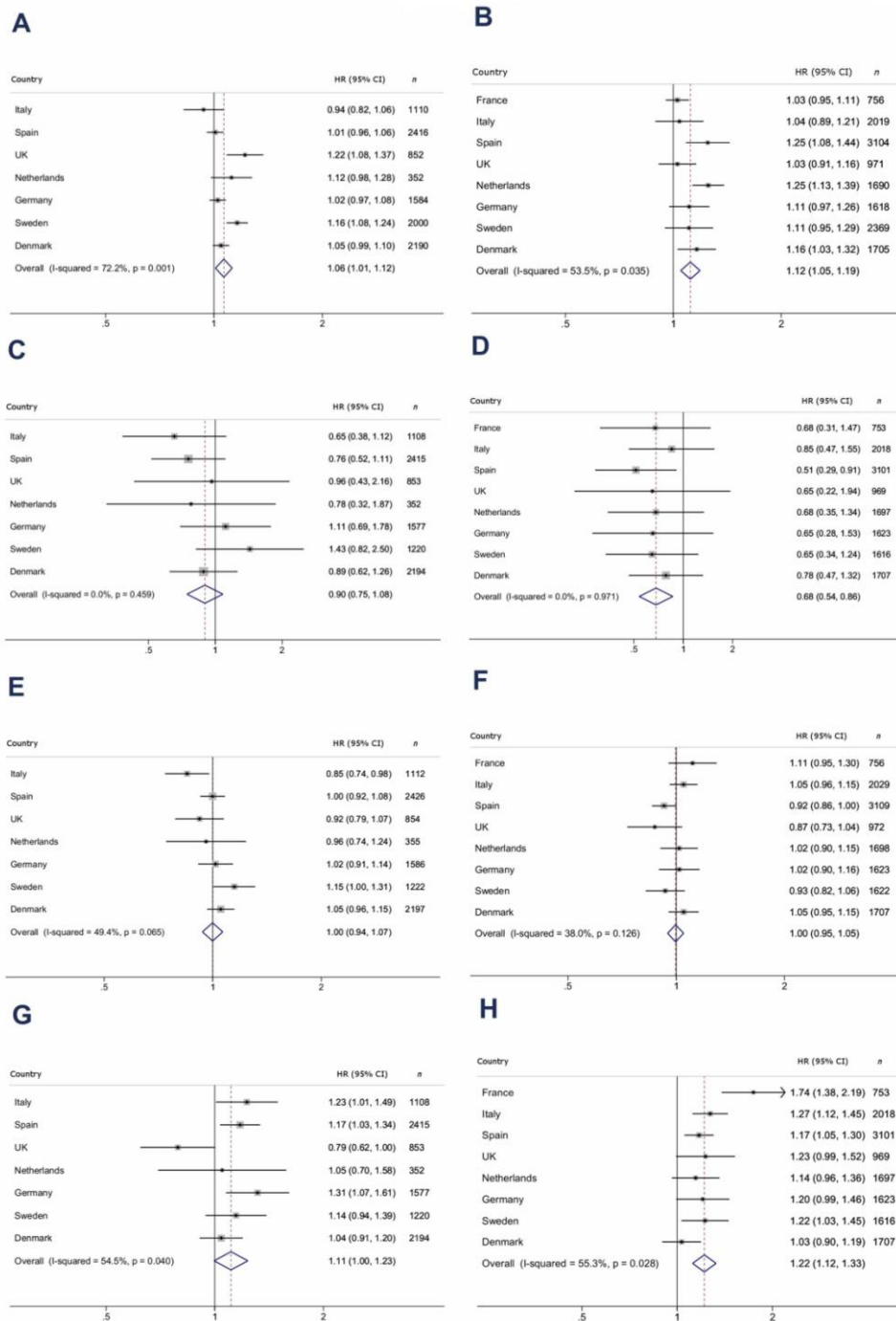


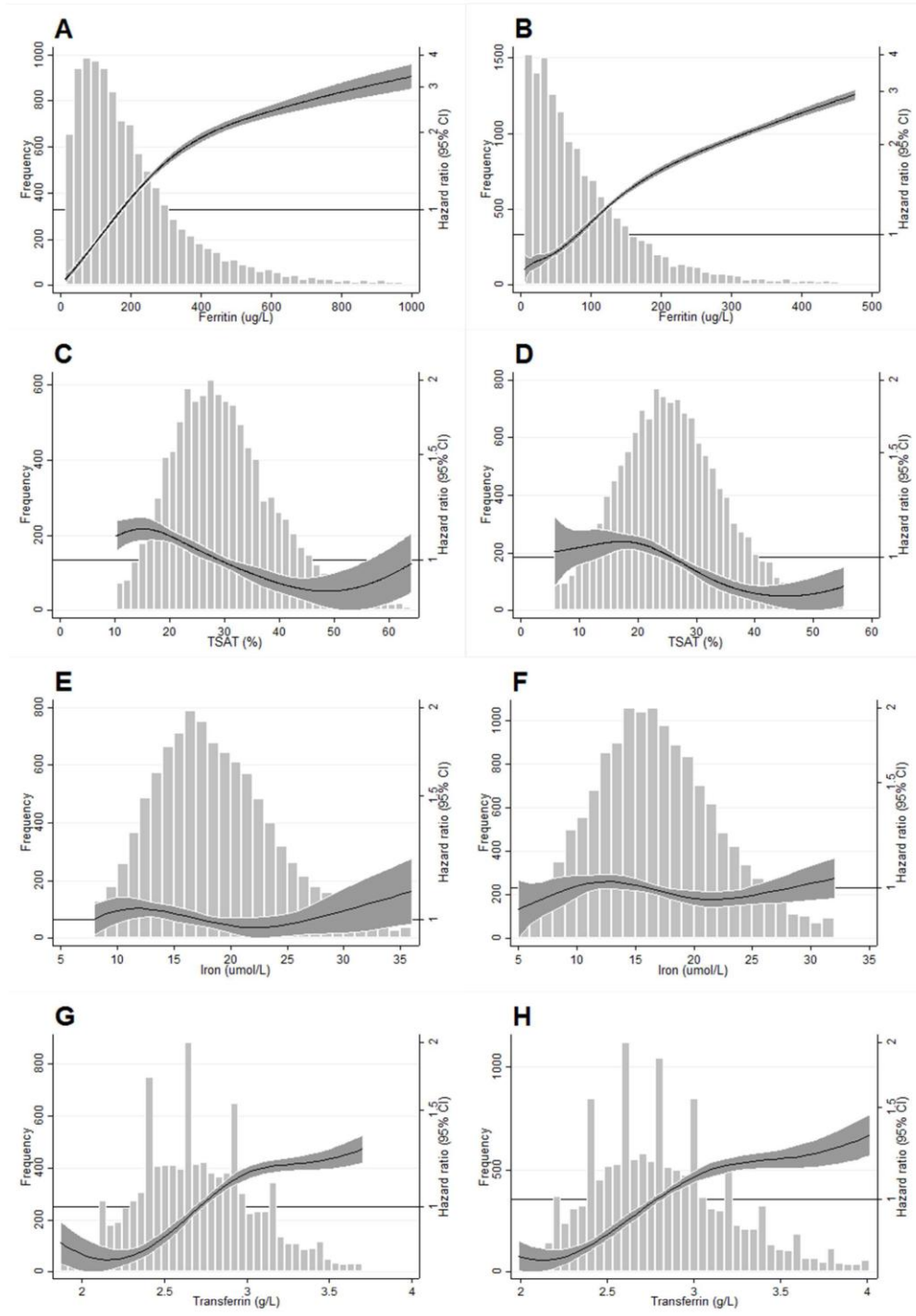
SUPPLEMENTARY DATA

Supplementary Figure S1. Hazard ratios (95% confidence intervals) of Type 2 Diabetes for the higher biomarker level as stated, by sex and meta-analyzed across countries. Per 100 µg/L higher level of ferritin in men (A) and women (B). Elevated TSAT (≥45% versus <45%) in men (C) and women (D). Per 5 µmol/L higher level of serum iron in men (E) and women (F). Per 0.5 g/L higher level of transferrin in men (G) and women (H). All figures are adjusted for age, center, BMI, physical activity, smoking status, level of education, hsCRP, ALT and GGT. The cohorts from all the centers in France, as well as from Naples and Utrecht consisted of women only. HR: Hazard Ratio; 95% CI: 95% confidence intervals



SUPPLEMENTARY DATA

Supplementary Figure S2. Unadjusted Hazard ratios for Type 2 Diabetes (T2D) by Ferritin, TSAT, Serum Iron and Transferrin levels in men and women. Ferritin in men (A) and women (B); TSAT in men (C) and women (D); serum iron in men (E) and women (F); transferrin in men (G) and women (H). The histogram represents the distribution of the biomarker in the given population.



SUPPLEMENTARY DATA

Supplementary Table S1. Mean (SD) and median (interquartile range) of Ferritin ($\mu\text{g/L}$) by BMI and waist circumference categories in men and women in the subcohort.

| | Ferritin ($\mu\text{g/L}$) | |
|---|------------------------------|------------------------------|
| | Mean (SD) | Median (interquartile range) |
| Men ($n=5,697$) | | |
| BMI (kg/m^2) | | |
| <25 | 159.7 (128.1) | 128 (74 - 212) |
| 25-30 | 191.5 (174.0) | 147 (82 - 247) |
| >30 | 235.7 (234.8) | 172 (92 - 289) |
| Waist circumference (cm) | | |
| <94 | 164.4 (138.2) | 132 (72 - 218) |
| 94-102 | 198.6 (190.7) | 147 (83 - 252) |
| ≥ 102 | 230.3 (218.3) | 174 (94 - 292) |
| Women ($n=9,485$) | | |
| BMI (kg/m^2) | | |
| <25 | 73.3 (70.2) | 55 (28 - 97) |
| 25-30 | 87.3 (99.6) | 62 (30 - 116) |
| >30 | 91.6 (103.3) | 61 (30 - 122) |
| Waist circumference (cm) | | |
| <80 | 73.2 (70.0) | 55 (28 - 97) |
| 80-88 | 85.6 (84.9) | 62 (30 - 115) |
| ≥ 88 | 94.7 (116.0) | 66 (31 - 125) |

SUPPLEMENTARY DATA

Supplementary Table S2. Multivariable linear regressions (age, sex and center adjusted) and correlations (unadjusted) of each biomarker with other variables in the subcohort.

| | Linear regression | | Correlation | |
|--|-------------------------|----------|-------------|----------|
| | β (95% CI) | <i>p</i> | <i>r</i> | <i>p</i> |
| Ferritin ($\mu\text{g/L}$) | | | | |
| TSAT (%) | 0.032 (0.030; 0.033) | <0.001 | 0.40 | <0.001 |
| Iron ($\mu\text{mol/L}$) | 0.038 (0.036; 0.040) | <0.001 | 0.27 | <0.001 |
| Transferrin (g/L) | -0.954 (-0.986; -0.922) | <0.001 | -0.47 | <0.001 |
| \log_e hsCRP (mg/L) | 0.092 (0.079; 0.106) | <0.001 | 0.13 | <0.001 |
| AST (U/L) | 0.012 (0.011; 0.014) | <0.001 | 0.23 | <0.001 |
| ALT (U/L) | 0.015 (0.014; 0.016) | <0.001 | 0.30 | <0.001 |
| \log_e GGT (U/L) | 0.400 (0.377; 0.424) | <0.001 | 0.41 | <0.001 |
| BMI (kg/m^2) | 0.013 (0.010; 0.017) | <0.001 | 0.13 | <0.001 |
| Dietary iron (mg/day) | 0.003 (-0.001; 0.006) | 0.149 | 0.13 | <0.001 |
| \log_e alcohol intake (g/day) | 0.073 (0.062; 0.084) | <0.001 | 0.26 | <0.001 |
| TSAT (%) | | | | |
| Iron ($\mu\text{mol/L}$) | 1.577 (1.565; 1.589) | <0.001 | 0.91 | <0.001 |
| Transferrin (g/L) | -9.509 (-9.900; -9.118) | <0.001 | -0.39 | <0.001 |
| \log_e hsCRP (mg/L) | -1.646 (-1.807; -1.485) | <0.001 | -0.15 | <0.001 |
| AST (U/L) | 0.080 (0.064; 0.097) | <0.001 | 0.11 | <0.001 |
| ALT (U/L) | 0.042 (0.028; 0.055) | <0.001 | 0.09 | <0.001 |
| \log_e GGT (U/L) | 1.414 (1.122; 1.706) | <0.001 | 0.14 | <0.001 |
| BMI (kg/m^2) | -0.312 (-0.354; -0.271) | <0.001 | -0.10 | <0.001 |
| Dietary iron (mg/day) | 0.010 (-0.034; 0.053) | 0.665 | 0.05 | <0.001 |
| \log_e alcohol intake (g/day) | 0.650 (0.513; 0.786) | <0.001 | 0.13 | <0.001 |
| Iron ($\mu\text{mol/L}$) | | | | |
| Transferrin (g/L) | -0.054 (-0.296; 0.189) | 0.665 | -0.02 | 0.0217 |
| \log_e hsCRP (mg/L) | -0.947 (-1.040; -0.854) | <0.001 | -0.16 | <0.001 |
| AST (U/L) | 0.081 (0.071; 0.090) | <0.001 | 0.16 | <0.001 |
| ALT (U/L) | 0.049 (0.042; 0.057) | <0.001 | 0.13 | <0.001 |
| \log_e GGT (U/L) | 1.207 (1.040; 1.374) | <0.001 | 0.15 | <0.001 |
| BMI (kg/m^2) | -0.135 (-0.159; -0.111) | <0.001 | -0.08 | <0.001 |
| Dietary iron (mg/day) | 0.019 (-0.006; 0.044) | 0.136 | 0.06 | <0.001 |
| \log_e alcohol intake (g/day) | 0.388 (0.310; 0.467) | <0.001 | 0.12 | <0.001 |
| Transferrin (g/L) | | | | |
| \log_e hsCRP (mg/L) | 0.008 (0.001; 0.014) | 0.019 | -0.01 | 0.335 |
| AST (U/L) | 0.004 (0.004; 0.005) | <0.001 | 0.07 | <0.001 |
| ALT (U/L) | 0.003 (0.003; 0.004) | <0.001 | 0.06 | <0.001 |
| \log_e GGT (U/L) | 0.047 (0.036; 0.059) | <0.001 | -0.02 | 0.039 |
| BMI (kg/m^2) | 0.009 (0.008; 0.011) | <0.001 | 0.06 | <0.001 |
| Dietary iron (mg/day) | 0.001 (-0.0003; 0.003) | 0.107 | -0.01 | 0.0886 |

SUPPLEMENTARY DATA

log_ealcohol intake (g/day) -0.004 (-0.009; 0.002) 0.176 -0.06 <0.001

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: Body Mass Index; GGT: gamma-glutamyl transpeptidase; hsCRP: high sensitivity C-reactive protein

Supplementary Table S3. Hazard ratios (95% confidence intervals) of Type 2 Diabetes per sex-specific standard deviation of Ferritin in men and women

| Sex | Biomarker | Model | HR (95% CI) | p value | Heterogeneity I ² (%) |
|------------------------------|---------------------------|-------|-------------------|---------|----------------------------------|
| Men (n = 10,504) | Ferritin (per SD*) | 1 | 1.32 (1.21; 1.45) | <0.001 | |
| | | 2 | 1.24 (1.14; 1.35) | <0.001 | |
| | | 3 | 1.12 (1.02; 1.23) | 0.021 | 72.2 |
| Women (n = 14,232) | Ferritin (per SD*) | 1 | 1.27 (1.19; 1.35) | <0.001 | |
| | | 2 | 1.19 (1.12; 1.27) | <0.001 | |
| | | 3 | 1.10 (1.04; 1.16) | 0.001 | 53.5 |

*Mean (SD) of ferritin in the subcohort: 188.2 (174.3) µg/l in men; 80.7 (86.9) µg/l in women.

Model 1: age and center adjusted

Model 2: further adjustment for BMI, physical activity, smoking status and level of education

Model 3: further adjustment for hsCRP, ALT and GGT

HR: Hazard Ratio; SD: standard deviation; 95% CI: 95% confidence intervals

SUPPLEMENTARY DATA

Supplementary Table S4. Hazard ratios (95% confidence intervals) of Type 2 Diabetes for Transferrin Saturation using varying cut-off points and per 5% higher level of TSAT in men and women.

| Sex | TSAT cut-off or per 5% higher level | HR (95% CI) | p value | Heterogeneity I² (%) |
|-------------------------------|--|--------------------|----------------|--|
| Men (n = 9,719) | ≥45% | 0.90 (0.75; 1.08) | 0.259 | 0.0 |
| | ≥50% | 0.90 (0.71; 1.15) | 0.403 | 0.0 |
| | ≥55% | 0.86 (0.63; 1.17) | 0.345 | 0.0 |
| | per 5% | 0.99 (0.95; 1.03) | 0.558 | 53.6 |
| Women (n = 13,484) | ≥45% | 0.68 (0.54; 0.86) | 0.002 | 0.0 |
| | ≥50% | 0.74(0.55; 1.01) | 0.059 | 0.0 |
| | ≥55% | 0.72 (0.49; 1.09) | 0.119 | 0.0 |
| | per 5% | 0.97 (0.94; 0.997) | 0.032 | 23.2 |

Adjusted for age, centre, BMI, physical activity, smoking status, level of education, hsCRP, ALT and GGT.

HR: Hazard Ratio; TSAT: Transferrin Saturation; 95% CI: 95% confidence intervals

SUPPLEMENTARY DATA

Supplementary Table S5. Hazard ratio (95% confidence intervals) of Type 2 Diabetes for 100 µg/L higher level of ferritin by sex in specific subgroups, adjusting for age, center, BMI, physical activity, smoking status, level of education, hsCRP, ALT and GGT and specified additional covariates.

| Subgroup | Sex | n | Model | HR (95% CI) | p |
|--------------------------------------|-------|--------|---------------------------|-------------------|--------|
| Menopausal status data available | Women | 13,450 | Model 3 | 1.10 (1.04; 1.17) | 0.001 |
| | | 13,450 | Model 3 + menopause | 1.11 (1.05; 1.18) | <0.001 |
| Alcohol intake data available | Men | 10,489 | Model 3 | 1.07 (1.02; 1.13) | 0.01 |
| | | 10,489 | Model 3 + alcohol intake | 1.07 (1.02; 1.13) | 0.001 |
| | Women | 14,224 | Model 3 | 1.12 (1.05; 1.19) | <0.001 |
| | | 14,224 | Model 3 + alcohol intake | 1.13 (1.16; 1.20) | <0.001 |
| Red meat intake data available | Men | 10,258 | Model 3 | 1.07 (1.02; 1.13) | 0.012 |
| | | 10,258 | Model 3 + red meat intake | 1.07 (1.01; 1.13) | 0.001 |
| | Women | 13,926 | Model 3 | 1.11 (1.05; 1.18) | 0.001 |
| | | 13,162 | Model 3 + red meat intake | 1.10 (1.03; 1.17) | 0.003 |
| Family history of T2D data available | Men | 5,051 | Model 3 | 1.13 (1.05; 1.21) | 0.001 |
| | | 5,051 | Model 3 + FH | 1.13 (1.05; 1.22) | 0.001 |
| | Women | 6,514 | Model 3 | 1.17 (1.06; 1.28) | 0.001 |
| | | 6,514 | Model 3 + FH | 1.15 (1.03; 1.27) | 0.01 |
| Waist circumference data available | Men | 9,672 | Model 3 | 1.05 (1.01; 1.10) | 0.02 |
| | | 9,672 | Model 3 + WC | 1.06 (1.01; 1.10) | 0.02 |
| | Women | 13,450 | Model 3 | 1.12 (1.05; 1.19) | <0.001 |
| | | 13,450 | Model 3 + WC | 1.10 (1.04; 1.17) | 0.001 |

Model 3 is adjusted for age, center, BMI, physical activity, smoking status, level of education, hsCRP, ALT and GGT

FH: family history of type 2 diabetes; HR: hazard ratio; WC: waist circumference; 95% CI: 95% confidence intervals