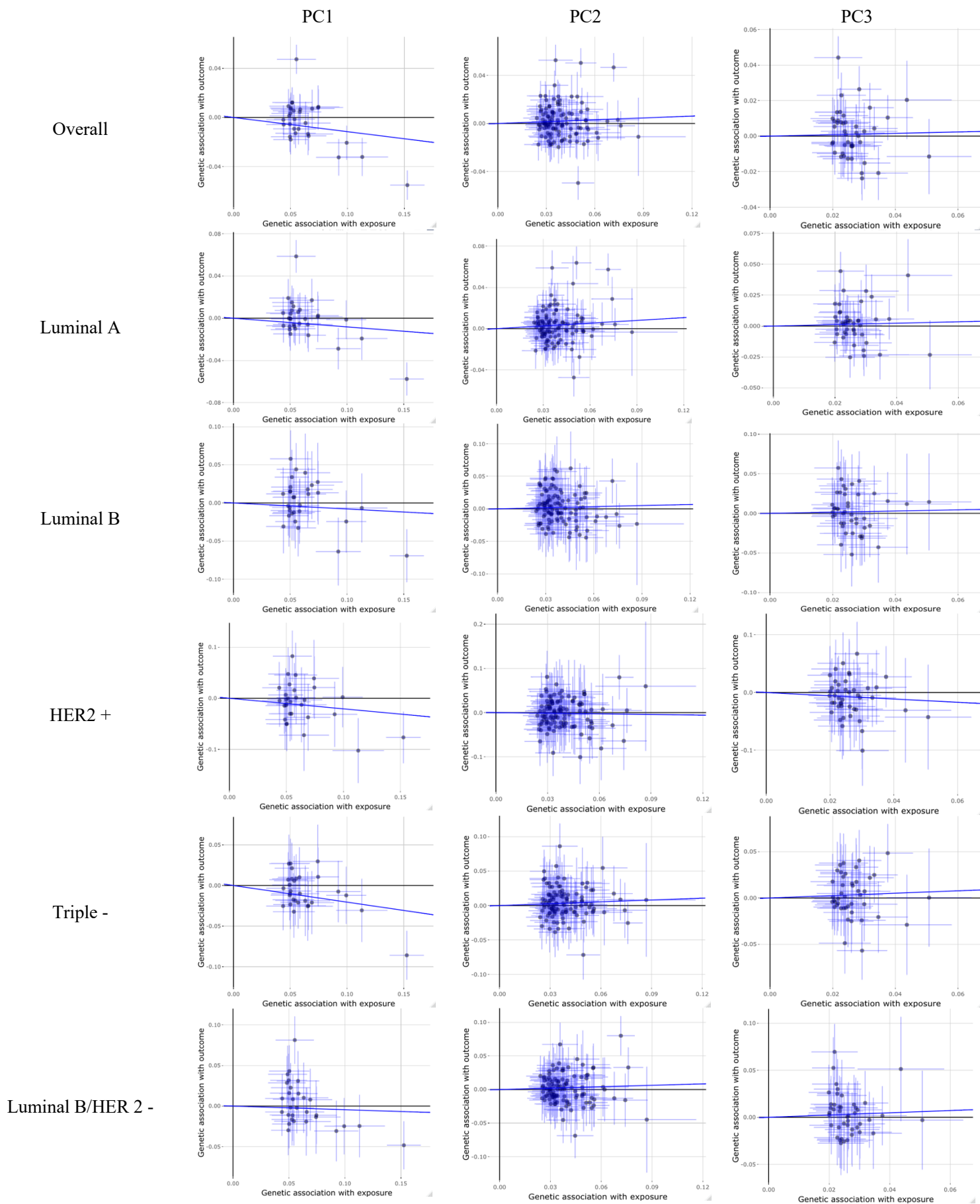


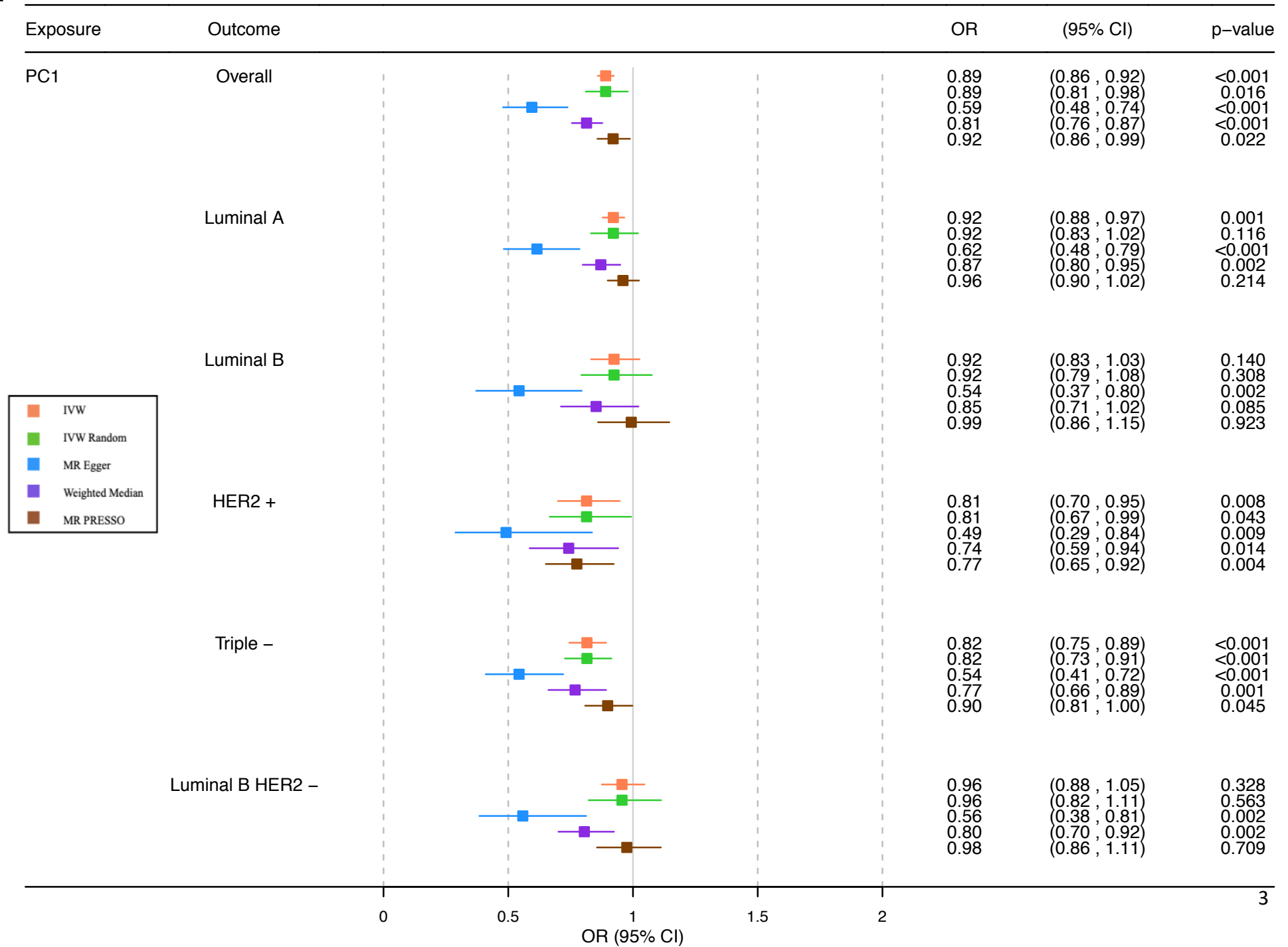
## Supplementary Figures and Tables

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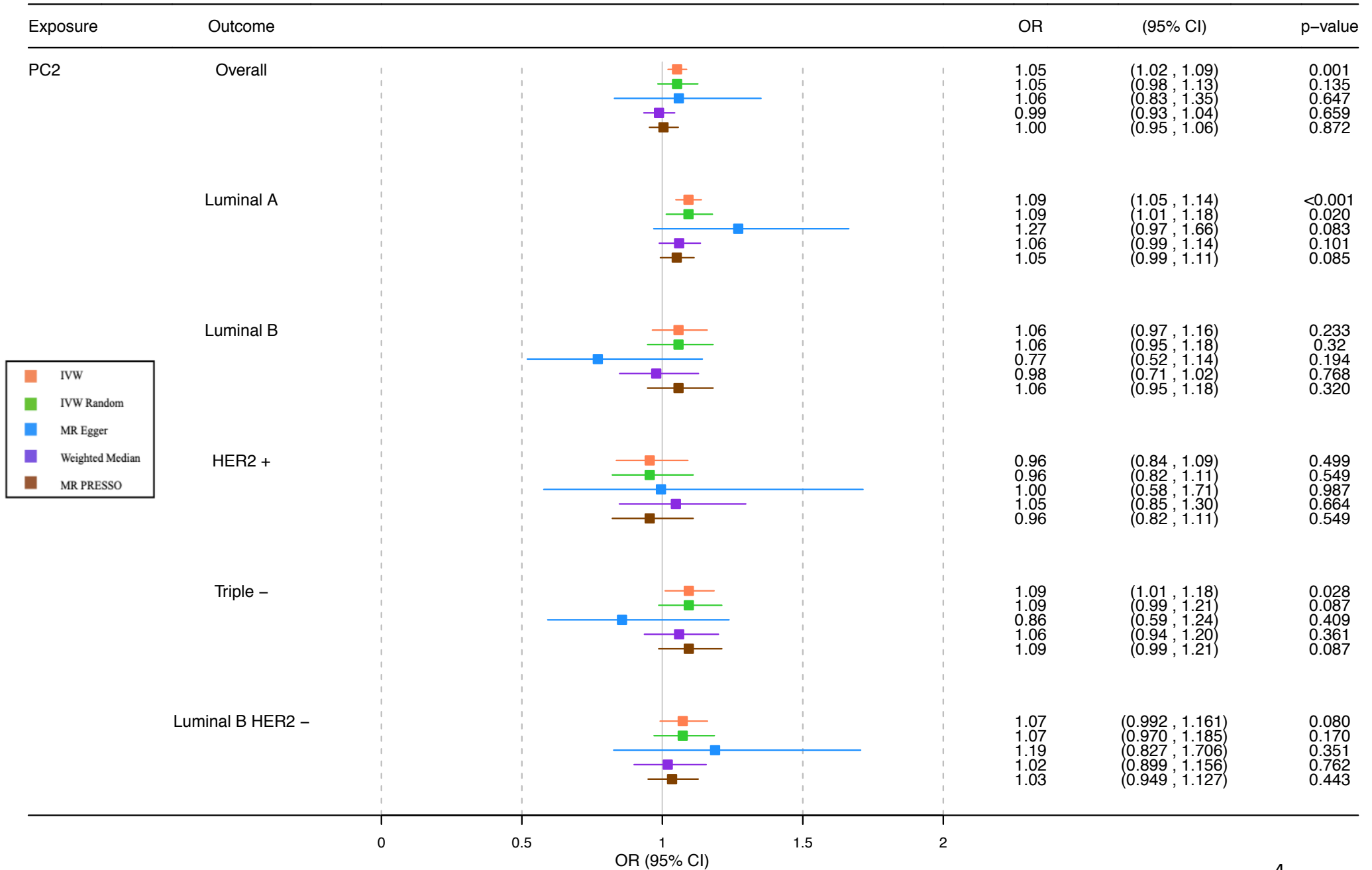


**Supplementary Figure 1.** Scatter plots of associations between body shapes and overall breast cancer and sub-types.

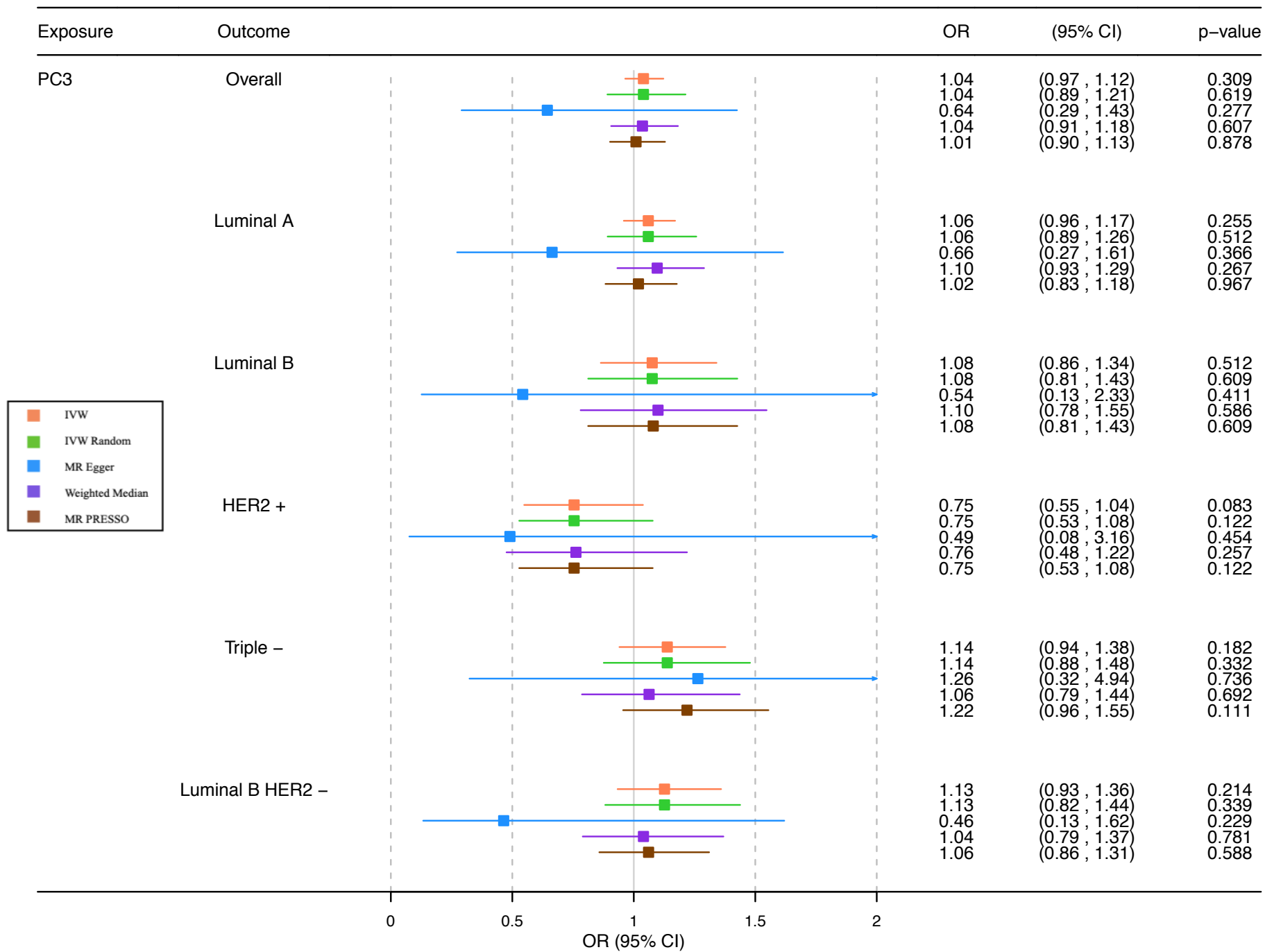
A



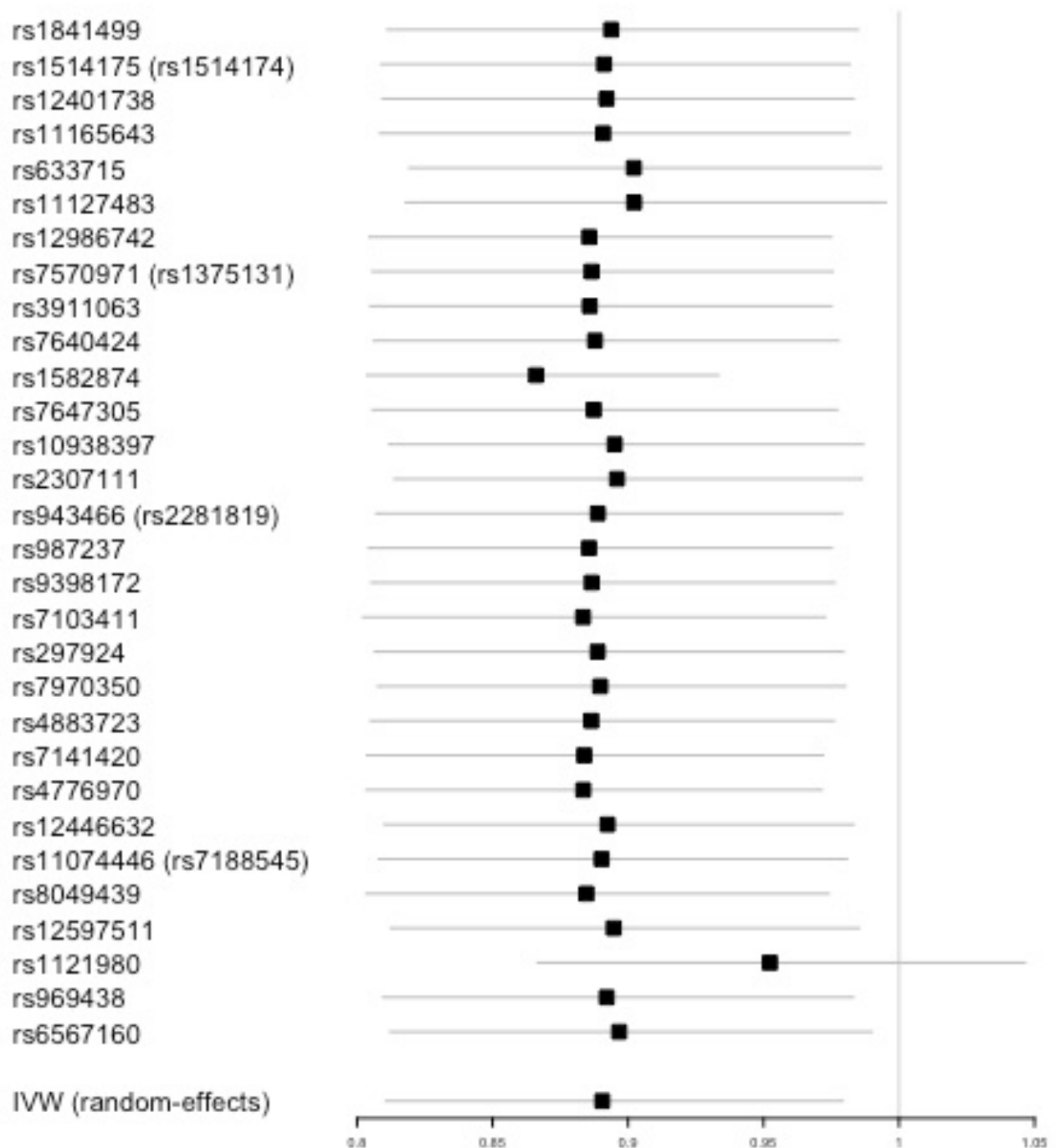
**B**



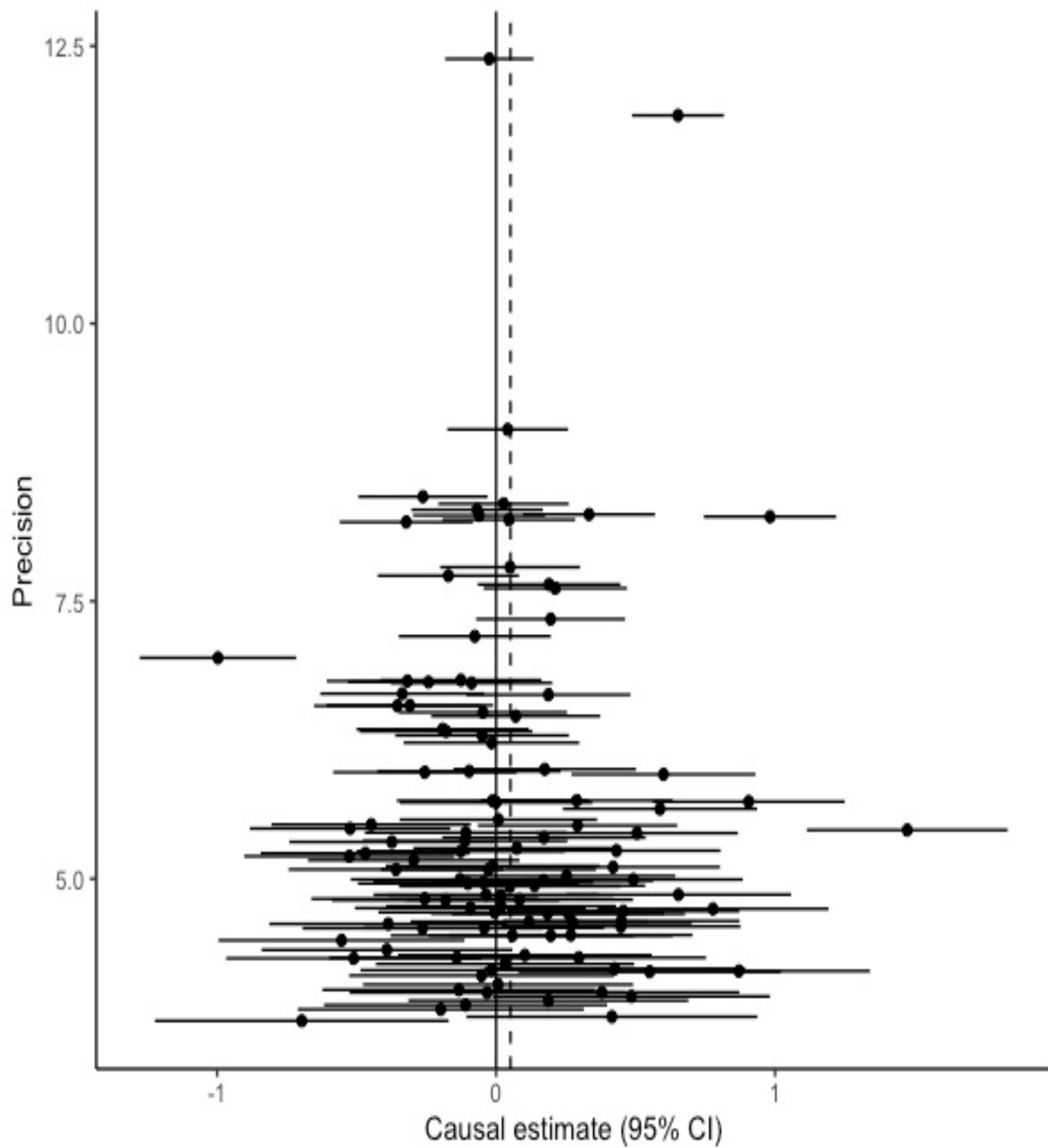
C



**Supplementary Figure 2.** Mendelian randomization estimates between body shape phenotype PC1 (A), PC2 (B) and PC3 (C) and overall and sub-types breast cancer risk using IVW (orange), IVW Random (green), MR Egger (blue), Weighted Median (violet) and MR PRESSO (brown) MR approaches. CI, confidence interval; OR, odds ratio.



**Supplementary Figure 3.** Leave-one SNP-out plot for PC1 and overall breast cancer risk.



**Supplementary Figure 4.** Funnel plot for PC2 and overall breast cancer risk.

|                    | PC1    | PC2    | PC3    |
|--------------------|--------|--------|--------|
| BMI                | 0.473  | -0.128 | -0.284 |
| Height             | 0.131  | 0.803  | 0.513  |
| Hip                | 0.444  | 0.197  | -0.399 |
| Waist              | 0.488  | -0.159 | 0.138  |
| Weight             | 0.486  | 0.186  | -0.056 |
| WHR                | 0.297  | -0.490 | 0.689  |
| Explained variance | 64.37% | 18.46% | 13.79% |

**Supplementary Table 1.** Loadings and explained variance of the three PCs.<sup>1</sup>

| Breast cancer GWAS sample size          |                                      |                          |
|-----------------------------------------|--------------------------------------|--------------------------|
| Breast cancer                           | Overall                              | Sub-types                |
| Cases                                   | 133,384                              | 106,278 (invasive cases) |
| Controls                                | 113,789                              | 91,477                   |
| Tumor marker sub-types GWAS sample size |                                      |                          |
| Estrogen Receptor status                | Negative                             | 16883                    |
|                                         | Positive                             | 69963                    |
|                                         | Unknown                              | 19432                    |
| Progesterone Receptor status            | Negative                             | 24260                    |
|                                         | Positive                             | 51546                    |
|                                         | Unknown                              | 30472                    |
| HER2 status                             | Negative                             | 47645                    |
|                                         | Positive                             | 9502                     |
|                                         | Unknown                              | 49131                    |
| Grade                                   | 1                                    | 15566                    |
|                                         | 2                                    | 37532                    |
|                                         | 3                                    | 24360                    |
|                                         | Unknown                              | 28820                    |
| Breast cancer sub-types description     |                                      |                          |
| Luminal A                               | ER+ and/or PR+, HER2-, grade 1 and 2 |                          |
| Luminal B                               | ER+ and/or PR+, HER2+                |                          |
| HER2 +                                  | ER-, PR-, HER2+                      |                          |
| Triple -                                | ER-, PR-, HER2 -                     |                          |
| Luminal B/HER 2 -                       | ER+ and/or PR+, HER2-, grade 3       |                          |

**Supplementary Table 2.** Sample size for overall breast cancer and sub-types GWAS as well as according to tumor marker (Estrogen Receptor (negative, positive and unknown), Progesterone Receptor (negative, positive and unknown), HER2 (negative, positive and unknown), and grade (1, 2, 3 and unknown)). Finally, sub-types studied description regarding tumor markers.<sup>2</sup>

| Outcome              | Exposure | Heterogeneity |     |         | Egger intercept |                |         |
|----------------------|----------|---------------|-----|---------|-----------------|----------------|---------|
|                      |          | Cochran's Q   | df  | p-value | Estimate        | 95% CI         | p-value |
| Overall              | PC1      | 199.5858      | 29  | <0.001  | 0.029           | 0.014 , 0.043  | <0.001  |
|                      | PC2      | 515.5738      | 113 | <0.001  | 0               | -0.010 , 0.009 | 0.961   |
|                      | PC3      | 180.1254      | 43  | <0.001  | 0.013           | -0.008 , 0.033 | 0.228   |
| Luminal A            | PC1      | 136.8719      | 29  | <0.001  | 0.029           | 0.012 , 0.045  | 0.001   |
|                      | PC2      | 368.3768      | 113 | <0.001  | -0.006          | -0.017 , 0.004 | 0.256   |
|                      | PC3      | 129.4055      | 43  | <0.001  | 0.012           | -0.011 , 0.036 | 0.293   |
| Luminal B            | PC1      | 60.9838       | 29  | 0.0005  | 0.038           | 0.012 , 0.063  | 0.003   |
|                      | PC2      | 162.6251      | 113 | 0.0016  | 0.013           | -0.003 , 0.028 | 0.1     |
|                      | PC3      | 70.7185       | 43  | 0.0049  | 0.018           | -0.02 , 0.056  | 0.348   |
| HER2 +               | PC1      | 49.9252       | 29  | 0.0092  | 0.036           | 0.001 , 0.071  | 0.046   |
|                      | PC2      | 143.6335      | 113 | 0.0273  | -0.002          | -0.023 , 0.02  | 0.876   |
|                      | PC3      | 54.0215       | 43  | 0.1209  | 0.011           | -0.037 , 0.06  | 0.644   |
| Triple -             | PC1      | 45.7765       | 29  | 0.0247  | 0.029           | 0.01 , 0.048   | 0.003   |
|                      | PC2      | 187.1135      | 113 | <0.001  | 0.01            | -0.004 , 0.025 | 0.175   |
|                      | PC3      | 81.4148       | 43  | 0.0004  | -0.003          | -0.038 , 0.033 | 0.878   |
| Luminal B/<br>HER2 - | PC1      | 82.7505       | 29  | <0.001  | 0.038           | 0.013 , 0.063  | 0.003   |
|                      | PC2      | 183.9729      | 113 | <0.001  | -0.004          | -0.018 , 0.01  | 0.565   |
|                      | PC3      | 72.6526       | 43  | 0.0031  | 0.023           | -0.009 , 0.056 | 0.156   |

**Supplementary Table 3.** Heterogeneity test and Egger intercept results for body shape phenotypes and overall breast cancer risk and sub-types.

| Breast Cancer    | PC1                    | PC2                                                            | PC3                                                          |
|------------------|------------------------|----------------------------------------------------------------|--------------------------------------------------------------|
| Overall          | rs1582874<br>rs1121980 | rs11205303<br>rs724016<br>rs6569648<br>rs11049611<br>rs3764419 | rs9425301<br>rs6726261<br>rs9838625<br>rs272885<br>rs1936809 |
|                  | $\rho = 0.130$         | $\rho = 0.013$                                                 | $\rho = 0.123$                                               |
| Luminal A        | rs1582874<br>rs1121980 | rs11205303<br>rs724016<br>rs6569648<br>rs11049611<br>rs1182199 | rs9838625<br>rs272885<br>rs1516883                           |
|                  | $\rho = 0.053$         | $\rho = 0.020$                                                 | $\rho = 0.038$                                               |
| Luminal B        | rs3911063<br>rs1121980 | -                                                              | -                                                            |
|                  | $\rho = 0.039$         |                                                                |                                                              |
| HER2 +           | rs1582874              | -                                                              | -                                                            |
|                  | $\rho = 0.692$         |                                                                |                                                              |
| Triple -         | rs1121980              | rs6569648<br>rs11049611                                        | rs9425301                                                    |
|                  | $\rho = 0.007$         | $\rho = 0.769$                                                 | $\rho = 0.545$                                               |
| Luminal B/HER2 - | rs1582874<br>rs1121980 | rs1415288<br>rs724016<br>rs11049611                            | rs9838625                                                    |
|                  | $\rho = 0.334$         | $\rho = 0.204$                                                 | $\rho = 0.266$                                               |

**Supplementary Table 4.** Genetic variants considered as outliers for overall and sub-types breast cancer and each body shape phenotype. We also provide P-distortion ( $\rho$ ) for each test performed.

## References

1. Ried JS, Jeff JM, Chu AY, Bragg-Gresham JL, Van Dongen J, Huffman JE, et al. A principal component meta-analysis on multiple anthropometric traits identifies novel loci for body shape. *Nat Commun.* 2016;7.
2. Zhang H, Ahearn TU, Lecarpentier J, Barnes D, Beesley J, Qi G, et al. Genome-wide association study identifies 32 novel breast cancer susceptibility loci from overall and subtype-specific analyses. *Nat Genet.* 2020;52(6).