Is Coffee Intake Associated with Obesity-Related Traits? . A Mendelian Randomization/Pleiotropy Approach Using United Kingdom Biobank (UKBB) Database

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Objectives: Epidemiological studies suggest that coffee intake (CI) is protective against body weight gain. We explored whether genetic determinants of CI are associated with obesity-related phenotypic traits, primarily body mass Index (BMI).

Methods: We leveraged information from ~354,000 individuals in the UKBB database (https://genetics.opentargets.org/) searching for genetic variants associated with CI (cutoff $P < 0.5E-8$). We further explored the association of these variants with BMI and other obesity-related traits (body fat percentage-BFP, obesity or waist circumference-WC) using summarized data from Neale's lab (http://www.nealelab.is/uk-biobank/).

Results: Twenty seven variants were significantly associated with CI, including rs2472297-CYP1A1/2 ($P = 3.4E-116$, beta(b) = 0.047) and rs4410790-AHR- ($P = 3.2E-95$, b = 0.039), which were previously reported to be associated with CI. Seventeen variants showed significant associations with BMI in the same direction (i.e., rs2472297-CYP1A1/2, $P = 1.2E-6$, b = 0.06; rs4410790-AHR, $P = 1.7E-4$, b = 0.04; rs589500-SEC16B, $P = 2.5E-59$, b = 0.22; rs1260326-GCKR, $P = 8.0E-6$, b = 0.05; rs3814424-MEF2C, $P = 6.3E-20$, b = 0.14; rs1189470082-AL355997.1, $P = 4.3E-8$, b = 0.07; rs9398171-LINC00222/FOXO3, $P = 6.1E-10$, b = 0.08; rs370535199-KBTBD2, $P = 9.2E-5$, b = 0.045; rs1057868-POR, $P = 9.9E-6$, b = 0.055; rs56094641-FTO, $P = 2.1E-219$, b = 0.26). The remaining 9 variants showed no associations with any obesity-related trait. One variant (rs57918684-MED13) showed a marginal and opposite effect. Beta coefficients for CI and BMI were significantly correlated (Spearman R: 0.69, $P < 0.0001$), which is compatible with a significant genetic correlation between both traits (rg = 0.24 ± 0.02, $P = 4.06E-23$). The positive association between CI and BMI is biologically supported by genetic correlations between CI and food intake (rg = 0.26 ± 0.07, $P = 1.0E-4$), BFP (rg = 0.16 ± 0.02, $P = 2.54E-13$) and WC (rg = 0.23 ± 0.02, $P = 2.0E-22$).

Conclusions: Variants associated with CI present direct pleiotropic effects on obesity-related traits such as BMI, BFP, and WC. If these are not causal relations, then from a Mendelian Randomization point of view, CI has an undesirable effect.

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