

Causal effects of modifiable behaviors on prostate cancer in Europeans and East Asians: a comprehensive Mendelian randomization study

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Text S1: Detailed analytic plan

- Framework: two-sample univariable and multivariable Mendelian randomization analysis
- Total proportion of phenotypic variation explained by SNPs: R^2
$$R^2 = \sum [2 \times (1 - \text{MAF}) \times \text{MAF} \times \beta^2 / (\text{SE}^2 \times N)]$$

β and SE: the coefficient and standard error for effect size
MAF: minor allele frequency for each SNP
N: sample size
- Instrument strength: F-statistic
$$F = (N - K - 1) / K \times [R^2 / (1 - R^2)]$$

N: sample size
K: total number of SNPs selected for MR analysis
 R^2 : total proportion of phenotypic variation explained by all the included SNPs
- Statistical power calculation: mRnd platform
(<https://shiny.cnsgenomics.com/mRnd/>)
- Bias estimate by sample overlapped: <https://sb452.shinyapps.io/overlap/>
- Primary MR analytical approach: random-effects inverse-variance weighted (IVW)
- Heterogeneity detection: Cochran's Q test with I^2 statistics
- Horizontal pleiotropy examination: MR-Egger intercept
- Outlier detection: MR-pleiotropy residual sum and outlier (MR-PRESSO), the radial regression method, and leave-one-out analyses
- Sensitivity analysis: MR-Egger regression, weighted-median, simple-mode, weighted-mode for UVMR; MR-least absolute shrinkage and selection operator (LASSO) method for MVMR
- Statistical software: All analyses were performed using the TwoSampleMR (v0.5.6), MendelianRandomization (v0.6.0), MRPRESSO (v1.0), RadialMR (v1.0) and MVMR (v0.3) packages in R4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Table S1. Characteristics of GWAS summary data for behaviors and PCa in European ancestry

Traits	GWAS ID	PubMed ID	Year	Sample size	No. SNPs	Units	Author	Consortium
Prostate cancer								
Discovery	ieu-b-85	29892016	2018	Cases: 79,148 Total: 140,254	20,346,368	N/A	Schumacher FR	PRACTICAL
Replication	finn-b- C3_PROSTATE	N/A	2021	Cases: 6,311 Total: 95,213	16,378,835	N/A	N/A	FinnGen
Tobacco smoking								
Ever smoking	ukb-b-20261	N/A	2018	461,066	9,851,867	N/A	Elsworth B	MRC-IEU
Smoking initiation	ieu-b-4877	30643251	2019	632,802	11,802,365	N/A	Liu M	GSCAN
Lifetime smoking index	N/A	31689377	2020	462,690	7,683,478	N/A	Wootton RE	UK Biobank
Alcohol drinking								
Alcohol frequency	ukb-b-5779	N/A	2018	462,346	9,851,867	SD	Elsworth B	MRC-IEU
Alcohol quantity	ieu-b-73	30643251	2019	335,394	11,887,865	SD	Liu M	GSCAN
Fruit intake								
Fresh fruit	ukb-b-3881	N/A	2018	446,462	9,851,867	SD	Elsworth B	MRC-IEU
Dried fruit	ukb-b-16576	N/A	2018	421,764	9,851,867	SD	Elsworth B	MRC-IEU
Vegetables intake								
Raw vegetable	ukb-b-1996	N/A	2018	435,435	9,851,867	SD	Elsworth B	MRC-IEU
Cooked vegetable	ukb-b-8089	N/A	2018	448,651	9,851,867	SD	Elsworth B	MRC-IEU
Physical activity								
Duration of vigorous activity	ukb-b-13932	N/A	2018	251,501	9,851,867	SD	Elsworth B	MRC-IEU
Duration of moderate activity	ukb-b-2346	N/A	2018	343,827	9,851,867	SD	Elsworth B	MRC-IEU

Duration of light activity	ukb-b-8865	N/A	2018	64,949	9,851,867	SD	Elsworth B	MRC-IEU
Sexual behavior								
Age of initiation	ebi-a- GCST90000047	34211149	2021	397,338	16,359,424	N/A	Mills MC	Human Reproductive Behaviour Consortium
No. of sexual partner	ukb-b-4256	N/A	2018	378,882	9,851,867	SD	Elsworth B	MRC-IEU
Sleep behavior								
Insomnia	ukb-b-3957	N/A	2018	462,341	9,851,867	SD	Elsworth B	MRC-IEU
Nap during day	ebi-a- GCST011494	33568662	2021	452,633	13,024,091	N/A	Dashti HS	UK Biobank and GIANT consortium
Daytime dozing	ukb-b-5776	N/A	2018	460,913	9,851,867	N/A	Elsworth B	MRC-IEU

GIANT, the Genetic Investigation of ANthropometric Traits; GSCAN, GWAS and Sequencing Consortium of Alcohol and Nicotine use; MRC-IEU, the Medical Research Council - Integrative Epidemiology Unit; PRACTICAL, Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome; N/A, not applicable

Table S2. Characteristics of GWAS summary data for behaviors and PCa in East Asian ancestry

Traits	GWAS ID	Year	Sample size	SNPs (n)	Author	Consortium
Prostate cancer						
Discovery	N/A	2022	Cases: 3,343 Total: 6,658	10,661,929	ChinaPCa	ChinaPCa
Replication	bbj-a-148	2019	Cases: 5,408 Total: 109,347	8,878,753	Ishigaki K	Biobank Japan
Tobacco smoking						
Ever smoking	ukb-e-20160_EAS	2020	2,649	82,146,731	Pan-UKB team	Pan-UKB
Alcohol drinking						
Alcohol frequency	ukb-e-1558_EAS	2020	2,658	8,256,422	Pan-UKB team	Pan-UKB
Fruit intake						
Fresh fruit	ukb-e-1309_EAS	2020	2,513	8,255,183	Pan-UKB team	Pan-UKB
Dried fruit	ukb-e-1319_EAS	2020	2,219	8,275,593	Pan-UKB team	Pan-UKB
Vegetables intake						
Raw vegetable	ukb-e-1299_EAS	2020	2,365	8,268,823	Pan-UKB team	Pan-UKB
Cooked vegetable	ukb-e-1289_EAS	2020	2,499	8,257,733	Pan-UKB team	Pan-UKB
Physical activity						
Duration of vigorous activity	ukb-e-914_EAS	2020	1,373	8,283,408	Pan-UKB team	Pan-UKB
Duration of moderate activity	ukb-e-894_EAS	2020	1,853	8,264,440	Pan-UKB team	Pan-UKB
Sexual behavior						
Age of initiation	ukb-e-2139_EAS	2020	1,711	8,345,332	Pan-UKB team	Pan-UKB
No. of sexual partner	ukb-e-2149_EAS	2020	1,559	8,326,030	Pan-UKB team	Pan-UKB

Sleep behavior						
Insomnia	ukb-e-1200_EAS	2020	2,654	8,256,478	Pan-UKB team	Pan-UKB
Nap during day	ukb-e-1190_EAS	2020	2,606	8,258,355	Pan-UKB team	Pan-UKB
Daytime dozing	ukb-e-1220_EAS	2020	2,582	8,260,991	Pan-UKB team	Pan-UKB

Table S3. Univariable MR result based on IVW method in European discovery

Factors	Effect size		Heterogeneity			Pleiotropy	
	OR	P	Q-stat	P	I ² (%)	MR-Egger intercept	P
Tobacco smoking							
Ever smoking	1.05 (0.75, 1.48)	0.770	101.85	0.018	27.35	0.00	0.666
Smoking initiation	0.92 (0.82, 1.02)	0.118	173.33	<0.001	51.54	0.01	0.373
Lifetime smoking index	0.75 (0.58, 0.97)	0.026	245.41	<0.001	57.62	0.01	0.135
Alcohol drinking							
Alcohol frequency	0.89 (0.80, 0.99)	0.038	149.60	<0.001	45.86	0.00	0.549
Alcohol quantity	0.94 (0.60, 1.48)	0.787	161.06	<0.001	80.13	-0.01	0.460
Fruit intake							
Fresh fruit	1.25 (0.83, 1.88)	0.283	92.16	<0.001	51.17	0.01	0.327
Dried fruit	1.15 (0.70, 1.89)	0.573	127.57	<0.001	73.35	0.02	0.191
Vegetable intake							
Raw vegetable	2.15 (0.87, 5.31)	0.096	54.90	<0.001	72.68	-0.01	0.833
Cooked vegetable	1.25 (0.61, 2.55)	0.536	38.52	<0.001	63.65	0.05	0.265
Physical activity							
Duration of vigorous activity	1.04 (0.54, 1.99)	0.903	0.98	0.612	0	0.04	0.508
Duration of moderate activity	1.24 (0.60, 2.57)	0.562	1.10	0.576	0	0.02	0.595
Duration of light activity	1.00 (1.00, 1.01)	0.468	1.78	0.411	0	0.03	0.650
Sexual behavior							
Age of initiation	1.18 (1.01, 1.38)	0.035	325.73	<0.001	58.55	<0.001	0.954
No. of sexual partners	0.90 (0.64, 1.26)	0.532	184.51	<0.001	70.19	-0.01	0.551
Sleep behavior							

Insomnia	1.17 (0.80, 1.71)	0.429	60.98	0.001	47.53	0.01	0.244
Nap during day	0.97 (0.77, 1.24)	0.825	125.90	0.011	26.93	0.00	0.861
Daytime dozing	0.90 (0.44, 1.87)	0.784	61.04	<0.001	59.04	-0.01	0.855

Table S4. Detection of outlying SNPs in European discovery by MR-PRESSO and radial regression

Factors	MR-PRESSO				Radial regression			
	Outlier	OR	95%CI	P value	Outlier	OR	95%CI	P value
Tobacco smoking								
Ever smoking	rs56166763	1.11	0.81-1.53	0.524	rs56166763	1.12	0.83-1.50	0.452
	rs2516436							
Smoking initiation	rs13145728	0.94	0.85-1.04	0.237	rs13145728	0.93	0.84-1.03	0.175
Lifetime smoking index	rs6778080	0.77	0.61-0.97	0.029	rs6778080	0.75	0.59-0.95	0.021
	rs7077678				rs7077678			
Alcohol drinking								
Alcohol frequency	rs8614	0.91	0.82-1.01	0.068	N/A			
Alcohol quantity	rs28929474				rs28929474			
	rs4752999	0.95	0.72-1.25	0.711	rs4752999	0.95	0.66-1.35	0.770
	rs6739804				rs6739804			
Fruit intake								
Fresh fruit	rs12044599	1.09	0.77-1.53	0.632	rs12044599	1.13	0.79-1.62	0.517
Dried fruit	rs11811826				rs11811826			
	rs4269101	1.45	1.04-2.03	0.038	rs4269101	1.48	1.06-2.06	0.030
	rs429358				rs429358			
	rs62084586				rs62084586			
Vegetable intake								
Raw vegetable	rs3095337	1.82	1.08-3.08	0.041	rs3095337	1.48	0.87-2.52	0.171
	rs3129962				rs3129962			
					rs8130508			

	rs8130508							
	rs9427220							
Cooked vegetable	rs2844672	0.91	0.63-1.31	0.610	rs2844672	0.91	0.62-1.31	0.611
Physical activity								
Duration of vigorous activity	N/A				N/A			
Duration of moderate activity	N/A				N/A			
Duration of light activity	N/A				N/A			
Sexual behavior								
Age of initiation	rs28929474				rs28929474			
	rs62177795	1.15	11.03-1.28	0.015	rs62177795	1.21	1.05-1.38	0.008
	rs7618715				rs7618715			
	rs809955				rs807478			
No. of sexual partner	rs2726461	0.92	0.70-1.21	0.551	rs2726461	0.94	0.71-1.26	0.696
	rs6908726				rs6908726			
Sleep behavior								
Insomnia	N/A				N/A			
Nap during day	N/A				N/A			
Daytime dozing	rs553314	0.67	0.36-1.26	0.231	rs553314	0.67	0.35-1.30	0.245
	rs6923811				rs6923811			

Table S5. Univariable MR result based on IVW method in European replication

Factors	Effect size		Heterogeneity			Pleiotropy	
	OR	P	Q-stat	P	I ² (%)	MR-Egger intercept	P
Tobacco smoking							
Ever smoking	1.31 (0.61-2.79)	0.485	80.17	0.292	7.70	-0.01	0.802
Smoking initiation	0.90 (0.73, 1.12)	0.335	97.04	0.082	18.59	-0.01	0.706
Lifetime smoking index	1.08 (0.71, 1.63)	0.720	107.91	0.618	0.00	0.00	0.643
Alcohol drinking							
Alcohol frequency	1.05 (0.82, 1.33)	0.704	128.08	0.006	28.95	0.00	0.725
Alcohol quantity	0.88 (0.39, 2.01)	0.765	69.33	<0.001	56.73	-0.03	0.172
Fruit intake							
Fresh fruit	2.32 (0.97, 5.52)	0.058	78.96	0.006	36.68	-0.02	0.185
Dried fruit	1.38 (0.67, 2.85)	0.378	51.63	0.044	30.27	0.00	0.975
Vegetable intake							
Raw vegetable	5.44 (1.20, 24.70)	0.028	25.35	0.064	36.89	0.02	0.547
Cooked vegetable	3.25 (0.64, 16.62)	0.157	36.62	0.001	59.04	-0.02	0.841
Physical activity							
Duration of vigorous activity	1.29 (0.25, 6.56)	0.762	0.03	0.984	0.00	-0.02	0.888
Duration of moderate activity	0.11 (0.01, 0.88)	0.037	1.45	0.484	0.00	0.02	0.849
Duration of light activity	1.00 (0.99, 1.00)	0.295	1.06	0.590	0.00	0.10	0.492
Sexual behavior							
Age of initiation	0.83 (0.63, 1.09)	0.187	169.82	0.034	18.74	0.00	0.886
No. of sexual partner	1.11 (0.66, 1.89)	0.691	69.01	0.097	20.30	-0.02	0.223
Sleep behavior							

Insomnia	0.97 (0.50, 1.86)	0.922	36.68	0.437	1.86	0.00	0.989
Nap during day	1.44 (0.81, 2.57)	0.215	117.01	0.035	22.23	0.00	0.809
Daytime dozing	2.24 (0.55, 9.09)	0.257	38.97	0.064	30.72	0.04	0.217

Table S6. Univariable MR result based on IVW method in East Asian discovery

Factors	Effect size		Heterogeneity			Pleiotropy	
	OR	P	Q-stat	P	I ² (%)	MR-Egger intercept	P
Tobacco smoking							
Ever smoking	1.05 (0.94, 1.17)	0.395	9.41	0.400	4.33	-0.04	0.742
Alcohol drinking							
Alcohol frequency	1.11 (1.00, 1.23)	0.050	1.80	0.773	0.00	-0.01	0.887
Fruit intake							
Fresh fruit	1.01 (0.73, 1.39)	0.971	5.96	0.311	16.05	-0.07	0.316
Dried fruit	1.06 (0.84, 1.34)	0.635	16.52	0.086	39.46	-0.04	0.672
Vegetable intake							
Raw vegetable	0.89 (0.68, 1.17)	0.416	0.64	0.727	0.00	-0.04	0.730
Cooked vegetable	1.04 (0.88, 1.23)	0.627	31.60	0.017	46.20	-0.01	0.800
Physical activity							
Duration of vigorous activity	0.93 (0.82, 1.06)	0.259	3.68	0.298	18.6	0.09	0.219
Duration of moderate activity	1.04 (0.88, 1.22)	0.801	0.12	0.944	0.00	0.02	0.835
Sexual behavior							
Age of initiation	0.93 (0.73, 1.19)	0.586	3.37	0.339	10.86	1.01	0.240
No. of sexual partners	0.84 (0.59, 1.21)	0.353	0.85	0.932	0.00	0.08	0.609
Sleep behavior							
Insomnia	0.86 (0.69, 1.07)	0.164	28.18	0.043	39.68	0.01	0.777
Nap during day	1.12 (0.98, 1.28)	0.104	8.85	0.784	0.00	-0.01	0.947
Daytime dozing	0.90 (0.66, 1.24)	0.535	12.13	0.595	0.00	0.03	0.520

Table S7. Univariable MR result based on IVW method in East Asian replication

Factors	Effect size		Heterogeneity			Pleiotropy	
	OR	P	Q-stat	P	I ² (%)	MR-Egger intercept	P
Tobacco smoking							
Ever smoking	0.99 (0.93, 1.06)	0.795	2.67	0.849	0.00	-0.06	0.436
Alcohol drinking							
Alcohol frequency	1.00 (0.94, 1.06)	0.887	0.19	0.979	0.00	-0.02	0.769
Fruit intake							
Fresh fruit	0.98 (0.84, 1.14)	0.797	2.70	0.609	0.00	0.01	0.713
Dried fruit	0.96 (0.80, 1.16)	0.666	26.20	<0.001	69.46	0.02	0.817
Vegetable intake							
Raw vegetable	1.08 (0.94, 1.24)	0.309	<0.01	1.000	0.00	0.00	0.993
Cooked vegetable	0.97 (0.91, 1.04)	0.386	13.22	0.721	0.00	0.03	0.248
Physical activity							
Duration of vigorous activity	0.96 (0.89, 1.03)	0.275	2.50	0.475	0.00	-0.01	0.876
Duration of moderate activity	0.96 (0.86, 1.08)	0.498	0.93	0.628	0.00	-0.04	0.516
Sexual behavior							
Age of initiation	0.97 (0.84, 1.12)	0.669	4.45	0.216	32.65	-0.51	0.242
No. of sexual partner	1.05 (0.86, 1.27)	0.637	5.09	0.278	21.48	0.03	0.761
Sleep behavior							
Insomnia	0.97 (0.88, 1.08)	0.589	10.99	0.687	0.00	-0.03	0.270
Nap during day	0.98 (0.89, 1.08)	0.669	17.05	0.148	29.60	-0.01	0.812
Daytime dozing	0.99 (0.85, 1.16)	0.929	25.63	0.042	41.48	0.00	0.926

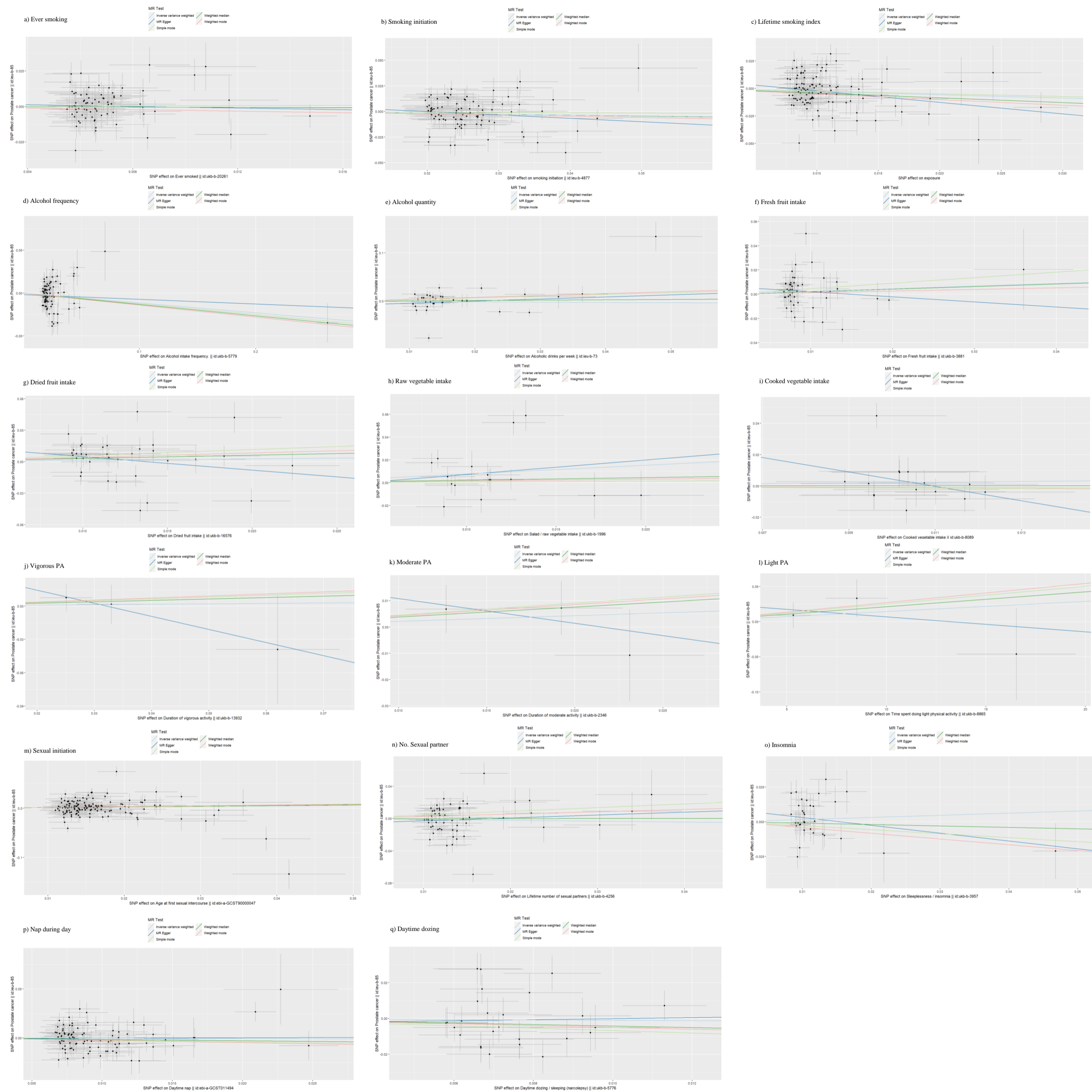


Figure S2. Scatter plots of the 15 behavioral factors in relation to PCa in the European discovery sample

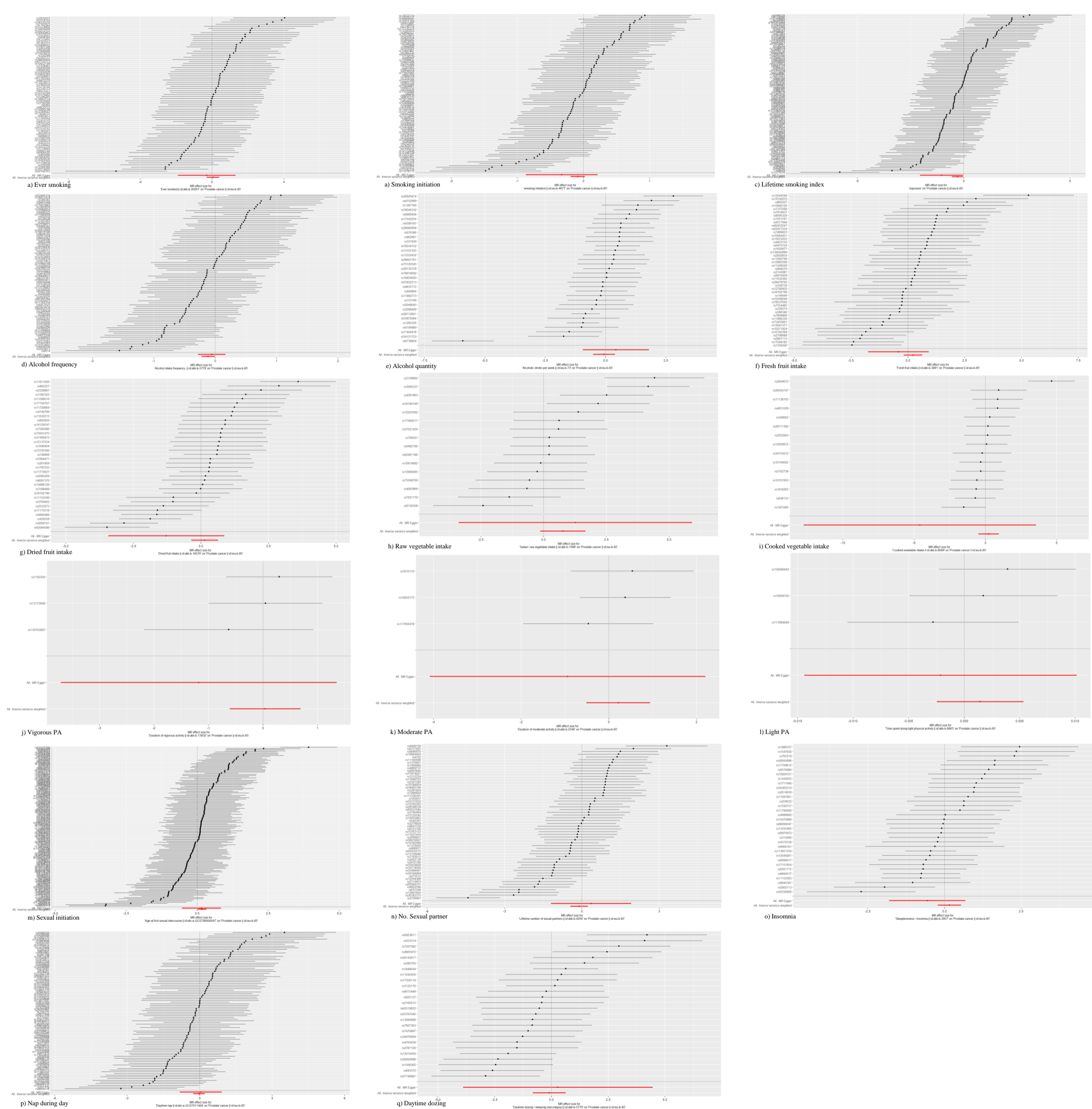


Figure S3. Forest plots of each single SNP of the 15 behavioral factors in relation to PCa in the European discovery sample



Figure S4. Funnel plots of each single SNP of the 15 behavioral factors in relation to PCa in the European discovery sample



Figure S5. Leave-one-out analyses of the 15 behavioral factors in relation to PCa in the European discovery sample

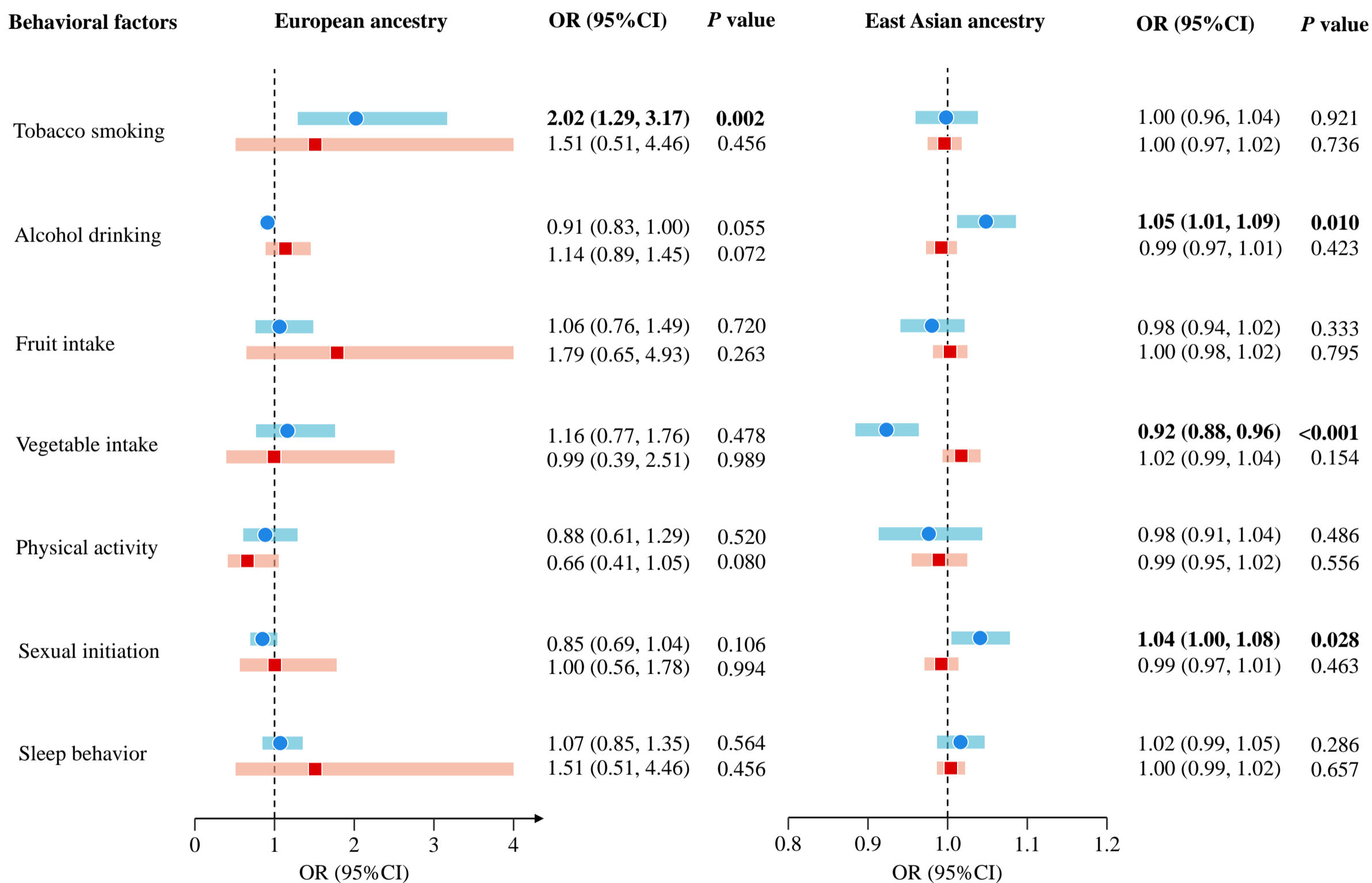


Figure S6. Causal effects of modifiable behavioral factors on prostate cancer by MVMR-LASSO in Europeans and East Asians

Discovery Replication

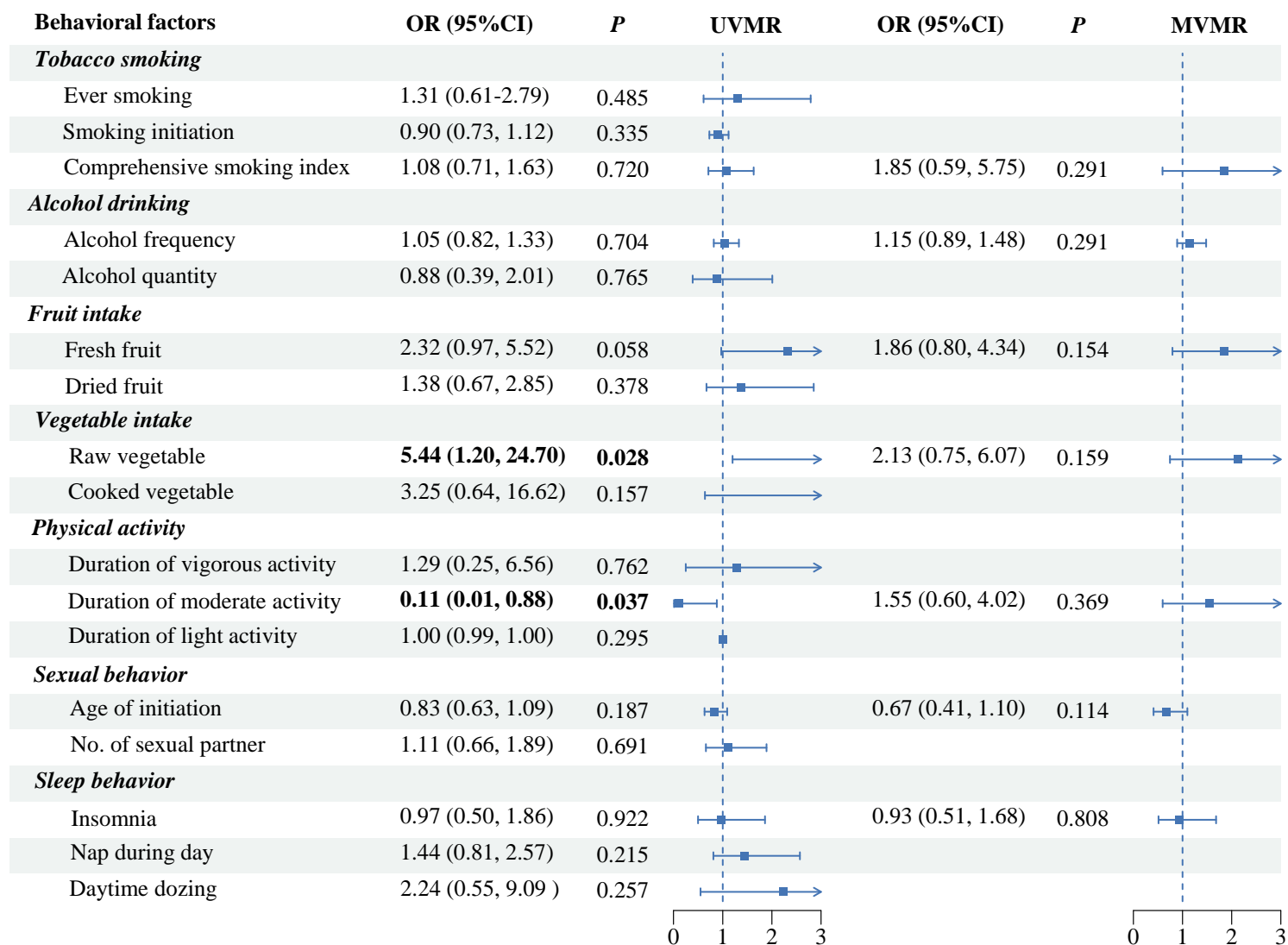


Figure S7. Causal effects of modifiable behaviors on prostate cancer by UVMR and MVMR in European replication sample

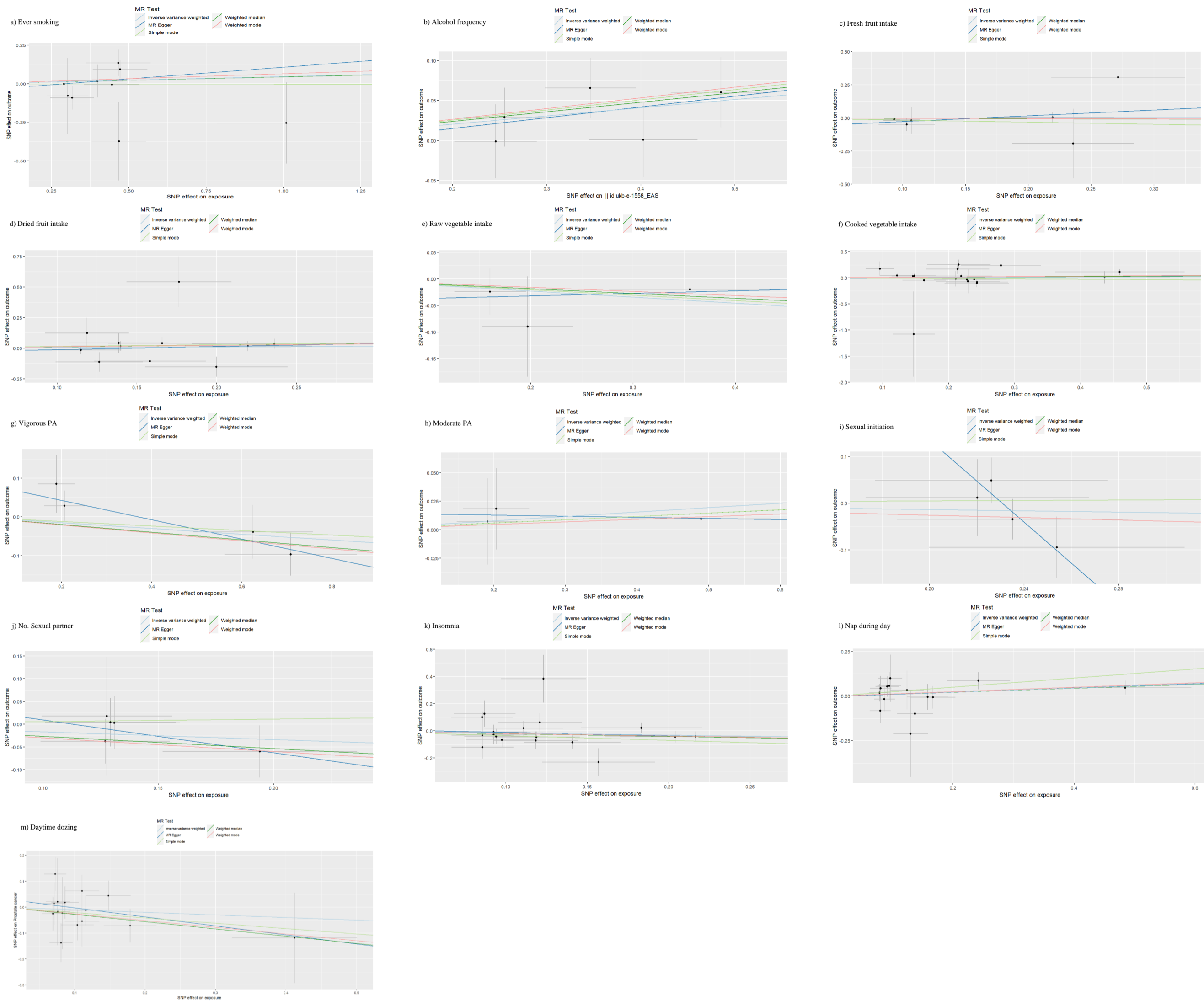


Figure S8. Scatter plots of the 12 behavioral factors in relation to PCa in the East Asian discovery sample



Figure S9. Forest plots of each single SNP of the 12 behavioral factors in relation to PCa in the East Asian discovery sample



Figure S10. Funnel plots of each single SNP of the 12 behavioral factors in relation to PCa in the East Asian discovery sample

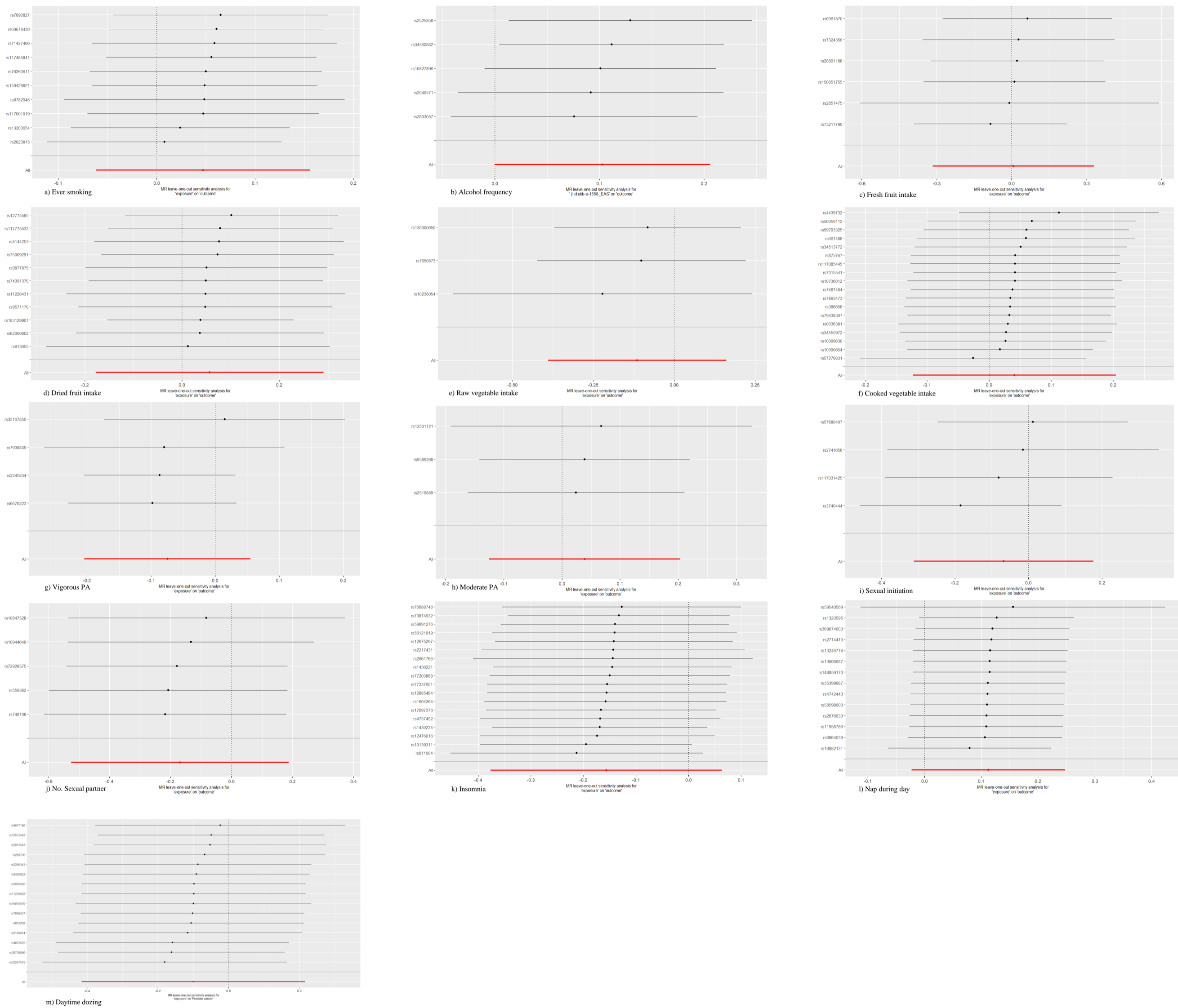


Figure S11. Leave-one-out analyses of the 12 behavioral factors in relation to PCa in the East Asian discovery sample

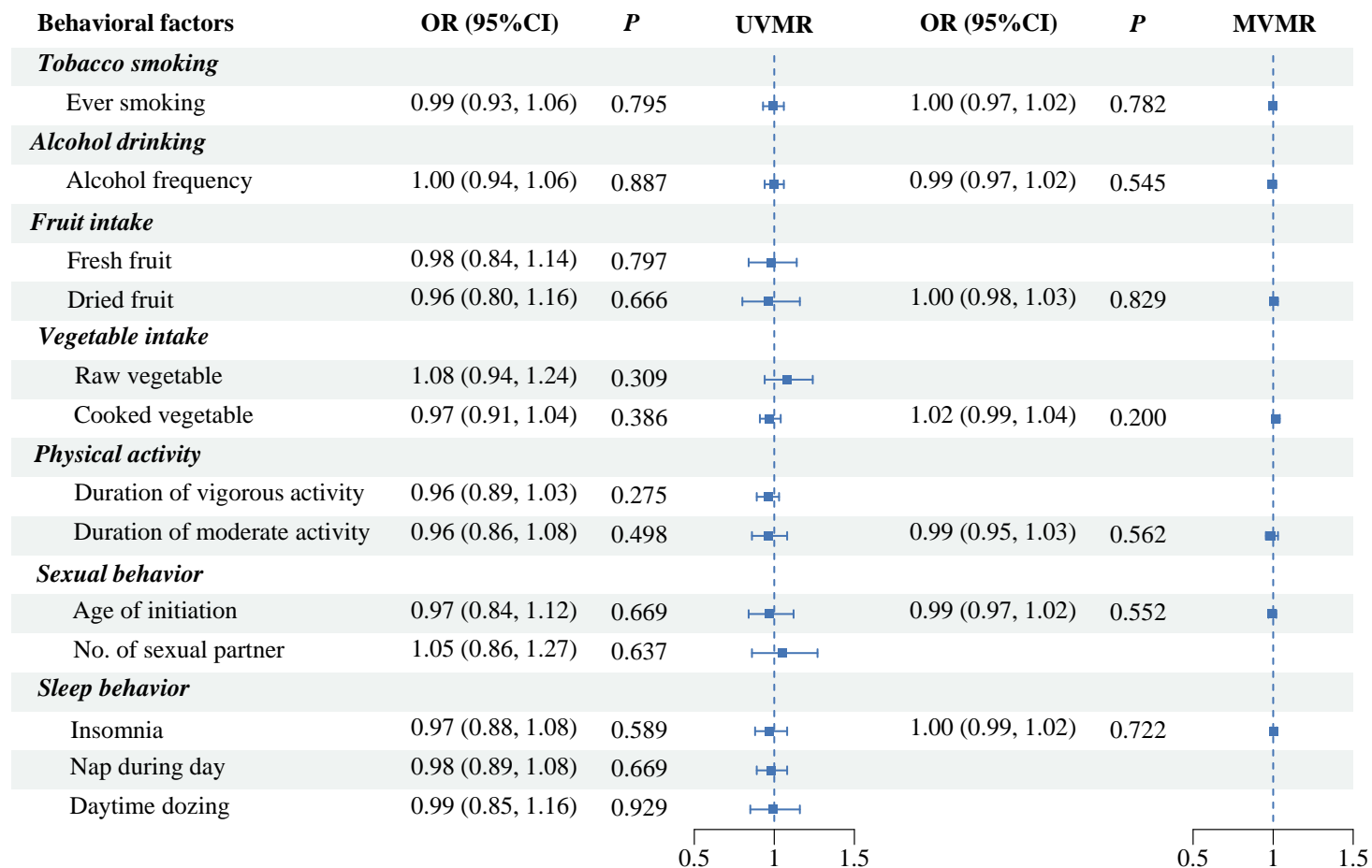


Figure S12. Causal effects of modifiable behaviors on prostate cancer by UVMR and MVMR in East Asian replication sample