Supplementary Table 1. The general characteristics of control and exposure groups

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variables\*\* | Control | Exposure | 2/*t*/*Z* | *P* |
| Gender |  |  |  |  |
| Male | 139 (58.4) | 390 (71.7) | 13.357b | <0.001 |
| Female | 99 (41.6) | 154 (28.3) |  |  |
| Age Grouping |  |  |  |  |
| ≤40 | 142 (59.7) | 273 (50.2) | 5.974b | 0.015 |
| ＞40 | 96 (40.3) | 271 (49.8) |  |  |
| Age (years) | 38.39±8.43 | 40.10±6.30 | 2.800a | 0.005 |
| Smoking Status |  |  |  |  |
| No | 197 (82.8) | 321 (59.0) | 41.817b | <0.001 |
| Yes | 41 (17.2) | 223 (41.0) |  |  |
| Drinking Status |  |  |  |  |
| No | 138 (58.0) | 248 (45.6) | 10.176b | 0.001 |
| Yes | 100 (42.0) | 296 (54.4) |  |  |
| BMI(kg/m2) |  |  |  |  |
| Low weight | 5 (2.1) | 12 (2.2) | 3.101b | 0.376 |
| Normal weight | 108 (45.4) | 224 (41.2) |  |  |
| Overweight | 101 (42.4) | 230 (42.3) |  |  |
| Obesity | 24 (10.1) | 78 (14.3) |  |  |
| Cumulative Exposure Dose | 0.07(0.06,0.09) | 1.12(0.34, 2.14) | 22.093c | <0.001 |
| 1-OHPYR | 1.78±0.98 | 4.44±1.15 | 19.953 a | <0.001 |
| 1-OHNAP | 3.02±0.92 | 4.08±1.20 | 3.151 a | 0.002 |
| 2-OHNAP | 3.31±0.10 | 4.49±1.03 | 9.792 a | <0.001 |
| 3-OHPHE | 0.99±1.12 | 2.96±1.06 | 16.828 a | <0.001 |
| mtDNAcn | 1.03±0.31 | 0.60±0.29 | 18.931 a | <0.001 |

\*\* Each variable is represented by the number of samples and percentage or mean±SD.

a *t*-test.

b2 test.

c Rank sum test.

Supplementary Table 2. The general characteristics on mtDNAcn

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Variable | | Control | |  | Exposure | | | *F* | *P* |
| n | mtDNAcn () | n | mtDNAcn () | |
| Gender | |  |  |  |  | |  |  |  |
|  | Male | 139 | 1.00±0.28 |  | 390 | | 0.59±0.30 | 201.939 | <0.001 |
|  | Female | 99 | 1.08±0.34 |  | 154 | | 0.62±0.29 | 133.108 | <0.001 |
|  | *F* |  | 3.085 |  |  | | 0.231 |  |  |
|  | *P* |  | 0.080 |  |  | | 0.631 |  |  |
| Age Grouping | |  |  |  |  | |  |  |  |
|  | ≤40 | 142 | 1.05±0.31 |  | 273 | | 0.60±0.28 | 223.722 | <0.001 |
|  | ＞40 | 96 | 1.01±0.30 |  | 271 | | 0.60±0.31 | 114.037 | <0.001 |
|  | *F* |  | 0.816 |  |  | | 0.062 |  |  |
|  | *P* |  | 0.367 |  |  | | 0.804 |  |  |
| Smoking Status | |  |  |  |  | |  |  |  |
|  | No | 197 | 1.04±0.32 |  | 321 | | 0.60±0.29 | 257.887 | <0.001 |
|  | Yes | 41 | 0.99±0.27 |  | 223 | | 0.59±0.29 | 64.900 | <0.001 |
|  | *F* |  | 0.030 |  |  | | 0.201 |  |  |
|  | *P* |  | 0.863 |  |  | | 0.654 |  |  |
| Drinking Status | |  |  |  |  | |  |  |  |
|  | No | 138 | 1.05±0.33 |  | 248 | | 0.61±0.30 | 168.387 | <0.001 |
|  | Yes | 100 | 1.01±0.27 |  | 296 | | 0.58±0.29 | 164.549 | <0.001 |
|  | *F* |  | 0.065 |  |  | | 0.650 |  |  |
|  | *P* |  | 0.800 |  |  | | 0.420 |  |  |
| BMI (kg/m2) | |  |  |  |  | |  |  |  |
| <24.0 | | 113 | 1.01±0.33 |  | 236 | | 0.62±0.30 | 115.357 | <0.001 |
| 24.0-27.9 | | 101 | 1.06±0.29 |  | 230 | | 0.58±0.28 | 194.732 | <0.001 |
| ≥28 | | 24 | 1.03±0.30 |  | 78 | | 0.58±0.33 | 32.382 | <0.001 |
| *F* | |  | 1.530 |  |  | | 0.783 |  |  |
| *P* | |  | 0.219 |  |  | | 0.458 |  |  |

Covariance analysis was used to analyze the effects of the general characteristics on mtDNAcn with the appropriate adjustment of gender, age (years), smoking index, drinking status, and BMI.

Supplementary Table 3. Distribution of SNP loci and Hardy-Weinberg equilibrium test

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Gene/SNPs | Genotype | Number | Genotype Frequency | Allele Frequency | Hardy-Weinberg 2 (*P*)\* |
| GSTT1 | - | 101 | 0.424 | - | - |
|  | + | 137 | 0.576 |  |  |
| GSTM1 | - | 130 | 0.546 | - | - |
|  | + | 108 | 0.454 |  |  |
| GSTP1 |  |  |  |  |  |
| rs1695 | AA | 148 | 0.622 | A: 0.790 | 0.039 (0.844) |
|  | AG | 80 | 0.336 | G: 0.210 |  |
|  | GG | 10 | 0.042 |  |  |
| CYP2E1 |  |  |  |  |  |
| rs6413432 | TT | 144 | 0.605 | T: 0.780 | 0.048 (0.827) |
|  | AT | 83 | 0.349 | A: 0.220 |  |
|  | AA | 11 | 0.046 |  |  |
| rs3813867 | GG | 133 | 0.559 | G: 0.742 | 0.509 (0.476) |
|  | CG | 87 | 0.366 | C: 0.258 |  |
|  | CC | 18 | 0.076 |  |  |

\*The Hardy-Weinberg test was performed using the control group.

Supplementary Table 4. The effect of metabolic enzyme gene polymorphism on 1-OHNAP

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Gene/SNPs | | | Control | | | |  | Exposure | | | | |
| n | 1-OHNAP () | | *P* |  | n | 1-OHNAP () | | | *P* |
| GSTT1 | | |  |  |  | |  |  | |  |  | |
|  | | - | 7 | 3.00±0.89 | Ref | |  | 96 | | 4.41±1.20 | Ref | |
|  | | + | 6 | 3.03±1.03 | 0.942 | |  | 142 | | 4.07±1.26 | 0.892 | |
| GSTM1 | | |  |  |  | |  |  | |  |  | |
|  | | - | 11 | 2.85±0.85 | Ref | |  | 129 | | 4.01±1.12 | Ref | |
|  | | + | 2 | 3.95±0.90 | 0.428 | |  | 109 | | 4.17±1.28 | 0.254 | |
| GSTP1 rs1695 | | |  |  |  | |  |  | |  |  | |
|  | AA | | 7 | 3.02±0.88 | Ref | |  | 160 | | 3.99±1.23 | Ref | |
|  | AG+GG | | 6 | 3.01±1.04 | 0.439 | |  | 78 | | 4.28±1.12 | 0.052 | |
| CYP2E1 rs6413432 | | |  |  |  | |  |  | |  |  | |
|  | | TT | 7 | 3.49±0.74 | Ref | |  | 147 | | 4.11±1.24 | Ref | |
|  | | AT+AA | 6 | 2.47±0.83 | 0.134 | |  | 91 | | 4.03±1.13 | 0.469 | |
| CYP2E1 rs3813867 | | |  |  |  | |  |  | |  |  | |
|  | | GG | 7 | 3.18±0.79 | Ref | |  | 138 | | 4.07±1.33 | Ref | |
|  | | CG+CC | 6 | 2.82±1.09 | 0.732 | |  | 100 | | 4.10±0.99 | 0.967 | |

Covariance analysis was used to compare 1-OHNAP among genotypes, adjusted for gender, age (years), smoking index, drinking status, and BMI.

Ref: The reference group when comparing.

Supplementary Table 5. The effect of metabolic enzyme gene polymorphism on 2-OHNAP

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Gene/SNPs | | | Control | | | | |  | Exposure | | | | |
| n | | 2-OHNAP () | | *P* |  | n | 2-OHNAP () | | | *P* |
| GSTT1 | | |  |  | |  | |  |  | |  |  | |
|  | | - | 38 | 3.32±0.85 | | Ref | |  | 136 | 4.47±0.99 | | Ref | |
|  | | + | 52 | 3.31±1.00 | | 0.743 | |  | 191 | 4.51±1.06 | | 0.435 | |
| GSTM1 | | |  |  | |  | |  |  |  | |  | |
|  | | - | 55 | 3.46±0.98 | | Ref | |  | 185 | 4.34±0.95 | | Ref | |
|  | | + | 35 | 3.08±0.81 | | 0.068 | |  | 142 | 4.69±1.10 | | 0.005 | |
| GSTP1 rs1695 | | |  |  | |  | |  |  |  | |  | |
|  | AA | | 53 | 3.32±0.86 | | Ref | |  | 219 | 4.48±1.01 | | Ref | |
|  | AG | | 33 | 3.24±1.07 | | 0.886 | |  | 99 | 4.48±1.08 | | 0.693 | |
|  | GG | | 4 | 3.87±0.58 | | 0.270 | |  | 9 | 4.78±0.97 | | 0.209 | |
|  | *Ptrend* | |  | 0.591 | |  | |  |  | 0.330 | |  | |
| CYP2E1 rs6413432 | | |  |  | |  | |  |  |  | |  | |
|  | | TT | 55 | 3.23±0.94 | | Ref | |  | 193 | 4.47±1.05 | | Ref | |
|  | | AT | 31 | 3.48±0.97 | | 0.327 | |  | 117 | 4.47±1.02 | | 0.836 | |
|  | | AA | 4 | 3.23±0.43 | | 0.986 | |  | 17 | 4.84±0.91 | | 0.062 | |
|  | | *Ptrend* |  | 0.476 | |  | |  |  | 0.315 | |  | |
| CYP2E1 rs3813867 | | |  |  | |  | |  |  |  | |  | |
|  | | GG | 50 | 3.25±0.89 | | Ref | |  | 204 | 4.47±1.09 | | Ref | |
|  | | CG | 36 | 3.36±1.03 | | 0.719 | |  | 107 | 4.55±0.91 | | 0.799 | |
|  | | CC | 4 | 3.67±0.50 | | 0.384 | |  | 16 | 4.42±1.08 | | 0.750 | |
|  | | *Ptrend* |  | 0.445 | |  | |  |  | 0.963 | |  | |

Covariance analysis was used to compare 2-OHNAP among genotypes, adjusted for gender, age (years), smoking index, drinking status, and BMI.

Multiple linear regression analyzed the trend of 2-OHNAP change with mutant allele loci, adjusting gender, age, smoking index, drinking status, BMI.

Ref: The reference group when comparing.

Supplementary Table 6. The effect of metabolic enzyme gene polymorphism on 3-OHPHE

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Gene/SNPs | | | Control | | | | |  | Exposure | | | |
| n | | 3-OHPHE () | | *P* |  | n | 3-OHPHE () | | *P* |
| GSTT1 | | |  |  | |  | |  |  |  |  | |
|  | | - | 47 | 1.12±1.10 | | Ref | |  | 151 | 2.98±0.98 | Ref | |
|  | | + | 64 | 0.90±1.13 | | 0.701 | |  | 207 | 2.95±1.12 | 0.781 | |
| GSTM1 | | |  |  | |  | |  |  |  |  | |
|  | | - | 62 | 0.85±0.78 | | Ref | |  | 208 | 2.88±1.05 | Ref | |
|  | | + | 49 | 1.18±1.42 | | 0.068 | |  | 150 | 3.06±1.08 | 0.005 | |
| GSTP1 rs1695 | | |  |  | |  | |  |  |  |  | |
|  | AA | | 69 | 0.90±1.04 | | Ref | |  | 240 | 2.93±1.00 | Ref | |
|  | AG | | 37 | 1.14±1.31 | | 0.103 | |  | 109 | 2.99±1.20 | 0.575 | |
|  | GG | | 5 | 1.24±0.29 | | 0.854 | |  | 9 | 3.45±0.92 | 0.201 | |
|  | *Ptrend* | |  | 0.203 | |  | |  |  | 0.270 |  | |
| CYP2E1 rs6413432 | | |  |  | |  | |  |  |  |  | |
|  | | TT | 66 | 0.85±0.88 | | Ref | |  | 212 | 3.01±1.03 | Ref | |
|  | | AT | 40 | 1.22±1.47 | | 0.216 | |  | 128 | 2.84±1.12 | 0.139 | |
|  | | AA | 5 | 1.03±0.34 | | 0.683 | |  | 18 | 3.24±0.96 | 0.244 | |
|  | | *Ptrend* |  | 0.510 | |  | |  |  | 0.750 |  | |
| CYP2E1 rs3813867 | | |  |  | |  | |  |  |  |  | |
|  | | GG | 59 | 0.93±0.83 | | Ref | |  | 219 | 2.96±1.13 | Ref | |
|  | | CG | 47 | 1.05±1.45 | | 0.857 | |  | 119 | 2.97±0.91 | 0.695 | |
|  | | CC | 5 | 1.13±0.42 | | 0.642 | |  | 20 | 2.91±1.18 | 0.623 | |
|  | | *Ptrend* |  | 0.901 | |  | |  |  | 0.565 |  | |

Covariance analysis was used to compare 3-OHPHE among genotypes, adjusted for gender, age (years), smoking index, drinking status, and BMI.

Multiple linear regression analyzed the trend of 3-OHPHE change with mutant allele loci, adjusting gender, age, smoking index, drinking status, BMI.

Ref: The reference group when comparing.