

Mendelian randomization highlights insomnia as a risk factor for pain diagnoses

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Supplementary document 1

FinnGen Data Freeze 5:

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Supplementary Table S1**ICD10 Diagnosis codes included in Finngen R5 Pain summary statistics category**

Subcategories of general pain as given in text	ICD10	Long name
x	G50.0	Trigeminal neuralgia
x	G50.1	Atypical facial pain
Ocular pain	H57.1	Ocular Pain
x	M54.0	Panniculitis affecting regions of neck and back
x	M54.1	Radiculopathy
x	M54.2	Cervicalgia
Low back pain	M54.5	Low back pain
x	M54.3	Sciatica
x	M54.4	Lumbago with sciatica
x	M54.6	Pain in thoracic spine
x	M54.8	Other dorsalgia
x	M54.9	Dorsalgia, unspecified
x	M79.0	Rheumatism, unspecified
x	M79.1	Myalgia
x	M79.2	Neuralgia and neuritis, unspecified
x	M79.3	Panniculitis, unspecified
Pain in limb	M79.6	Pain in limb
x	M79.7	Fibromyalgia
x	G54.6	Phantom limb syndrome with pain
x	K07.6	Temporomandibular joint disorders
Pain in joint	M25.5	Pain in joint
Pain in abdomen and pelvic area	R10	Abdominal and pelvic pain
x	R51	Headache
x	R52	Pain, not elsewhere classified
Pain in throat and chest	R07	Pain in throat and chest

Pain in throat and chest not included in general pain summary statistics

Supplementary Table S2

Sensitivity analysis results

MR Egger intercept

outcome	exposure	egger_intercept	se	P-value
Lane insomnia	Finngen R5 Pain	-0.001118827	0.002511883	0.674501
Pain	Jansen insomnia	0.00224489	0.002656084	0.398888
Low back pain	Jansen insomnia	-0.003216347	0.00506841	0.526427
Ocular pain	Jansen insomnia	0.007294743	0.01506718	0.628813
Joint pain	Jansen insomnia	-0.005641462	0.00471268	0.232699
Limb pain	Jansen insomnia	-0.00434495	0.004699	0.356266
Throat and chest pain	Jansen insomnia	0.009326415	0.003790137	0.014719
Abdominal and pelvic area pain	Jansen insomnia	0.003933862	0.003158162	0.214369

MR PRESSO

outcome	exposure	Global test p-value
Lane insomnia	Finngen R5 Pain	0.95

Exposure	Outcome	MR Analysis	Causal Estimate	Sd	T-stat	P-value	Global test P-value
Jansen insomnia	Finngen R5 Pain	Raw	0.3876021	0.035258	10.99324	7.21E-23	<2e-04
Jansen insomnia	Finngen R5 Pain	Outlier-corrected	0.3792089	0.034425	11.01563	6.38E-23	

Exposure	Outcome	Distortion test p-value
Jansen insomnia	Finngen R5 Pain	0.8174
Jansen insomnia	Finngen R5 Pain	x

Lane insomnia=Data from Lane et al. (2019), doi: 10.1038/s41588-019-0361-7

Jansen insomnia=Data from Jansen et al. (2019), doi:10.1038/s41588-018-0333-3

Supplementary Table S3

Analysis based on using the multisite chronic pain (MCP) data from Johnston et al. 2019

doi:<https://doi.org/10.1371/journal.pgen.1008164>

outcome	exposure	method	nSNP	P-value	OR [95% CI]
Insomnia (Lane et al. 2019)	MCP	MR Egger	64	9.37E-02	1.19 [0.97-1.44]
Insomnia (Lane et al. 2019)	MCP	Weighted median	64	1.03E-20	1.22 [1.17-1.28]
Insomnia (Lane et al. 2019)	MCP	IVW	64	1.58E-36	1.32 [1.26-1.38]

MR Egger intercept test for pleiotropy P-value: 0.28

MR Presso outlier corrected P-value: 1.59E-18

outcome	exposure	method	nSNP	P-value	OR [95% CI]
MCP	Insomnia (Jansen et al. 2019)	MR Egger	232	2.94E-03	1.22 [1.07-1.38]
MCP	Insomnia (Jansen et al. 2019)	Weighted median	232	6.62E-26	1.23 [1.18-1.28]
MCP	Insomnia (Jansen et al. 2019)	IVW	232	2.04E-81	1.36 [1.32-1.41]

MR Egger intercept test for pleiotropy P-value: 0.07

MR Presso outlier corrected P-value: 4.23E-53

Supplementary Table S4

Lead variants used in this study.

SNP ID	Jansen et al.	Lane et al.	Johnston et al.	FinnGen Pain Proxy SNPs	Jansen et al.
	Table S6	Table S2	Table S7		
rs1015438	Yes	x	x	x	
rs1031654	Yes	Yes	x	x	
rs1038093	Yes	x	x	x	
rs10502966	Yes	x	x	x	
rs1064213	Yes	x	x	x	
rs1064939	Yes	x	x	x	
rs10756571	Yes	x	x	x	
rs10758593	Yes	x	x	x	
rs10761240	Yes	x	x	x	
rs10800992	Yes	x	x	x	
rs10825503	Yes	x	x	x	
rs10865954	Yes	Yes	x	x	
rs10898940	Yes	x	x	x	
rs10928256	Yes	x	x	x	
rs10944696	Yes	x	x	x	
rs10947428	Yes	x	x	x	
rs10947690	Yes	Yes	x	x	
rs10947987	Yes	x	x	x	
rs10955647	Yes	x	x	x	
rs11001276	Yes	x	x	x	
rs11090039	Yes	x	x	x	
rs11119409	Yes	x	x	x	
rs11126082	Yes	x	x	x	rs4671158
rs11149313	Yes	x	x	x	
rs113851554	Yes	Yes	x	x	
rs1147852	Yes	x	x	x	
rs11588755	Yes	x	x	x	
rs11605348	Yes	x	x	x	
rs116466468	Yes	x	x	x	
rs11650304	Yes	x	x	x	rs77563750
rs1167132	Yes	x	x	x	
rs11679943	Yes	x	x	x	
rs11722569	Yes	x	x	x	
rs11756035	Yes	x	x	x	
rs117630493	Yes	x	x	x	
rs11803128	Yes	x	x	x	
rs118166957	Yes	x	x	x	
rs11838830	Yes	x	x	x	
rs12030482	Yes	x	x	x	rs17115350
rs12187443	Yes	x	x	x	
rs12251016	Yes	x	x	x	rs10828247
rs12310246	Yes	x	x	x	
rs12454003	Yes	x	x	x	rs12458369
rs12520974	Yes	x	x	x	
rs12540241	Yes	x	x	x	
rs12605642	Yes	x	x	x	

rs12614369	Yes	x	x	x	
rs1264419	Yes	x	x	x	rs1264421
rs12666306	Yes	x	x	x	
rs12790660	Yes	x	x	x	
rs1289939	Yes	x	x	x	
rs12912299	Yes	x	x	x	
rs12917449	Yes	x	x	x	
rs12924275	Yes	x	x	x	
rs12983032	Yes	x	x	x	
rs12991815	Yes	x	x	x	rs6747972
rs13010288	Yes	x	x	x	
rs13135092	Yes	x	Yes	x	
rs13138995	Yes	x	x	x	
rs1357685	Yes	x	x	x	
rs138014720	Yes	x	x	x	rs138916547
rs138678612	Yes	x	x	x	
rs1519102	Yes	x	x	x	rs2049019
rs152555	Yes	x	x	x	
rs1530938	Yes	x	x	x	
rs1536053	Yes	x	x	x	
rs1553754	Yes	x	x	x	
rs1567084	Yes	x	x	x	
rs1580173	Yes	x	x	x	
rs1620977	Yes	x	x	x	
rs16903122	Yes	x	x	x	
rs16990210	Yes	x	x	x	
rs17005118	Yes	x	x	x	
rs17025198	Yes	x	x	x	
rs17083297	Yes	x	x	x	
rs17223714	Yes	x	x	x	
rs1731951	Yes	x	x	x	rs1731947
rs17324524	Yes	x	x	x	
rs17367725	Yes	x	x	x	
rs17520265	Yes	x	x	x	
rs17643634	Yes	x	x	x	
rs176644	Yes	x	x	x	
rs1861412	Yes	x	x	x	
rs190073	Yes	x	x	x	
rs1927902	Yes	x	x	x	
rs1937447	Yes	x	x	x	
rs2030672	Yes	x	x	x	
rs2089358	Yes	x	x	x	
rs214934	Yes	x	x	x	rs214932
rs2216427	Yes	x	x	x	rs2543163
rs2221119	Yes	x	x	x	rs1391954
rs224029	Yes	x	x	x	
rs2286729	Yes	x	x	x	
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rs2388840	Yes	x	x	x	

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rs2447094	Yes	x	x	x	
rs2491124	Yes	x	x	x	
rs2598293	Yes	x	x	x	
rs2737240	Yes	x	x	x	
rs2792990	Yes	x	x	x	rs2596692
rs2815757	Yes	x	x	x	
rs2838787	Yes	x	x	x	
rs28552587	Yes	x	x	x	
rs28582096	Yes	x	x	x	
rs28611339	Yes	x	x	x	
rs2867690	Yes	x	x	x	
rs2903385	Yes	x	x	x	
rs3131638	Yes	x	x	x	
rs314281	Yes	x	x	x	
rs3184470	Yes	x	x	x	
rs324017	Yes	Yes	x	x	
rs34036083	Yes	x	x	x	
rs34214423	Yes	x	x	x	
rs34490907	Yes	x	x	x	rs191981826
rs34967082	Yes	x	x	x	
rs35110063	Yes	x	x	x	
rs35322724	Yes	x	x	x	
rs35539975	Yes	x	x	x	
rs37445	Yes	x	x	x	
rs3774751	Yes	x	x	x	
rs3902952	Yes	x	x	x	
rs4090240	Yes	x	x	x	
rs4238755	Yes	x	x	x	
rs4260410	Yes	x	x	x	
rs429358	Yes	x	x	x	
rs4502882	Yes	x	x	x	
rs45453598	Yes	x	x	x	
rs4588900	Yes	x	x	x	
rs4592425	Yes	x	x	x	
rs4643373	Yes	x	x	x	
rs4664299	Yes	x	x	x	
rs4699157	Yes	x	x	x	
rs4702	Yes	x	x	x	
rs4709655	Yes	x	x	x	
rs4767645	Yes	x	x	x	
rs4788203	Yes	x	x	x	
rs4790076	Yes	x	x	x	
rs4858708	Yes	x	x	x	rs1604010
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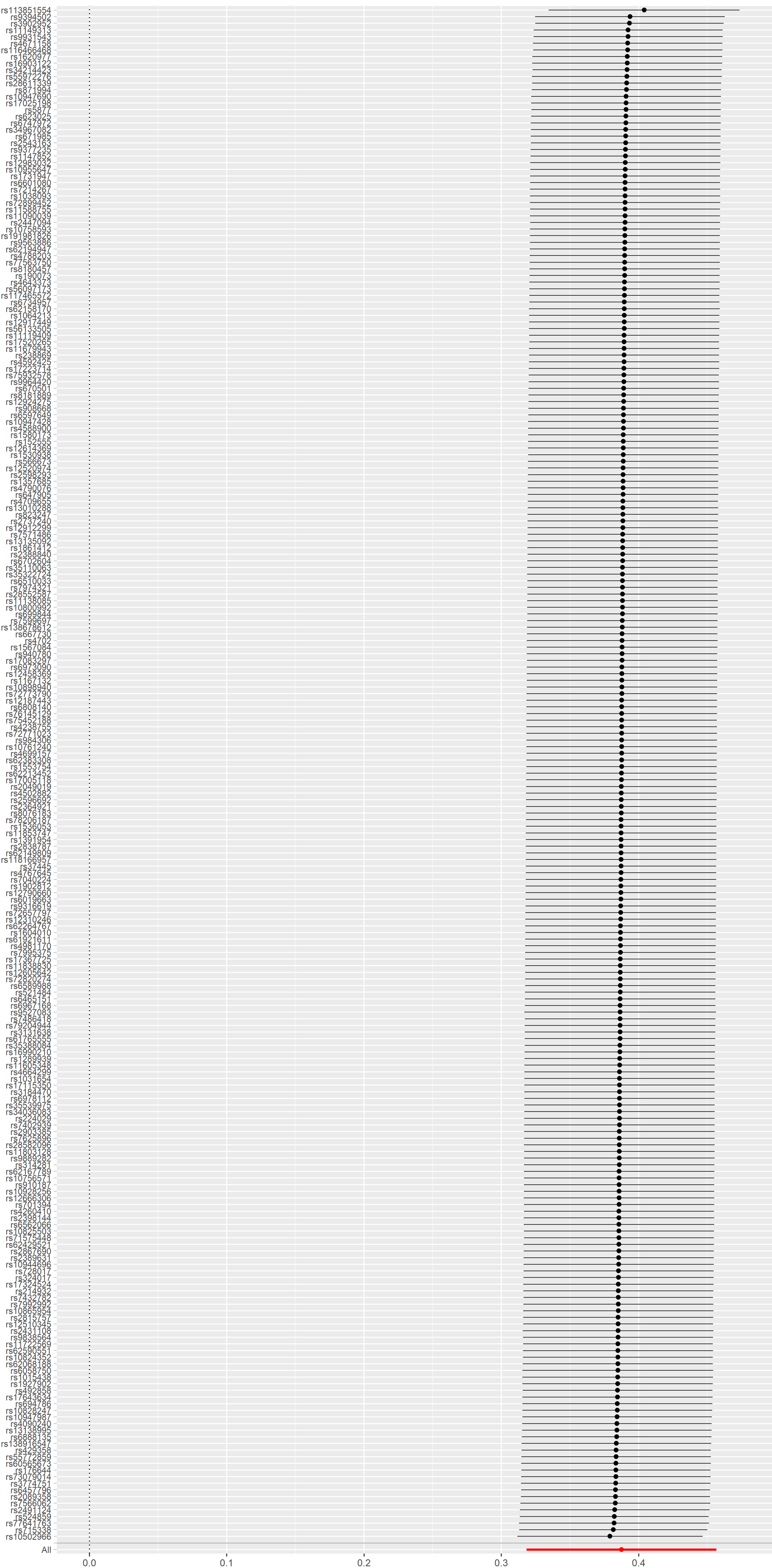
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rs6019663	Yes	x	x	x	
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rs6119267	Yes	x	x	x	rs6058750
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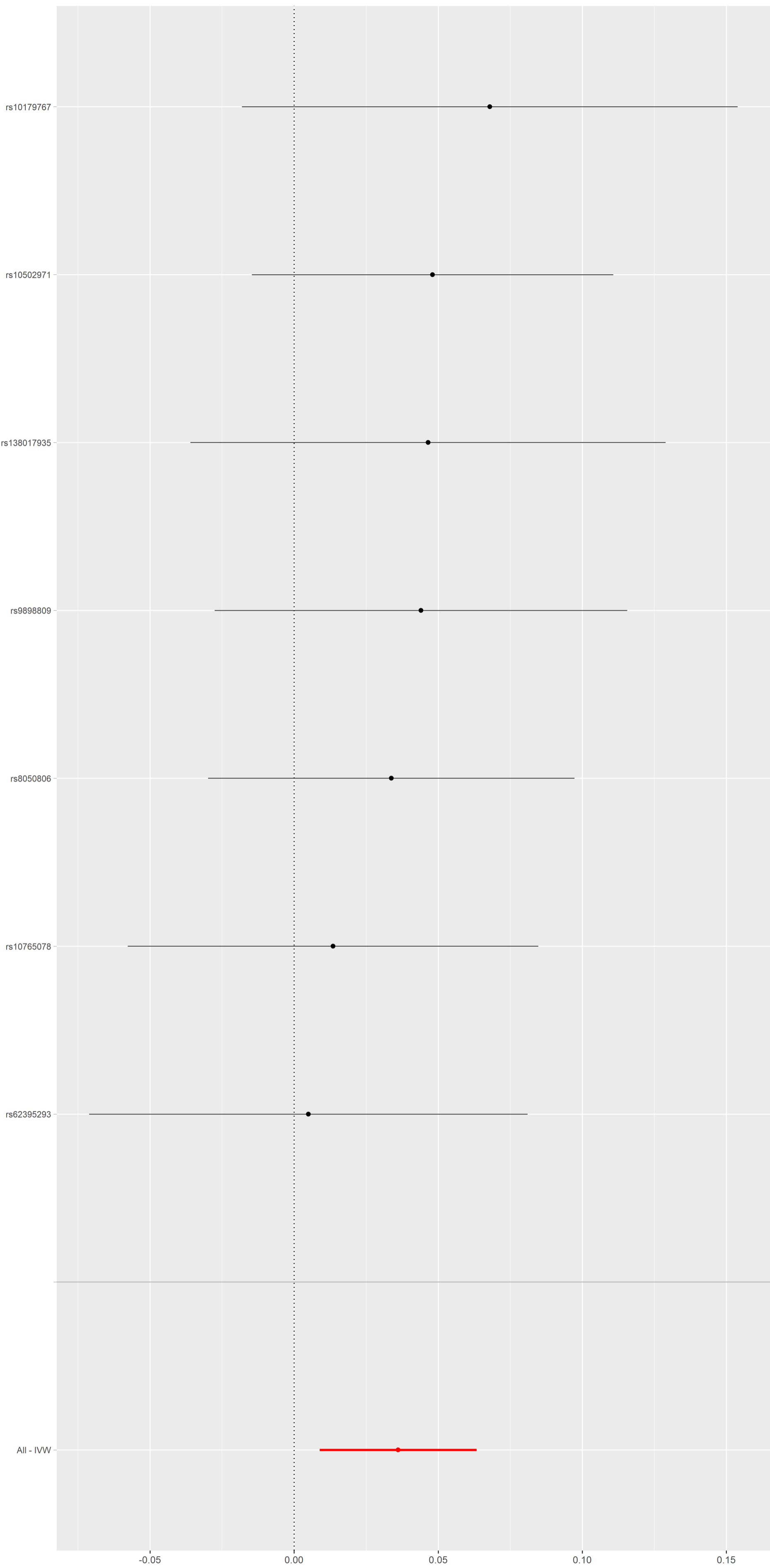
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rs314280	x	Yes	x	x
rs3104778	x	Yes	x	x
rs302165	x	Yes	x	x
rs2956278	x	Yes	x	x
rs28061	x	Yes	x	x
rs2644128	x	Yes	x	x
rs2613503	x	Yes	x	x
rs2296580	x	Yes	x	x
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rs2062113	x	Yes	x	x
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rs11635495	x	Yes	x	x
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rs2759694	x	x	Yes	x
rs6561715	x	x	Yes	x
rs1443914	x	x	Yes	x
rs7987501	x	x	Yes	x
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rs2006281	x	x	Yes	x
rs2386584	x	x	Yes	x
rs285026	x	x	Yes	x
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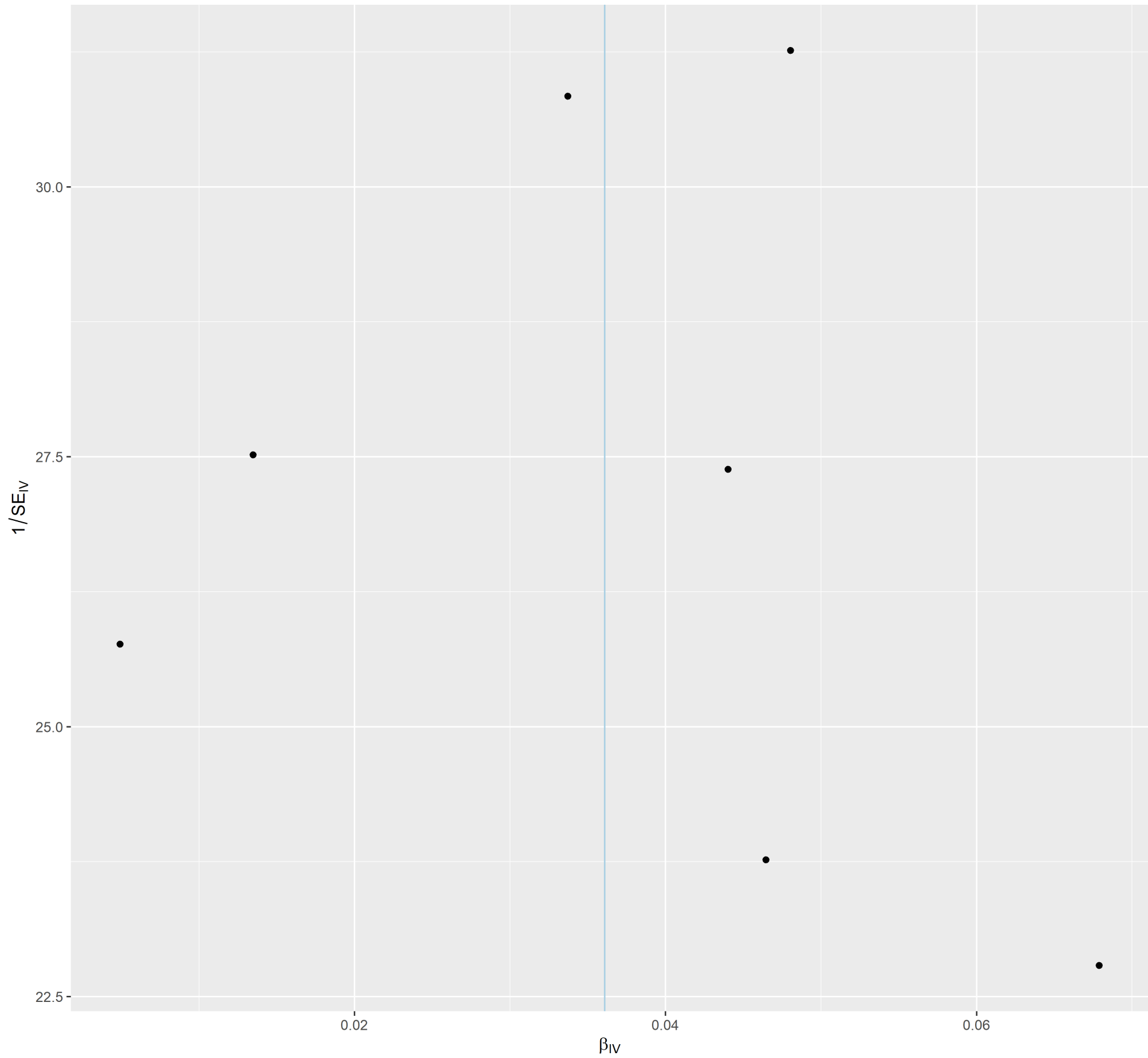
Supplementary Figure 1. Jansen et al. insomnia instruments have positive effect size on pain outcome.
 A leave-one-out plot of the IVW effects of the Jansen et al. insomnia exposure instruments on the general pain outcome analysis.



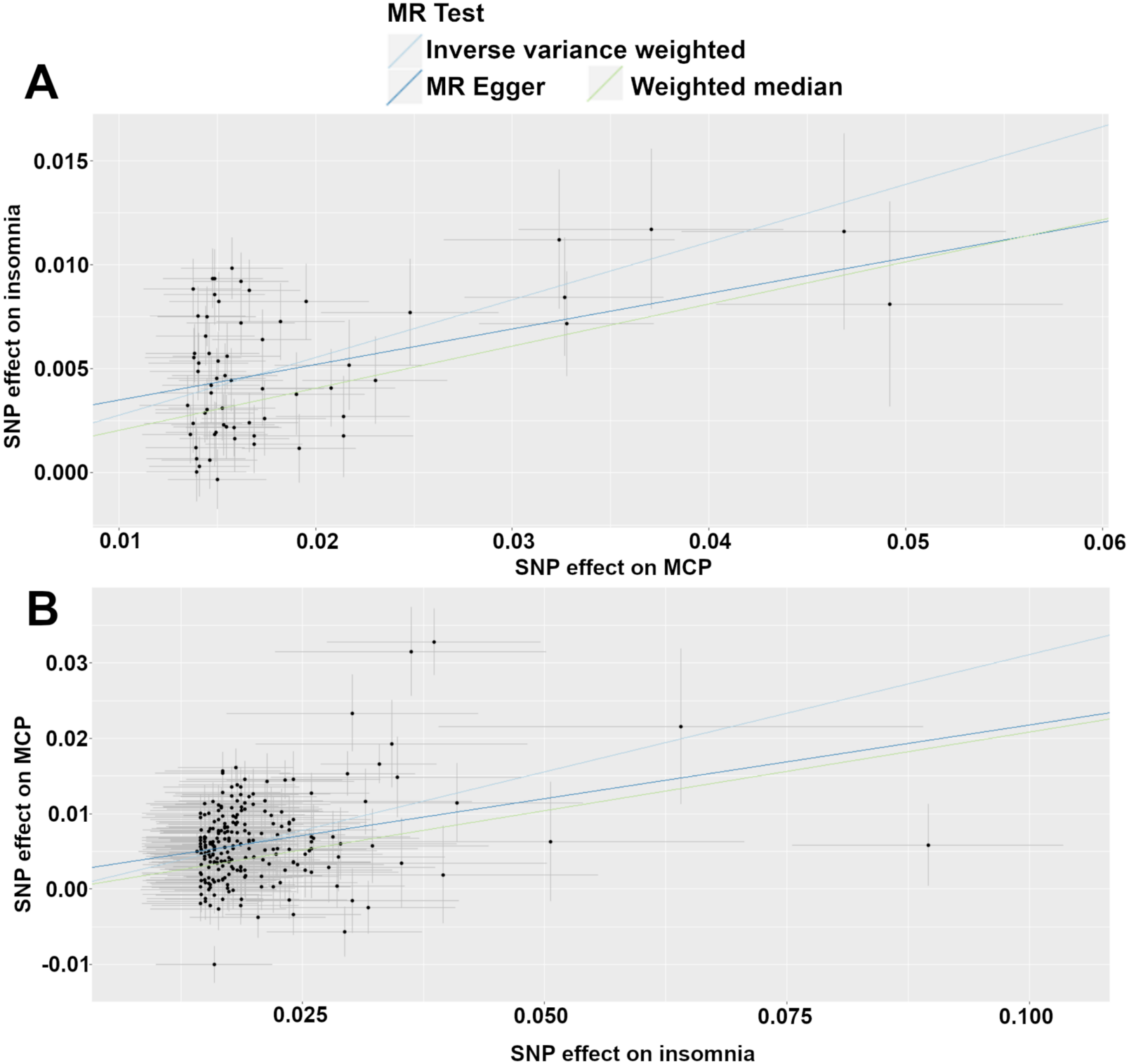
Supplementary Figure 2. FinnGen pain demonstrates a significant positive effect size on Lane UKBB outcome. Forest plot of the MR-based effect sizes of FinnGen pain exposure instruments on Lane et al. insomnia outcome.

MR Method

Inverse variance weighted



Supplementary Figure 3. General pain instruments show no significant pleiotropy or experimental bias. A funnel plot of the IVW analysis for FinnGen general pain instruments as exposure on Lane et al. insomnia outcome.



Supplementary Figure 4. MCP-insomnia MR analysis shows similar effects as FinnGen general pain-insomnia. Combined MR Egger, weighted median and IVW scatter plots of Johnston et al. MCP lead SNPs as exposure and Lane et al. insomnia summary statistics as outcome (A), and Jansen et al. insomnia lead SNPs as exposure for an MCP outcome (B).



Supplementary Figure 5. Filtered Jansen et al. insomnia instruments have positive effect size on pain outcome.
 A leave-one-out plot of the IVW effects of the Jansen et al. insomnia exposure instruments not significantly associated to other UKBB sleep trait analyses on general pain as outcome.