

## Supplemental Material

Causal association between mTOR-Dependent EIF-4E and EIF-4A circulating protein levels and Type 2 Diabetes: A Mendelian Randomization Study

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# SUPPLEMENTAL TABLES

**Supplemental Table S1: SNPs associated with exposure to mTOR targets:**

| <b>Protein</b> | <b>SNP</b>  | <b>Beta</b> | <b>SE</b> | <b>Effect</b> | <b>Other</b> | <b>p-Value</b> | <b>Chrpos</b> |
|----------------|-------------|-------------|-----------|---------------|--------------|----------------|---------------|
| <b>EIF-4E</b>  | rsID        | Exposure    | Exposure  | Allele        | Allele       | Exposure       | Exposure      |
| 1              | rs2209485   | 0.1637      | 0.034     | t             | c            | 1.51E-06       | 10:20905192   |
| 2              | rs74842834  | 0.4443      | 0.0947    | t             | g            | 2.69E-06       | 11:23204504   |
| 3              | rs192206210 | -0.5846     | 0.1211    | t             | g            | 1.41E-06       | 15:87118467   |
| 4              | rs138236097 | -0.2673     | 0.0583    | a             | g            | 4.47E-06       | 16:47761066   |
| 5              | rs741454    | -0.1426     | 0.031     | t             | c            | 4.17E-06       | 19:29350614   |
| 6              | rs11084300  | 0.1585      | 0.0272    | t             | c            | 5.75E-09       | 19:54311090   |
| 7              | rs3848582   | -0.1776     | 0.0364    | a             | g            | 1.07E-06       | 19:54317794   |
| 8              | rs62143198  | 0.4669      | 0.0296    | a             | g            | 6.76E-56       | 19:54320939   |
| 9              | rs149036167 | 0.5168      | 0.108     | t             | c            | 1.70E-06       | 2:119720418   |
| 10             | rs62130614  | 0.4606      | 0.0999    | t             | g            | 3.98E-06       | 2:29505824    |
| 11             | rs113679228 | 0.3464      | 0.0732    | a             | g            | 2.24E-06       | 4:138007589   |
| 12             | rs12640699  | 0.1574      | 0.0341    | a             | c            | 4.07E-06       | 4:167757172   |
| 13             | rs142569846 | 0.2303      | 0.0468    | t             | g            | 8.71E-07       | 5:116455931   |
| 14             | rs192028145 | 0.5295      | 0.1025    | a             | g            | 2.40E-07       | 5:66685975    |
| 15             | rs116934738 | -0.3758     | 0.077     | t             | c            | 1.05E-06       | 8:87691869    |
| 16             | rs2772577   | 0.1361      | 0.0292    | a             | g            | 3.02E-06       | 9:24547232    |
|                |             |             |           |               |              |                |               |
| <b>EIF-4A</b>  | SNP         | Beta        | SE        | Effect        | Other        | p-Value        | Chrpos        |
|                | rsID        | Exposure    | Exposure  | Allele        | Allele       | Exposure       | Exposure      |
| 1              | rs74512707  | 0.1785      | 0.0385    | a             | g            | 3.55E-06       | 12:95350637   |
| 2              | rs151270869 | 0.4543      | 0.0938    | a             | g            | 1.29E-06       | 15:86409988   |
| 3              | rs3859507   | 0.1777      | 0.0327    | t             | g            | 5.75E-08       | 19:54295370   |
| 4              | rs11084300  | 0.1431      | 0.0272    | t             | c            | 1.48E-07       | 19:54311090   |
| 5              | rs34436714  | 0.4687      | 0.0291    | a             | c            | 2.00E-58       | 19:54327313   |
| 6              | rs146117463 | -0.2062     | 0.042     | a             | g            | 9.33E-07       | 19:54329672   |
| 7              | rs34131899  | -0.2829     | 0.0591    | a             | g            | 1.70E-06       | 2:29058128    |
| 8              | rs6792693   | -0.134      | 0.0286    | a             | g            | 2.82E-06       | 3:27245225    |
| 9              | rs1447676   | -0.1182     | 0.0257    | t             | c            | 4.37E-06       | 3:74143047    |
| 10             | rs2462049   | 0.1159      | 0.0249    | t             | g            | 3.31E-06       | 7:85099898    |
| 11             | rs1931094   | 0.1163      | 0.0253    | a             | g            | 4.27E-06       | 9:87844548    |
|                |             |             |           |               |              |                |               |
| <b>EIF-4G3</b> | SNP         | Beta        | SE        | Effect        | Other        | p-Value        | Chrpos        |
|                | rsID        | Exposure    | Exposure  | Allele        | Allele       | Exposure       | Exposure      |
| 1              | rs7955609   | 0.1251      | 0.0263    | a             | g            | 2.00E-06       | 12:116387486  |
| 2              | rs112309230 | 0.5745      | 0.1158    | t             | c            | 6.92E-07       | 12:127417047  |
| 3              | rs143862167 | -0.204      | 0.044     | t             | c            | 3.55E-06       | 12:39641451   |
| 4              | rs704       | 0.1618      | 0.0245    | a             | g            | 4.27E-11       | 17:26694861   |
| 5              | rs142978915 | 0.4055      | 0.0885    | t             | c            | 4.57E-06       | 3:53892603    |
| 6              | rs1411879   | 0.4092      | 0.089     | a             | g            | 4.27E-06       | 9:3762150     |

**Supplemental Table 1 SNPs associated with exposure to mTOR targets—Continued**

| <b>EIF-4EBP2</b> | <b>SNP</b>  | <b>Beta</b> | <b>SE</b> | <b>Effect</b> | <b>Other</b> | <b>p-Value</b> | <b>Chrpos</b> |
|------------------|-------------|-------------|-----------|---------------|--------------|----------------|---------------|
|                  | rsID        | Exposure    | Exposure  | Allele        | Allele       | Exposure       | Exposure      |
| 1                | rs10864412  | -0.1334     | 0.0254    | a             | g            | 1.58E-07       | 1:9425722     |
| 2                | rs10733789  | -0.1254     | 0.0272    | t             | c            | 4.07E-06       | 10:64948684   |
| 3                | rs72743058  | -0.3839     | 0.0827    | a             | g            | 3.47E-06       | 15:58881788   |
| 4                | rs79943794  | -0.357      | 0.0766    | t             | c            | 3.16E-06       | 15:90454175   |
| 5                | rs2745108   | 0.1927      | 0.0402    | t             | c            | 1.58E-06       | 16:1547477    |
| 6                | rs2575348   | 0.1527      | 0.0333    | t             | c            | 4.47E-06       | 16:1846089    |
| 7                | rs79613514  | -0.3407     | 0.0738    | t             | c            | 3.89E-06       | 2:167837496   |
| 8                | rs17003636  | -0.4607     | 0.0984    | t             | c            | 2.88E-06       | 21:21934726   |
| 9                | rs113664570 | 0.2666      | 0.0584    | t             | c            | 4.90E-06       | 3:14547897    |
| 10               | rs72806713  | -0.1366     | 0.0296    | t             | c            | 3.89E-06       | 5:152342669   |
| 11               | rs76802510  | -0.2684     | 0.0496    | t             | c            | 6.46E-08       | 7:113007324   |
| 12               | rs4734879   | 0.1343      | 0.028     | a             | g            | 1.62E-06       | 8:106583124   |
|                  |             |             |           |               |              |                |               |
| <b>RP-S6K</b>    | <b>SNP</b>  | <b>Beta</b> | <b>SE</b> | <b>Effect</b> | <b>Other</b> | <b>p-Value</b> | <b>Chrpos</b> |
|                  | rsID        | Exposure    | Exposure  | Allele        | Allele       | Exposure       | Exposure      |
| 1                | rs1355191   | -0.125      | 0.0263    | t             | c            | 1.95E-06       | 11:119496472  |
| 2                | rs77394885  | -0.5291     | 0.1122    | a             | c            | 2.40E-06       | 15:83650787   |
| 3                | rs3859503   | -0.1892     | 0.0333    | a             | c            | 1.35E-08       | 19:54294400   |
| 4                | rs148800371 | 0.1637      | 0.0327    | t             | g            | 5.50E-07       | 19:54305398   |
| 5                | rs62143197  | 0.5347      | 0.029     | a             | g            | 8.13E-76       | 19:54320716   |
| 6                | rs117021160 | 0.2834      | 0.0433    | t             | c            | 6.17E-11       | 19:54333199   |
| 7                | rs75688971  | -0.4179     | 0.0836    | t             | c            | 5.75E-07       | 20:58296885   |
| 8                | rs58565824  | 0.4607      | 0.0937    | t             | c            | 8.91E-07       | 3:22584610    |
| 9                | rs9833044   | -0.319      | 0.0635    | t             | c            | 5.13E-07       | 3:27587457    |
| 10               | rs35747952  | 0.3736      | 0.0809    | t             | c            | 3.89E-06       | 4:145934089   |
| 11               | rs1381968   | 0.3462      | 0.0746    | t             | c            | 3.55E-06       | 5:101423444   |
| 12               | rs62398809  | 0.1129      | 0.0247    | a             | g            | 4.90E-06       | 5:152488248   |
| 13               | rs148897689 | 0.4496      | 0.0943    | a             | g            | 1.91E-06       | 5:39170760    |
| 14               | rs72881486  | 0.3633      | 0.0745    | a             | g            | 1.07E-06       | 6:68218559    |
| 15               | rs79777011  | 0.1634      | 0.0346    | a             | c            | 2.29E-06       | 7:58384       |
| 16               | rs7017005   | 0.1213      | 0.0256    | a             | g            | 2.14E-06       | 8:56752146    |

## SUPPLEMENTAL TABLE S2

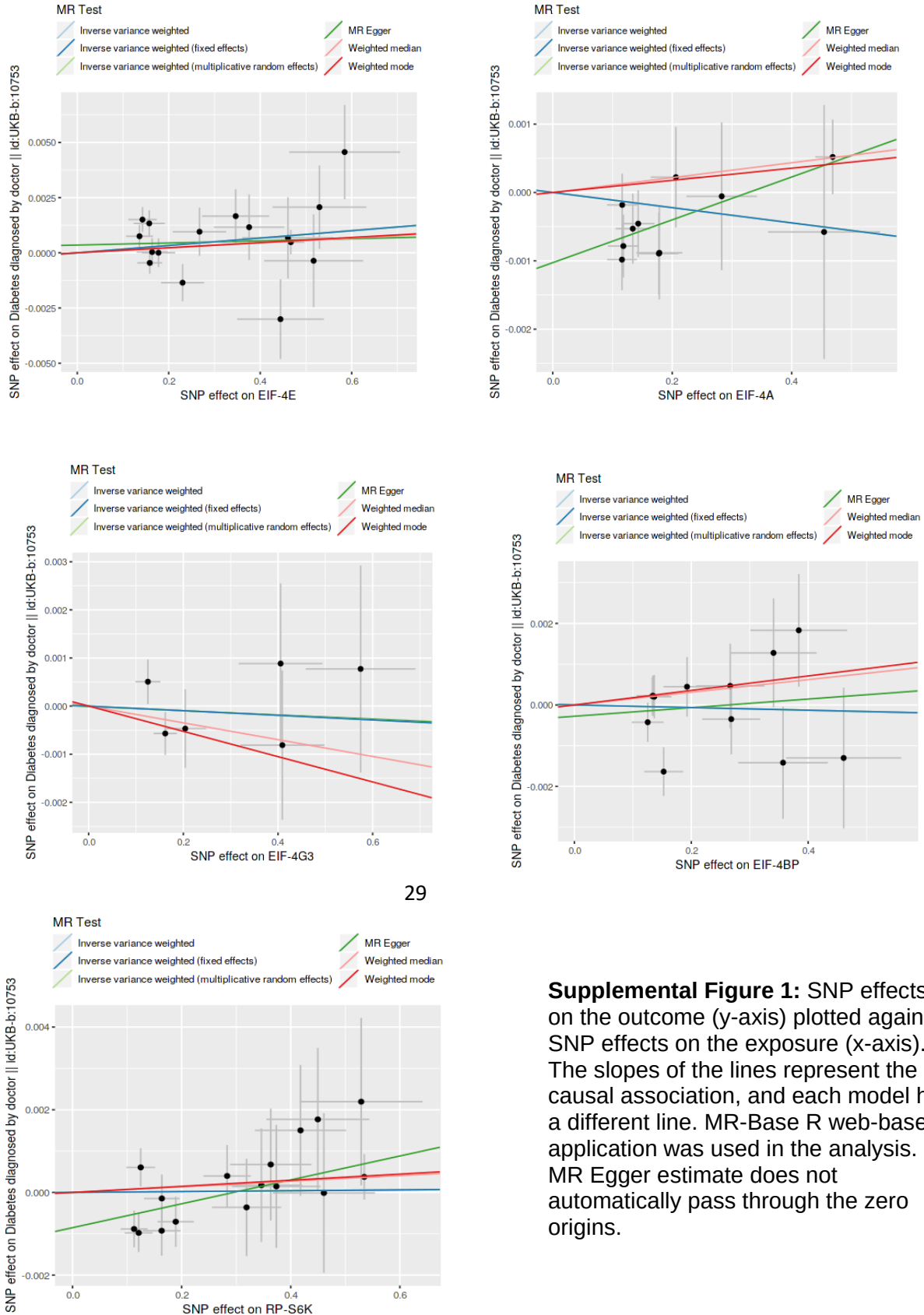
**Table S2 Supplement**

T-Distribution and F-Statistics of the Beta. Exposure Variable on Diabetes Health Outcome

| Exposure ID | Causal Estimate<br>(beta) | SD      | T-Stat   | P-value  | MR-PRESSO<br>Global |
|-------------|---------------------------|---------|----------|----------|---------------------|
| EIF-4E      | -0.06552                  | 0.02219 | -2.95269 | 0.00987  | 0.9053              |
| EIF-4A      | -0.09210                  | 0.02039 | -4.51705 | 0.00195  | 0.9885              |
| EIF-4G3     | 0.07317                   | 0.04368 | 1.67513  | 0.15475  | 0.6732              |
| EIF-4EBP    | -0.04147                  | 0.04646 | -0.89259 | -0.39118 | 0.1056              |
| RP-S6K      | -0.05583                  | 0.03157 | -1.76819 | 0.09735  | 0.2552              |

## SUPPLEMENTAL FIGURES

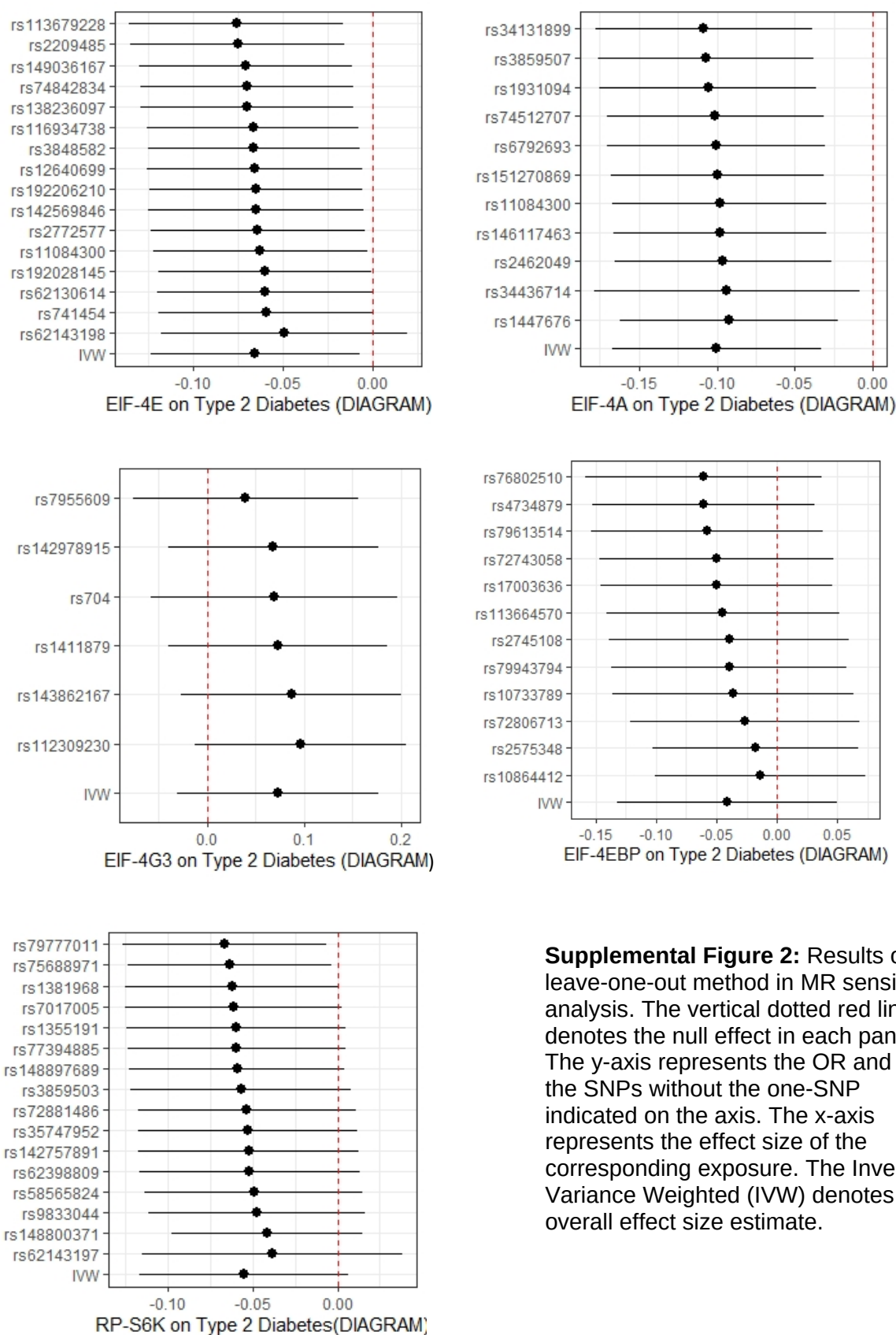
Supplemental Figure S1: Scatter Plot Analysis and Comparison Between MR Models



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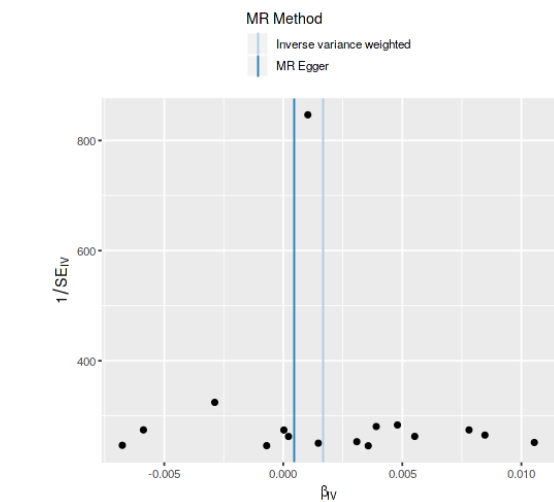
**Supplemental Figure 1:** SNP effects on the outcome (y-axis) plotted against SNP effects on the exposure (x-axis). The slopes of the lines represent the causal association, and each model has a different line. MR-Base R web-based application was used in the analysis. MR Egger estimate does not automatically pass through the zero origins.

**Supplemental Figure 2: Leave-One-Out- Sensitivity Analysis**

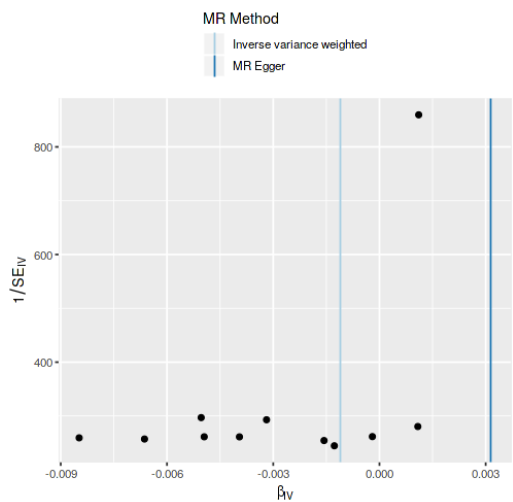


**Supplemental Figure 2:** Results of the leave-one-out method in MR sensitivity analysis. The vertical dotted red line denotes the null effect in each panel. The y-axis represents the OR and CI of the SNPs without the one-SNP indicated on the axis. The x-axis represents the effect size of the corresponding exposure. The Inverse Variance Weighted (IVW) denotes the overall effect size estimate.

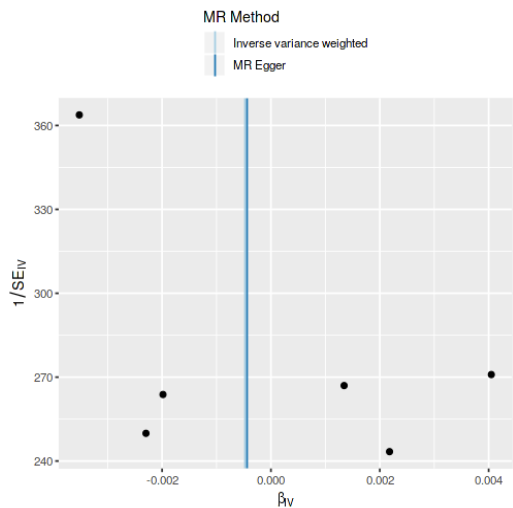
SUPPLEMENTAL FIGURE 3: Funnel plot Comparison Between MR Methods



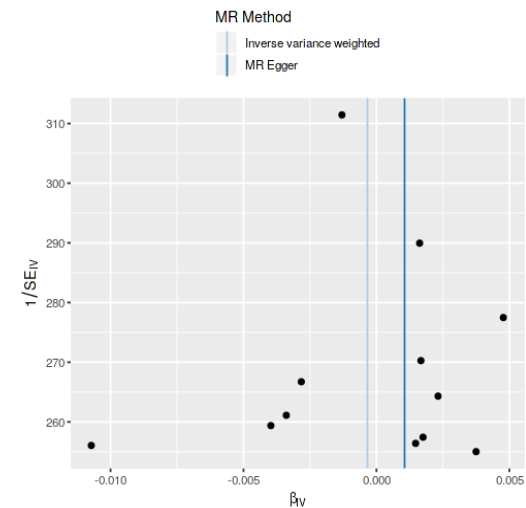
Funnel plot analysis for EIF-4E



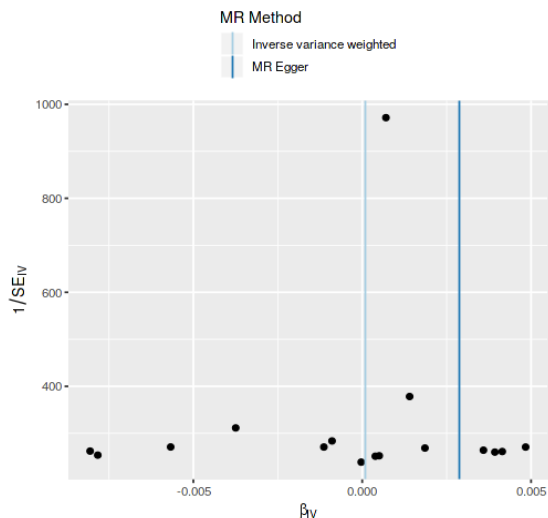
Funnel plot analysis for EIF-4A



Funnel plot analysis for EIF-4G3



Funnel plot analysis for EIF-4E-BP



Funnel plot analysis for RP-S6K

**Supplemental Figure 3:** Funnel plot analysis to assess heterogeneity. The vertical lines represent the causal estimates using all SNPs combined into a single instrument for each of the MR models (IVW, and MR Egger). The x-axis represents the causal estimate, and the y-axis represents the inverse of the instrument strength. MR-Base R package and web application were used in the analysis.