No evidence for a causal relationship between cancers and Parkinson's disease

Konstantin Senkevich, MD, PhD,[1,2] Sara Bandres-Ciga, PhD,[3] Eric Yu, BSc,[1,4] Upekha E. Liyanage, MBBS, PhD,[5] International Parkinson Disease Genomics Consortium (IPDGC), Alastair J Noyce, MRCP, PhD,[6,7] Ziv Gan-Or, MD, PhD[1,2,4*]

[1]Montreal Neurological Institute, McGill University, Montréal, QC, H3A 1A1, Canada
[2]Department of Neurology and neurosurgery, McGill University, Montréal, QC, H3A 0G4, Canada, Canada
[3]Molecular Genetics Section, Laboratory of Neurogenetics, NIA, NIH, Bethesda, MD, USA
[4]Department of Human Genetics, McGill University, Montréal, QC, H3A 1A1, Canada
[5]Cancer and Population Studies group, Population Health department,
QIMR Berghofer Medical Research Institute, Locked Bag 2000, Royal Brisbane Hospital,
Queensland 4006, Australia
[6]Preventive Neurology Unit, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK
[7]Department of Clinical and Movement Neurosciences, University College London Institute of Neurology, London, UK

*Corresponding author:
Ziv Gan-Or
Department of Neurology and Neurosurgery
McGill University
1033 Pine Avenue, West,
Ludmer Pavilion, room 312
Montreal, QC, H3A 1A1,
Phone: +1-514-398-5845
Fax. +1-514 398-8248
Email: ziv.gan-or@mcgill.ca

Text word count: 1948 words

Keywords: Parkinson's disease; Mendelian randomization; Cancer; Melanoma

Abstract

Background: Epidemiological data suggest that cancer patients have a reduced risk of subsequent Parkinson's disease (PD) development, but the prevalence of PD in melanoma patients is often reported to be increased. Causal relationships between cancers and PD have not been fully explored.

Objectives: To study causal relationship between different cancers and PD.

Methods: We used GWAS summary statistics of 15 different types of cancers and two-sample Mendelian randomization to study the causal relationship with PD.

Results: There was no evidence to support a causal relationship between the studied cancers and PD. We also performed reverse analyses between PD and cancers with available full summary statistics (melanoma, breast, prostate, endometrial and keratinocyte cancers) and did not find evidence of causal relationship.

Conclusions: We found no evidence to support a causal relationship between cancer and PD and the previously reported associations could be a result of genetic pleiotropy, shared biology or biases.

Introduction

Parkinson's disease (PD) is a complex disorder, influenced by numerous environmental and genetic factors. Observational studies have suggested associations between PD and different types of cancers (lung, skin, pancreatic cancers and others) [1-7], such that cancer patients have lower risk of subsequent PD development [8] and overall PD is associated with a reduced risk of subsequent cancer development [1, 2]. However, risk of PD is increased in melanoma patients [9] and the prevalence of melanoma and brain tumors may be increased in patients with PD [3-6]. In the absence of a causal effect, apparent associations may be explained by confounding factors (such as toxins that casually influence the risk of specific cancers and PD), shared genetic susceptibility or biological pathways, or ascertainment bias [10, 11].

In Mendelian randomization (MR), similar to randomized control trials, single-nucleotide polymorphism (SNPs) are used to randomly divide participants into two groups defined by genotype, assuming that genotype distribution is a random process during meiosis, and therefore it should not be affected by confounders. MR uses SNPs associated with an exposure of interest (such as cancer susceptibility) as proxies to determine the causal association between that exposure and an outcome [12]. Summary level data from genome wide associational studies (GWASs) are used to construct instrumental variables (IVs) from GWAS significant SNPs. In the current study, we performed bi-directional MR to examine whether certain types of cancers have causal relationships with PD and vice versa.

Methods

Mendelian randomization

For the construction of genetic instruments, we selected studies from the GWAS Catalog [13] using the R package MRInstruments [14, 15]. First, we searched for traits using keywords "cancer",

72 “carcinoma”, “glioma”, “lymphoma”, “leukemia”, “melanoma”. We then selected the most recent
73 available GWAS for each cancer, with a minimum of 1000 cases and at least the same number of
74 controls of European ancestry. Additionally, recent GWASs on melanoma [16] and combined analysis
75 of keratinocyte cancers [17] were added as they were not available in the GWAS catalog. Fifteen
76 studies were selected for this part of the analysis **(Supplementary Table 1)**. UK biobank (UKB)
77 participants were included in some of these studies (colorectal cancer, combined analysis of
78 keratinocyte cancers, endometrial cancer, lung cancer, melanoma, uterine fibroids).

79 To perform MR in the reverse direction (the causal relationship between PD and different
80 cancer types) we required full summary statistics which we obtained through GWAS Catalog or direct
81 contact with authors. We were able to collect full summary statistics for melanoma [16], breast [18],
82 prostate [19], endometrial [20] and keratinocyte cancers (basal cell and squamous cell carcinoma) [17].

83 We used GWAS summary statistics from the latest PD GWAS excluding 23andMe and UKB
84 data, to avoid potential bias due to overlapping samples [21]. After the exclusions, a total of 15,056
85 PD patients and 12,637 controls were included in the summary statistics [21].

86 We constructed genetic instruments for cancer susceptibility and PD using SNPs with GWAS
87 significant *p*-values ($<5\times10^{-8}$) from each study. The extracted data included rs-numbers, log odds
88 ratios, standard errors, *p*-values, alleles, and effect allele frequency. SNPs for each exposure were
89 clumped using standard parameters (clumping window of 10,000 kb, r^2 cutoff 0.001) to discard
90 variants in LD. Additionally, we calculated r^2, which reflects the proportion of variability explained
91 by genetic variants and F-statistics to estimate the strength of IVs selected for exposures as previously
92 described [22, 23]. We calculated estimated power to detect an equivalent effect size of OR 1.2 on PD
93 risk utilizing an online Mendelian randomization power calculation
94 (https://sb452.shinyapps.io/power/) [24].

MR methods implemented in the Two-sample MR R package [14, 15] were used and are described in detail elsewhere [25-27]. Firstly, we performed Steiger filtering to exclude SNPs that explain more variance in the outcome than in the exposure [15]. We then used the inverse variance weighted (IVW) method, in which we pooled estimates from individual Wald ratios for each SNP and meta-analyzed using random effects [25-27]. We applied MR Egger to detect net directional pleiotropy and provide a better estimate of the true causal effect allowing to detect possible violations of instrumental variable assumptions [27]. Additionally, we used weighted median (WM) which is a median of the weighted estimates and provides consistent effect even if 50% of IVs are invalid [28]. These sensitivity analyses were performed to explore heterogeneity and horizontal pleiotropy. Heterogeneity was tested using Cochran's Q test in the IVW and MR-Egger methods [29]. For each method, we constructed funnel plots to detect pleiotropic outliers **(Supplementary Figure 1-6)**. Additionally, we performed MR-PRESSO test to detect outlier SNPs which may be biasing estimates through horizontal pleiotropy, and then adjust for them [30].

Data availability:

All code used in the current study is available at https://github.com/gan-orlab/MR_Cancers-PD

Results

Mendelian randomization does not support a causal role for different cancers and PD

We selected 15 cancer GWAS studies for MR analysis **(Table 1)**. The variance in the exposure variables explained by SNPs ranged from 0.016 to 0.059 **(Table 2)**. All instruments had F-statistics of >10, which is the standard cut-off applied to indicate sufficient instrument strength **(Table 2; Supplementary Table 1)**.

No causal effect of any cancer on PD was observed applying various MR methods **(Table 1; Supplementary Table 1, Supplementary Figure 1-2)**.

To test for potential violations of MR assumptions, we performed sensitivity analyses. Significant heterogeneity was apparent for cutaneous squamous cell carcinoma (IVW, Q *p*-value=0.02) and combined analysis of keratinocyte cancers (MR Egger, Q *p*-value=0.012; IVW, Q *p*-value=0.012, **Supplementary Table 2, Supplementary Figure 3**).

Tests for pleiotropy were performed to detect SNPs affecting the outcome through alternative pathways. There was some evidence for net horizontal pleiotropy for brain tumors (p=0.011) and cutaneous squamous cell carcinoma (p=0.029, **Supplementary Table 2**) which may have resulted in bias to IVW estimates, but the slopes from Egger regression were imprecisely estimated. Using MR-PRESSO, we detected an outlier SNP for cutaneous squamous cell carcinoma (rs4710154). The distortion test did not suggest significant changes in the effect estimates after this outlier was removed **(Supplementary Table 2)**. The sensitivity analyses revealed no clear evidence for bias in the IVW estimate due to invalid instruments with other cancers.

Additionally, we performed reverse MR with melanoma, keratinocyte, prostate, endometrial and breast cancers for which we had full summary statistics using PD-associated SNPs as exposure and cancer summary statistics as outcome and did not find any evidence for causal relationships **(Supplementary Table 3; Supplementary Figure 4-6)**. We found evidence for directional pleiotropy between PD and breast cancer and keratinocyte cancers, and a borderline distortion test with MR-PRESSO for breast cancer **(Supplementary Table 3)**. MR-PRESSO identified an outlier SNP for both PD and breast and prostate cancer (rs4630591). Additionally, the rs510306 SNP was found to be an outlier for prostate cancer. For keratinocyte cancers, three outlier SNPs were detected (rs4630591, rs6599388 and rs4889603).

Discussion

In the current study, we performed a comprehensive analysis to examine whether the reported associations between different cancers **(Table 1)** and PD may be causal. Our results provide no

evidence to support causal effects, and indicate that the observed associations may be due to other reasons including shared biology, confounders or biases. MR methods have limited availability and statistical power to differentiate horizontal and vertical pleiotropy, but high power to detect pleiotropy itself. Although MR can help reduce confounding and the possibility of reverse causality, a recent study demonstrated that MR is not immune to survival bias [31]. PD is an age-related disease and inverse observational study associations may occur spuriously if the exposure of interest (here cancer) causes premature mortality. This situation is known as 'survivor bias' and can occur in case-control settings, including in MR studies. On the other hand, early mortality from cancer could reduce cancer prevalence in PD [8]. The higher occurrence of brain cancers in PD might be related to closer medical attention (i.e., more frequent MRI in PD patients compared to the general population).

The most thoroughly studied genetic relationship between cancer and PD is for melanoma [32]. Previous MR studies did not demonstrate evidence of a causal relationship between PD and melanoma [22]. However, a recent, comprehensive analysis suggested a significant genetic correlation between melanoma and PD, with gene expression overlap [10], that could probably explain the increased frequency of melanoma in PD. One of the possible explanations for the link between cancers and PD is pleiotropy. In our study, we only examined causality using MR and did not estimate possible shared biology. To study possible shared biology, methods such as linkage disequilibrium score regression and transcriptome wide association study can be used to examine correlations between two traits occurring through shared genetic architecture. Unfortunately, we were only able to collect full summary statistics of mostly sex-specific cancers (prostate, breast, endometrial cancers), which cannot be used with the PD GWAS data since it is not sex-stratified. This approach should be used in future studies. We cannot rule out that pleiotropic effects within the IVs cancel out each other if they have effects in opposite direction. There are genes involved in pathogenesis of both PD and cancers. It was suggested that familial PD genes (*PINK1*, *DJ1*, *LRRK2 etc.*) may play a role in cancers [33-35].

GPNMB variants were associated with PD [36] and overexpression of GPNMB have been demonstrated in PD as well as in various cancers including melanoma [37, 38].

In our analyses using MR-PRESSO, we identified a few outlier SNPs. For cutaneous squamous cell carcinoma and PD, the rs4710154 SNP, located near the *FGFR1OP* gene, was an outlier. This gene was previously implicated in skin cancer and in several inflammatory disorders including Crohn's disease [39]. This SNP was not previously associated with PD. Another outlier SNP, rs4630591, near the *KANSL1* gene (encoding for KAT8 Regulatory NSL Complex Subunit 1) was identified for PD and breast and prostate cancers. This gene has been previously reported as the first cancer predisposition fusion gene [40], and this SNP was associated with breast cancer in transcriptome wide association study [41]. The rs510306 SNP near the *IGSF9B* gene has not been previously implicated in prostate cancer. For PD and keratinocyte cancers, three outlier SNPs were detected (rs4630591, rs6599388 and rs4889603). The rs6599388 SNP is located in *TMEM175* and rs4889603 is located in *STX1B*, both of which have not been previously associated with skin cancers.

Our study has several limitations. This is a European-based study, and these associations or lack thereof should be studied in other populations. We excluded UKB data to decrease the chance of overlapping samples between studies, which can result in bias. As a result, some of our MR analyses might have not enough power to detect the causal effect. Lack of availability of sex-specific PD GWAS data is the another limitation, which would be important for studying the causal effect of sex-specific cancers, or with cancers that have meaningful sex differences [42]. We performed bi-directional MR with PD and cancers with available full summary statistics (melanoma, breast, prostate, endometrial and keratinocyte cancers) and did not find evidence of a causal relationships. One more limitation is that MR relies on the quality of the GWAS used for the MR, and thus, limited by the GWAS quality.

Additionally, we could not consider in the current analysis important environmental exposures that would be of interest for stratified analyses (e.g. smoking in lung cancer; hormone levels in sex-

driven cancers). Thus, it is possible that we missed some causal effects due to gene-environment interaction or imperfect phenotype consideration.

To conclude, our results do not support a causal relationship between the tested cancers and PD, and suggest that the observed associations could be a result of genetic pleiotropy, shared biology or biases. Once larger datasets become available, as well as sex-specific PD datasets, additional MR studies should be performed on cancers and PD.

Acknowledgments including sources of support

We would like to thank the relevant consortia for making their data available. We would like to also thank all members of the International Parkinson Disease Genomics Consortium (IPDGC). For a complete overview of members, acknowledgements and funding, please see http://pdgenetics.org/partners. This study was financially supported by grants from the Michael J. Fox Foundation, the Canadian Consortium on Neurodegeneration in Aging (CCNA), the Canada First Research Excellence Fund (CFREF), awarded to McGill University for the Healthy Brains for Healthy Lives initiative (HBHL), and Parkinson Canada. ZGO is supported by the Fonds de recherche du Québec - Santé (FRQS) Chercheurs-boursiers award, in collaboration with Parkinson Quebec, and by the Young Investigator Award by Parkinson Canada. KS is supported by a postdoctoral fellowship from the Canada First Research Excellence Fund (CFREF), awarded to McGill University for the Healthy Brains for Healthy Lives initiative (HBHL). We would like to also thank Stuart MacGregor, Matthew Law and David Whiteman from QIMR Berghofer Medical Research Institute, Locked Bag 2000, Royal Brisbane Hospital, Queensland 4006, Australia for providing summary statistics data on keratinocytes cancers. The endometrial cancer genome-wide association analyses were supported by the National Health and Medical Research Council of Australia (APP552402, APP1031333, APP1109286, APP1111246 and APP1061779), the U.S. National Institutes of Health (R01-CA134958), European Research Council (EU FP7 Grant), Wellcome Trust Centre for Human Genetics (090532/Z/09Z) and Cancer Research UK. OncoArray genotyping of ECAC cases was performed with the generous assistance of the Ovarian Cancer Association Consortium (OCAC), which was funded through grants from the U.S. National Institutes of Health (CA1X01HG007491-01 (C.I. Amos), U19-CA148112 (T.A. Sellers), R01-CA149429 (C.M. Phelan) and R01-CA058598 (M.T. Goodman); Canadian Institutes of Health Research (MOP-86727 (L.E. Kelemen)) and the Ovarian Cancer Research Fund (A. Berchuck). We particularly thank the efforts of Cathy Phelan. OncoArray genotyping of the BCAC controls was funded by Genome Canada Grant GPH-129344, NIH Grant

U19 CA148065, and Cancer UK Grant C1287/A16563. All studies and funders are listed in O'Mara et al (2018). The breast cancer genome-wide association analyses were supported by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research, the 'Ministère de l'Économie, de la Science et de l'Innovation du Québec' through Genome Québec and grant PSR-SIIRI-701, The National Institutes of Health (U19 CA148065, X01HG007492), Cancer Research UK (C1287/A10118, C1287/A16563, C1287/A10710) and The European Union (HEALTH-F2-2009-223175 and H2020 633784 and 634935). All studies and funders supported breast cancer GWAS are listed in Michailidou et al., (Nature, 2017). For acknowledgements for the melanoma meta-analysis see Landi et al (Nature genetics, 2020). We would like to thank The PRACTICAL consortium, CRUK, BPC3, CAPS, PEGASUS. The Prostate cancer genome-wide association analyses are supported by the Canadian Institutes of Health Research, European Commission's Seventh Framework Programme grant agreement n° 223175 (HEALTH-F2-2009-223175), Cancer Research UK Grants C5047/A7357, C1287/A10118, C1287/A16563, C5047/A3354, C5047/A10692, C16913/A6135, and The National Institute of Health (NIH) Cancer Post-Cancer GWAS initiative grant: No. 1 U19 CA 148537-01 (the GAME-ON initiative). We would also like to thank the following for funding support: The Institute of Cancer Research and The Everyman Campaign, The Prostate Cancer Research Foundation, Prostate Research Campaign UK (now PCUK), The Orchid Cancer Appeal, Rosetrees Trust, The National Cancer Research Network UK, The National Cancer Research Institute (NCRI) UK. We are grateful for support of NIHR funding to the NIHR Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust. The Prostate Cancer Program of Cancer Council Victoria also acknowledge grant support from The National Health and Medical Research Council, Australia (126402, 209057, 251533, 396414, 450104, 504700, 504702, 504715, 623204, 940394, 614296,), VicHealth, Cancer Council Victoria, The Prostate Cancer Foundation of Australia, The Whitten Foundation, PricewaterhouseCoopers, and Tattersall's. EAO, DMK, and EMK acknowledge the Intramural Program of the National Human Genome Research Institute for their

support. Genotyping of the OncoArray was funded by the US National Institutes of Health (NIH) [U19 CA 148537 for ELucidating Loci Involved in Prostate cancer SuscEptibility (ELLIPSE) project and X01HG007492 to the Center for Inherited Disease Research (CIDR) under contract number HHSN2682012000008I] and by Cancer Research UK grant A8197/A16565. Additional analytic support was provided by NIH NCI U01 CA188392 (PI: Schumacher). Funding for the iCOGS infrastructure came from: the European Community's Seventh Framework Programme under grant agreement n° 223175 (HEALTH-F2-2009-223175) (COGS), Cancer Research UK (C1287/A10118, C1287/A 10710, C12292/A11174, C1281/A12014, C5047/A8384, C5047/A15007, C5047/A10692, C8197/A16565), the National Institutes of Health (CA128978) and Post-Cancer GWAS initiative (1U19 CA148537, 1U19 CA148065 and 1U19 CA148112 – the GAME-ON initiative), the Department of Defence (W81XWH-10-1-0341), the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer, Komen Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund. The BPC3 was supported by the U.S. National Institutes of Health, National Cancer Institute (cooperative agreements U01-CA98233 to D.J.H., U01-CA98710 to S.M.G., U01-CA98216 toE.R., and U01-CA98758 to B.E.H., and Intramural Research Program of NIH/National Cancer Institute, Division of Cancer Epidemiology and Genetics). CAPS GWAS study was supported by the Swedish Cancer Foundation (grant no 09-0677, 11-484, 12-823), the Cancer Risk Prediction Center (CRisP; www.crispcenter.org), a Linneus Centre (Contract ID 70867902) financed by the Swedish Research Council, Swedish Research Council (grant no K2010-70X-20430-04-3, 2014-2269). PEGASUS was supported by the Intramural Research Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health. This research was supported in part by the Intramural Research Program of the NIH, National institute on Aging.

Conflict of Interest:

ZGO has received consulting fees from Lysosomal Therapeutics Inc., Idorsia, Prevail Therapeutics, Denali, Ono Therapeutics, Neuron23, Handl Therapeutics, Deerfield and Inception Sciences (now Ventus). None of these companies were involved in any parts of preparing, drafting and publishing this study. AJN received grants from the Barts Charity, Parkinson's UK and Aligning Science Across Parkinson's; and honoraria from Britannia, BIAL, AbbVie, Global Kinetics Corporation, Profile, Biogen, and Roche. The rest of the authors have nothing to report.

References

[1] Bajaj A, Driver JA, Schernhammer ES (2010) Parkinson's disease and cancer risk: a systematic review and meta-analysis. *Cancer Causes & Control* **21**, 697-707.

[2] Chen C, Zheng H, Hu Z (2017) Association between Parkinson's disease and risk of prostate cancer in different populations: An updated meta-analysis. *Sci Rep* **7**, 13449.

[3] Huang P, Yang XD, Chen SD, Xiao Q (2015) The association between Parkinson's disease and melanoma: a systematic review and meta-analysis. *Transl Neurodegener* **4**, 21.

[4] Ryu HJ, Park JH, Choi M, Jung JH, Han K, Kwon DY, Kim DH, Park YG (2020) Parkinson's disease and skin cancer risk: a nationwide population-based cohort study in Korea. *J Eur Acad Dermatol Venereol*.

[5] Tang CF, Lu MK, Muo CH, Tsai CH, Kao CH (2016) Increased risk of brain tumor in patients with Parkinson's disease: a nationwide cohort study in Taiwan. *Acta Neurol Scand* **134**, 148-153.

[6] Ye R, Shen T, Jiang Y, Xu L, Si X, Zhang B (2016) The Relationship between Parkinson Disease and Brain Tumor: A Meta-Analysis. *PLoS One* **11**, e0164388.

[7] Zhang P, Liu B (2019) Association between Parkinson's Disease and Risk of Cancer: A PRISMA-compliant Meta-analysis. *ACS Chemical Neuroscience* **10**, 4430-4439.

[8] Cui X, Liew Z, Hansen J, Lee PC, Arah OA, Ritz B (2019) Cancers Preceding Parkinson's Disease after Adjustment for Bias in a Danish Population-Based Case-Control Study. *Neuroepidemiology* **52**, 136-143.

[9] Dalvin LA, Damento GM, Yawn BP, Abbott BA, Hodge DO, Pulido JS (2017) Parkinson Disease and Melanoma: Confirming and Reexamining an Association. *Mayo Clinic Proceedings* **92**, 1070-1079.

[10] Dube U, Ibanez L, Budde JP, Benitez BA, Davis AA, Harari O, Iles MM, Law MH, Brown KM, Agee M, Alipanahi B, Auton A, Bell RK, Bryc K, Elson SL, Fontanillas P, Furlotte NA, Hinds DA, Huber KE, Kleinman A, Litterman NK, McCreight JC, McIntyre MH, Mountain JL, Noblin ES, Northover CAM, Pitts SJ, Sathirapongsasuti JF, Sazonova OV, Shelton JF, Shringarpure S, Tian C, Tung JY, Vacic V, Wilson CH, Law MH, Bishop DT, Lee JE, Brossard M, Martin NG, Moses EK, Song F, Barrett JH, Kumar R, Easton DF, Pharoah PD, Swerdlow AJ, Kypreou KP, Taylor JC, Harland M, Randerson-Moor J, Akslen LA, Andresen PA, Avril MF, Azizi E, Scarrà GB, Brown KM, Debniak T, Duffy DL, Elder DE, Fang S, Friedman E, Galan P, Ghiorzo P, Gillanders EM, Goldstein AM, Gruis NA, Hansson J, Helsing P, Hočevar M, Höiom V, Ingvar C, Kanetsky PA, Chen WV, Landi MT, Lang J, Lathrop GM, Lubiński J, Mackie RM, Mann GJ, Molven A, Montgomery GW, Novaković S, Olsson H, Puig S, Puig-Butille JA, Wu W, Qureshi AA, Radford-Smith GL, van der Stoep N, van Doorn R, Whiteman DC, Craig JE, Schadendorf E, Simms LA, Burdon KP, Nyholt DR, Pooley KA, Orr N, Stratigos AJ, Cust AE, Ward SV, Hayward NK, Han J, Schulze HJ, Dunning AM, Bishop JA, Demenais F, Amos CI, MacGregor S, Iles MM, Cruchaga C, andMe Research T, Melanoma-Meta-analysis C, Geno MELC, Essen-Heidelberg I, Group SDHS, Q M, Investigators Q, Investigators A, Group AMS (2020) Overlapping genetic architecture between Parkinson disease and melanoma. *Acta Neuropathologica* **139**, 347-364.

[11] Freedman DM, Wu J, Chen H, Engels EA, Enewold LR, Freedman ND, Goedert JJ, Kuncl RW, Gail MH, Pfeiffer RM (2016) Associations between cancer and Parkinson's disease in U.S. elderly adults. *International Journal of Epidemiology* **45**, 741-751.

[12] Burgess S, Small DS, Thompson SG (2017) A review of instrumental variable estimators for Mendelian randomization. *Statistical methods in medical research* **26**, 2333-2355.

[13] Buniello A, MacArthur JAL, Cerezo M, Harris LW, Hayhurst J, Malangone C, McMahon A, Morales J, Mountjoy E, Sollis E, Suveges D, Vrousgou O, Whetzel PL, Amode R, Guillen JA, Riat HS, Trevanion SJ, Hall P, Junkins H, Flicek P, Burdett T, Hindorff LA, Cunningham F, Parkinson H (2019) The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. *Nucleic Acids Res* **47**, D1005-d1012.

[14] Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, Laurin C, Burgess S, Bowden J, Langdon R (2018) The MR-Base platform supports systematic causal inference across the human phenome. *Elife* **7**, e34408.

[15] Hemani G, Tilling K, Davey Smith G (2017) Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS genetics* **13**, e1007081.

[16] Landi MT, Bishop DT, MacGregor S, Machiela MJ, Stratigos AJ, Ghiorzo P, Brossard M, Calista D, Choi J, Fargnoli MC, Zhang T, Rodolfo M, Trower AJ, Menin C, Martinez J, Hadjisavvas A, Song L, Stefanaki I, Scolyer R, Yang R, Goldstein AM, Potrony M, Kypreou KP, Pastorino L, Queirolo P, Pellegrini C, Cattaneo L, Zawistowski M, Gimenez-Xavier P, Rodriguez A, Elefanti L, Manoukian S, Rivoltini L, Smith BH, Loizidou MA, Del Regno L, Massi D, Mandala M, Khosrotehrani K, Akslen LA, Amos CI, Andresen PA, Avril M-F, Azizi E, Soyer HP, Bataille V, Dalmasso B, Bowdler LM, Burdon KP, Chen WV, Codd V, Craig JE, Dębniak T, Falchi M, Fang S, Friedman E, Simi S, Galan P, Garcia-Casado Z, Gillanders EM, Gordon S, Green A, Gruis NA, Hansson J, Harland M, Harris J, Helsing P, Henders A, Hočevar M, Höiom V, Hunter D, Ingvar C, Kumar R, Lang J, Lathrop GM, Lee JE, Li X, Lubiński J, Mackie RM, Malt M, Malvehy J, McAloney K, Mohamdi H, Molven A, Moses EK, Neale RE, Novaković S, Nyholt DR, Olsson H, Orr N, Fritsche LG, Puig-Butille JA, Qureshi AA, Radford-Smith GL, Randerson-Moor J, Requena C, Rowe C, Samani NJ, Sanna M, Schadendorf D, Schulze H-J, Simms LA, Smithers M, Song F, Swerdlow AJ, van der Stoep N, Kukutsch NA, Visconti A, Wallace L, Ward SV, Wheeler L, Sturm RA, Hutchinson A, Jones K, Malasky M, Vogt A, Zhou W, Pooley KA, Elder DE, Han J, Hicks B, Hayward NK, Kanetsky PA, Brummett C, Montgomery GW, Olsen CM, Hayward C, Dunning AM, Martin NG, Evangelou E, Mann GJ, Long G, Pharoah PDP, Easton DF, Barrett JH, Cust AE, Abecasis G, Duffy DL, Whiteman DC, Gogas H, De Nicolo A, Tucker MA, Newton-Bishop JA, Peris K, Chanock SJ, Demenais F, Brown KM, Puig S, Nagore E, Shi J, Iles MM, Law MH, Geno MELC, Q M, Investigators Q, Group AMS, andMe, The SDHSG, Investigators IBD, Essen-Heidelberg I, Investigators A, MelaNostrum C (2020) Genome-wide association meta-analyses combining multiple risk phenotypes provide insights into the genetic architecture of cutaneous melanoma susceptibility. *Nature Genetics* **52**, 494-504.

[17] Liyanage UE, Law MH, Han X, An J, Ong JS, Gharahkhani P, Gordon S, Neale RE, Olsen CM, MacGregor S, Whiteman DC (2019) Combined analysis of keratinocyte cancers identifies novel genome-wide loci. *Hum Mol Genet* **28**, 3148-3160.

[18] Michailidou K, Lindström S, Dennis J, Beesley J, Hui S, Kar S, Lemaçon A, Soucy P, Glubb D, Rostamianfar A, Bolla MK, Wang Q, Tyrer J, Dicks E, Lee A, Wang Z, Allen J, Keeman R, Eilber U, French JD, Qing Chen X, Fachal L, McCue K, McCart Reed AE, Ghoussaini M, Carroll JS, Jiang X, Finucane H, Adams M, Adank MA, Ahsan H, Aittomäki K, Anton-Culver H, Antonenkova NN, Arndt V, Aronson KJ, Arun B, Auer PL, Bacot F, Barrdahl M, Baynes C, Beckmann MW, Behrens S, Benitez J, Bermisheva M, Bernstein L, Blomqvist C, Bogdanova NV, Bojesen SE, Bonanni B, Børresen-Dale AL, Brand JS, Brauch H, Brennan P, Brenner H, Brinton L, Broberg P, Brock IW, Broeks A, Brooks-Wilson A, Brucker SY, Brüning T, Burwinkel B, Butterbach K, Cai Q, Cai H, Caldés T, Canzian F, Carracedo A, Carter BD, Castelao JE, Chan TL, David Cheng TY, Seng Chia K, Choi JY, Christiansen H, Clarke CL, Collée M, Conroy DM, Cordina-Duverger E, Cornelissen S, Cox DG, Cox A, Cross SS, Cunningham JM, Czene K, Daly MB, Devilee P, Doheny KF, Dörk T, Dos-Santos-Silva I, Dumont M, Durcan L, Dwek M, Eccles DM, Ekici AB, Eliassen AH, Ellberg C, Elvira M, Engel C, Eriksson M, Fasching PA, Figueroa J, Flesch-Janys D, Fletcher O, Flyger H, Fritschi L, Gaborieau V, Gabrielson M, Gago-Dominguez M, Gao YT, Gapstur SM, García-Sáenz JA, Gaudet MM, Georgoulias V, Giles GG, Glendon G, Goldberg MS, Goldgar DE, González-Neira A, Grenaker Alnæs GI, Grip M, Gronwald J, Grundy A, Guénel P, Haeberle L, Hahnen E, Haiman CA, Håkansson N, Hamann U, Hamel N, Hankinson S, Harrington P, Hart SN, Hartikainen JM, Hartman M, Hein A, Heyworth J, Hicks B, Hillemanns P, Ho DN, Hollestelle A, Hooning MJ, Hoover RN, Hopper JL, Hou MF, Hsiung CN, Huang G, Humphreys K, Ishiguro J, Ito H, Iwasaki M, Iwata H, Jakubowska A, Janni W, John EM, Johnson N, Jones K, Jones M, Jukkola-Vuorinen A, Kaaks R, Kabisch M, Kaczmarek K, Kang D, Kasuga Y, Kerin MJ, Khan S, Khusnutdinova E, Kiiski JI, Kim SW, Knight JA, Kosma VM, Kristensen VN, Krüger U, Kwong A, Lambrechts D, Le Marchand L, Lee E, Lee MH, Lee JW, Neng Lee C, Lejbkowicz F, Li J, Lilyquist J, Lindblom A, Lissowska J, Lo WY, Loibl S, Long J, Lophatananon A, Lubinski J, Luccarini C, Lux MP, Ma ESK, MacInnis RJ, Maishman T, Makalic E, Malone KE, Kostovska IM, Mannermaa A, Manoukian S, Manson JE, Margolin S, Mariapun S,

Martinez ME, Matsuo K, Mavroudis D, McKay J, McLean C, Meijers-Heijboer H, Meindl A, Menéndez P, Menon U, Meyer J, Miao H, Miller N, Taib NAM, Muir K, Mulligan AM, Mulot C, Neuhausen SL, Nevanlinna H, Neven P, Nielsen SF, Noh DY, Nordestgaard BG, Norman A, Olopade OI, Olson JE, Olsson H, Olswold C, Orr N, Pankratz VS, Park SK, Park-Simon TW, Lloyd R, Perez JIA, Peterlongo P, Peto J, Phillips KA, Pinchev M, Plaseska-Karanfilska D, Prentice R, Presneau N, Prokofyeva D, Pugh E, Pylkäs K, Rack B, Radice P, Rahman N, Rennert G, Rennert HS, Rhenius V, Romero A, Romm J, Ruddy KJ, Rüdiger T, Rudolph A, Ruebner M, Rutgers EJT, Saloustros E, Sandler DP, Sangrajrang S, Sawyer EJ, Schmidt DF, Schmutzler RK, Schneeweiss A, Schoemaker MJ, Schumacher F, Schürmann P, Scott RJ, Scott C, Seal S, Seynaeve C, Shah M, Sharma P, Shen CY, Sheng G, Sherman ME, Shrubsole MJ, Shu XO, Smeets A, Sohn C, Southey MC, Spinelli JJ, Stegmaier C, Stewart-Brown S, Stone J, Stram DO, Surowy H, Swerdlow A, Tamimi R, Taylor JA, Tengström M, Teo SH, Beth Terry M, Tessier DC, Thanasitthichai S, Thöne K, Tollenaar R, Tomlinson I, Tong L, Torres D, Truong T, Tseng CC, Tsugane S, Ulmer HU, Ursin G, Untch M, Vachon C, van Asperen CJ, Van Den Berg D, van den Ouweland AMW, van der Kolk L, van der Luijt RB, Vincent D, Vollenweider J, Waisfisz Q, Wang-Gohrke S, Weinberg CR, Wendt C, Whittemore AS, Wildiers H, Willett W, Winqvist R, Wolk A, Wu AH, Xia L, Yamaji T, Yang XR, Har Yip C, Yoo KY, Yu JC, Zheng W, Zheng Y, Zhu B, Ziogas A, Ziv E, Lakhani SR, Antoniou AC, Droit A, Andrulis IL, Amos CI, Couch FJ, Pharoah PDP, Chang-Claude J, Hall P, Hunter DJ, Milne RL, García-Closas M, Schmidt MK, Chanock SJ, Dunning AM, Edwards SL, Bader GD, Chenevix-Trench G, Simard J, Kraft P, Easton DF (2017) Association analysis identifies 65 new breast cancer risk loci. *Nature* **551**, 92-94.

[19] Schumacher FR, Al Olama AA, Berndt SI, Benlloch S, Ahmed M, Saunders EJ, Dadaev T, Leongamornlert D, Anokian E, Cieza-Borrella C, Goh C, Brook MN, Sheng X, Fachal L, Dennis J, Tyrer J, Muir K, Lophatananon A, Stevens VL, Gapstur SM, Carter BD, Tangen CM, Goodman PJ, Thompson IM, Jr., Batra J, Chambers S, Moya L, Clements J, Horvath L, Tilley W, Risbridger GP, Gronberg H, Aly M, Nordström T, Pharoah P, Pashayan N, Schleutker J, Tammela TLJ, Sipeky C, Auvinen A, Albanes D, Weinstein S, Wolk A, Håkansson N, West CML, Dunning AM, Burnet N, Mucci LA, Giovannucci E, Andriole GL, Cussenot O, Cancel-Tassin G, Koutros S, Beane Freeman LE, Sorensen KD, Orntoft TF, Borre M, Maehle L, Grindedal EM, Neal DE, Donovan JL, Hamdy FC, Martin RM, Travis RC, Key TJ, Hamilton RJ, Fleshner NE, Finelli A, Ingles SA, Stern MC, Rosenstein BS, Kerns SL, Ostrer H, Lu YJ, Zhang HW, Feng N, Mao X, Guo X, Wang G, Sun Z, Giles GG, Southey MC, MacInnis RJ, FitzGerald LM, Kibel AS, Drake BF, Vega A, Gómez-Caamaño A, Szulkin R, Eklund M, Kogevinas M, Llorca J, Castaño-Vinyals G, Penney KL, Stampfer M, Park JY, Sellers TA, Lin HY, Stanford JL, Cybulski C, Wokolorczyk D, Lubinski J, Ostrander EA, Geybels MS, Nordestgaard BG, Nielsen SF, Weischer M, Bisbjerg R, Røder MA, Iversen P, Brenner H, Cuk K, Holleczek B, Maier C, Luedeke M, Schnoeller T, Kim J, Logothetis CJ, John EM, Teixeira MR, Paulo P, Cardoso M, Neuhausen SL, Steele L, Ding YC, De Ruyck K, De Meerleer G, Ost P, Razack A, Lim J, Teo SH, Lin DW, Newcomb LF, Lessel D, Gamulin M, Kulis T, Kaneva R, Usmani N, Singhal S, Slavov C, Mitev V, Parliament M, Claessens F, Joniau S, Van den Broeck T, Larkin S, Townsend PA, Aukim-Hastie C, Gago-Dominguez M, Castelao JE, Martinez ME, Roobol MJ, Jenster G, van Schaik RHN, Menegaux F, Truong T, Koudou YA, Xu J, Khaw KT, Cannon-Albright L, Pandha H, Michael A, Thibodeau SN, McDonnell SK, Schaid DJ, Lindstrom S, Turman C, Ma J, Hunter DJ, Riboli E, Siddiq A, Canzian F, Kolonel LN, Le Marchand L, Hoover RN, Machiela MJ, Cui Z, Kraft P, Amos CI, Conti DV, Easton DF, Wiklund F, Chanock SJ, Henderson BE, Kote-Jarai Z, Haiman CA, Eeles RA (2018) Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. *Nat Genet* **50**, 928-936.

[20] O'Mara TA, Glubb DM, Amant F, Annibali D, Ashton K, Attia J, Auer PL, Beckmann MW, Black A, Bolla MK, Brauch H, Brenner H, Brinton L, Buchanan DD, Burwinkel B, Chang-Claude J, Chanock SJ, Chen C, Chen MM, Cheng THT, Clarke CL, Clendenning M, Cook LS, Couch FJ, Cox A, Crous-Bous M, Czene K, Day F, Dennis J, Depreeuw J, Doherty JA, Dörk T, Dowdy SC, Dürst M, Ekici AB, Fasching PA, Fridley BL, Friedenreich CM, Fritschi L, Fung J, García-Closas M, Gaudet MM, Giles GG, Goode EL, Gorman M, Haiman CA, Hall P, Hankison SE, Healey CS, Hein A, Hillemanns P, Hodgson S, Hoivik EA, Holliday EG, Hopper JL, Hunter DJ, Jones A, Krakstad C, Kristensen VN, Lambrechts D, Marchand LL, Liang X,

Lindblom A, Lissowska J, Long J, Lu L, Magliocco AM, Martin L, McEvoy M, Meindl A, Michailidou K, Milne RL, Mints M, Montgomery GW, Nassir R, Olsson H, Orlow I, Otton G, Palles C, Perry JRB, Peto J, Pooler L, Prescott J, Proietto T, Rebbeck TR, Risch HA, Rogers PAW, Rübner M, Runnebaum I, Sacerdote C, Sarto GE, Schumacher F, Scott RJ, Setiawan VW, Shah M, Sheng X, Shu XO, Southey MC, Swerdlow AJ, Tham E, Trovik J, Turman C, Tyrer JP, Vachon C, VanDen Berg D, Vanderstichele A, Wang Z, Webb PM, Wentzensen N, Werner HMJ, Winham SJ, Wolk A, Xia L, Xiang YB, Yang HP, Yu H, Zheng W, Pharoah PDP, Dunning AM, Kraft P, De Vivo I, Tomlinson I, Easton DF, Spurdle AB, Thompson DJ (2018) Identification of nine new susceptibility loci for endometrial cancer. *Nat Commun* **9**, 3166.

[21] Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D, Tan M, Kia DA, Noyce AJ, Xue A, Bras J, Young E, von Coelln R, Simon-Sanchez J, Schulte C, Sharma M, Krohn L, Pihlstrom L, Siitonen A, Iwaki H, Leonard H, Faghri F, Gibbs JR, Hernandez DG, Scholz SW, Botia JA, Martinez M, Corvol JC, Lesage S, Jankovic J, Shulman LM, Sutherland M, Tienari P, Majamaa K, Toft M, Andreassen OA, Bangale T, Brice A, Yang J, Gan-Or Z, Gasser T, Heutink P, Shulman JM, Wood NW, Hinds DA, Hardy JA, Morris HR, Gratten J, Visscher PM, Graham RR, Singleton AB, andMe Research T, System Genomics of Parkinson's Disease C, International Parkinson's Disease Genomics C (2019) Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet Neurol* **18**, 1091-1102.

[22] Noyce AJ, Bandres-Ciga S, Kim J, Heilbron K, Kia D, Hemani G, Xue A, Lawlor DA, Smith GD, Duran R, Gan-Or Z, Blauwendraat C, Gibbs JR, Hinds DA, Yang J, Visscher P, Cuzick J, Morris H, Hardy J, Wood NW, Nalls MA, Singleton AB (2019) The Parkinson's Disease Mendelian Randomization Research Portal. *Mov Disord* **34**, 1864-1872.

[23] Burgess S, Thompson SG, Collaboration CCG (2011) Avoiding bias from weak instruments in Mendelian randomization studies. *International Journal of Epidemiology* **40**, 755-764.

[24] Burgess S (2014) Sample size and power calculations in Mendelian randomization with a single instrumental variable and a binary outcome. *Int J Epidemiol* **43**, 922-929.

[25] Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG (2017) Sensitivity Analyses for Robust Causal Inference from Mendelian Randomization Analyses with Multiple Genetic Variants. *Epidemiology* **28**, 30-42.

[26] Burgess S, Butterworth A, Thompson SG (2013) Mendelian Randomization Analysis With Multiple Genetic Variants Using Summarized Data. *Genetic Epidemiology* **37**, 658-665.

[27] Bowden J, Davey Smith G, Burgess S (2015) Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *International Journal of Epidemiology* **44**, 512-525.

[28] Bowden J, Davey Smith G, Haycock PC, Burgess S (2016) Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genet Epidemiol* **40**, 304-314.

[29] Bowden J, Del Greco MF, Minelli C, Zhao Q, Lawlor DA, Sheehan NA, Thompson J, Davey Smith G (2019) Improving the accuracy of two-sample summary-data Mendelian randomization: moving beyond the NOME assumption. *Int J Epidemiol* **48**, 728-742.

[30] Verbanck M, Chen C-Y, Neale B, Do R (2018) Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nature Genetics* **50**, 693-698.

[31] Smit RAJ, Trompet S, Dekkers OM, Jukema JW, le Cessie S (2019) Survival Bias in Mendelian Randomization Studies: A Threat to Causal Inference. *Epidemiology* **30**, 813-816.

[32] Inzelberg R, Flash S, Friedman E, Azizi E (2016) Cutaneous malignant melanoma and Parkinson disease: Common pathways? *Ann Neurol* **80**, 811-820.

[33] Kawate T, Tsuchiya B, Iwaya K (2017) Expression of DJ-1 in Cancer Cells: Its Correlation with Clinical Significance. *Adv Exp Med Biol* **1037**, 45-59.

[34] Mencke P, Hanss Z, Boussaad I, Sugier PE, Elbaz A, Krüger R (2020) Bidirectional Relation Between Parkinson's Disease and Glioblastoma Multiforme. *Front Neurol* **11**, 898.

[35] Filippou PS, Outeiro TF (2020) Cancer and Parkinson's Disease: Common Targets, Emerging Hopes. *Mov Disord*.
[36] Rudakou U, Yu E, Krohn L, Ruskey JA, Asayesh F, Dauvilliers Y, Spiegelman D, Greenbaum L, Fahn S, Waters CH, Dupré N, Rouleau GA, Hassin-Baer S, Fon EA, Alcalay RN, Gan-Or Z (2020) Targeted sequencing of Parkinson's disease loci genes highlights SYT11, FGF20 and other associations. *Brain*.
[37] Moloney EB, Moskites A, Ferrari EJ, Isacson O, Hallett PJ (2018) The glycoprotein GPNMB is selectively elevated in the substantia nigra of Parkinson's disease patients and increases after lysosomal stress. *Neurobiology of Disease* **120**, 1-11.
[38] Taya M, Hammes SR (2018) Glycoprotein Non-Metastatic Melanoma Protein B (GPNMB) and Cancer: A Novel Potential Therapeutic Target. *Steroids* **133**, 102-107.
[39] Yang SK, Hong M, Zhao W, Jung Y, Baek J, Tayebi N, Kim KM, Ye BD, Kim KJ, Park SH, Lee I, Lee EJ, Kim WH, Cheon JH, Kim YH, Jang BI, Kim HS, Choi JH, Koo JS, Lee JH, Jung SA, Lee YJ, Jang JY, Shin HD, Kang D, Youn HS, Liu J, Song K (2014) Genome-wide association study of Crohn's disease in Koreans revealed three new susceptibility loci and common attributes of genetic susceptibility across ethnic populations. *Gut* **63**, 80-87.
[40] Zhou J, Li XL, Chen ZR, Chng WJ (2017) Tumor-derived exosomes in colorectal cancer progression and their clinical applications. *Oncotarget* **8**, 100781-100790.
[41] Wu L, Shi W, Long J, Guo X, Michailidou K, Beesley J, Bolla MK, Shu XO, Lu Y, Cai Q, Al-Ejeh F, Rozali E, Wang Q, Dennis J, Li B, Zeng C, Feng H, Gusev A, Barfield RT, Andrulis IL, Anton-Culver H, Arndt V, Aronson KJ, Auer PL, Barrdahl M, Baynes C, Beckmann MW, Benitez J, Bermisheva M, Blomqvist C, Bogdanova NV, Bojesen SE, Brauch H, Brenner H, Brinton L, Broberg P, Brucker SY, Burwinkel B, Caldés T, Canzian F, Carter BD, Castelao JE, Chang-Claude J, Chen X, Cheng TD, Christiansen H, Clarke CL, Collée M, Cornelissen S, Couch FJ, Cox D, Cox A, Cross SS, Cunningham JM, Czene K, Daly MB, Devilee P, Doheny KF, Dörk T, Dos-Santos-Silva I, Dumont M, Dwek M, Eccles DM, Eilber U, Eliassen AH, Engel C, Eriksson M, Fachal L, Fasching PA, Figueroa J, Flesch-Janys D, Fletcher O, Flyger H, Fritschi L, Gabrielson M, Gago-Dominguez M, Gapstur SM, García-Closas M, Gaudet MM, Ghoussaini M, Giles GG, Goldberg MS, Goldgar DE, González-Neira A, Guénel P, Hahnen E, Haiman CA, Håkansson N, Hall P, Hallberg E, Hamann U, Harrington P, Hein A, Hicks B, Hillemanns P, Hollestelle A, Hoover RN, Hopper JL, Huang G, Humphreys K, Hunter DJ, Jakubowska A, Janni W, John EM, Johnson N, Jones K, Jones ME, Jung A, Kaaks R, Kerin MJ, Khusnutdinova E, Kosma VM, Kristensen VN, Lambrechts D, Le Marchand L, Li J, Lindström S, Lissowska J, Lo WY, Loibl S, Lubinski J, Luccarini C, Lux MP, MacInnis RJ, Maishman T, Kostovska IM, Mannermaa A, Manson JE, Margolin S, Mavroudis D, Meijers-Heijboer H, Meindl A, Menon U, Meyer J, Mulligan AM, Neuhausen SL, Nevanlinna H, Neven P, Nielsen SF, Nordestgaard BG, Olopade OI, Olson JE, Olsson H, Peterlongo P, Peto J, Plaseska-Karanfilska D, Prentice R, Presneau N, Pylkäs K, Rack B, Radice P, Rahman N, Rennert G, Rennert HS, Rhenius V, Romero A, Romm J, Rudolph A, Saloustros E, Sandler DP, Sawyer EJ, Schmidt MK, Schmutzler RK, Schneeweiss A, Scott RJ, Scott CG, Seal S, Shah M, Shrubsole MJ, Smeets A, Southey MC, Spinelli JJ, Stone J, Surowy H, Swerdlow AJ, Tamimi RM, Tapper W, Taylor JA, Terry MB, Tessier DC, Thomas A, Thöne K, Tollenaar R, Torres D, Truong T, Untch M, Vachon C, Van Den Berg D, Vincent D, Waisfisz Q, Weinberg CR, Wendt C, Whittemore AS, Wildiers H, Willett WC, Winqvist R, Wolk A, Xia L, Yang XR, Ziogas A, Ziv E, Dunning AM, Pharoah PDP, Simard J, Milne RL, Edwards SL, Kraft P, Easton DF, Chenevix-Trench G, Zheng W (2018) A transcriptome-wide association study of 229,000 women identifies new candidate susceptibility genes for breast cancer. *Nat Genet* **50**, 968-978.
[42] Rubin JB, Lagas JS, Broestl L, Sponagel J, Rockwell N, Rhee G, Rosen SF, Chen S, Klein RS, Imoukhuede P, Luo J (2020) Sex differences in cancer mechanisms. *Biol Sex Differ* **11**, 17.
[43] Law PJ, Berndt SI, Speedy HE, Camp NJ, Sava GP, Skibola CF, Holroyd A, Joseph V, Sunter NJ, Nieters A, Bea S, Monnereau A, Martin-Garcia D, Goldin LR, Clot G, Teras LR, Quintela I, Birmann BM, Jayne S, Cozen W, Majid A, Smedby KE, Lan Q, Dearden C, Brooks-Wilson AR, Hall AG, Purdue MP, Mainou-Fowler T, Vajdic CM, Jackson GH, Cocco P, Marr H, Zhang Y, Zheng T, Giles GG, Lawrence C, Call TG, Liebow M, Melbye M, Glimelius B, Mansouri L, Glenn M, Curtin K, Diver WR, Link BK, Conde L, Bracci

PM, Holly EA, Jackson RD, Tinker LF, Benavente Y, Boffetta P, Brennan P, Maynadie M, McKay J, Albanes D, Weinstein S, Wang Z, Caporaso NE, Morton LM, Severson RK, Riboli E, Vineis P, Vermeulen RC, Southey MC, Milne RL, Clavel J, Topka S, Spinelli JJ, Kraft P, Ennas MG, Summerfield G, Ferri GM, Harris RJ, Miligi L, Pettitt AR, North KE, Allsup DJ, Fraumeni JF, Bailey JR, Offit K, Pratt G, Hjalgrim H, Pepper C, Chanock SJ, Fegan C, Rosenquist R, de Sanjose S, Carracedo A, Dyer MJ, Catovsky D, Campo E, Cerhan JR, Allan JM, Rothman N, Houlston R, Slager S (2017) Genome-wide association analysis implicates dysregulation of immunity genes in chronic lymphocytic leukaemia. *Nat Commun* **8**, 14175.

[44] Law PJ, Timofeeva M, Fernandez-Rozadilla C, Broderick P, Studd J, Fernandez-Tajes J, Farrington S, Svinti V, Palles C, Orlando G, Sud A, Holroyd A, Penegar S, Theodoratou E, Vaughan-Shaw P, Campbell H, Zgaga L, Hayward C, Campbell A, Harris S, Deary IJ, Starr J, Gatcombe L, Pinna M, Briggs S, Martin L, Jaeger E, Sharma-Oates A, East J, Leedham S, Arnold R, Johnstone E, Wang H, Kerr D, Kerr R, Maughan T, Kaplan R, Al-Tassan N, Palin K, Hänninen UA, Cajuso T, Tanskanen T, Kondelin J, Kaasinen E, Sarin AP, Eriksson JG, Rissanen H, Knekt P, Pukkala E, Jousilahti P, Salomaa V, Ripatti S, Palotie A, Renkonen-Sinisalo L, Lepistö A, Böhm J, Mecklin JP, Buchanan DD, Win AK, Hopper J, Jenkins ME, Lindor NM, Newcomb PA, Gallinger S, Duggan D, Casey G, Hoffmann P, Nöthen MM, Jöckel KH, Easton DF, Pharoah PDP, Peto J, Canzian F, Swerdlow A, Eeles RA, Kote-Jarai Z, Muir K, Pashayan N, Harkin A, Allan K, McQueen J, Paul J, Iveson T, Saunders M, Butterbach K, Chang-Claude J, Hoffmeister M, Brenner H, Kirac I, Matošević P, Hofer P, Brezina S, Gsur A, Cheadle JP, Aaltonen LA, Tomlinson I, Houlston RS, Dunlop MG (2019) Association analyses identify 31 new risk loci for colorectal cancer susceptibility. *Nat Commun* **10**, 2154.

[45] Chahal HS, Lin Y, Ransohoff KJ, Hinds DA, Wu W, Dai HJ, Qureshi AA, Li WQ, Kraft P, Tang JY, Han J, Sarin KY (2016) Genome-wide association study identifies novel susceptibility loci for cutaneous squamous cell carcinoma. *Nat Commun* **7**, 12048.

[46] McKay JD, Hung RJ, Han Y, Zong X, Carreras-Torres R, Christiani DC, Caporaso NE, Johansson M, Xiao X, Li Y, Byun J, Dunning A, Pooley KA, Qian DC, Ji X, Liu G, Timofeeva MN, Bojesen SE, Wu X, Le Marchand L, Albanes D, Bickeböller H, Aldrich MC, Bush WS, Tardon A, Rennert G, Teare MD, Field JK, Kiemeney LA, Lazarus P, Haugen A, Lam S, Schabath MB, Andrew AS, Shen H, Hong YC, Yuan JM, Bertazzi PA, Pesatori AC, Ye Y, Diao N, Su L, Zhang R, Brhane Y, Leighl N, Johansen JS, Mellemgaard A, Saliba W, Haiman CA, Wilkens LR, Fernandez-Somoano A, Fernandez-Tardon G, van der Heijden HFM, Kim JH, Dai J, Hu Z, Davies MPA, Marcus MW, Brunnström H, Manjer J, Melander O, Muller DC, Overvad K, Trichopoulou A, Tumino R, Doherty JA, Barnett MP, Chen C, Goodman GE, Cox A, Taylor F, Woll P, Brüske I, Wichmann HE, Manz J, Muley TR, Risch A, Rosenberger A, Grankvist K, Johansson M, Shepherd FA, Tsao MS, Arnold SM, Haura EB, Bolca C, Holcatova I, Janout V, Kontic M, Lissowska J, Mukeria A, Ognjanovic S, Orlowski TM, Scelo G, Swiatkowska B, Zaridze D, Bakke P, Skaug V, Zienolddiny S, Duell EJ, Butler LM, Koh WP, Gao YT, Houlston RS, McLaughlin J, Stevens VL, Joubert P, Lamontagne M, Nickle DC, Obeidat M, Timens W, Zhu B, Song L, Kachuri L, Artigas MS, Tobin MD, Wain LV, Rafnar T, Thorgeirsson TE, Reginsson GW, Stefansson K, Hancock DB, Bierut LJ, Spitz MR, Gaddis NC, Lutz SM, Gu F, Johnson EO, Kamal A, Pikielny C, Zhu D, Lindströem S, Jiang X, Tyndale RF, Chenevix-Trench G, Beesley J, Bossé Y, Chanock S, Brennan P, Landi MT, Amos CI (2017) Large-scale association analysis identifies new lung cancer susceptibility loci and heterogeneity in genetic susceptibility across histological subtypes. *Nat Genet* **49**, 1126-1132.

[47] Sud A, Thomsen H, Law PJ, Försti A, Filho M, Holroyd A, Broderick P, Orlando G, Lenive O, Wright L, Cooke R, Easton D, Pharoah P, Dunning A, Peto J, Canzian F, Eeles R, Kote-Jarai Z, Muir K, Pashayan N, Hoffmann P, Nöthen MM, Jöckel KH, Strandmann EPV, Lightfoot T, Kane E, Roman E, Lake A, Montgomery D, Jarrett RF, Swerdlow AJ, Engert A, Orr N, Hemminki K, Houlston RS (2017) Genome-wide association study of classical Hodgkin lymphoma identifies key regulators of disease susceptibility. *Nat Commun* **8**, 1892.

[48] Melin BS, Barnholtz-Sloan JS, Wrensch MR, Johansen C, Il'yasova D, Kinnersley B, Ostrom QT, Labreche K, Chen Y, Armstrong G, Liu Y, Eckel-Passow JE, Decker PA, Labussière M, Idbaih A, Hoang-Xuan K, Di Stefano AL, Mokhtari K, Delattre JY, Broderick P, Galan P, Gousias K, Schramm J,

Schoemaker MJ, Fleming SJ, Herms S, Heilmann S, Nöthen MM, Wichmann HE, Schreiber S, Swerdlow A, Lathrop M, Simon M, Sanson M, Andersson U, Rajaraman P, Chanock S, Linet M, Wang Z, Yeager M, Wiencke JK, Hansen H, McCoy L, Rice T, Kosel ML, Sicotte H, Amos CI, Bernstein JL, Davis F, Lachance D, Lau C, Merrell RT, Shildkraut J, Ali-Osman F, Sadetzki S, Scheurer M, Shete S, Lai RK, Claus EB, Olson SH, Jenkins RB, Houlston RS, Bondy ML (2017) Genome-wide association study of glioma subtypes identifies specific differences in genetic susceptibility to glioblastoma and non-glioblastoma tumors. *Nat Genet* **49**, 789-794.

[49] Lesseur C, Diergaarde B, Olshan AF, Wünsch-Filho V, Ness AR, Liu G, Lacko M, Eluf-Neto J, Franceschi S, Lagiou P, Macfarlane GJ, Richiardi L, Boccia S, Polesel J, Kjaerheim K, Zaridze D, Johansson M, Menezes AM, Curado MP, Robinson M, Ahrens W, Canova C, Znaor A, Castellsagué X, Conway DI, Holcátová I, Mates D, Vilensky M, Healy CM, Szeszenia-Dąbrowska N, Fabiánová E, Lissowska J, Grandis JR, Weissler MC, Tajara EH, Nunes FD, de Carvalho MB, Thomas S, Hung RJ, Peters WH, Herrero R, Cadoni G, Bueno-de-Mesquita HB, Steffen A, Agudo A, Shangina O, Xiao X, Gaborieau V, Chabrier A, Anantharaman D, Boffetta P, Amos CI, McKay JD, Brennan P (2016) Genome-wide association analyses identify new susceptibility loci for oral cavity and pharyngeal cancer. *Nat Genet* **48**, 1544-1550.

[50] Klein AP, Wolpin BM, Risch HA, Stolzenberg-Solomon RZ, Mocci E, Zhang M, Canzian F, Childs EJ, Hoskins JW, Jermusyk A, Zhong J, Chen F, Albanes D, Andreotti G, Arslan AA, Babic A, Bamlet WR, Beane-Freeman L, Berndt SI, Blackford A, Borges M, Borgida A, Bracci PM, Brais L, Brennan P, Brenner H, Bueno-de-Mesquita B, Buring J, Campa D, Capurso G, Cavestro GM, Chaffee KG, Chung CC, Cleary S, Cotterchio M, Dijk F, Duell EJ, Foretova L, Fuchs C, Funel N, Gallinger S, JM MG, Gazouli M, Giles GG, Giovannucci E, Goggins M, Goodman GE, Goodman PJ, Hackert T, Haiman C, Hartge P, Hasan M, Hegyi P, Helzlsouer KJ, Herman J, Holcatova I, Holly EA, Hoover R, Hung RJ, Jacobs EJ, Jamroziak K, Janout V, Kaaks R, Khaw KT, Klein EA, Kogevinas M, Kooperberg C, Kulke MH, Kupcinskas J, Kurtz RJ, Laheru D, Landi S, Lawlor RT, Lee IM, LeMarchand L, Lu L, Malats N, Mambrini A, Mannisto S, Milne RL, Mohelníková-Duchoňová B, Neale RE, Neoptolemos JP, Oberg AL, Olson SH, Orlow I, Pasquali C, Patel AV, Peters U, Pezzilli R, Porta M, Real FX, Rothman N, Scelo G, Sesso HD, Severi G, Shu XO, Silverman D, Smith JP, Soucek P, Sund M, Talar-Wojnarowska R, Tavano F, Thornquist MD, Tobias GS, Van Den Eeden SK, Vashist Y, Visvanathan K, Vodicka P, Wactawski-Wende J, Wang Z, Wentzensen N, White E, Yu H, Yu K, Zeleniuch-Jacquotte A, Zheng W, Kraft P, Li D, Chanock S, Obazee O, Petersen GM, Amundadottir LT (2018) Genome-wide meta-analysis identifies five new susceptibility loci for pancreatic cancer. *Nat Commun* **9**, 556.

[51] Scelo G, Purdue MP, Brown KM, Johansson M, Wang Z, Eckel-Passow JE, Ye Y, Hofmann JN, Choi J, Foll M, Gaborieau V, Machiela MJ, Colli LM, Li P, Sampson JN, Abedi-Ardekani B, Besse C, Blanche H, Boland A, Burdette L, Chabrier A, Durand G, Le Calvez-Kelm F, Prokhortchouk E, Robinot N, Skryabin KG, Wozniak MB, Yeager M, Basta-Jovanovic G, Dzamic Z, Foretova L, Holcatova I, Janout V, Mates D, Mukeriya A, Rascu S, Zaridze D, Bencko V, Cybulski C, Fabianova E, Jinga V, Lissowska J, Lubinski J, Navratilova M, Rudnai P, Szeszenia-Dabrowska N, Benhamou S, Cancel-Tassin G, Cussenot O, Baglietto L, Boeing H, Khaw KT, Weiderpass E, Ljungberg B, Sitaram RT, Bruinsma F, Jordan SJ, Severi G, Winship I, Hveem K, Vatten LJ, Fletcher T, Koppova K, Larsson SC, Wolk A, Banks RE, Selby PJ, Easton DF, Pharoah P, Andreotti G, Freeman LEB, Koutros S, Albanes D, Männistö S, Weinstein S, Clark PE, Edwards TL, Lipworth L, Gapstur SM, Stevens VL, Carol H, Freedman ML, Pomerantz MM, Cho E, Kraft P, Preston MA, Wilson KM, Michael Gaziano J, Sesso HD, Black A, Freedman ND, Huang WY, Anema JG, Kahnoski RJ, Lane BR, Noyes SL, Petillo D, Teh BT, Peters U, White E, Anderson GL, Johnson L, Luo J, Buring J, Lee IM, Chow WH, Moore LE, Wood C, Eisen T, Henrion M, Larkin J, Barman P, Leibovich BC, Choueiri TK, Mark Lathrop G, Rothman N, Deleuze JF, McKay JD, Parker AS, Wu X, Houlston RS, Brennan P, Chanock SJ (2017) Genome-wide association study identifies multiple risk loci for renal cell carcinoma. *Nat Commun* **8**, 15724.

[52] Rafnar T, Gunnarsson B, Stefansson OA, Sulem P, Ingason A, Frigge ML, Stefansdottir L, Sigurdsson JK, Tragante V, Steinthorsdottir V, Styrkarsdottir U, Stacey SN, Gudmundsson J, Arnadottir GA, Oddsson A, Zink F, Halldorsson G, Sveinbjornsson G, Kristjansson RP, Davidsson OB, Salvarsdottir A,

635 Thoroddsen A, Helgadottir EA, Kristjansdottir K, Ingthorsson O, Gudmundsson V, Geirsson RT,
636 Arnadottir R, Gudbjartsson DF, Masson G, Asselbergs FW, Jonasson JG, Olafsson K, Thorsteinsdottir
637 U, Halldorsson BV, Thorleifsson G, Stefansson K (2018) Variants associating with uterine leiomyoma
638 highlight genetic background shared by various cancers and hormone-related traits. *Nat Commun* **9**,
639 3636.

640

641

642

643 **Table 1. List of all cancer GWAS studies selected for Mendelian randomization analysis**

Trait	Study	Initial sample size		Replication sample size		Power
		Cases	Controls	Cases	Controls	
Breast cancer	Michailidou et al., 2017[18]	76,192	63,082	46,785	70,064	100.00%
Chronic lymphocytic leukemia	Law et al., 2017[43]	4,478	13,213	1,722	4,385	80.70%
Colorectal cancer	Law et al., 2019[44]	31,197	61,770	-	-	38%
Cutaneous squamous cell carcinoma	Chahal et al., 2016[45]	6579	280,558	825	11,518	74.50%
Combined analysis of keratinocyte cancers	Liyanage et al., 2019[17]	31,787	619,351	-	-	63.00%
Endometrial cancer	O'Mara et al., 2018[20]	12,906	108,979	-	-	71.50%
Lung cancer	McKay et al., 2017[46]	23,223	16,964	-	-	71.50%
Lymphoma	Sud et al., 2017[47]	1,278	14,325	1,586	3,069	90.60%
Melanoma	Landi et al., 2020[16]	36,760	375,188	-	-	68.30%
Non-glioblastoma glioma/Glioma	Melin et al., 2017[48]	12,469	18,190	-	-	93.10%
Oral cavity and pharyngeal cancer	Lesseur et al., 2016[49]	6,009	6,585	-	-	95.60%
Pancreatic cancer	Klein et al., 2018[50]	9,040	12,496	2,737	4,752	82.80%
Prostate cancer	Schumacher et al., 2018[19]	79,148	61,106	-	-	57.00%
Renal cell carcinoma	Scelo et al., 2015[51]	10,784	20,406	3,182	6,301	71.50%
Uterine fibroids	Rafnar et al., 2018[52]	16,595	52,3330	-	-	64.90%

644

645

Table 2. MR analysis between exposure (cancers) and outcome (PD).

Exposure	N, SNPs included	r^2	F-statistics	MR Egger			Inverse variance weighted		
				b	se	pval	b	se	pval
Breast cancer	107	0.016	38.5	0.075	0.065	0.247	0.032	0.033	0.337
Chronic lymphocytic leukemia	7	0.035	106.11	0.047	0.640	0.944	0.099	0.077	0.197
Colorectal cancer	35	0.02	53.8	-0.002	0.273	0.994	0.042	0.057	0.460
Cutaneous squamous cell carcinoma	23	0.03	405.2	-0.097	0.077	0.223	0.051	0.048	0.288
Combined analysis of keratinocyte cancers	68	0.023	216.6	-0.018	0.053	0.732	0.017	0.031	0.586
Endometrial cancer	13	0.028	271.4	-0.106	0.252	0.681	-0.014	0.059	0.808
Lung cancer	10	0.029	120.4	0.000	0.121	0.999	0.049	0.053	0.355
Lymphoma	5	0.047	236.2	0.325	0.288	0.341	-0.013	0.068	0.845
Melanoma	45	0.026	244.37	-0.035	0.053	0.507	-0.002	0.032	0.950
Non-glioblastoma glioma/Glioma	19	0.052	88.03	0.102	0.049	0.052	-0.021	0.023	0.356
Oral cavity and pharyngeal cancer	4	0.059	198.2	0.008	0.376	0.986	0.094	0.064	0.144
Pancreatic cancer	16	0.037	68.9	-0.221	0.152	0.168	0.003	0.041	0.934
Prostate cancer	74	0.02	38.9	-0.091	0.060	0.130	-0.022	0.028	0.443
Renal cell carcinoma	8	0.028	148.02	-0.145	0.241	0.569	-0.031	0.084	0.707
Uterine fibroids	18	0.024	732.5	0.164	0.185	0.388	-0.014	0.073	0.854

PD, Parkinson's disease; N, number; r^2, proportion of variance in exposure variable explained by SNPs; F, statistics 'strength' of the genetic instrumental variable; b, beta; se, standard error, pval, p-value.

Suplementary Table 1. MR analysis between exposure (cancers) and outcome (PD)

Exposure	N, SNPs	R2	F-statistics	MR Egger			Inverse variance weighted			Simple mode			Weighted mode		
				b	se	pval	b	se	pval	b	se	pval	b	se	pval
Breast cancer	107	0.016	38.5	0.08	0.06	0.25	0.03	0.03	0.34	-0.01	0.13	0.92	0.01	0.07	0.84
Chronic lymphocytic leukemia	7	0.035	106.11	0.05	0.64	0.94	0.10	0.08	0.20	-0.03	0.15	0.87	-0.03	0.12	0.83
Colorectal cancer	35	0.02	53.8	0.00	0.27	0.99	0.04	0.06	0.46	-0.13	0.19	0.51	-0.16	0.18	0.37
Cutaneous squamous cell carcinoma	23	0.03	405.2	-0.10	0.08	0.22	0.05	0.05	0.29	0.19	0.11	0.09	0.00	0.06	0.99
Combined analysis of keratinocyte cancers	68	0.023	216.6	-0.02	0.05	0.73	0.02	0.03	0.59	-0.02	0.08	0.78	0.00	0.04	1.00
Endometrial cancer	13	0.028	271.4	-0.11	0.25	0.68	-0.01	0.06	0.81	-0.04	0.12	0.73	0.04	0.11	0.73
Lung cancer	10	0.029	120.4	0.00	0.12	1.00	0.05	0.05	0.36	0.04	0.12	0.74	0.08	0.08	0.35
Lymphoma	5	0.047	236.2	0.33	0.29	0.34	-0.01	0.07	0.85	-0.02	0.11	0.85	-0.03	0.10	0.79
Melanoma	45	0.026	244.37	-0.04	0.05	0.51	0.00	0.03	0.95	-0.07	0.09	0.40	-0.05	0.04	0.31
Non-glioblastoma glioma/Glioma	19	0.052	88.03	0.10	0.05	0.05	-0.02	0.02	0.36	-0.05	0.06	0.43	-0.02	0.04	0.57
Oral cavity and pharyngeal cancer	4	0.059	198.2	0.01	0.38	0.99	0.09	0.06	0.14	0.18	0.12	0.22	0.17	0.11	0.22
Pancreatic cancer	16	0.037	68.9	-0.22	0.15	0.17	0.00	0.04	0.93	-0.02	0.10	0.88	0.02	0.08	0.82
Prostate cancer	74	0.02	38.9	-0.09	0.06	0.13	-0.02	0.03	0.44	-0.07	0.08	0.36	0.00	0.05	0.94
Renal cell carcinoma	8	0.028	148.02	-0.15	0.24	0.57	-0.03	0.08	0.71	0.12	0.18	0.52	0.13	0.13	0.34
Uterine fibroids	18	0.024	732.5	0.16	0.19	0.39	-0.01	0.07	0.85	0.12	0.19	0.54	0.15	0.15	0.34

R2- proportion of variance in exposure variable explained by SNPs; F-statistics ‘strength’ of the genetic instrumenral variable b- beta; se- standart error, pval - p-value

Supplementary Table 2. Heterogeneity tests and tests for directional horizontal pleiotropy between Cancers and PD

	Heterogeneity tests						Test for directional horizontal pleiotropy				
	MR Egger			Inverse variance weighted			egger intercept	se	pval	MR-PRESSO global	MR-PRESSO distortion test
Exposure	Q	Q_df	Q_pval	Q	Q_df	Q_pval				pval	pval
Breast cancer	115.83	105	0.22	116.51	106	0.23	0.00	0.01	0.43	0.18	NA
Chronic lymphocytic leukemia	8.09	5	0.15	8.10	6	0.23	0.01	0.10	0.94	0.25	NA
Colorectal cancer	34.79	33	0.38	34.82	34	0.43	0.00	0.02	0.87	0.37	NA
Cutaneous squamous cell carcinoma	29.94	21	0.09	37.73	22	0.02	0.03	0.01	0.03	0.01	0.14
Combined analysis of keratinocyte cancers	94.79	66	0.01	95.76	67	0.01	0.01	0.01	0.41	0.01	NA
Endometrial cancer	5.50	11	0.91	5.64	12	0.93	0.01	0.03	0.72	0.94	NA
Lung cancer	8.34	8	0.40	8.56	9	0.48	0.01	0.02	0.66	0.43	NA
Lymphoma	3.23	3	0.36	4.79	4	0.31	-0.08	0.07	0.32	0.39	NA
Melanoma	54.34	43	0.12	55.13	44	0.12	0.01	0.01	0.43	0.11	NA
Non-glioblastoma glioma/Glioma	9.37	17	0.93	17.57	18	0.49	-0.04	0.01	0.01	0.30	NA
Oral cavity and pharyngeal cancer	4.48	2	0.11	4.60	3	0.20	0.02	0.09	0.84	0.02	NA
Pancreatic cancer	11.44	14	0.65	13.78	15	0.54	0.04	0.03	0.15	0.50	NA
Prostate cancer	57.22	70	0.86	58.98	71	0.85	0.01	0.01	0.19	0.82	NA
Renal cell carcinoma	8.97	6	0.18	9.35	7	0.23	0.02	0.03	0.63	0.20	NA
Uterine fibroids	22.90	16	0.12	24.46	17	0.11	-0.02	0.02	0.31	0.12	NA

Q- Cochran's Q test, df- degrees of freedom, se- standart error, pval- p-value, NA for distortion test if non outliers were avaliable

Suplementary Table 3. Reverse MR analysis between exposure (Parkinson's disease) and outcome (cancers)

Outcome	N, SNPs	MR Egger			Weighted median			Inverse variance weighted			Simple mode			Weighted mode		
		b	se	pval	b	se	pval	b	se	pval	b	se	pval	b	se	pval
Breast cancer	15	0.01	0.06	0.82	0.02	0.02	0.38	0.04	0.02	0.08	-0.02	0.03	0.59	0.00	0.02	0.86
Endometrial cancer	15	-0.03	0.10	0.78	-0.04	0.04	0.31	-0.02	0.04	0.54	0.04	0.08	0.66	-0.04	0.06	0.47
Melanoma	14	0.00	0.06	0.99	-0.01	0.03	0.64	0.02	0.02	0.47	-0.01	0.05	0.81	-0.01	0.04	0.74
Prostate cancer	15	-0.08	0.05	0.13	0.00	0.02	0.88	0.02	0.02	0.40	0.00	0.04	0.99	0.00	0.03	0.98
Keratinocyte cancers	15	0.05	0.08	0.55	0.04	0.03	0.24	0.00	0.03	0.91	0.08	0.06	0.22	0.10	0.04	0.02

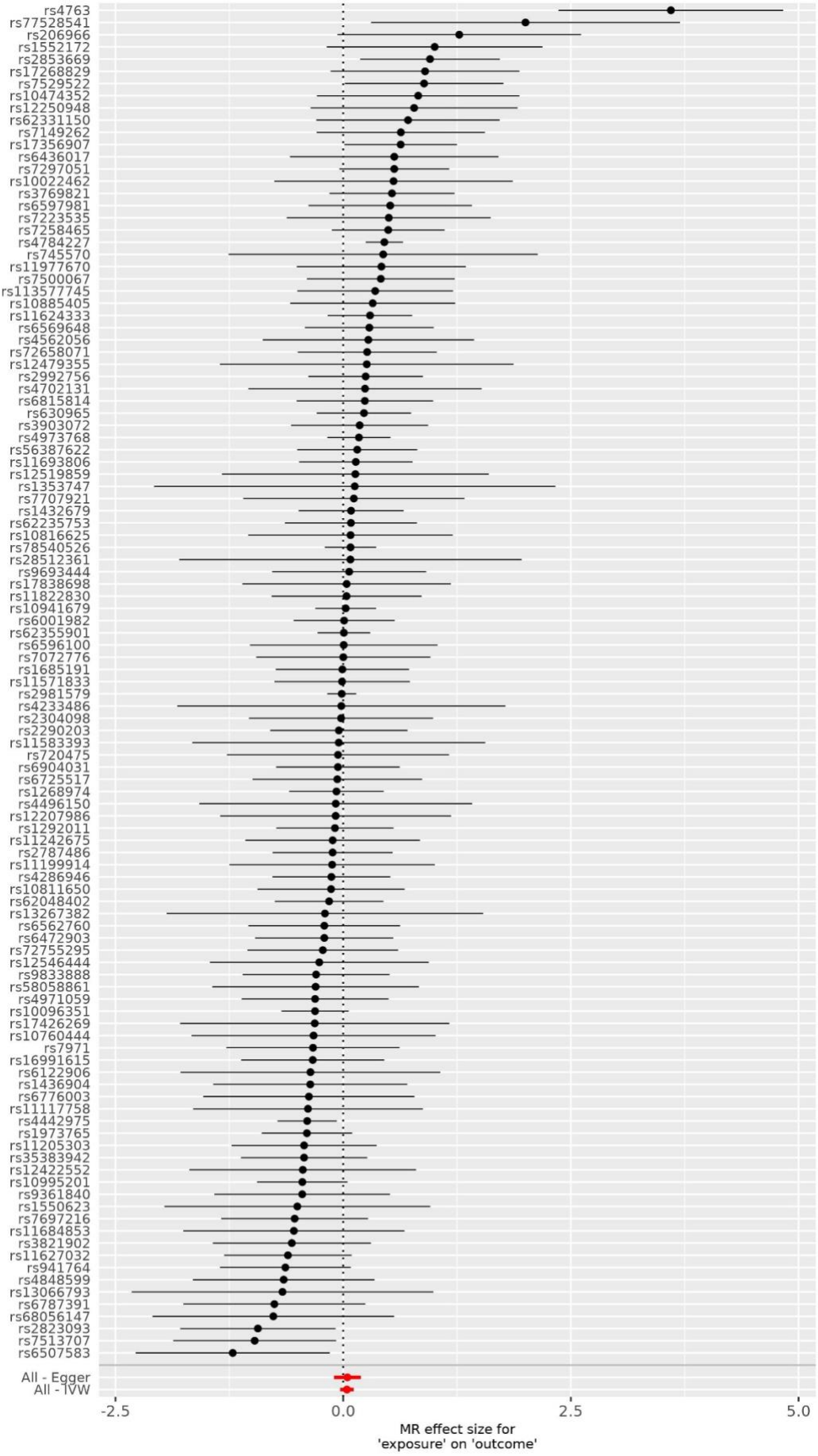
Outcome	N, SNPs	Heterogeneity tests						Test for directional horizontal pleiotropy				
		MR Egger			Inverse variance weighted						MR-PRESSO global	MR-PRESSO distortion test
		Q	Q_df	Q_pval	Q	Q_df	Q_pval	egger_intercept	se	pval	pval	pval
Breast cancer	15	49.72	13	0.00	50.38	14	0.00	0.00	0.01	0.68	<0.001	0.05
Endometrial cancer	15	21.80	13	0.06	21.81	14	0.08	0.00	0.02	0.95	0.07	NA
Melanoma	14	12.62	12	0.40	12.70	13	0.47	0.00	0.01	0.78	0.51	NA
Prostate cancer	15	20.29	13	0.09	27.29	14	0.02	0.02	0.01	0.05	0.02	0.22
Keratinocyte cancers	15	38.22	13	0.00	39.35	14	0.00	-0.01	0.01	0.55	<0.001	0.60

b- beta; se- standart error, pval - p-value

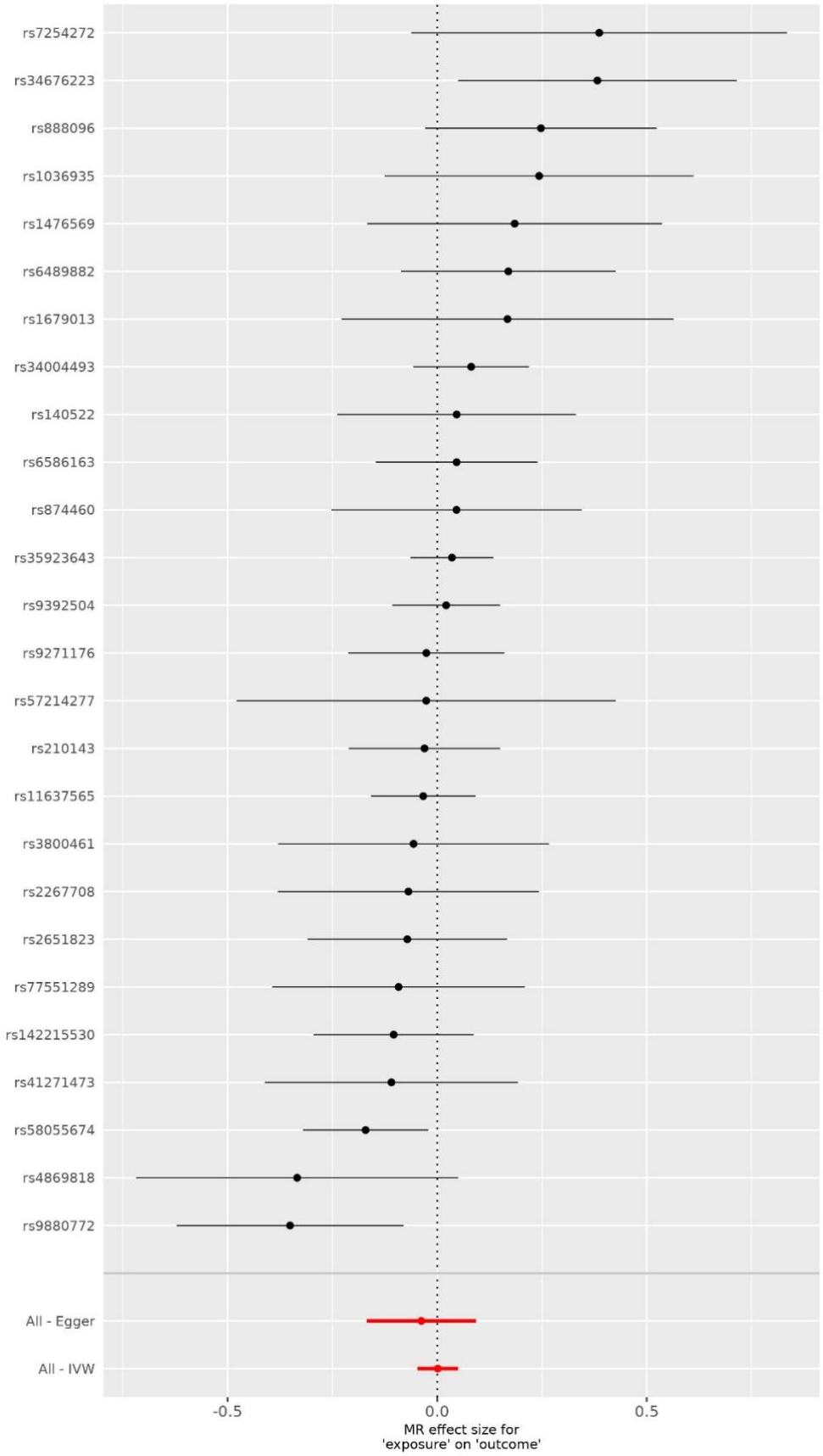
Supplementary Figure 1. Forest plots showing point estimates of the exposures of interest, Exposure of interest at the top of each forest plot.

Black points represent log-odds ratio of each SNP on the risk of PD. Red points represent the log-odds ration when combining all SNPs together (Inverse variance weighted and MR Egger methods). Lines from points represent 95% confidence intervals.

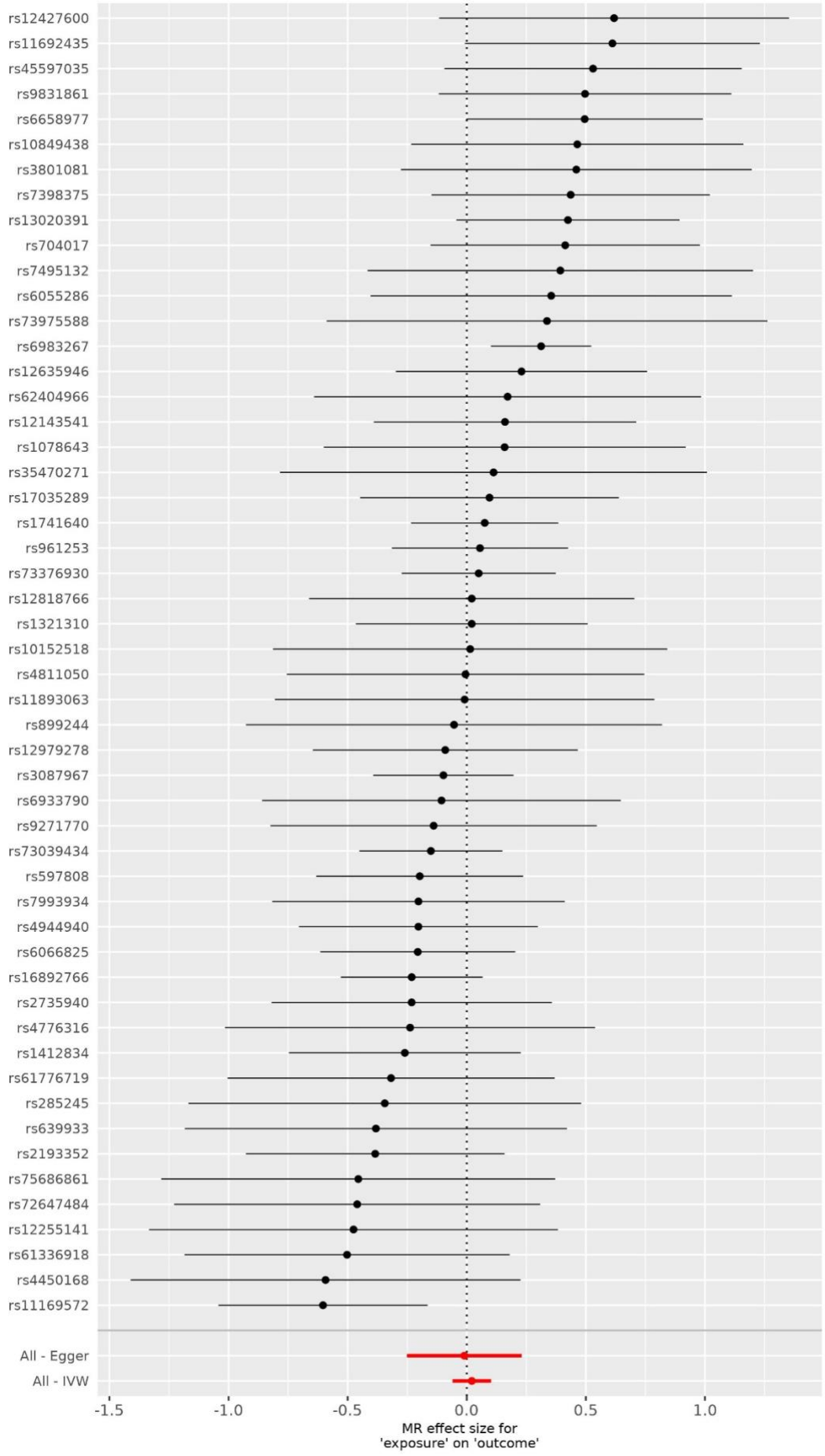
Breast cancer as exposure



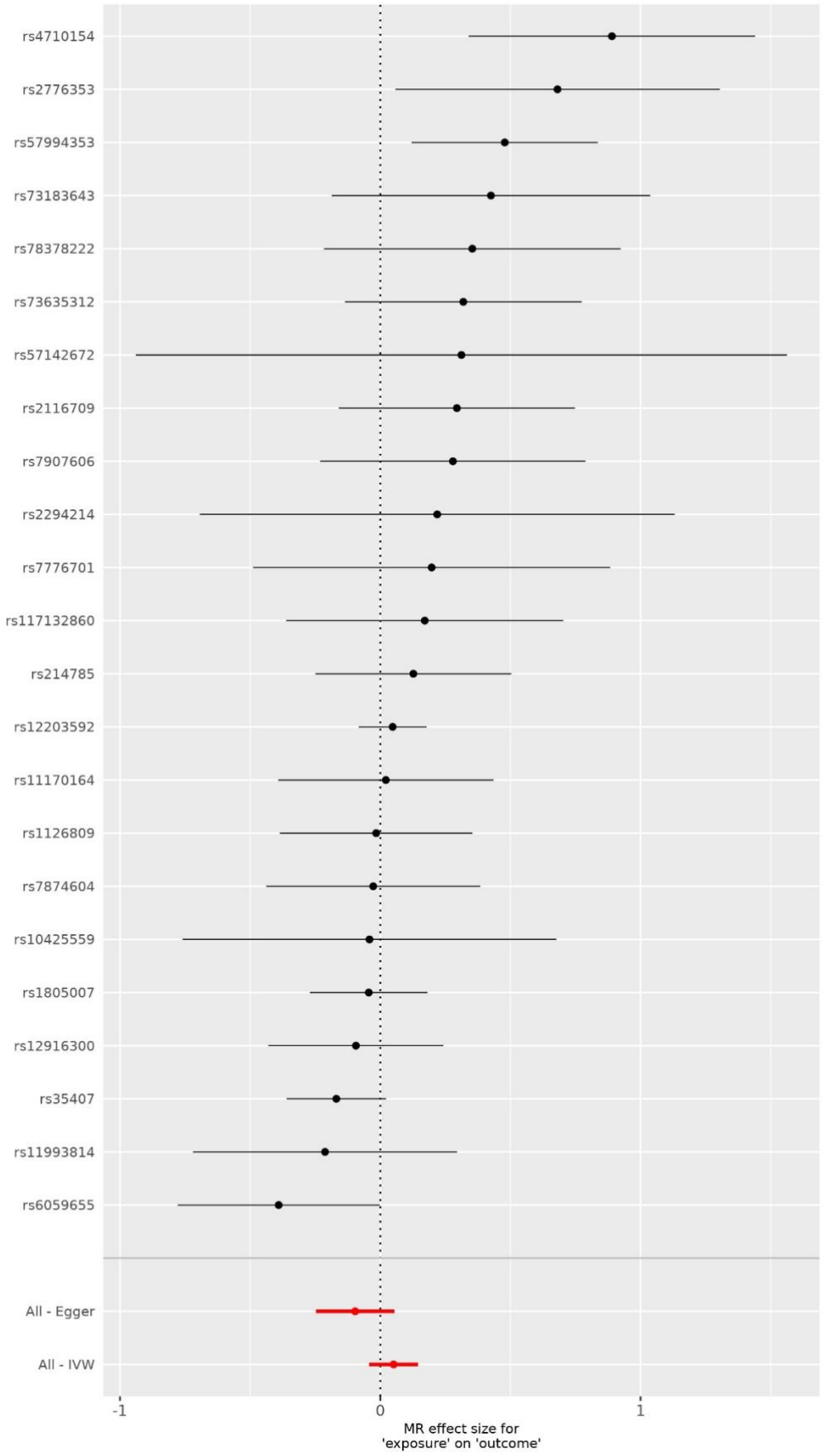
Chronic lymphocytic leukemia as exposure



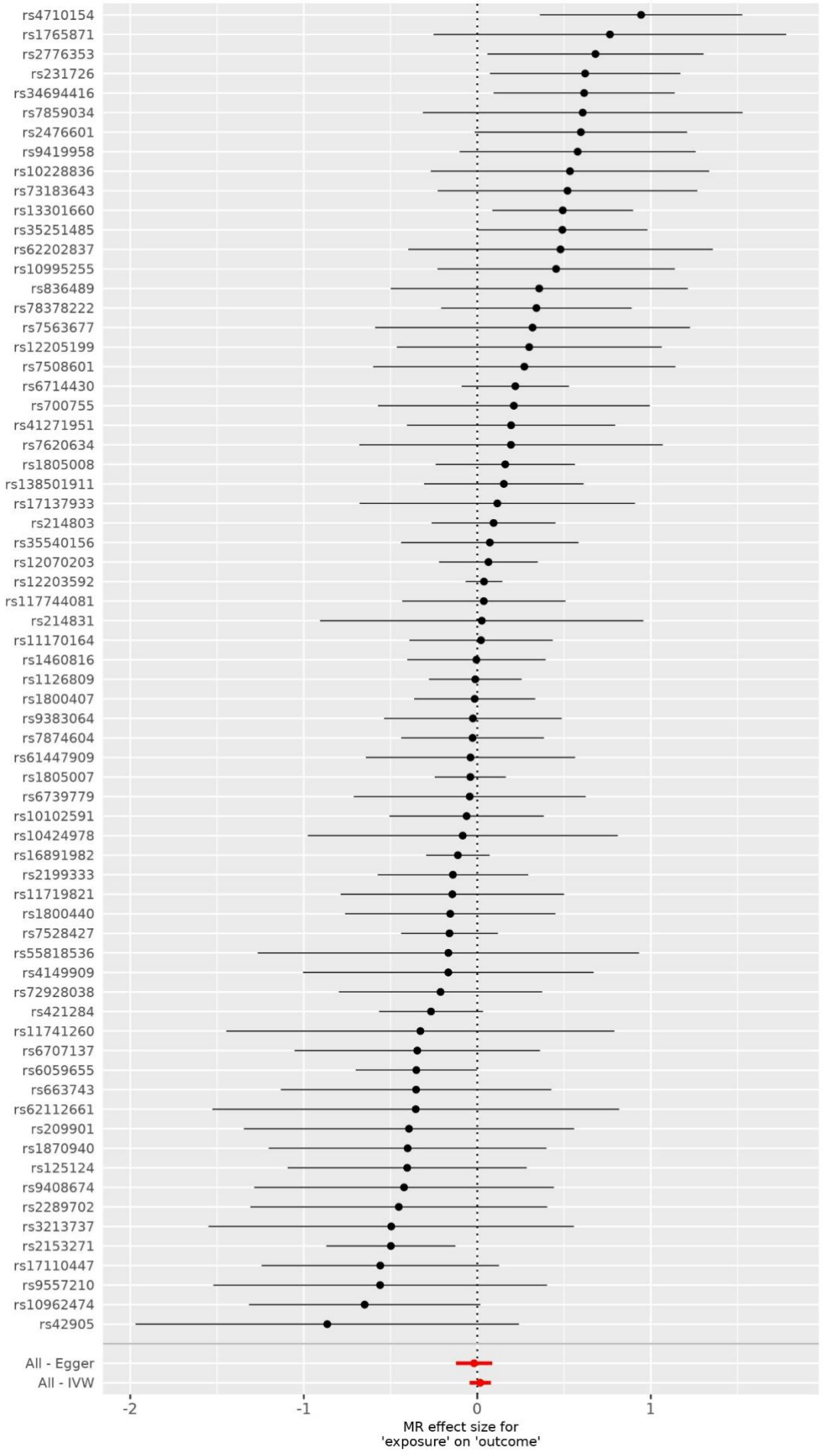
Colorectal cancer as exposure



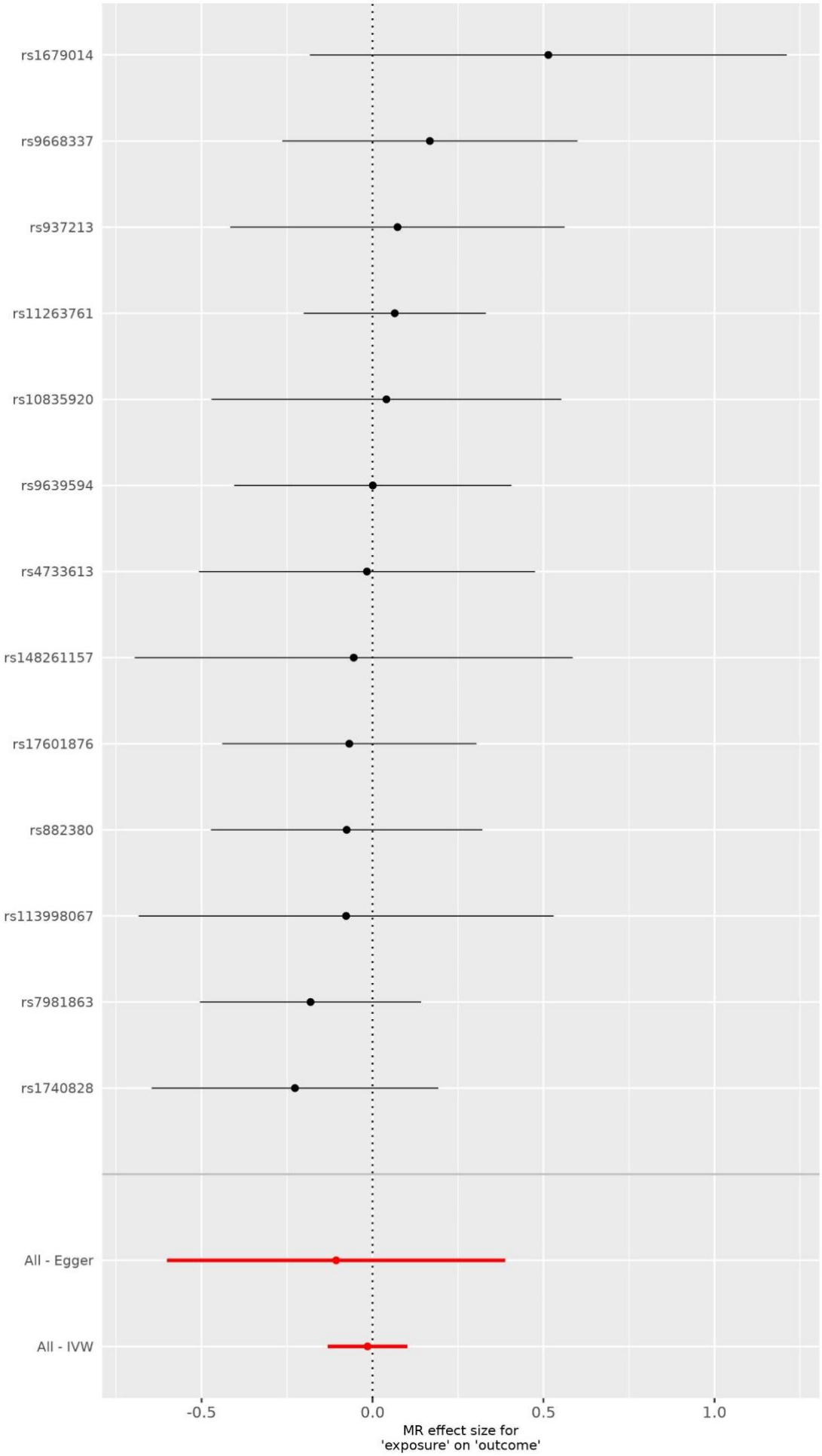
Cutaneous squamous cell carcinoma as exposure



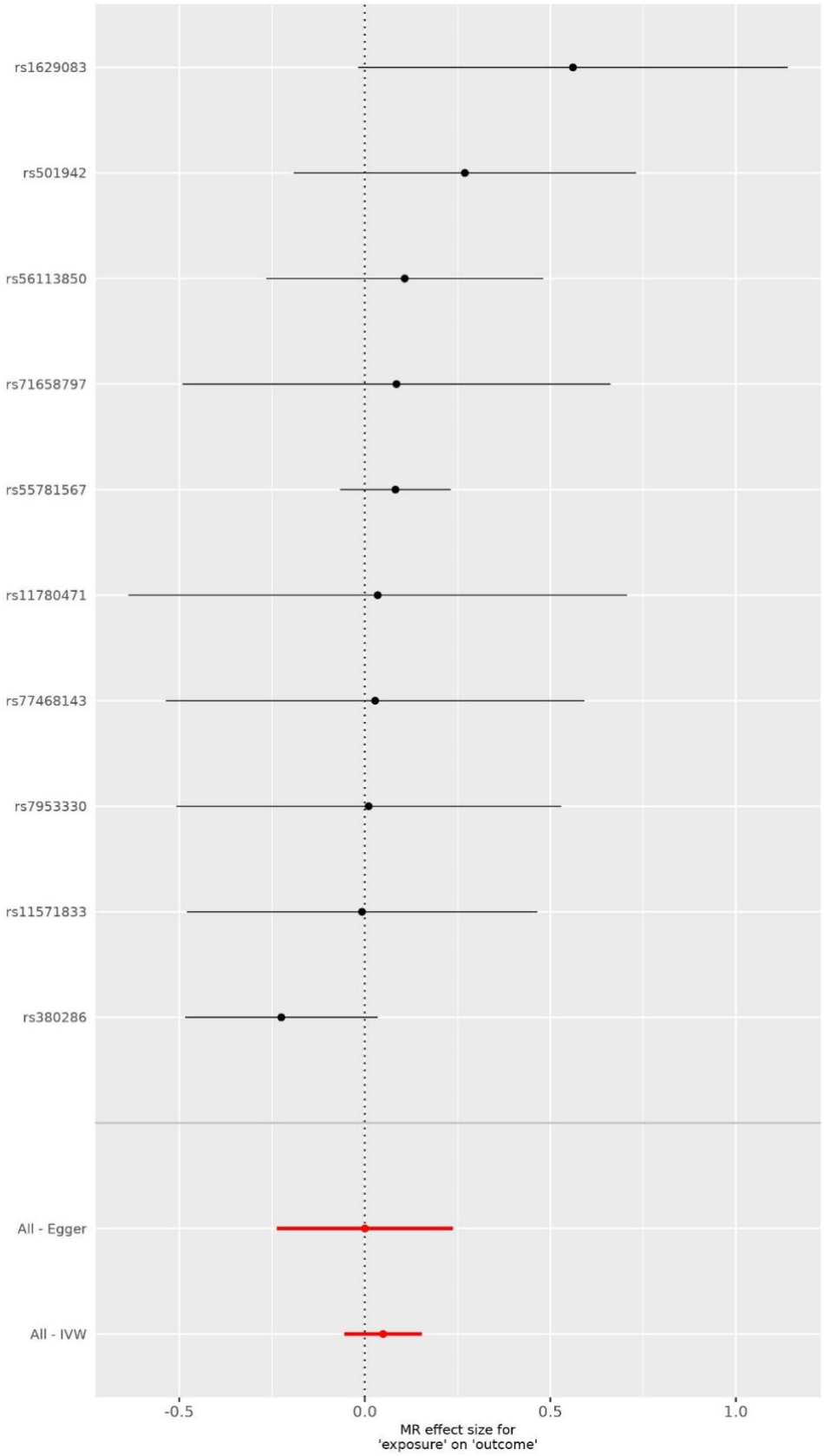
Combined analysis of keratinocyte cancers as exposure



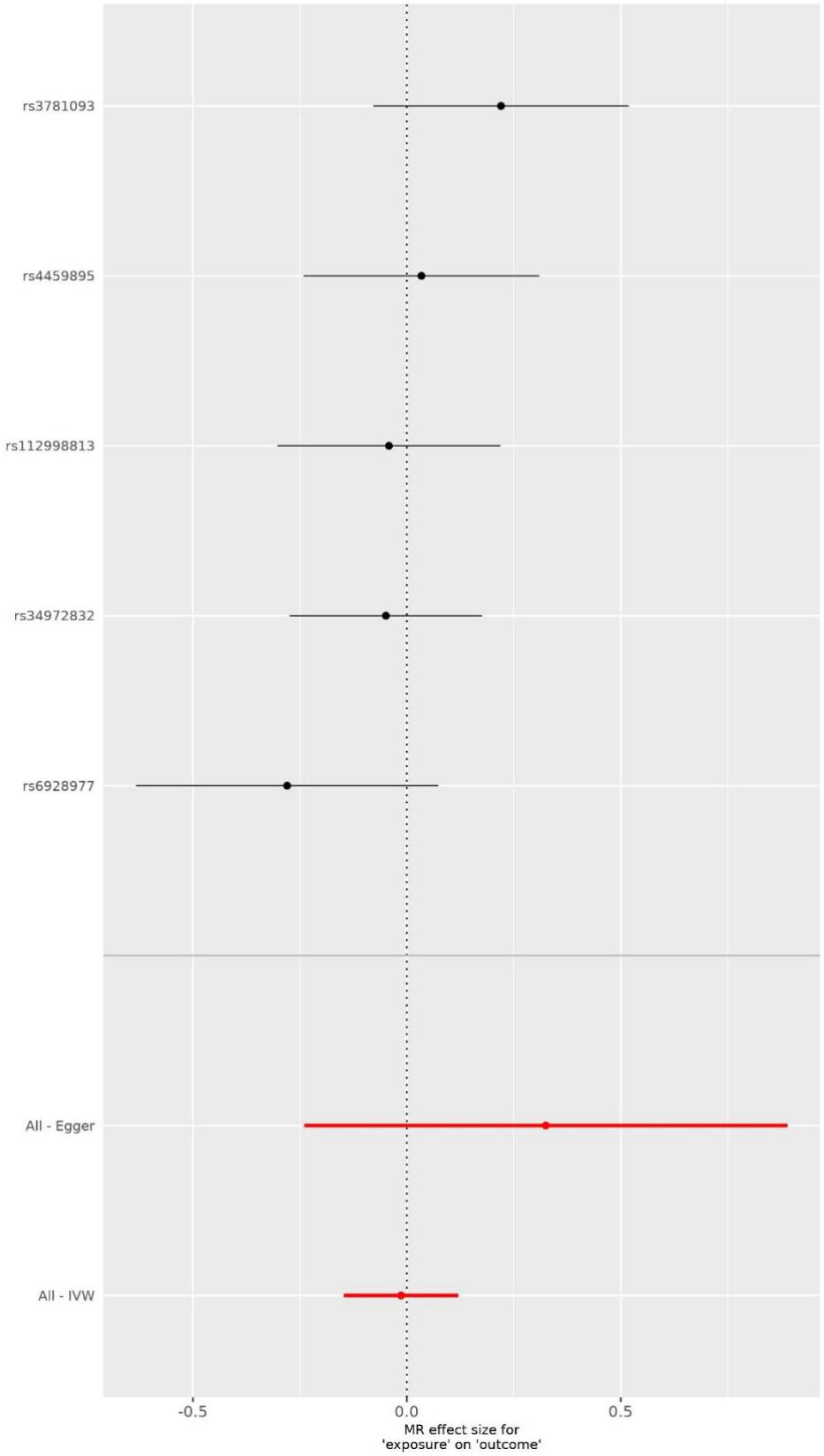
Endometrial cancer as exposure



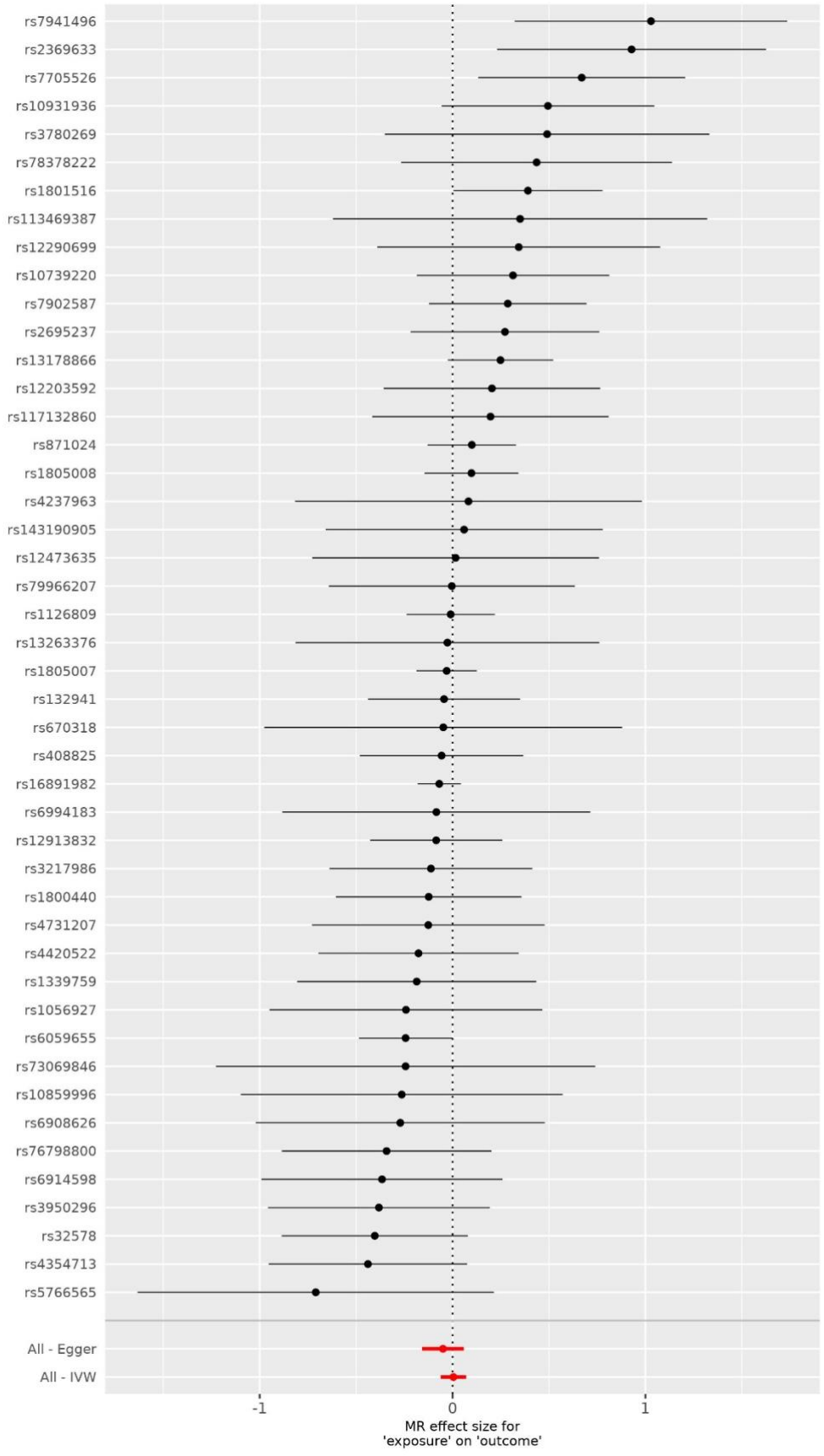
Lung cancer as exposure



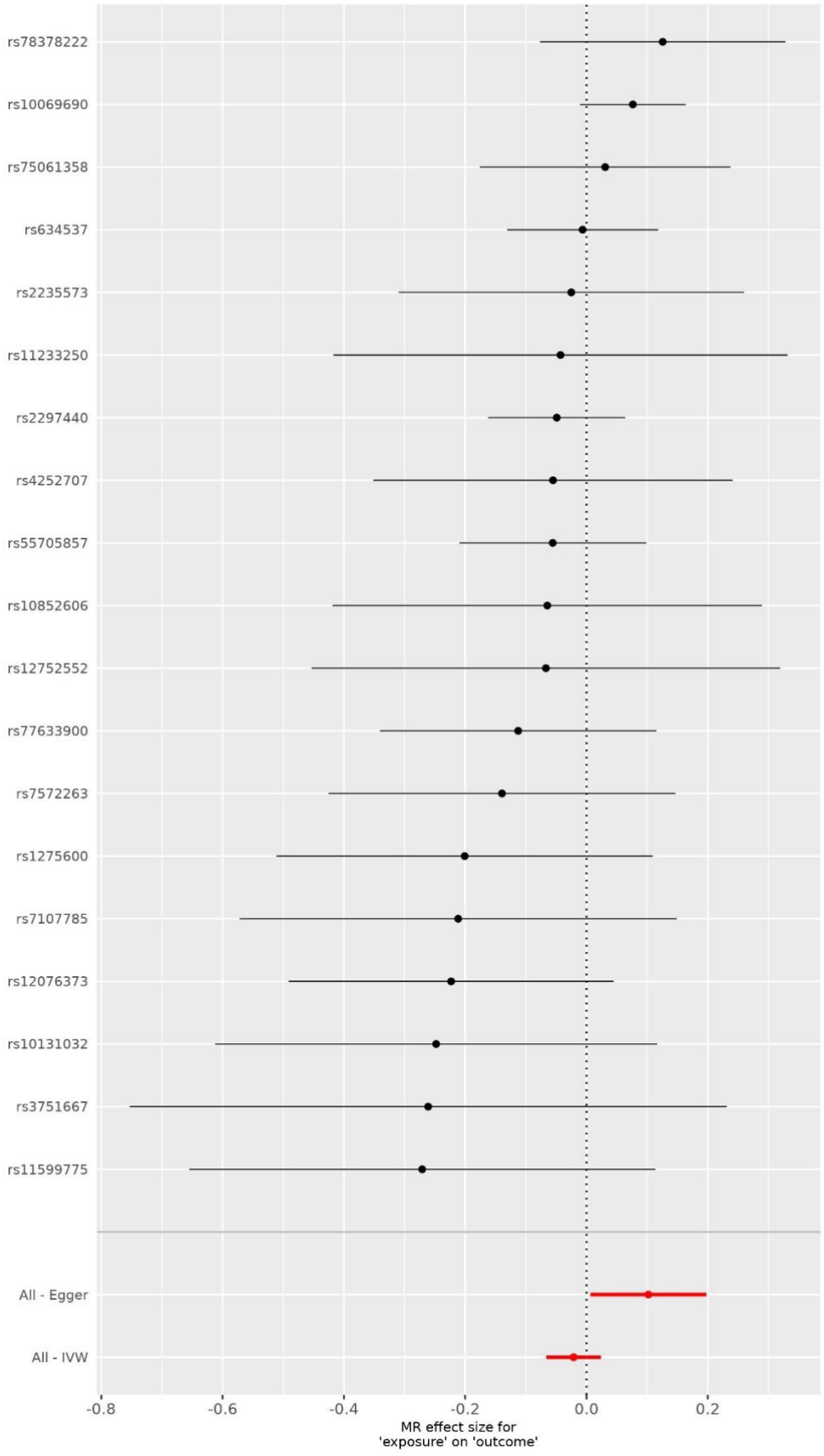
Lymphoma as exposure



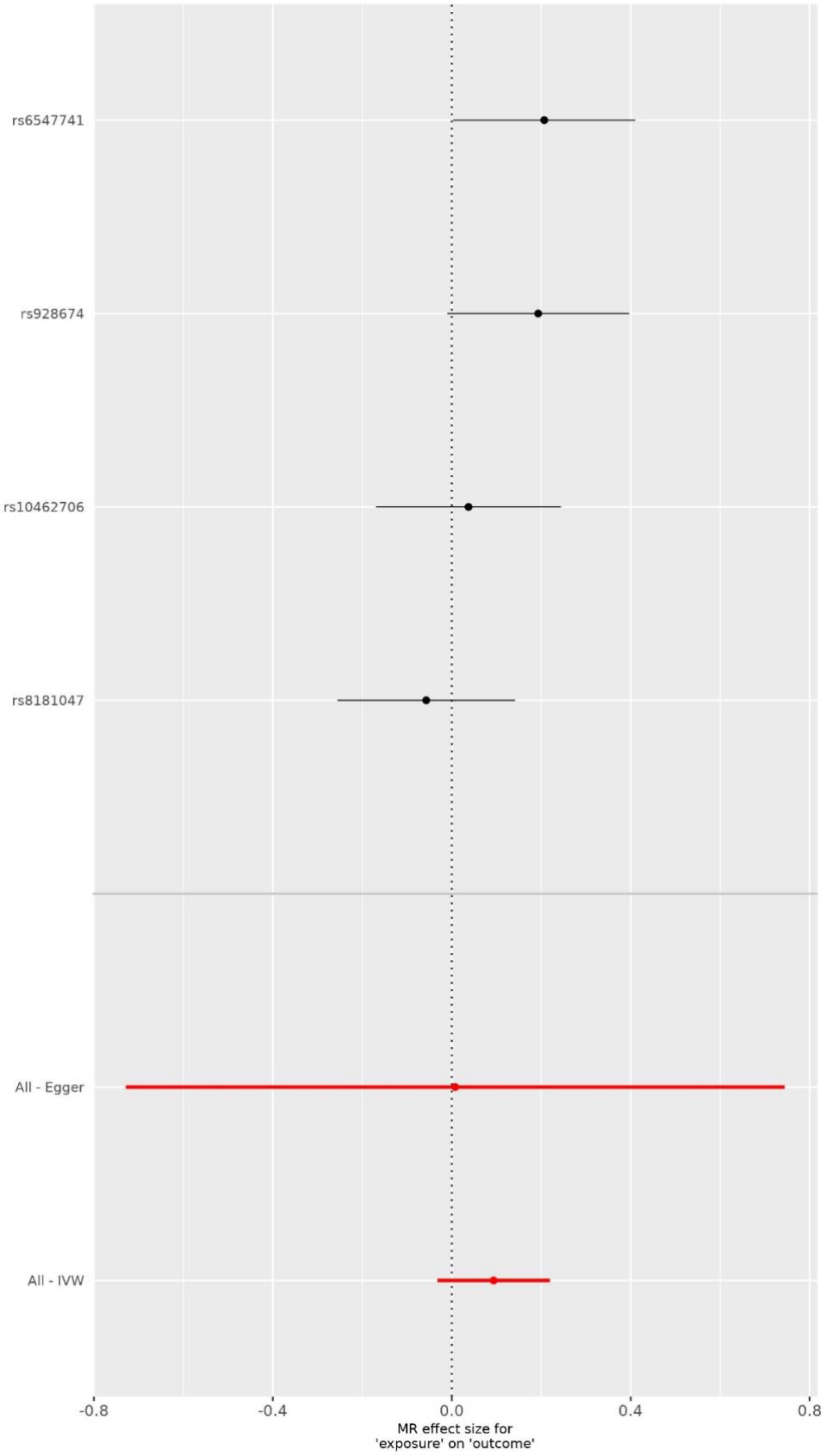
Melanoma as exposure



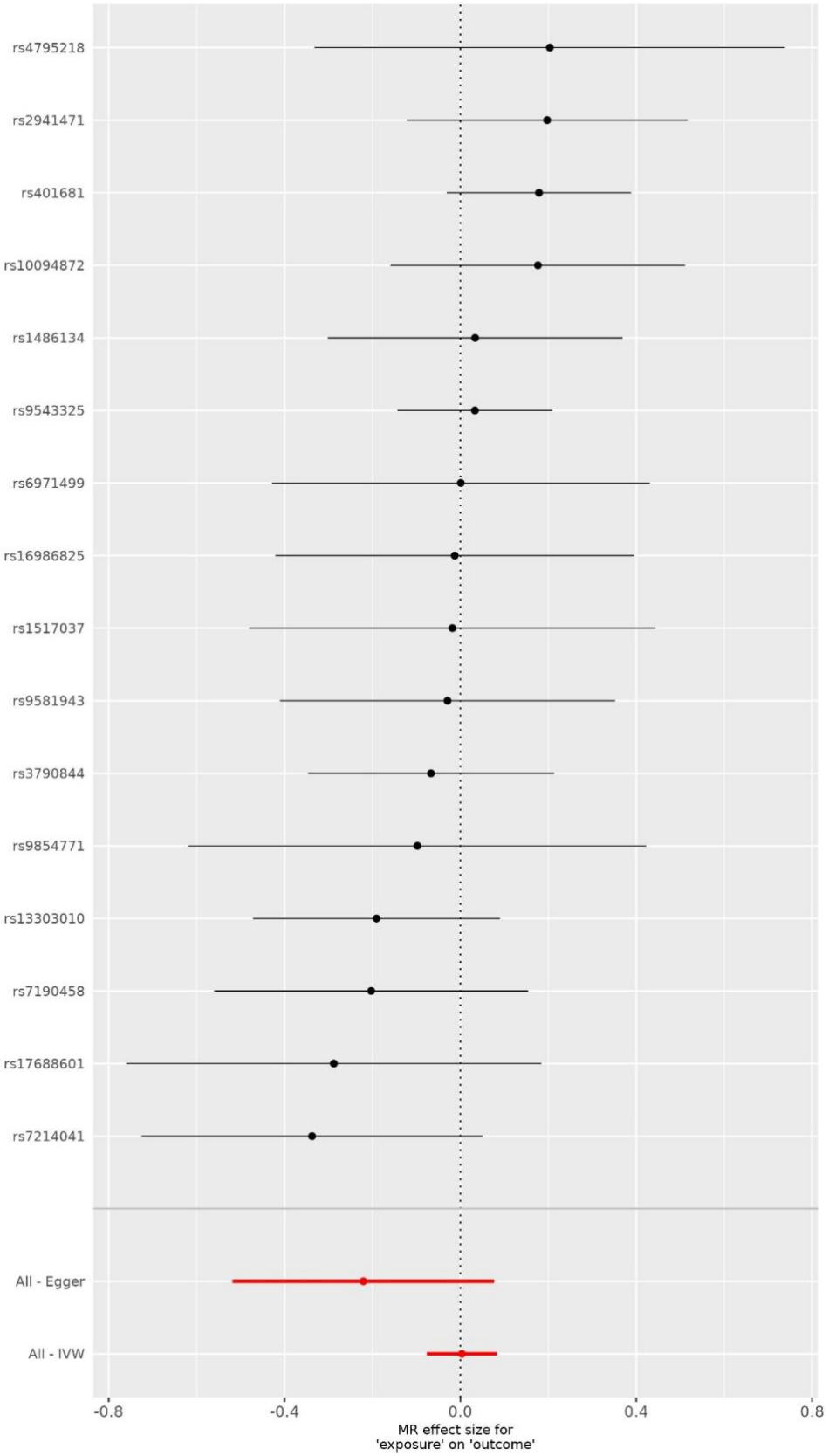
Non-glioblastoma glioma/glioma as exposure



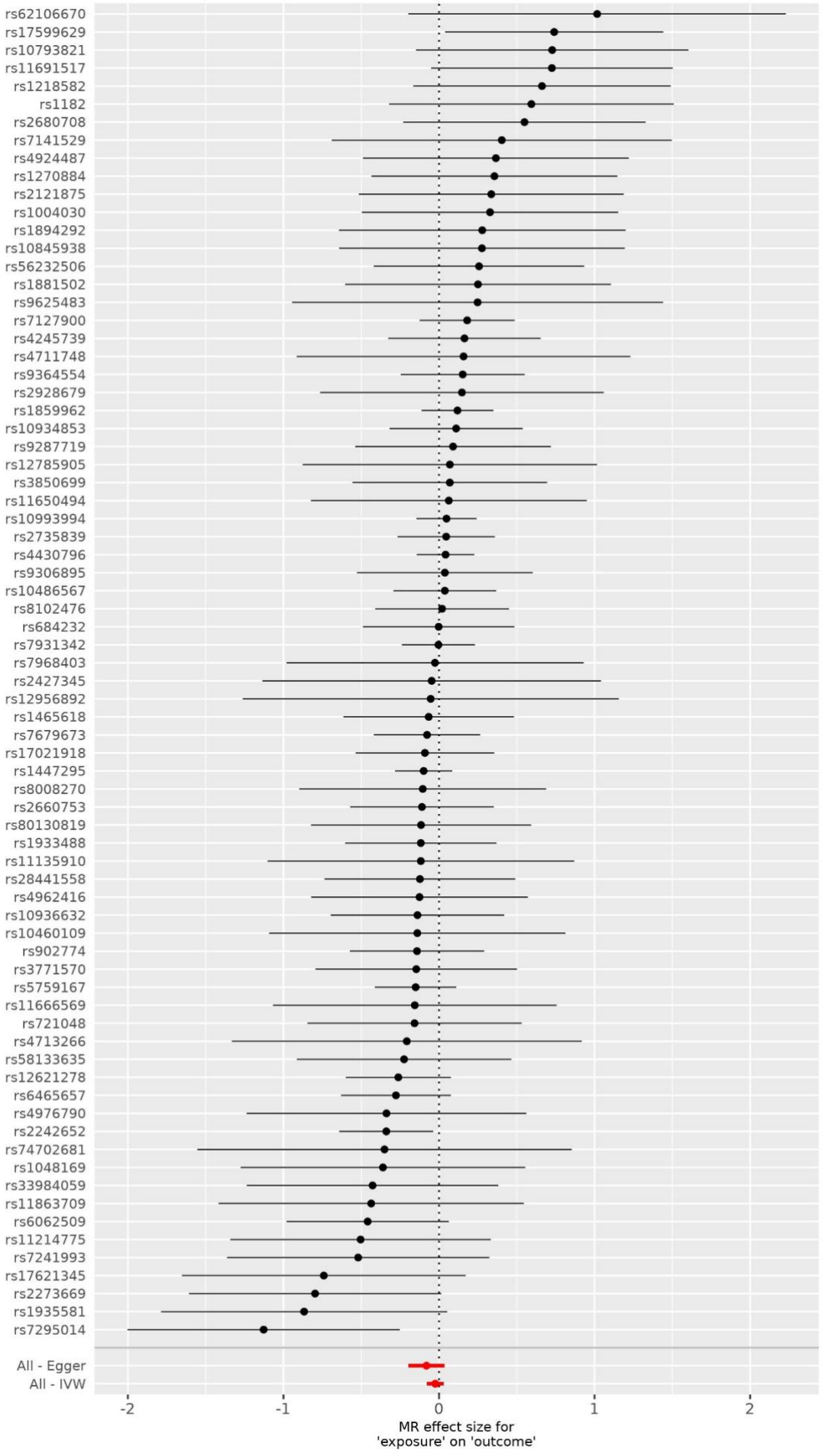
Oral cavity and pharyngeal cancer as exposure



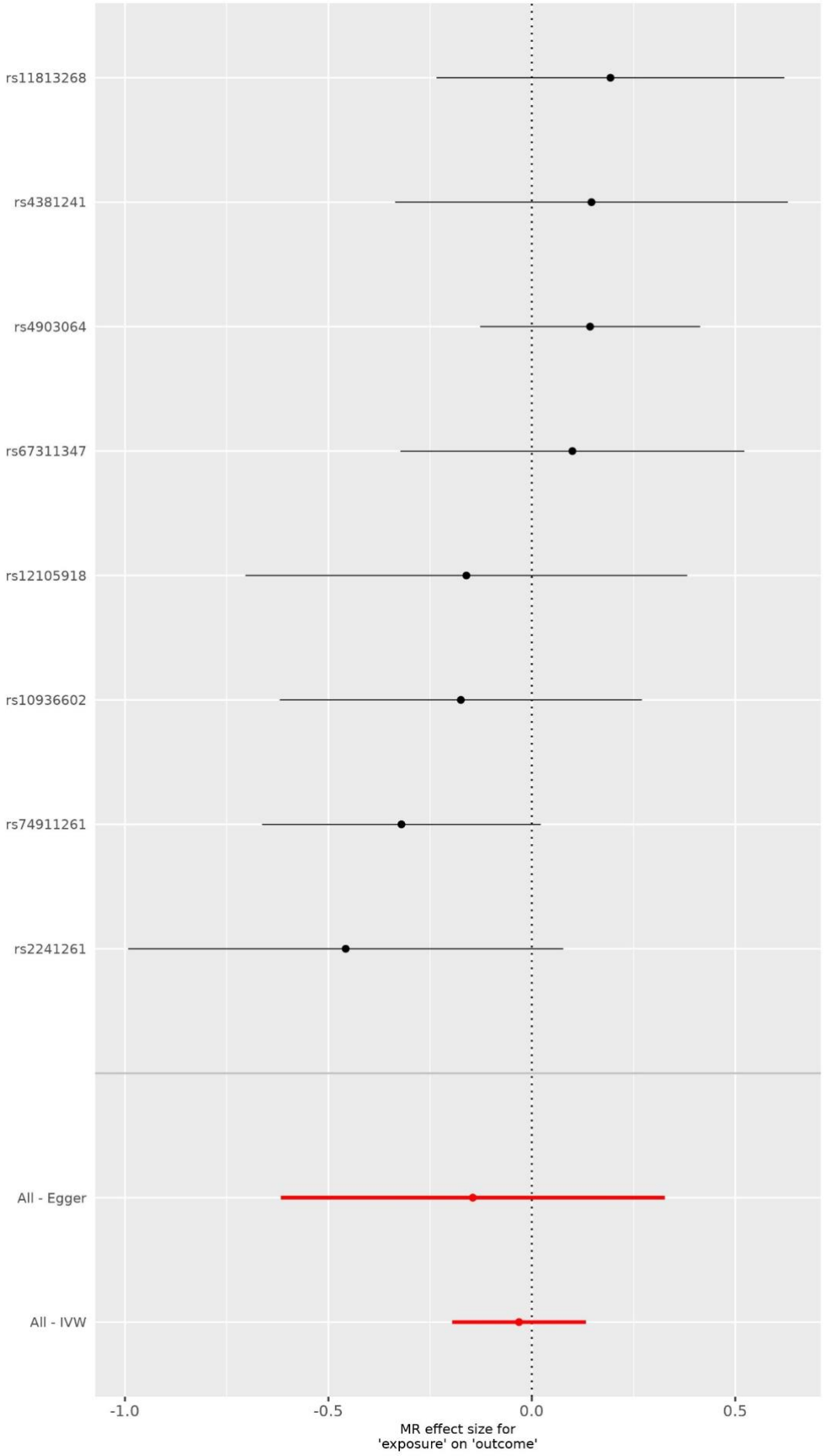
Pancreatic cancer



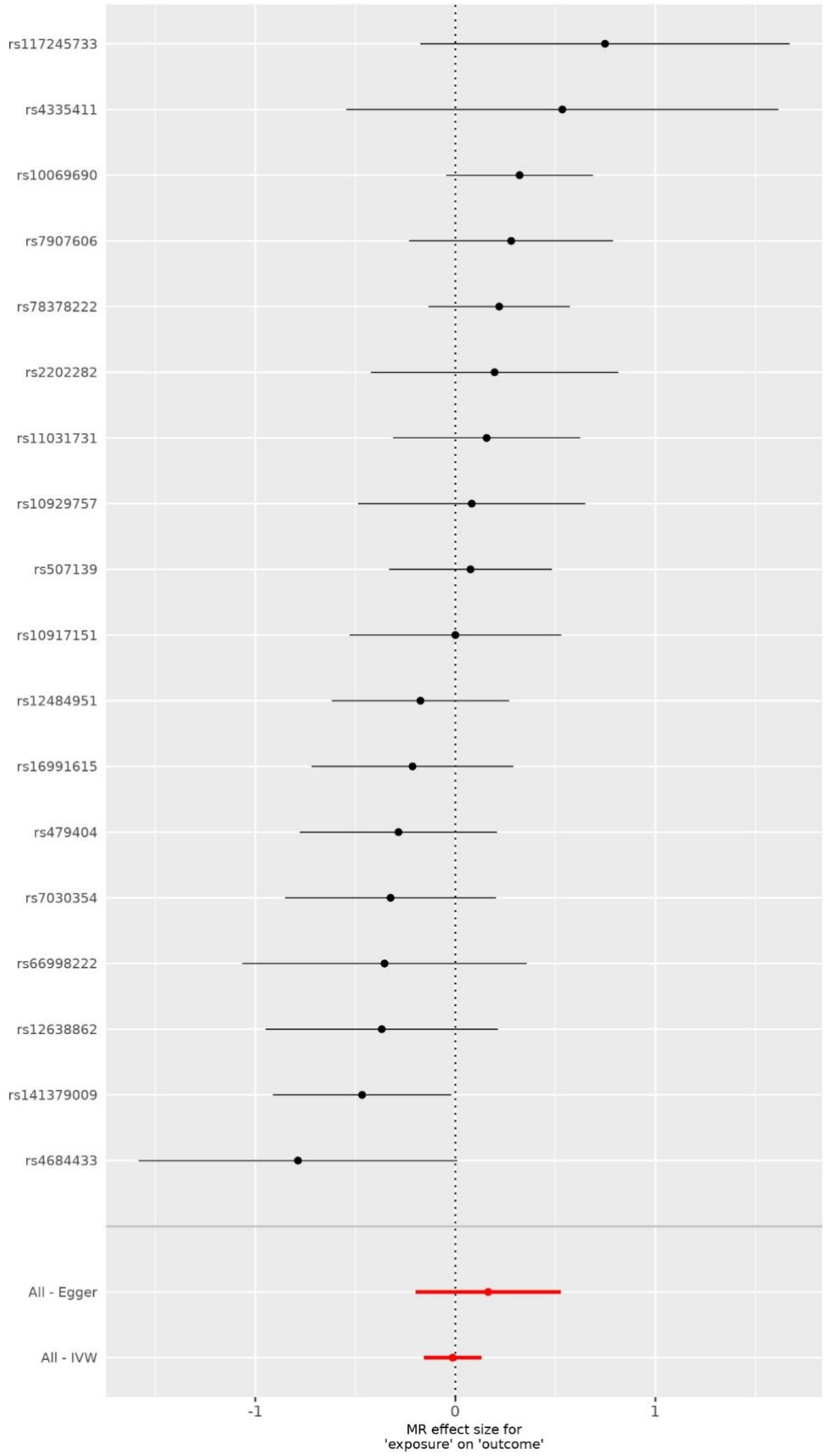
Prostate cancer



Renal cell carcinoma



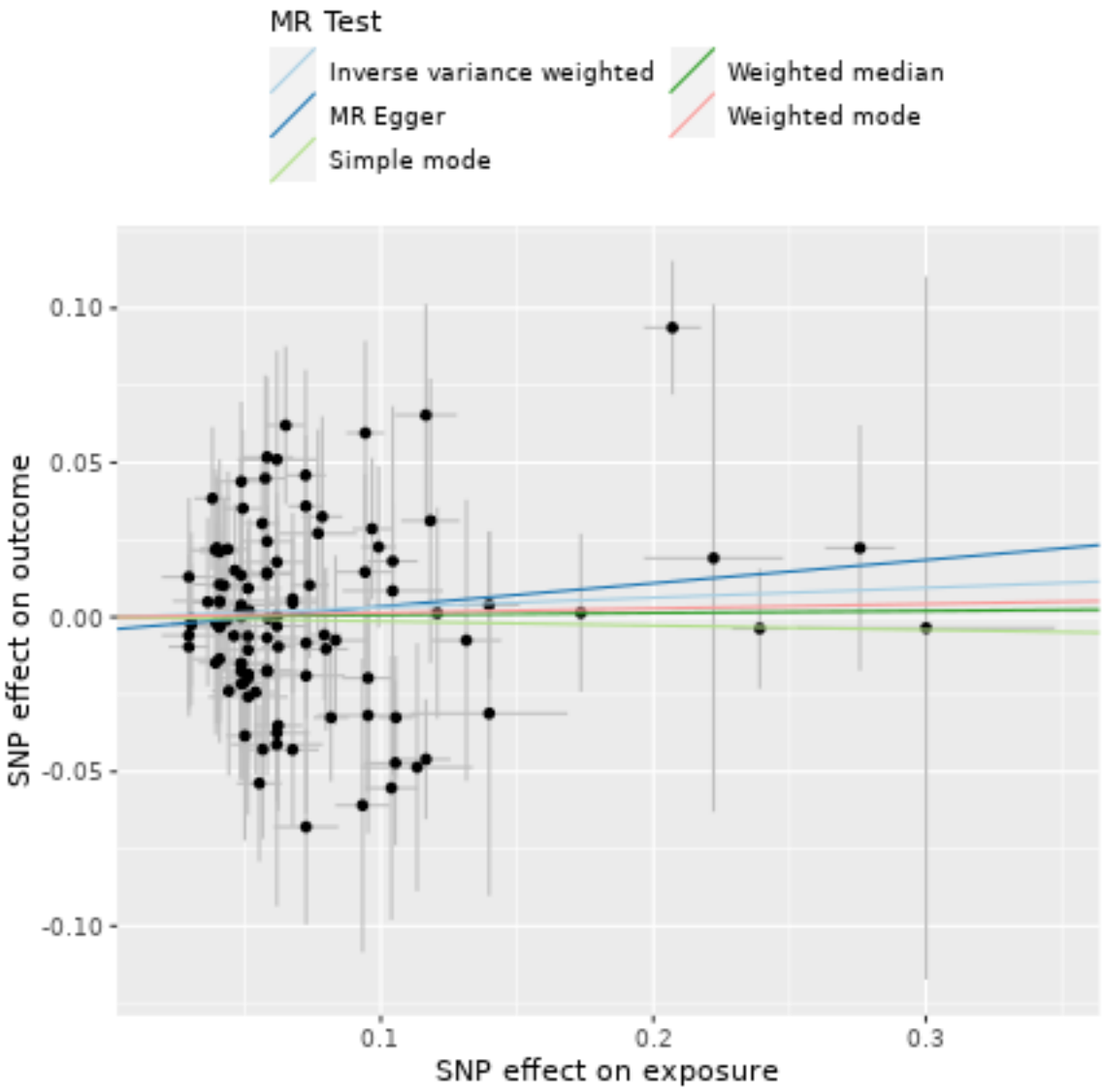
Uterine fibroids



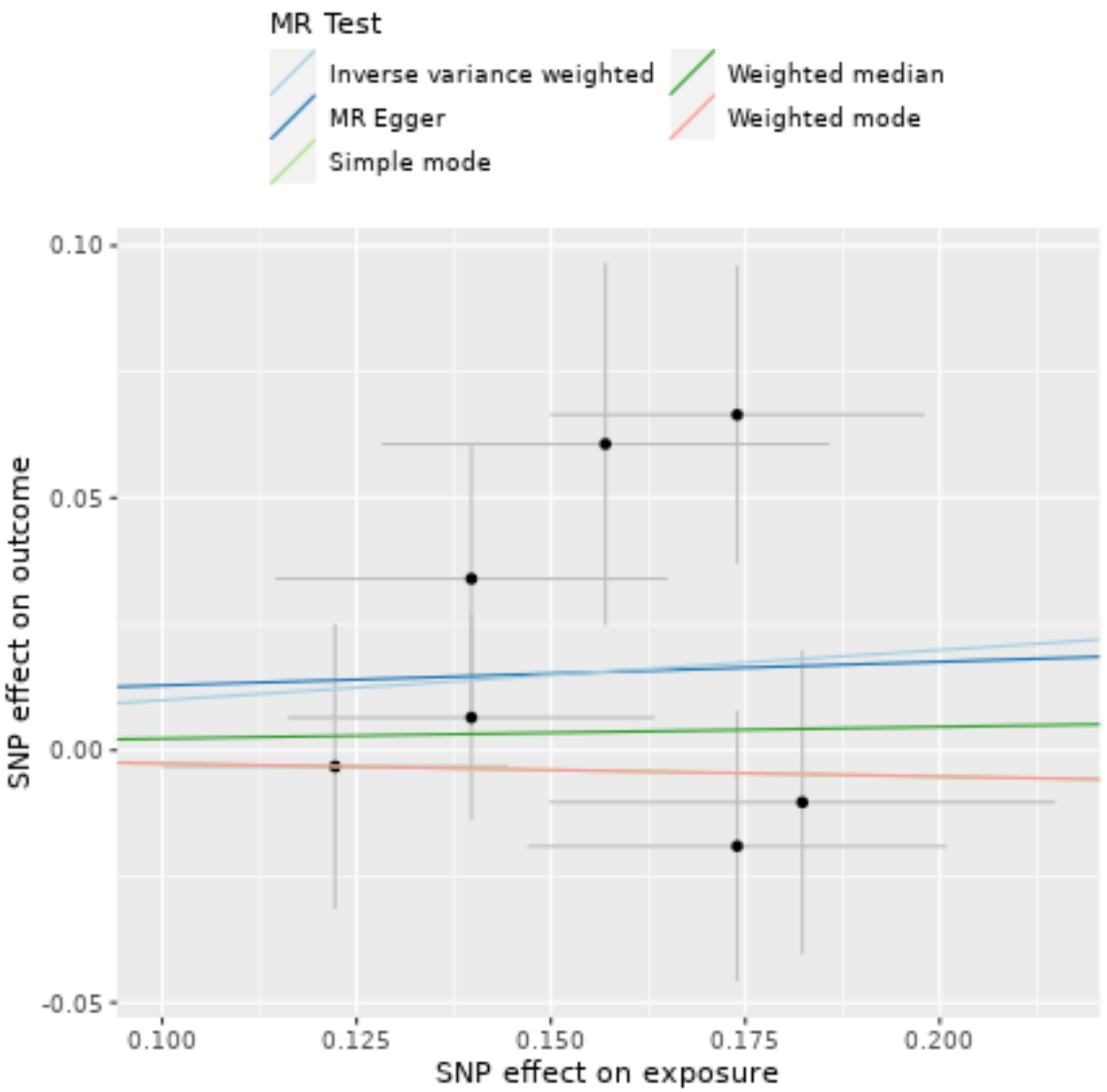
Supplementary Figure 2. PD without UKBB. Plots showing point estimates of the exposures of interest; Exposure of interest at the top of each plot.

A plot relating the effect sizes of the SNP-exposure association and the SNP-outcome associations with standard error bars. Lines correspond to causal estimates using each of the methods.

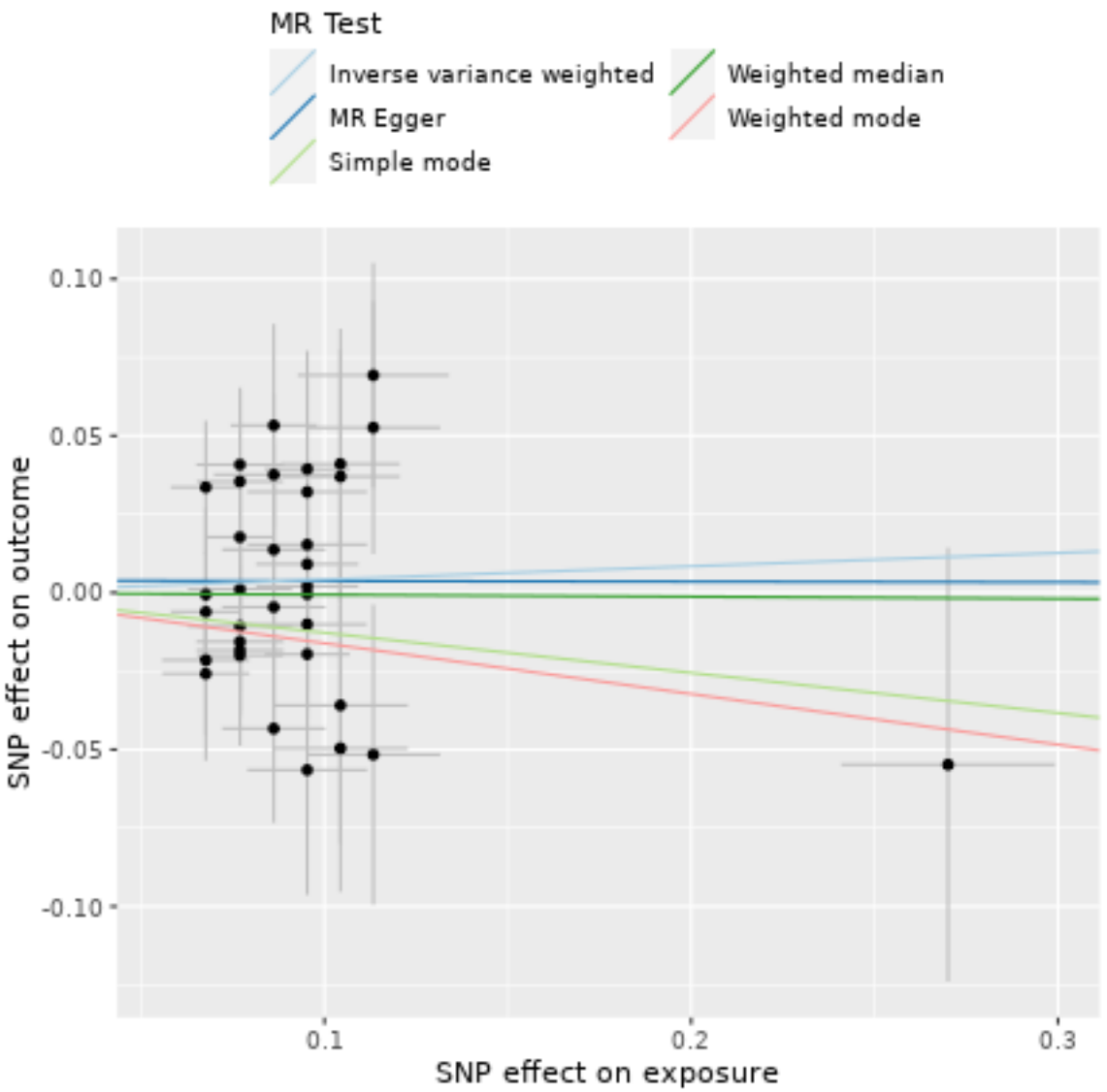
Breast cancer as exposure



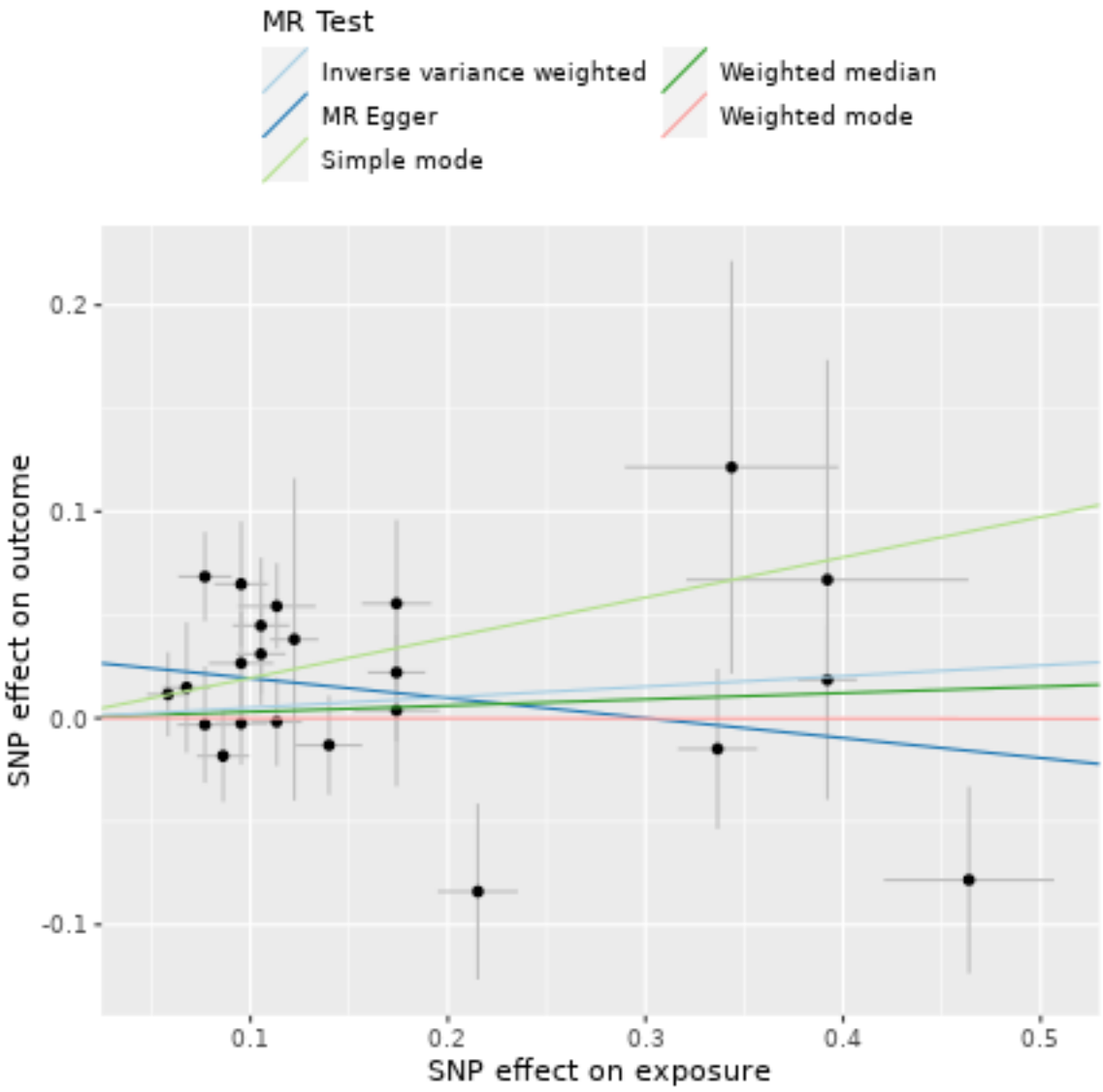
Chronic lymphocytic leukemia as exposure



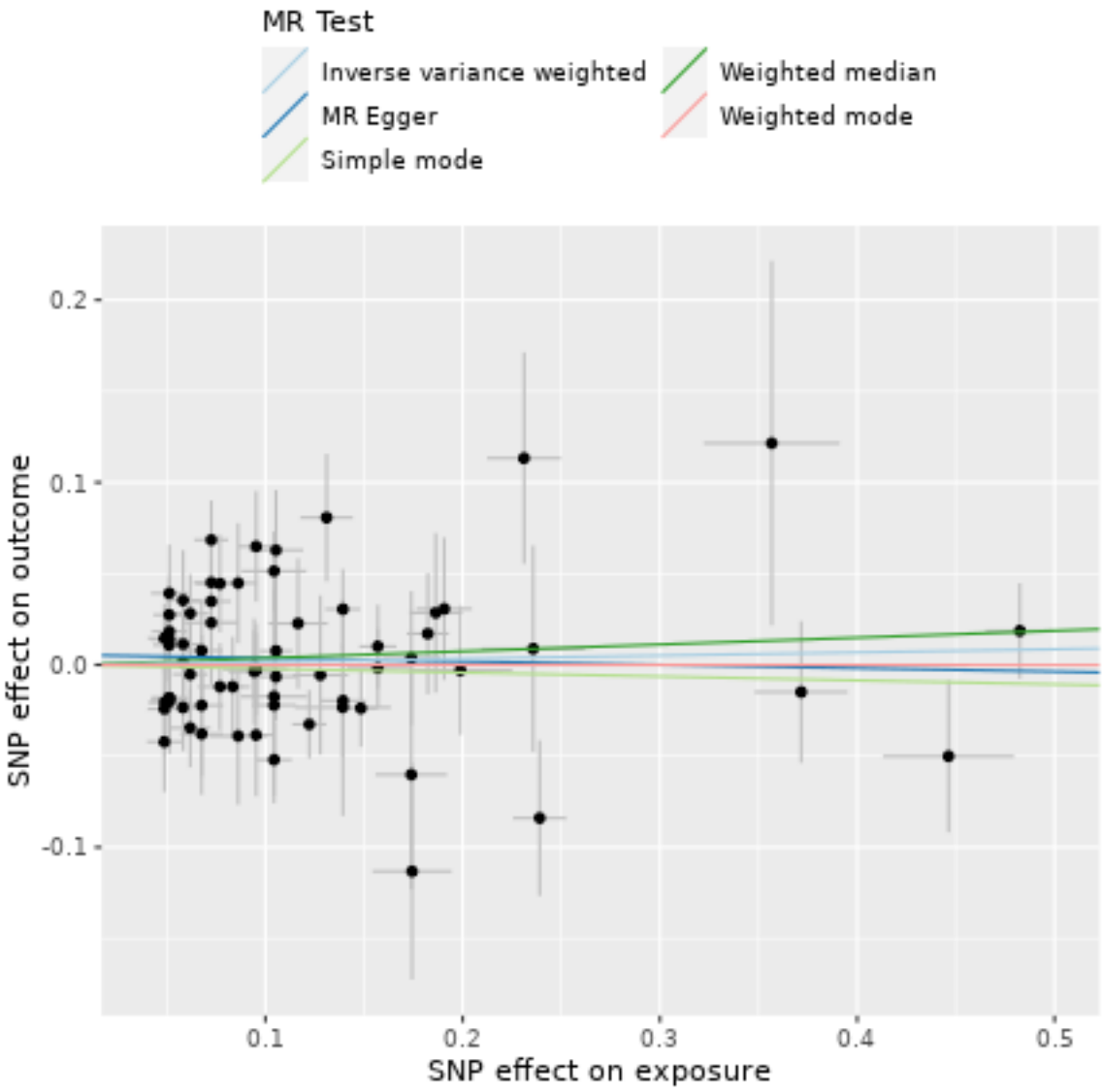
Colorectal cancer as exposure



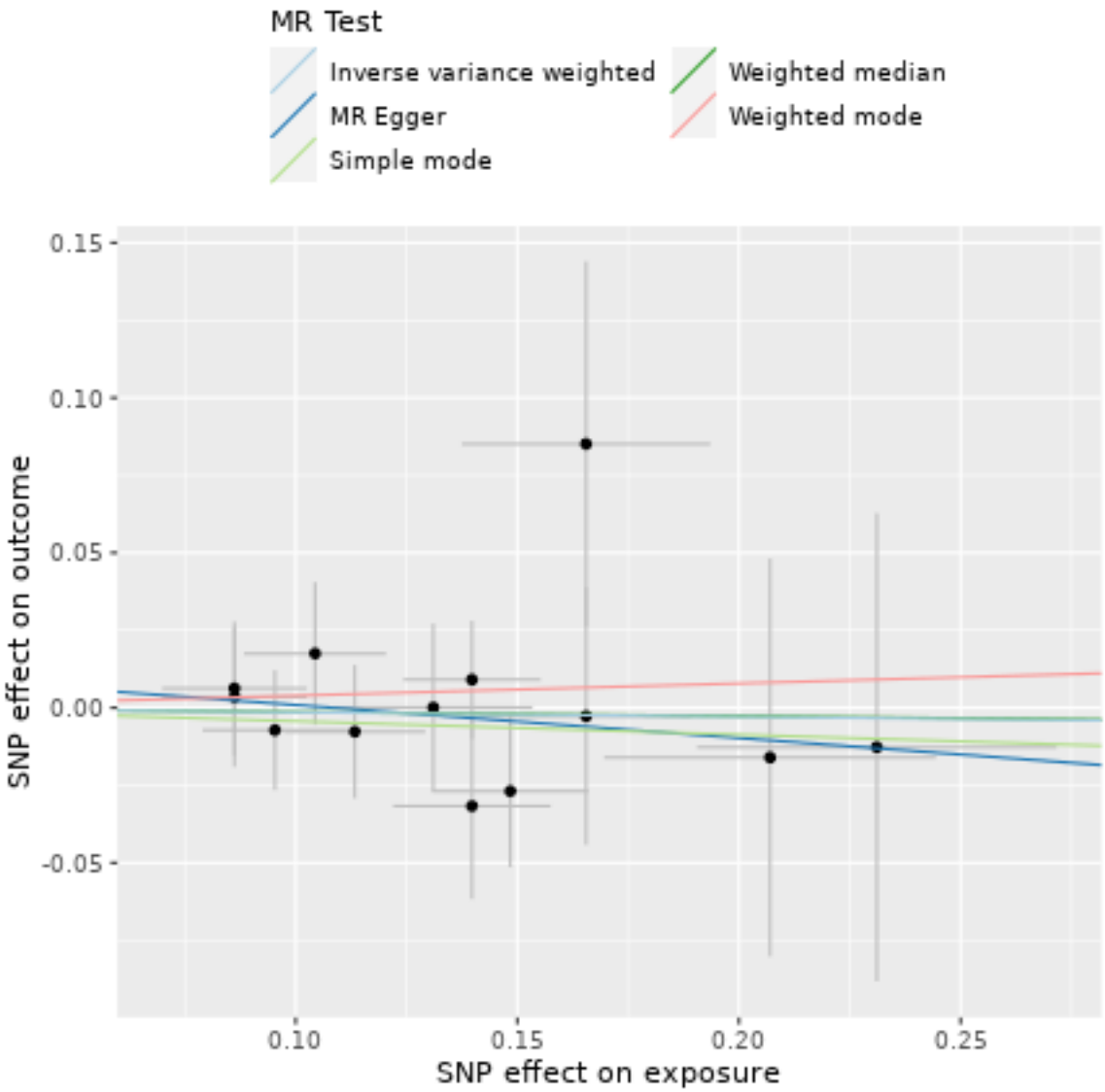
Cutaneous squamous cell carcinoma as exposure



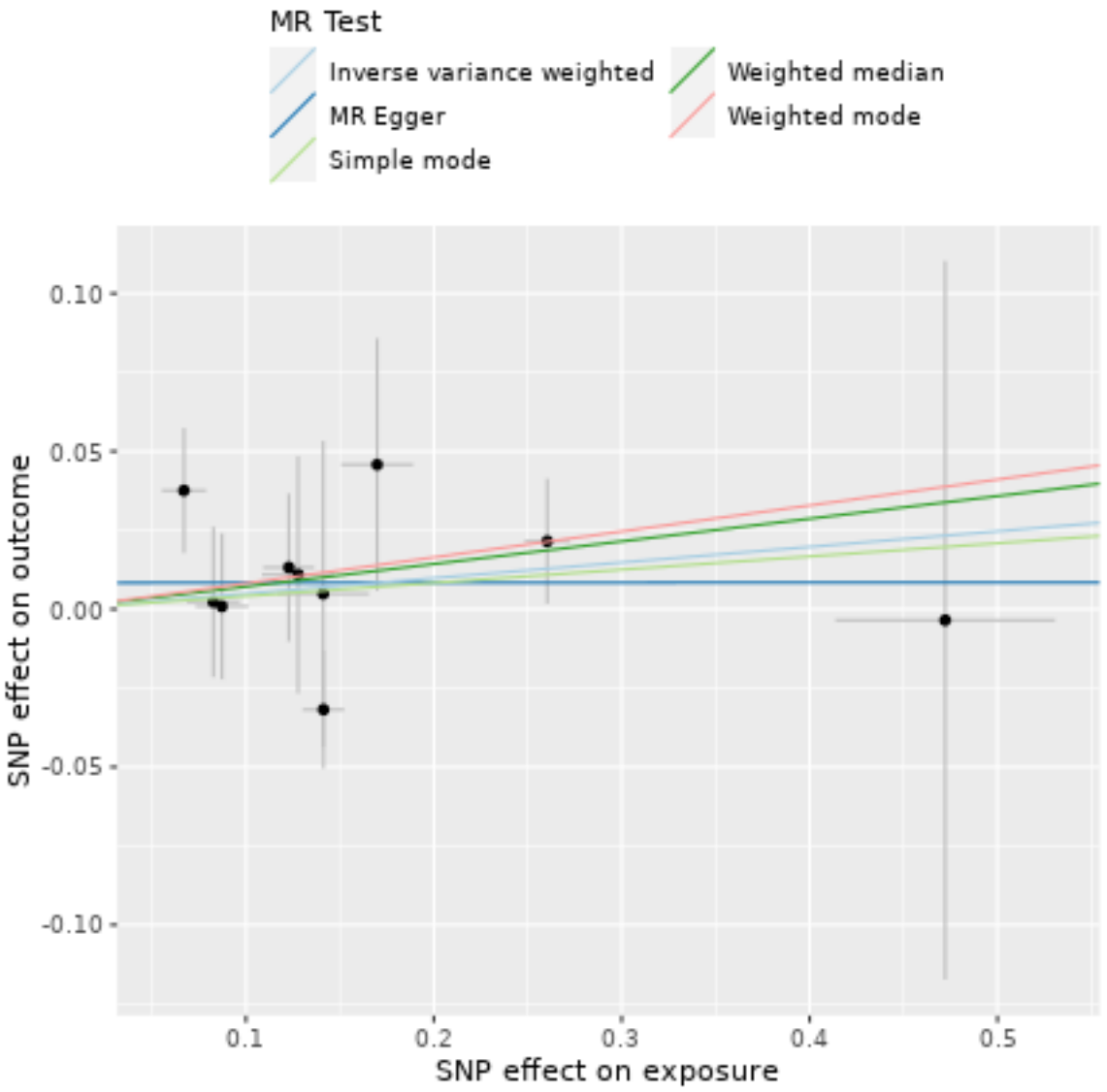
Combined analysis of keratinocyte cancers as exposure



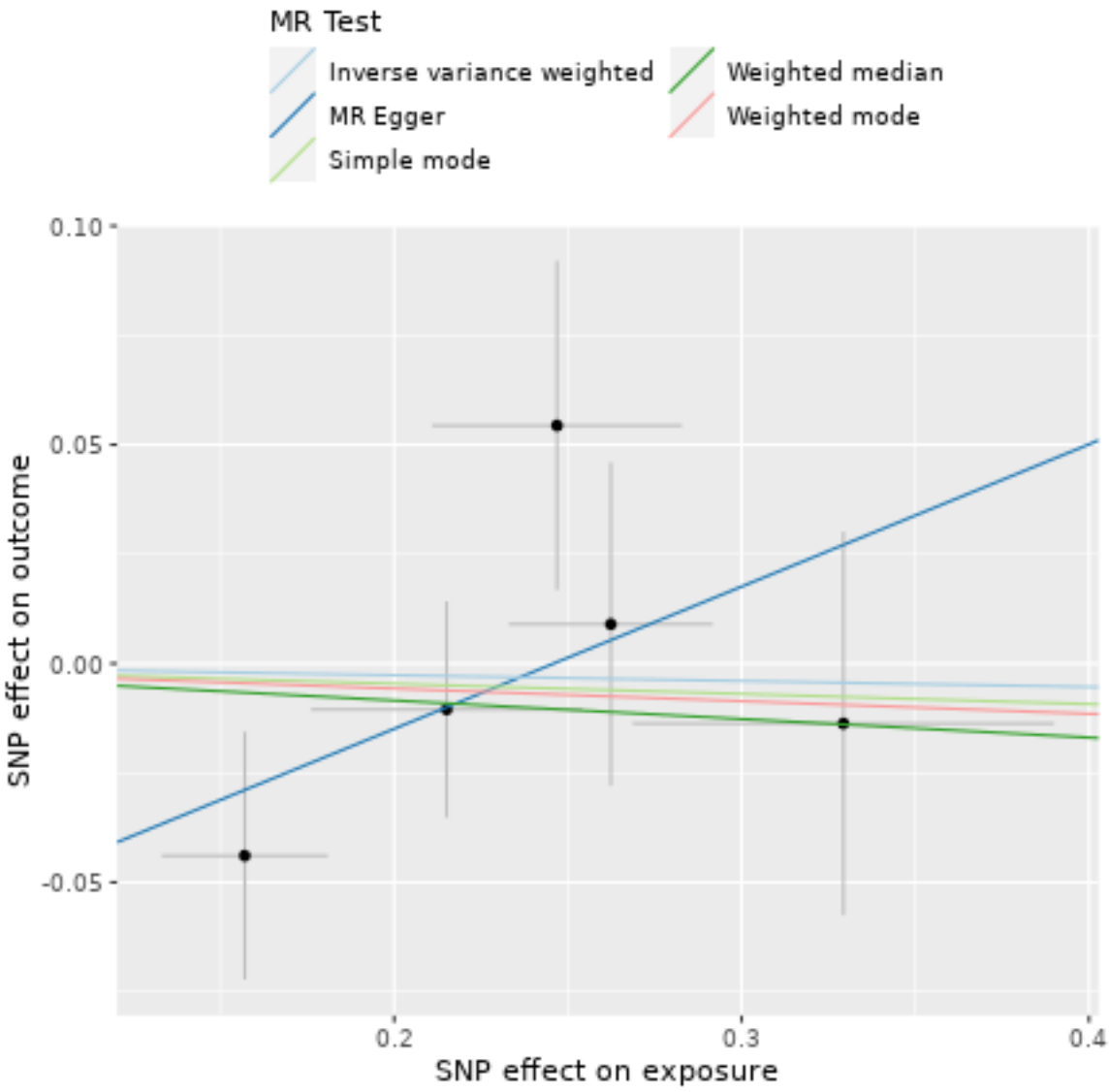
Endometrial cancer as exposure



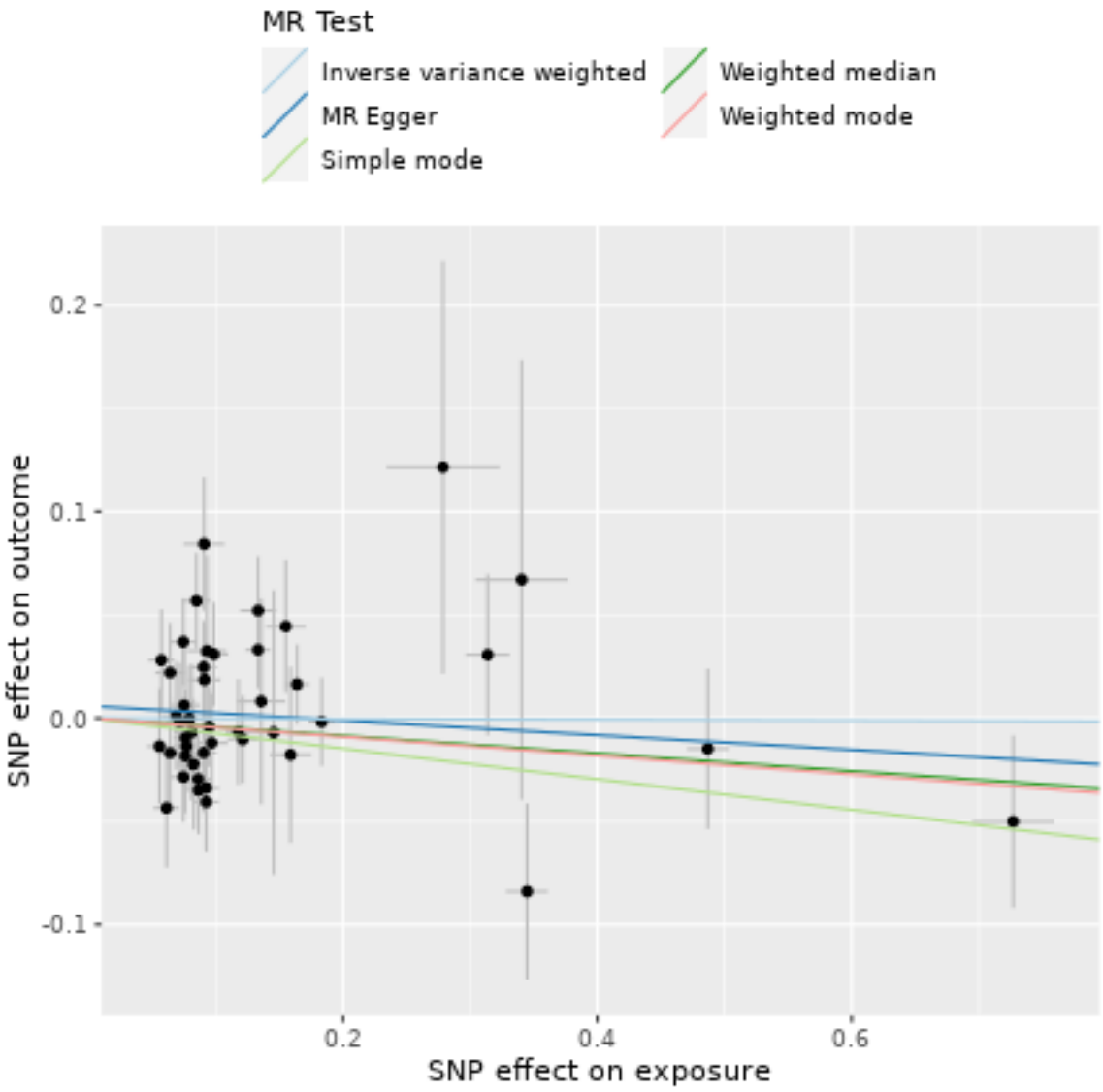
Lung cancer as exposure



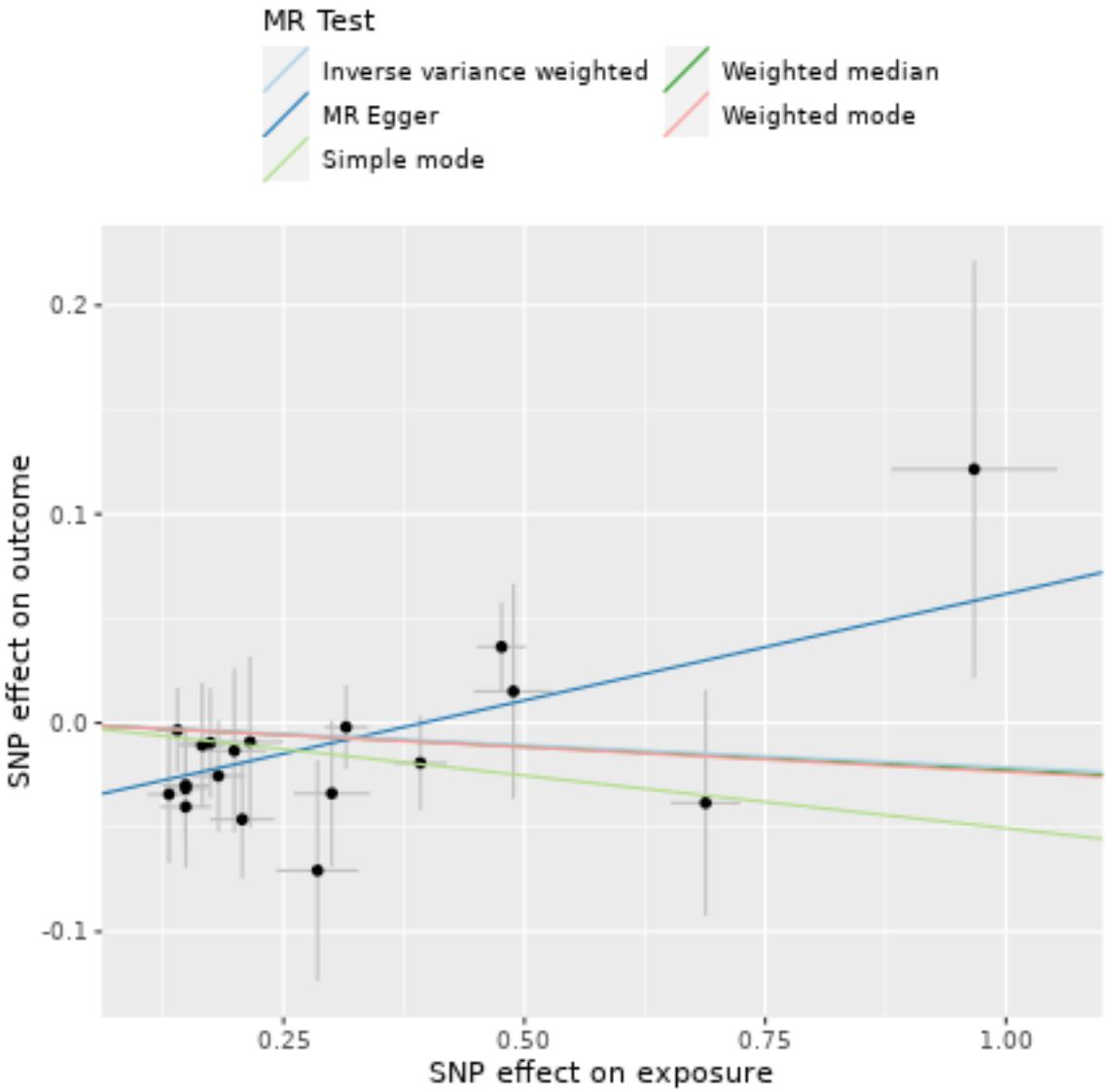
Lymphoma as exposure



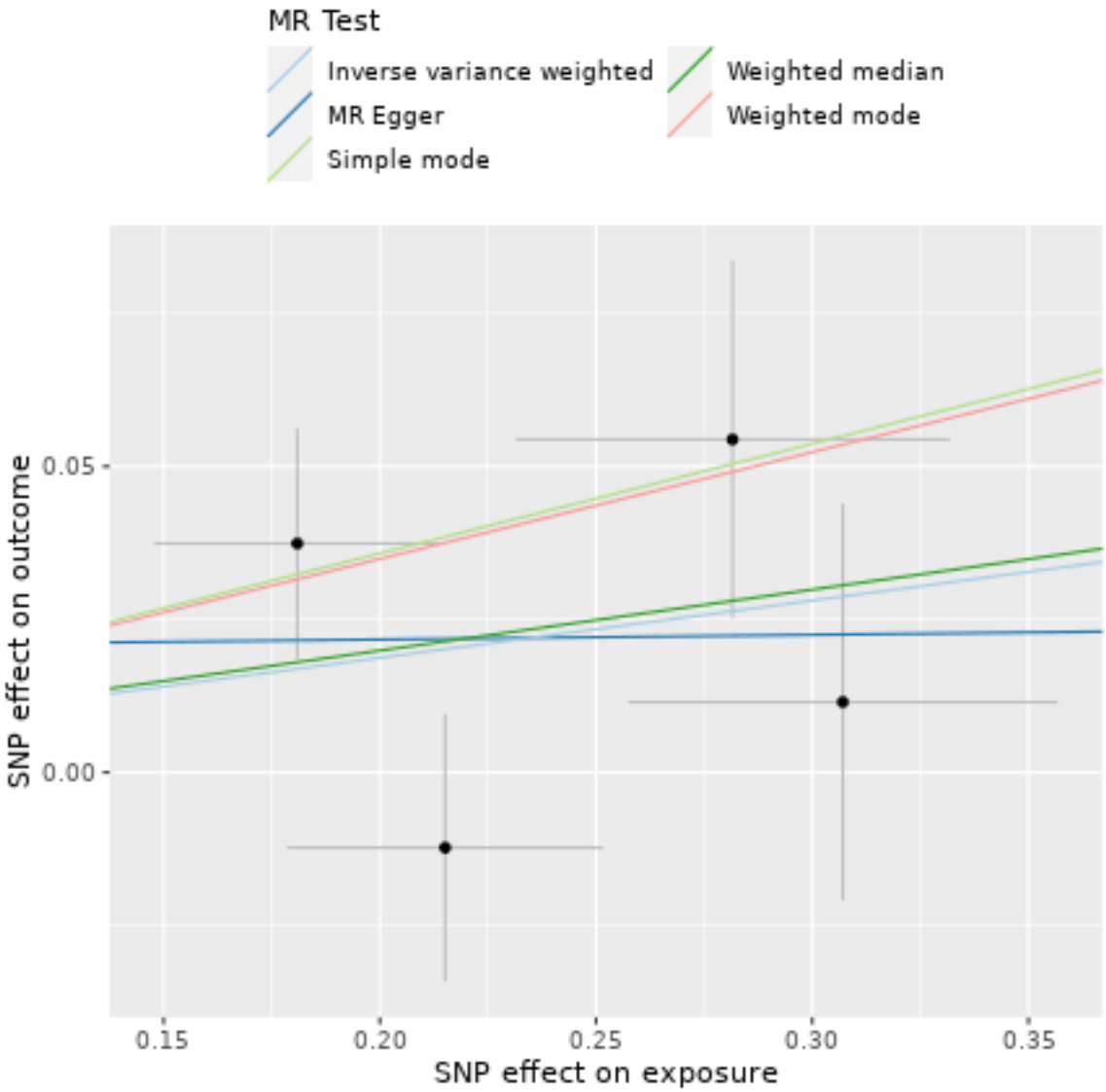
Melanoma as exposure



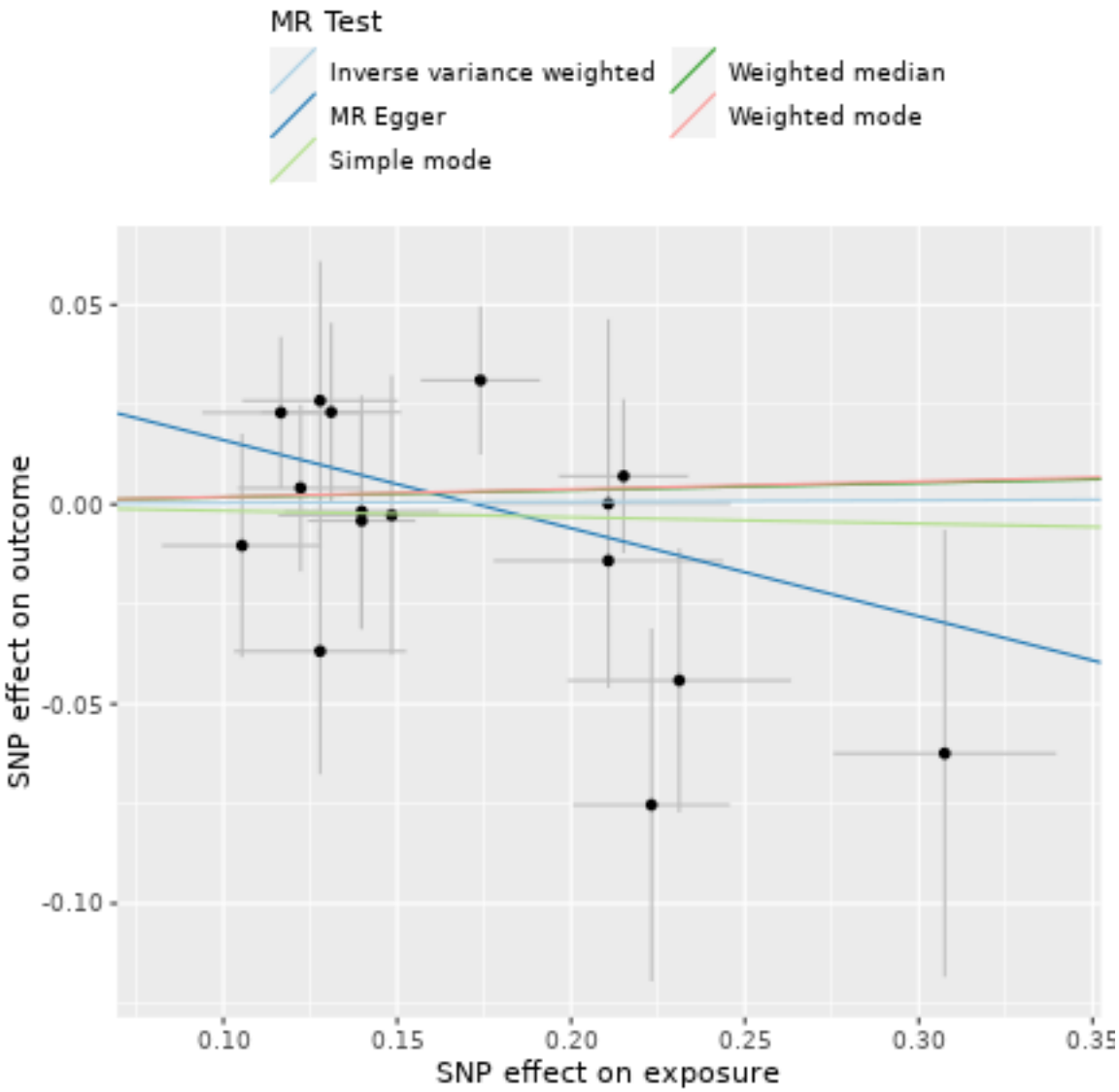
Non-glioblastoma glioma/Glioma as exposure



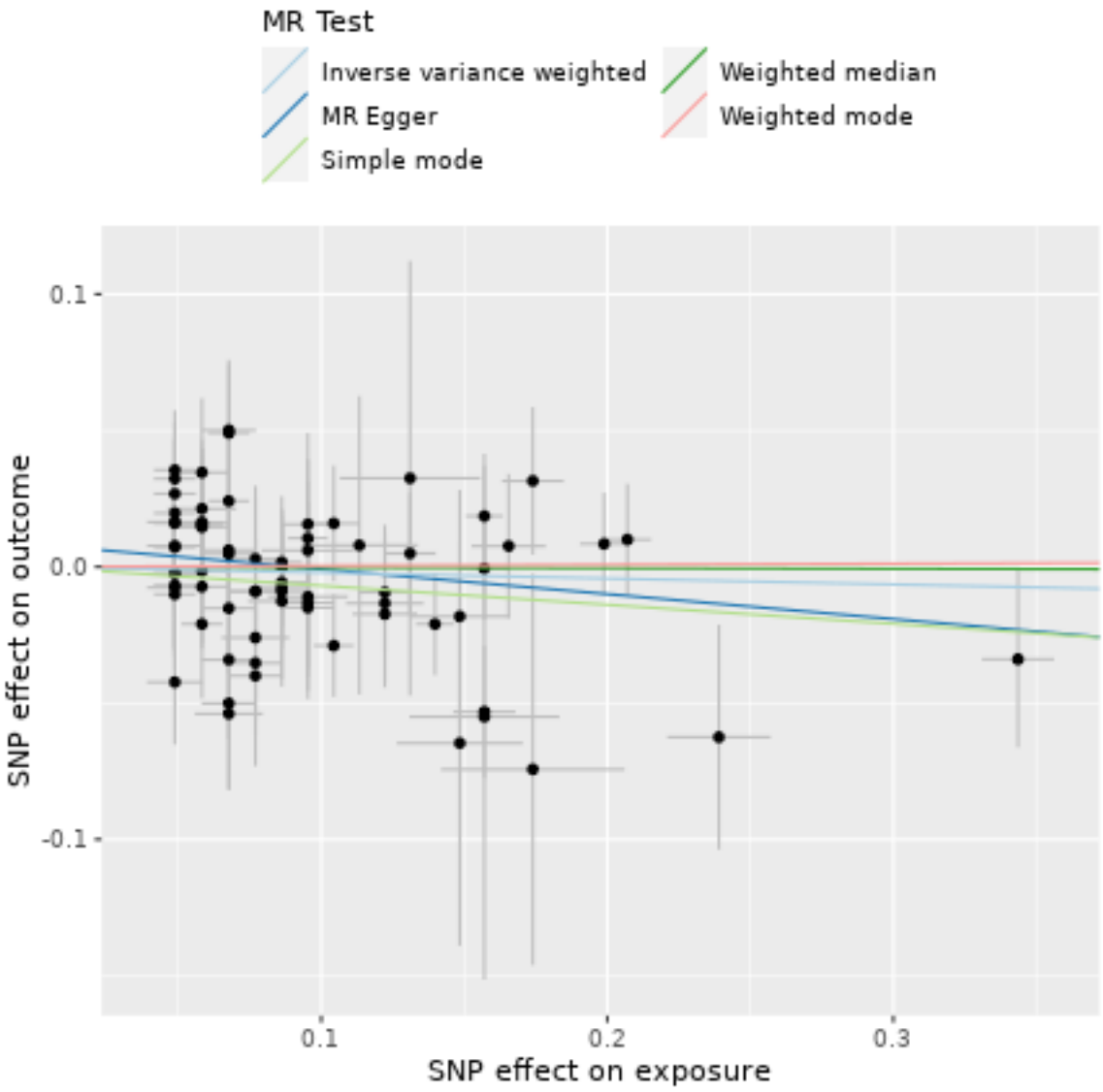
Oral cavity and pharyngeal cancer as exposure



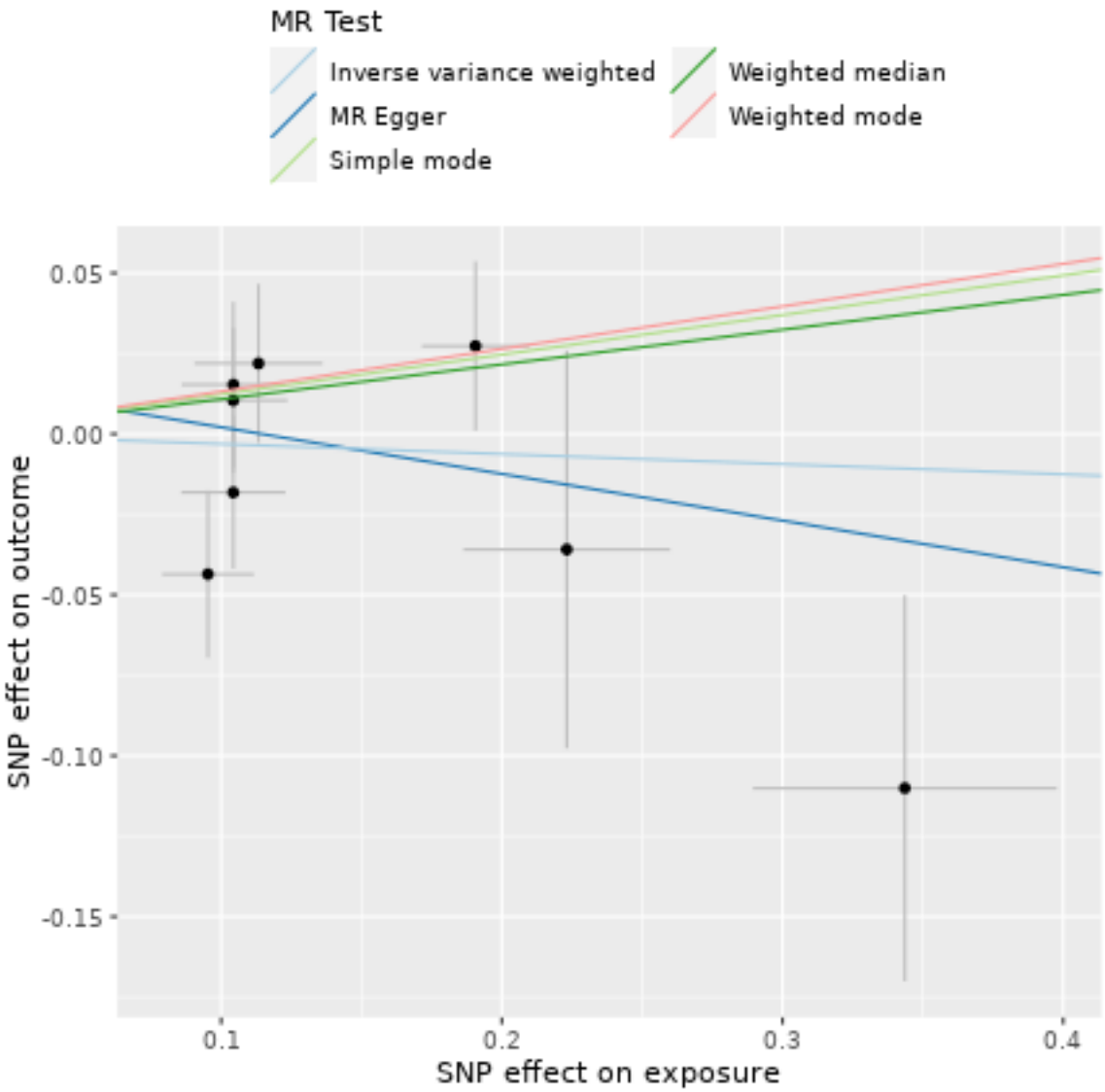
Pancreatic cancer as exposure



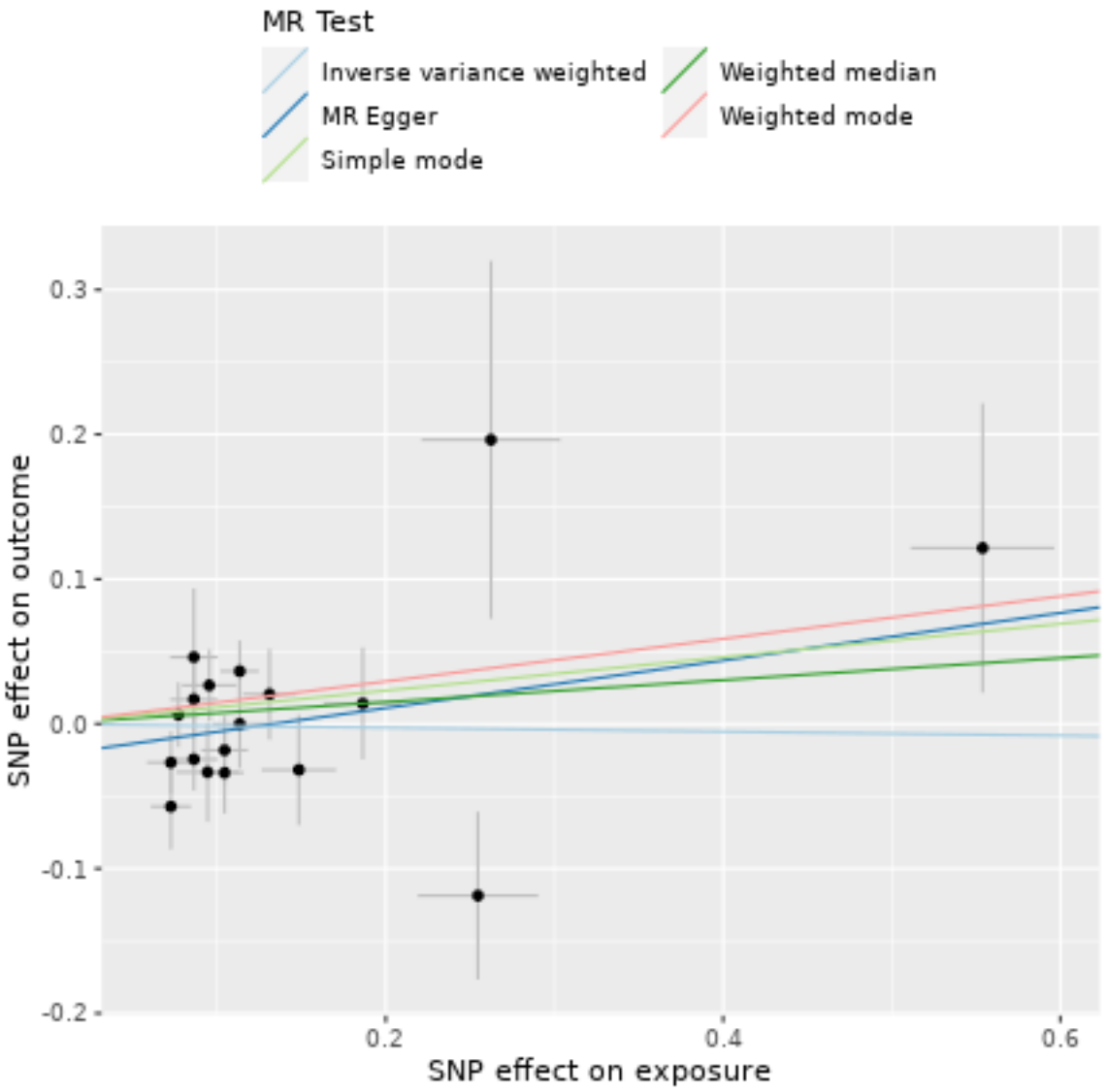
Prostate cancer as exposure



Renal cell carcinoma as exposure

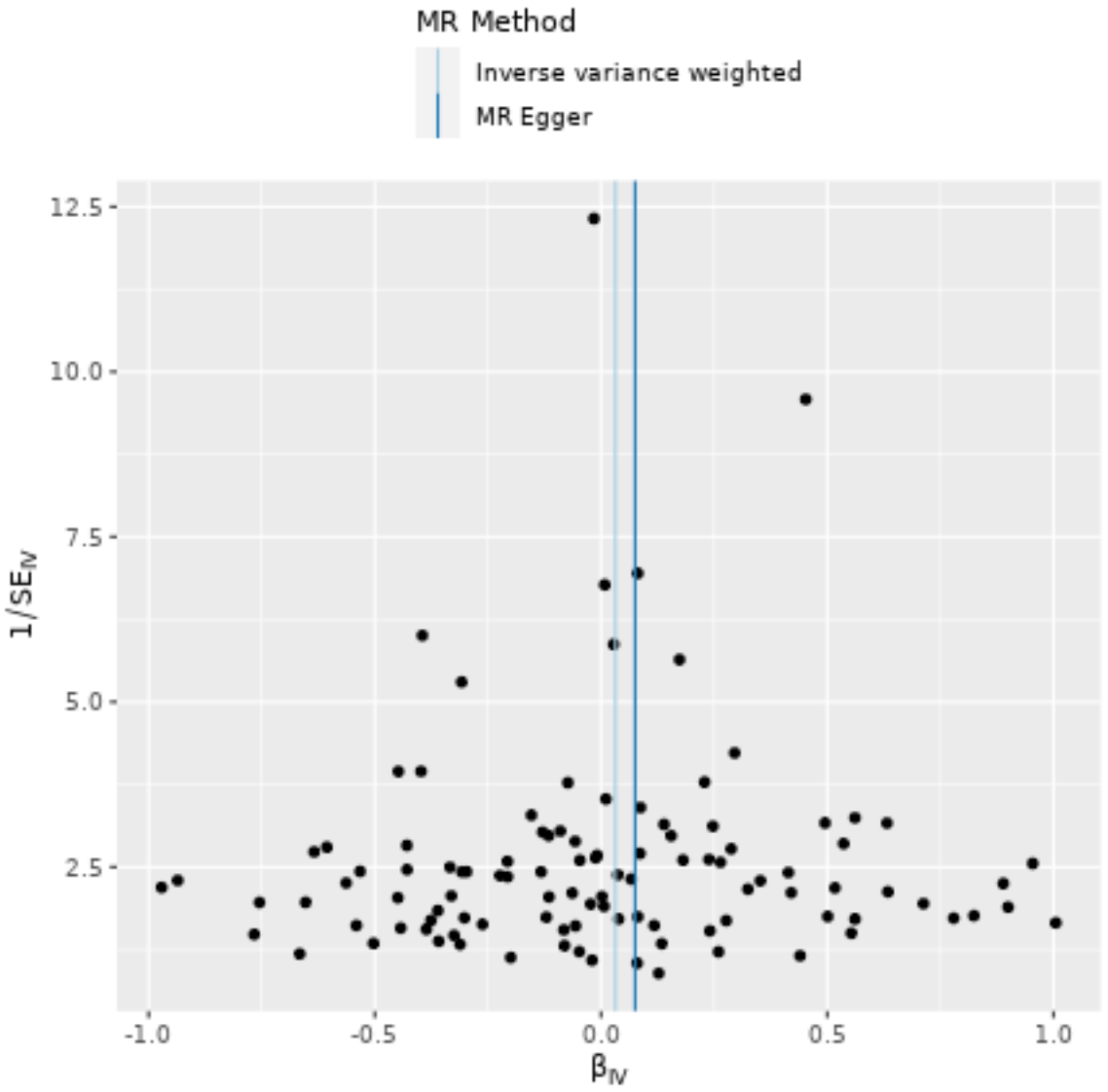


Uterine fibroids as exposure

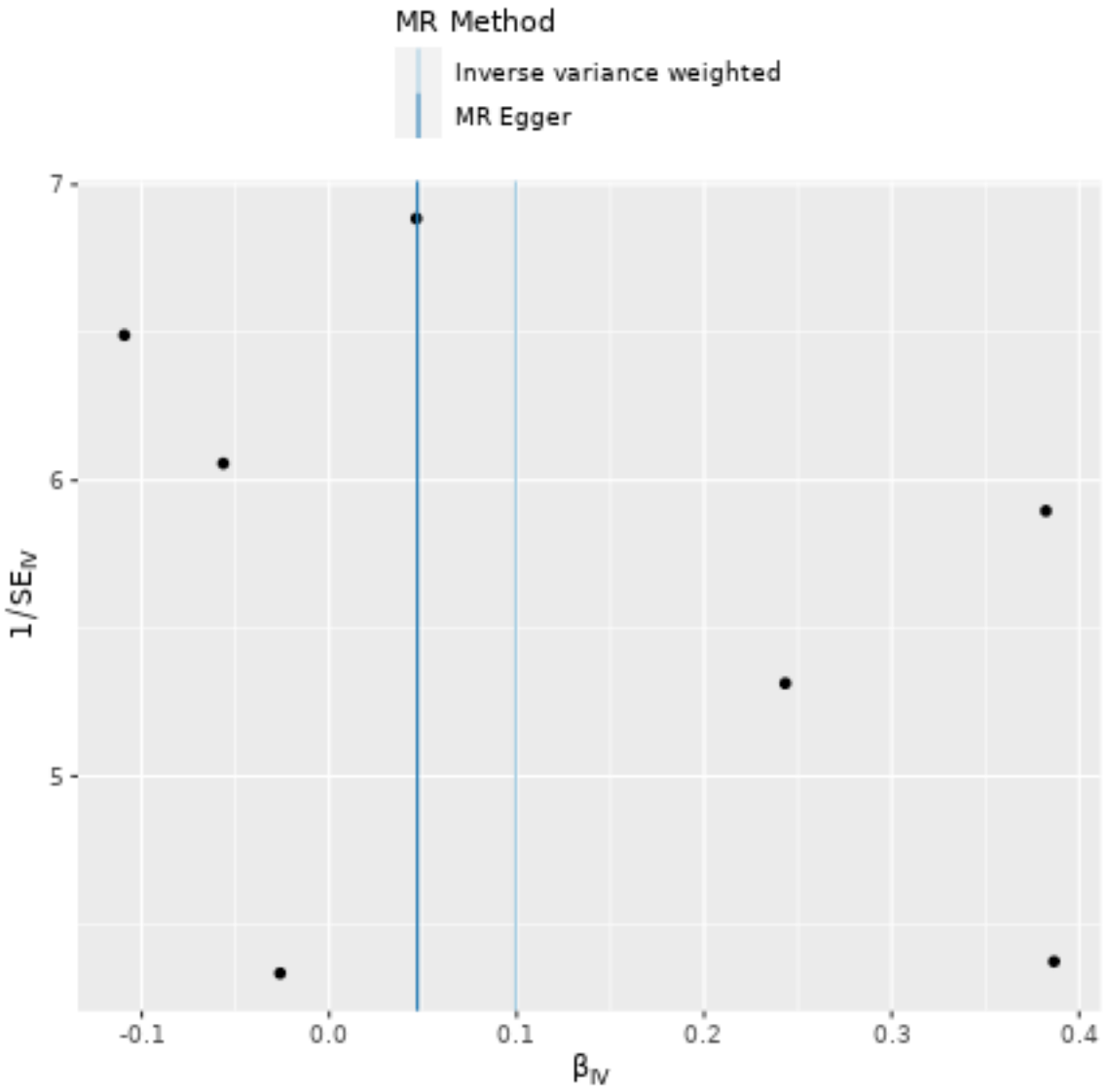


Supplementary Figure 3. PD without UKBB. Funnel plots evaluated the presence of possible heterogeneity across the estimates. Exposure of interest at the top of each plot.
Each SNPs represented by dots. Inverse variance weighted and MR Egger method averaged causal effect of all SNPs.

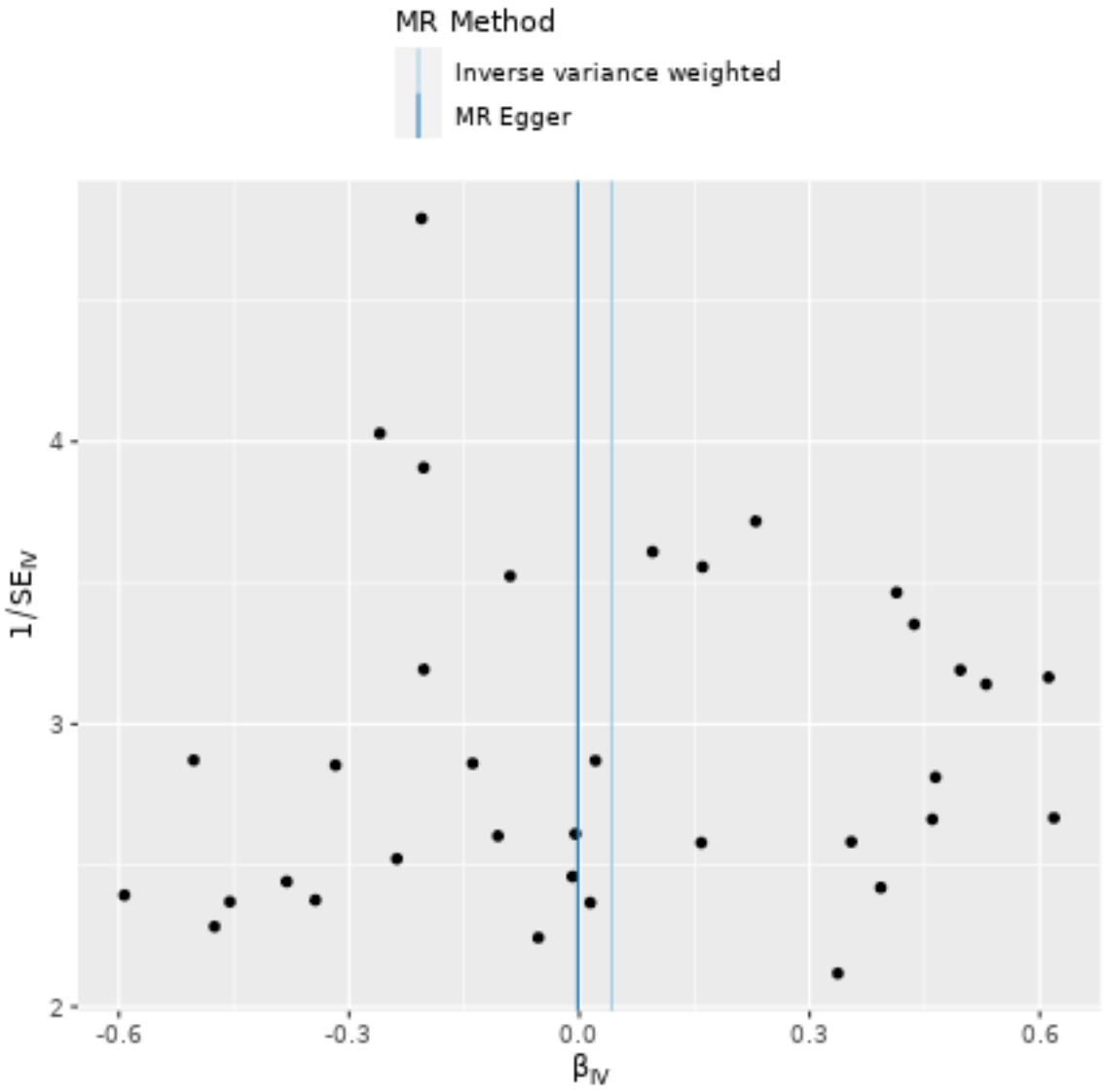
Breast cancer as exposure



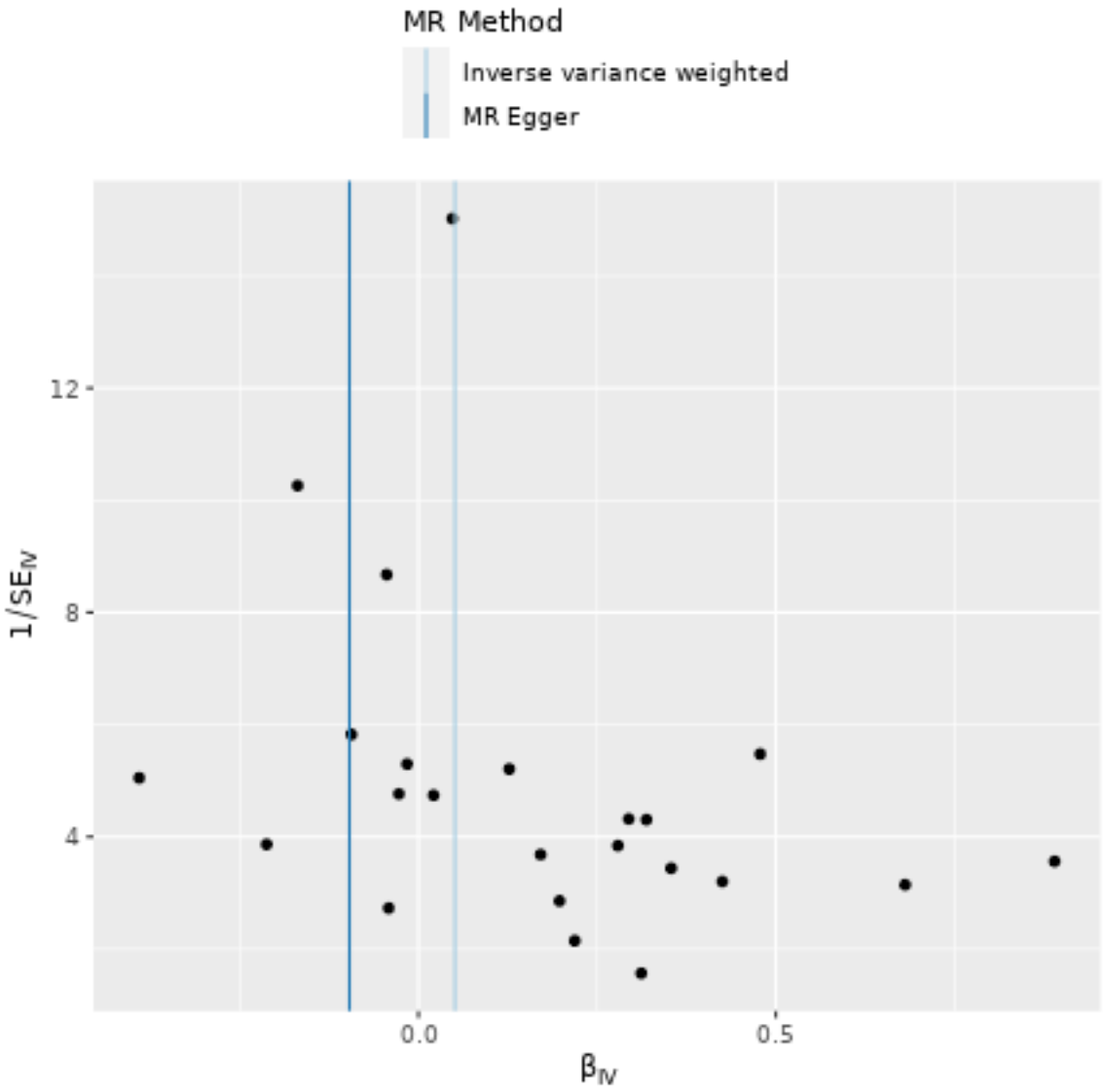
Chronic lymphocytic leukemia as exposure



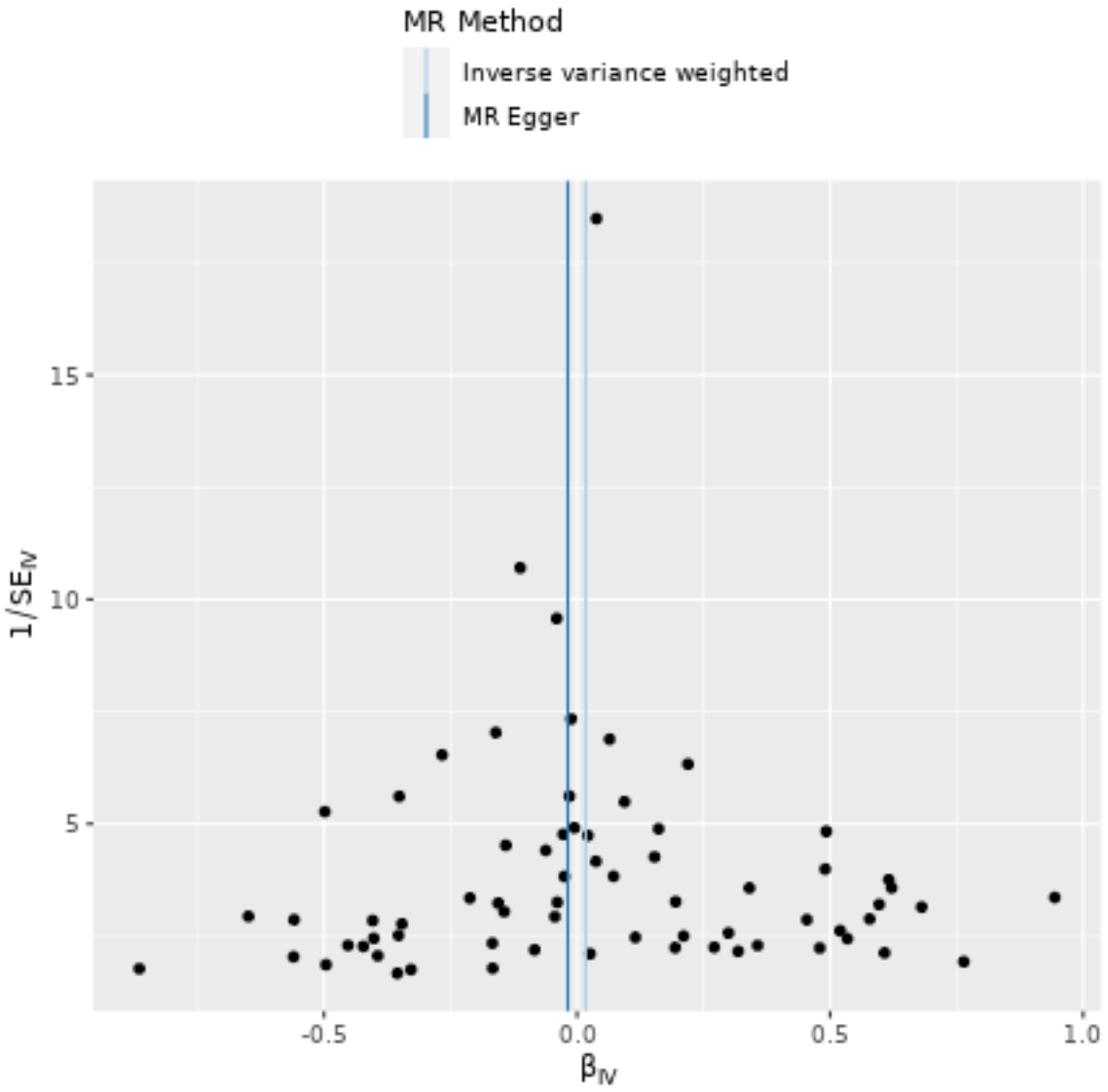
Colorectal cancer as exposure



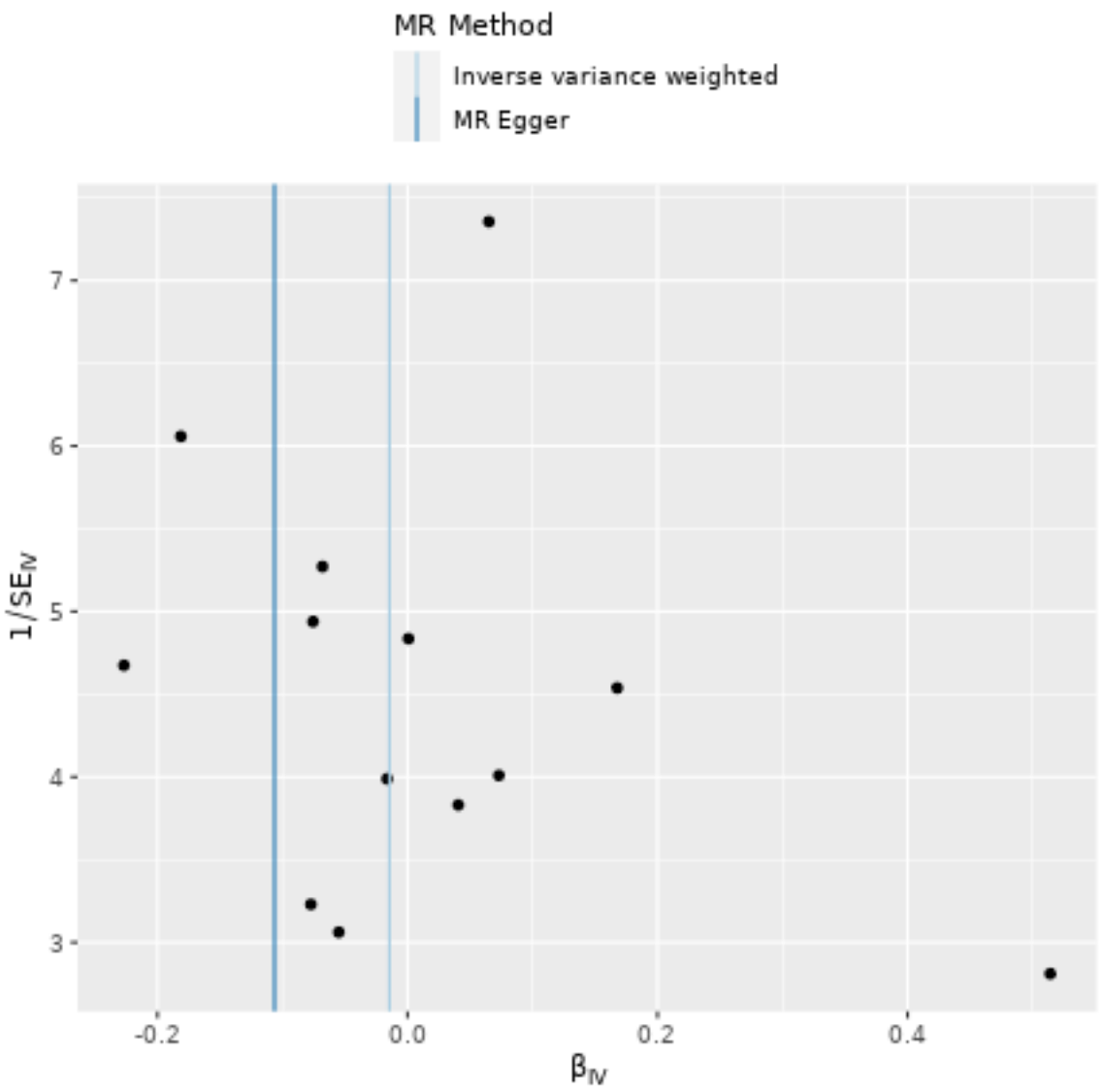
Cutaneous squamous cell carcinoma as exposure



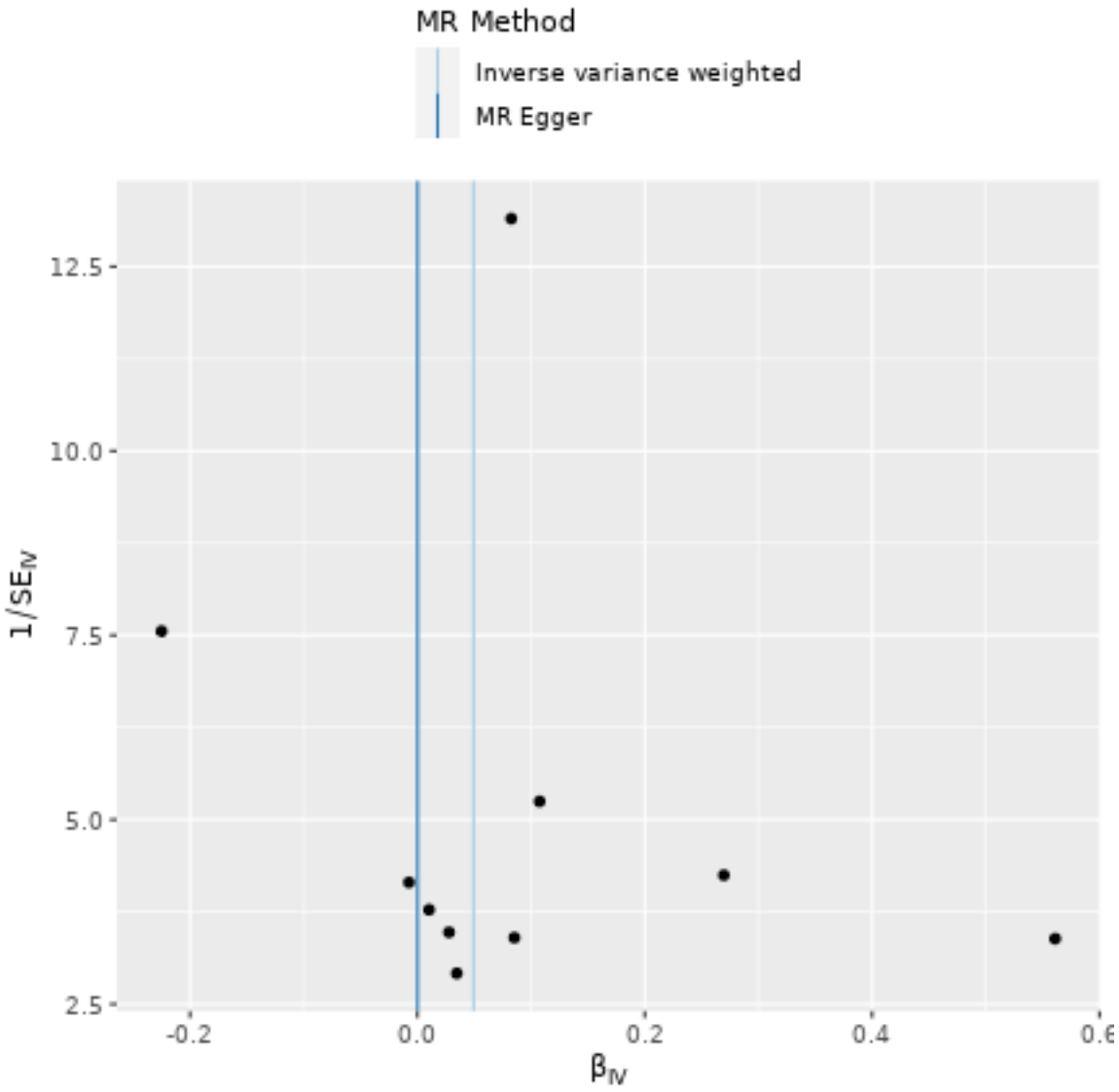
Combined analysis of keratinocyte cancers as exposure



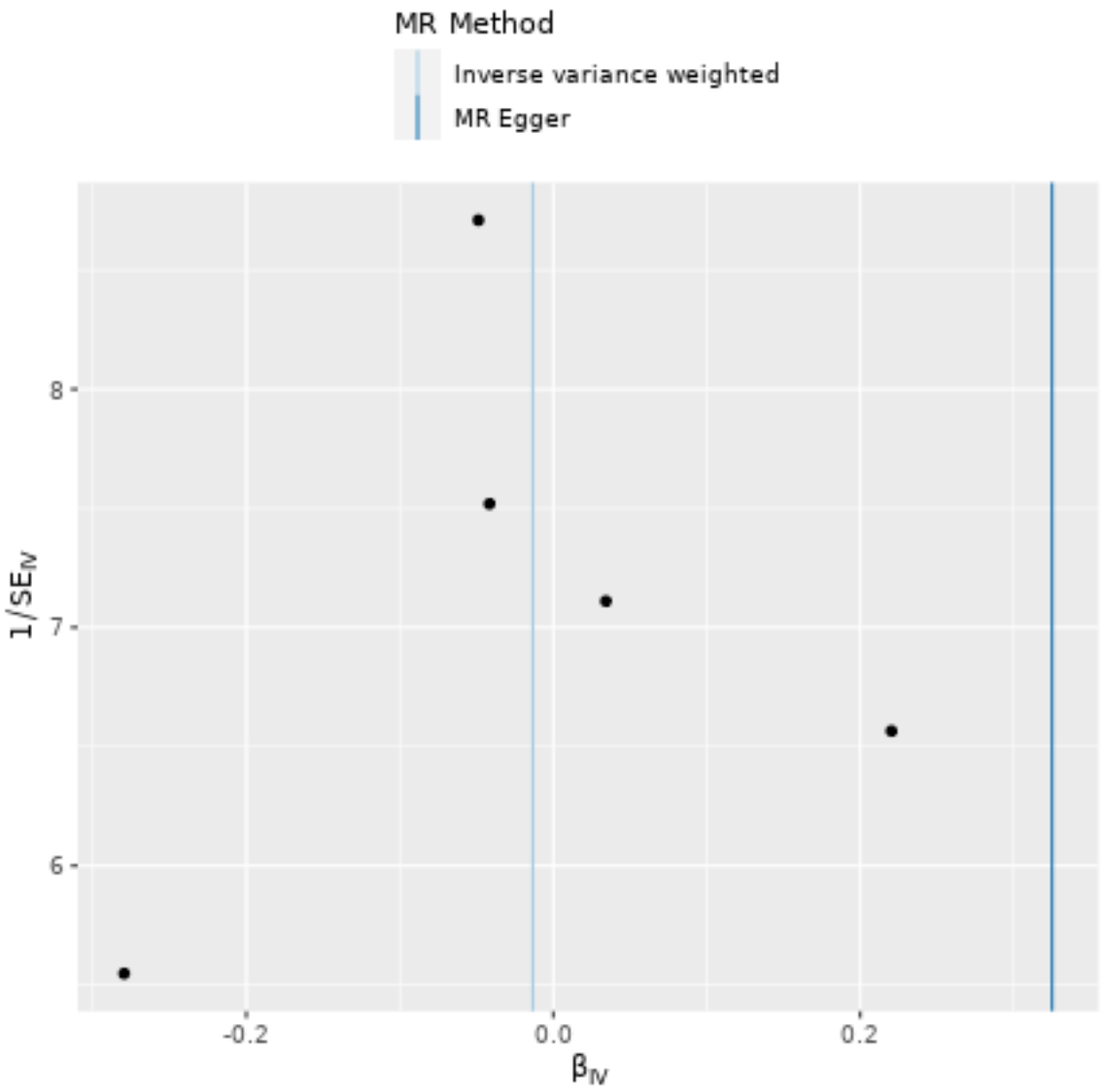
Endometrial cancer as exposure



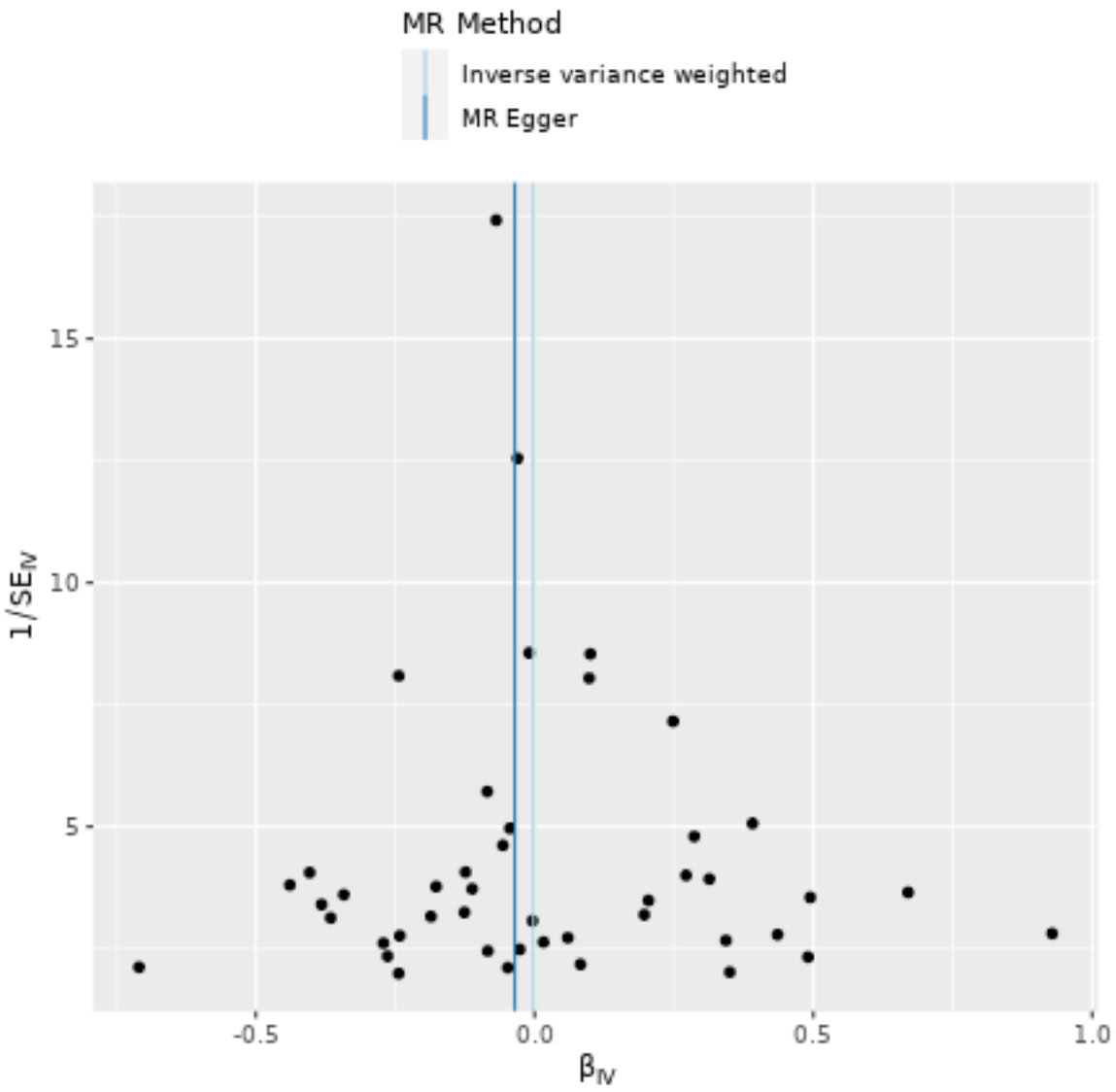
Lung cancer as exposure



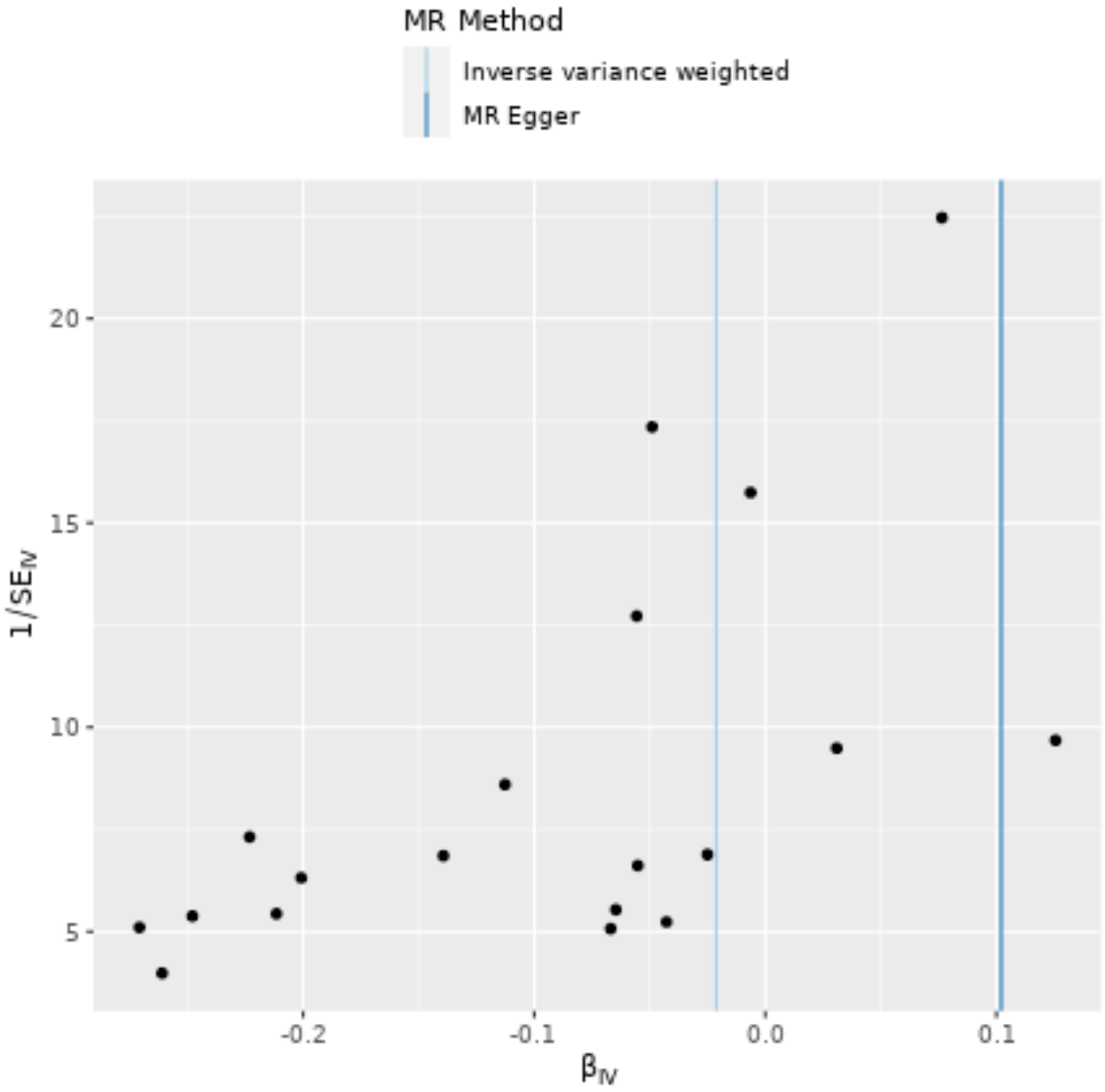
Lymphoma as exposure



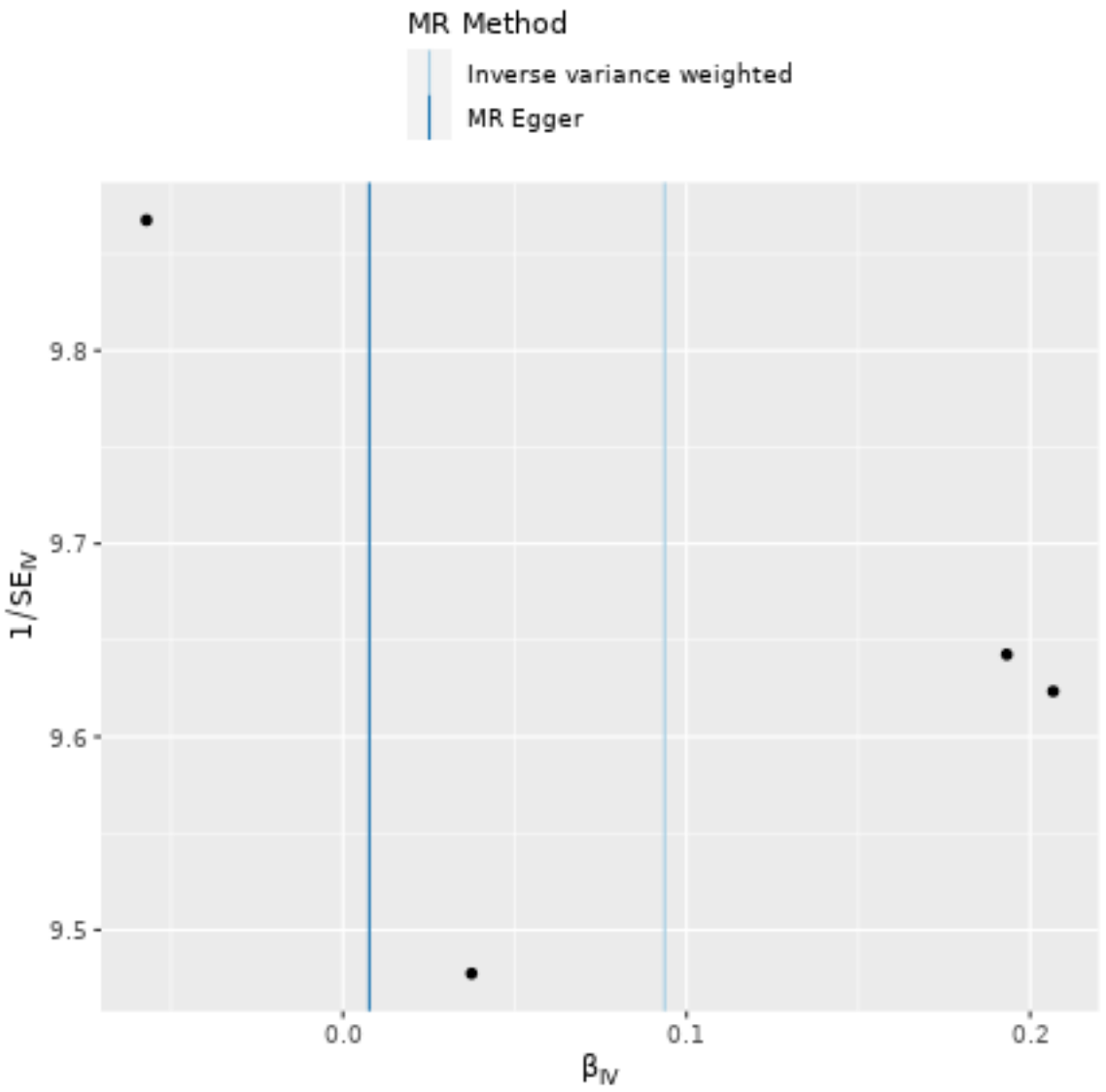
Melanoma as exposure



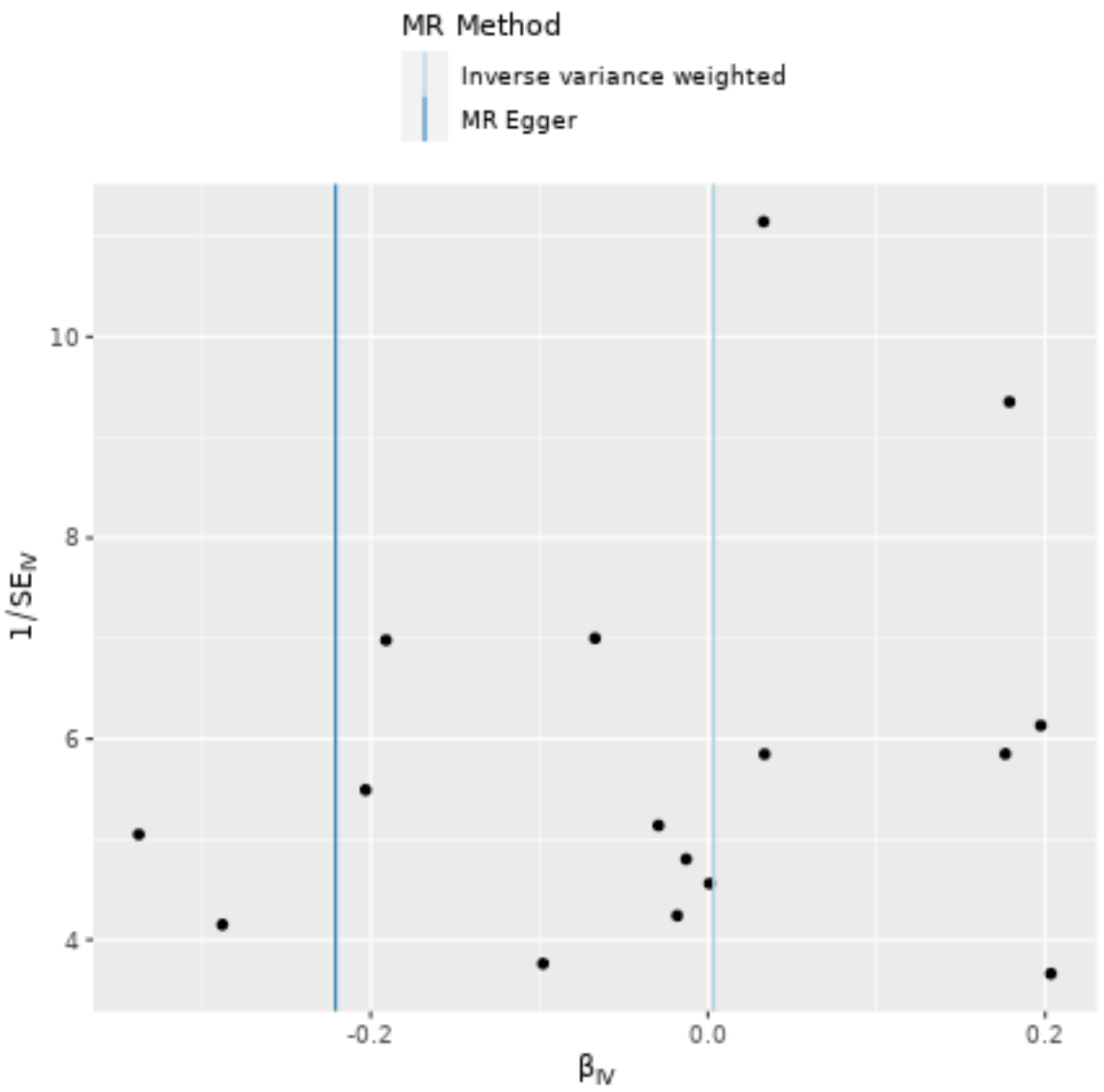
Non-glioblastoma glioma/Glioma as exposure



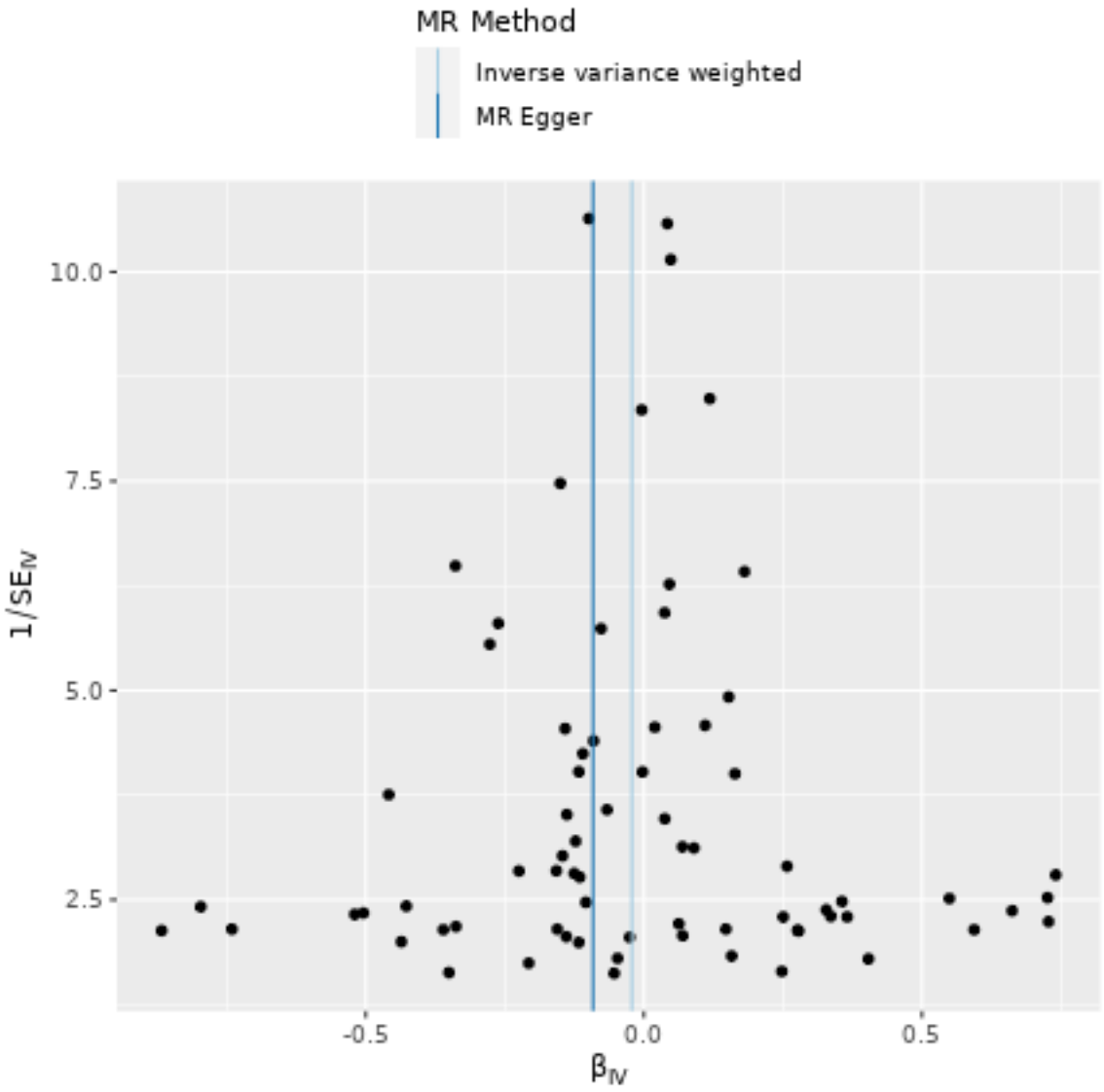
Oral cavity and pharyngeal cancer as exposure



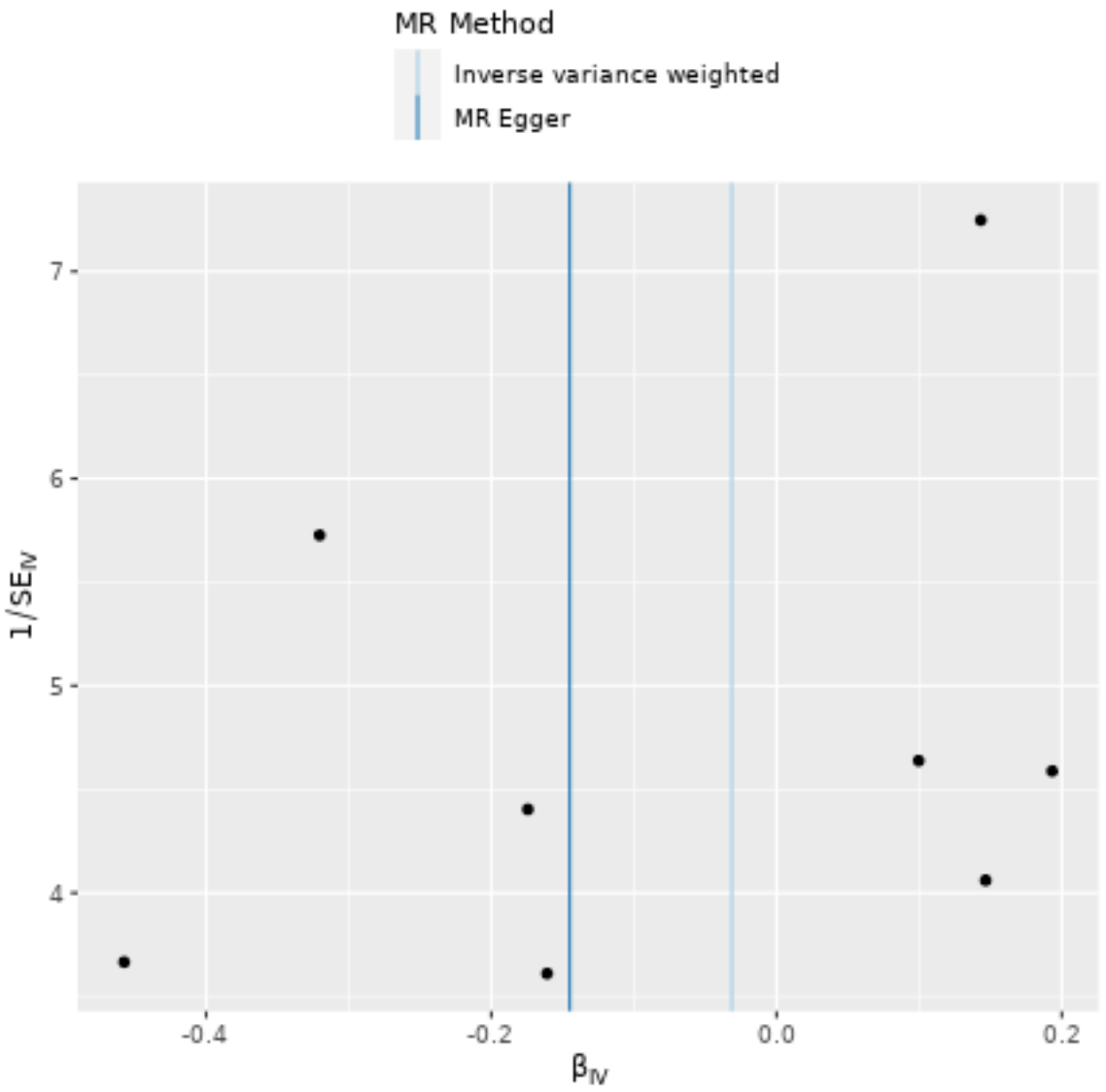
Pancreatic cancer as exposure



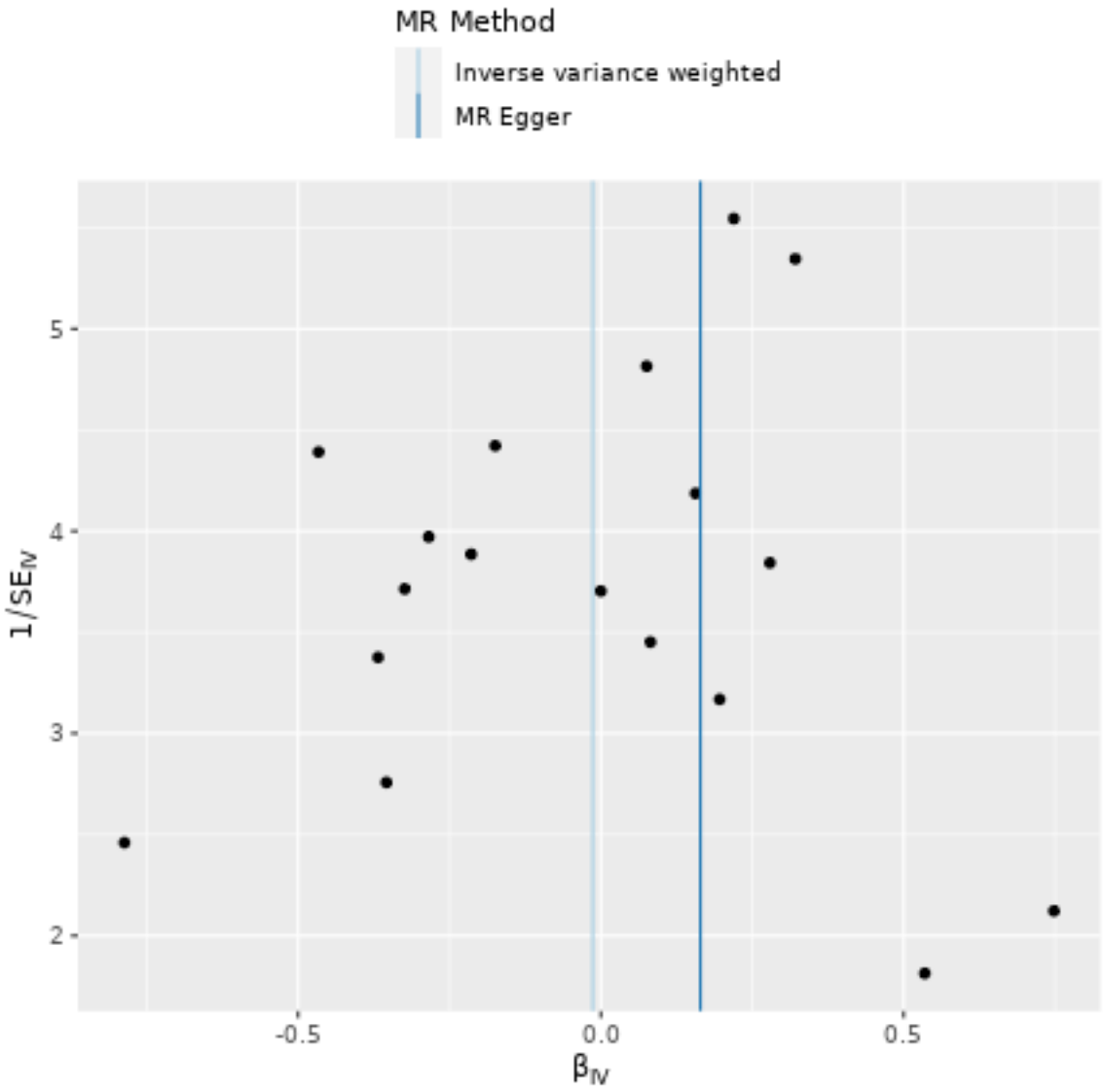
Prostate cancer as exposure



Renal cell carcinoma as exposure

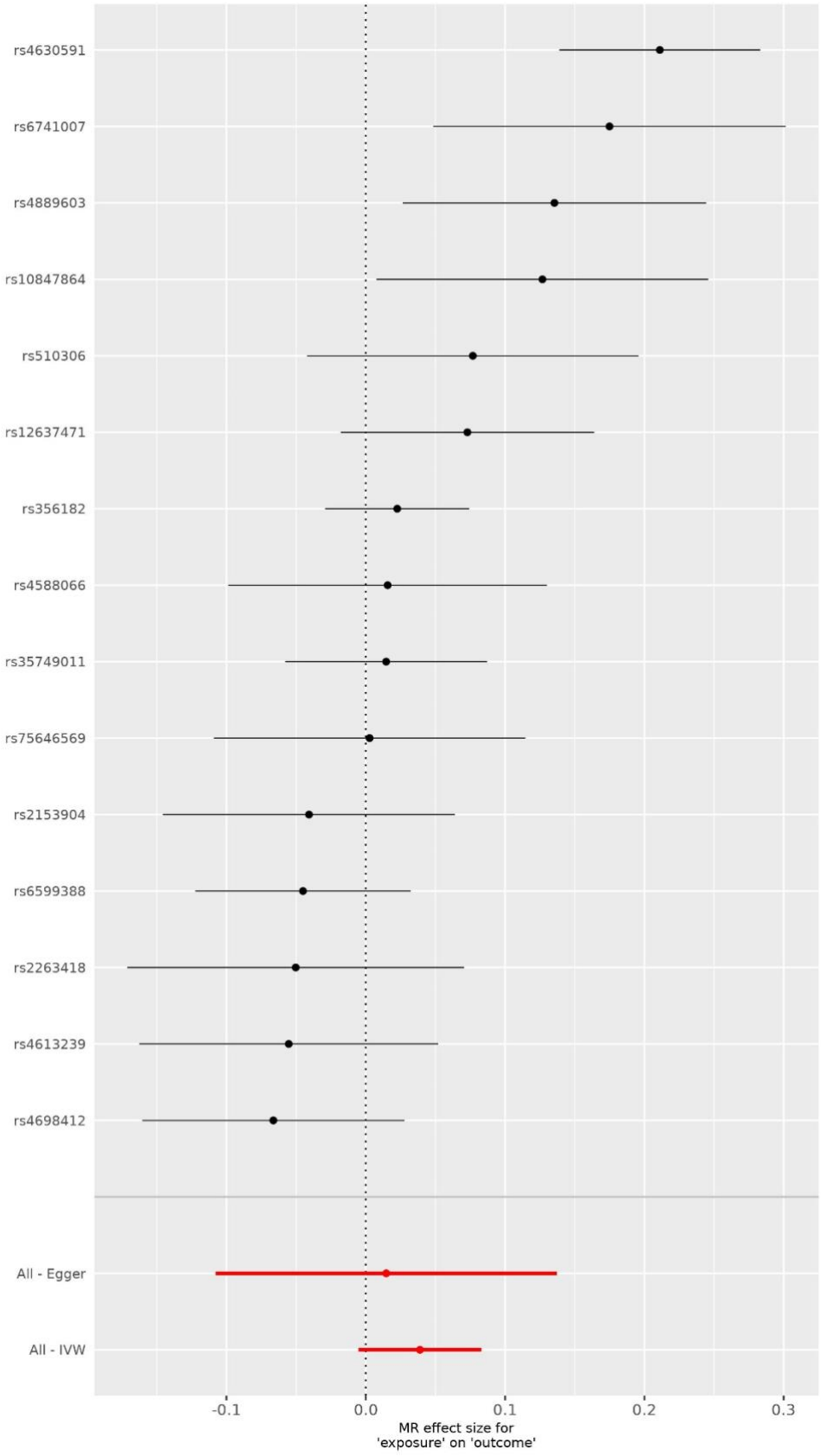


Uterine fibroids as exposure

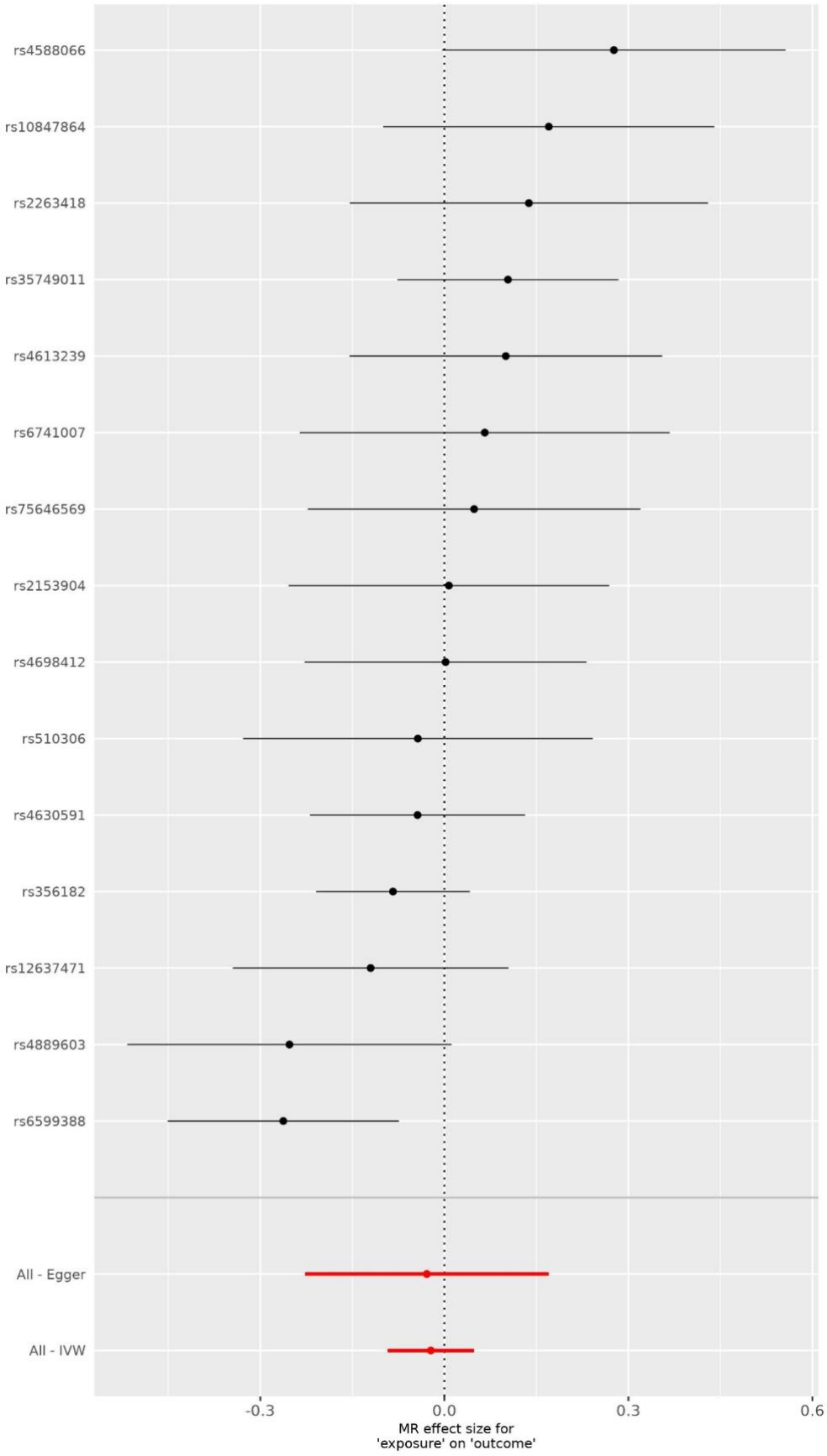


Supplementary Figure 4. Reverse MR (PD as exposure; Cancers as outcome). Forest plots showing point estimates of the exposures of interest, Exposure of interest at the top of each forest plot

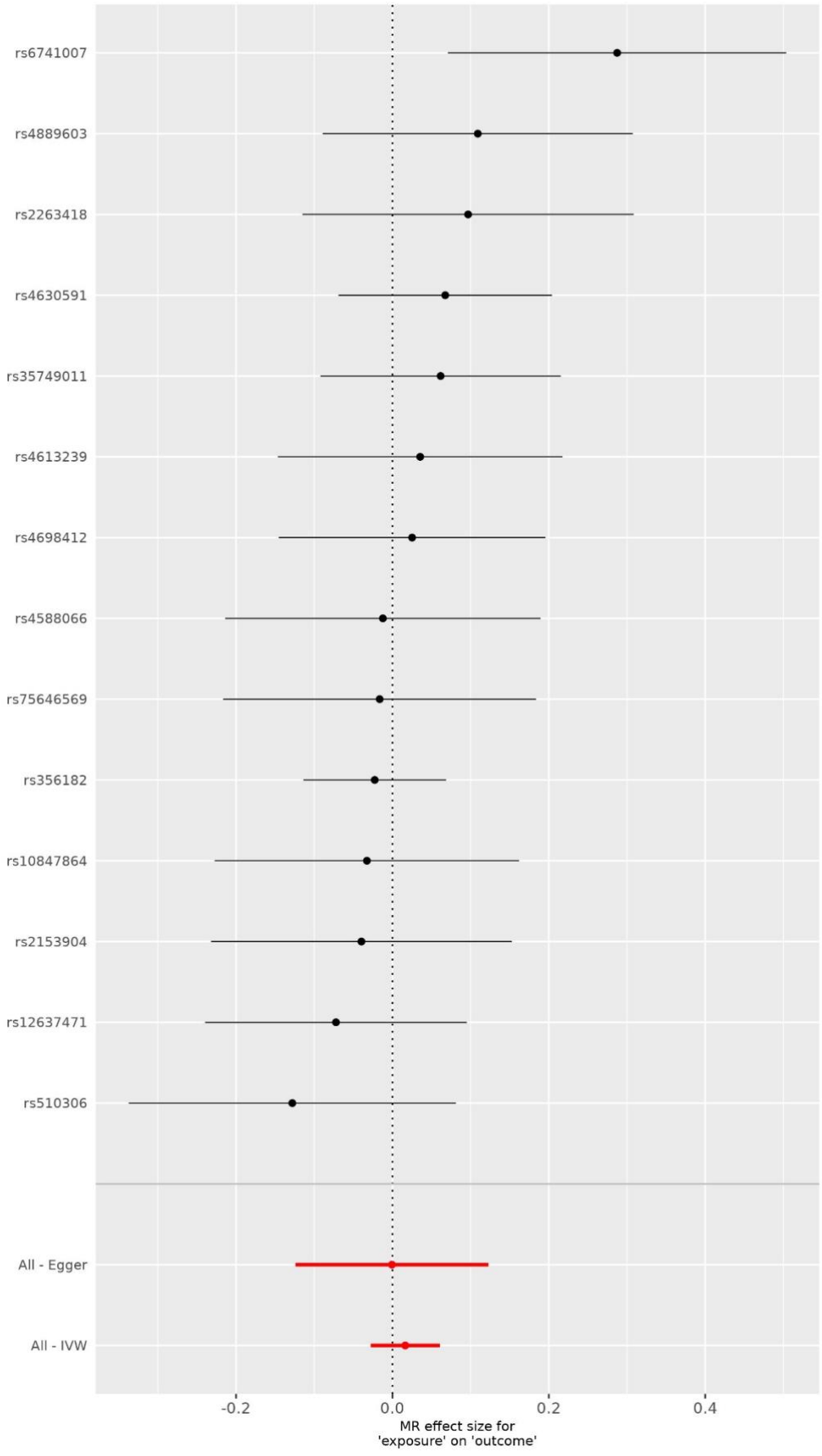
Breast cancer as outcome



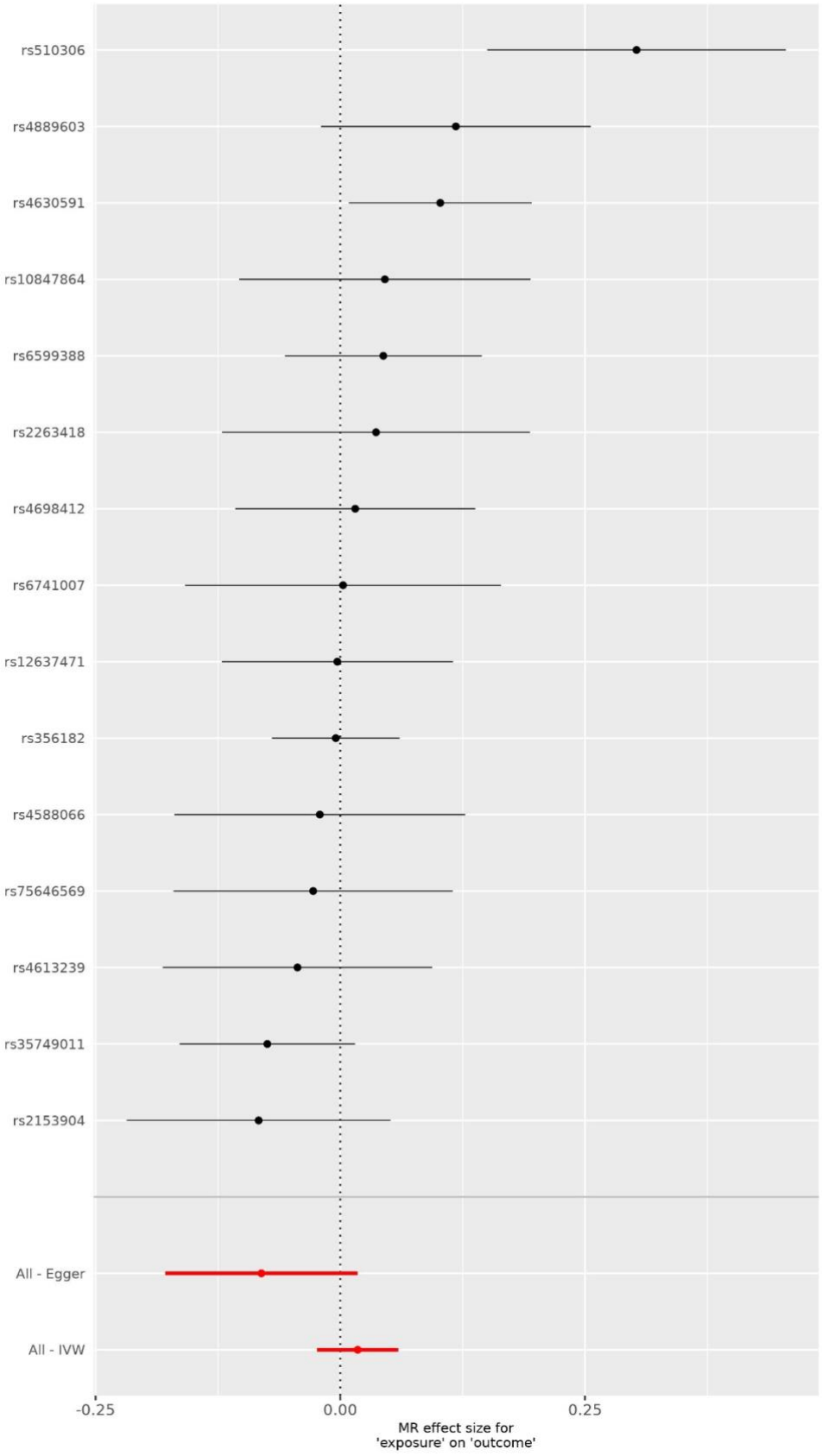
Endometrial cancer as outcome



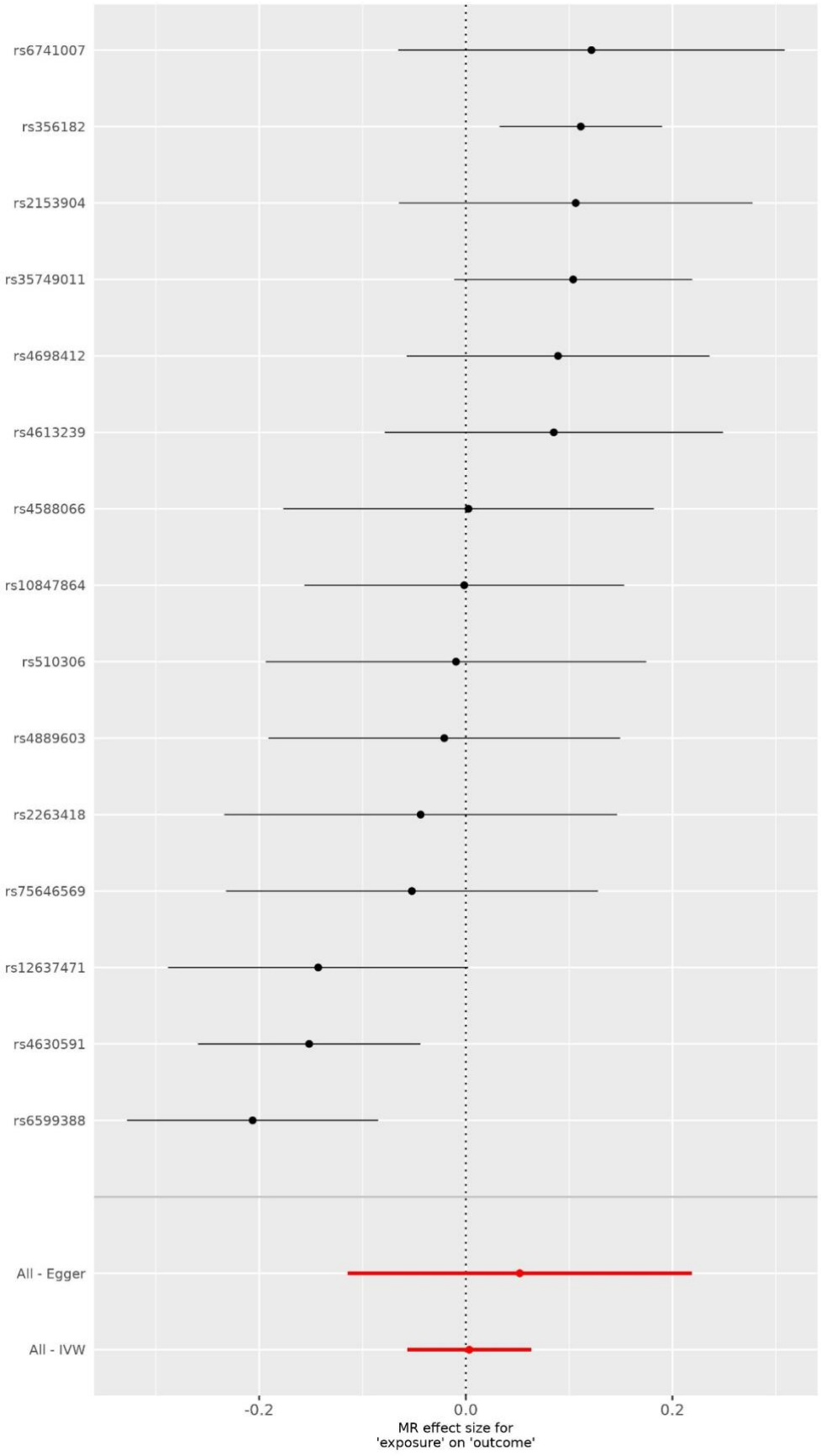
Melanoma as outcome



Prostate as outcome

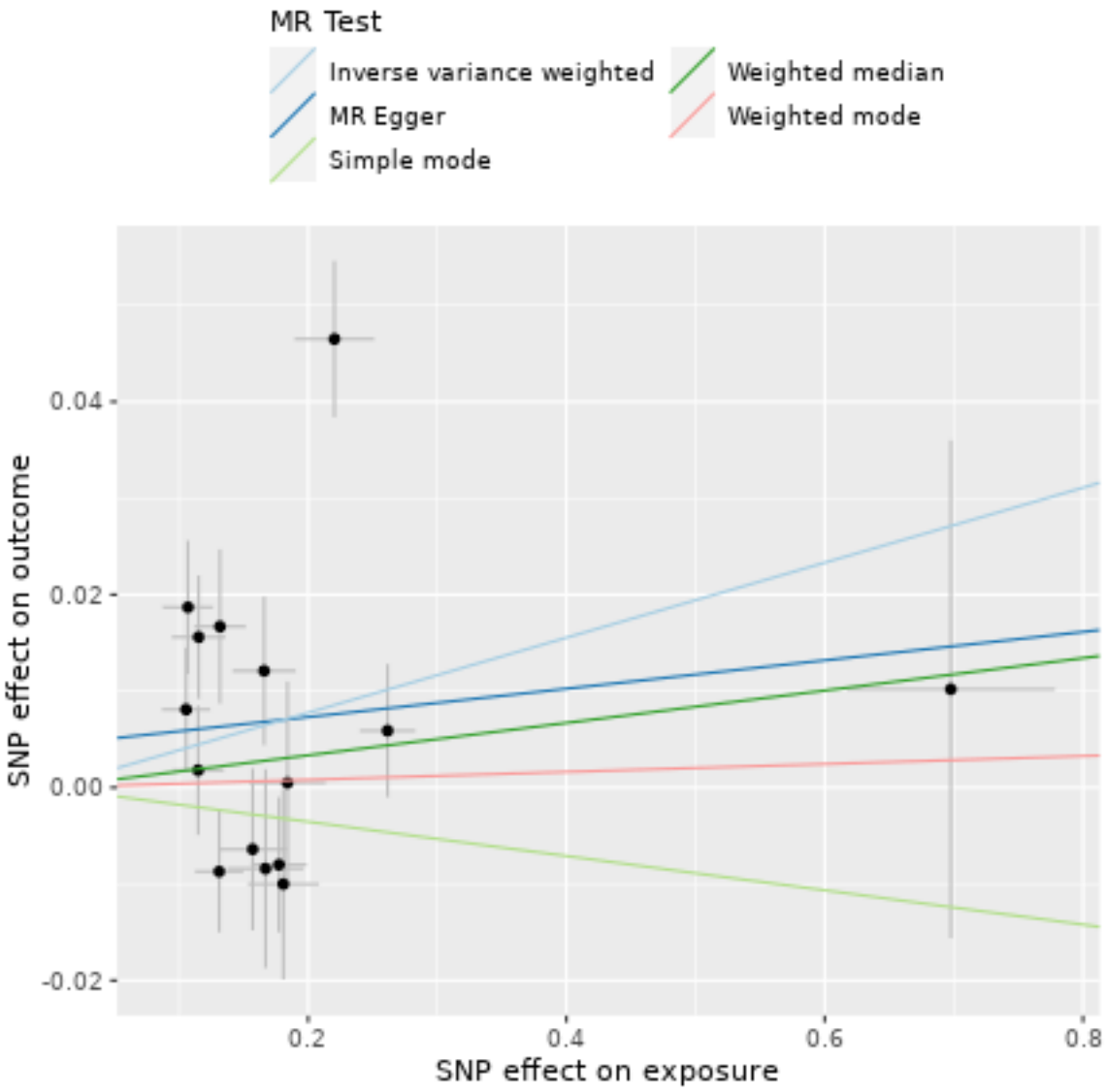


Keratinocytes cancers

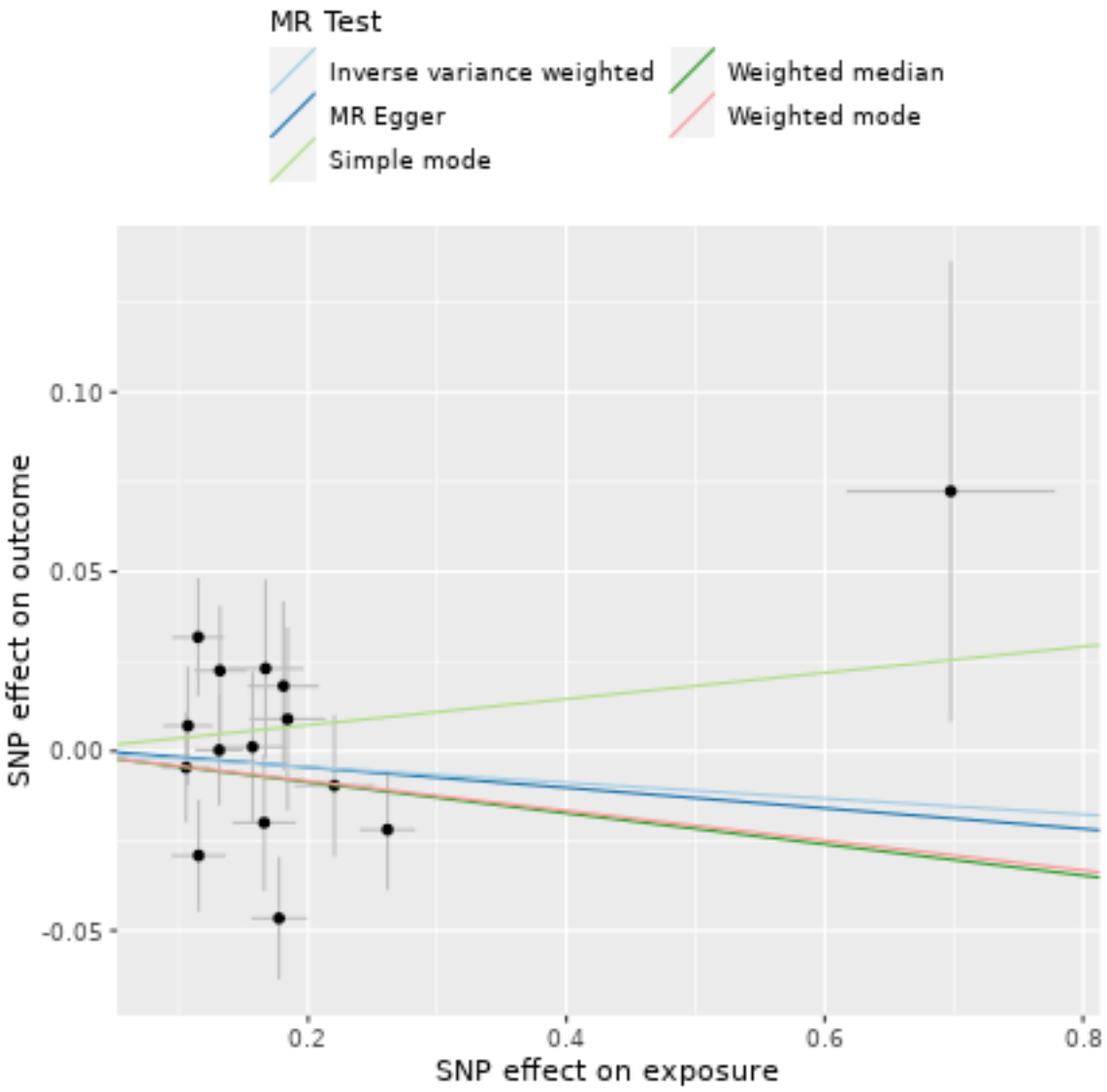


Supplementary Figure 5. Reverse MR (PD as exposure; Cancers as outcome). Plots showing point estimates of the exposures of interest; Exposure of interest at the top of each plot

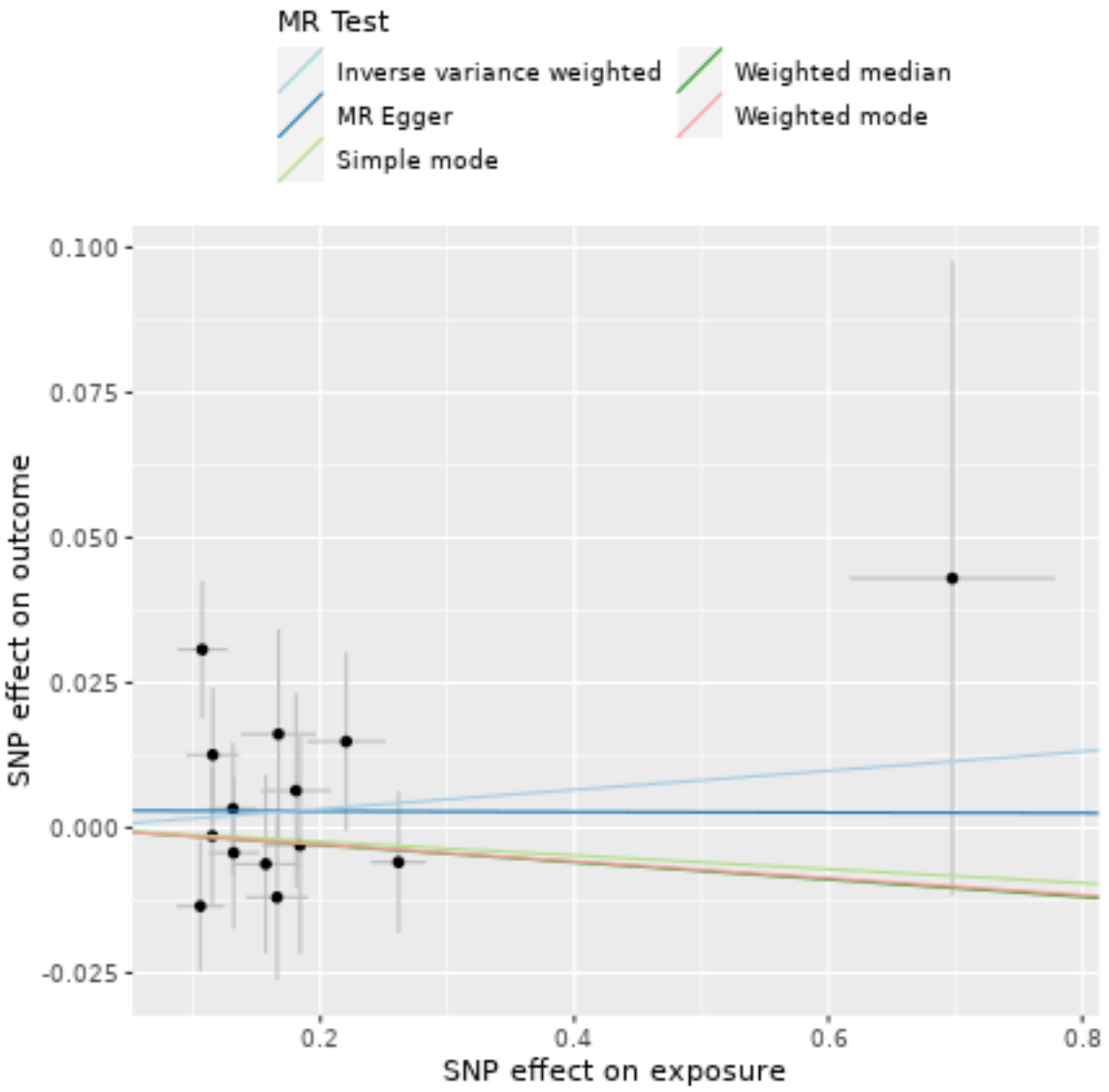
Breast cancer as outcome



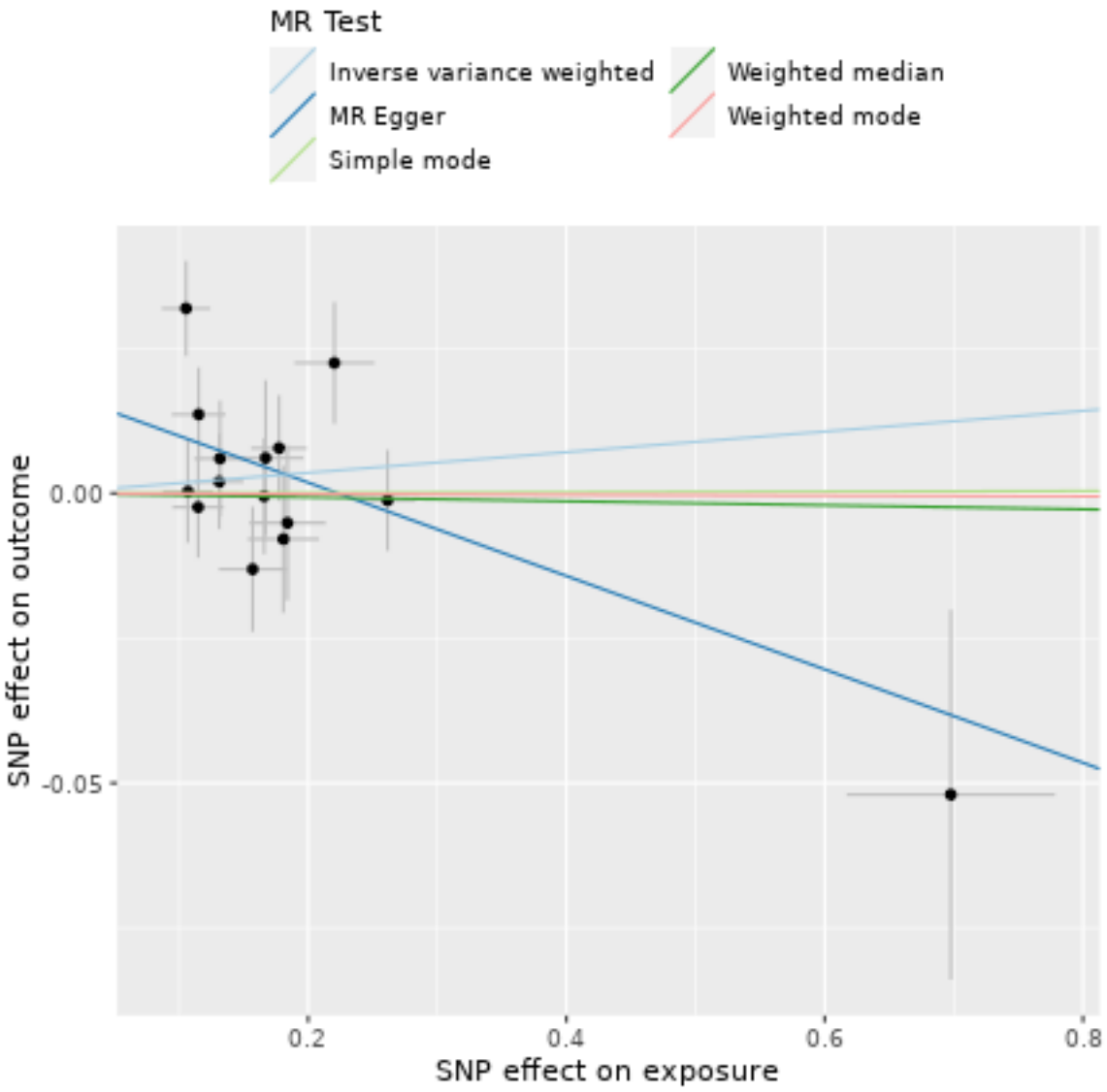
Endometrial cancer as outcome



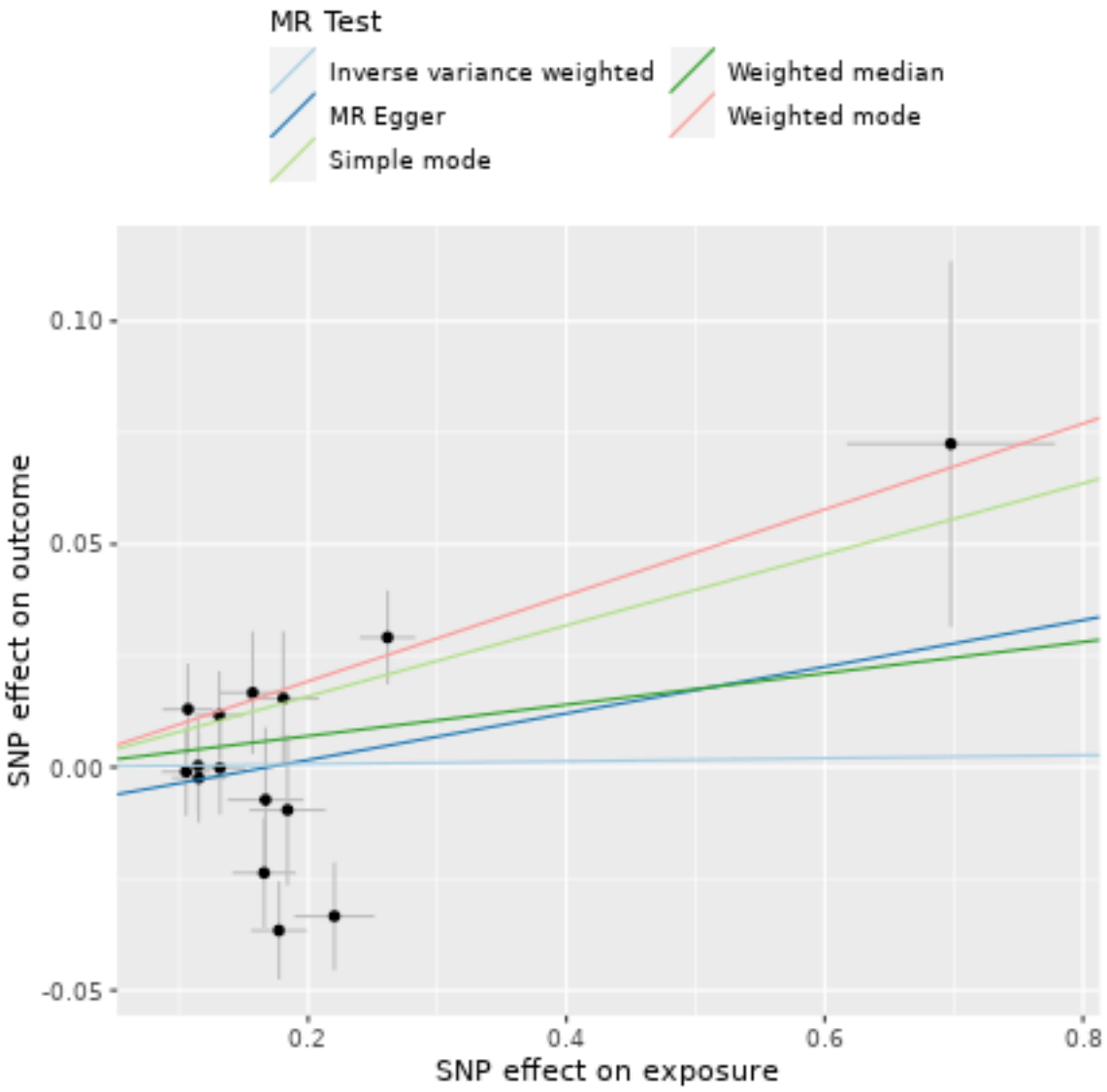
Melanoma as outcome



Prostate as outcome

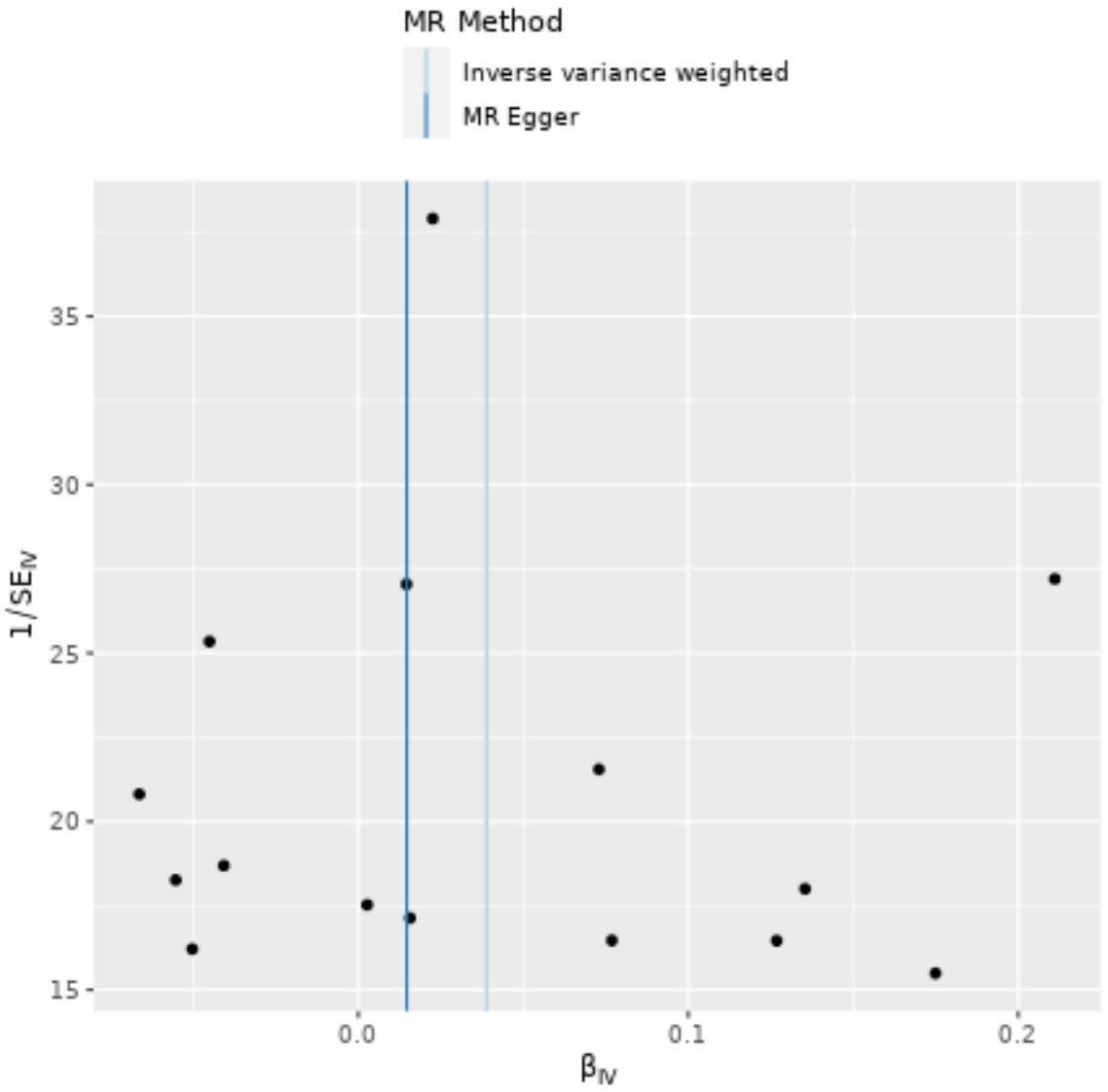


Keratinocytes cancers

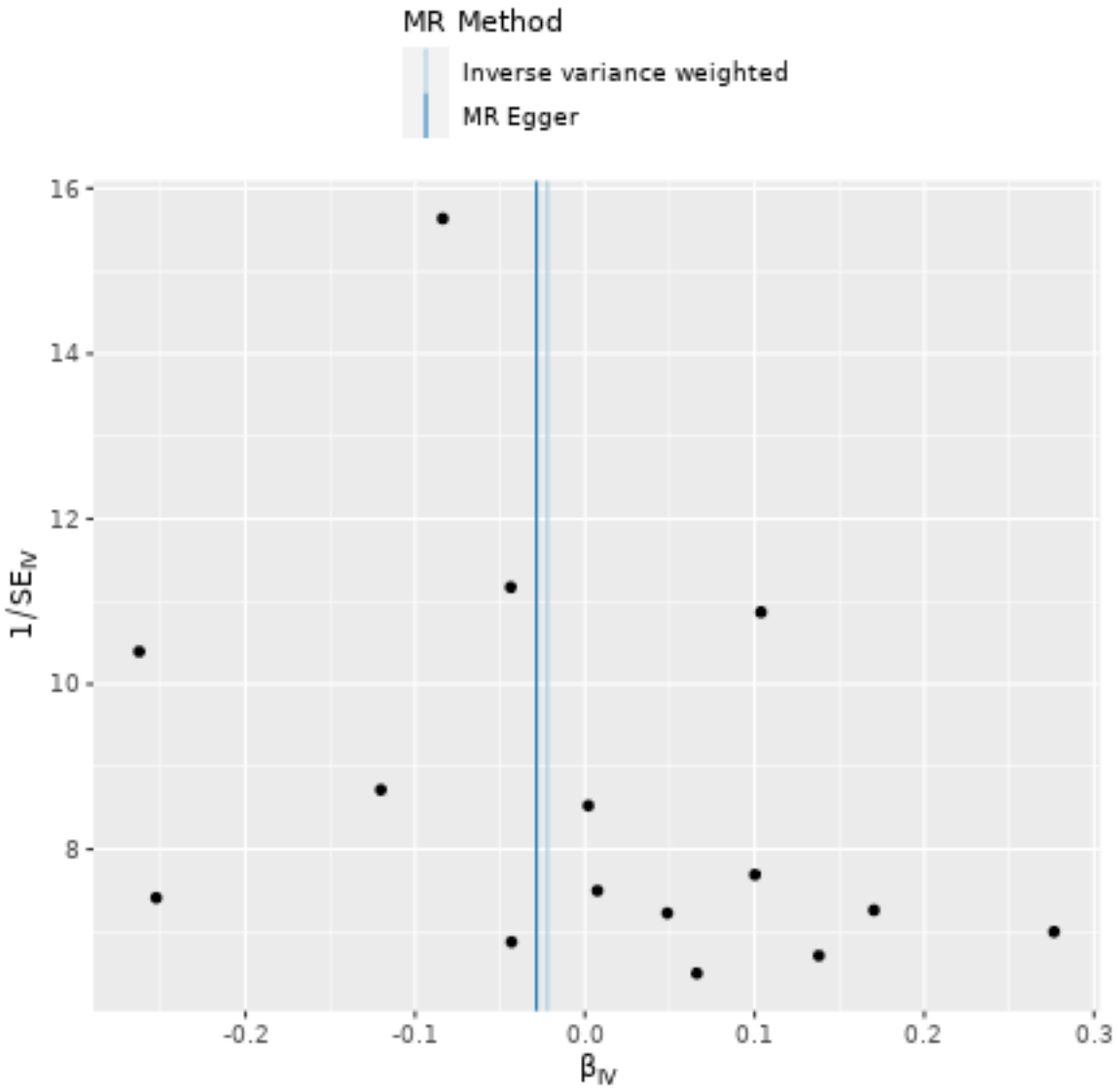


Supplementary Figure 6. Reverse MR (PD as exposure; Cancers as outcome). Funnel plots evaluated the presence of possible heterogeneity across the estimates. Exposure of interest at the top of each plot

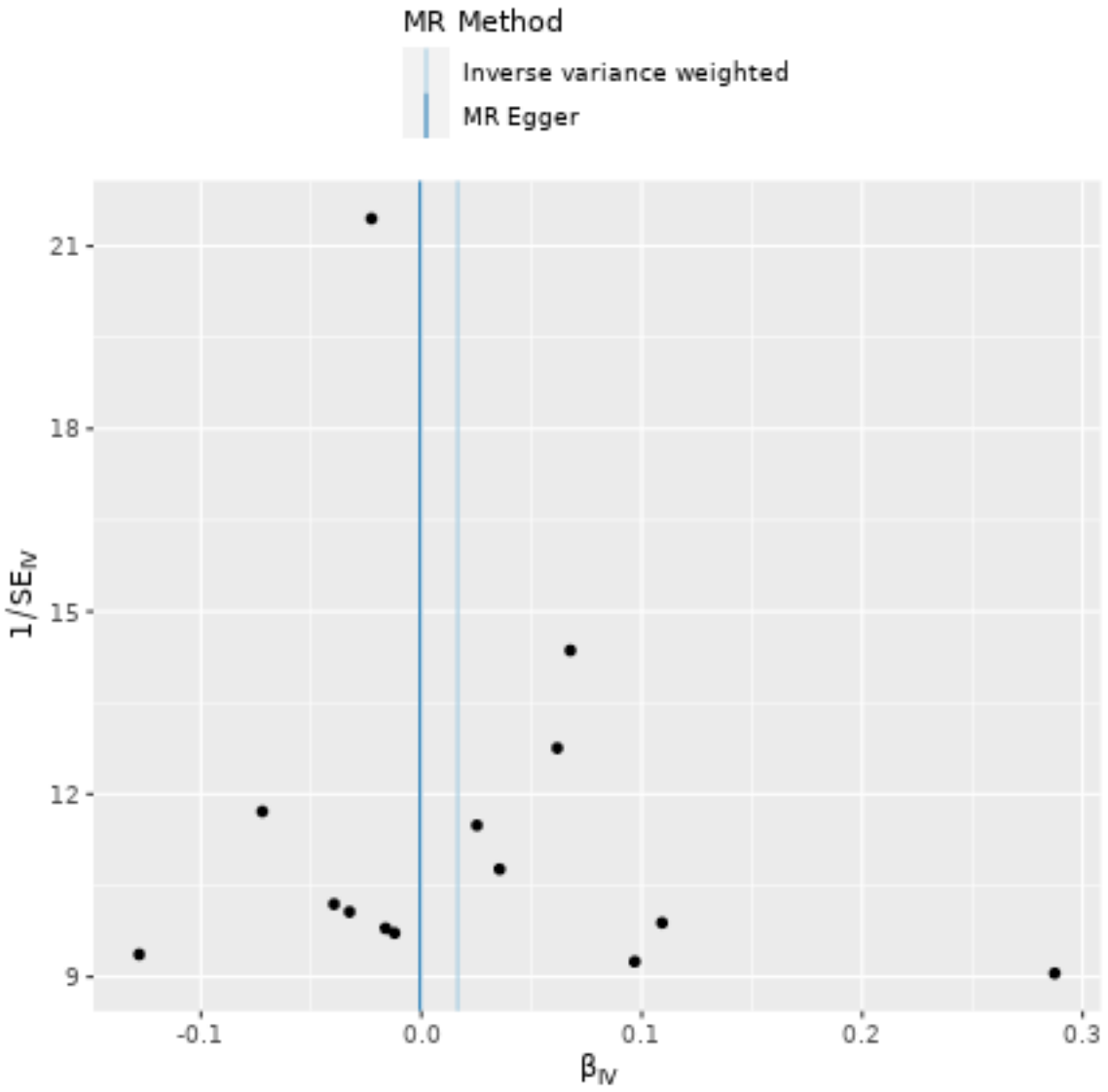
Breast cancer as outcome



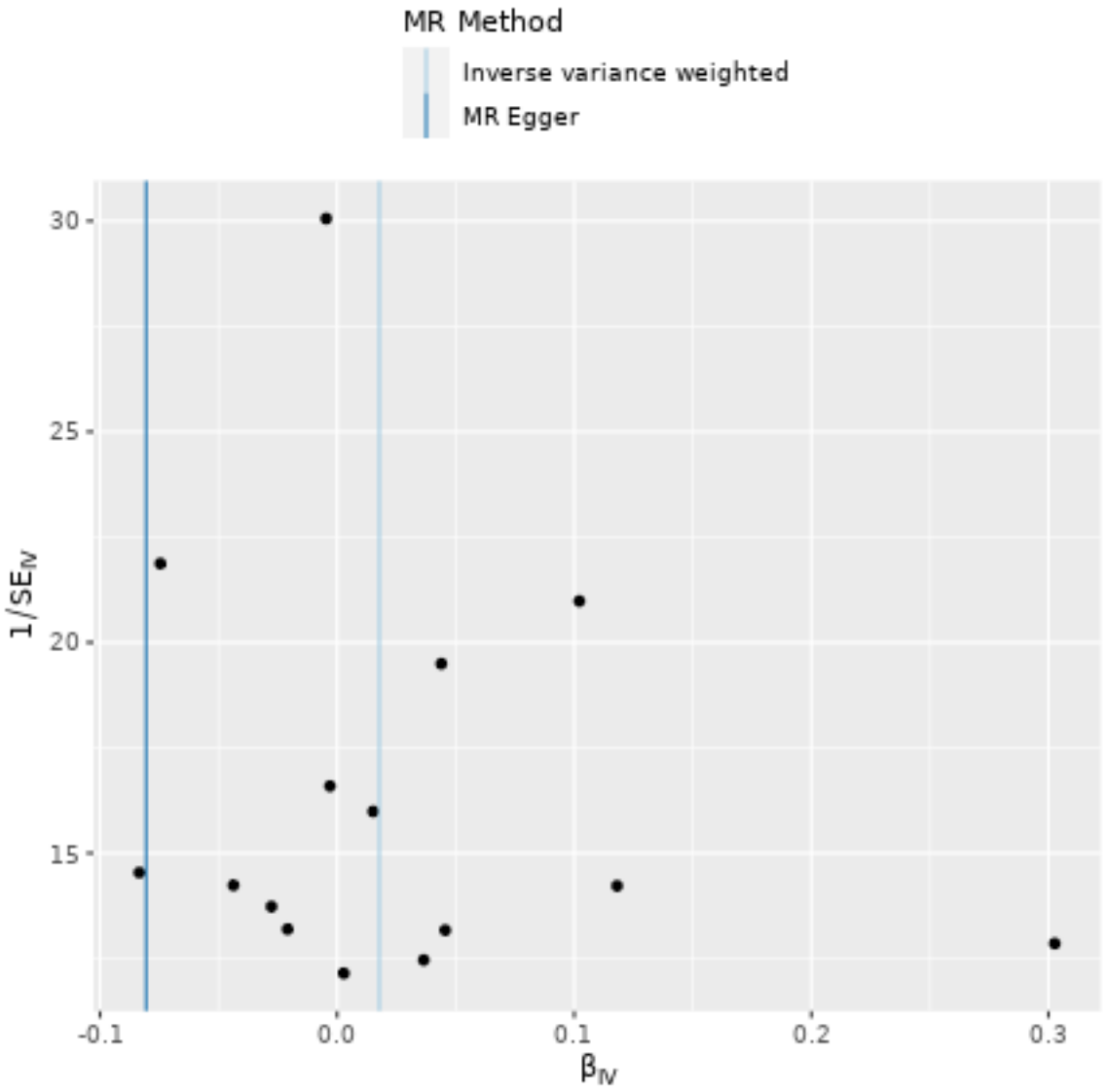
Endometrial cancer as outcome



Melanoma as outcome



Prostate cancer as outcome



Keratinocytes cancers