|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **T1 evaluation** | |  |  |
| **P** | **Included** | **Not included** |  |  |
|  | **558** | **674** |  | N |
| <0.001 | 57.7±6.6 | 60.2±6.9 |  | Age (y) |
| 0.013 | 97 (17.4) | 156 (23.1) | ≥2 | AP Class, n (%) |
|  | 460 (82.6) | 518 (76.9) | <2 |  |
| <0.001 | 531 (95.2) | 595 (88.3) |  | Males, n (%) |
| <0.001 | 114 (20.5) | 280 (41.7) | Elementary | Education, n (%) |
|  | 279 (50.2) | 285 (42.4) | High school |  |
|  | 163 (29.3) | 107 (15.9) | Academic |  |
| 0.22 | 53 (9.5) | 88 (13.1) | Currently | Smoking, n (%) |
|  | 341 (61.1) | 386 (57.3) | Former |  |
|  | 164 (29.4) | 200 (29.7) | Never |  |
| 0.496 | 208 (37.3) | 264 (39.2) | Yes | Beta-blockers treatment, n (%) |
| 0.001 | 222 (39.8) | 331 (49.1) | Yes | Nitrates treatment, n (%) |
| 0.060 | 263 (47.1) | 354 (52.5) | Yes | Calcium channel blockers treatment, n (%) |
| 0.823 | 136 (24.4) | 168 (24.9) |  | PCI or CABG in the BIP, n (%) |
| 0.43 | 428 (76.7) | 504 (74.9) | Yes | Previous MI, n (%) |
| 0.006 | (6.8) 38 | 77 (11.4) | Yes | Diabetes, n (%) |
| 0.016 | 123 (23.3) | 188 (29.7) | Yes | Insulin resistance†, n (%) |
|  |  |  | Yes | CKD§, n (%) |
| 0.51  0.10 | 174 (31.2)  17 (3.0) | 222 (33.3)  11 (1.6) | Yes  Yes | History of hypertension, n (%) |
| History of PAD, n (%) |
| 0.06 | 1 (0.2) | 7 (1.0) | Yes | History of stroke, n (%) |
| 0.72 | 15 (2.7) | 16 (2.4) | Yes | History of COPD, n (%) |
| <0.001 | 170.2±6.7 | 168 ± 7.6 |  | Height (cm) |
| 0.038 | 26.0 (24.5-28.0) | 26.4 (24.6-28.7) |  | BMI\* (kg/m2) |
| <0.001 | 130±17.4 | 134 ± 19 |  | Systolic BP (mmHg) |
| 0.06 | 81±9.4 | 82 ± 10 |  | Diastolic BP (mmHg) |
| 0.01 | 213±17.6 | 211±18 |  | Total cholesterol (mg/dL) |
| 0.05 | 149.5±16.5 | 148±17 |  | LDL cholesterol (mg/dL) |
| 0.15 | 34.9±5.4 | 34.5±5.4 |  | HDL cholesterol (mg/dL) |
| 0.54 | (179-105) 137 | 136 (106-171) |  | Triglycerides\* (mg/dL) |
| 0.003 | 1.15±0.14 | 1.11±0.14 |  | Creatinine (ml/dl) |
| 0.02 | (292-377) 332 | 338 (299-392) |  | Fibrinogen\* (mg/dL) |
| 0.1 | (7.3-5.4) 6.2 | 6.4 (5.5-7.5) |  | White blood counts\* (×109/L) |
| <0.001 | (4.7-1.5) 2.6 | 3.5 (1.9-6.7) |  | C-reactive protein (mg/dL) |

**Supplemental table 1:** Baseline characteristics of the BIP sample of 1,232 participants: 674 individuals that did not participate in the T1 evaluation compared to those (n=558) included at the T1 evaluation.

† Defined as homeostatic model assessment of insulin resistance (HOMA-IR) in the top quartile (≥1.60); § Defined as Estimated glomerular filtration rate, eGFR<60 ml/min/m2; \*Median and interquartile range (IQR) is presented for variables with skewed distributions;BP, indicates blood pressure; cIMT, Common carotid intima-media thickness; CVR, Cerebrovascular reactivity; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; NYHA, New York Heart Association functional class.

**Supplemental table 2:** Characteristics of the BIP Neurocognitive study by angina pectoris (AP) severity class

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| ***P*** | **AP Class<2** | | **AP Class≥2** |  |  | |
|  | N=301 | | N=50 |  |  | |
| *Baseline* | | | | |  | |
| 0.175 | 6.4±56.5 | 6.8±57.9 | |  | Age (years, mean±std.) | |
| 0.05 | 54 (17.9) | 13 (26.0) | | Elementary | Education, n (%) | |
| 141 (46.8) | 26 (52.0) | | High school |
| 106 (35.2) | 11 (22.0) | | Academic |
| 0.046 | 85 (28.2) | 20 (40.0) | | Middle East | Birthplace, n (%) | |
| 135 (44.9) | 22 (44.0) | | Europe |
| 81 (26.9) | 8 (16.0) | | Israel |
| 880.8 | 20 (6.6) | 5 (10.0) | | Currently | Smoking, n (%) | |
| 194 (64.5) | 28 (56.0) | | Former |
| 87 (28.9) | 17 (34.0) | | Never |
| 0.007 | 103 (34.2) | 27 (54.0) | | Yes | Beta-blockers treatment, n (%) | |
| 0.001> | 96 (31.9) | 39 (78.0) | | Yes | Nitrates treatment, n (%) | |
| 0.001> | 119 (39.5) | 32 (64.0) | | Yes | Calcium channel blockers treatment, n (%) | |
| 0.023 | 74 (24.6) | 20 (40.0) | | Yes | PCI or CABG in the BIP, n (%) | |
| 0.240 | 239 (79.4) | 36 (72.0) | | Yes | Previous MI, n (%) | |
| 0.936 | 29 (9.6) | 5 (10.0) | | Yes | Diabetes, n (%) | |
| 0.010 | 64 (22.3) | 19 (39.6) | | Yes | Insulin resistance†, n (%) | |
| 0.883 | 81 (27.0) | 13 (26.0) | | Yes | CKD §, n (%) | |
| 0.001> | 273 (90.7) | 24 (48.0) | | <2 | NYHA class, n (%) | |
| 28 (9.3) | 26 (52.0) | | ≥2 |
| 0.011 | 223 (75.3) | 29 (58.0) | | Yes | Any physical activity, n (%) | |
| 0.664 | 3±26.2 | 3±26.4 | |  | BMI (kg/m2) | |
| 0.821 | 16±128 | 18±129 | |  | Systolic BP (mmHg, mean±std.) | |
| 0.588 | 10±80 | 10±81 | |  | Diastolic BP (mmHg, mean±std.) | |
| 0.048 | 17±214 | 17±209 | |  | Total cholesterol (mg/dL, mean±std.) | |
| 0.040 | 17±150 | 16±144 | |  | LDL cholesterol (mg/dL, mean±std.) | |
| 0.036 | 5±35 | 5±33 | |  | HDL cholesterol (mg/dL, mean±std.) | |
| 0.465 | 136 (106-180) | 134 (120-209) | |  | Triglycerides (mg/dL)\* | |
| 0.101 | 2.3 (1.2-4.2) | 2.3 (2.0-5.9) | |  | C-reactive protein (mg/dL)\* | |
|  | *T1 evaluation* | | | |  | |
| 0.208 | 6.4±71.7 | 6.7±72.9 | |  | Age (years, mean±std.) |
| 0.210 | 230 (78.5) | 33 (70.2) | | Yes | Increased cIMT(≥0.93mm) and/or Bilateral carotid plaques, n (%) |
| 0.048 | 115 (40.9) | 25 (56.8) | | Yes | Impaired CVR, n (%) |
| 0.026 | 42 (14.0) | 13 (26.5) | | GDS≥5 | Depressive symptoms, n (%) |
| 0.018 | 139 (46.8) | 29 (65.9) | | ≤97 | Median Global Cognitive Score, n (%) |
| 158 (53.2) | 15 (34.1) | | >98 |  |
|  | *T2 evaluation* | | | |  |
| 0.230 | 6.4±77.0 | 6.7±78.1 | |  | Age (years, mean±std.) |
| 0.033 | 79 (26.2) | 21 (42.0) | |  | Frailty, n (%) |

† Defined as homeostatic model assessment of insulin resistance (HOMA-IR) in the top quartile (≥1.60); § CKD, Chronic Kidney Diseases defined as Estimated glomerular filtration rate, eGFR<60 ml/min/m2; \* Median and interquartile range (IQR) is presented for variables with skewed distributions; BP, indicates blood pressure; CABG, Coronary Artery Bypass Grafting; cIMT, Common carotid intima-media thickness; CVR, Cerebrovascular reactivity; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MI, myocardial infarction; NYHA, New York Heart Association functional class; PCI, percutaneous coronary intervention.

**Supplemental table 3:** Multinomial logistic regression for association between AP severity (≥2 vs. <2) and pre-frailty and frailty (reference outcome value is robust)

|  |  |  |  |
| --- | --- | --- | --- |
| **Model** | **Frailty Status** | **OR\* (95% CI)** | **P** |
| 1 | Robust | 1.00 (ref.) |  |
| Pre-frail | 1.71 (1.36-2.16) | 0.178 |
| Frail | 2.83 (1.12-7.19) | 0.028 |
| 2 | Robust | 1.00 (ref.) |  |
| Pre-frail | 3.03 (1.06-8.65) | 0.039 |
| Frail | 5.11 (1.56-16.70) | 0.007 |
| 3 | Robust | 1.00 (ref.) |  |
| Pre-frail | 3.24 (1.09-9.68) | 0.035 |
| Frail | 3.50 (0.99-12.41) | 0.053 |
| 4 | Robust | 1.00 (ref.) |  |
| Pre-frail | 2.56 (0.836-2.33) | 0.102 |
| Frail | 3.95 (1.12-14.05) | 0.034 |
| 5 | Robust | 1.00 (ref.) |  |
| Pre-frail | 2.57 (0.84-7.87) | 0.098 |
| Frail | 5.23 (1.44-19.05) | 0.012 |
| 6 | Robust | 1.00 (ref.) |  |
| Pre-frail | 2.73 (1.49-5.00) | <0.001 |
| Frail | 5.68 (2.94-10.99) | <0.001 |

**Model 1** = age, education (≥12 vs. <12 years), birthplace (Europa, Middle East vs. Israel); **Model 2** = model 1 + BMI (continues), systolic BP (continues), physical activity, diabetes, previous MI, CKD, NYHA functional class (≥2 vs. <2), insulin resistance (top quartile vs. others) and CRP (top tertile vs. others); **Model 3** = model 2 + impaired CVR vs. normal and increased cIMT and/or bilateral carotid plaques vs. normal cIMT and without bilateral carotid plaques at T2; **Model 4** = model 2 + global cognitive score and depressive symptoms (GDS≥5) at T1; **Model 5**= model 3 after excluding subjects with stroke and dementia at T2 (n=56); **Model 6** = model 3 applying IPW method; CI, confidence interval.