| **Supplementary information Table 1a. PESA cohort characteristics.** | | | | |
|---|---|---|---|---|
| | **Overall cohort (n=400)** | **CTR (n=105)** | **AT (n=295)** | **p-value** |
| Age, yrs | 56 ± 4 | 55 ± 4 | 56 ± 4 | 0.16 |
| Men, n (%) | 310 (78%) | 76 (72%) | 234 (79%) | 0.17 |
| **Cardiovascular risk factors** | | | | |
| Family history of CV disease, n (%) | 104 (26%) | 17 (16%) | 87 (30%) | 0.009 |
| Smoking, n (%) | 96 (24%) | 16 (15%) | 80 (27%) | 0.016 |
| BMI, $kg/m^2$ | 26.8 ± 3.7 | 26.3 ± 3.5 | 26.9 ± 3.7 | 0.097 |
| Waist circumference, cm | 94.6 ± 10.9 | 92.8 ± 9.9 | 95.2 ± 11.1 | 0.046 |
| Obesity, n (%) | 66 (17%) | 16 (15%) | 50 (17%) | 0.76 |
| Visceral fat | 11.8 ± 4.5 | 11.9 ± 5.5 | 11.8 ± 3.9 | 0.82 |
| DBP, mm Hg | 73.8 ± 8.8 | 71.6 ± 9.4 | 74.5 ± 8.5 | 0.006 |
| SBP, mm Hg | 119.6 ± 14.1 | 115.8 ± 14.8 | 120.9 ± 13.6 | 0.002 |
| Hypertension, n (%) | 123 (31%) | 17 (16%) | 106 (36%) | 0.00012 |
| Family history of hypertension, n (%) | 83 (21%) | 14 (13%) | 69 (23%) | 0.035 |
| Family history of hypercholesterolemia, n (%) | 179 (45%) | 28 (27%) | 151 (51%) | 1.28E-05 |
| **Treatments** | | | | |
| Antihypertensive therapy, n (%) | 80 (20%) | 14 (13%) | 66 (22.4%) | 0.048 |
| Lipid-lowering therapy, n (%) | 98 (24.5%) | 11 (11%) | 87 (29.5%) | 6.12E-05 |
| **Biochemistry** | | | | |
| Total cholesterol, mg/dL | 208.6 ± 36.8 | 203.3 ± 33.2 | 210.5 ± 37.8 | 0.066 |
| Oxidized LDL-C, mg/dL | 72.5 ± 29.7 | 67.8 ± 24.9 | 74.1 ± 31.1 | 0.062 |
| LDL-C, mg/dL | 134.6 ± 31.7 | 131.1 ± 29.2 | 135.9 ± 32.4 | 0.17 |
| *HDL-C, mg/dL | 50.7 (43.9-60.4) | 52.4 (44.9-61.1) | 50.1 (43.8-59.9) | 0.45 |
| *Lipoprotein, mg/dL | 18.6 (8.9-49.9) | 14.8 (5.6-38.8) | 20.9 (10.0-53.5) | 0.027 |
| *Triglyceride, mg/dL | 87 (64-121) | 80 (60-107) | 91 (68-124) | 0.004 |
| Fasting glucose, mg/dL | 87.9 ± 9.3 | 85.3 ± 8.5 | 88.9 ± 9.4 | 0.000326 |
| HbA1c, % | 5.43 ± 0.36 | 5.36 ± 0.30 | 5.45 ± 0.38 | 0.031 |
| Uric acid, mg/dL | 5.9 ± 1.2 | 5.6 ± 1.2 | 5.9 ± 1.2 | 0.018 |
| Hemoglobin, g/dL | 15.1 ± 1.2 | 14.8 ± 1.2 | 15.2 ± 1.1 | 0.009 |
| **Inflammatory marker** | | | | |
| hs-CRP, mg/dL | 0.13 (0.07-0.32) | 0.11 (0.06-0.24) | 0.14 (0.07-0.36) | 0.091 |
| **Biomarkers** | | | | |
| *ImP, nMol | 28.0 (19.9-41.2) | 26.0 (17.9-34.8) | 28.7 (20.7-42.9) | 0.012 |

| | | | | |
|---|---|---|---|---|
| *Histidine, µMol | 78.8 (72.3-85.1) | 79.3 (72.8-84.7) | 78.5 (72.1-85.4) | 0.80 |
| *Urocanic acid, nMol | 10.0 (7.2-13.9) | 10.1 (7.2-14.0) | 10.0 (7.1-13.9) | 0.55 |
| **Kidney and Liver function** | | | | |
| *Creatinine, mg/dL | 0.85 (0.77-0.95) | 0.85 (0.79-0.99) | 0.85 (0.77-0.94) | 0.095 |
| *Albumin:creatinine | 5.7 (4.3-8.2) | 5.2 (3.8-7.2) | 6.1 (4.7-8.5) | 0.001 |
| *ALT, mg/dL | 22 (17-30) | 20 (16-30) | 23 (17-30) | 0.043 |
| *AST, mg/dL | 20 (17-24) | 20 (17-24) | 21 (18-24) | 0.18 |
| *GGT, mg/dL | 24 (17-35) | 23 (16-31) | 24 (17-39) | 0.21 |
| **CV risk factor score** | | | | |
| SCORE (n,%) | | | | |
| Low (<1%) | 158 (40%) | 63 (60%) | 95 (33%) | 8.22E-07 |
| Moderate (1-5%) | 232 (58%) | 40 (38%) | 192 (66%) | 8.22E-07 |
| High (>5%) | 7 (2%) | 2 (2%) | 5 (2%) | 0.90 |

Data as mean ± SD, n(%) or median and interquartile range (*). P-values were calculated by the two-sided Student t-test (continuous parametric data) or two-sided by Mann-Witney U test (continuous nonparametric data) or two-sided Fisher's Exact test (categorical variables). Abbreviations: BMI, body mass index; CV, cardiovascular disease; DBP, diastolic blood pressure; HbA1c, glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure

| **Supplementary information Table 1b. PESA cohort characteristics by tertiles of Imidazole Propionate levels.** | | | | |
|---|---|---|---|---|
| **Variables** | **1st Tertile** | **2nd Tertile** | **3rd Tertile** | **p-value** |
| | **(lowest)** | **(intermediate)** | **(highest)** | |
| N | 134 | 133 | 133 | |
| Age, yrs | 56 ± 4 | 56 ± 4 | 56.3 ± 4 | 0.28 |
| Men, n (%) | 90 (67%) | 104 (78%) | 116 (87%) | 0.0004 |
| BMI, $kg/m^2$ | 26 ± 3.8 | 26.6 ± 3.4 | 27.8 ± 3.6 | 0.0003 |
| DBP, mm Hg | 73.2 ± 9.6 | 72.3 ± 7.1 | 75.8 ± 9.3 | 0.0037 |
| SBP, mm Hg | 118 ± 14.3 | 118 ± 11.6 | 122 ± 15.8 | 0.022 |
| Fasting glucose, mg/dL | 86.6 ± 9.8 | 87.4 ± 9.1 | 89.8 ± 8.9 | 0.015 |
| HDL-C, mg/dL | 55.2 ± 15.4 | 54 ± 13.6 | 50.9 ± 12.0 | 0.031 |
| LDL-C, mg/dL | 133 ± 30.3 | 137 ± 33.2 | 134 ± 31.6 | 0.63 |
| Total cholesterol, mg/dL | 208 ± 34.2 | 211 ± 38.7 | 207 ± 37.4 | 0.57 |
| Family history of CV disease, n (%) | 31 (23%) | 37 (28%) | 36 (27%) | 0.64 |
| Smoking, n (%) | 26 (19%) | 36 (27%) | 34 (26%) | 0.3 |
| Hypertension, n (%) | 40 (30%) | 35 (26%) | 48 (36%) | 0.22 |
| *Creatinine, mg/dL | 0.82 (0.75-0.93) | 0.85 (0.79-0.96) | 0.87 (0.79-0.98) | 0.0074 |
| *Visceral fat | 11 (8.5-13) | 11.5 (9.5-13.5) | 12.5 (10-15) | 0.0036 |
| *HbA1c, % | 5.4 (5.2-5.6) | 5.4 (5.1-5.6) | 5.4 (5.2-5.7) | 0.12 |
| *hs-CRP, mg/dL | 0.11 (0.05-0.24) | 0.15 (0.08-0.42) | 0.14 (0.07-0.33) | 0.017 |
| *Triglyceride, mg/dL | 82 (60-117) | 87.5 (68-114.5) | 90 (64-131) | 0.13 |
| *SCORE2 | 1 (0.47-1.9) | 1.23 (0.66-1.82) | 1.34 (0.88-2.23) | 0.0024 |
| **CAC score categories** | | | | 0.021 |
| 0 | 70 (56%) | 55 (44%) | 52 (41%) | |
| 0-99 | 36 (29%) | 40 (32%) | 45 (36%) | |
| 100-399 | 12 (10%) | 18 (15%) | 19 (15%) | |
| >400 | 7 (6%) | 11 (9%) | 10 (8%) | |
| ***Endpoints** | | | | |
| Atherosclerosis (AT), n(%) | 91 (68%) | 98(74%) | 106(80%) | 0.029 |
| Active atherosclerosis, n(%) | 61 (46%) | 72 (54%) | 88 (66%) | 0.001 |

| | | | | |
|---|---|---|---|---|
| Extent of atherosclerosis (summed ordinal value), n(%) | 0(0-2) | 3(2-5) | 5(3-6) | <0.001 |
| 0 | 50 (37%) | 37 (28%) | 28 (21%) | <0.001 |
| 1-2 | 21 (16%) | 27 (20%) | 28 (21%) | |
| 3-4 | 36 (27%) | 34 (26%) | 41 (31%) | |
| >4 | 27 (20%) | 35 (26%) | 36 (27%) | |

Data as mean ± SD or median and interquartile range (*). Categorical variables are shown by absolute count and percentage. Subjects with the same ImP concentration are assigned to the same tertile. Continuous variables were compared across tertiles of ImP by ANOVA or non-parametric Kruskal Wallis tests as appropriate, whereas nominal variables by applying the Cohran-Armitage test (dichotomous variables) and the Jonckheere-Terpstra test (ordinal variable) for trend. All tests were two tailed and the level of statistical significance was pre-specified at p-value<0.05. Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HbA1c, glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

| **Supplementary information Table 2a. IGT cohort characteristics.** | | | | |
|---|---|---|---|---|
| | **Overall cohort (n=1844)** | **CTR (n=529)** | **AT (n=1315)** | **p-value** |
| Age, yrs | 58 ± 5 | 57 ± 5 | 59 ± 5 | 2.13E-19 |
| Men, n (%) | 841 (46%) | 150 (29%) | 691 (53%) | 1.53E-21 |
| **Cardiovascular risk factors** | | | | |
| Family history of CVD, n (%) | 142 (8%) | 32 (6%) | 110 (9%) | 0.089 |
| Smoking, n (%) | 157 (9%) | 29 (6%) | 128 (10%) | 0.003 |
| BMI, kg/m$^2$ | 27.7 ± 4.4 | 27.2 ± 4.3 | 28 ± 4.4 | 0.00024 |
| Waist, cm | 97.9 ± 12.5 | 94.9 ± 11.9 | 99.2 ± 12.6 | 8.80E-12 |
| Obesity, n (%) | 507 (27%) | 126 (24%) | 382 (29%) | 0.025 |
| Abdominal visceral fat area, cm$^2$ | 169.6 ± 88.3 | 143.9 ± 74.2 | 180 ± 91.4 | 1.94E-15 |
| DBP, mm Hg | 80.9 ± 9.2 | 79.4 ± 9.1 | 81.5 ± 9.3 | 0.000004 |
| SBP, mm Hg | 126.9 ± 15.7 | 122.6 ± 14.9 | 128.7 ± 15.7 | 2.31E-14 |
| Hypertension, n (%) | 704 (38%) | 197 (38%) | 709 (54%) | 1.05E-10 |
| **Treatments** | | | | |
| Antihypertensive therapy, n (%) | 364 (22%) | 60 (13%) | 304 (26%) | 7.61E-09 |
| Lipid-lowering therapy, n (%) | 163 (9%) | 13 (3%) | 132 (12%) | 5.93E-09 |
| **Biochemistry** | | | | |
| Total cholesterol, mg/dL | 217.0 ± 40.1 | 215.1 ± 38.3 | 217.8 ± 40.8 | 0.18 |
| LDL-C, mg/dL | 143.6 ± 37.2 | 139.2 ± 36.4 | 145.4 ± 37.5 | 0.001 |
| *HDL-c, mg/dL | 61.9 (50.3-77.3) | 69.7 (58.1-85.1) | 61.9 (50.3-73.5) | 1.25E-13 |
| *Triglyceride, mg/dL | 97.5 (71.8-132.9) | 87.7 (64.7-124) | 97.5 (75.3-141.8) | 1.05E-08 |
| Fasting glucose, mg/dL | 104.4 ± 12.9 | 101.6 ± 10.3 | 105.5 ± 13.7 | 7.30E-9 |
| HbA1c, mmol/L | 35.5 ± 4.1 | 34.8 ± 3.4 | 35.8 ± 4.3 | 0.000002 |
| Uric acid, mg/dL | 5.3 ± 1.3 | 5.0 ± 1.2 | 5.5 ± 1.3 | 6.60E-13 |
| Hemoglobin, g/dL | 14.3 ± 1.1 | 14.1 ± 1.2 | 14.4 ± 1.1 | 3.53E-11 |
| *ImP, nMol | 7 (5-11) | 7 (5-10) | 7 (5-11) | 0.0004 |
| *Urocanic acid, nMol | 112 (81-158) | 118 (88-158) | 111 (80-157) | 0.68 |
| *Histidine, µMol | 76 (69-84) | 76 (69-85) | 76 (69-83) | 0.57 |
| **Inflammatory marker** | | | | |
| *hs-CRP, mg/dL | 0.11 (0.07-0.24) | 0.10 (0.06-0.21) | 0.12 (0.07-0.25) | 0.00013 |
| **Kidney and liver function** | | | | |
| *Creatinine, mg/dL | 0.89 (0.79-1.02) | 0.86 (0.77-0.98) | 0.92 (0.81-1.03) | 3.48E-07 |
| *eGFR, mL/min/1.73m$^2$ | 80.8 (73.6-88.4) | 82.2 (74.7-89.9) | 80.3 (73-88) | 0.05 |

| | | | | |
|---|---|---|---|---|
| *ALT, ukat/L | 0.43 (0.34-0.56) | 0.40 (0.32-0.51) | 0.44 (0.35-0.59) | 1.78E-08 |
| *GGT, ukat/L | 0.38 (0.27-0.59) | 0.32 (0.24-0.49) | 0.40 (0.28-0.63) | 1.06E-12 |
| **CV risk factor scores** | | | | |
| SCORE (n, %) | | | | |
| Low <5% | 1116 (62%) | 426 (24%) | 690 (39%) | 0 |
| Moderate 5-10% | 599 (34%) | 89 (5%) | 510 (29%) | 0 |
| High >10% | 92 (6%) | 1 (1%) | 91 (6%) | 0 |

Data as mean ± SD, n(%) or median and interquartile range (*). P-values were calculated by the two-sided Student t-test (continuous parametric data) or two-sided by Mann-Witney U test (continuous nonparametric data) or two-sided Fisher's Exact test (categorical variables). Abbreviations: BMI, body mass index; CV, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated Glomerular filtration rate; HbA1c, glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

| **Supplementary information Table 2b. IGT cohort characteristics by tertiles of Imidazole Propionate levels.** | | | | |
|---|---|---|---|---|
| **Variables** | **1st Tertile** | **2nd Tertile** | **3rd Tertile** | **p-value** |
| | **(lowest)** | **(intermediate)** | **(highest)** | |
| N | 813 | 482 | 549 | |
| Age, yrs | 58 ± 5 | 58 ± 5 | 58 ± 5 | 0.63 |
| Men, n (%) | 229 (28%) | 263 (55%) | 349 (64%) | 1.00E-25 |
| Smoking, n (%) | 53 (7%) | 48 (10%) | 56 (10%) | 0.024 |
| Family history of CV disease, n (%) | 70 (9%) | 40 (8%) | 32 (6%) | 0.14 |
| BMI, kg/m$^2$ | 27 ± 4.1 | 28.2 ± 4.5 | 28.3 ± 4.4 | 5.05E-09 |
| DBP, mm Hg | 80 ± 9.2 | 81.7 ± 9.0 | 81.4 ± 9.4 | 0.001 |
| SBP, mm Hg | 125 ± 15.8 | 128 ± 15.0 | 128 ± 0.2 | 0.001 |
| Glucose (mmol /L) | 102.6 ± 10.8 | 106 ± 14.7 | 106 ± 13.8 | 1.07E-07 |
| LDL-C (mmol/L) | 144.3 ± 37.9 | 143.1 ± 36.7 | 142.7 ± 36.8 | 0.74 |
| HDL-C, mmol/L | 70.0 ± 19.2 | 63.5 ± 19.0 | 61.1 ± 18.6 | 7.03E-18 |
| *Waist, cm | 94 (86-103) | 100 (91-108) | 101 (91-109) | 8.11E-18 |
| *HbA1c, mmol/mol | 35 (33-37) | 35 (33-38) | 35 (33-38) | 0.023 |
| *TG (mmol/L) | 88.57 (69.08-124.00) | 97.43 (73.51-141.71) | 106.28 (78.83-150.57) | 2.53E-09 |
| *hs-CRP, mg/dL | 0.1 (0.06-0.22) | 0.12 (0.07-0.25) | 0.12 (0.0.7-0.27) | 0.001 |
| *Creatinine, mg/dL | 0.85 (76-95) | 93 (82-1.04) | 0.96 (0.84-1.06) | 1.00E-25 |
| *Hemoglobin, g/dL | 14.0 (13.3-14.7) | 14.4 (13.6-15.2) | 14.6 (13.8-15.2) | 1.02E-19 |
| *eGFR, mL/min/173m$^2$ | 82.6 (75.4 - 90.0) | 79 (72.3-87.5) | 79.7 (71.8 - 86.8) | 4.60E-08 |
| *Histidine, µMol | 75 (68-81) | 76 (70-85) | 78 (71-86) | 9.50E-09 |
| *Urocanic acid, nM | 110 (80-149) | 112 (83-170) | 118 (83-161) | 0.043 |
| *SCORE2 | 3.46 (2.15 - 5.26) | 4.39 (2.93-6.99) | 4.95 (3.075 -7.41) | 1.51E-23 |
| **CAC score categories, n(%)** | | | | 8.79E-05 |
| 0 | 510 (63%) | 251 (53%) | 277 (51%) | |
| 1-99 | 224 (28%) | 157 (33%) | 182 (34%) | |
| 100-399 | 51 (6%) | 46 (10%) | 58 (11%) | |
| >400 | 21 (3%) | 21 (4%) | 26 (5%) | |
| ***Endpoints** | | | | |

| | | | | |
|---|---|---|---|---|
| Atherosclerosis (AT), n (%) | 537 (66%) | 335 (70%) | 400 (73%) | 0.028 |
| Extent of atherosclerosis (summed ordinal value), n (%) | 1 (0-2) | 1 (0-2) | 1 (0-2) | 6.54E-05 |
| 0 | 276 (34%) | 147 (31%) | 149 (27%) | 6.32E-05 |
| 1 | 254 (31%) | 125 (26%) | 153 (28%) | |
| 2 | 168 (21%) | 108 (22%) | 112 (20%) | |
| 3 | 75 (9%) | 52 (11%) | 90 (16%) | |
| 4 | 26 (3%) | 32 (7%) | 29 (5%) | |
| 5 | 14 (2%) | 18 (4%) | 16 (3%) | |

Data as mean ± SD or median and interquartile range (*). Categorical variables are shown by absolute count and percentage. Subjects with the same ImP concentration are assigned to the same tertile. Continuous variables were compared across tertiles of ImP by ANOVA or non-parametric Kruskal Wallis tests as appropriate, whereas nominal variables by applying the Cohran-Armitage test (dichotomous variables) and the Jonckheere-Terpstra test (ordinal variable) for trend. All tests were two tailed and the level of statistical significance was pre-specified at p-value<0.05. Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated Glomerular filtration rate; HbA1c, glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

**Supplementary information Table 3 (relative to Figure 2g).** Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) from regression models assessing the association between ImP and key atherosclerosis outcomes (presence and extent of AT) in the PESA and IGT cohorts.

| | **AT** | | **Extent of AT** | |
|---|---|---|---|---|
| | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
| PESA cohort | 1.76 (1.22-2.54) | 1.69 (1.13-2.52) | *1.68 (1.21-2.33) | *1.47 (1.04-2.1) |
| IGT cohort | *1.37 (1.13-1.67) | *1.25 (1.00-1.55) | *1.54 (1.31-1.80) | *1.35 (1.14-1.61) |

ORs correspond to 1-SD increase in ImP levels. AT defined as femoral and carotid plaques in PESA; carotid plaques in IGT. * ORs are presented per comparison of the 80th versus 20th percentiles of ImP distribution (dose-response models) in view of the non-linear association. ORs are adjusted for age, sex, smoking, creatinine, family history of CVD, haemoglobin, hypertension and LDL-C (PESA cohort) and age, smoking, family history of CVD, hypertension, LDL-C, Hb1Ac, hsCRP and ALT (IGT cohort).

| **Supplementary information Table 4. PESA cohort characteristics stratified by $^{18}$F-FDG uptake.** | | | | | | |
|---|---|---|---|---|---|---|
| | **CTR (n=105)** | **FDG$^{neg}$ (n=74)** | **FDG+_A (n=57)** | **FDG+_BM (n=40)** | **FDG+_SYS (n=124)** | **Significance** |
| Age, yrs | 55 ± 4 | 55 ± 5 | 56 ± 5 | 56 ± 4 | 56 ± 4 | 0.29 |
| Men, n (%) | 76 (72%) | 48 (65%) | 32 (80%) | 46 (81%) | 108 (87%) | d=0.007 |
| **Cardiovascular risk factors** | | | | | | |
| Family history of CV disease, n (%) | 17 (16%) | 24 (32%) | 8 (20%) | 10 (18%) | 45 (36%) | a=0.018, d=0.001 |
| Active smoking, n (%) | 16 (15%) | 22 (30%) | 10 (25%) | 17 (30%) | 31 (25%) | a=0.026, b= 0.04 |
| BMI kg/m$^2$ | 26.3 ± 3.5 | 24.1 ± 3.0 | 25.8 ± 2.7 | 28.0 ± 4.1 | 28.9 ± 3.1 | 2.02E-21 |
| Waist circumference, cm | 92.8 ± 9.9 | 96.3 ± 10.9 | 95.8 ± 10.8 | 94.6 ± 12.7 | 94.5 ± 11.1 | 0.28 |
| Obesity, n (%) | 16 (15%) | 1 (1%) | 7 (18%) | 3 (5%) | 39 (32%) | a=0.001, d= 0.005 |
| Visceral fat | 11.9 ± 5.5 | 9 ± 3.4 | 10.8 ± 2.8 | 12.4 ± 4.0 | 13.7 ± 3.7 | 2.28E-7 |
| DBP, mm Hg | 71.6 ± 9.4 | 72 ± 9.4 | 74.2 ± 6.7 | 73.8 ± 7.7 | 76.5 ± 8.6 | 0.00026 |
| SBP, mm Hg | 115.8 ± 14.8 | 118.5 ± 14.7 | 119.5 ± 12.5 | 119.6 ± 12.3 | 123.5 ± 13.7 | 0.0013 |
| Hypertension, n (%) | 17 (16%) | 23 (31%) | 9 (23%) | 17 (30%) | 57 (46%) | a=0.028, b=0.046, d=0 |
| Family history of hypertension, n (%) | 14 (13%) | 14 (19%) | 7 (18%) | 12 (21%) | 36 (29%) | d= 0.006 |
| Family history of hypercholesterolemia, n (%) | 28 (27%) | 29 (39%) | 26 (65%) | 29 (51%) | 67 (54%) | b= 0.003, c=0, d=0 |
| **Treatments** | | | | | | |
| Antihypertensive therapy, n (%) | 14 (13%) | 14 (19%) | 5 (13%) | 12 (21%) | 35 (28%) | d= 0.006 |
| Lipid-lowering therapy, n (%) | 11 (11%) | 12 (16%) | 20 (50%) | 16 (28%) | 39 (31%) | b= 0.007, c=0, d=0 |
| **Biochemistry** | | | | | | |
| Total cholesterol, mg/dL | 203.3 ± 33.2 | 216.8 ± 34.8 | 203.9 ± 34.7 | 209.6 ± 44.4 | 210.2 ± 38.5 | 0.13 |
| Oxidized LDL-C, mg/dL | 67.8 ± 24.9 | 72.1 ± 28.0 | 74.3 ± 26.9 | 80.7 ± 39.7 | 73.1 ± 31.5 | 0.20 |
| LDL-C, mg/dL | 131.1 ± 29.2 | 137.8 ± 30.0 | 131.1 ± 30.4 | 136.3 ± 40.0 | 136.8 ± 32.3 | 0.50 |
| *HDL-C, mg/dL | 52.4 (44.9-61.1) | 59 (50.5-70.9) | 49.6 (43.9-59.1) | 50.8 (45.4-57.1) | 46.6 (41.4-54.9) | 1.93E-08 |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Lipoprotein, mg/dL | 14.8 (5.6-38.8) | 17.95 (8.3-64) | 23 (6.6-49.6) | 25.55 (12.35-71) | 22.8 (10-53.1) | 0.15 |
| *Triglyceride, mg/dL | 80 (60-107) | 70 (57-98.5) | 90 (71-127.5) | 86.5 (66.8-123) | 109 (78.5-131) | 3.88E-07 |
| Fasting glucose, mg/dL | 85.3 ± 8.5 | 85.6 ± 10.1 | 87.1 ± 7.6 | 91.5 ± 8.4 | 90.8 ± 9.5 | 0.000001 |
| HbA1c, % | 5.36 ± 0.30 | 5.35 ± 0.31 | 5.44 ± 0.38 | 5.45 ± 0.38 | 5.53 ± 0.41 | 0.0037 |
| Uric acid, mg/dL | 5.6 ± 1.2 | 5.5 ± 1.2 | 5.9 ± 1.2 | 5.9 ± 1.1 | 6.7 ± 1.2 | 0.000003 |
| Hemoglobin, g/dL | 14.8 ± 1.2 | 14.9 ± 1.2 | 15.3 ± 1.1 | 15.5 ± 1.1 | 15.2 ± 1.1 | 0.0029 |
| **Inflammatory marker** | | | | | | |
| *hs-CRP, mg/dL | 0.11 (0.06-0.24) | 0.1 (0.04-0.27) | 0.12 (0.06-0.25) | 0.13 (0.07-0.33) | 0.19 (0.09-0.56) | 0.00052 |
| **Biomarkers** | | | | | | |
| *ImP, nMol | 26.0 (17.9-34.8) | 24.8 (19.5-33.1) | 28.5 (18.7-40.9) | 33.7 (25.2-44.1) | 29.5 (22.3-47.3) | 0.002 |
| *Histidine, µMol | 79.3 (72.8-84.7) | 79.4 (71.9-85.9) | 79.2 (72.9-85.6) | 79.4 (71.5-85.3) | 77.4 (71.8-83.8) | 0.80 |
| *Urocanic acid, nMol | 10.1 (7.2-14.0) | 9.9 (6.2-13.9) | 9.6 (7.2-13.8) | 10.9 (7.5-15.1) | 10.2 (7.3-14.1) | 0.92 |
| **Kidney and Liver function** | | | | | | |
| *Creatinine, mg/dL | 0.85 (0.79-0.99) | 0.82 (0.73-0.89) | 0.87 (0.78-0.98) | 0.85 (0.79-0.93) | 0.86 (0.77-0.95) | 0.72 |
| *Albumin:creatinine | 5.2 (3.8-7.2) | 6.8 (5.2-8.8) | 6.5 (4.9-9.0) | 5.5 (3.7-8.0) | 6.0 (4.6-8.4) | 0.0056 |
| *ALT, mg/dL | 20 (16-30) | 18 (15-27) | 21 (17-27) | 23 (18-29) | 27 (20-33) | 8.96E-05 |
| *AST, mg/dL | 20 (17-24) | 20 (17-24) | 21 (18-24) | 19 (17-22) | 21 (18-25) | 0.22 |
| *GGT, mg/dL | 23 (16-31) | 20 (13-28) | 24 (16-34) | 24 (18-39) | 27 (20-44) | 0.0013 |
| **CV risk factor score** | | | | | | |
| SCORE (n,%) | | | | | | |
| Low (<1%) | 63 (60%) | 31 (42%) | 17 (43%) | 18 (32%) | 29 (24%) | b=0, d=0 |
| Moderate (1-5%) | 40 (38%) | 39 (53%) | 23 (58%) | 38 (67%) | 92 (75%) | b=0, d=0 |
| High (>5%) | 2 (2%) | 3 (4%) | 0 (0%) | 1 (2%) | 1 (1%) | - |

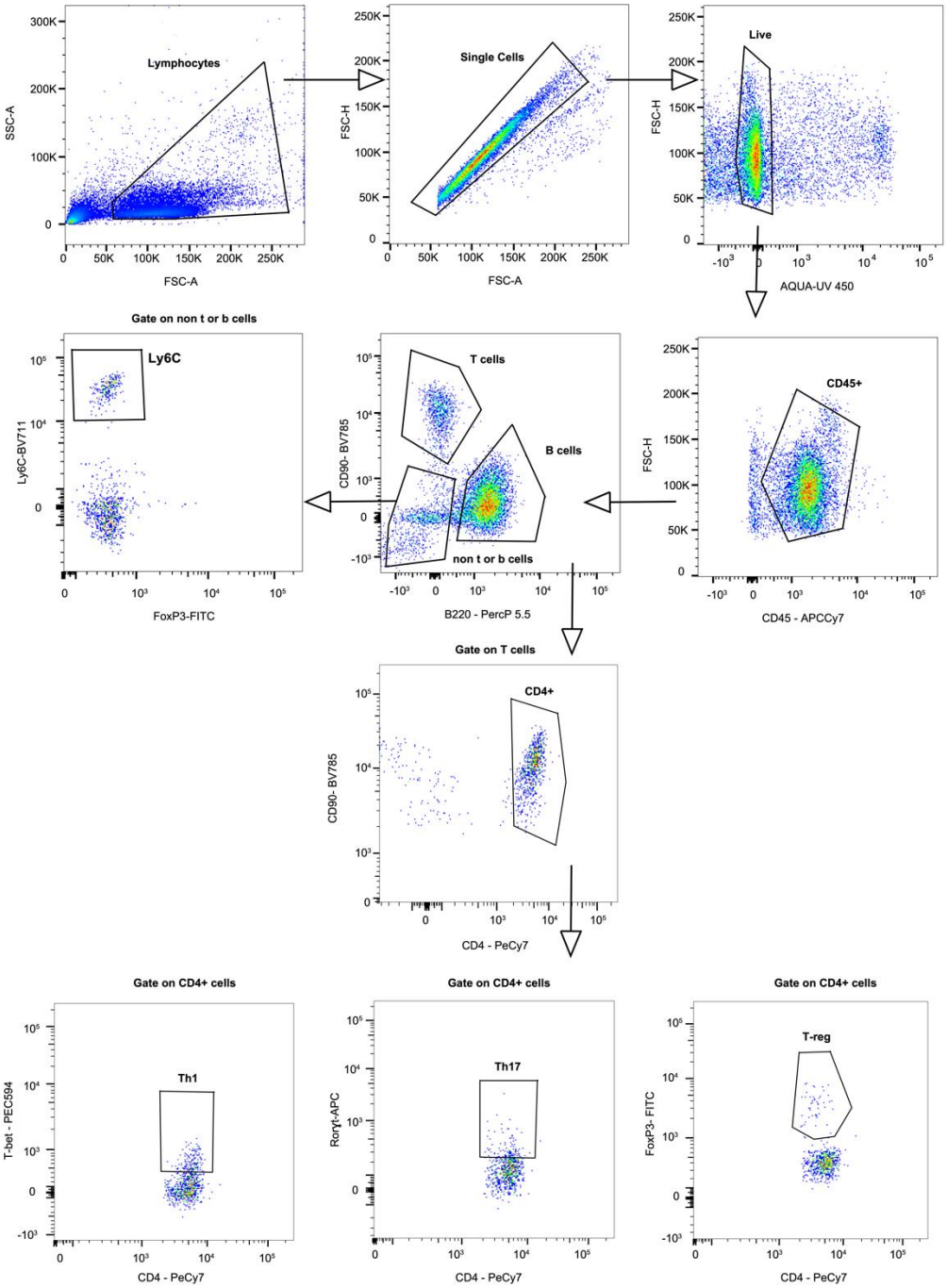
Data as mean ± SD, n(%) or median and interquartile range (*). P-values were calculated by One-way ANOVA with post-hoc Tukey HSD test (continuous parametric data) or Kruskal-Wallis with post-hoc Dunn's test (continuous nonparametric data) or Fisher's Exact test (categorical variables). All tests were two-tailed and the level of statistical significance was pre-specified at p-value<0.05. a, b, c, d are indicatives of p-value <0.05 for the comparisons $FDG^{neg}$ vs CTR, FDG+_A vs CTR, FDG+_BM vs CTR, FDG+_SYS vs CTR, respectively. Abbreviations: BMI, body mass index; CV, cardiovascular disease; DBP, diastolic blood pressure; HbA1c, glycosylated haemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

**Supplementary information Table 5 (relative to Figure 2k).** Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) from multinominal regression model assessing the association between ImP and the presence and activity of atherosclerosis in the PESA cohort.

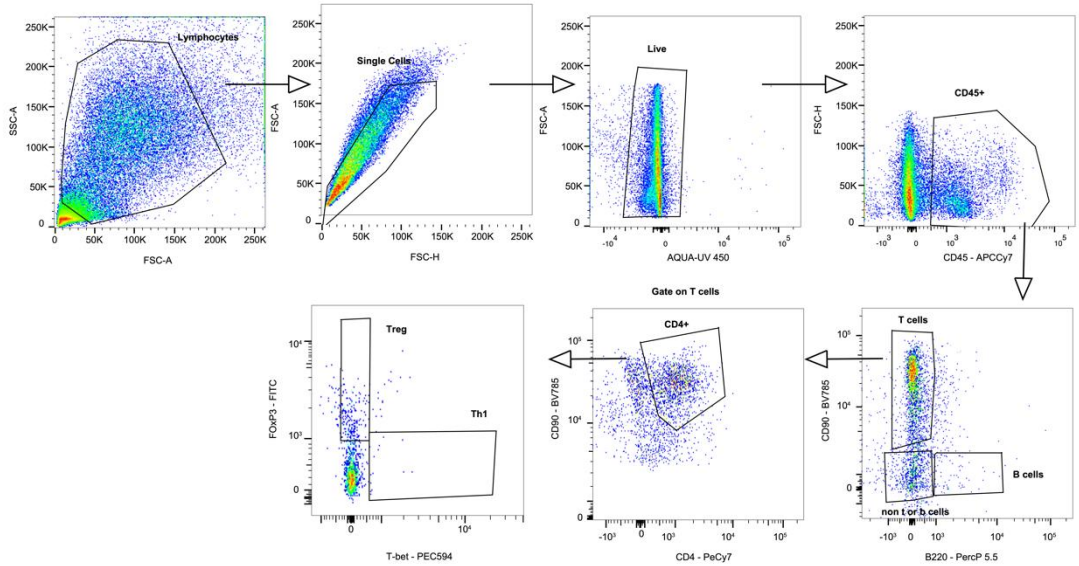
| | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|
| $FDG^{neg}$ | 1.26 (0.78-2.03) | 1.26 (0.80-1.99) |
| FDG+_A | 1.80 (1.16-2.79) | 1.67 (1.08-2.57) |
| FDG+_BM | 2.01 (1.29-3.13) | 1.80 (1.16-2.80) |
| FDG+_SYS | 1.98 (1.34-2.94) | 1.76 (1.19-2.59) |

No atherosclerosis (CTR) is used as the reference category. ORs correspond to 1-SD increase in ImP levels. ORs are adjusted for age, sex, smoking, glucose, hs-CRP and haemoglobin concentration. Abbreviations: $FDG^{neg}$, inactive atherosclerosis (negative 18F-FDG uptake in any compartment); FDG+_A, vascular inflammation (arterial 18F-FDG uptake), FDG+_BM, bone marrow (BM) activation (18F-FDG uptake in BM); FDG+_SYS and systemic inflammation (concurrent arterial and BM 18F-FDG uptake).

**Supplementary information Figure 1, Gating strategy for flow cytometry analysis of blood (relative to Fig. 3c,3d, 4c,4j, 4k, ED Fig. 4a, ED Fig. 4g-i and ED Fig. 7e,f)**



**Supplementary Information Figure 2, Gating strategy for flow cytometry analysis of B, T, Th1 and Treg cells in aorta (relative to Fig. 4f, ED Fig. 4i and ED Fig. 7g-i)**




**Supplementary information Figure 3, Gating strategy for flow cytometry analysis of macrophages subsets in aorta (relative to Fig. 4g and ED Fig. 7j)**