# SUPPLEMENTAL MATERIAL

**Table S1:** Power estimates of hazard ratios for incident CVD based on rs4680 G(val) allele frequencies over range of GAF from 0.3-0.6.

| GAF | HR | Power |
|---|---|---|
| 0.30 | 0.70 | 0.98 |
| | 0.75 | 0.91 |
| | 0.80 | 0.74 |
| 0.40 | 0.70 | 0.99 |
| | 0.75 | 0.95 |
| | 0.80 | 0.80 |
| 0.50 | 0.70 | 0.99 |
| | 0.75 | 0.96 |
| | 0.80 | 0.83 |
| 0.60 | 0.70 | 0.99 |
| | 0.75 | 0.96 |
| | 0.80 | 0.82 |

Abbreviations: HR=Hazard Ratio; GAF= Gene allele frequency

**Table S2:** Demographics, baseline characteristics and aspirin use by *COMT* rs4818 genotype use in MESA.

| | CC | GC | GG |
|---|---|---|---|
| **Participants, n** | 2888 (47.7) | 2515 (41.6) | 649 (10.7) |
| **Demographic data** | | | |
| Age | 62.1 (10.1) | 62.3 (10.4) | 63.0 (10.5) |
| Female | 1501 (52.0) | 1315 (52.3) | 340 (52.4) |
| Race/ethnicity | | | |
| White | 828 (28.7) | 1129 (44.9) | 379 (58.4) |
| Black | 981 (34.0) | 528 (12.9) | 72 (11.1) |
| Hispanic | 733 (25.4) | 533 (21.0) | 110 (17.0) |
| Asian | 346 (12.0) | 325 (21.2) | 88 (13.6) |
| **Medical History** | | | |
| History of diabetes | 395 (13.7) | 312 (12.4) | 54 (8.4) |
| Current smoker | 373 (12.9) | 338 (13.4) | 66 (10.2) |
| Aspirin Use at Exam 1 (%) | 579 (20.1) | 512 (20.4) | 126 (19.4) |
| **Physical Exam** | | | |
| Body mass index, $kg/m^2$ | 28.7 (5.7) | 28.1 (5.4) | 27.8 (5.1) |
| Systolic blood pressure, mmHg | 127.5 (21.7) | 126.0 (21.6) | 124.8 (20.7) |
| Diastolic blood pressure, mmHg | 72.3 (10.4) | 71.5 (10.3) | 71.2 (9.7) |
| **Laboratory Measurements** | | | |
| HDL cholesterol, mg/dL | 50.6 (14.7) | 50.8 (14.9) | 51.0 (14.4) |
| Triglycerides, mg/dL | 131.3 (87.7) | 134.9 (96.9) | 133.9 (79.2) |
| Total cholesterol, mg/dL | 193.5 (35.8) | 194.6 (36.6) | 195.2 (34.3) |

**Table S3:** Distribution of *COMT* rs4818 and rs4680 genotypes by race in MESA.

| | rs4818 | | | | | rs4680 | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Race** | **GG** | **GC** | **CC** | **MAF (G)** | **HWE** | **AA** | **AG** | **GG** | **MAF (A)** | **HWE** | **LD $r^2$** |
| **Overall** | 677 | 2635 | 3004 | 0.32 | <0.01 | 1106 | 2928 | 2316 | 0.40 | <0.001 | 0.31 |
| **White** | 406 | 1206 | 869 | 0.41 | >0.05 | 655 | 1236 | 593 | 0.51 | >0.05 | 0.72 |
| **Black** | 74 | 547 | 1018 | 0.21 | >0.05 | 178 | 685 | 806 | 0.31 | >0.05 | 0.12 |
| **Hispanic** | 109 | 555 | 764 | 0.27 | >0.05 | 211 | 704 | 514 | 0.39 | >0.05 | 0.24 |
| **Asian** | 88 | 327 | 353 | 0.33 | >0.05 | 62 | 303 | 403 | 0.28 | >0.05 | 0.19 |

Abbreviations: MAF = minor allele frequency; HWE = Hardy-Weinberg Equilibrium; LD = Linkage disequilibrium

**Table S4:** Parameter estimates of COMT rs4818 and rs4680 (per G allele) association with baseline cardiometabolic risk factors.

| | | All | | | White | | | Black | | | Hispanic | | | Asian | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Risk Factor** | | **Beta** | **SE** | **P** | **Beta** | **SE** | **P** | **Beta** | **SE** | **P** | **Beta** | **SE** | **P** | **Beta** | **SE** | **P** |
| **Fibrinogen,** | rs4818 | -3.65 | 1.35 | 0.007 | -0.81 | 2.11 | 0.70 | -2.29 | 3.03 | 0.45 | -4.94 | 3.02 | 0.10 | -9.70 | 3.06 | 0.002 |
| **mg/dL** | rs4680 | 0.53 | 1.29 | 0.68 | 0.84 | 1.96 | 0.67 | 1.70 | 2.78 | 0.54 | -1.43 | 2.89 | 0.62 | 0.54 | 3.31 | 0.87 |
| **CRP, mg/L** | rs4818 | -0.06 | 0.10 | 0.58 | 0.32 | 0.16 | 0.05 | -0.19 | 0.33 | 0.58 | -0.44 | 0.23 | 0.05 | -0.31 | 0.20 | 0.12 |
| | rs4680 | 0.17 | 0.11 | 0.11 | 0.33 | 0.15 | 0.03 | 0.09 | 0.27 | 0.74 | 0.003 | 0.22 | 0.99 | -0.01 | 0.27 | 0.97 |
| **ICAM, ng/mL** | rs4818 | -1.05 | 2.22 | 0.64 | -2.86 | 2.93 | 0.33 | 10.52 | 7.85 | 0.18 | -3.22 | 5.84 | 0.58 | 1.09 | 4.95 | 0.82 |
| | rs4680 | -1.12 | 2.11 | 0.59 | -1.20 | 2.77 | 0.66 | 3.83 | 6.92 | 0.58 | -0.34 | 5.66 | 0.95 | -3.97 | 4.91 | 0.42 |
| **IL-6, pg/mL** | rs4818 | -0.02 | 0.02 | 0.44 | 0.03 | 0.04 | 0.37 | -0.01 | 0.06 | 0.91 | -0.05 | 0.05 | 0.30 | -0.09 | 0.05 | 0.08 |
| | rs4680 | 0.02 | 0.04 | 0.50 | 0.02 | 0.03 | 0.47 | 0.03 | 0.05 | 0.59 | 0.10 | 0.04 | 0.02 | -0.10 | 0.06 | 0.13 |
| **SBP, mmHg** | rs4818 | -0.23 | 0.39 | 0.56 | 0.13 | 0.56 | 0.81 | -0.12 | 0.93 | 0.90 | -0.49 | 0.83 | 0.55 | -1.28 | 1.08 | 0.24 |
| | rs4680 | 0.01 | 0.36 | 0.99 | 0.17 | 0.52 | 0.74 | 0.21 | 0.78 | 0.78 | -0.45 | 0.76 | 0.55 | -0.16 | 1.07 | 0.88 |
| **DBP, mmHg** | rs4818 | 0.03 | 0.19 | 0.88 | 0.16 | 0.28 | 0.55 | 0.03 | 0.46 | 0.96 | -0.25 | 0.38 | 0.52 | 0.06 | 0.52 | 0.91 |
| | rs4680 | 0.03 | 0.18 | 0.85 | 0.09 | 0.26 | 0.74 | -0.03 | 0.37 | 0.94 | -0.30 | 0.36 | 0.41 | 0.71 | 0.56 | 0.21 |
| **Hemoglobin** | rs4818 | -0.02 | 0.02 | 0.22 | 0.00 | 0.02 | 0.95 | -0.07 | 0.05 | 0.15 | -0.05 | 0.06 | 0.34 | -0.07 | 0.04 | 0.12 |
| **A1c, %** | rs4680 | -0.02 | 0.01 | 0.20 | -0.01 | 0.02 | 0.41 | -0.01 | 0.04 | 0.86 | -0.02 | 0.06 | 0.69 | -0.08 | 0.05 | 0.12 |
| **Fasting** | rs4818 | -0.45 | 0.48 | 0.35 | 0.69 | 0.59 | 0.24 | -3.36 | 1.34 | 0.01 | -2.50 | 1.74 | 0.15 | -2.36 | 1.39 | 0.09 |
| **glucose, mg/dl** | rs4680 | -1.15 | 0.96 | 0.23 | 0.44 | 0.52 | 0.40 | -1.69 | 1.21 | 0.16 | -0.86 | 1.64 | 0.60 | -3.86 | 1.65 | 0.02 |
| **Triglycerides,** | rs4818 | 0.17 | 1.66 | 0.92 | -1.57 | 4.38 | 0.72 | -0.12 | 4.71 | 0.98 | 0.60 | 2.56 | 0.81 | 0.51 | 3.00 | 0.86 |
| **mg/dL** | rs4680 | -3.42 | 1.83 | 0.06 | 0.06 | 2.43 | 0.98 | -4.14 | 3.33 | 0.21 | -5.88 | 3.47 | 0.09 | -8.52 | 4.90 | 0.08 |
| **HDL-C,** | rs4818 | 0.03 | 0.26 | 0.89 | -0.05 | 0.41 | 0.90 | -0.07 | 0.64 | 0.91 | 0.42 | 0.51 | 0.42 | -0.22 | 0.62 | 0.72 |
| **mg/dL** | rs4680 | 0.33 | 0.24 | 0.17 | -0.03 | 0.40 | 0.93 | 0.43 | 0.52 | 0.41 | 0.60 | 0.44 | 0.18 | 0.59 | 0.69 | 0.39 |
| **LDL-C,** | rs4818 | 0.08 | 0.63 | 0.90 | 0.75 | 0.92 | 0.42 | -0.69 | 1.53 | 0.65 | -0.79 | 1.37 | 0.56 | 0.10 | 1.55 | 0.95 |
| **mg/dL** | rs4680 | -0.14 | 0.58 | 0.81 | 0.13 | 0.86 | 0.88 | -1.11 | 1.24 | 0.37 | -0.74 | 1.27 | 0.56 | 1.79 | 1.76 | 0.31 |

**Table S5:** *COMT* rs4818 and rs4680 gene dosage (per allele*) association with rates of CVD stratified by race and sex.

| SNP | Females | | | Males | | |
|---|---|---|---|---|---|---|
| **Race/Ethnicity** | **Events/N** | **HR 95% CI** | **P** | **Events/N** | **HR, 95% CI** | **P** |
| **rs4818** | | | | | | |
| **Overall** | 226/3271 | 0.93 [0.75-1.14] | 0.48 | 298/2977 | 0.80 [0.67-0.97] | 0.02 |
| **White** | 97/1300 | 1.04 [0.77-1.41] | 0.80 | 117/1179 | 0.85 [0.65-1.11] | 0.24 |
| **Black** | 55/846 | 0.77 [0.45-1.32] | 0.34 | 75/729 | 0.87 [0.58-1.32] | 0.52 |
| **Hispanic** | 54/736 | 0.75 [0.47-1.18] | 0.21 | 83/690 | 0.67 [0.46-0.98] | 0.04 |
| **Asian** | 20/389 | 0.94 [0.50-1.79] | 0.86 | 23/379 | 0.83 [0.42-1.64] | 0.59 |
| **rs4680** | | | | | | |
| **Overall** | 226/3271 | 0.95 [0.78-1.15] | 0.59 | 298/2977 | 0.95 [0.79-1.14] | 0.59 |
| **White** | 97/1300 | 1.14 [0.85-1.52] | 0.38 | 117/1179 | 0.95 [0.73-1.22] | 0.68 |
| **Black** | 55/846 | 0.88 [0.61-1.29] | 0.52 | 75/729 | 1.04 [0.72-1.48] | 0.84 |
| **Hispanic** | 54/736 | 0.75 [0.51-1.11] | 0.15 | 83/690 | 1.04 [0.76-1.43] | 0.79 |
| **Asian** | 20/389 | 0.89 [0.43-1.81] | 0.74 | 23/379 | 0.55 [0.30-1.03] | 0.06 |

Abbreviations: HR = Hazard ratio

* Allele key: rs4818 coded allele = G; rs4680 coded allele = G

**Table S6:** Hormone replacement therapy (HRT) use among women assessed at Exam 1 and rates of CVD by *COMT* rs4818 and rs4680 genotype stratified by HRT use and race.

| | | Hormone replacement therapy (HRT) use ever | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **SNP** | **Race/ethnicity** | **Total (%)** | **CC** | **GC** | **GG** | **HRT ever – no*** | **HRT ever – yes*** | **$P_{interaction}$** |
| **rs4818** | **Overall** | 1540 (51.1) | 708 (49.6) | 647 (51.2) | 185 (57.6) | 1.22 [0.74-2.02], 0.44 | 0.64 [0.45-0.89], 0.009 | 0.047 |
| | **White** | 772 (64.1) | 269 (64.7) | 367 (62.2) | 136 (68.3) | 2.20 [1.34-3.07], 0.002 | 0.59 [0.39-0.89], 0.01 | 0.02 |
| | **Black** | 384 (47.4) | 241 (48.5) | 127 (45.0) | 16 (50.0) | 0.94 [0.49-1.78], 0.84 | 0.96 [0.41-2.30], 0.94 | 0.97 |
| | **Hispanic** | 268 (40.6) | 144 (39.9) | 107 (42.3) | 17 (37.0) | 0.83 [0.51-1.34], 0.44 | 0.62 [0.17-1.31], 0.46 | 0.39 |
| | **Asian** | 116 (34.2) | 54 (34.8) | 46 (32.9) | 16 (36.4) | 1.28 [0.53-3.07], 0.58 | 0.59 [0.22-1.58], 0.30 | 0.84 |
| | | | **met/met** | **val/met** | **val/val** | | | |
| **rs4680** | **Overall** | 1701 (55.4) | 296 (57.7) | 723 (51.8) | 521 (47.1) | 1.14 [0.66-1.95], 0.64 | 0.75 [0.56-1.02], 0.07 | 0.26 |
| | **White** | 772 (64.1) | 205 (66.8) | 381 (63.0) | 186 (62.5) | 2.39 [1.42-4.01], 0.001 | 0.72 [0.49-1.04], 0.08 | 2E-04 |
| | **Black** | 419 (50.9) | 45 (50.6) | 158 (47.9) | 181 (46.2) | 0.93 [0.57-1.53], 0.78 | 0.96 [0.47-1.95], 0.91 | 0.43 |
| | **Hispanic** | 302 (45.1) | 39 (41.5) | 138 (40.8) | 91 (39.9) | 0.83 [0.54-1.28], 0.40 | 0.59 [0.22-1.61], 0.31 | 0.26 |
| | **Asian** | 137 (39.6) | 7 (30.4) | 46 (37.4) | 63 (32.6) | 0.81 [0.30-2.19], 0.68 | 0.88 [0.30-2.61], 0.82 | 0.24 |

Random effects meta-analysis of HRT ever and never use. $I^2$ for rs4818 HRT no = 65.1; HRT yes = 0. $I^2$ for rs4680 HRT no = 72.7; HRT yes = 0

**Table S7:** Aspirin user (%) > 3 days/week by *COMT* rs4818 genotype at the five MESA exams.

| | rs4818 genotype | | |
|---|---|---|---|
| **Exam** | **CC** | **GC** | **GG** |
| **1** | 577 (20.0) | 511 (20.3) | 125 (19.3) |
| **2** | 863 (31.6) | 762 (31.4) | 185 (29.2) |
| **3** | 886 (33.9) | 799 (34.6) | 195 (32.3) |
| **4** | 944 (37.2) | 824 (36.4) | 216 (36.0) |
| **5** | 905 (45.2) | 825 (44.4) | 215 (44.4) |

**Supplementary Table S8:** *COMT* rs4818 and rs4680 gene dosage (per allele*) association with rates of CVD stratified by time-varying aspirin and HRT ever use among white women.

| SNP | Aspirin | No HRT<br>HR [95% CI], P | Ever HRT<br>HR [95% CI], P |
|---|---|---|---|
| **rs4818** | **<3 days/week** | 3.13 [1.53-6.39], 0.002 | 0.34 [0.16-0.69], 0.004 |
| | **≥3 days/week** | 1.99 [0.90-4.40], 0.09 | 0.80 [0.42-1.52], 0.49 |
| | **$P_{interaction}$** | 0.39 | 0.08 |
| **rs4680** | **<3 days/week** | 3.02 [1.38-6.58], 0.006 | 0.46 [0.25-0.85], 0.01 |
| | **≥3 days/week** | 2.25 [0.97-5.24], 0.06 | 1.27 [0.69-2.35], 0.45 |
| | **$P_{interaction}$** | 0.613 | 0.02 |

* Allele key: rs4818 coded allele = G; rs4680 coded allele = G