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Assessment of Causal Effects of Visceral Adipose Tissue on Risk of Cancers: A Mendelian Randomization Study

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Abstract

Background: Despite the established association between obesity and cancer risk, it remains unclear whether visceral obesity is causally related to cancer risk and whether it is more pro-oncogenic than total body fat.

Methods: We conducted two-sample Mendelian randomization (MR) analysis to assess the causal effects of visceral adipose tissue (VAT) on six common cancers. For exposure data, 221 genetic variants associated with the predicted volume of VAT in 325,153 Europeans from UK Biobank were used as instrumental variables. Genetic association data of six common cancers (breast, lung, colorectal, ovarian, pancreatic, and prostate cancers) were obtained from large-scale consortia with an average of 19,576 cases and 43,272 controls. We performed univariable MR with five MR methods [inverse-variance weighted (IVW), MR-Egger regression, weighted median, MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO), and Radial MR] and multivariable MR to estimate the effect of VAT independent of body mass index (BMI). Finally, we performed a series of sensitivity analyses as validation of primary MR results.

Results: Two associations survived the false discovery rate correction for multiple testing (q-value < 0.05): in IVW, the odds ratios (95% CIs) per unit increase in genetically determined VAT were 1.65 (1.03 to 2.62) for pancreatic cancer and 1.47 (1.20 to 1.82) for lung squamous-cell carcinoma, respectively, which showed the same directions and overlapped confidence intervals with MR-Egger regression and weighted median results. There were no outlier variants identified by MR-PRESSO and no evidence supporting the presence of heterogeneity and pleiotropy in sensitivity analyses.

Although with wider confidence intervals that included the null, multivariable MR results for these two cancers showed the same directions and similar effect sizes as in IVW, which were independent of the effect from BMI. There was no evidence for a causal effect of VAT on the risk of other types of cancer.

Conclusions: Our findings suggest that lifelong exposure to elevated volumes of VAT might increase the risk of pancreatic cancer and lung squamous-cell carcinoma, highlighting the importance to reveal the underlying mechanisms for intervention targets.

Keywords: Mendelian randomization, visceral adipose tissue, cancers, causal inference

Key Messages

- We conducted a systematic two-sample Mendelian randomization (MR) analysis to estimate the causal effects of viscera adipose tissue (VAT) on six common cancers.
- Univariable and multivariable MR results suggested that genetically determined VAT might increase the risk of pancreatic cancer and lung squamous-cell carcinoma, which were independent of the effect from body mass index (BMI).
- Future studies are needed to clarify the non-linear relationships between VAT and cancer risks.

Introduction

The prevalence of excess body weight and the associated cancer burden have been rising worldwide. Epidemiologic studies have shown that obesity, measured by body mass index (BMI), is associated with 13 different types of cancers(1). However, BMI is an indirect indicator and does not reflect the difference between fat and lean body mass, nor does it reflect the location of adipose (i.e., central, peripheral, or in the organ at risk). It is known that central adiposity, primarily referring to visceral adipose tissue (VAT), is more harmful than adipose from other locations(2), resulting in a metabolic, hormonal and inflammatory milieu that features tumor promotion(3). An increasing number of studies indicated that VAT represents a risk factor for metabolic disorders as well as some types of cancers(4-6). Accurate measurement of VAT depends on imaging methods such as magnetic resonance imaging (MRI) and computed tomography (CT), limiting its broad application to the general population. Therefore, previous studies were largely limited by small sample sizes. Moreover, due to their observational nature, these studies were likely subject to residual confounding and reverse causation, restricting their ability for causal inference.

In contrast to observational studies with the above limitations, Mendelian randomization (MR) offers an approach to efficiently and reliably investigate the potential causal relationships between increased VAT and cancer risks. MR is considered as ‘nature’s randomized control trial’(7), using genetic variants robustly associated with the exposure of interest to explore causal effects on the outcomes(8), which can therefore address the limitations above in observational studies. In this study,

we performed two-sample MR analyses to evaluate the causal effects of VAT on the risk of different cancers and whether the estimates were independent of BMI.

Methods

Study design

The flow chart of our study design is shown in Figure 1. Firstly, we identified genetic variants as instrumental variables (IVs) for VAT. Secondly, we collected the summary data containing all single nucleotide polymorphisms (SNPs) from the large-scale genome-wide association studies (GWASes) for cancers; Thirdly, we performed univariable two-sample MR with five MR methods, including inverse-variance weighted (IVW), MR-Egger regression, weighted median, MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO), and Radial regression of MR (Radial MR). Fourthly, we conducted a series of sensitivity analyses and multivariable MR (to adjust for BMI); Finally, we compared our MR results with observational studies by performing a systematic review.

Selection of genetic predictors of VAT

UK Biobank recruited more than 500,000 individuals aged 37–73 years old across the United Kingdom between 2006 and 2010. It aimed to identify the phenotypic and health-related information by following up participants over time. All participants gave written informed consent for data collection, analysis, and record linkage. A recent study constructed 2 sub-cohorts to predict VAT in UK Biobank: one was called VAT-

training dataset measured by dual energy x-ray absorptiometry (DXA, GE Healthcare Lunar iDXA scanner) and used to create prediction models; and the other was called VAT-application dataset, in which VAT was calculated according to the prediction models [coefficient of determination = 0.76 (0.74 to 0.78)]. After screening and quality control, a total of 4,198 and 325,153 participants enrolled in the training dataset for model construction and application dataset for genome-wide association (GWA) analyses, respectively(9). In total, 11 predictors (age, menopause status in females, waist circumference, hip circumference, height, weight, and impedance of limbs and whole body) distributed on 20 different linear and interaction terms (age × weight, waist circumference × weight, et al.) were included in the prediction models. Two reduced prediction models (menopause status, hip circumference, and 5 bio-electrical impedance predictors were omitted in males, and age, menopause status, height, right arm and right leg impedance were omitted in females), which included only regression terms with p-values < 0.05, were developed for use in the clinic, while the two full models included all terms. Overall, the training and application datasets had similar characteristics, and the median depot of VAT was ~2.5 times larger in males than females. GWA analyses for predicted VAT were performed using linear regression models in males (N = 164,004) and females (N = 161,149) separately, and the sex-combined associations were subsequently computed using a fixed-effect meta-analysis. GWAS summary data for predicted VAT are available at https://www.ebi.ac.uk/gwas/downloads/summary-statistics (Study Accession ID: GCST008744 for combined sexes, GCST008743 for males only, and GCST008742 for

females only).

Among the SNPs available in each GWAS summary dataset, we selected SNPs robustly associated with VAT as instrumental variables (IVs) ($P < 5 \times 10^{-8}$, IV Assumption 1, Figure 2). To minimize the influence of linkage disequilibrium (LD), which may bias the results of randomized allele allocation, a stringent condition (LD threshold of $r^2 < 0.001$ and distance located 10000 kb apart from each other) was set to ensure that the genetic instruments selected for VAT are conditionally independent to each other. *F*-statistic represents the strength of the relationship between IVs and VAT. Generally, $F > 10$ may attenuate bias produced by weak IVs(10).

Similarly, we extracted BMI GWAS summary data for combined sexes from a meta-analysis of GWASes including 681,275 participants(11) and sex-specific data from another meta-analysis of GWASes including 152,893 males and 171,977 females (12), respectively. These data were from the Genetic Investigation of ANthropometric Traits (GIANT) consortium (https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files).

Selection of cancer outcomes

We collected summary data of six common types of cancers from large-scale consortia: breast cancer from Breast Cancer Association Consortium (BCAC)(13), lung cancer from International Lung Cancer Consortium (ILCCO)(14), colorectal cancer from Genetic Epidemiology Research in Adult Health and Aging (GERA)(15), ovarian

cancer from Ovarian Cancer Association Consortium (OCAC)(16), pancreatic cancer from Pancreatic Cancer Cohort Consortium (PANSCAN)(17), and prostate cancer from Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL)(15). Summary statistics of the largest available GWAS were extracted from the MR-Base database(18). The participants had an identical genetic background (European ancestry), and to our knowledge, there was no sample overlap between the exposure and outcome GWASes.

Comparison with observational studies

To compare the MR results with observational results reported by previous epidemiological studies, we searched the electronic databases of PubMed, Medline, and Embase from database inception to October 15, 2021, with no language restrictions, for studies in humans of the associations between visceral adipose tissue volume and cancer incidence for six cancer types: colorectal (colon and rectum), lung (adenocarcinoma and squamous cell carcinoma), and pancreatic cancers for combined sexes, breast (premenopausal and postmenopausal) and ovarian cancers for females, and prostate cancer for males. Our core search consisted of terms related to VAT (visceral adipose tissue, VAT, and visceral fat), combined with the terms for each cancer type (Table S1, Figure S1, and see Supplementary Methods for the details of review protocol).

Statistical Analysis

Two-sample Mendelian randomization

As shown in Figure 2, we estimated the causal effect of VAT on cancers using a classic MR model: $\beta_{\text{causal effect}} = \beta_{ZY} / \beta_{ZX}$ (β_{ZX} and β_{ZY} represent the regression coefficient of SNPs on VAT and cancers, respectively)(8, 19). Ideally, a valid instrument should satisfy 3 assumptions (Figure 2): (1) must be truly associated with VAT (in this study, defined as the genetic association with $P < 5 \times 10^{-8}$); (2) not associated with confounders of VAT and cancers; and (3) should only be associated with the cancers through VAT.

To evaluate the causal effects of VAT on cancer risk by combining multiple SNPs, we conducted a two-sample Mendelian randomization(20) analysis using four primary methods, including IVW(21), MR-Egger regression(22), weighted median(23)，and MR-PRESSO(24). The IVW is a conventional method to obtain an MR estimate performing a meta-analysis of each Wald ratio for multiple SNPs. The weighted median estimator makes the median effect of SNPs, allowing up to 50% of the invalid SNPs. The MR-Egger regression, with a relaxed criterion, allows the presence of horizontal pleiotropy across SNPs. It requires the InSIDE (Instrument Strength Independent of Direct Effect) assumption to be satisfied(22). However, it has less power and provides wider confidence intervals than the IVW. The MR-PRESSO regresses the SNP-outcome estimates against the SNP-exposure estimates to test for outlier SNPs and outputs a corrected MR estimate. In addition, we used Radial regression of MR (Radial MR) as an alternative method of MR-PRESSO to identify outlier SNPs(25).

When examining the effects of VAT on sex-specific cancers such as ovarian cancer, breast cancer, and prostate cancer, we used the VAT GWAS results from the same sex

as the exposure GWAS data. For example, we used the VAT GWAS results from women in the analysis for breast cancer. For other cancers, sex-combined GWAS results for VAT were used. All results were corrected for multiple testing using the false discovery rate (FDR) method, and FDR *q*-values were provided.

MR sensitivity analyses

We evaluated the heterogeneity of the results using the Cochran's Q-test(26) and detected the potential presence of horizontal pleiotropy using the MR-Egger intercept tests. We also performed the leave-one-out analysis by eliminating SNPs one by one and recomputing the effect. Once heterogeneity or horizontal pleiotropy was noted, we recomputed IVW and MR-Egger estimates after removing the outlier SNPs identified by MR-PRESSO or Radial MR.

Multivariable Mendelian randomization

MR analysis adjusted for potential confounders has a distinct advantage in favor of specifying the independent effect of VAT on the outcome. As BMI is highly correlated with VAT, and BMI has been reported to be related to several cancers(27-29), we additionally used multivariable MR (MVMR) analysis to estimate the direct causal effects of VAT on the risk of six cancers independent of the effect from BMI.

Based on the analyses above, we took the IVW results as the primary causal effect estimates and considered the consistency of the results across all MR methods. In this study, we defined the evidence for a potential causal effect when the following criteria

were met: (1) one of the IVW and MVMR results had an FDR q-value < 0.05; (2) IVW and MVMR showed the same effect direction and overlapped confidence intervals; (3) other MR methods showed the same effect direction and similar effect sizes with IVW and MVMR; and (4) there was no evidence of horizontal pleiotropy (i.e. p-value for Egger intercept > 0.05).

MR analyses were performed in R (version 4.0.4) with R packages 'vroom', 'tidyr', 'tibble', 'dplyr', 'TwoSampleMR'(18), 'MR-PRESSO'(24), 'RadialMR'(25), and 'MVMR'(30). FDR q-values were estimated using the R package 'fdrtool'.

Results

Participant characteristics and instruments

The characteristics of the participants from UK Biobank, GIANT, and consortia of cancer outcomes are shown in Table 1. We selected 221, 96, and 70 SNPs as instruments for predicted VAT (Table S2-S4) in combined sexes, males, and females, respectively. The F-statistic ranged from 901.13 to 1260.80, reflecting strong instrument strength. We also selected 490, 30, and 37 BMI-associated SNPs for combined sexes, males, and females, respectively, to perform multivariable MR analysis.

Estimation of causal effects of VAT on cancers

Univariable two-sample MR results

Table 2 shows the results of univariable MR analysis for the effect of increased VAT on cancer risks. IVW results showed that genetically increased VAT was associated with a

higher risk for pancreatic cancer (OR=1.65, 95% CI=1.03 to 2.62), total lung cancer (OR=1.24, 95% CI=1.06 to 1.45) and its subtype lung squamous-cell carcinoma (OR=1.47, 95% CI=1.20 to 1.82). Of these, the results from other MR methods were largely consistent with the IVW results for pancreatic cancer ($P < 0.05$ in both MR-Egger regression and weighted median). The association between increased VAT and lung squamous-cell carcinoma showed similar effect sizes and overlapped confidence intervals across different univariable MR methods. Subsequently, the IVW results for pancreatic cancer, total lung cancer, and lung squamous-cell carcinoma survived the multiple testing correction (FDR q-value < 0.05). There was little evidence to support an association between genetically increased VAT and other cancer types.

MR sensitivity analysis results

We conducted a series of sensitivity analyses to evaluate the heterogeneity and potential horizontal pleiotropy (Table 2). Cochran's Q-test showed evidence ($P_h < 0.05$) for the presence of heterogeneity in the IVW results for high-serous ovarian cancer, endometroid ovarian cancer, breast cancer and its subtype ER+ breast cancer, lung cancer and its subtype lung adenocarcinoma, and prostate cancer ($P_h < 0.05$). The MR-Egger intercept tests showed the presence of unbalanced horizontal pleiotropy ($P_{intercept} < 0.05$) for breast cancer and pancreatic cancer. MR-PRESSO and Radial MR did not identify any outlier SNPs for pancreatic cancer. The funnel plots showed a relatively symmetrical distribution of variant effects for pancreatic cancer and lung squamous-cell carcinoma, indicating an absence of directional pleiotropy (Figure 4). The leave-

one-out analysis found that the MR estimates remained stable when sequentially dropping a single SNP out (Figure S2-S7).

Multivariable MR results adjusted for BMI

Although the associations of VAT with pancreatic cancer (OR=1.35, 95% CI=0.63 to 2.93) and lung squamous-cell carcinoma (OR=1.40, 95% CI=0.97 to 2.01) were attenuated in multivariable MR with the adjustment for BMI, they still showed the same effect direction and overlapped confidence intervals with the IVW results. There was no evidence for a causal relationship between VAT and the risk of any other types of cancer (Figure 3).

Discussion

In this study, we performed MR analyses to evaluate the causal relationship between VAT and the risk of six common cancers. We found that genetically increased VAT had a causal effect on the risk of pancreatic cancer and lung squamous-cell carcinoma. However, some of our findings were inconsistent with previous observational studies (Table 3 and Figure 3).

Few observational studies have specifically investigated the association between VAT and ovarian cancer, and most published studies have only focused on BMI or weight circumference (WC) as the exposure(31, 32). It has been reported that the adipocytes in the tumor microenvironment may result in the metastasis, growth and angiogenesis of ovarian cancer(33). However, we found that ovarian cancer and its subtypes were

not causally affected by VAT in our MR analysis. For lung cancer, we failed to retrieve any publications describing the association of VAT with lung cancer and its subtypes. A meta-analysis of prospective studies suggests that abdominal obesity, measured by WC, may play a critical role in the development of lung cancer(34). We observed a causal relationship between VAT and a higher risk of lung squamous-cell carcinoma, other than lung adenocarcinoma.

Notably, lung squamous-cell carcinoma has been demonstrated to be remarkably distinct from the other subtype. The underlying mechanisms may be attributable to the following two aspects. Firstly, different cell types differ in their ability to repair DNA damage, which is associated with chronic inflammation caused by obesity(35). Compared with subcutaneous adiposity, visceral adiposity is more metabolically active and may be more strongly linked with chronic inflammation(36). Then more cytokines and adipokines are released, which promote DNA damage and dysregulation of DNA repair pathways, increasing the mutation rate and leading to the transformation of healthy tissues to cancer(37), especially for repair deficient cells. Secondly, different cancer types may have different susceptibility to environmental influences. For instance, lung squamous-cell carcinoma originates from squamous metaplasia of bronchial epithelium, which is more vulnerable to environmental factors(38-40). Further observational studies focusing on the association between VAT and ovarian and lung cancer subtypes and tissue-specific basic research are needed to reveal the possible mechanisms.

Since VAT is in close proximity to the pancreas, they may directly interact with each

other. For example, increased VAT leads to fatty infiltration in the pancreas and is correlated with pancreatic intraepithelial neoplasia (PanIN), which has a high risk of conversion to pancreatic ductal adenocarcinoma (PDAC)(41). Similarly, our MR results showed a causal relationship between genetically determined VAT and pancreatic cancer, which was supported by further sensitivity analysis.

We did not find evidence for a causal effect of VAT on breast cancer and its two subtypes in either univariable or multivariable MR analysis. In contrast, most observational studies have reported a positive association between VAT and breast cancer risk(42, 43). As VAT is more metabolically active than subcutaneous adipose tissue (SAT), the increased levels of adipokines such as IL-6, IL-1β, and leptin contribute to insulin resistance(44, 45), which is in turn associated with an increased risk of breast cancer(46, 47). Moreover, hyposecretion of adiponectin due to VAT accumulation has been associated with increased proliferation of tumor cells in breast cancer(45, 48). It has been reported that the association between BMI and breast cancer is complicated by different menopausal statuses. More specifically, the inverse association between adult BMI and premenopausal breast cancer is consistently supported by previous studies, while MR results for postmenopausal breast cancer are in contrast with conventional observational studies in favor of a positive association. The discrepancy may be partly attributed to early life body shape and postmenopausal weight gain (27, 28).

There was no evidence supporting the VAT as a causal factor on the risk of colorectal cancer or prostate cancer in our study. Although meta-analysis and observational studies have found that increased VAT measured by CT is linked to the etiology of colorectal

adenoma and colorectal cancer(49-53), these studies were all based on Asian populations, which may not be generalizable to other ethnic groups. The evidence of European populations came from a small case-control study, which did not show different volumes of visceral fat between cases and controls (P = 0.156)(54). On the other hand, CT-measured VAT has been shown as a risk factor (OR=4.6, 95% CI=2.6 to 8.2) for prostate cancer in a case-control study(55). No association between VAT and the risk of total prostate cancer (OR=1.02, 95% CI=0.88 to 1.19) was found in another prospective study including 1832 participants(56). These observational studies, nonetheless, might have suffered from issues such as small sample sizes, reverse causality, and residual confounding.

Strength and limitations

To the best of our knowledge, this study is the first to systematically assess the causal effect of VAT on multiple cancer risks using MR. We applied a series of sensitivity analyses and multivariable MR to test the assumptions of MR and minimize the influence of potential confounders and horizontal pleiotropy. Given that the profound differences of male/female proportions between the exposure and outcome populations could be a potential confounder, which might substantially influence the direction or magnitude of causal relationships between VAT and sex-specific cancers, we conducted sex-specific MR analyses to reduce the bias of causal effect estimation and make our MR results more reliable.

Notably, there are also four major limitations in our study. First, as the training models for the VAT prediction was established on a relatively small subset of data, GWAS

results for predicted VAT may not reflect genetic associations with the true volume of VAT, and the IVs selected from these GWAS results was likely to introduce biases. Second, these IVs could only explain a small part of the variation in VAT, resulting in limited statistical power and imprecision of MR estimates. Third, to ensure the consistency of genetic background, only European-ancestry participants were included in our MR analysis, limiting the generalizability of the conclusions to other ethnic groups. Fourth, we could not rule out the possibility that the association between VAT and cancer risks may be non-linear. Current MR methods based on summary-level data assume that the exposure-outcome relationship is linear when estimating causal effects. Therefore, this possible non-linear relation should be investigated using individual-level data in future research.

Conclusions

In summary, this MR study suggests that lifelong exposure to elevated volumes of VAT might increase the risk of pancreatic cancer and lung squamous-cell carcinoma. Further studies are needed to determine the reliability of VAT as a predictor of cancer risks, evaluate the mediating mechanisms for potential intervention targets, and explore the possible non-linear relationship using individual-level data.

List of abbreviations

BCAC, Breast Cancer Association Consortium; BIA, bioelectrical impedance analysis; BMI, Body mass index; CI, Confidence interval; CT, Computed tomography; DXA,

Dual energy x-ray absorptiometry; ER, Estrogen receptor; GERA, Genetic Epidemiology Research in Adult Health and Aging; GIANT, The Genetic Investigation of ANthropometric Traits; GWAS, Genome-wide association studies; IARC, The International Agency for Research on Cancer; ILCCO, International Lung Cancer Consortium; IVs, Instrumental variables; IVW, Inverse-variance weighted; LD, Linkage disequilibrium; MR, Mendelian randomization; MRI, Magnetic resonance imaging; MR-PRESSO, Mendelian randomization-Pleiotropy Residual Sum and Outlier; MVMR, multivariable Mendelian randomization; OCAC, Ovarian Cancer Association Consortium; OR, Odds ratio; PanIN, Pancreatic intraepithelial neoplasia; PANSCAN, Pancreatic Cancer Cohort Consortium; PDAC, Pancreatic ductal adenocarcinoma; PRACTICAL, Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome; SAT, Subcutaneous adipose tissue; SNP, Single variant polymorphisms; VAT, Visceral adipose tissue; WC, Waist circumference; WHR, Waist-hip ratio.

Ethics approval

The UK Biobank study has ethical approval from the North West Multicentre Research Ethics Committee (MREC). For cancer-related consortia, all participating studies were approved by their appropriate ethics review board and all participants provided informed written consent.

Data availability

The datasets were derived from sources in the public domain: GWAS Catalog (https://www.ebi.ac.uk/gwas/home) and MR-Base (https://www.mrbase.org/).

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

YL, HBT, and PYH: Formal analysis; Statistic analysis; Writing original draft. JW, PZD., and YLL.: Data collection. JZ and LW: Methodology; Writing review and editing; Supervision.

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Table 1. Characteristics of cancer consortia and UK Biobank datasets.

Variables	Consortium	SNPs*	Cases/Controls	Sample size	Population
Exposure					
VAT (sex-combined)	UK Biobank	221	Not relevant	325,153	European-ancestry
VAT (male)	UK Biobank	96	Not relevant	164,004	European-ancestry
VAT (female)	UK Biobank	70	Not relevant	161,149	European-ancestry
Outcomes					
Ovarian cancer	OCAC	70	25,509/40,941	66,450	European-ancestry
Low grade mucinous	OCAC	70	1,149/40,941	42,090	European-ancestry
Invasive mucinous	OCAC	70	1,417/40,941	42,358	European-ancestry
Low grade serous	OCAC	70	1,012/40,941	41,953	European-ancestry
High grade serous	OCAC	70	13,037/40,941	53,978	European-ancestry
Endometrioid	OCAC	70	2,810/40,941	43,751	European-ancestry
Clear cell	OCAC	70	1,366/40,941	42,090	European-ancestry
Pancreatic cancer	PANSCAN	118	1,896/1,939	3,835	European-ancestry
Breast cancer	BCAC	70	122,977/105,974	228,951	European-ancestry
ER+	BCAC	70	69,501/105,974	175,475	European-ancestry
ER-	BCAC	70	21,468/105,974	127,442	European-ancestry
Lung cancer	ILCCO	206	11,348/15,861	27,209	European-ancestry
Adenocarcinoma	ILCCO	206	3,442/14,894	18,336	European-ancestry
Squamous-cell carcinoma	ILCCO	206	3,275/15,038	18,313	European-ancestry
Colorectal cancer	GERA	172	3,793/50,525	54,318	European-ancestry
Prostate cancer	PRACTICAL	96	46,939/27,910	74,849	European-ancestry

*Numbers for the exposure represent the total number of VAT instrumental SNPs; numbers for the outcomes represent the number of VAT instrumental SNPs (either sex-combined or sex-specific, whichever is the most appropriate) available in each outcome GWAS.

VAT, visceral adipose tissue; BMI, body mass index; SNP, single nucleotide polymorphism; ER, estrogen receptor; GIANT, The Genetic Investigation of ANthropometric Traits; BCAC, Breast Cancer Association Consortium; ILCCO, International Lung Cancer Consortium; GERA, Genetic Epidemiology Research in Adult Health and Aging; OCAC, Ovarian Cancer Association Consortium; PANSCAN, Pancreatic Cancer Cohort Consortium; PRACTICAL, Prostate Cancer

Association Group to Investigate Cancer Associated Alterations in the Genome; GWAS, genome-wide association study.

Table 2. Two-sample Mendelian randomization results for the effect of visceral adipose tissue on the risk of different types of cancer.

Outcomes	Methods	Odds ratio (95% CI)	*p*-value	*q*-value[a]	Q-statistics	P_h	Egger intercept	$P_{intercept}$
Ovarian cancer	MR-Egger	1.13 (0.67-1.89)	6.62E-01	1.66E-01	75.56	8.49E-02	-0.001 (-0.015-0.015)	9.90E-01
	Inverse-variance weighted	1.12 (0.96-1.31)	1.44E-01	1.13E-01	75.56	9.94E-02		
	Weighted median	1.05 (0.85-1.30)	6.32E-01	5.25E-01				
	MR-PRESSO	1.12 (0.97-1.30)	1.38E-01	1.49E-01				
Ovarian cancer	MR-Egger	0.74 (0.14-3.84)	7.23E-01	1.74E-01	68.79	2.31E-01	0.023 (-0.031-0.061)	5.14E-01
(Low-mucinous)	Inverse-variance weighted	1.26 (0.78-2.03)	3.52E-01	1.64E-01	69.27	2.46E-01		
	Weighted median	0.91 (0.44-1.89)	7.94E-01	5.81E-01				
Ovarian cancer	MR-Egger	2.85 (0.67-12.10)	1.61E-01	9.69E-02	65.77	3.15E-01	-0.027 (-0.067-0.014)	1.97E-01
(Invasive mucinous)	Inverse-variance weighted	1.14 (0.74-1.74)	5.54E-01	1.85E-01	67.60	2.92E-01		
	Weighted median	1.65 (0.89-3.05)	1.11E-01	1.92E-01				
Ovarian cancer	MR-Egger	1.91 (0.31-11.78)	4.88E-01	1.45E-01	72.57	1.47E-01	-0.025 (-0.076-0.026)	3.44E-01
(Low-serous)	Inverse-variance weighted	0.82 (0.48-1.40)	4.69E-01	1.78E-01	73.65	1.48E-01		
	Weighted median	0.93 (0.42-2.03)	8.49E-01	5.98E-01				
Ovarian cancer	MR-Egger	0.84 (0.44-1.59)	5.97E-01	1.59E-01	79.80	4.46E-02	0.007 (-0.011-0.025)	4.48E-01
(High-serous)	Inverse-variance weighted	1.07 (0.88-1.29)	5.03E-01	1.81E-01	80.57	4.74E-02		
	Weighted median	1.20 (0.92-1.55)	1.74E-01	2.35E-01				
	MR-PRESSO	1.08 (0.90-1.30)	4.08E-01	2.71E-01				
Ovarian cancer	MR-Egger	1.80 (0.57-5.66)	3.20E-01	1.16E-01	79.17	4.93E-02	-0.002 (-0.034-0.031)	9.13E-01
(Endometrioid)	Inverse-variance weighted	1.39 (1.00-1.94)	4.97E-02	5.62E-02	79.19	5.87E-02		
	Weighted median	1.38 (0.86-2.21)	1.78E-01	2.37E-01				
Ovarian cancer	MR-Egger	4.28 (0.94-19.58)	6.55E-02	8.01E-02	71.17	1.75E-01	-0.035 (-0.077-0.008)	1.14E-01
(Clear cell)	Inverse-variance weighted	1.30 (0.83-2.04)	2.49E-01	1.45E-01	74.17	1.38E-01		
	Weighted median	1.73 (0.91-3.29)	9.73E-02	1.92E-01				

Pancreatic cancer	MR-Egger	6.19 (1.57-24.45)	1.05E-02	3.79E-02*	115.39	4.46E-01	-0.030 (-0.05--0.001)	4.72E-02
	Inverse-variance weighted	1.65 (1.03-2.62)	3.53E-02	4.80E-02*	119.47	3.69E-01		
	Weighted median	2.23 (1.10-4.51)	2.63E-02	1.92E-01				
Breast cancer	MR-Egger	0.66 (0.42-1.02)	6.69E-02	8.05E-02	111.33	4.98E-06	0.013 (0.001-0.024)	3.62E-02
	Inverse-variance weighted	1.05 (0.94-1.17)	4.00E-01	1.70E-01	121.02	4.76E-07		
	Weighted median	1.11 (0.98-1.26)	9.09E-02	1.16E-01				
	MR-PRESSO	1.06 (0.95-1.17)	4.49E-01	1.92E-01				
Breast cancer	MR-Egger	0.67 (0.42-1.09)	1.11E-01	9.10E-02	93.65	4.86E-04	0.012 (-0.001-0.025)	6.46E-02
(ER+)	Inverse-variance weighted	1.05 (0.93-1.19)	4.09E-01	1.71E-01	99.94	1.45E-04		
	Weighted median	1.02 (0.88-1.17)	8.19E-01	5.89E-01				
	MR-PRESSO	0.98 (0.88-1.10)	7.61E-01	3.98E-01				
Breast cancer	MR-Egger	0.71 (0.41-1.24)	2.38E-01	1.08E-01	62.39	2.30E-01	0.007 (-0.007-0.022)	3.40E-01
(ER-)	Inverse-variance weighted	0.93 (0.81-1.07)	3.00E-01	1.55E-01	63.43	2.31E-01		
	Weighted median	0.89 (0.72-1.09)	2.54E-01	3.08E-01				
	MR-PRESSO	0.90 (0.78-1.03)	1.46E-01	1.53E-01				
Lung cancer	MR-Egger	1.21 (0.75-1.94)	4.37E-01	1.37E-01	267.59	9.94E-04	0.006 (-0.009-0.106)	9.12E-01
	Inverse-variance weighted	1.24 (1.06-1.45)	6.90E-03	1.56E-02*	267.60	1.16E-03		
	Weighted median	1.21 (0.96-1.50)	1.03E-01	1.92E-01				
	MR-PRESSO	1.24 (1.07-1.45)	4.81E-03	1.01E-02*				
Lung cancer	MR-Egger	0.87 (0.44-1.76)	7.07E-01	1.71E-01	253.86	8.85E-03	0.004 (-0.011-0.018)	6.20E-01
(Adenocarcinoma)	Inverse-variance weighted	1.03 (0.82-1.30)	7.79E-01	2.35E-01	254.17	9.71E-03		
	Weighted median	1.09 (0.78-1.51)	6.11E-01	5.17E-01				
	MR-PRESSO	1.09 (0.87-1.37)	4.56E-01	2.84E-01				
Lung cancer	MR-Egger	1.62 (0.84-3.13)	1.50E-01	9.59E-02	210.37	2.94E-01	-0.002 (-0.016-0.012)	7.59E-01
(Squamous-cell carcinoma)	Inverse-variance weighted	1.47 (1.20-1.82)	3.22E-04	1.46E-03*	210.47	3.09E-01		
	Weighted median	1.32(0.94-1.86)	1.13E-01	1.92E-01				

	MR-PRESSO	1.44 (1.17-1.76)	6.50E-04	2.72E-03*				
Colorectal cancer	MR-Egger	1.32 (0.76-2.30)	3.21E-01	1.16E-01	223.75	2.45E-01	-0.005 (-0.017-0.007)	3.90E-01
	Inverse-variance weighted	1.05 (0.88-1.26)	5.78E-01	1.87E-01	224.54	2.49E-01		
	Weighted median	0.99 (0.74-1.33)	9.47E-01	6.24E-01				
Prostate cancer	MR-Egger	0.85 (0.64-1.13)	2.69E-01	1.12E-01	128.39	1.66E-03	0.004 (-0.004-0.122)	2.89E-01
	Inverse-variance weighted	0.99 (0.91-1.07)	7.51E-01	2.28E-01	130.11	1.51E-03		
	Weighted median	0.99 (0.88-1.11)	8.19E-01	4.85E-01				
	MR-PRESSO	0.98 (0.90-1.07)	6.61E-01	5.89E-01				

[a] Estimated by the false discovery rate (FDR) method for multiple testing correction.

* q-value < 0.05.

ER, estrogen receptor; NA, not applicable; P_h, p-value for heterogeneity; $P_{intercept}$, p-value for intercept of MR-Egger regression.

Table 3. Observational studies on the associations between visceral obesity and cancer risks.

Cancer types	Visceral obesity	Study design	Population	Sample size	Age (yr)	Findings	First author
Breast cancer	MRI-measured VAT	Nested case-control study	European American (19.3%) African American (16.2%) Native Hawaiian (11.2%) Japanese American (32.8%) Latino (20.5%)	Case: 950 Control: 950	Case: 66.8±7.9 Control: 67.0±7.8	Risk factor OR (95% CI) by increasing tertiles: 1.00, 1.09 (0.86–1.39), 1.48 (1.16–1.89); P_{trend}=0.002	Le Marchand L, et al. (43)
	CT-measured VAT	Case-control study	East Asian	Case: 234 Control: 211	Case: 52.6 Control: 52.3	No significance Pre-menopause: Tertile3 vs Tertile1, OR=0.98 (0.49-1.93); Post-menopause: Tertile3 vs Tertile1, OR=1.84 (0.81-3.76)	Kim et al. (57)
	BIA-measured VAT	Case-control study	Southeast Asian	Case: 56 control: 56	Case: 47±8 Control: 42±9	No significance Per unit increase: Crude OR=1.01(0.91-1.13)	Zunura'in et al. (58)
Colorectal cancer	MRI-measured VAT	Nested case-control study	European American (14.2%) African American (21.7%) Native Hawaiian (6.6%) Japanese American (32.6%) Latino (24.9%)	Case: 831 Control: 831	Case: 69.9±7.8 Control: 70.5±7.9	No significance (P=0.84) OR (95% CI) by increasing tertiles: 1.00, 0.98 (0.68–1.39), 1.24 (0.88–1.76); P_{trend}=0.08	Le Marchand L, et al. (43)
	CT-measured VAT	Cross-sectional study	East Asian	200	50.9±8.5	Risk factor OR 4.07 (95% CI: 1.01-16.43, P = 0.03) for those with VAT over 136.61 cm^2 relative to those with VAT under 67.23 cm^2.	Oh TH, et al. (53)

	CT-measured VAT	Case-control study	East Asian	Case: 22 Control: 66	Case: 53.8±7.9 Control: 53.8±7.7	OR (95% CI) for the lowest to highest tertile of visceral fat area of 1 (reference), 2.17 (0.45-10.46), and 5.92 (1.22-28.65), respectively (P_{trend} = 0.02).	Yamamoto S, et al.(59)
	CT-measured VAT	Cross-sectional study	East Asian postmenopausal women	398	60.73±8.55	Highest versus the lowest visceral fat tertiles were 2.96 (1.38–6.33)	Lee J, et al.(60)
	CT-measured VAT	Case-control study	European	Case: 23 Control: 50	Case: 57±9.7 Control: 59±9.2	VFA was not different in the colorectal carcinoma groups than controls (P = 0.156).	Erarslan E, et al. (54)
Prostate cancer	CT-measured VAT	Case-control study	European	Case: 63 Control: 63	Case: 71.0±7.3 Control: 68.9±10.5	Risk factor OR (95% CI), 4.6 (2.6-8.2) per SD increased visceral fat	von Hafe P, et al. (55)
	CT-measured VAT	Prospective cohort studies	European	1,832	NA	No association between VAT and the risk of total prostate cancer: HR 1.02 (0.88-1.19)	Dickerman BA, et al. (56)
	CT-measured VAT	Cross-sectional analysis	African American (62.7%)	308	Non-black: 65.4±6.4 Black: 63.4 ± 6.5	Risk factor Tertile 3 vs Tertile 1: OR=2.12 (1.07–4.22)	Allott et al. (61)

VAT, visceral adipose tissue; CT, computed tomography; MRI, magnetic resonance imaging; BIA, bioelectrical impedance analysis.

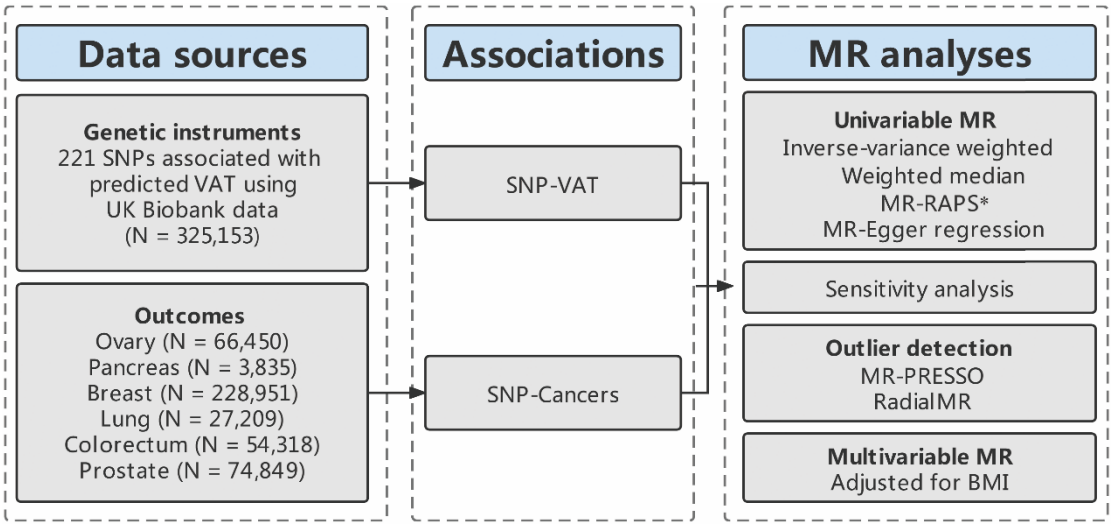


Figure 1. Study design.

*Only in the Supplementary material.

MR, Mendelian randomization; SNP, single nucleotide polymorphism; VAT, visceral adipose issue; BMI, body mass index; MR-RAPS, MR-Robust adjusted profile score; MR-PRESSO, MR-Pleiotropy Residual Sum and Outlier.

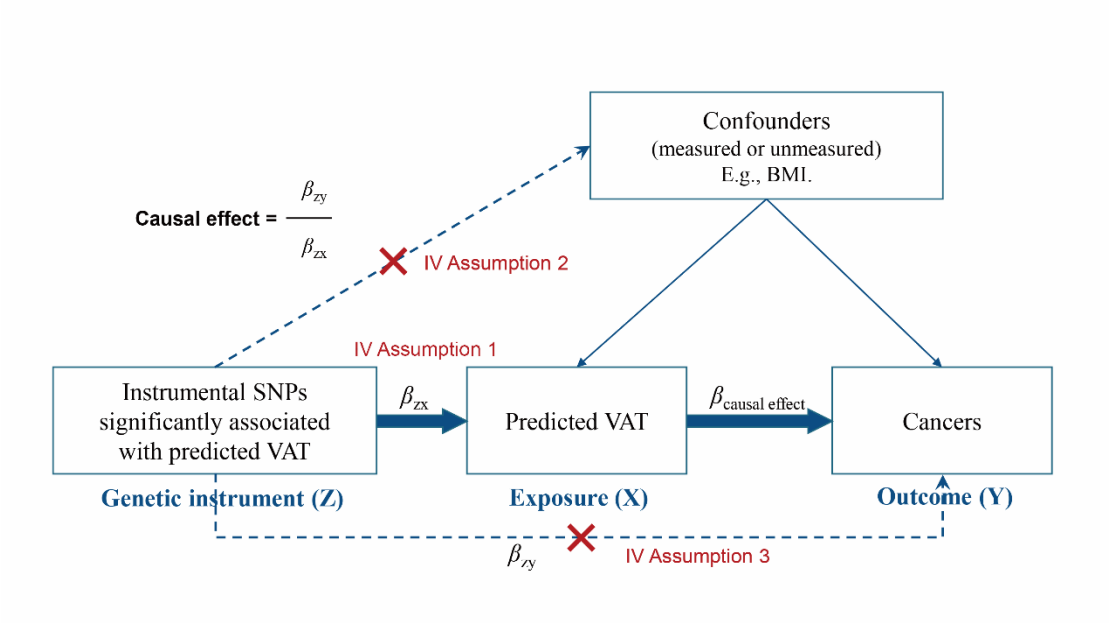


Figure 2. Core assumptions of Mendelian randomization.

SNP, single nucleotide polymorphism; VAT, visceral adipose tissue; IV, instrumental variable; BMI, body mass index.

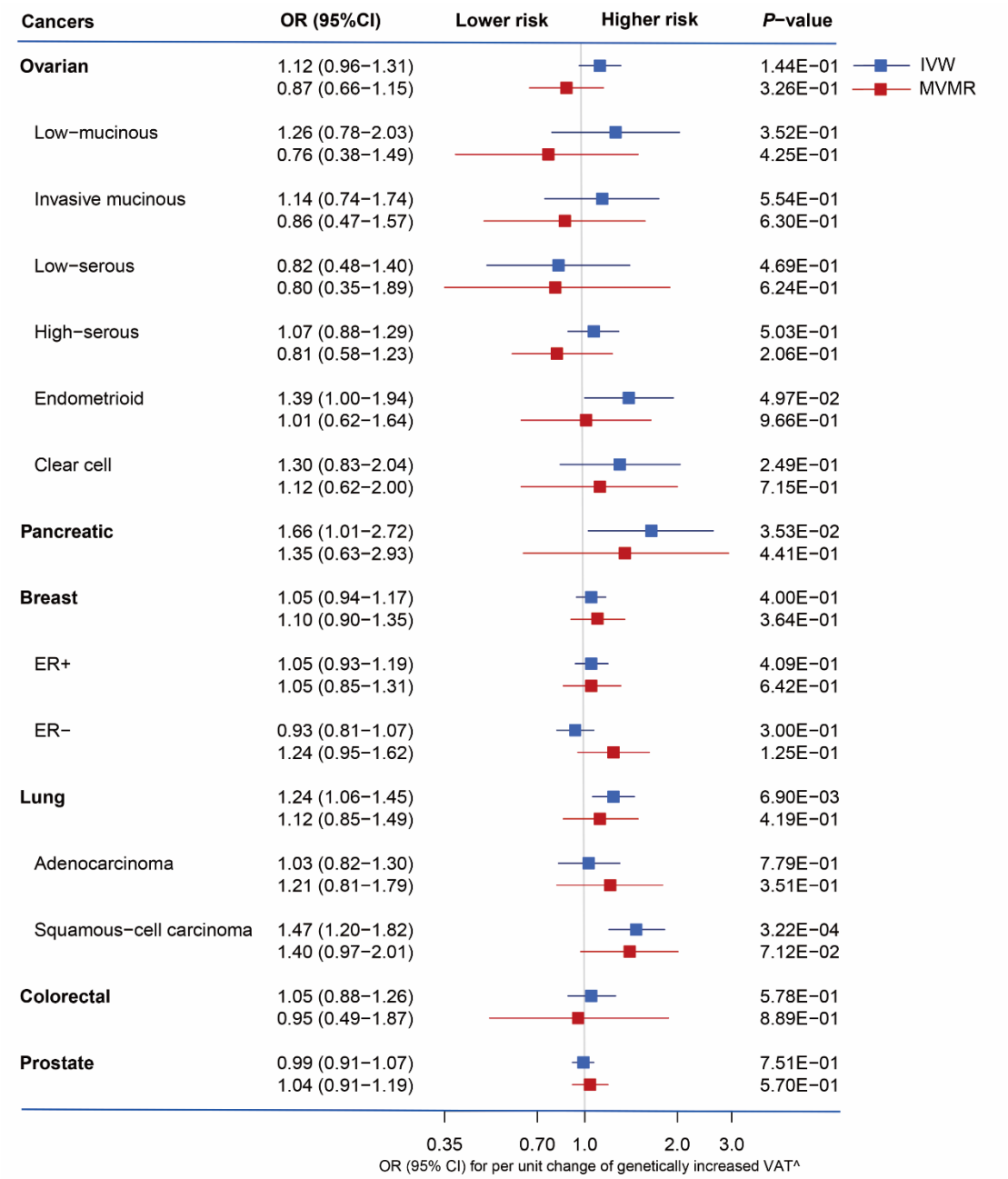


Figure 3. Comparison of the results between univariable and multivariable Mandelian randomization for the effect of visceral adipose tissue on cancer risks (outlier SNPs have been removed).

ER, estrogen receptor; VAT, visceral adipose tissue; IVW, inverse-variance weighted; MVMR, multivariable Mendelian randomization.

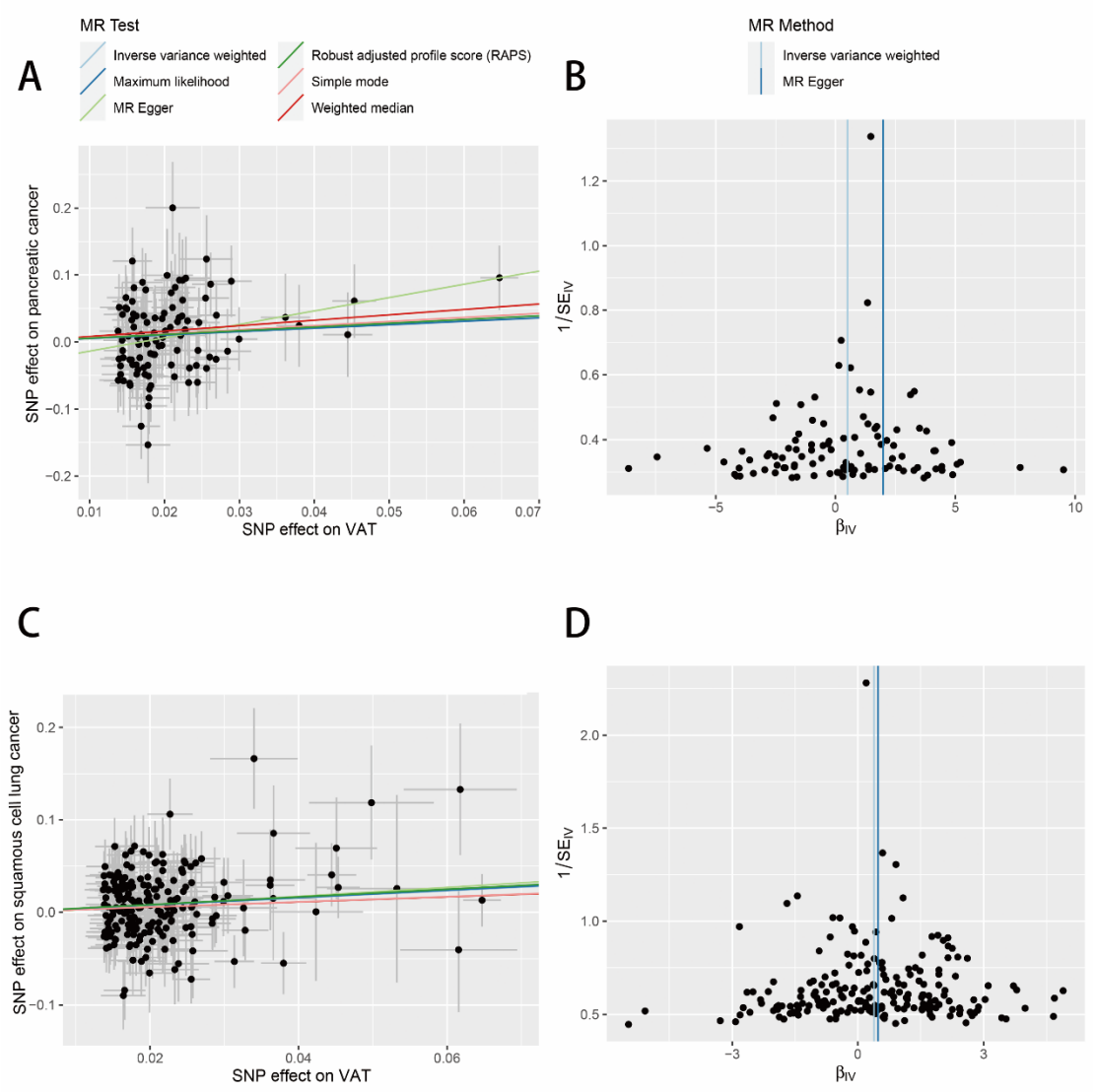


Figure 4. Scatter plots and funnel plots for effects of visceral adipose tissue on pancreatic cancer (A, B) and lung squamous-cell carcinoma (C, D).

VAT, visceral adipose tissue; MR, Mendelian randomization.

Supplementary materials

A systematic review of observational studies for the associations between visceral adipose tissue volume and incidence of six common cancers

1. Research question

The associations visceral adipose tissue volume and the risk of common cancers.

2. Search strategy

We performed a comprehensive literature search to identify relevant studies that reported the associations between visceral adipose tissue (VAT) and the incidence for six common cancers: colorectal (colon and rectum), lung (adenocarcinoma and squamous cell carcinoma), and pancreatic cancer, breast (premenopausal and postmenopausal), ovarian cancer, and prostate cancer. We searched the electronic databases of PubMed, Medline, and Embase from database inception to October 15, 2021. The search strategies consisted of terms related to "VAT" and each "cancer type". The detailed search strategy and full search terms are provided in the Table S1.

3. Selection of articles

3.1 Inclusion criteria

The studies could be included in the literature review:

- PubMed, Medline, and Embase (from the commencements to October 15, 2021).
- Present results from an epidemiologic study of one of the following types:
    - Prospective cohort study
    - Nested case-control study
    - Case-cohort study
    - Historical cohort study
- Must have as outcome of interest cancer incidence (six common cancers).
- Have to present results on the relevant exposures (VAT measured by CT, MRI, BIA, or DXA).

3.2 Exclusion criteria

The studies to be excluded from the literature review:

- Out of the research topic.
- Published as not full reports, such as conference abstracts and letters to editors.
- Do not report measure of association between the VAT and the risk of any of the cancers investigated.

- Visceral adiposity is measured by waist circumference or waist-hip ratio.
- Studies of cancer prognosis (survivor or mortality rather than incidence).
- Studies of cancer precursors (for example colorectal adenoma).

4. Exposure

- CT-measured VAT (cm^2)
- MRI-measured VAT (cm^2)
- DXA-measured VAT
- BIA- measured VAT

5. Outcomes

The outcomes of interest are the incidence of ovarian cancer, breast cancer, pancreatic cancer, lung cancer, colorectal cancer, and prostate cancer.

6. Data extraction and quality control

One investigator (HBT) extracted data, which was checked by two others (PYH and YL). We used following information including authors, study types and patient characteristics, number of cases and controls, mean age, and risk estimates and 95% CIs (either with one VAT category as a referent group or per SD/unit incremental VAT increase). Populations were categorised by different genetic backgrounds.

All the data will be checked by a second investigator, checking if the confidence intervals contain the effect estimates and if they are symmetrical, checking that the sum of cases and controls exposure add up to the total number of individuals. If there are errors, another investigator will reextract the data and check them again.

Table S1 Literature search strategy and results.

Electronic databases	Search Strategies	Results
PubMed	(((visceral adipose tissue[Title/Abstract]) OR (visceral fat[Title/Abstract])) OR (VAT[Title/Abstract]))) AND ((((((Ovarian cancer[Title/Abstract]) OR (Pancreatic cancer[Title/Abstract])) OR (breast cancer[Title/Abstract])) OR (lung cancer[Title/Abstract])) OR (colorectal cancer[Title/Abstract])) OR (prostate cancer[Title/Abstract])) AND (humans[Filter])	291
Medline	#1 TI=(visceral adipose tissue OR visceral fat OR VAT) OR AB=(visceral adipose tissue OR visceral fat OR VAT) #2 TI=(Ovarian cancer OR Pancreatic cancer OR breast cancer OR lung cancer OR colorectal cancer OR prostate cancer) OR AB=(Ovarian cancer OR Pancreatic cancer OR breast cancer OR lung cancer OR colorectal cancer OR prostate cancer) #3 (#1) AND #2 and Humans (MeSH)	1491
Embase	#1 'visceral adipose tissue':ab,ti OR 'visceral fat':ab,ti OR vat:ab,ti #2 'Ovarian cancer':ab,ti OR 'Pancreatic cancer':ab,ti OR 'breast cancer':ab,ti OR 'lung cancer':ab,ti OR 'colorectal cancer':ab,ti OR 'prostate cancer':ab,ti #3 #1 AND #2 AND [humans]/lim	686

Table S2. Single-nucleotide polymorphisms associated with predicted VAT (sex combined).

SNP	EA	OA	samplesize	beta	se	pval	eaf	exposure
rs10057588	G	A	324221	-0.014532	0.002643	3.84E-08	0.691693	vata
rs10182458	G	A	322841	0.026141	0.002481	5.90E-26	0.441494	vata
rs10187101	T	C	323622	-0.017221	0.002585	2.69E-11	0.711861	vata
rs10423928	A	T	325114	-0.032776	0.003126	1.01E-25	0.828075	vata
rs10510025	T	C	322500	0.016399	0.002888	1.36E-08	0.633586	vata
rs10740991	G	C	323883	0.025669	0.002758	1.33E-20	0.854433	vata
rs10756714	G	A	323642	-0.019681	0.002499	3.35E-15	0.621805	vata
rs10773302	G	T	324145	-0.017215	0.002798	7.66E-10	0.803315	vata
rs10789334	A	G	324609	-0.018469	0.002957	4.24E-10	0.915136	vata
rs10896012	C	T	324254	0.022404	0.003008	9.46E-14	0.863219	vata
rs10938398	A	G	324435	0.028359	0.002504	1.00E-29	0.675319	vata
rs11030112	A	G	324702	0.031329	0.002648	2.65E-32	0.75599	vata
rs11126734	A	C	325114	-0.015361	0.0025	7.97E-10	0.654153	vata
rs111363146	C	T	323532	0.019821	0.003599	3.64E-08	0.932907	vata
rs11150745	G	A	322528	-0.019427	0.002665	3.11E-13	0.789936	vata
rs11161044	G	C	322820	-0.01731	0.003165	4.52E-08	0.659145	vata
rs111610668	G	A	322989	-0.017001	0.002558	2.99E-11	0.852037	vata
rs11173521	T	G	323219	0.014127	0.002514	1.93E-08	0.398163	vata
rs112108364	G	T	322772	0.017346	0.00276	3.27E-10	0.860224	vata
rs113211479	A	G	324189	0.024395	0.00252	3.70E-22	0.663738	vata
rs113866544	C	T	324632	0.036628	0.004939	1.20E-13	0.926318	vata
rs114067739	A	C	324678	-0.036585	0.005725	1.66E-10	0.97524	vata
rs11679338	C	T	325114	-0.017248	0.002614	4.20E-11	0.715855	vata
rs117151227	C	T	324417	-0.06175	0.007611	4.95E-16	0.977236	vata
rs117176448	G	C	325114	0.024786	0.004202	3.67E-09	0.96266	vata
rs11776713	C	T	325114	-0.015107	0.002475	1.04E-09	0.626198	vata
rs11880870	G	A	323866	-0.018489	0.002476	8.09E-14	0.321086	vata
rs11896591	G	A	322210	0.0137	0.002488	3.65E-08	0.63758	vata
rs11917587	A	G	323623	0.01441	0.002506	8.94E-09	0.483626	vata
rs12001634	A	T	323854	-0.016126	0.002623	7.88E-10	0.53115	vata
rs12101386	T	G	322889	-0.016409	0.00301	4.98E-08	0.858027	vata
rs12103006	A	G	323178	-0.016629	0.002506	3.25E-11	0.533347	vata
rs12200046	T	C	324344	0.021769	0.003741	5.90E-09	0.93151	vata
rs1225060	A	G	322033	0.02316	0.002779	7.88E-17	0.835064	vata
rs1229984	T	C	325114	-0.049819	0.008386	2.84E-09	0.841454	vata
rs12335914	C	G	323031	0.01602	0.002489	1.22E-10	0.616014	vata
rs12409875	A	G	325114	-0.014311	0.002473	7.21E-09	0.644369	vata
rs12435171	G	A	322855	0.01625	0.002739	2.98E-09	0.38758	vata
rs12459368	G	A	325114	-0.019853	0.002792	1.15E-12	0.694489	vata
rs12477088	C	T	323965	-0.020348	0.002516	6.17E-16	0.533147	vata
rs12632423	A	G	325114	-0.022742	0.004061	2.14E-08	0.839856	vata
rs12739999	A	G	323586	0.021677	0.003305	5.46E-11	0.615615	vata
rs13017207	A	G	324531	-0.019643	0.002535	9.17E-15	0.716254	vata
rs13062093	G	T	324896	0.019749	0.002569	1.51E-14	0.631589	vata
rs13075615	T	C	323732	-0.021721	0.003473	3.97E-10	0.930711	vata
rs13097150	T	C	323462	0.015351	0.002561	2.03E-09	0.699481	vata
rs13135092	G	A	323401	0.032562	0.004539	7.31E-13	0.97504	vata
rs13192865	A	G	324560	-0.018173	0.002801	8.76E-11	0.813299	vata
rs13263674	G	A	323413	0.017056	0.002737	4.65E-10	0.861422	vata
rs13337177	T	G	322583	-0.022824	0.003245	2.02E-12	0.790935	vata
rs13393304	A	G	325114	-0.044471	0.003277	6.12E-42	0.877396	vata
rs1446585	G	A	325114	-0.016894	0.002964	1.21E-08	0.189896	vata
rs145350287	A	T	325114	-0.042363	0.006311	1.92E-11	0.990016	vata
rs1454687	C	G	324927	0.023007	0.002476	1.49E-20	0.453474	vata
rs1474518	C	T	322216	-0.018117	0.002934	6.62E-10	0.761382	vata
rs148168215	T	A	323100	-0.05324	0.00941	1.54E-08	0.984026	vata

rs1559677	G	A	325042	0.014851	0.002528	4.22E-09	0.441494	vata
rs1591726	T	C	323016	0.022329	0.002655	4.06E-17	0.589058	vata
rs1652376	T	G	325114	-0.020877	0.002483	4.17E-17	0.389776	vata
rs17239176	C	T	322836	-0.016621	0.002994	2.85E-08	0.896366	vata
rs1724557	C	A	322469	0.015577	0.002525	6.87E-10	0.372204	vata
rs17589357	C	T	322647	-0.019914	0.003482	1.07E-08	0.936901	vata
rs1762509	A	G	322088	0.0157	0.002624	2.20E-09	0.77476	vata
rs17682873	T	C	323466	0.019578	0.003536	3.07E-08	0.924321	vata
rs17770336	T	C	324999	0.024723	0.002641	7.85E-21	0.790136	vata
rs1834144	A	C	323386	-0.018118	0.002568	1.72E-12	0.554912	vata
rs1928496	C	T	325114	-0.02106	0.002827	9.30E-14	0.745607	vata
rs2020942	T	C	323155	0.015158	0.002536	2.28E-09	0.745008	vata
rs2102278	G	A	323517	0.015695	0.002657	3.48E-09	0.455072	vata
rs215628	C	T	323995	0.015755	0.00255	6.48E-10	0.397764	vata
rs2172131	T	C	325114	0.016871	0.002512	1.85E-11	0.70647	vata
rs217669	C	T	325114	0.017486	0.002783	3.32E-10	0.642372	vata
rs2253310	C	G	323636	-0.020934	0.002563	3.16E-16	0.470248	vata
rs2285640	G	A	325114	0.019966	0.002477	7.58E-16	0.591653	vata
rs2304608	A	C	324911	0.02986	0.003408	1.91E-18	0.701478	vata
rs2307111	C	T	325114	-0.026014	0.002536	1.08E-24	0.384385	vata
rs2448916	A	C	323289	-0.014048	0.00255	3.60E-08	0.471645	vata
rs245775	A	G	323699	-0.01959	0.002789	2.16E-12	0.759385	vata
rs2472297	T	C	325114	0.016566	0.002795	3.08E-09	0.934305	vata
rs247975	T	C	322641	-0.014386	0.002489	7.46E-09	0.630791	vata
rs2481665	C	T	325114	-0.017842	0.00249	7.82E-13	0.813498	vata
rs2499468	C	A	323581	-0.015629	0.002605	1.98E-09	0.77476	vata
rs2537621	C	G	324115	0.014625	0.002572	1.29E-08	0.675919	vata
rs254024	T	G	324907	0.015587	0.002495	4.19E-10	0.582867	vata
rs264932	A	G	323856	0.013946	0.002533	3.69E-08	0.82488	vata
rs2667761	C	T	322975	-0.015918	0.002584	7.27E-10	0.491813	vata
rs2678204	G	T	323592	0.023059	0.002615	1.16E-18	0.744808	vata
rs2730806	T	A	322359	0.01646	0.002483	3.35E-11	0.438698	vata
rs2744973	T	C	324438	0.021408	0.002696	2.01E-15	0.591254	vata
rs2799465	C	T	323945	0.021307	0.003663	6.02E-09	0.711262	vata
rs2804477	A	G	325114	0.021072	0.003614	5.52E-09	0.848642	vata
rs2926614	T	C	322213	-0.022405	0.003232	4.16E-12	0.763978	vata
rs2926864	A	G	323005	0.017481	0.002624	2.68E-11	0.813498	vata
rs2962082	A	G	322814	-0.015355	0.002488	6.72E-10	0.613618	vata
rs329124	G	A	323838	-0.013782	0.002514	4.22E-08	0.538139	vata
rs34431565	T	G	325029	-0.033976	0.005913	9.14E-09	0.966653	vata
rs34811474	A	G	325114	-0.019089	0.002927	6.96E-11	0.925919	vata
rs35060985	A	G	322405	0.023354	0.002675	2.52E-18	0.700679	vata
rs35697587	G	A	324734	0.01669	0.002477	1.62E-11	0.407348	vata
rs35972789	A	C	325114	-0.039582	0.006481	1.01E-09	0.989816	vata
rs362307	T	C	322041	0.028696	0.004787	2.04E-09	0.972444	vata
rs3759094	T	C	321924	-0.015213	0.002628	7.05E-09	0.732827	vata
rs3774063	T	C	324850	0.023817	0.004106	6.63E-09	0.959465	vata
rs3784692	C	T	324075	-0.024385	0.002531	5.70E-22	0.462859	vata
rs3787075	G	C	325079	0.017758	0.002622	1.26E-11	0.694688	vata
rs3791687	T	A	323613	0.019128	0.002973	1.24E-10	0.692492	vata
rs3803253	A	G	323928	-0.016288	0.002729	2.39E-09	0.797324	vata
rs3826408	T	C	325114	0.014336	0.002485	7.95E-09	0.613419	vata
rs3843540	C	T	324190	-0.025588	0.003487	2.17E-13	0.597644	vata
rs3943933	A	T	324890	0.016588	0.002478	2.18E-11	0.426717	vata
rs40067	A	G	322239	-0.024457	0.003314	1.59E-13	0.738419	vata
rs4073582	A	G	324342	-0.017506	0.002582	1.20E-11	0.834265	vata
rs4148866	T	C	325114	0.015278	0.002517	1.28E-09	0.603235	vata
rs4239060	A	G	325114	-0.025591	0.003183	8.98E-16	0.864617	vata

rs429358	C	T	325114	-0.030445	0.003412	4.57E-19	0.849441	vata
rs4399192	G	T	323570	0.017783	0.002957	1.81E-09	0.725839	vata
rs4402589	T	G	323678	-0.026273	0.002495	6.17E-26	0.454473	vata
rs4419475	T	A	323444	0.013869	0.00252	3.71E-08	0.417931	vata
rs4482463	C	A	323457	0.03618	0.004715	1.68E-14	0.777756	vata
rs4500930	T	C	325114	0.01708	0.002608	5.75E-11	0.632388	vata
rs4558773	A	G	324345	0.017229	0.002576	2.24E-11	0.715655	vata
rs4562625	C	G	323590	0.014987	0.002543	3.76E-09	0.665535	vata
rs4807179	G	A	322506	-0.014609	0.002578	1.45E-08	0.39397	vata
rs4808762	C	T	325114	0.028893	0.00273	3.55E-26	0.791134	vata
rs4809221	G	A	323696	-0.014607	0.00264	3.15E-08	0.651757	vata
rs4842920	T	G	323875	-0.015407	0.00276	2.38E-08	0.882188	vata
rs4872376	C	T	324164	-0.013799	0.002481	2.67E-08	0.551917	vata
rs4929923	T	C	325114	-0.017976	0.002588	3.78E-12	0.532947	vata
rs496072	T	C	323896	0.01392	0.002521	3.35E-08	0.295327	vata
rs538656	T	G	325026	0.045345	0.002918	1.79E-54	0.724241	vata
rs539515	C	A	325065	0.037989	0.003052	1.43E-35	0.805312	vata
rs55726687	A	G	323945	0.022673	0.003036	8.12E-14	0.848442	vata
rs55742087	T	C	323102	-0.023318	0.003208	3.61E-13	0.847045	vata
rs55769038	G	A	323474	-0.015855	0.002525	3.38E-10	0.372404	vata
rs55911231	T	C	324133	0.014803	0.00252	4.25E-09	0.558706	vata
rs56094641	G	A	324955	0.064693	0.002522	3.82E-145	0.771166	vata
rs56356382	C	T	323312	-0.021676	0.003156	6.51E-12	0.795128	vata
rs57241669	G	A	324556	-0.025746	0.004686	3.93E-08	0.811701	vata
rs577525	T	C	323776	-0.017668	0.002498	1.52E-12	0.402955	vata
rs58120873	A	G	322036	-0.024819	0.004463	2.67E-08	0.937899	vata
rs59066241	G	T	322704	0.021192	0.003872	4.42E-08	0.766773	vata
rs60377014	T	C	322953	-0.020335	0.003468	4.53E-09	0.881589	vata
rs6096886	G	A	324695	-0.02839	0.003156	2.35E-19	0.826677	vata
rs61537964	G	C	323948	-0.023085	0.004003	8.11E-09	0.856629	vata
rs61813293	T	G	325114	0.023662	0.003526	1.93E-11	0.952875	vata
rs61903695	G	A	324835	0.016831	0.002839	3.04E-09	0.854433	vata
rs61910767	T	C	323505	-0.022872	0.003335	6.95E-12	0.946086	vata
rs62024481	T	C	323761	-0.017694	0.003099	1.13E-08	0.845048	vata
rs62084234	G	A	325057	0.025467	0.003125	3.68E-16	0.703275	vata
rs62104473	T	C	322872	0.019245	0.002646	3.50E-13	0.832468	vata
rs62183012	C	T	324358	-0.016234	0.002736	2.97E-09	0.879393	vata
rs62190394	T	C	324759	0.021935	0.002668	2.02E-16	0.723642	vata
rs62261725	G	A	322321	-0.021448	0.002648	5.52E-16	0.711062	vata
rs62262093	T	C	324915	-0.029926	0.002477	1.34E-33	0.364816	vata
rs62413414	T	C	325114	0.019767	0.003436	8.78E-09	0.926518	vata
rs62473743	A	G	323843	0.019795	0.003416	6.82E-09	0.734425	vata
rs62477685	T	A	325065	-0.019496	0.002509	7.78E-15	0.553714	vata
rs6433243	T	C	324216	0.016183	0.002596	4.56E-10	0.649361	vata
rs6536575	T	C	322381	-0.014075	0.002485	1.48E-08	0.49381	vata
rs653958	G	A	324074	0.018684	0.002566	3.28E-13	0.683906	vata
rs66679256	T	C	324288	0.018499	0.002497	1.29E-13	0.555911	vata
rs669696	A	C	324321	-0.02424	0.002518	6.15E-22	0.714058	vata
rs6739755	A	G	322339	0.022714	0.002541	3.95E-19	0.708267	vata
rs67463976	C	G	325114	0.016257	0.002508	9.11E-11	0.510982	vata
rs684214	T	C	323015	0.017916	0.002759	8.35E-11	0.769768	vata
rs7021721	C	G	324024	-0.015437	0.002739	1.74E-08	0.722644	vata
rs7035637	A	G	323688	0.018669	0.00282	3.57E-11	0.667133	vata
rs704061	C	T	323375	0.016452	0.00249	3.94E-11	0.500998	vata
rs7132908	A	G	325114	0.025531	0.002547	1.19E-23	0.748003	vata
rs7156625	A	G	324807	0.026865	0.00298	1.99E-19	0.804712	vata
rs7165759	A	G	324151	-0.017496	0.002707	1.02E-10	0.727835	vata
rs71658797	A	T	323248	0.034701	0.003785	4.79E-20	0.971446	vata

rs719802	T	C	325114	0.017379	0.00254	7.84E-12	0.493411	vata
rs72663503	T	C	323372	0.020887	0.002958	1.65E-12	0.881589	vata
rs72892910	T	G	323472	0.036156	0.003304	7.24E-28	0.820288	vata
rs72995085	C	T	324503	-0.021479	0.003248	3.77E-11	0.908746	vata
rs73033486	A	G	323417	0.020665	0.003728	2.97E-08	0.904952	vata
rs7308188	C	T	323422	-0.018701	0.002854	5.70E-11	0.553914	vata
rs73213484	T	A	323573	-0.021093	0.003588	4.13E-09	0.838658	vata
rs7324067	T	C	324537	-0.016533	0.002904	1.24E-08	0.775359	vata
rs74934567	G	A	325114	-0.021982	0.003411	1.16E-10	0.881989	vata
rs7498665	G	A	325114	0.026914	0.002528	1.83E-26	0.738618	vata
rs754635	C	G	324543	-0.023016	0.00389	3.28E-09	0.765575	vata
rs7550711	T	C	324515	0.061533	0.007867	5.20E-15	0.98782	vata
rs7586854	T	C	323097	-0.01449	0.002486	5.60E-09	0.397564	vata
rs76040172	A	G	323693	-0.045091	0.005505	2.60E-16	0.935304	vata
rs76111507	T	C	325114	-0.075379	0.006568	1.72E-30	0.988818	vata
rs76327888	T	G	323909	0.02295	0.003287	2.90E-12	0.710463	vata
rs7649970	T	C	325024	0.025485	0.003791	1.78E-11	0.880192	vata
rs7654647	T	A	324904	0.015545	0.00252	6.86E-10	0.700479	vata
rs7724430	A	C	324842	0.013927	0.002503	2.65E-08	0.469649	vata
rs7773094	C	T	325114	-0.017653	0.003098	1.21E-08	0.738419	vata
rs778094	G	A	323092	0.014975	0.002514	2.57E-09	0.341653	vata
rs7788950	A	G	322071	-0.017485	0.003207	4.99E-08	0.811102	vata
rs7822494	C	T	324916	-0.016237	0.002486	6.53E-11	0.549121	vata
rs7845090	G	A	322372	0.020056	0.002753	3.19E-13	0.640575	vata
rs7849553	C	A	323575	0.014133	0.002492	1.42E-08	0.592851	vata
rs7864091	A	G	324607	0.018599	0.003353	2.92E-08	0.828474	vata
rs78719460	A	G	324340	0.015898	0.002676	2.83E-09	0.863618	vata
rs7893571	G	T	322258	-0.017855	0.002632	1.17E-11	0.796126	vata
rs7942037	C	G	324418	-0.016889	0.002577	5.64E-11	0.711062	vata
rs7982447	C	T	322286	0.020754	0.003081	1.62E-11	0.701877	vata
rs8015400	C	A	325114	-0.019946	0.00265	5.22E-14	0.552516	vata
rs8074454	C	G	324664	0.017448	0.002638	3.75E-11	0.70627	vata
rs809955	A	G	323934	-0.015843	0.002573	7.45E-10	0.646366	vata
rs8103728	C	G	323039	-0.015244	0.002643	8.02E-09	0.617612	vata
rs879620	C	T	322283	-0.020561	0.002558	9.02E-16	0.34405	vata
rs916289	T	C	321870	-0.013815	0.0025	3.26E-08	0.713658	vata
rs9277979	T	C	324506	0.023072	0.003227	8.77E-13	0.882388	vata
rs9304665	T	A	323925	-0.016544	0.002933	1.70E-08	0.520767	vata
rs9320823	T	C	324853	-0.023205	0.002532	4.92E-20	0.689497	vata
rs9358912	T	G	324205	-0.024581	0.002789	1.22E-18	0.634385	vata
rs9471333	C	T	324508	0.024393	0.002487	1.06E-22	0.547524	vata
rs9512696	A	G	324813	-0.014388	0.00262	3.97E-08	0.470847	vata
rs9522285	A	G	323786	0.018717	0.002514	9.61E-14	0.716254	vata
rs9569934	T	C	322683	-0.018832	0.003201	4.04E-09	0.773363	vata
rs9641499	A	C	323441	-0.017768	0.002501	1.20E-12	0.603435	vata
rs9832402	G	A	323791	-0.016956	0.002858	2.99E-09	0.685304	vata
rs9843340	C	T	324821	-0.022145	0.003469	1.74E-10	0.93131	vata
rs9925945	C	A	323455	-0.017496	0.002838	7.04E-10	0.781949	vata
rs9989141	C	T	322205	-0.020101	0.002581	6.77E-15	0.50599	vata

Table S3. Single-nucleotide polymorphisms associated with predicted VAT (male).

SNP	EA	OA	samplesize	beta	se	pval	eaf	exposure
rs1421085	C	T	163965	0.07084	0.003545	1.02E-88	0.771366	vatm
rs7240682	G	C	162453	0.04463	0.004182	1.41E-26	0.777756	vatm
rs4423631	T	C	163353	-0.04833	0.004612	1.10E-25	0.838658	vatm
rs6265	T	C	163965	-0.04316	0.004438	2.38E-22	0.798722	vatm
rs6795703	C	T	163903	-0.03104	0.003486	5.49E-19	0.353235	vatm
rs7132908	A	G	163965	0.03175	0.003583	7.91E-19	0.748003	vatm
rs11637027	G	T	163148	-0.03141	0.003562	1.17E-18	0.450879	vatm
rs10938398	A	G	163633	0.03069	0.00352	2.89E-18	0.675319	vatm
rs72892910	T	G	163172	0.04007	0.004652	7.20E-18	0.820288	vatm
rs113211479	A	G	163533	0.03013	0.003546	1.96E-17	0.663738	vatm
rs2613500	T	C	163278	-0.03708	0.004385	2.80E-17	0.91274	vatm
rs6739755	A	G	162546	0.03012	0.003575	3.68E-17	0.708267	vatm
rs28479795	T	C	163521	0.0348	0.004209	1.38E-16	0.816494	vatm
rs27741	A	G	163366	0.02917	0.003537	1.63E-16	0.61242	vatm
rs112862634	C	G	163673	0.04089	0.005185	3.13E-15	0.749401	vatm
rs2066295	G	A	163965	-0.03258	0.00416	4.87E-15	0.816294	vatm
rs543874	G	A	163965	0.03359	0.004294	5.17E-15	0.804912	vatm
rs7239575	C	T	163883	-0.02725	0.00349	5.83E-15	0.413339	vatm
rs76111507	T	C	163965	-0.07222	0.009273	6.84E-15	0.988818	vatm
rs11666033	T	C	163865	0.02991	0.003851	8.13E-15	0.834265	vatm
rs10423928	A	T	163965	-0.03389	0.0044	1.35E-14	0.828075	vatm
rs4402589	T	G	163222	-0.02661	0.003514	3.70E-14	0.454473	vatm
rs9320823	T	C	163820	-0.02673	0.003563	6.33E-14	0.689497	vatm
rs12498044	A	G	163714	0.02912	0.003905	8.76E-14	0.847644	vatm
rs58939796	T	G	163544	-0.028	0.003805	1.87E-13	0.696086	vatm
rs1412239	G	C	163523	0.02701	0.003717	3.72E-13	0.795727	vatm
rs6063776	T	C	163419	-0.03196	0.004455	7.34E-13	0.863818	vatm
rs2384061	A	G	162910	0.02491	0.003524	1.58E-12	0.557708	vatm
rs1454687	C	G	163871	0.02389	0.003487	7.36E-12	0.453474	vatm
rs2307111	C	T	163965	-0.02445	0.003573	7.79E-12	0.384385	vatm
rs11127908	C	G	163404	-0.02477	0.003645	1.09E-11	0.592452	vatm
rs9469899	A	G	162584	0.02476	0.003645	1.10E-11	0.539736	vatm
rs2926614	T	C	162521	-0.03028	0.004547	2.77E-11	0.763978	vatm
rs17024393	C	T	163600	0.07366	0.01114	3.82E-11	0.968051	vatm
rs17325374	G	A	163216	0.02479	0.003752	3.92E-11	0.778554	vatm
rs3740390	T	C	163684	0.04253	0.00646	4.61E-11	0.842851	vatm
rs10740991	G	C	163352	0.02556	0.003884	4.68E-11	0.854433	vatm
rs935166	G	A	162788	0.02283	0.003494	6.50E-11	0.292332	vatm
rs12369179	T	C	163055	-0.03976	0.006092	6.74E-11	0.971046	vatm
rs10838137	A	C	162506	0.02418	0.003721	8.09E-11	0.644369	vatm
rs2678207	T	C	163518	0.02389	0.003691	9.59E-11	0.749002	vatm
rs1591726	T	C	162888	0.02419	0.00374	9.88E-11	0.589058	vatm
rs35697587	G	A	163779	0.02243	0.003487	1.25E-10	0.407348	vatm
rs55957513	C	T	163121	0.02356	0.003681	1.55E-10	0.734625	vatm
rs1724557	C	A	162645	0.0226	0.003551	1.97E-10	0.372204	vatm
rs28671107	C	A	162936	-0.02421	0.003806	2.01E-10	0.633786	vatm
rs2269610	C	G	163839	0.02855	0.004501	2.24E-10	0.865815	vatm
rs62136859	A	G	163833	-0.02381	0.003759	2.39E-10	0.470447	vatm
rs7804577	C	T	163299	0.03524	0.005566	2.44E-10	0.921725	vatm
rs62052816	T	G	162569	-0.0223	0.003554	3.52E-10	0.740016	vatm
rs12439200	A	G	162872	-0.02565	0.004111	4.44E-10	0.764577	vatm
rs4757136	T	A	162706	-0.02209	0.003552	4.98E-10	0.398562	vatm
rs11883756	T	C	163600	-0.02202	0.003546	5.28E-10	0.503994	vatm
rs62086892	T	G	162652	0.0235	0.003786	5.44E-10	0.440695	vatm
rs34045288	T	C	163712	0.02264	0.003694	8.84E-10	0.748602	vatm
rs4930349	A	G	162750	-0.02226	0.003644	1.01E-09	0.620407	vatm

rs151390	T	C	162822	0.02369	0.003888	1.10E-09	0.777556 vatm
rs79733879	T	C	163791	0.03402	0.0056	1.24E-09	0.954473 vatm
rs9603697	T	C	162508	0.02263	0.00373	1.30E-09	0.678115 vatm
rs11150745	G	A	162664	-0.02253	0.003747	1.81E-09	0.789936 vatm
rs14259	G	A	163138	-0.02303	0.003844	2.06E-09	0.714657 vatm
rs10027920	A	G	163060	0.02096	0.003499	2.12E-09	0.386781 vatm
rs17207196	T	C	163965	-0.02117	0.003536	2.14E-09	0.553115 vatm
rs217667	T	C	162841	0.02399	0.00404	2.88E-09	0.687899 vatm
rs879620	C	T	162502	-0.02133	0.003602	3.18E-09	0.34405 vatm
rs7806283	A	G	162501	-0.02081	0.003522	3.46E-09	0.719449 vatm
rs113866544	C	T	163733	0.04102	0.006951	3.63E-09	0.926318 vatm
rs7893571	G	T	162522	-0.02187	0.003706	3.65E-09	0.796126 vatm
rs7610493	C	G	163923	-0.02874	0.004878	3.86E-09	0.927915 vatm
rs9522279	T	C	162700	0.0207	0.003535	4.78E-09	0.707069 vatm
rs10209325	C	T	163824	0.02092	0.003601	6.33E-09	0.560503 vatm
rs77354155	T	C	163341	-0.06232	0.01076	6.90E-09	0.979233 vatm
rs10962547	A	T	163260	0.02682	0.004646	7.84E-09	0.791334 vatm
rs3907875	C	T	163840	0.02159	0.003746	8.29E-09	0.560104 vatm
rs869400	T	G	162809	-0.02602	0.004519	8.58E-09	0.838059 vatm
rs2038646	C	G	163582	-0.02038	0.003555	9.89E-09	0.497204 vatm
rs7308188	C	T	163051	-0.02301	0.004018	1.02E-08	0.553914 vatm
rs12740972	G	C	162713	-0.02019	0.003534	1.11E-08	0.716853 vatm
rs10131761	A	T	162763	-0.02542	0.004476	1.36E-08	0.792732 vatm
rs12001634	A	T	163306	-0.02092	0.003698	1.54E-08	0.53115 vatm
rs12049202	T	C	163728	0.02468	0.004379	1.73E-08	0.803115 vatm
rs2481665	C	T	163965	-0.01967	0.003506	2.03E-08	0.813498 vatm
rs62104473	T	C	162871	0.02089	0.003725	2.04E-08	0.832468 vatm
rs35957544	G	T	163329	0.01983	0.003538	2.08E-08	0.344649 vatm
rs9827823	C	T	163733	-0.02731	0.004879	2.16E-08	0.753195 vatm
rs9847186	A	G	163064	-0.01976	0.003531	2.21E-08	0.564497 vatm
rs245767	A	G	163538	-0.02191	0.003925	2.39E-08	0.790935 vatm
rs3803253	A	G	163329	-0.02142	0.003838	2.40E-08	0.797324 vatm
rs13082065	T	C	163429	-0.01979	0.003549	2.45E-08	0.564497 vatm
rs6545039	T	C	163965	-0.01946	0.003497	2.63E-08	0.529752 vatm
rs9783665	T	A	163807	0.02028	0.003652	2.82E-08	0.502396 vatm
rs6536575	T	C	162556	-0.01936	0.003501	3.23E-08	0.49381 vatm
rs9569934	T	C	162752	-0.02469	0.0045	4.08E-08	0.773363 vatm
rs6491247	T	C	163551	0.02359	0.004301	4.14E-08	0.636182 vatm
rs9601103	A	G	163219	0.02248	0.004108	4.46E-08	0.85643 vatm
rs719802	T	C	163965	0.01954	0.003577	4.72E-08	0.493411 vatm

Table S4. Single-nucleotide polymorphisms associated with predicted VAT (female).

SNP	EA	OA	samplesize	beta	se	pval	eaf	exposure
rs1013402	G	A	161035	0.02907	0.003755	9.82E-15	0.786941	vatf
rs10187101	T	C	160401	-0.02188	0.003671	2.53E-09	0.711861	vatf
rs10423928	A	T	161149	-0.03164	0.004442	1.07E-12	0.828075	vatf
rs10506965	T	G	159552	0.02247	0.003553	2.56E-10	0.458866	vatf
rs10890168	A	G	159720	0.01931	0.003541	4.94E-08	0.566893	vatf
rs10896012	C	T	160750	0.02738	0.004274	1.49E-10	0.863219	vatf
rs111610668	G	A	160083	-0.01991	0.003629	4.12E-08	0.852037	vatf
rs112154095	T	C	159707	-0.02472	0.004516	4.40E-08	0.928315	vatf
rs11669862	T	C	159657	-0.01951	0.003529	3.21E-08	0.30611	vatf
rs12072739	G	A	161149	0.02432	0.004229	8.93E-09	0.801917	vatf
rs12459368	G	A	161149	-0.023	0.003965	6.60E-09	0.694489	vatf
rs12577464	G	A	161036	0.02315	0.003816	1.31E-09	0.702676	vatf
rs12889731	T	C	160355	0.02161	0.003828	1.65E-08	0.773363	vatf
rs13017207	A	G	160881	-0.02234	0.003599	5.43E-10	0.716254	vatf
rs13130484	T	C	159936	0.02608	0.003573	2.91E-13	0.673722	vatf
rs13292699	C	A	160760	-0.02163	0.003553	1.15E-09	0.627196	vatf
rs1343431	A	C	160479	0.02123	0.003678	7.83E-09	0.503794	vatf
rs141127214	T	C	160184	0.05431	0.009105	2.46E-09	0.991813	vatf
rs1454687	C	G	161056	0.02211	0.003515	3.20E-10	0.453474	vatf
rs16951304	C	T	161149	-0.02764	0.004338	1.88E-10	0.690296	vatf
rs17141778	C	G	160989	0.021	0.003564	3.80E-09	0.511581	vatf
rs17770336	T	C	161093	0.02307	0.003756	8.14E-10	0.790136	vatf
rs1834144	A	C	160330	-0.02061	0.003648	1.61E-08	0.554912	vatf
rs1928496	C	T	161149	-0.02227	0.004006	2.73E-08	0.745607	vatf
rs205283	G	A	159798	0.02171	0.003697	4.32E-09	0.408147	vatf
rs2307111	C	T	161149	-0.0276	0.003599	1.76E-14	0.384385	vatf
rs2404324	G	A	160955	-0.02977	0.004862	9.20E-10	0.4998	vatf
rs2667762	G	A	160092	-0.02183	0.003666	2.64E-09	0.46266	vatf
rs2678204	G	T	160397	0.02251	0.00371	1.30E-09	0.744808	vatf
rs2861692	C	T	160520	-0.02382	0.003951	1.66E-09	0.707668	vatf
rs34422	A	G	159813	-0.02902	0.004419	5.18E-11	0.764577	vatf
rs35587371	A	T	160493	0.02636	0.003835	6.35E-12	0.863219	vatf
rs3736166	C	G	159924	0.02274	0.003532	1.22E-10	0.590455	vatf
rs3800228	T	G	159962	-0.02584	0.003915	4.15E-11	0.489018	vatf
rs429358	C	T	161149	-0.03593	0.004857	1.39E-13	0.849441	vatf
rs4366093	T	C	159585	-0.02063	0.003782	4.91E-08	0.828674	vatf
rs4576255	G	T	161012	-0.0204	0.0036	1.46E-08	0.694289	vatf
rs4759318	T	C	159777	0.02134	0.003665	5.79E-09	0.719249	vatf
rs4790841	T	C	159799	-0.03108	0.004883	1.96E-10	0.901158	vatf
rs4808846	G	A	159974	-0.01925	0.003523	4.65E-08	0.291134	vatf
rs4864900	T	A	159664	0.01949	0.00357	4.77E-08	0.357628	vatf
rs538656	T	G	161111	0.04797	0.004134	4.05E-31	0.724241	vatf
rs539515	C	A	161122	0.04247	0.004336	1.19E-22	0.805312	vatf
rs55726687	A	G	160610	0.02394	0.004305	2.68E-08	0.848442	vatf
rs56094641	G	A	161070	0.05855	0.003588	8.12E-60	0.771166	vatf
rs56813533	T	A	160850	-0.0283	0.003631	6.64E-15	0.64357	vatf
rs57636386	C	T	160645	-0.04007	0.006436	4.78E-10	0.770966	vatf
rs6021948	A	T	159808	-0.02218	0.003776	4.29E-09	0.585663	vatf
rs62084208	T	C	160155	0.02639	0.004466	3.45E-09	0.703474	vatf
rs62107261	C	T	160590	-0.08131	0.008262	7.56E-23	0.983027	vatf
rs62120394	A	G	159781	0.02842	0.003902	3.28E-13	0.83107	vatf
rs62262093	T	C	161046	-0.02884	0.003521	2.66E-16	0.364816	vatf
rs669696	A	C	160758	-0.02651	0.003581	1.33E-13	0.714058	vatf
rs6744646	A	G	160845	-0.04125	0.004663	9.16E-19	0.834665	vatf
rs6870983	T	C	160054	-0.02597	0.004335	2.09E-09	0.722045	vatf
rs6877910	C	A	160982	-0.03106	0.0056	2.93E-08	0.897764	vatf

rs71658797	A	T	160251	0.03104	0.005357	6.92E-09	0.971446	vatf
rs72892910	T	G	160300	0.03217	0.004694	7.23E-12	0.820288	vatf
rs7306275	A	G	160924	0.02011	0.003648	3.54E-08	0.753994	vatf
rs74593044	G	C	161149	0.03999	0.006475	6.62E-10	0.971446	vatf
rs7498665	G	A	161149	0.0252	0.00359	2.22E-12	0.738618	vatf
rs7596229	G	A	159686	-0.02952	0.005089	6.63E-09	0.903355	vatf
rs76040172	A	G	160452	-0.04853	0.007831	5.74E-10	0.935304	vatf
rs7612999	A	G	160029	0.02524	0.00411	8.22E-10	0.749002	vatf
rs77848049	A	G	160884	0.03615	0.004268	2.48E-17	0.841254	vatf
rs7935521	A	G	159836	-0.02342	0.003544	3.84E-11	0.621605	vatf
rs8103728	C	G	160127	-0.0208	0.003752	2.98E-08	0.617612	vatf
rs9471333	C	T	160854	0.0254	0.003539	7.18E-13	0.547524	vatf
rs9482772	C	T	159935	0.02419	0.003548	9.30E-12	0.600639	vatf
rs9935834	G	C	160906	-0.02859	0.004742	1.66E-09	0.783147	vatf

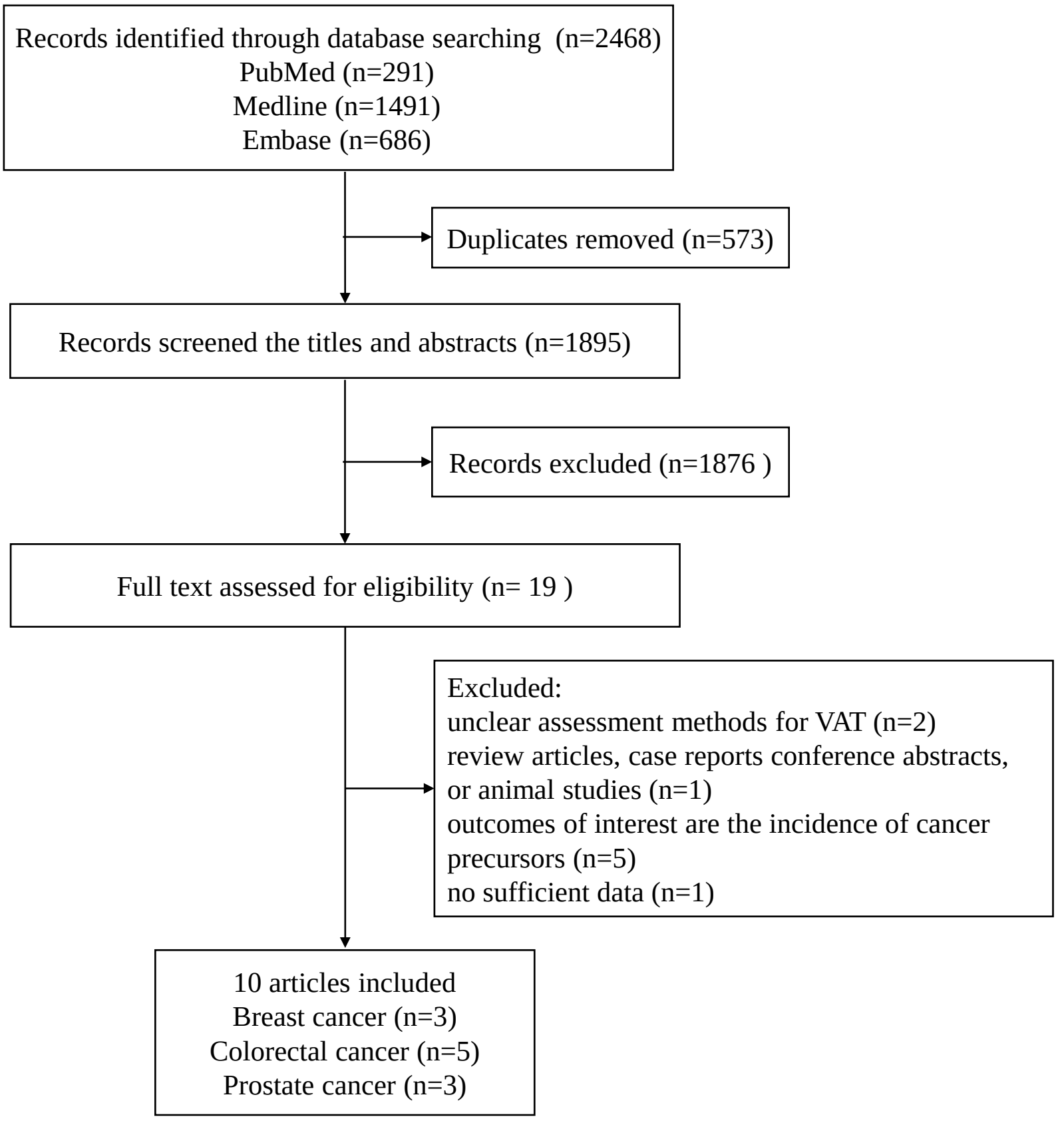
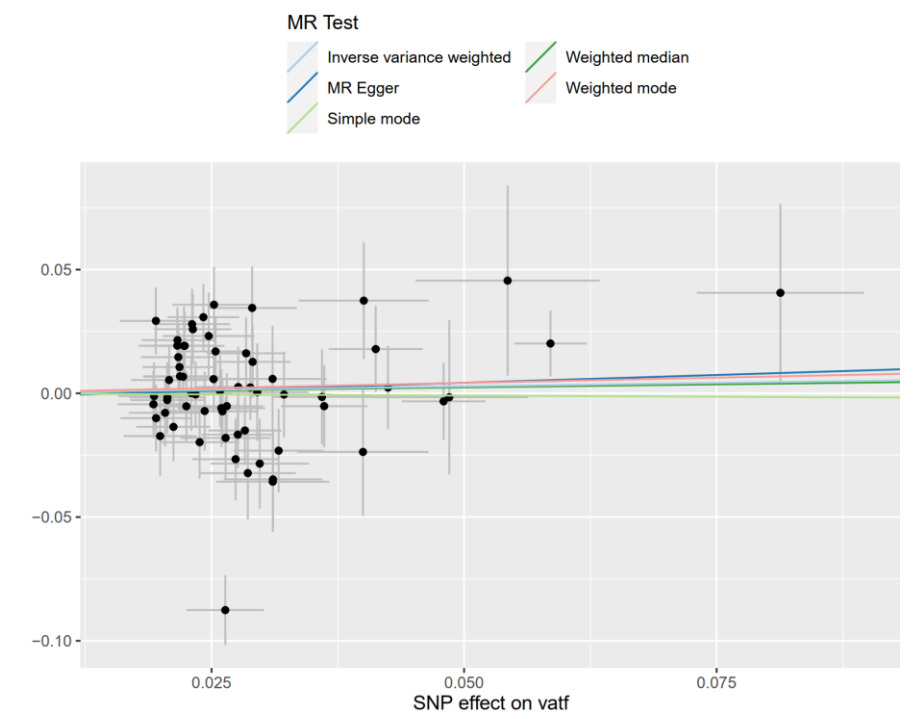
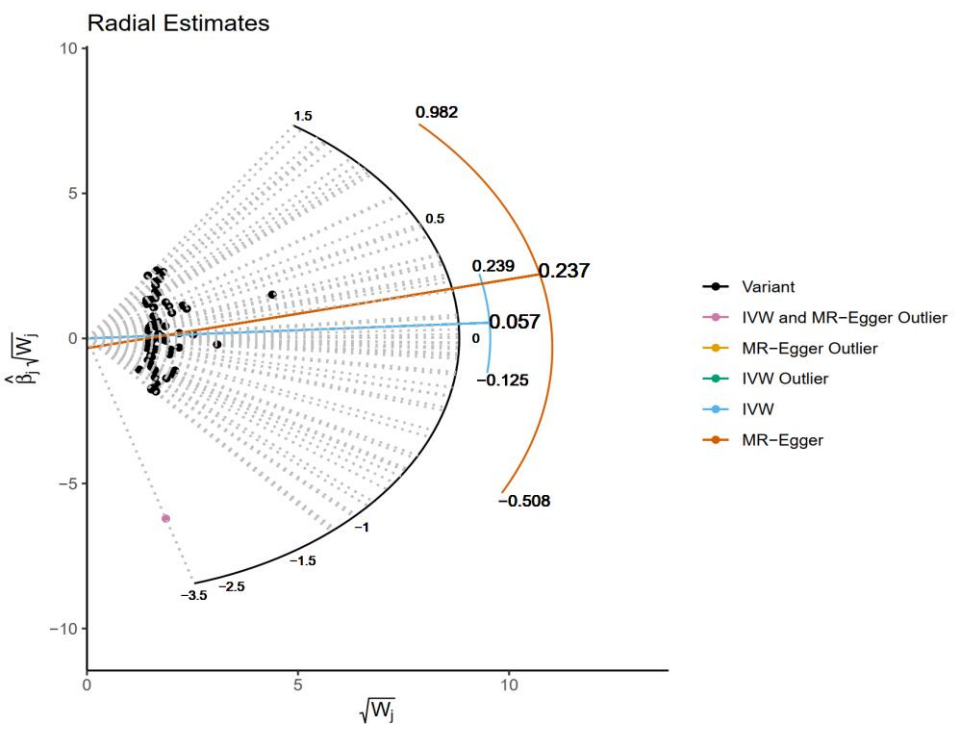
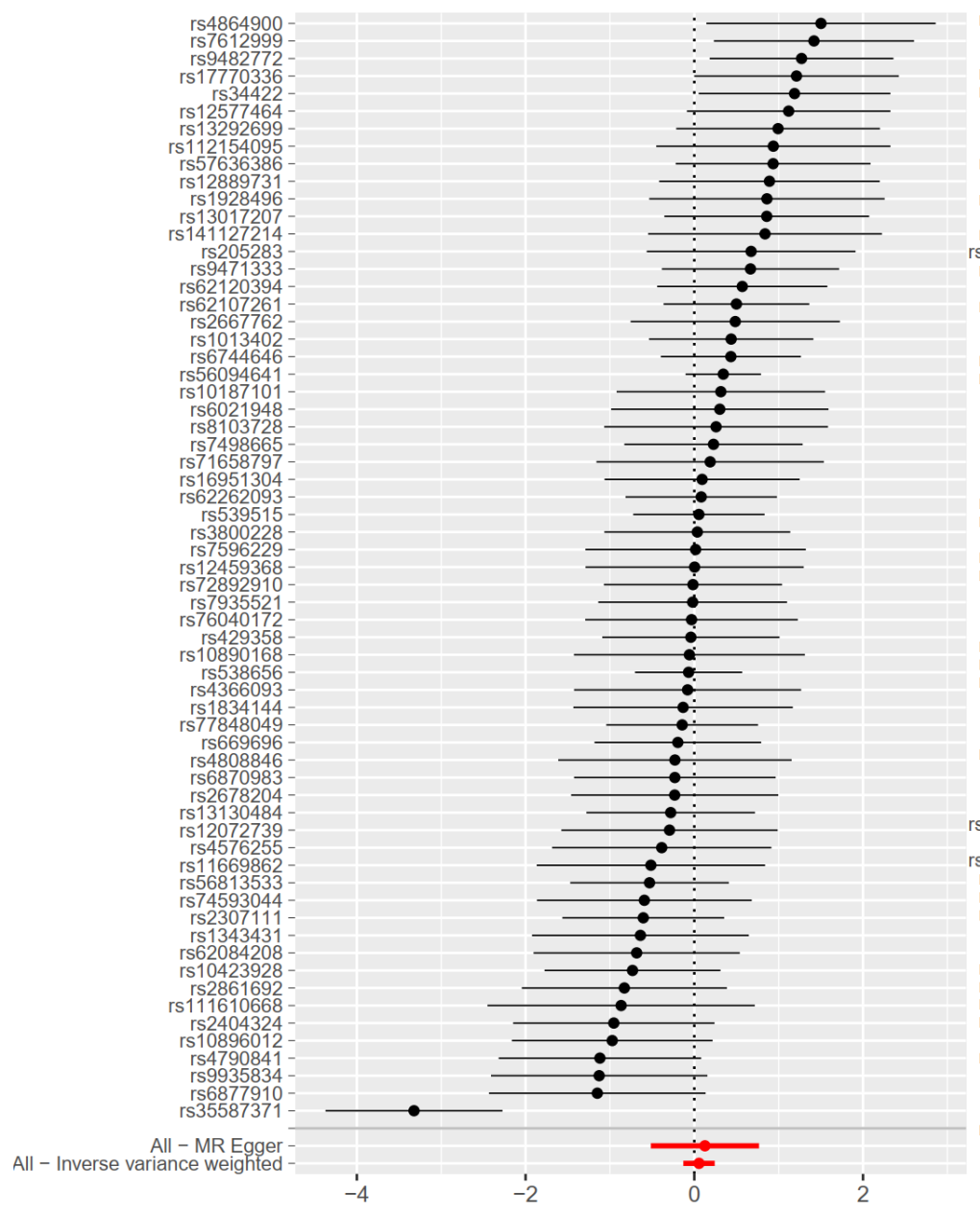


Figure S1: Flow diagram of search strategy and study selection for literature review.







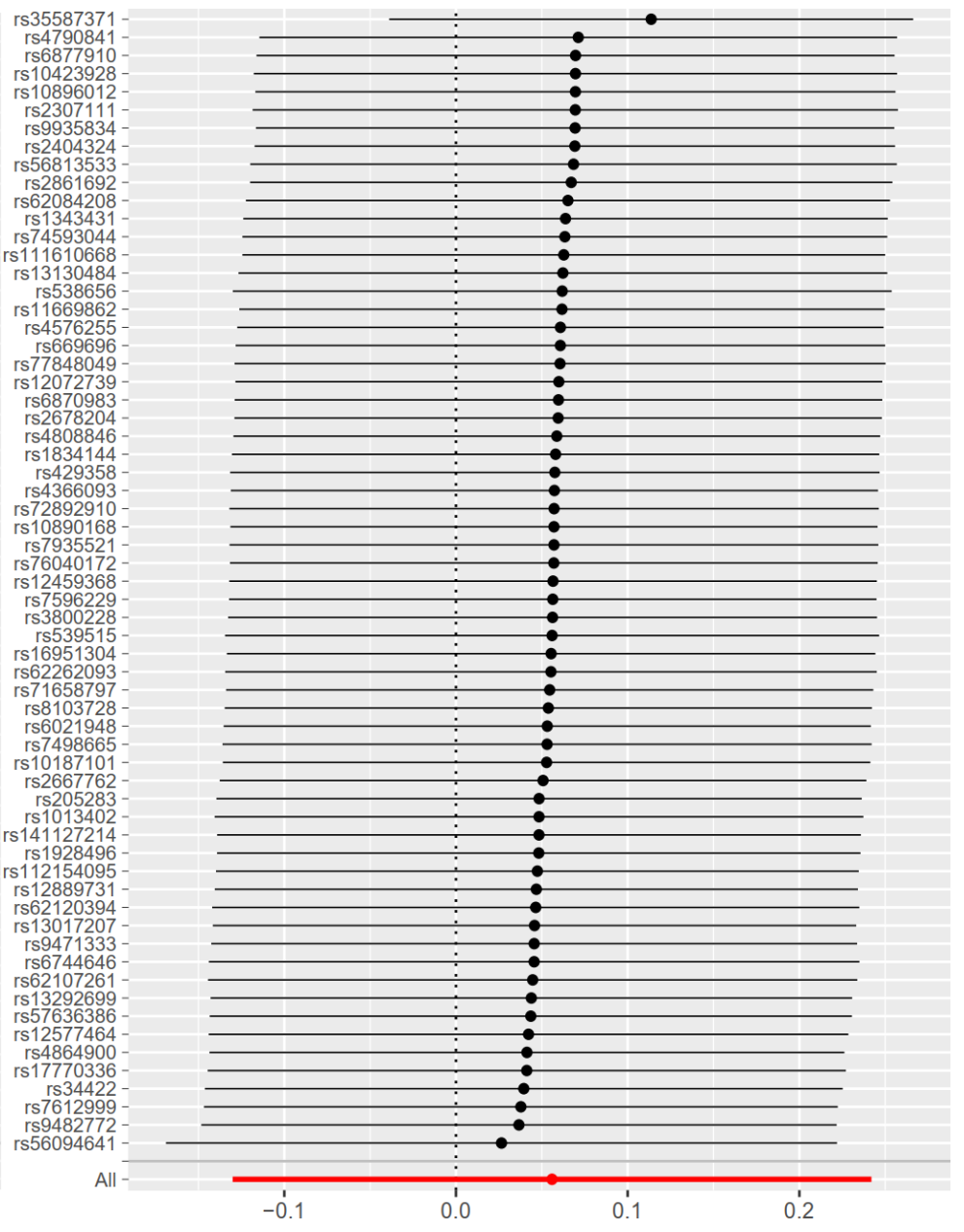


Figure S2-1. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on ovarian cancer.

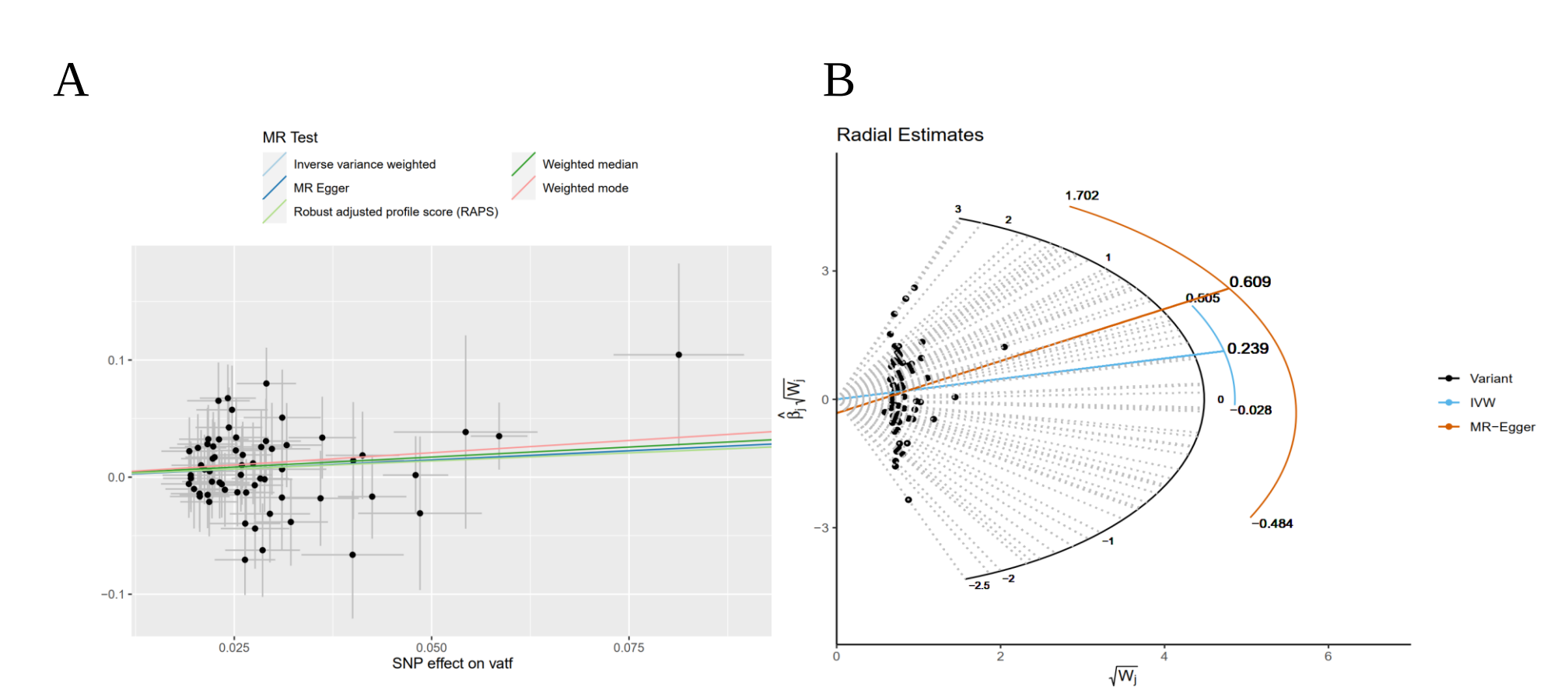


Figure S2-2. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on low malignant mucinous ovarian cancer.

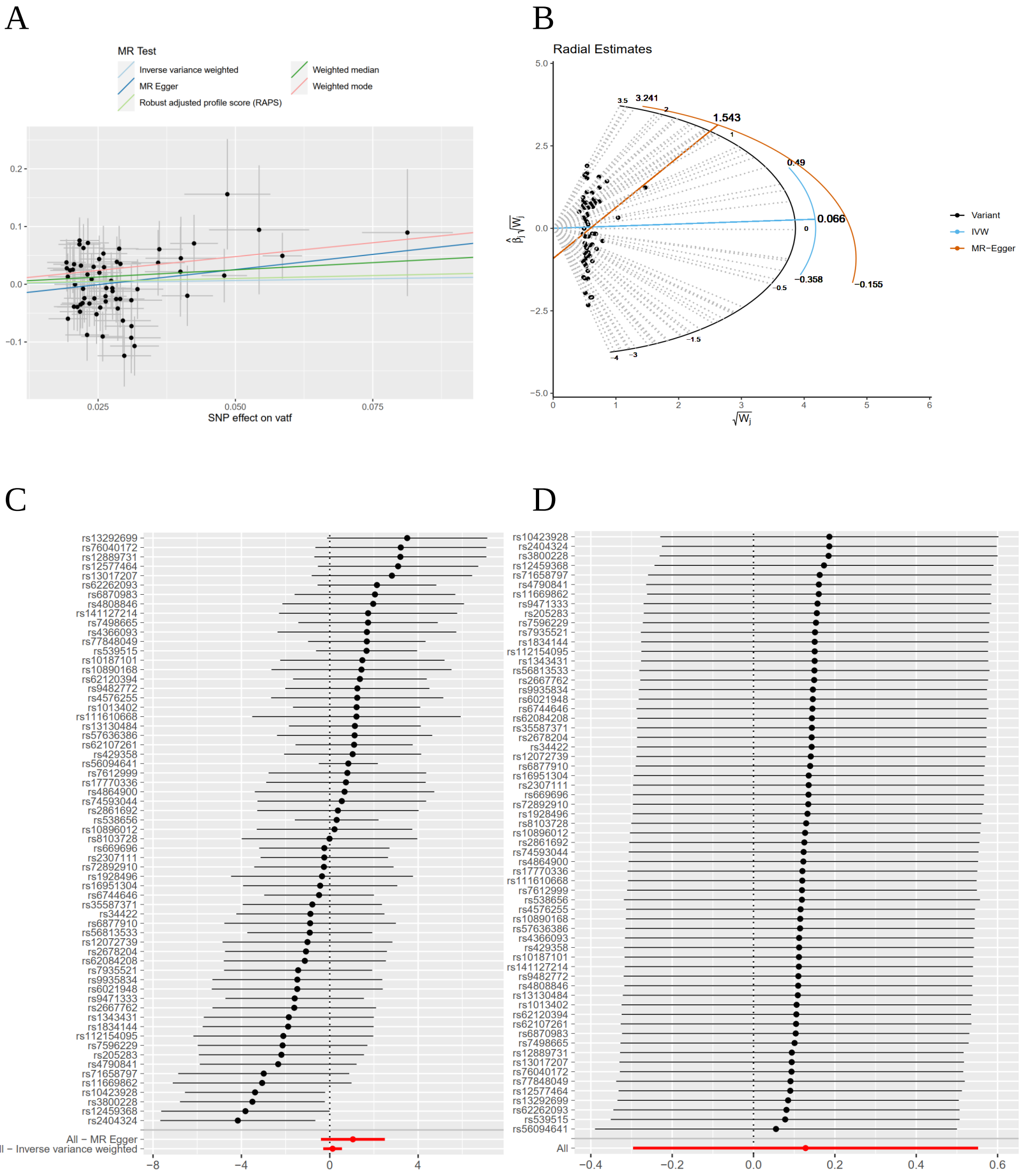
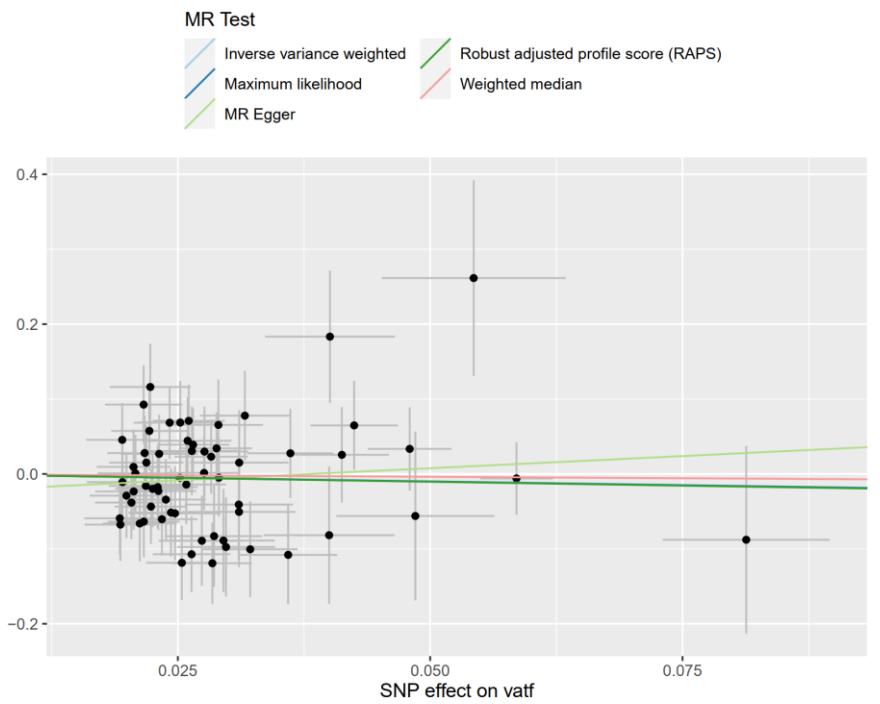
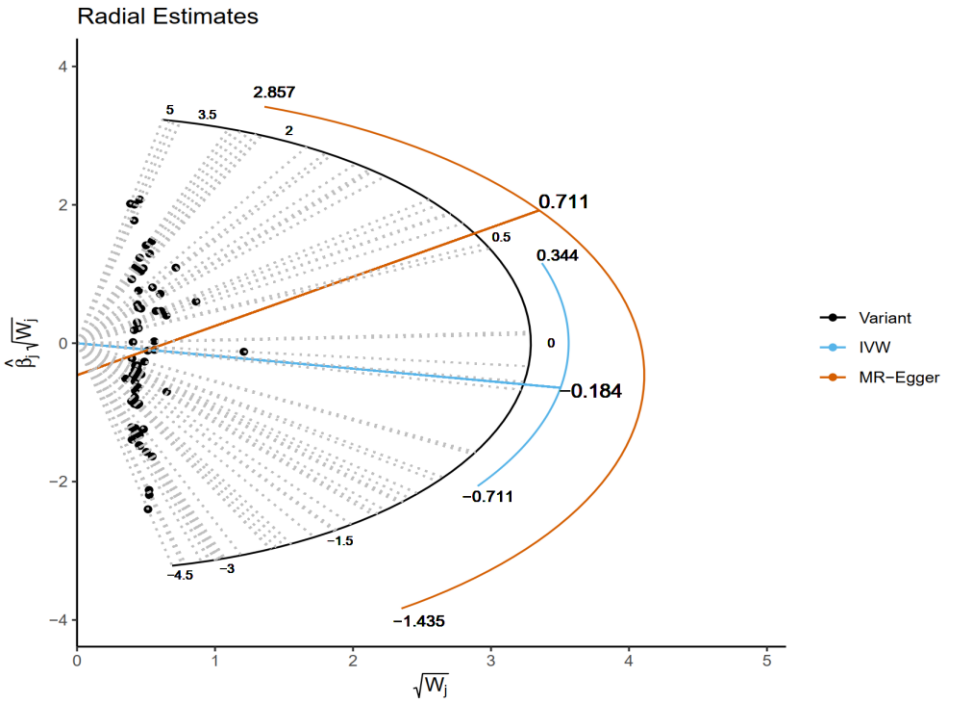


Figure S2-3. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on invasive mucinous ovarian cancer.

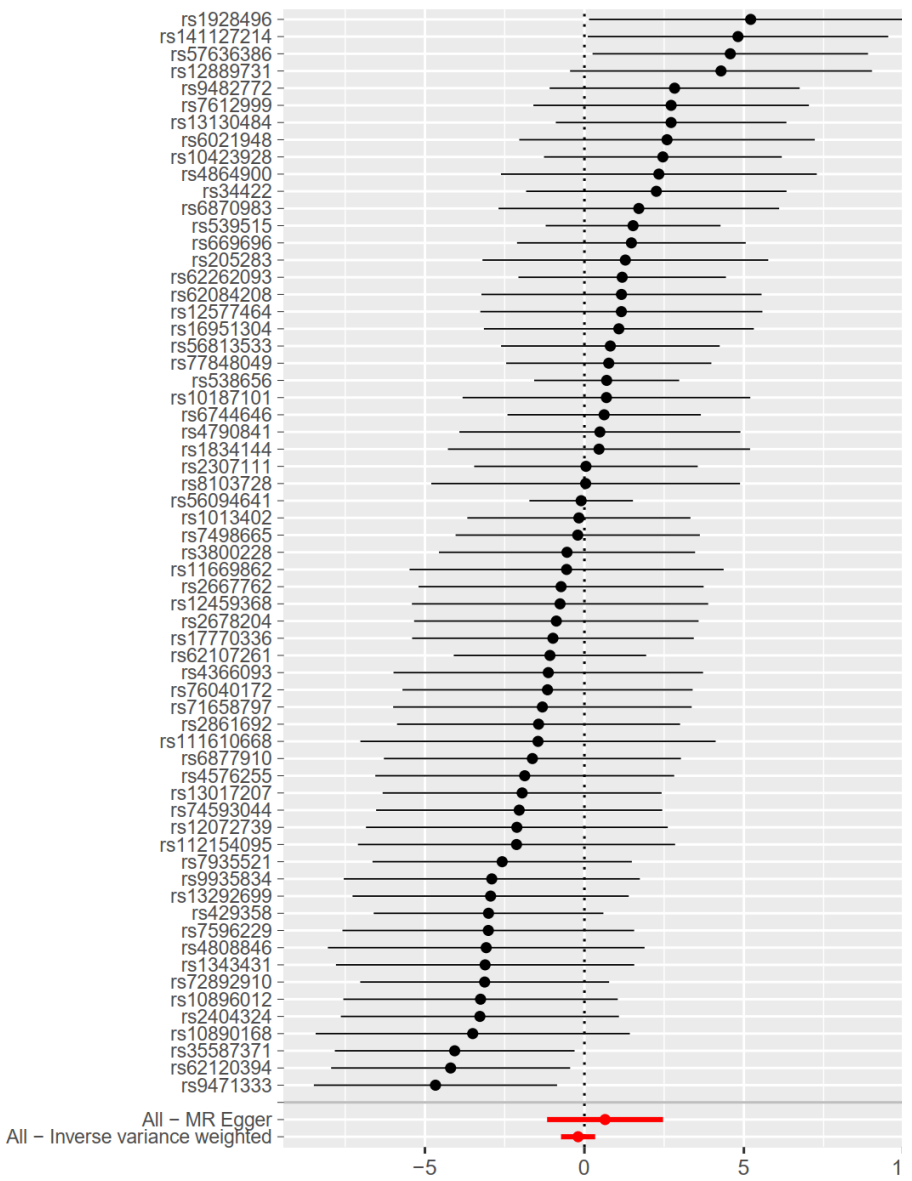
A



B



C



D

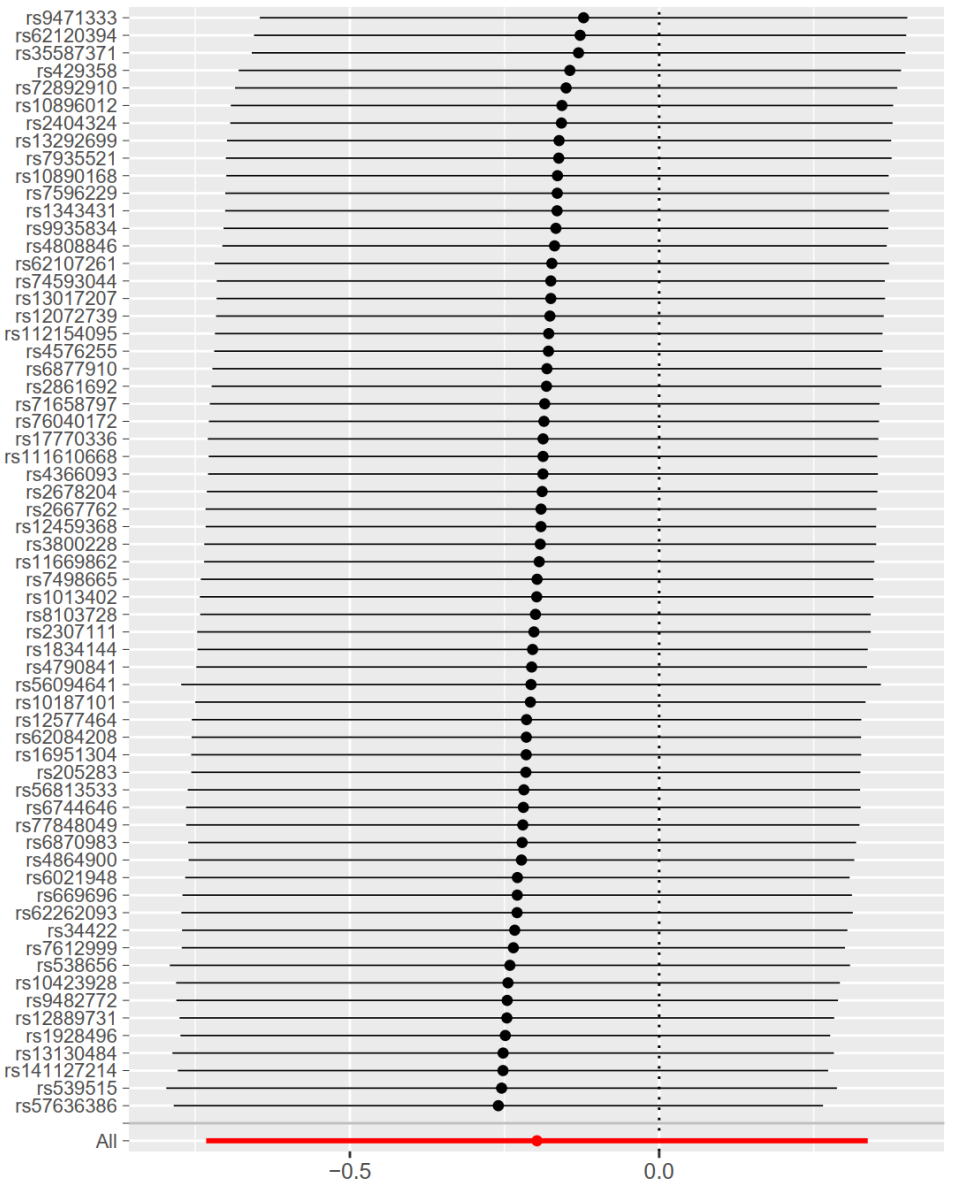
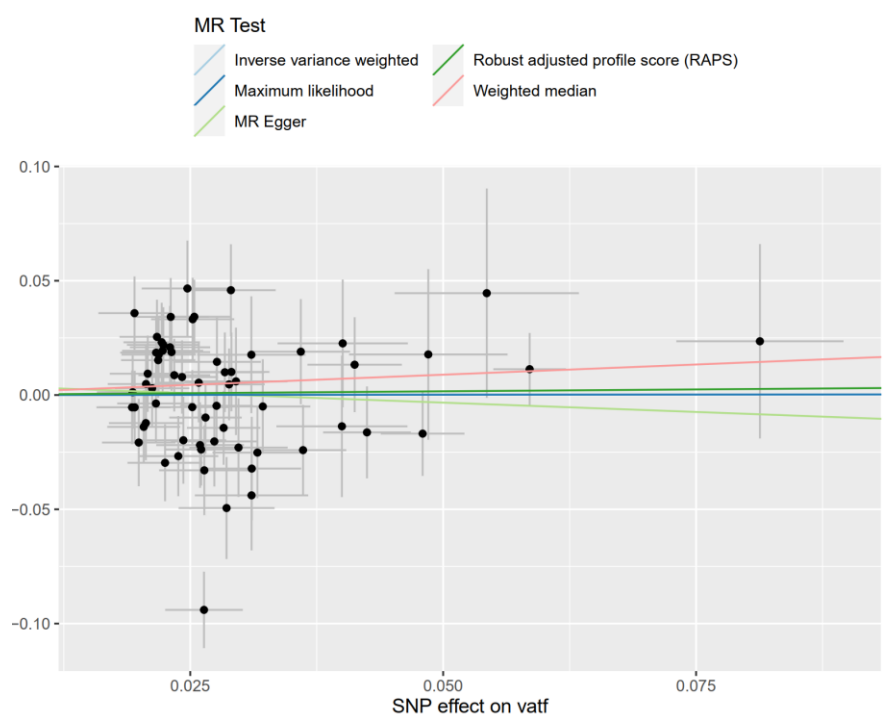
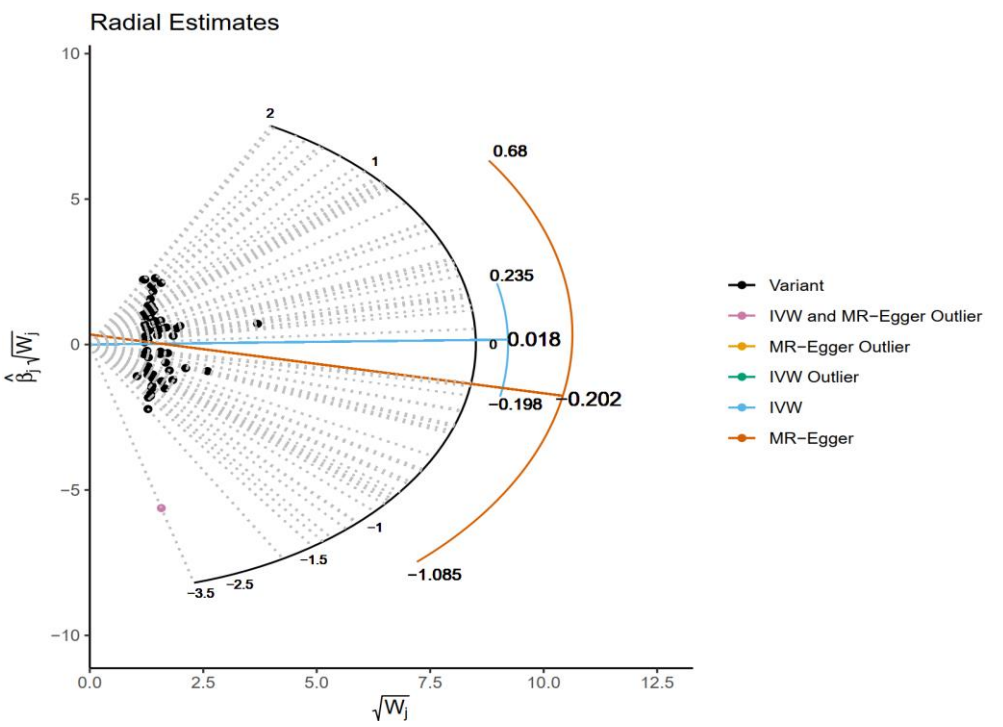
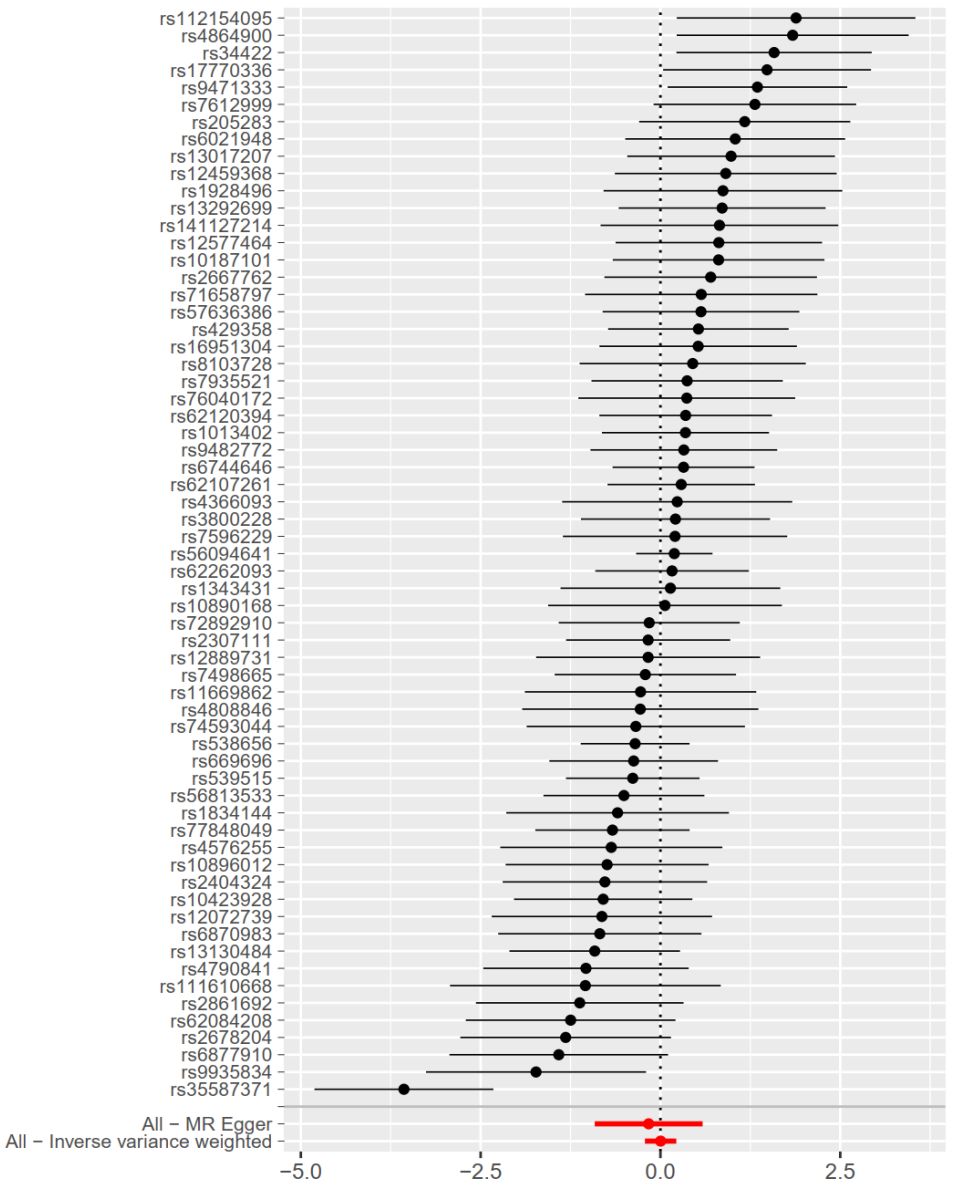


Figure S2-4. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on low grade serous ovarian cancer.







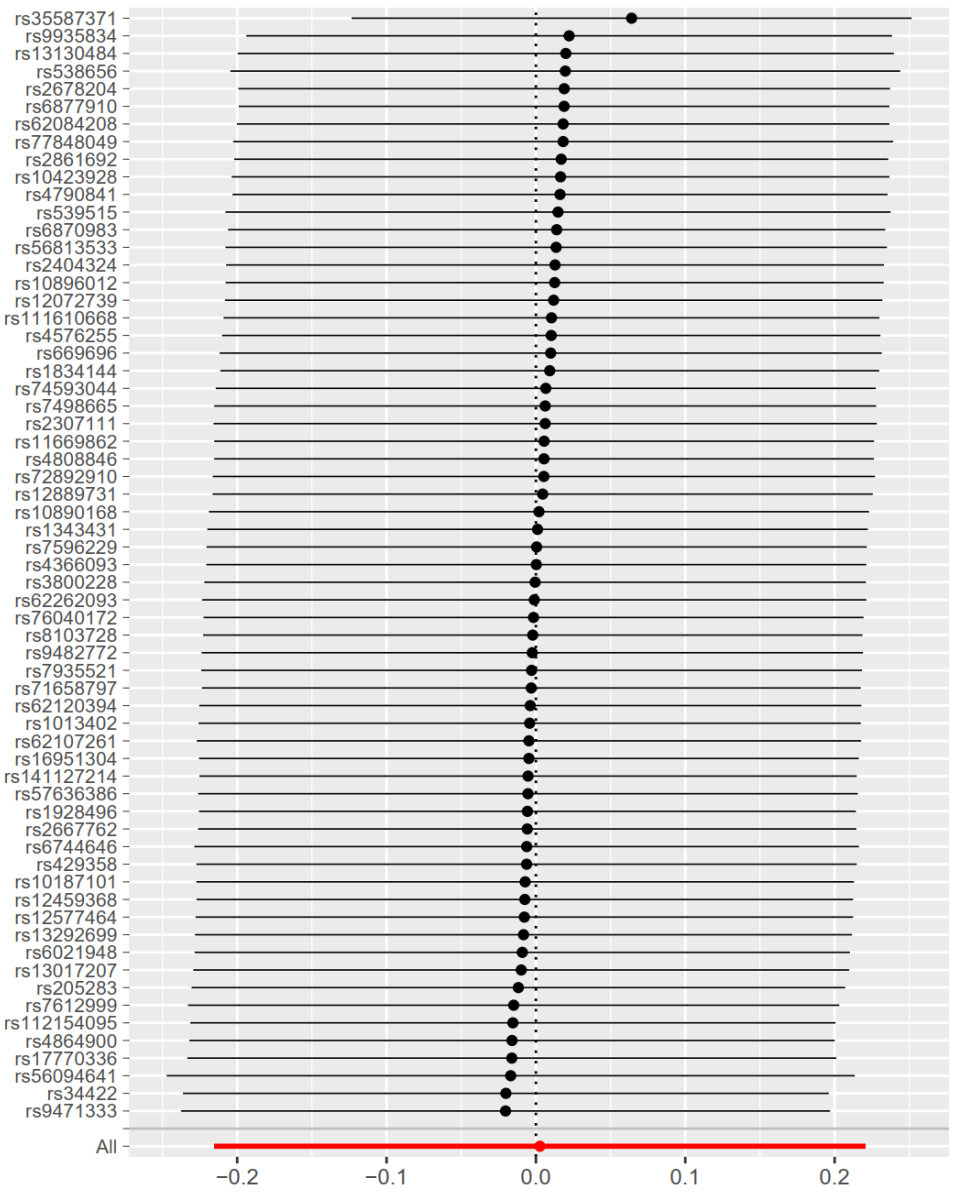
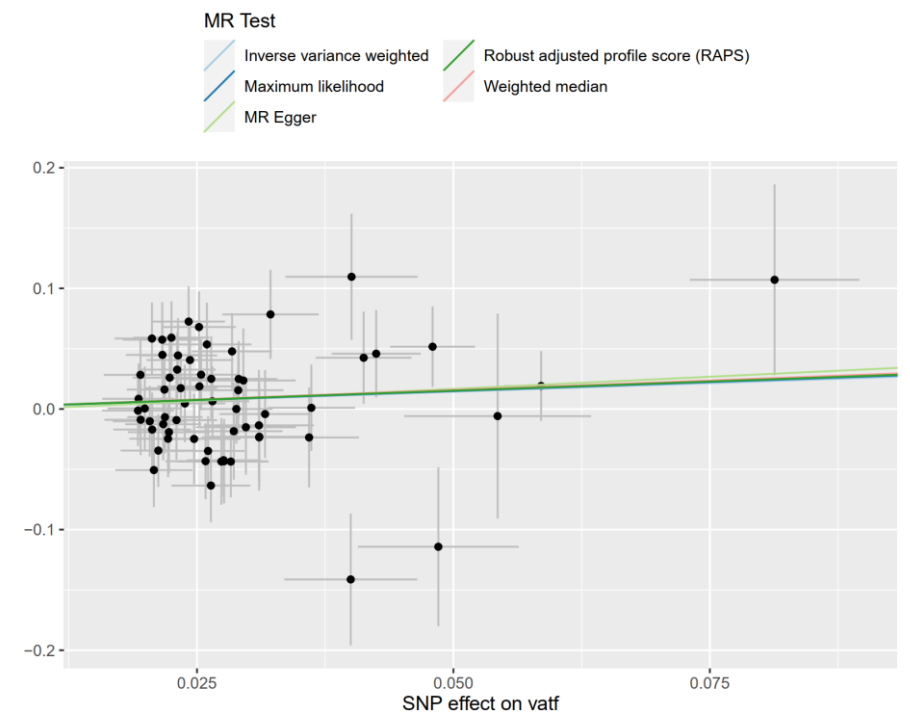
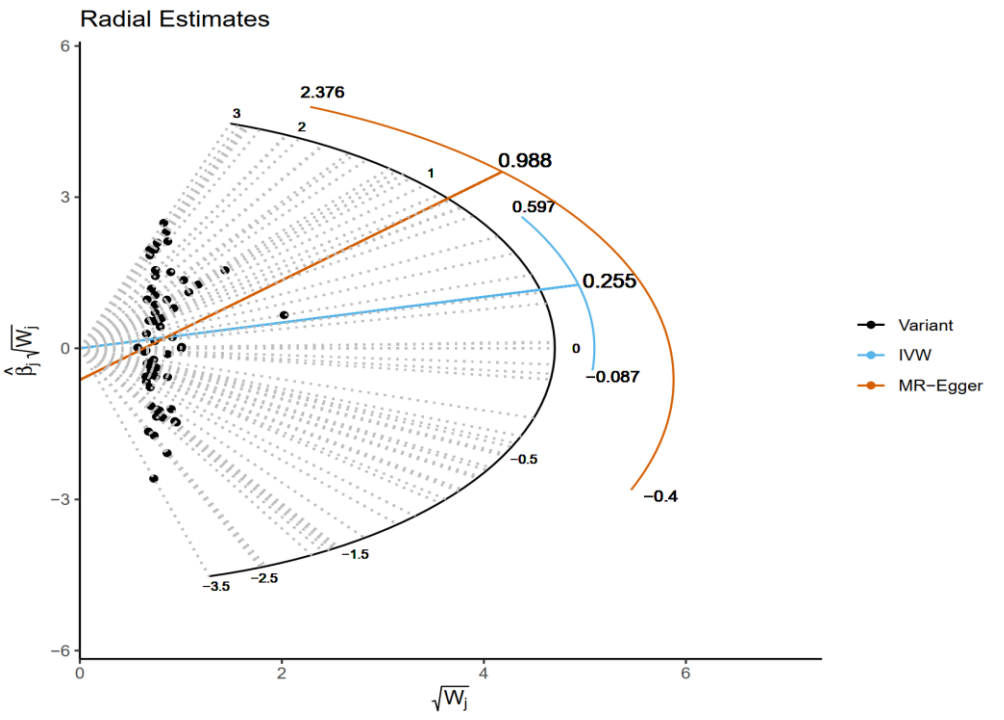
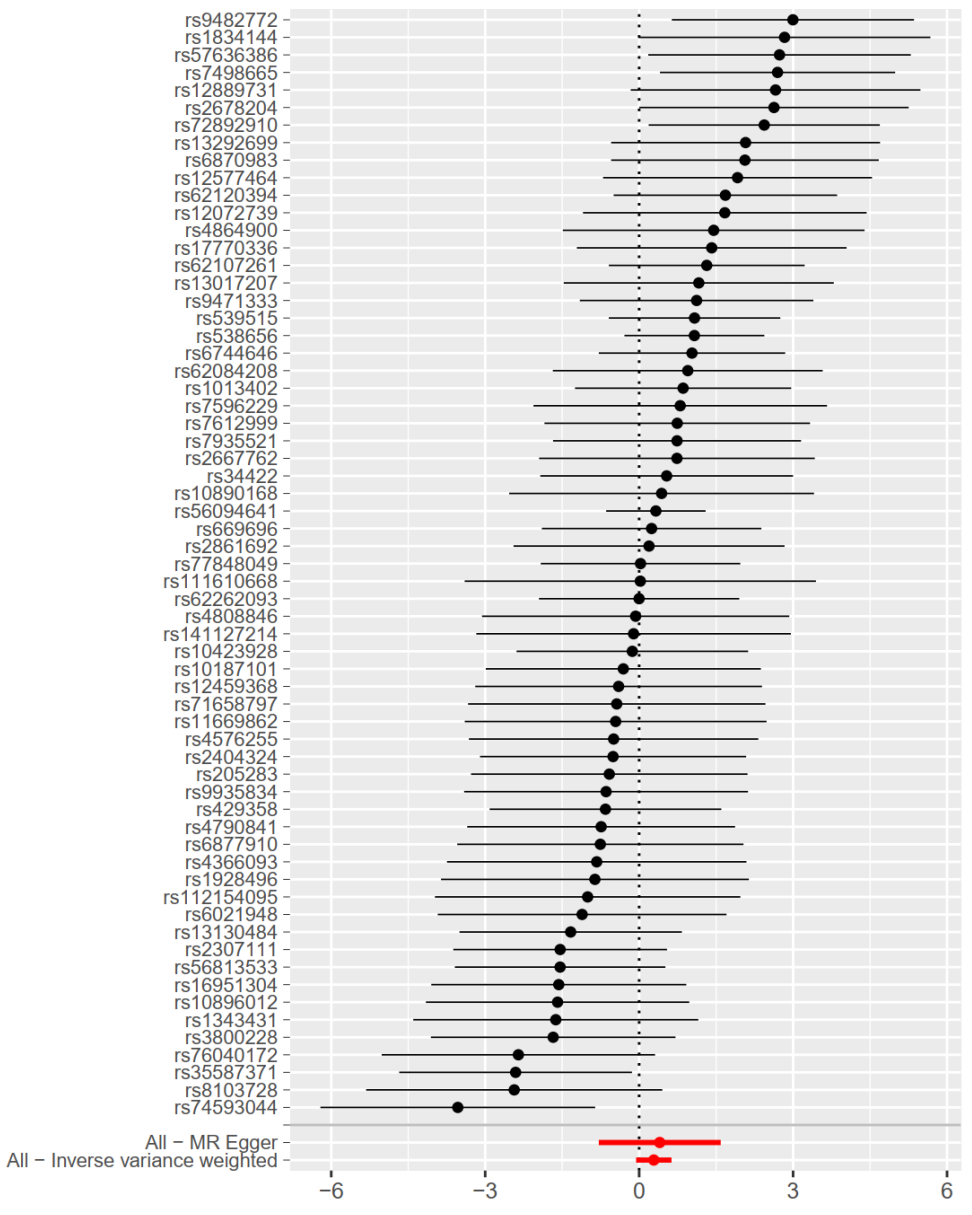


Figure S2-5. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on high grade serous ovarian cancer.







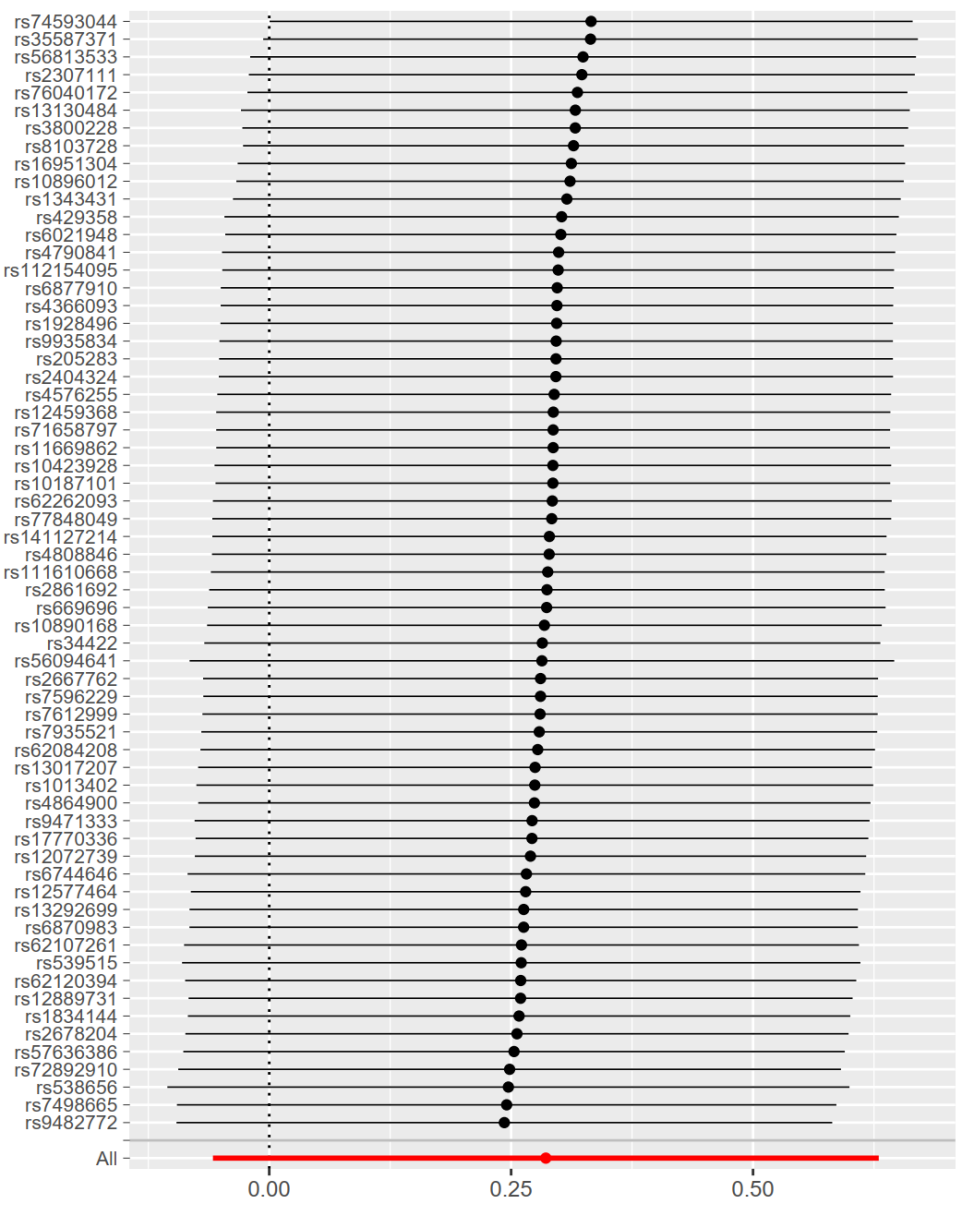
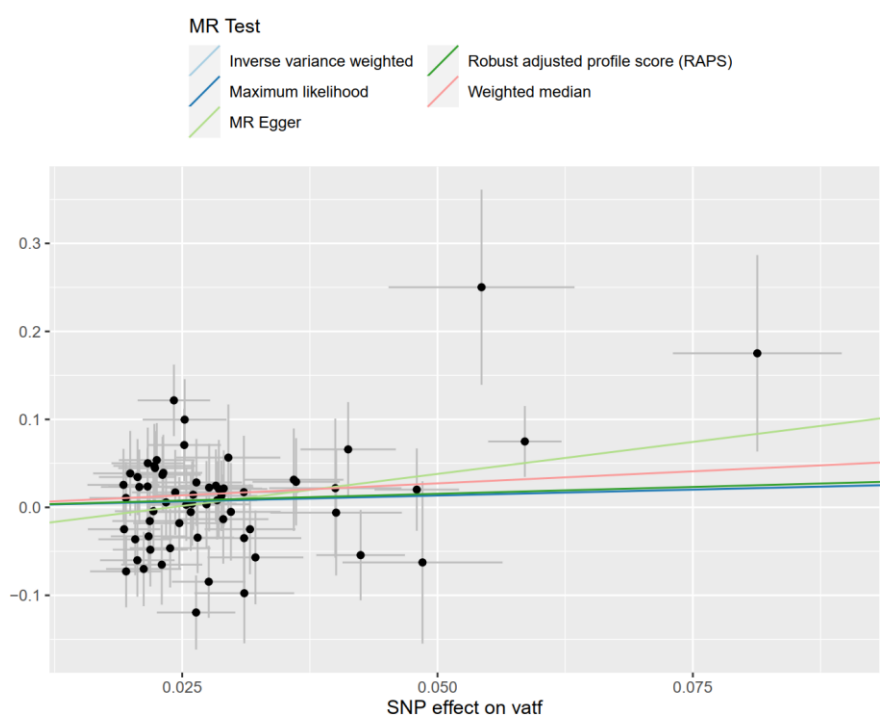
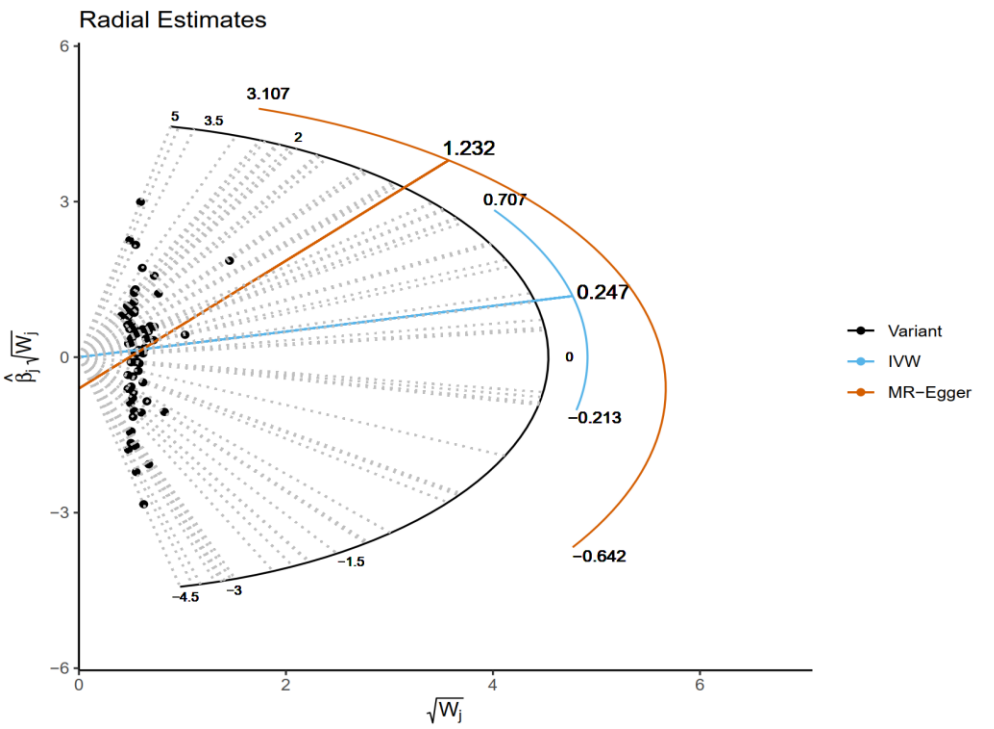
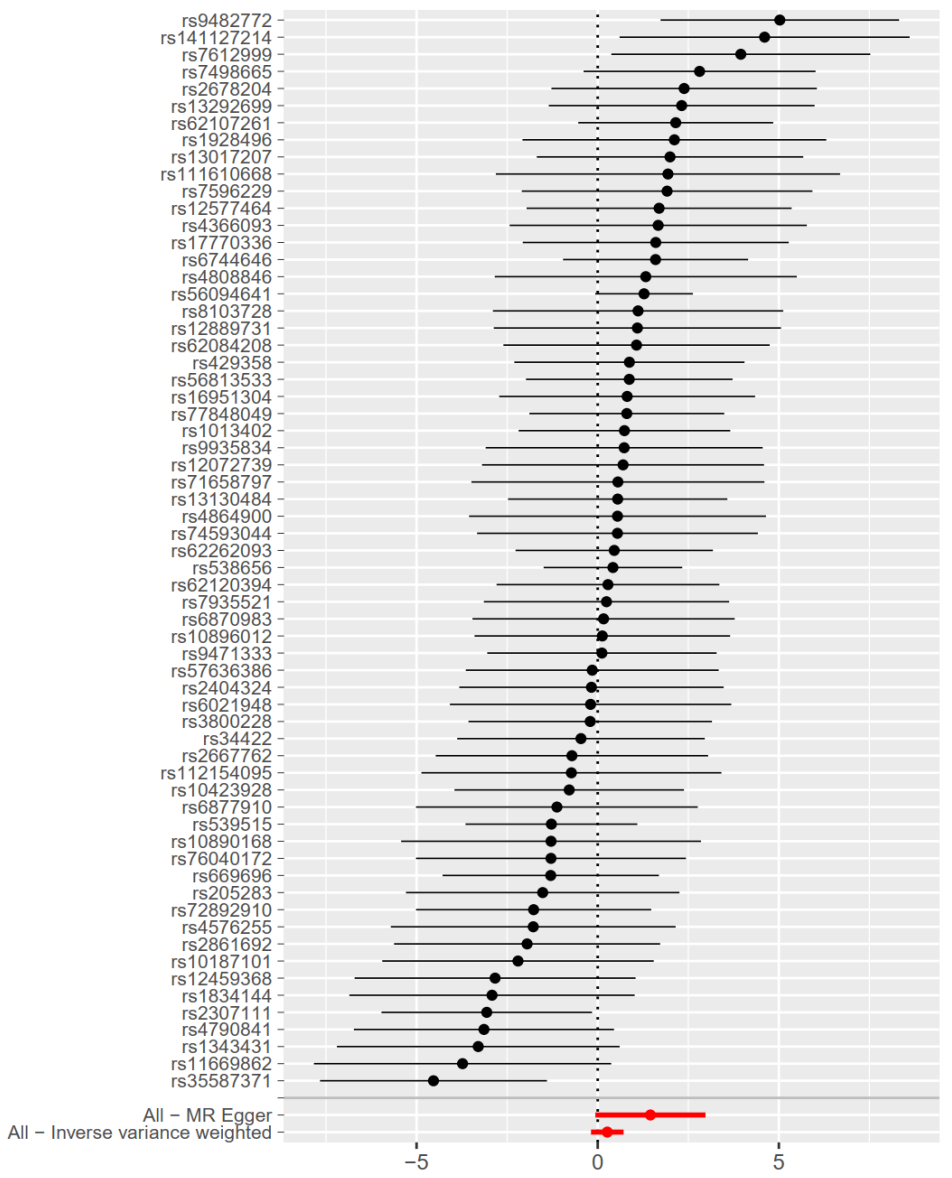


Figure S2-6. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on endometrioid ovarian cancer.







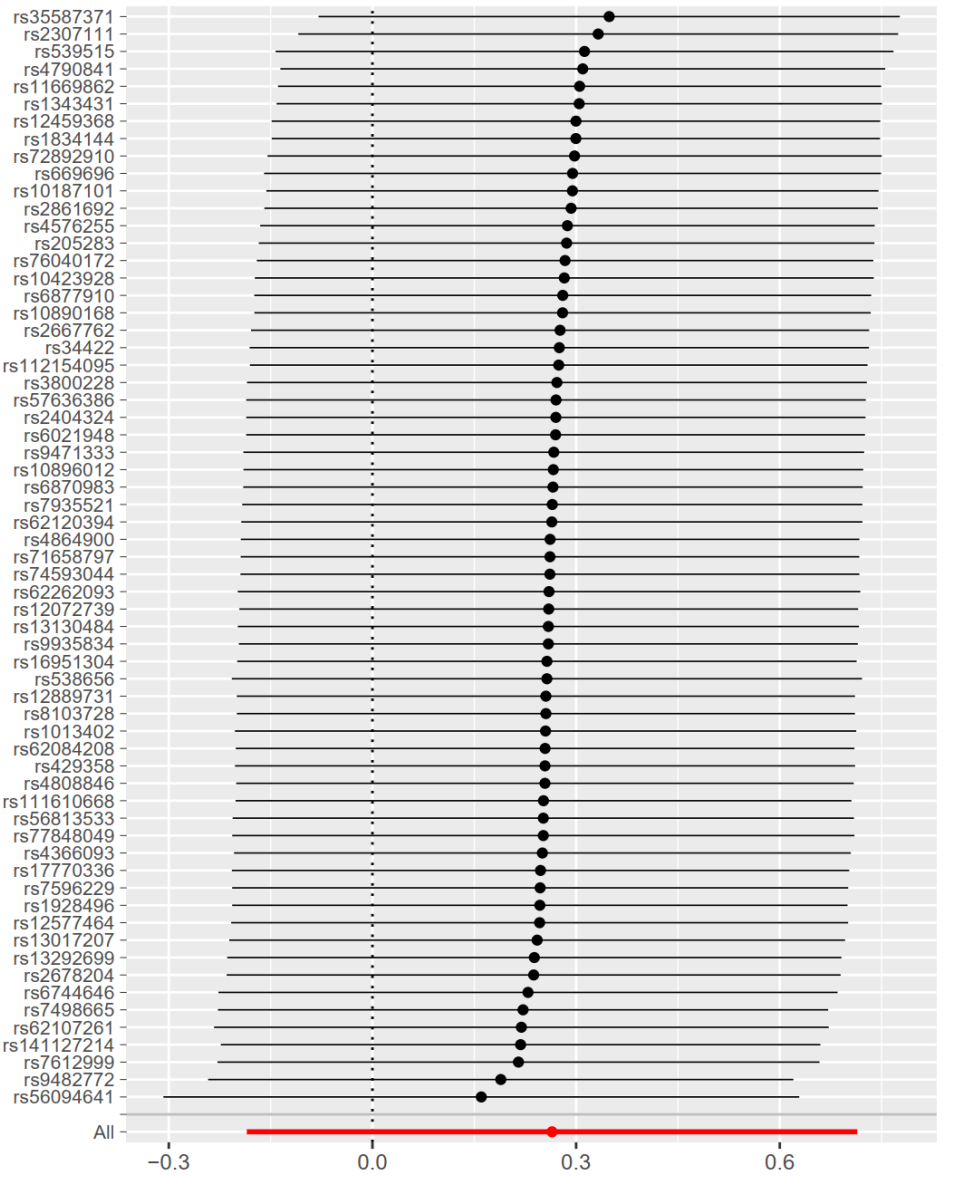
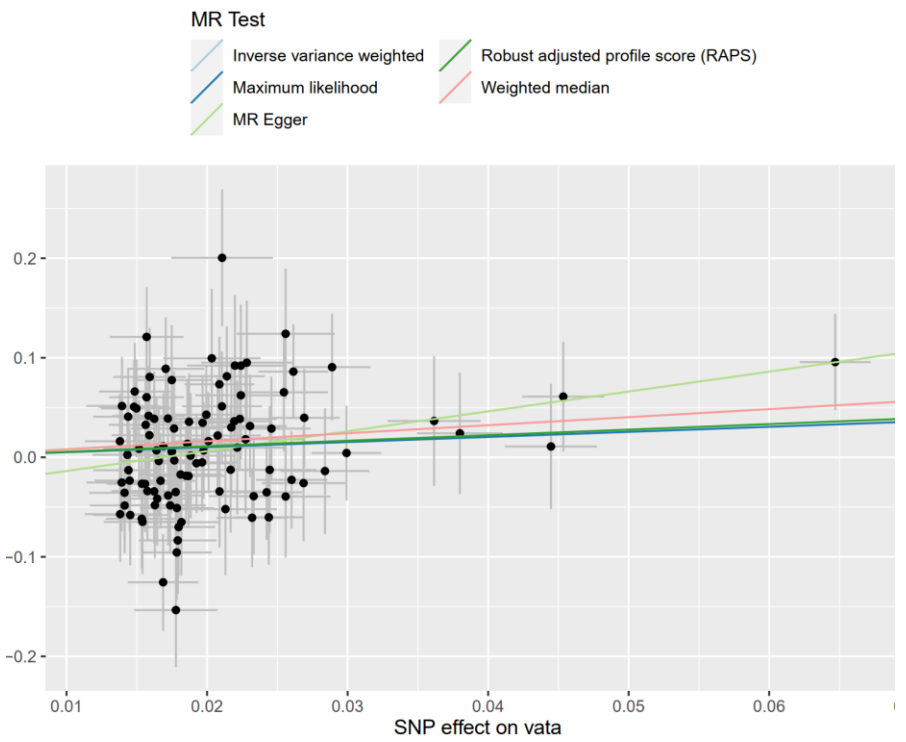
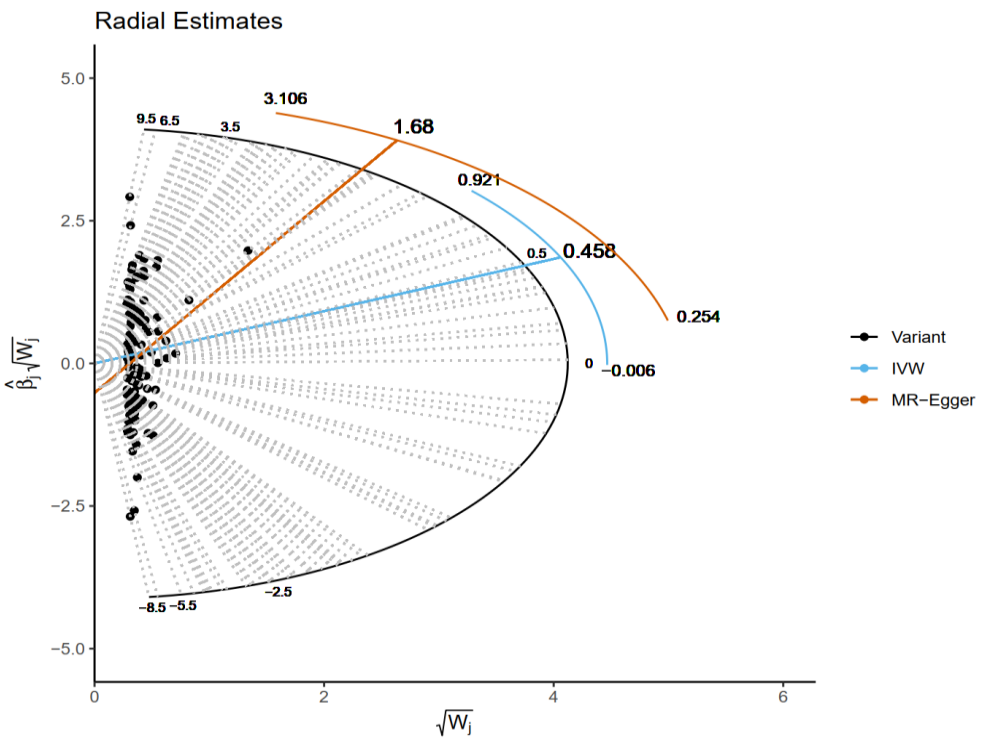


Figure S2-7. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on clear cell ovarian cancer.

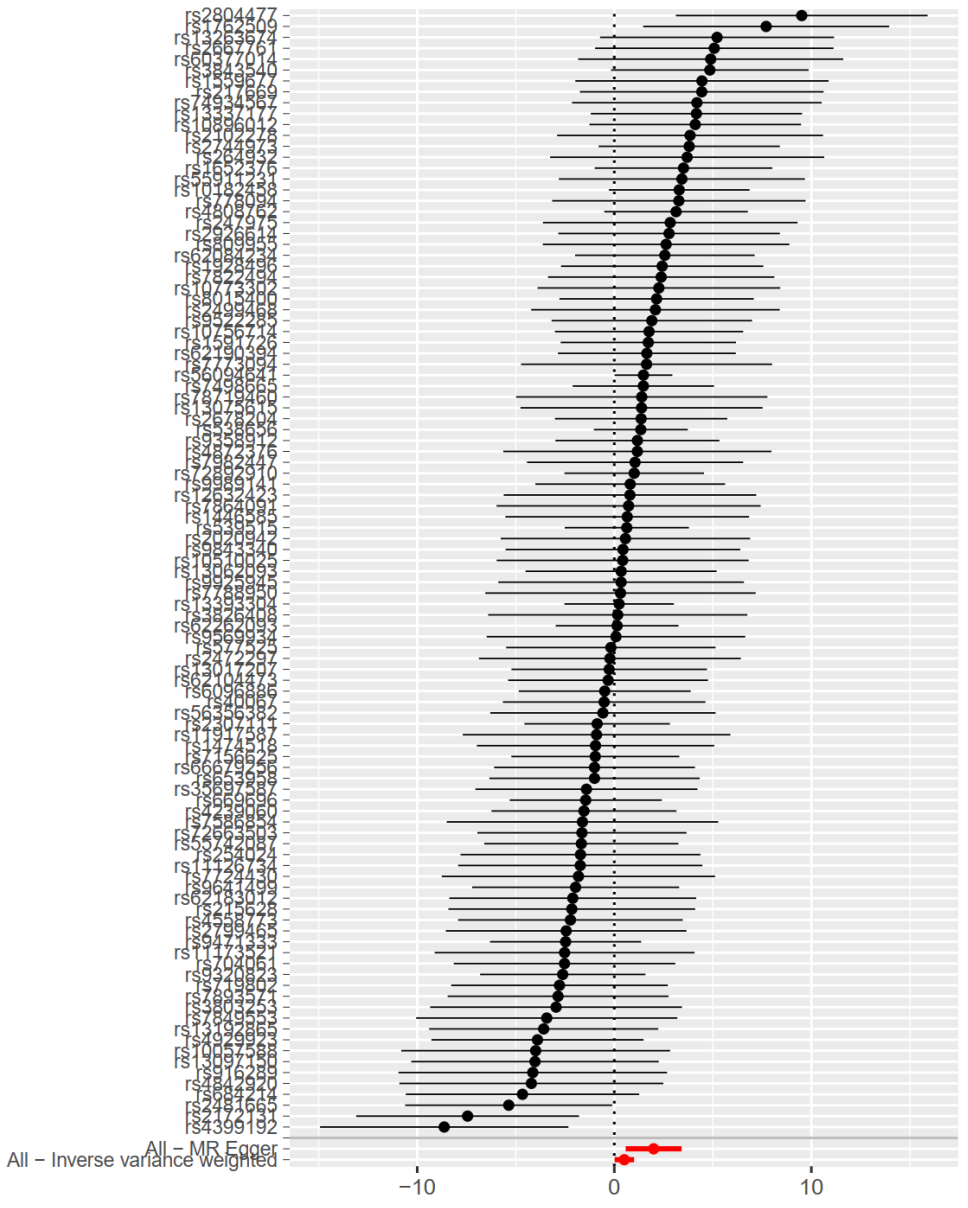
A



B



C



D

Figure S3. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on pancreatic cancer.

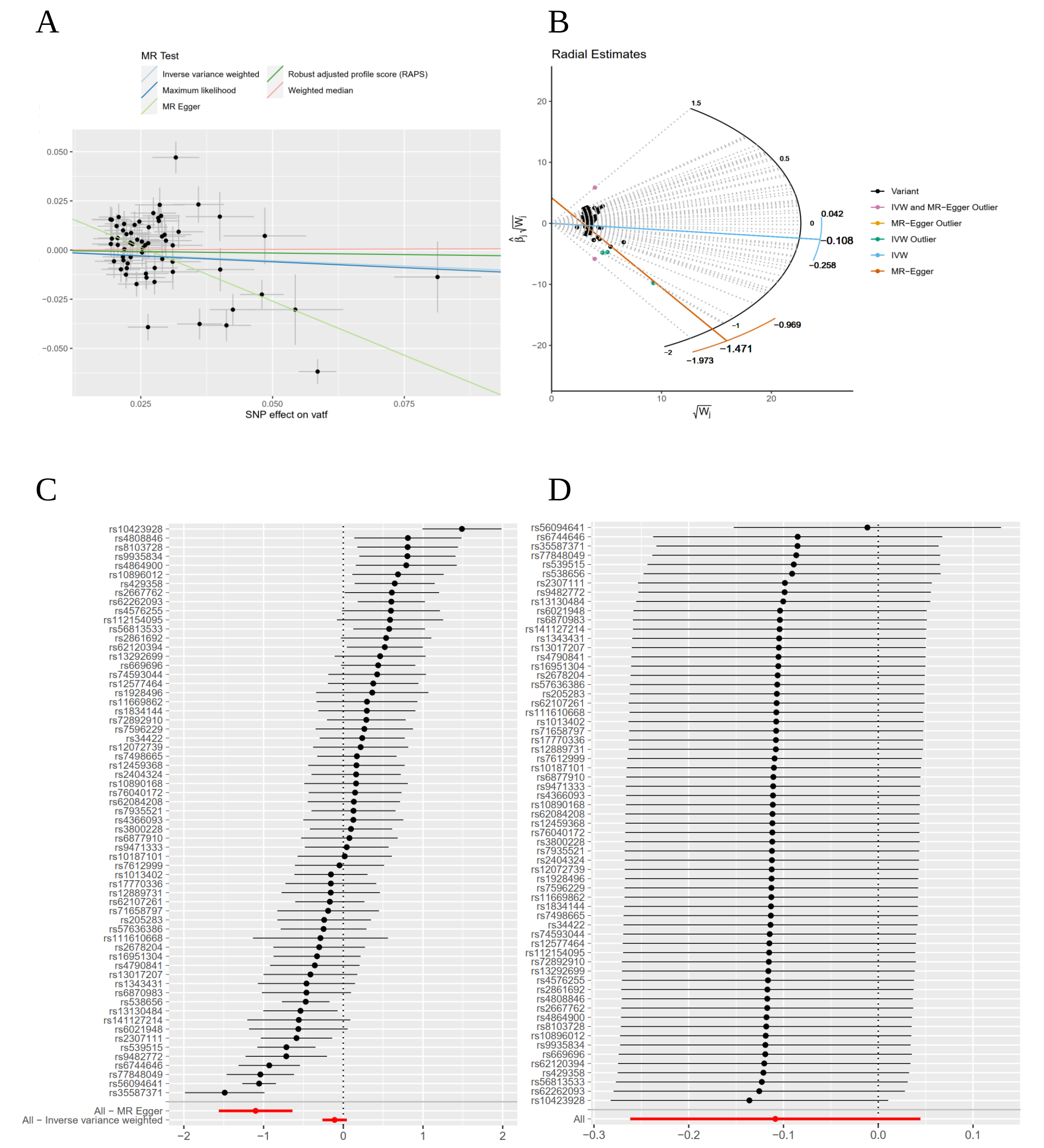
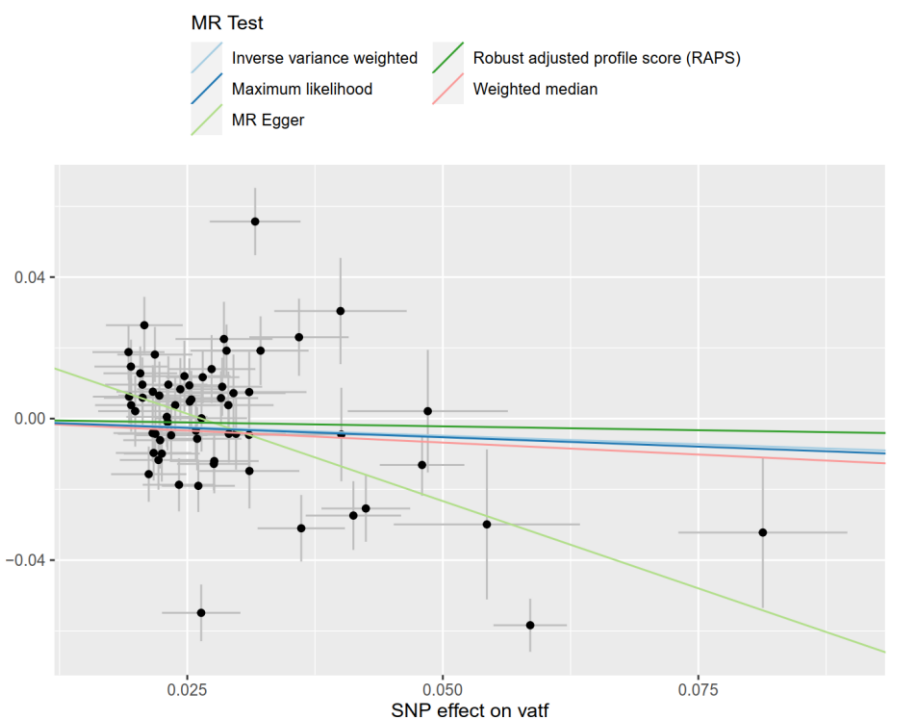
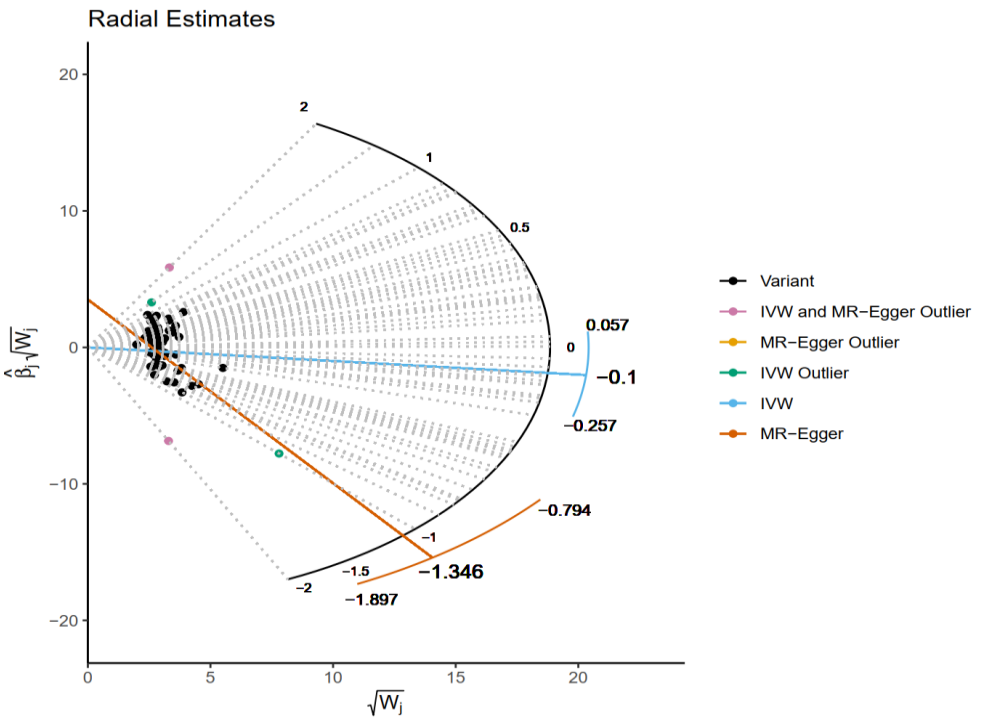


Figure S4-1. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on breast cancer.

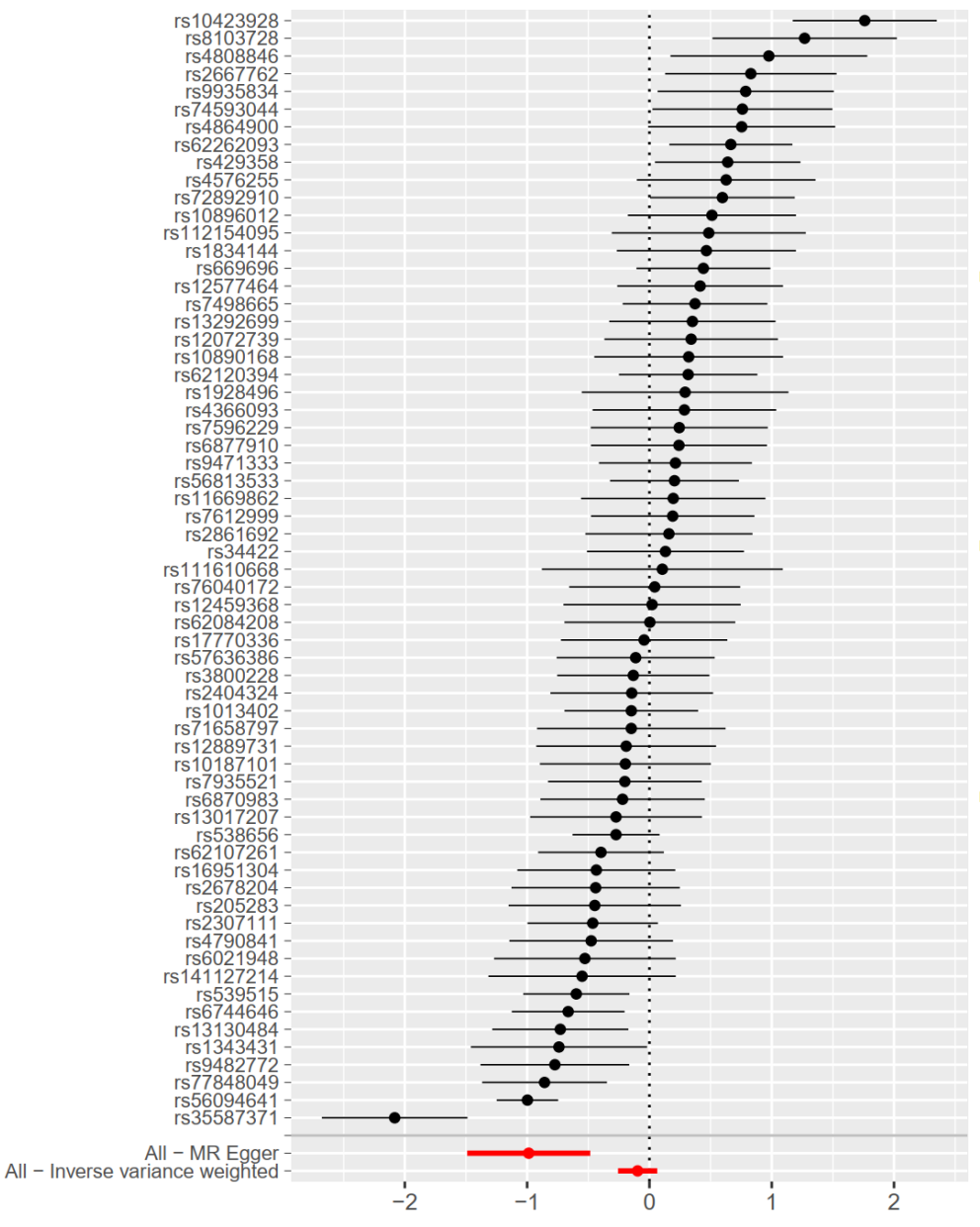
A



B



C



D

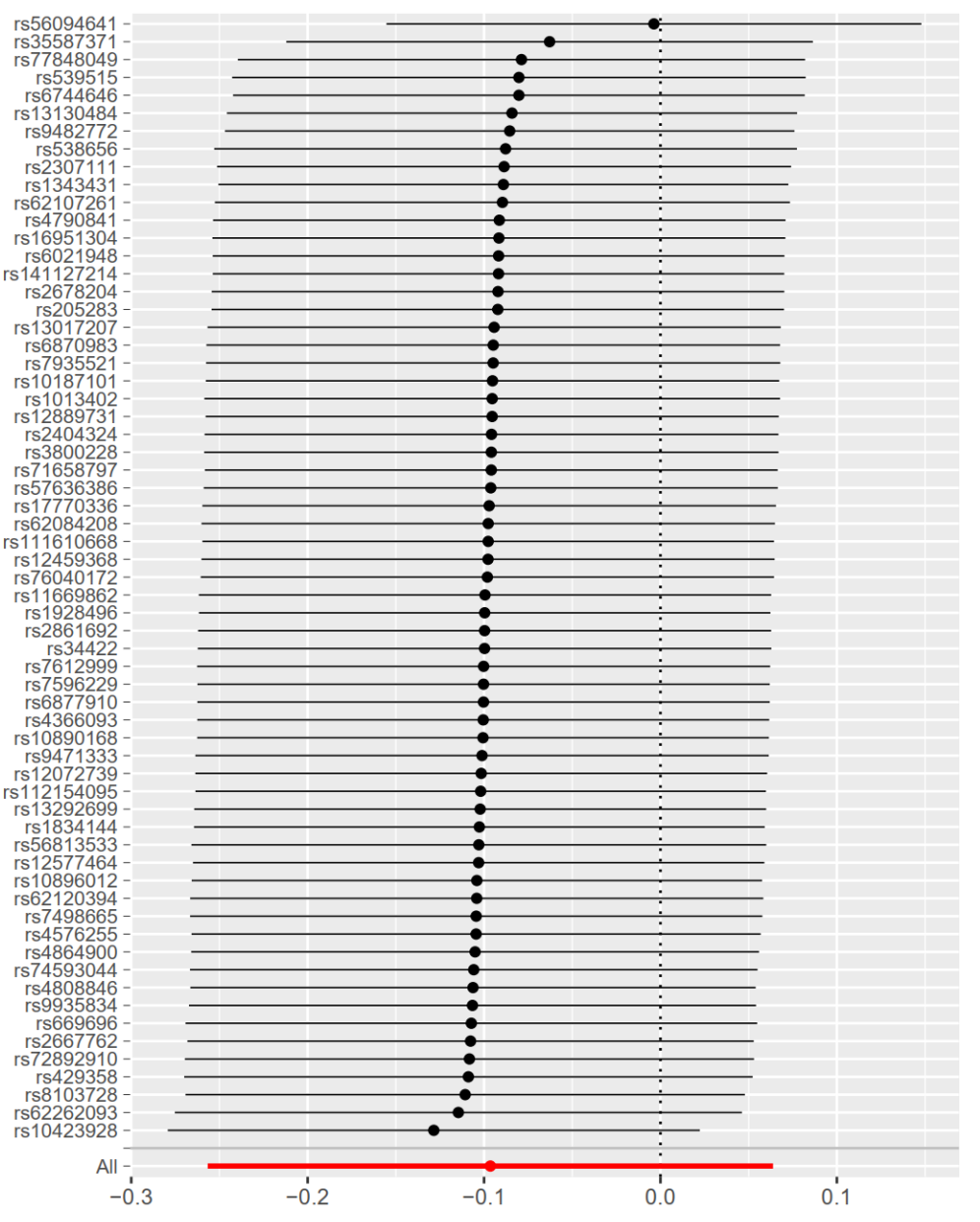


Figure S4-2. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on ER+ breast cancer.

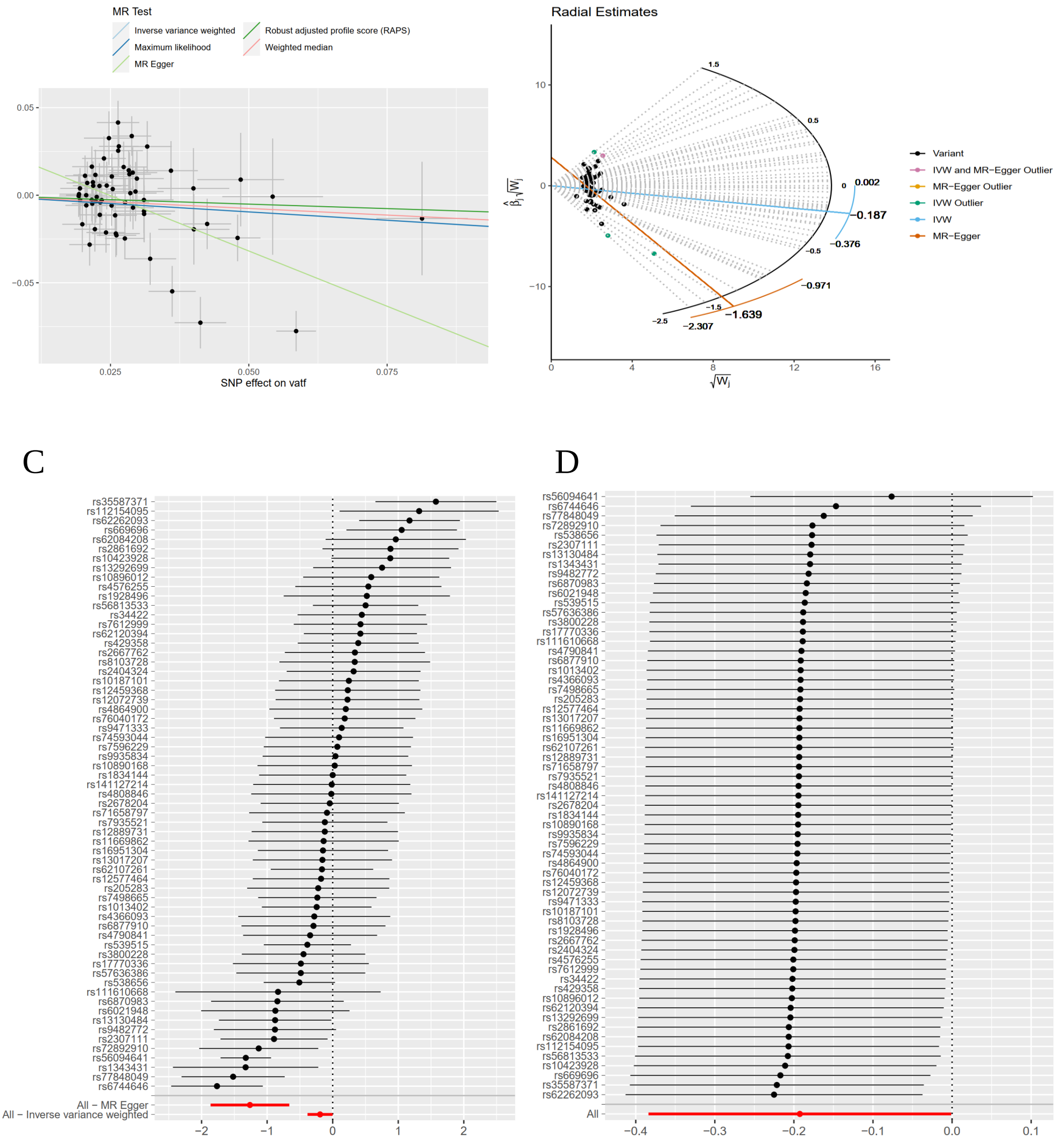
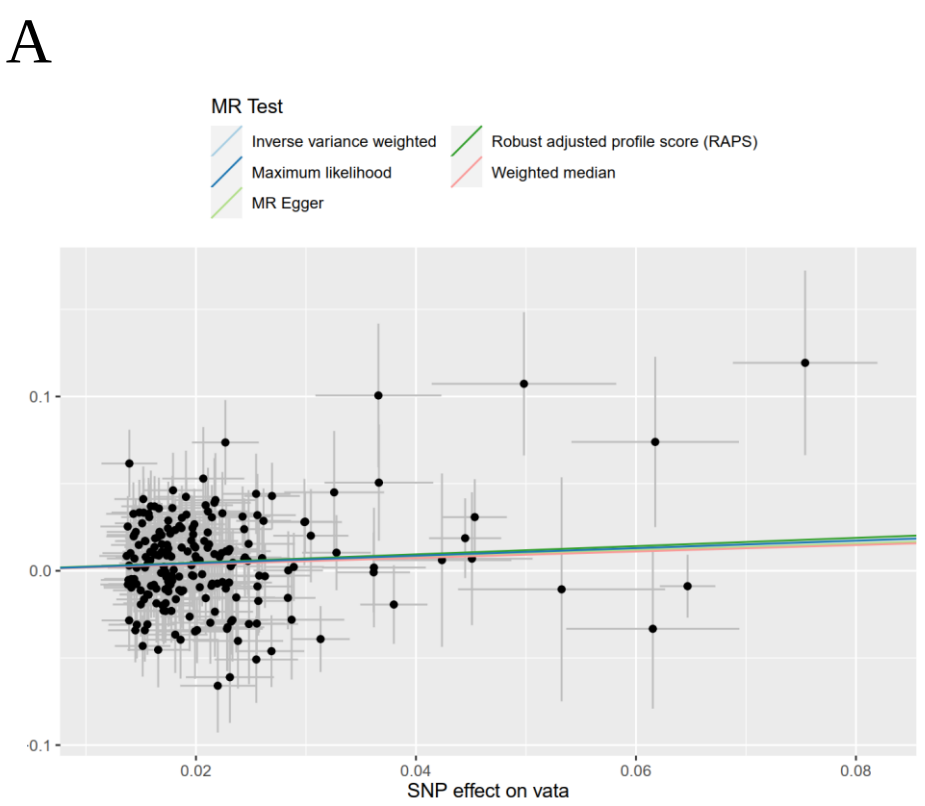
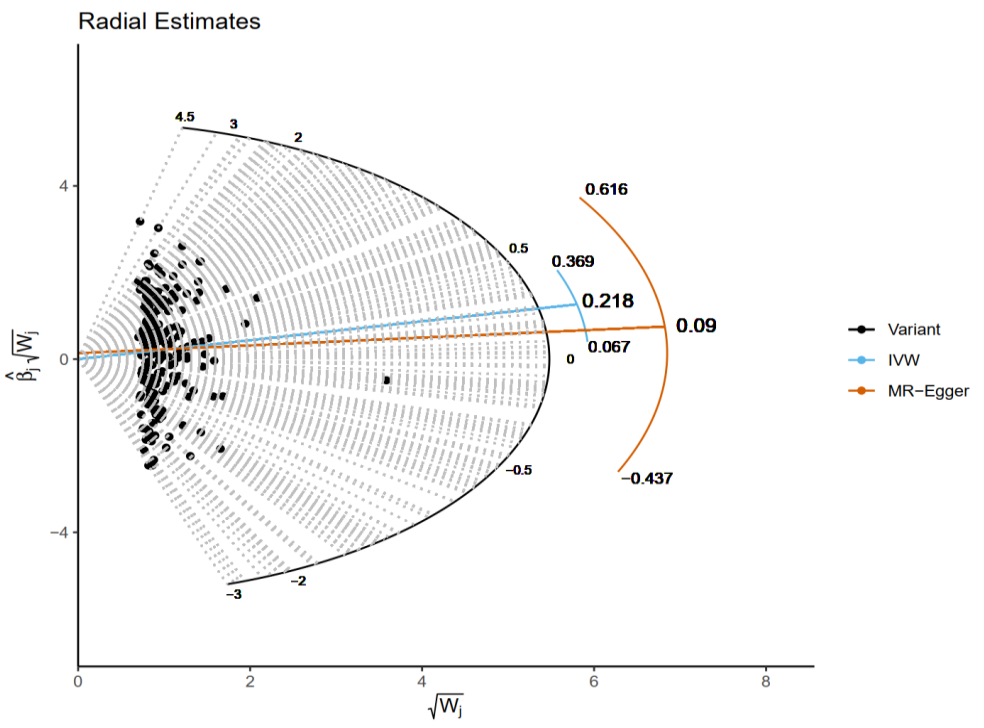
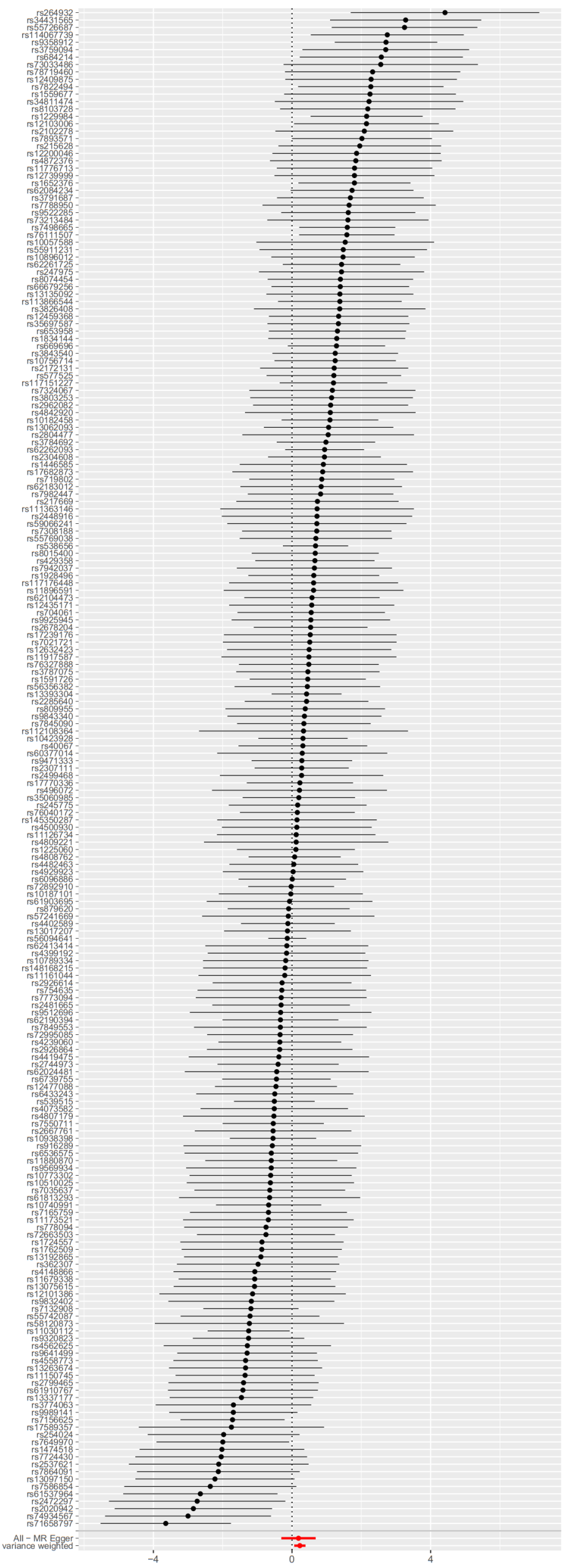


Figure S4-3. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on ER- breast cancer.







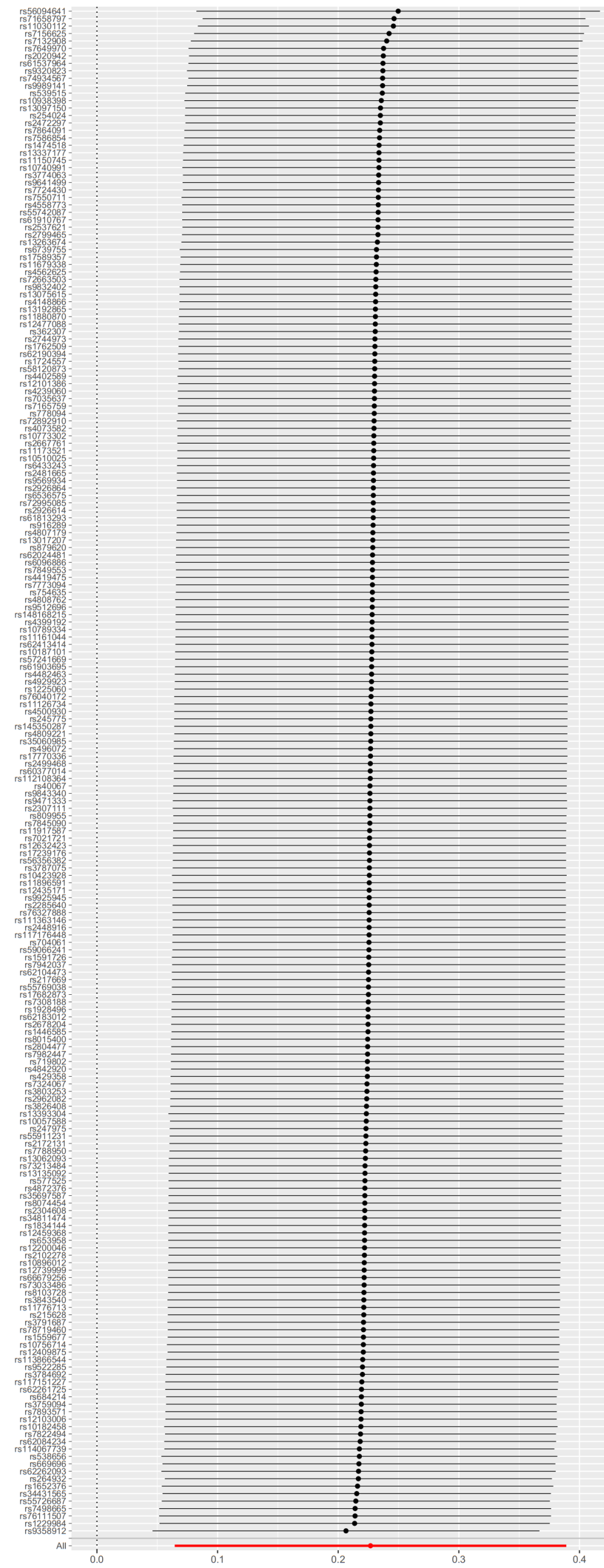
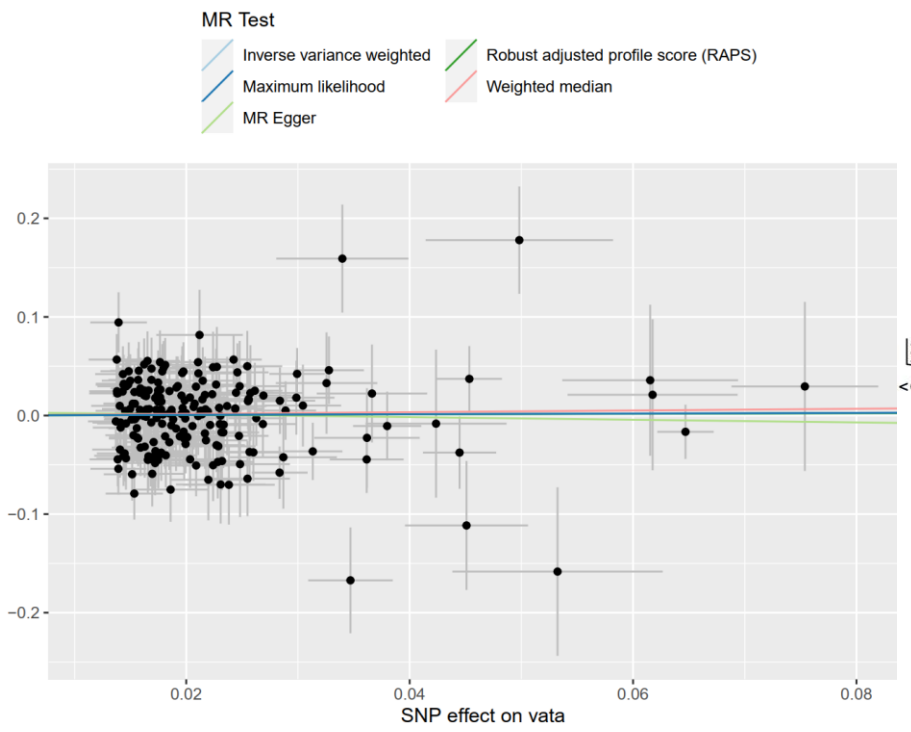
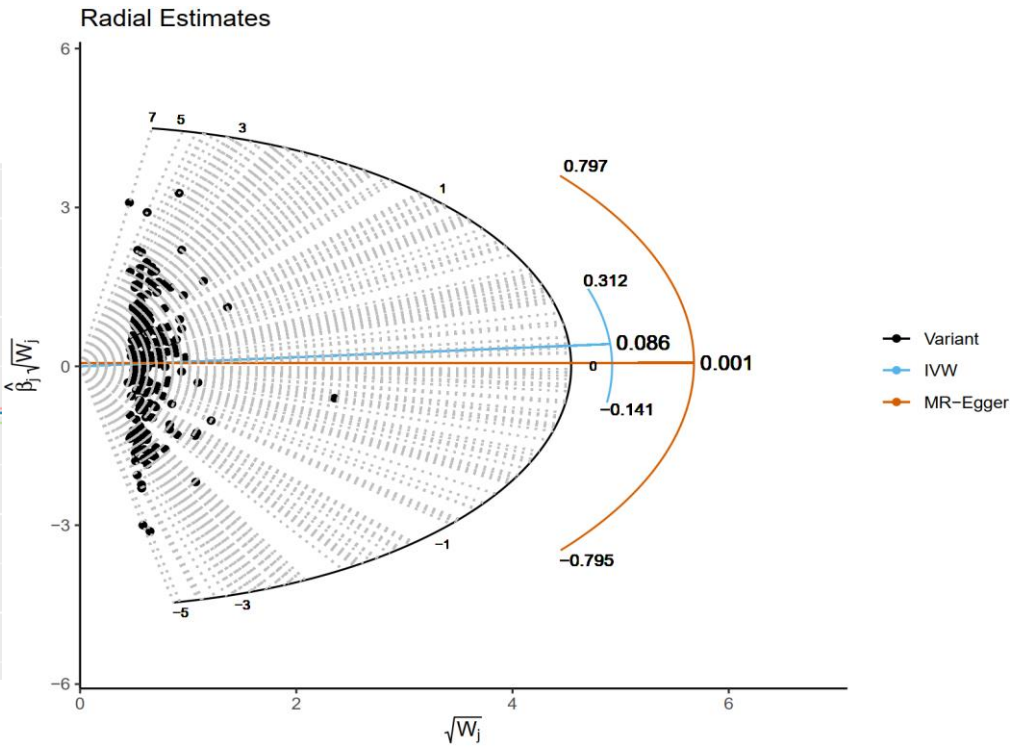


Figure S5-1. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on lung cancer.

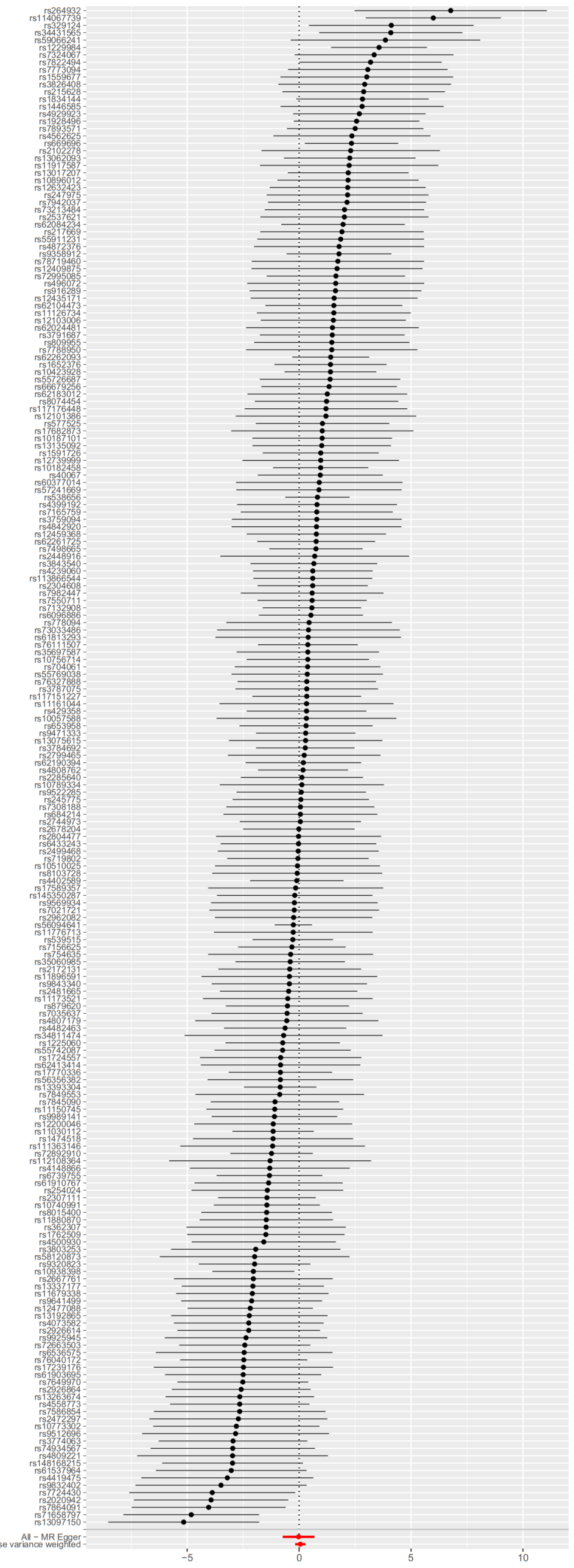
A



B



C



D

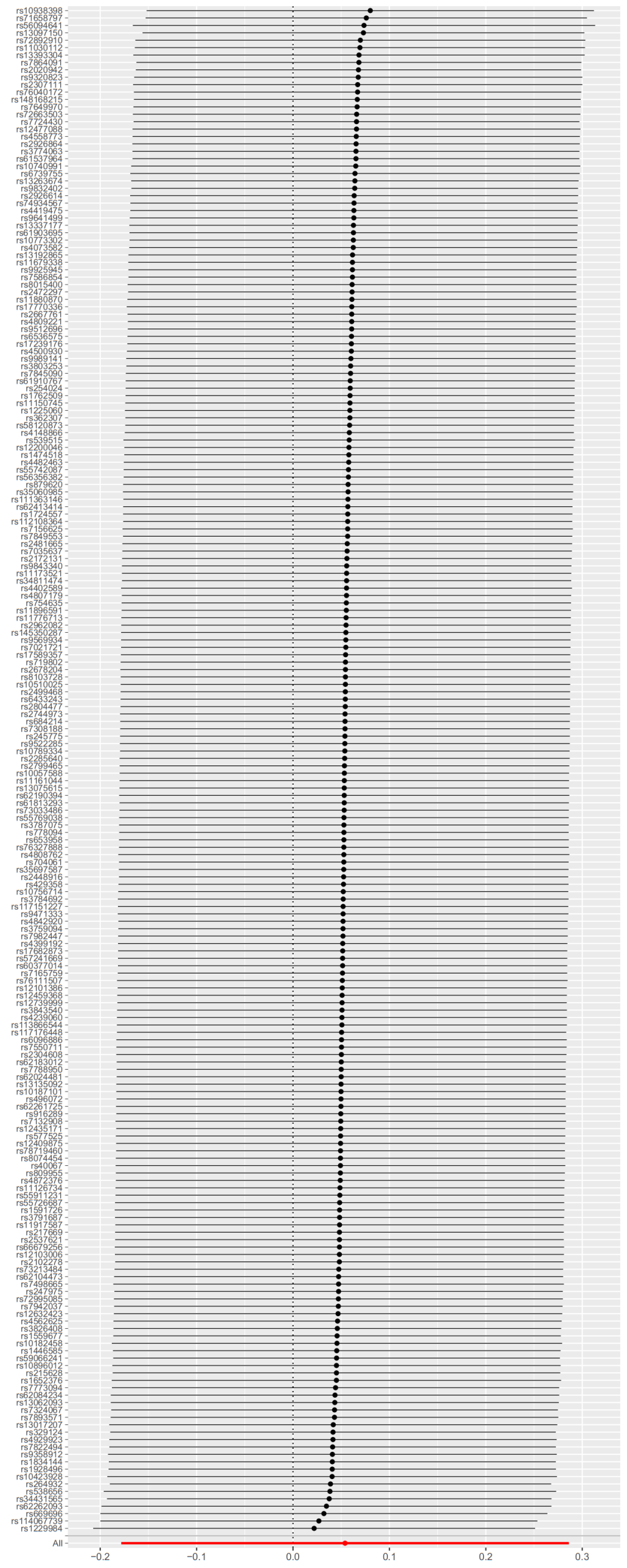
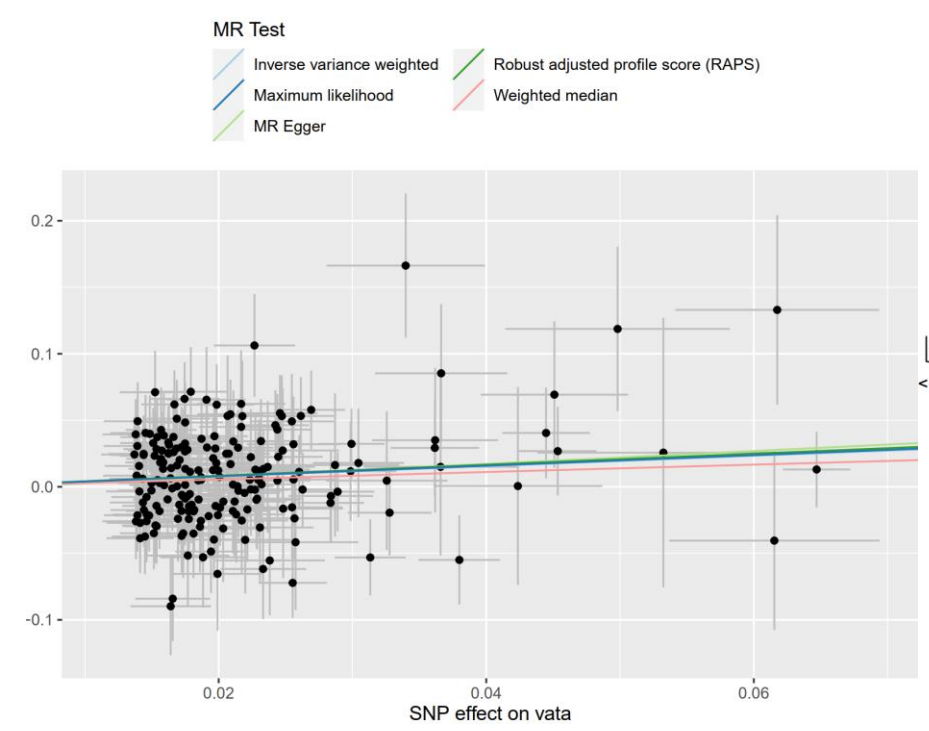
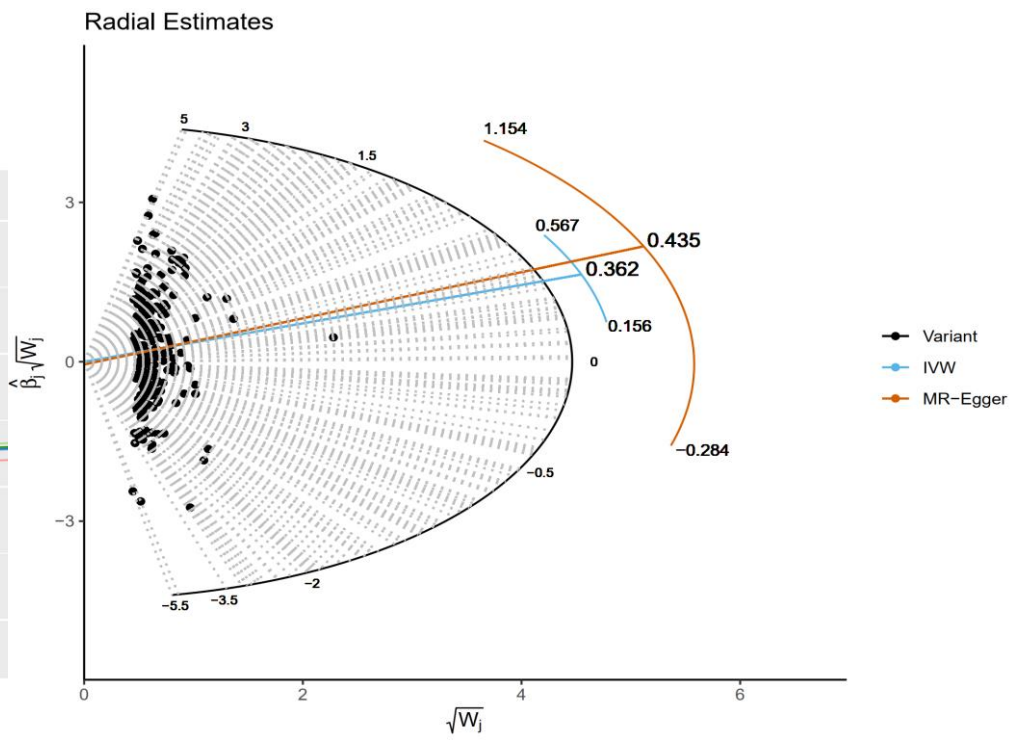
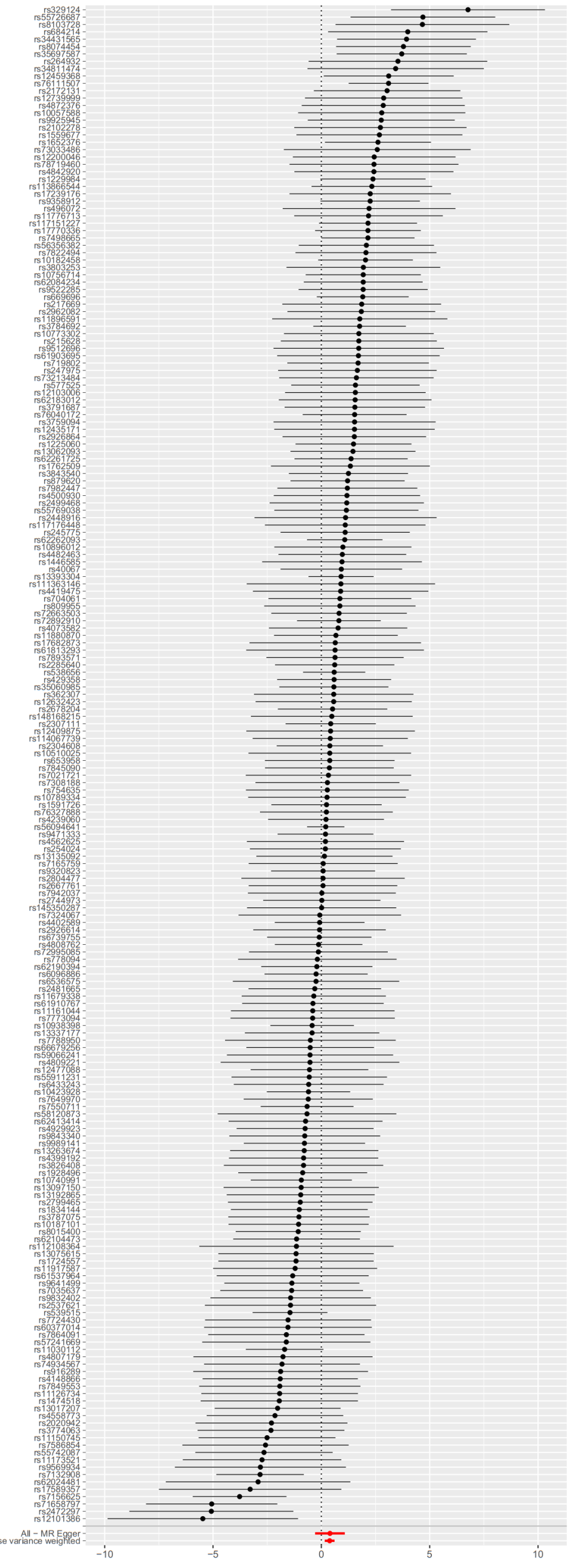


Figure S5-2. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on lung adenocarcinoma.







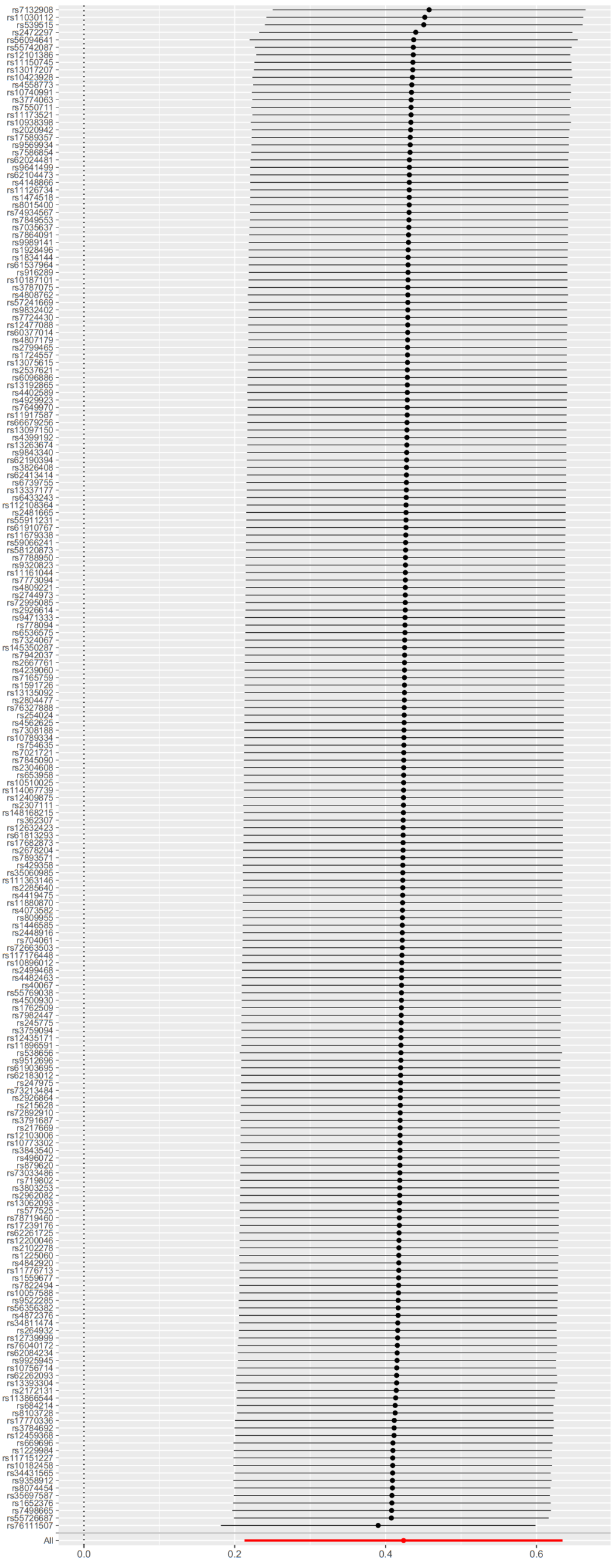
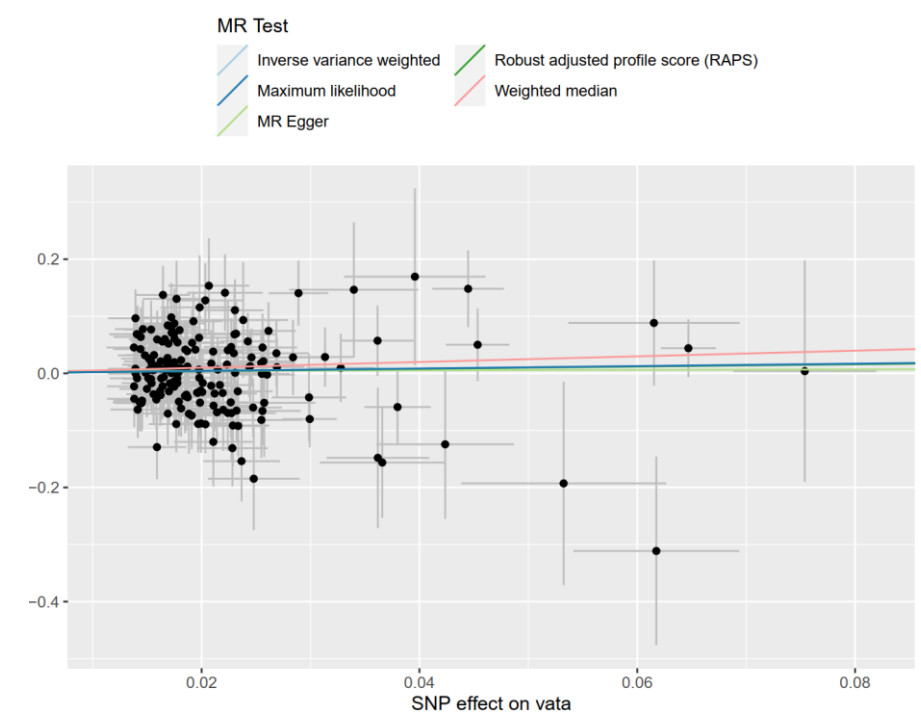
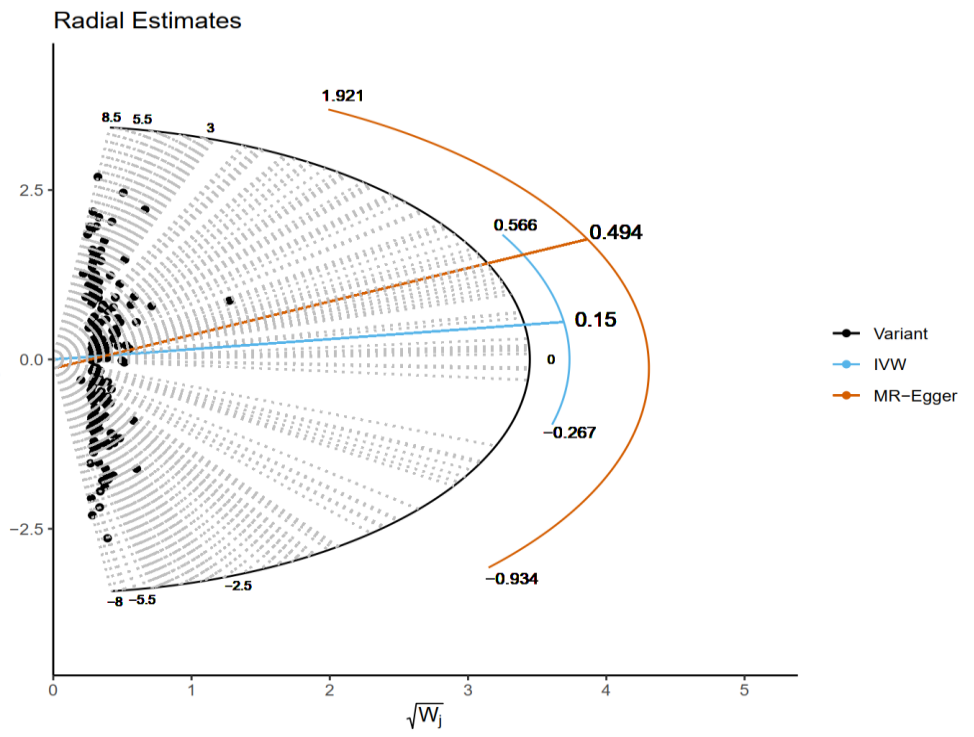
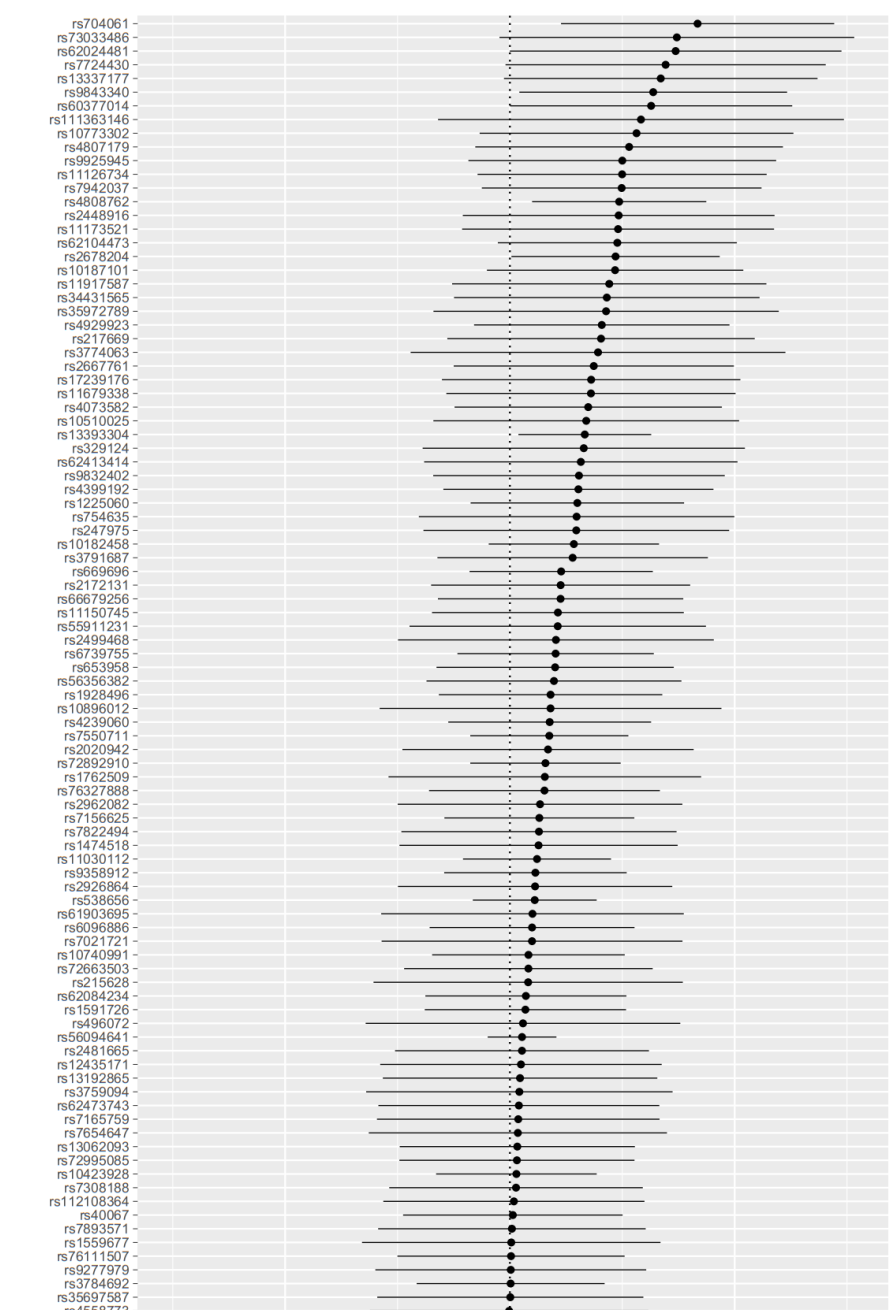


Figure S5-3. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on lung squamous cell carcinoma.







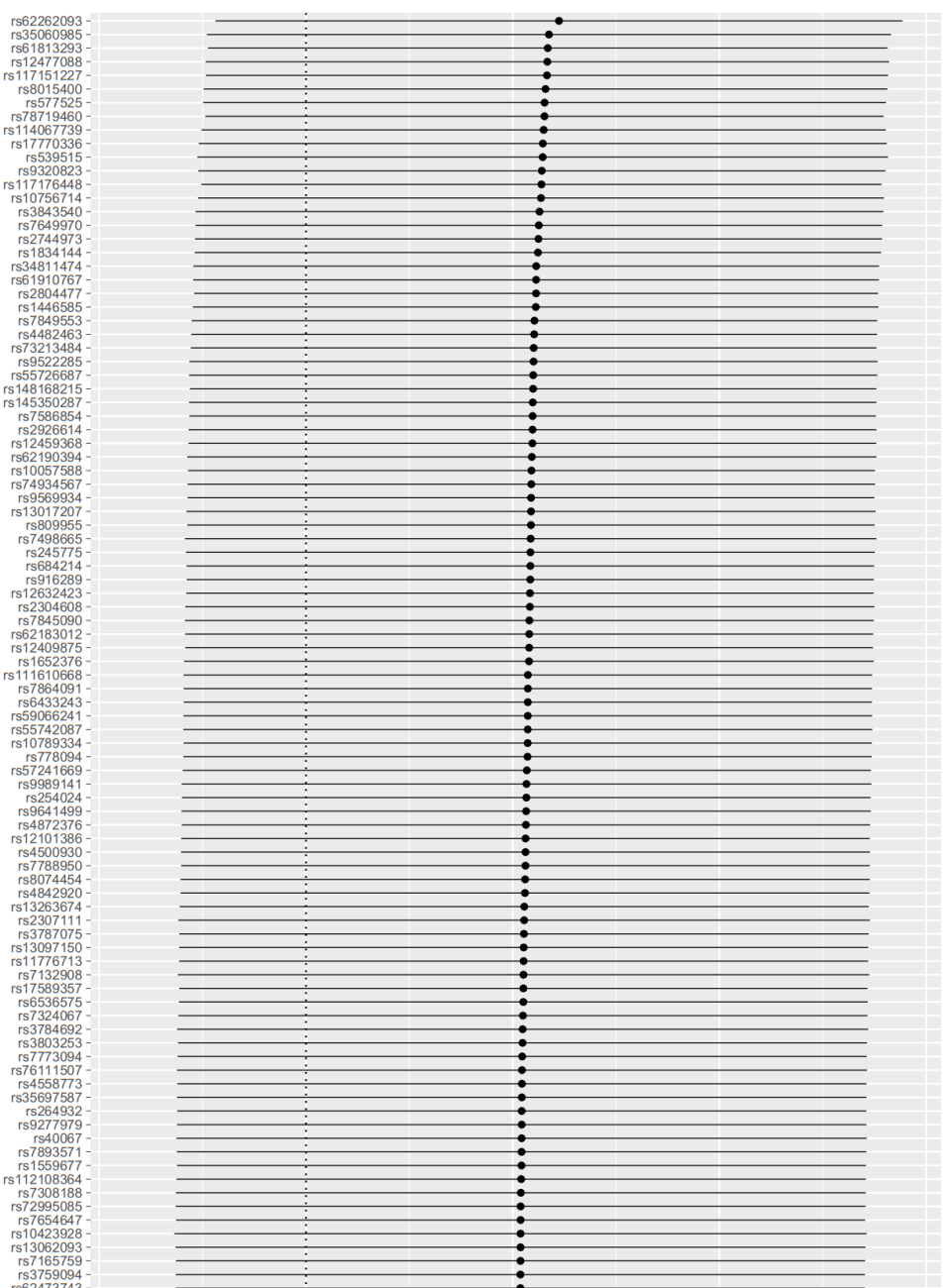
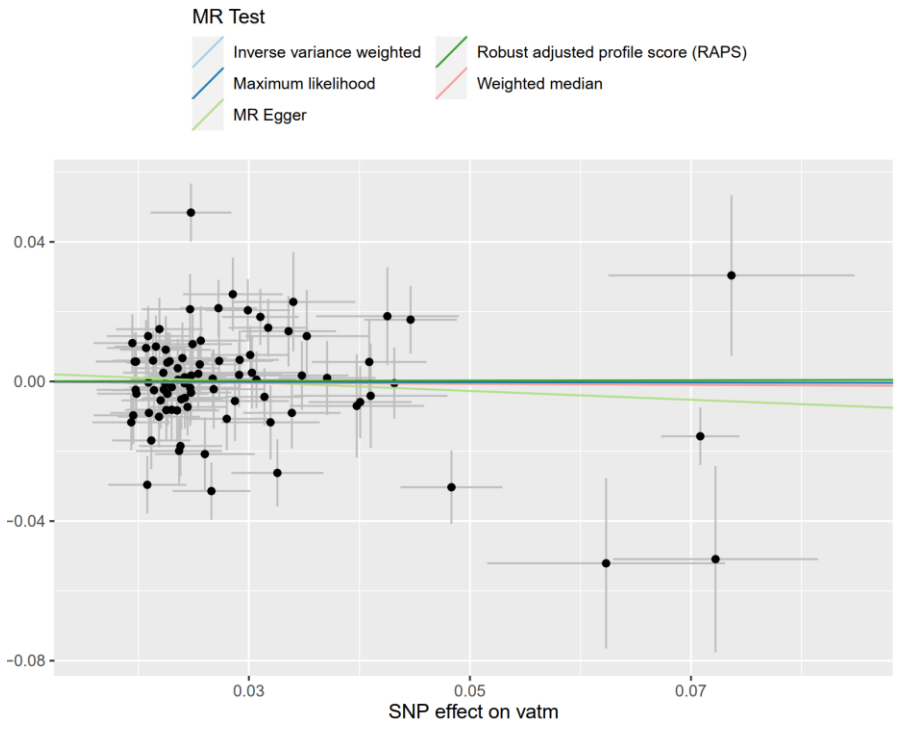
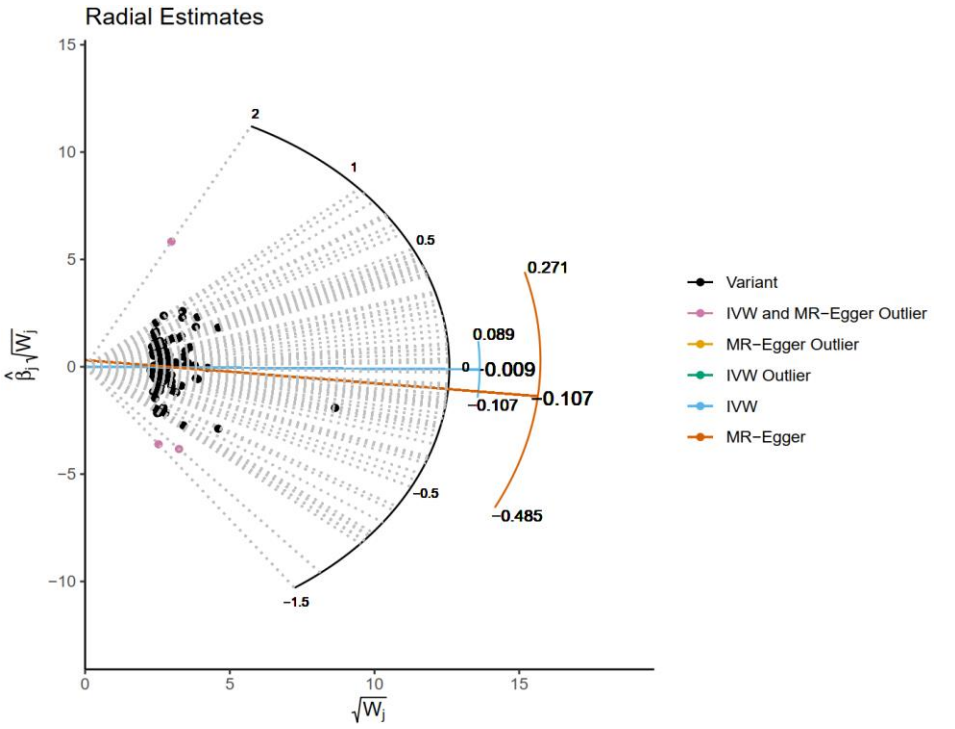


Figure S6. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on colorectal cancer.

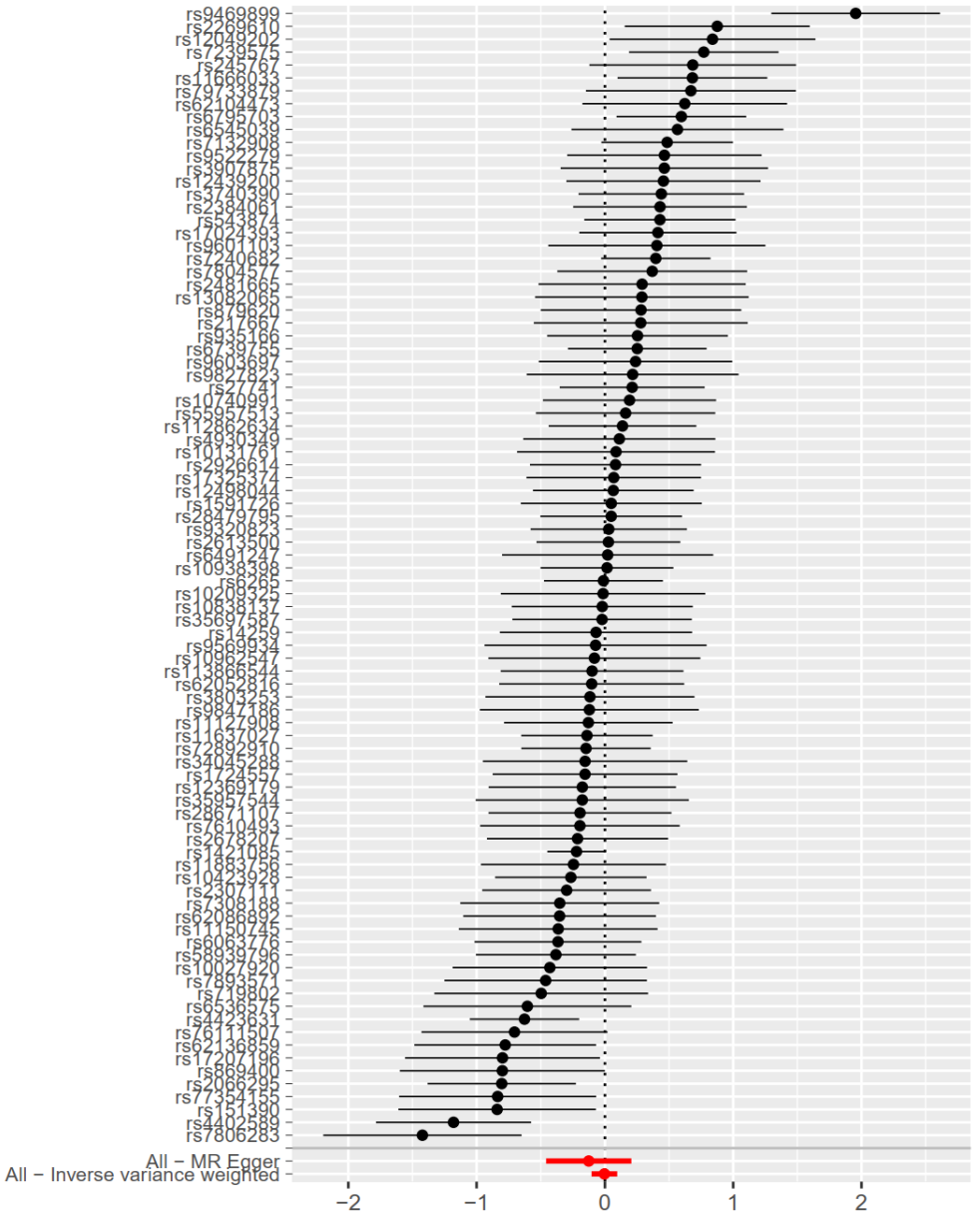
A



B



C



D

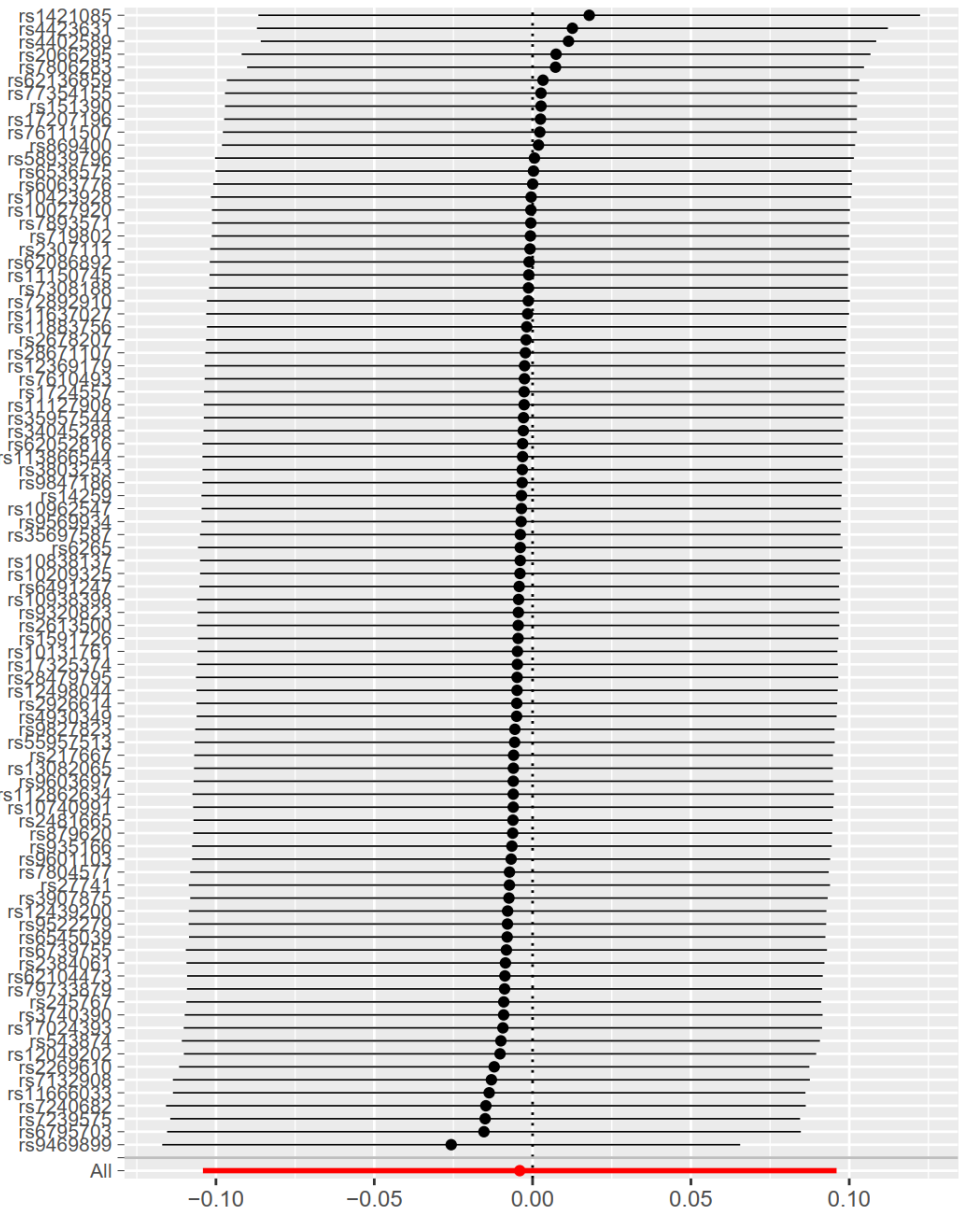


Figure S7. Scatter plot (A), plot for RadialMR (B), forest plot (C), and leave-one-out test (D) for VAT on prostate cancer.