Table S4.

1. Mendelian randomization analysis: effect of genetically predicted combined FG and FI on CRC risk

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Analytic Method** | **HR**¶ | **(95% CI)** | ***p*** | **p-het†** |
| **< Analyzed 38 combined FG and FI genetic instruments\* >** | | | | |
| Inverse-variance weighted | 11.84 | (0.138 – 1.02E+03) | 0.2679 | 0.1577 |
| Weighted median | 9.90 | (0.024 – 4.05E+03) | 0.4551 |  |
| Penalized weighted median | 9.24 | (0.029 – 2.95E+03) | 0.4497 |  |
| MR-Egger: intercept | 0.98 | (0.871 – 1.098) | 0.7006 |  |
|  | | | | |
| **< Analyzed 3 combined FG and FI genetic instruments¥ >** | | | | |
| Inverse-variance weighted | 138.16 | (1.27E-09 – 1.51E+13) | 0.4919 | 0.0811 |
| Weighted median | 34.15 | (0.003 – 4.45E+05) | 0.4651 |  |
| Penalized weighted median | 16.39 | (0.001 – 1.98E+05) | 0.5598 |  |
| MR-Egger: intercept | 1.57 | (0.026 – 9.59E+01) | 0.3978 |  |

CI, confidence interval; CRC colorectal cancer; FG, fasting glucose; FI, fasting insulin; HR, hazard ratio; MR, Mendelian randomization; p-het, p value for heterogeneity test.

¶ The MR estimate (except weighted/penalized weighted medians) was adjusted for a correlation between FG/FI phenotypes and CRC within the same population.

† p-het for heterogeneity test of MR estimates across genetic instruments was estimated via Cochran’s Q test.

\* Genetic instruments with nominal significance as well as significance after the Bonferroni multiple comparison correction were included.

¥ Only genetic instruments with statistical significance after the Bonferroni multiple comparison correction were included.

Table S4.

1. Mendelian randomization analysis: effect of genetically predicted FG on CRC risk

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Analytic Method** | **HR**¶ | **(95% CI)** | ***p*** | **p-het†** |
| **< Analyzed 34 FG genetic instruments\* >** | | | | |
| Inverse-variance weighted | 34.13 | **(**0.004– 2.67E+05**)** | 0.4287 | 0.0905 |
| Weighted median | 7763.63 | **(**0.072– 8.40E+08**)** | 0.1299 |  |
| Penalized weighted median | 6687.10 | **(**0.027– 1.65E+09**)** | 0.1644 |  |
| MR-Egger: intercept | 0.88 | **(**0.682– 1.126**)** | 0.2923 |  |
|  | | | | |
| **< Analyzed 2 FG genetic instruments¥ >** | | | | |
| Inverse-variance weighted | 4.14E+07 | **(**6.73E-89– 2.54E+103**)** | 0.4967 | 0.0779 |
| Weighted median | 4.14E+07 | **(**4.29E-05– 3.99E+19**)** | 0.2129 |  |
| Penalized weighted median | 4.14E+07 | **(**4.73E-04– 3.62E+18**)** | 0.1725 |  |
| MR-Egger: intercept | N/A | N/A | N/A |  |

CI, confidence interval; CRC colorectal cancer; FG, fasting glucose; FI, fasting insulin; HR, hazard ratio; MR, Mendelian randomization; N/A, not available; p-het, p value for heterogeneity test.

¶ The MR estimate (except weighted/penalized weighted medians) was adjusted for a correlation between FG phenotype and CRC within the same population.

† p-het for heterogeneity test of MR estimates across genetic instruments was estimated via Cochran’s Q test.

\* FG genetic instruments with nominal significance as well as significance after the Bonferroni multiple comparison correction were included.

¥ Only FG genetic instruments with statistical significance after the Bonferroni multiple comparison correction were included.

Table S4.

1. Mendelian randomization analysis: effect of genetically predicted FI on CRC risk

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Analytic Method** | **HR**¶ | **(95% CI)** | ***p*** | **p-het†** |
| **< Analyzed 4 FI genetic instruments\* >** | | | | |
| Inverse-variance weighted | 7.99 | (0.081 – 7.89E+02) | 0.2455 | 0.7623 |
| Weighted median | 7.05 | (0.026 – 1.91E+03) | 0.4944 |  |
| Penalized weighted median | 7.05 | (0.023 – 2.13E+03) | 0.5026 |  |
| MR-Egger: intercept | 0.67 | (0.409 – 1.085) | 0.0698 |  |
|  | | | | |
| **< Analyzed 1 FI genetic instruments¥ >** | | | | |
| Inverse-variance weighted | 16.76 | (0.006 – 4.49E+04) | 0.4839 |  |
| Weighted median | N/A | N/A | N/A |  |
| Penalized weighted median | N/A | N/A | N/A |  |
| MR-Egger: intercept | N/A | N/A | N/A |  |

CI, confidence interval; CRC colorectal cancer; FG, fasting glucose; FI, fasting insulin; HR, hazard ratio; MR, Mendelian randomization; N/A, not available; p-het, p value for heterogeneity test.

¶ The MR estimate (except weighted/penalized weighted medians) was adjusted for a correlation between FI phenotype and CRC within the same population.

† p-het for heterogeneity test of MR estimates across genetic instruments was estimated via Cochran’s Q test.

\* FI genetic instruments with nominal significance as well as significance after the Bonferroni multiple comparison correction were included.

¥ Only FI genetic instruments with statistical significance after the Bonferroni multiple comparison correction were included.