**Supplemental Table S1. Basic Information of three SNPs for BMI independent leptin GRS1[a] reaching genome-wide significance ($P<5\times10^{-8}$)**

| Chromosome Position | rsID | Coded Allele | Non-coded Allele | $R^2$ | Function | Nearest Gene | Population |
|---|---|---|---|---|---|---|---|
| 2:27742603 | rs780093 | C | T | 0.995 | intron variant | GCKR | European American |
| 7:127860163 | rs10487505 | G | C | 0.989 | intron variant | LEP | European American |
| 20:37333012 | rs6071166 | C | A | 0.973 | intergenic | SLC32A1 | European American |

BMI=body mass index

[a] Genetic risk scores 1 (GRS1) for leptin was generated by summing leptin increasing alleles of 3 SNPs adjusted for body mass index (BMI), weighted by their corresponding effect sizes reported by Kilpelainen et al.

**Supplemental Table S2. Basic Information of three SNPs for BMI dependent leptin GRS2[a] reaching genome-wide significance ($P<5\times10^{-8}$)**

| Chromosome Position | rsID | Coded Allele | Non-coded Allele | $R^2$ | Function | Nearest Gene | Population |
|---|---|---|---|---|---|---|---|
| 2:27742603 | rs780093 | C | T | 0.995 | intron variant | GCKR | European American |
| 3:156798775 | rs900400 | T | C | 0.691 | upstream variant 2KB | CCNL1 | European American |
| 16:53813450 | rs8043757 | A | T | 0.999 | intron variant | FTO | European American |

BMI=body mass index

[a] Genetic risk scores 2 (GRS2) for leptin was generated by summing leptin increasing alleles of 3 SNPs unadjusted for body mass index (BMI), weighted by their corresponding effect sizes reported by Kilpelainen et al.

**Supplemental Table S3. Association of BMI independent Leptin GRS1[a] with Baseline Lipids among Overall, Drinking, and Non-Drinking Participants without treating for Lipids of the Framingham Heart Study 3rd Generation Cohort, Respectively.**

| | Age, sex, BMI, waist adjusted model | | $P_{interaction}$[b] | Fully adjusted model[c] | | $P_{interaction}$[d] |
|---|---|---|---|---|---|---|
| | Beta( SE) | *P* | | Beta( SE) | *P* | |
| HDL-C | | | | | | |
| Overall | 5.25 (7.44) | 0.48 | | 7.59 (7.47) | 0.31 | |
| Not current drinkers | 18.83 (19.59) | 0.34 | 0.86 | 20.43 (20.23) | 0.31 | 0.83 |
| Current drinkers | 6.22 (7.97) | 0.44 | | 7.19 (8) | 0.37 | |
| LDL-C | | | | | | |
| Overall | 14.86 (16.06) | 0.35 | | 13.43 (16.2) | 0.41 | |
| Not current drinkers | 36.1 (49.22) | 0.46 | 0.51 | 27.18 (50.69) | 0.59 | 0.61 |
| Current drinkers | 12.19 (17.05) | 0.47 | | 10.48 (17.11) | 0.54 | |
| log-TG | | | | | | |
| Overall | -0.69 (0.27) | 0.01 | | -0.72 (0.27) | 0.007 | |
| Not current drinkers | -1.72 (0.84) | 0.04 | 0.20 | -1.61 (0.86) | 0.06 | 0.21 |
| Current drinkers | -0.58 (0.28) | 0.04 | | -0.6 (0.28) | 0.03 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Total cholesterol | | | | | | |
| Overall | -0.09 (18.19) | 1.00 | | -0.67 (18.26) | 0.97 | |
| Not current drinkers | 3.78 (55.05) | 0.95 | 0.94 | -2.29 (56.42) | 0.97 | 0.97 |
| Current drinkers | 0.98 (19.29) | 0.96 | | -0.34 (19.32) | 0.99 | |

BMI=body mass index; GRS=Genetic Risk Score; HDL-C=High-density lipoprotein cholesterol; LDL-C=Low-density lipoprotein cholesterol; log-TG=logarithmically transformed triglycerides; SE=standard error

[a] Genetic risk scores 1 (GRS1) for leptin was generated by summing leptin increasing alleles of 3 SNPs adjusted for body mass index (BMI), weighted by their corresponding effect sizes reported by Kilpelainen et al;
[b] Assessed by adding an interaction term, drinking×GRS along with the drinking variable to the age, sex, BMI and waist adjusted model among the overall participants;
[c] Adjusted for age, sex, education, smoking, drinking, BMI, waist, and physical activity among the overall sample;
[d] Assessed by adding an interaction term, drinking×GRS to the fully adjusted model among the overall participants.

**Supplemental Table S4. Association of BMI dependent Leptin GRS2[a] with Baseline Lipids among Overall, Drinking, and Non-Drinking Participants without treating for Lipids of the Framingham Heart Study 3rd Generation Cohort, Respectively.**

| | Age, sex, BMI, waist adjusted model | | $P_{interaction}$[b] | Fully adjusted model[c] | | $P_{interaction}$[d] |
|---|---|---|---|---|---|---|
| | Beta( SE) | *P* | | Beta( SE) | *P* | |
| HDL-C | | | | | | |
| Overall | -9.73 (6.50) | 0.13 | | -9.66 (6.53) | 0.14 | |
| Not current drinkers | -2.61 (17.44) | 0.88 | 0.72 | -1.22 (17.77) | 0.95 | 0.68 |
| Current drinkers | -10.52 (6.94) | 0.13 | | -10.19 (6.99) | 0.15 | |
| LDL-C | | | | | | |
| Overall | -0.42 (14.02) | 0.98 | | -1.56 (14.17) | 0.91 | |
| Not current drinkers | -83.19 (43.58) | 0.06 | 0.07 | -94.12 (44.22) | 0.03 | 0.05 |
| Current drinkers | 9.71 (14.86) | 0.51 | | 7.61 (14.96) | 0.61 | |
| log-TG | | | | | | |
| Overall | -0.63 (0.23) | 0.007 | | -0.63 (0.23) | 0.007 | |
| Not current drinkers | -2.09 (0.74) | 0.005 | 0.04 | -2.00 (0.75) | 0.008 | 0.05 |
| Current drinkers | -0.45 (0.25) | 0.07 | | -0.47 (0.25) | 0.05 | |
| Total cholesterol | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Overall | -25.28 (15.87) | 0.11 | | -26.38 (15.97) | 0.10 | |
| Not current drinkers | -136.15 (48.44) | 0.005 | 0.03 | -144.29 (48.92) | 0.003 | 0.02 |
| Current drinkers | -10.96 (16.82) | 0.51 | | -13.64 (16.90) | 0.42 | |

BMI=body mass index; GRS=Genetic Risk Score; HDL-C=High-density lipoprotein cholesterol; LDL-C=Low-density lipoprotein cholesterol; log-TG=logarithmically transformed triglycerides; SE=standard error

[a] Genetic risk scores 2 (GRS2) for leptin was generated by summing leptin increasing alleles of 3 SNPs unadjusted for body mass index (BMI), weighted by their corresponding effect sizes reported by Kilpelainen et al;
[b] Assessed by adding an interaction term, drinking×GRS along with the drinking variable to the age, sex, BMI and waist adjusted model among the overall participants;
[c] Adjusted for age, sex, education, smoking, drinking, BMI, waist, and physical activity among the overall sample;
[d] Assessed by adding an interaction term, drinking×GRS to the fully adjusted model among the overall participants.

**Supplemental Table S5. Association of BMI independent Leptin GRS1[a] with Baseline Lipids among Overall, Drinking, and Non-Drinking Participants without treating for Lipids and Diabetes of the Framingham Heart Study 3rd Generation Cohort, Respectively.**

| | Age, sex, BMI, waist adjusted model | | $P_{interaction}$[b] | Fully adjusted model[c] | | $P_{interaction}$[d] |
|---|---|---|---|---|---|---|
| | Beta( SE) | *P* | | Beta( SE) | *P* | |
| HDL-C | | | | | | |
| Overall | 5.64 (7.47) | 0.45 | | 8.00 (7.49) | 0.29 | |
| Not current drinkers | 20.89 (19.62) | 0.29 | 0.72 | 22.51 (20.25) | 0.27 | 0.69 |
| Current drinkers | 6.22 (7.98) | 0.44 | | 7.17 (8.02) | 0.37 | |
| LDL-C | | | | | | |
| Overall | 15.29 (16.11) | 0.34 | | 13.42 (16.27) | 0.41 | |
| Not current drinkers | 33.51 (49.77) | 0.50 | 0.58 | 24.63 (51.26) | 0.63 | 0.68 |
| Current drinkers | 12.68 (17.09) | 0.46 | | 10.99 (17.16) | 0.52 | |
| log-TG | | | | | | |
| Overall | -0.66 (0.27) | 0.01 | | -0.69 (0.27) | 0.01 | |
| Not current drinkers | -1.60 (0.85) | 0.06 | 0.23 | -1.46 (0.86) | 0.09 | 0.25 |
| Current drinkers | -0.57 (0.28) | 0.04 | | -0.59 (0.28) | 0.04 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Total cholesterol | | | | | | |
| Overall | 1.17 (18.24) | 0.95 | | 0.14 (18.33) | 0.99 | |
| Not current drinkers | 6.19 (55.64) | 0.91 | 0.93 | 1.04 (57.03) | 0.99 | 0.99 |
| Current drinkers | 1.56 (19.35) | 0.94 | | 0.26 (19.38) | 0.99 | |

BMI=body mass index; GRS=Genetic Risk Score; HDL-C =High-density lipoprotein cholesterol; LDL-C =Low-density lipoprotein cholesterol; log-TG=logarithmically transformed triglycerides; SE=standard error

[a] Genetic risk scores 1 (GRS1) for leptin was generated by summing leptin increasing alleles of 3 SNPs adjusted for body mass index (BMI), weighted by their corresponding effect sizes reported by Kilpelainen et al;
[b] Assessed by adding an interaction term, drinking×GRS along with the drinking variable to the age, sex, BMI and waist adjusted model among the overall participants;
[c] Adjusted for age, sex, education, smoking, drinking, BMI, waist, and physical activity among the overall sample;
[d] Assessed by adding an interaction term, drinking×GRS to the fully adjusted model among the overall participants.

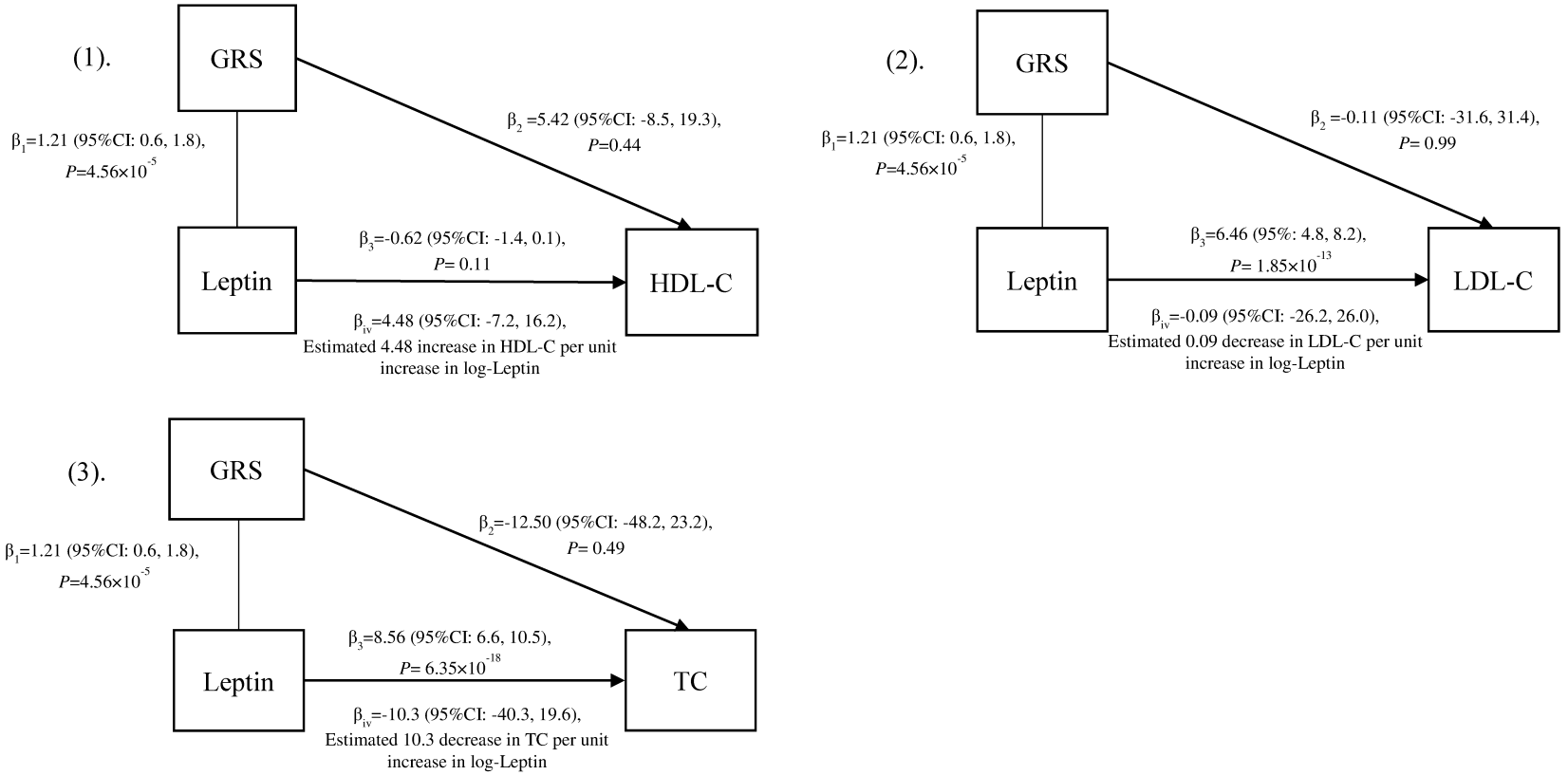
**Supplemental Table S6. Association of BMI dependent Leptin GRS2[a] with Baseline Lipids among Overall, Drinking, and Non-Drinking Participants without treating for Lipids and Diabetes of the Framingham Heart Study 3rd Generation Cohort, respectively.**

| | Age, sex, BMI, waist adjusted model | | $P_{interaction}$[b] | Fully adjusted model[c] | | $P_{interaction}$[d] |
|---|---|---|---|---|---|---|
| | Beta( SE) | *P* | | Beta( SE) | *P* | |
| HDL-C | | | | | | |
| Overall | -10.39 (6.52) | 0.11 | | -10.48 (6.55) | 0.11 | |
| Not current drinkers | -8.18 (17.54) | 0.64 | 0.95 | -7.77 (17.87) | 0.66 | 0.92 |
| Current drinkers | -10.58 (6.96) | 0.13 | | -10.32 (7.01) | 0.14 | |
| LDL-C | | | | | | |
| Overall | -1.58 (14.07) | 0.91 | | -3.3 (14.22) | 0.82 | |
| Not current drinkers | -95.04 (44.19) | 0.03 | 0.04 | -105.66 (44.81) | 0.02 | 0.03 |
| Current drinkers | 8.84 (14.90) | 0.55 | | 6.84 (15.00) | 0.65 | |
| log-TG | | | | | | |
| Overall | -0.62 (0.23) | 0.008 | 0.06 | -0.62 (0.23) | 0.008 | 0.08 |
| Not current drinkers | -2.00 (0.75) | 0.008 | | -1.87 (0.76) | 0.01 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Current drinkers | -0.45 (0.25) | 0.07 | | -0.48 (0.25) | 0.05 | |
| Total cholesterol | | | | | | |
| Overall | -26.72 (15.92) | 0.09 | | -28.67 (16.03) | 0.07 | |
| Not current drinkers | -150.52 (49.04) | 0.002 | 0.01 | -158.43 (49.51) | 0.002 | 0.01 |
| Current drinkers | -12.06 (16.87) | 0.47 | | -14.69 (16.95) | 0.39 | |

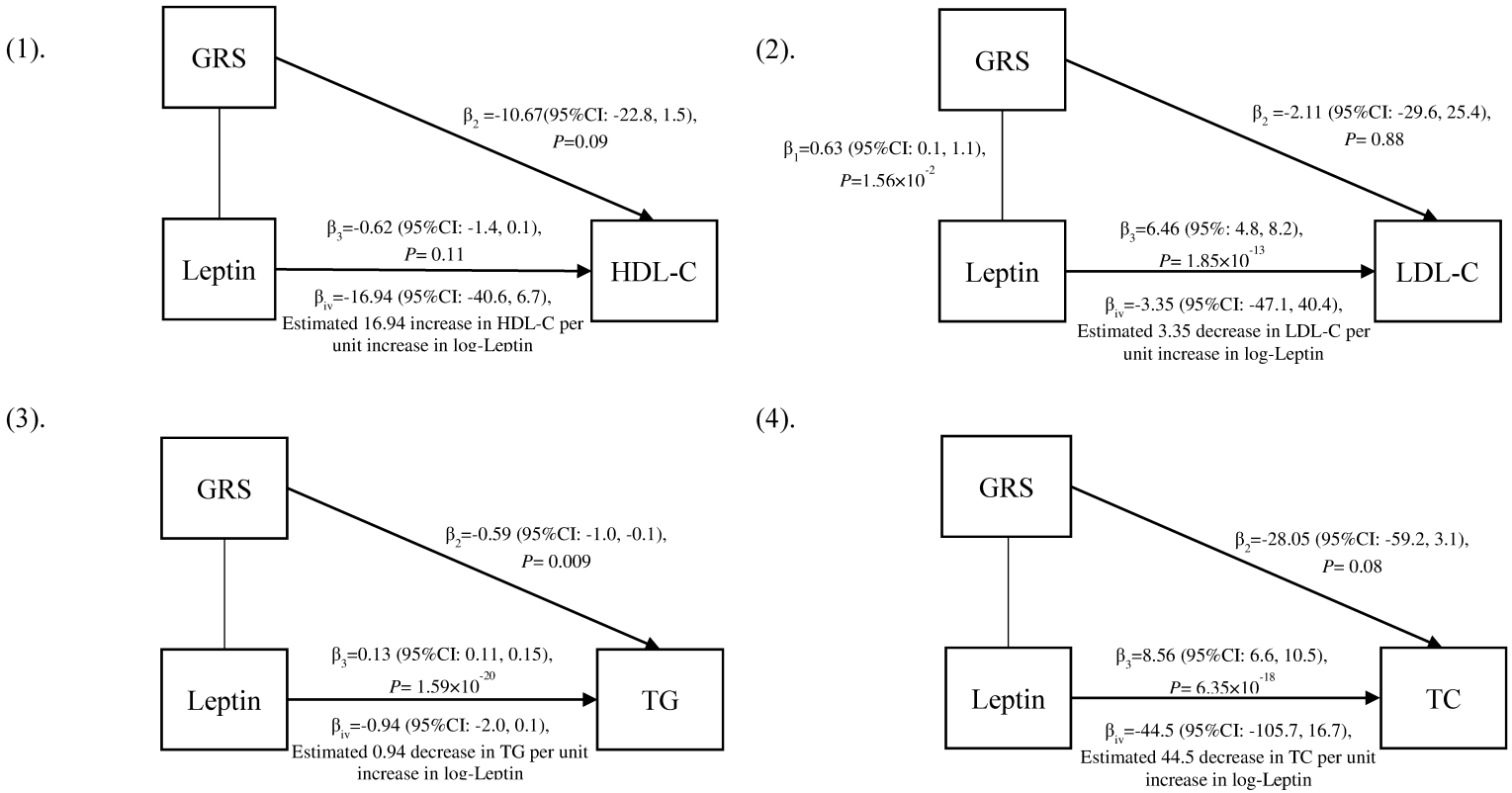
BMI=body mass index; GRS=Genetic Risk Score; HDL-C=High-density lipoprotein cholesterol; LDL-C=Low-density lipoprotein cholesterol; log-TG=logarithmically transformed triglycerides; SE=standard error

[a] Genetic risk scores 2 (GRS2) for leptin was generated by summing leptin increasing alleles of 3 SNPs unadjusted for body mass index (BMI), weighted by their corresponding effect sizes reported by Kilpelainen et al;
[b] Assessed by adding an interaction term, drinking×GRS along with the drinking variable to the age, sex, BMI and waist adjusted model among the overall participants;
[c] Adjusted for age, sex, education, smoking, drinking, BMI, waist, and physical activity among the overall sample;
[d] Assessed by adding an interaction term, drinking×GRS to the fully adjusted model among the overall participants.




**Supplemental Figure S1. The relationship between Leptin, Genetic Risk Score 1 (GRS1) for Leptin and Lipids in Framingham Heart Study the 3rd Generation cohort.**

1. The relationship between leptin, genetic risk score for leptin and high density lipoprotein cholesterol (HDL-C)
2. The relationship between leptin, genetic risk score for leptin and low density lipoprotein cholesterol (LDL-C)
3. The relationship between leptin, genetic risk score for leptin and total cholesterol (TC)




**Supplemental Figure S2. The relationship between Leptin, Genetic Risk Score 2 (GRS2) for Leptin and Lipids in Framingham Heart Study the 3rd Generation cohort.**

1. The relationship between leptin, genetic risk score for leptin and high density lipoprotein cholesterol (HDL-C)
2. The relationship between leptin, genetic risk score for leptin and low density lipoprotein cholesterol (LDL-C)
3. The relationship between leptin, genetic risk score for leptin and triglycerides (TG)

4. The relationship between leptin, genetic risk score for leptin and total cholesterol (TC)