Supplementary

Table S1 Post-hoc power calculation for the IVW analyses

Exposure	Outcome	Data source	Sample size	Ratio cases to controls	Variance explained (R^2)	Causal effect (OR according to IVW)	Significance level	Power (%)
Insomnia (female and male)	Kidney cancer	FinnGen	289,360	0.007741949	0.0056492	1.2440	0.05	11.7
Insomnia (male)	Prostate cancer	FinnGen	133,164	0.110181078	0.0031011	1.5893	0.05	80.4
Insomnia (male)	Prostate cancer	PRACTICAL	140,254	1.295257422	0.0032084	1.1791	0.05	41.0
Insomnia (male)	Prostate cancer	Combined	273,418	0.510146144	0.0032084	1.2951	0.05	95.2
Insomnia (female and male)	Bladder cancer	FinnGen	289,190	0.007149897	0.0056492	0.4823	0.05	69.7
Insomnia (female and male)	Calculus of kidney and ureter	FinnGen	376,406	0.026488098	0.005598	1.2664	0.05	40.5
Insomnia (female and male)	Neurogenic bladder	FinnGen	330,619	0.007981683	0.005598	1.4302	0.05	27.6
Insomnia (female and male)	Cystitis	FinnGen	346,081	0.055121783	0.005598	1.8121	0.05	100.0
Insomnia (male)	Prostatitis	FinnGen	123,057	0.031517976	0.0031011	3.5298	0.05	98.9
Insomnia (male)	Benign prostatic hyperplasia	FinnGen	149,363	0.252026455	0.0031011	1.3188	0.05	66.6
Insomnia (male)	Male infertility	FinnGen	120,568	0.010654082	0.0031011	0.9552	0.05	3.1
Insomnia (female)	Female infertility	FinnGen	120,706	0.122178424	0.0072485	1.2795	0.05	62.2

N represents the sample size; beta is the effect for the genetic variant (SNP) of interest; SE(beta) is the standard error of genetic effect; EAF is the effect allele frequency. R^2 was calculated as follows: $R^2 = 2 \times (beta^2) \times EAF \times (1 - EAF)/[2 \times (beta^2) \times EAF \times (1 - EAF) + SE(beta)^2 \times 2 \times N \times EAF \times (1 - EAF)]$. IVW, inverse variance weighted; OR, odds ratio; PRACTICAL, prostate cancer association group to investigate cancer associated alterations in the genome.

Table S2 Summary of GWAS datasets employed in the present MR study

	Unit	Sample size	Number of cases	Number of controls	Data source	Population	Year
Exposure							
Insomnia	Event	2,365,010	593,724	1,771,286	UK Biobank, 23andMe	European	2022
Outcome							
Malignant neoplasm of kidney, except pelvis	Event	289,360	2,223	287,137	FinnGen (R9 release)	European	2023
Prostate cancer	Event	133,164	13,216	119,948	FinnGen (R9 release)	European	2023
Prostate cancer	Event	140,254	79,148	61,106	PRACTICAL	European	2018
Bladder cancer	Event	289,190	2,053	287,137	FinnGen (R9 release)	European	2023
Calculus of kidney and ureter	Event	376,406	9,713	366,693	FinnGen (R9 release)	European	2023
Neurogenic bladder	Event	330,619	2,618	328,001	FinnGen (R9 release)	European	2023
Cystitis	Event	346,081	18,080	328,001	FinnGen (R9 release)	European	2023
Prostatitis	Event	123,057	3,760	119,297	FinnGen (R9 release)	European	2023
Benign prostatic hyperplasia	Event	149,363	30,066	119,297	FinnGen (R9 release)	European	2023
Male infertility	Event	120,568	1,271	119,297	FinnGen (R9 release)	European	2023
Female infertility	Event	120,706	13,142	107,564	FinnGen (R9 release)	European	2023

GWAS, genome-wide association study; MR, Mendelian randomization; PRACTICAL, prostate cancer association group to investigate cancer associated alterations in the genome.

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Table S3 Associations of genetically predicted insomnia with 10 urological and reproductive outcomes in sensitivity analyses

Outcome & data source	No. of SNPs	MR-PRESSO				Maximum likelihood				MR-Egger				Weighted median			
		OR	LB	UB	P	OR	LB	UB	P	OR	LB	UB	P	OR	LB	UB	P
Kidney cancer & FinnGen	240	1.30	0.76	2.21	0.34	1.24	0.69	2.23	0.46	0.55	0.07	4.29	0.57	1.24	0.53	2.89	0.62
Prostate cancer & FinnGen	62	1.29	0.83	2.00	0.26	1.60	1.04	2.46	0.03	5.41	0.97	30.28	0.059	1.71	0.93	3.14	0.08
Prostate cancer & PRACTICAL	64	1.11	0.84	1.46	0.49	1.18	0.93	1.52	0.18	1.49	0.43	5.13	0.53	1.01	0.68	1.48	0.97
Prostate cancer & Combined	NA	1.16	0.92	1.46	0.22	1.27	1.03	1.57	0.03	2.32	0.85	6.33	0.10	1.18	0.85	1.63	0.33
Bladder cancer & FinnGen	239	0.59	0.33	1.08	0.09	0.47	0.25	0.88	0.02	0.77	0.08	7.21	0.82	0.45	0.18	1.13	0.09
Calculus of kidney and ureter & FinnGen	239	1.26	0.92	1.73	0.15	1.26	0.95	1.68	0.11	0.54	0.16	1.80	0.32	1.27	0.82	1.98	0.29
Neurogenic bladder & FinnGen	239	1.56	0.91	2.69	0.11	1.43	0.83	2.45	0.19	2.74	0.36	20.72	0.33	1.37	0.62	3.03	0.44
Cystitis & FinnGen	239	1.68	1.37	2.06	<0.001	1.79	1.44	2.21	<0.001	1.14	0.54	2.40	0.74	2.03	1.47	2.79	<0.001
Prostatitis & FinnGen	62	3.20	1.65	6.21	0.001	3.58	1.75	7.34	<0.001	2.94	0.19	44.75	0.44	2.87	1.03	7.97	0.043
Benign prostatic hyperplasia & FinnGen	62	1.41	1.03	1.92	0.04	1.32	0.97	1.81	0.08	0.97	0.27	3.45	0.96	1.29	0.82	2.03	0.28
Male infertility & FinnGen	62	0.93	0.29	2.99	0.91	0.96	0.28	3.25	0.94	0.43	0.00	69.71	0.75	0.71	0.12	4.05	0.70
Female infertility & FinnGen	156	1.29	1.01	1.66	0.045	1.28	0.99	1.67	0.06	6.50	1.72	24.51	0.006	1.13	0.77	1.64	0.53

SNPs, single nucleotide polymorphisms; MR-PRESSO, Mendelian randomization-Pleiotropy Residual Sum and Outlier; OR, odds ratio; LB, lower bound of the 95% confidence interval; UB, upper bound of the 95% confidence interval; NA, not available; PRACTICAL, prostate cancer association group to investigate cancer associated alterations in the genome.

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Table S4 The results of Cochrane's Q, pleiotropy test and MR-PRESSO

Outcome & data source	Heterogeneity test Q statistic (P value)	Egger intercept (P value)	MR-PRESSO (Raw)				MR-PRESSO (Outlier-corrected)				Outliers	P value for global test	P value for distortion test[†]
			OR	LB	UB	P value	OR	LB	UB	P value			
Kidney cancer & FinnGen	225.47 (0.71)	0.006 (0.42)	1.30	0.76	2.21	0.34	NA	NA	NA	NA	0	0.67	NA
Prostate cancer & FinnGen	67.12 (0.25)	−0.012 (0.15)	1.29	0.83	2.00	0.26	NA	NA	NA	NA	0	0.09	NA
Prostate cancer & PRACTICAL	100.45 (0.001)	−0.002 (0.71)	1.11	0.84	1.46	0.49	1.15	0.88	1.51	0.32	1	0.001	0.81
Bladder cancer & FinnGen	248.64 (0.29)	−0.004 (0.67)	0.59	0.33	1.08	0.09	NA	NA	NA	NA	0	0.15	NA
Calculus of kidney and ureter & FinnGen	337.97 (<0.001)	0.007 (0.15)	1.26	0.92	1.73	0.15	1.27	0.94	1.72	0.13	2	<0.001	0.97
Neurogenic bladder & FinnGen	267.86 (0.08)	−0.005 (0.51)	1.56	0.91	2.69	0.11	NA	NA	NA	NA	0	0.03	NA
Cystitis & FinnGen	228.31 (0.65)	0.004 (0.20)	1.68	1.37	2.06	<0.001	NA	NA	NA	NA	0	0.28	NA
Prostatitis & FinnGen	54.66 (0.67)	0.002 (0.89)	3.20	1.65	6.21	0.001	NA	NA	NA	NA	0	0.42	NA
Benign prostatic hyperplasia & FinnGen	68.99 (0.20)	0.003 (0.63)	1.41	1.03	1.92	0.04	NA	NA	NA	NA	0	0.13	NA
Male infertility & FinnGen	72.33 (0.13)	0.008 (0.75)	0.93	0.29	2.99	0.91	NA	NA	NA	NA	0	0.28	NA
Female infertility & FinnGen	165.83 (0.24)	−0.015 (0.02)	1.29	1.01	1.66	0.045	NA	NA	NA	NA	0	0.20	NA

[†], P value for distortion test were derived from MR-PRESSO test and P value <0.05 indicates a difference between estimates before and after outlier removal. MR-PRESSO, Mendelian randomization-Pleiotropy Residual Sum and Outlier; OR, odds ratio; LB, lower bound of the 95% confidence interval; UB, upper bound of the 95% confidence interval; NA, not available (if no outliers were detected); PRACTICAL, prostate cancer association group to investigate cancer associated alterations in the genome.

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