

Supplementary Material:

Genome-wide association study investigating short and long sleep duration: a cross-population meta-analysis

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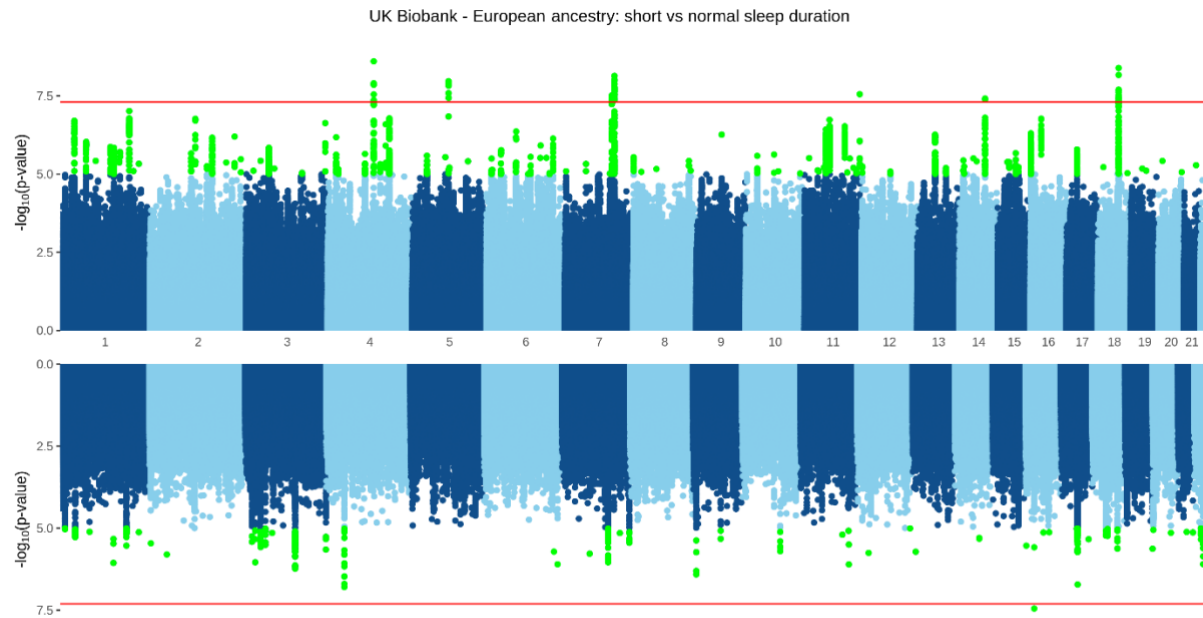
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1. Results from primary studies

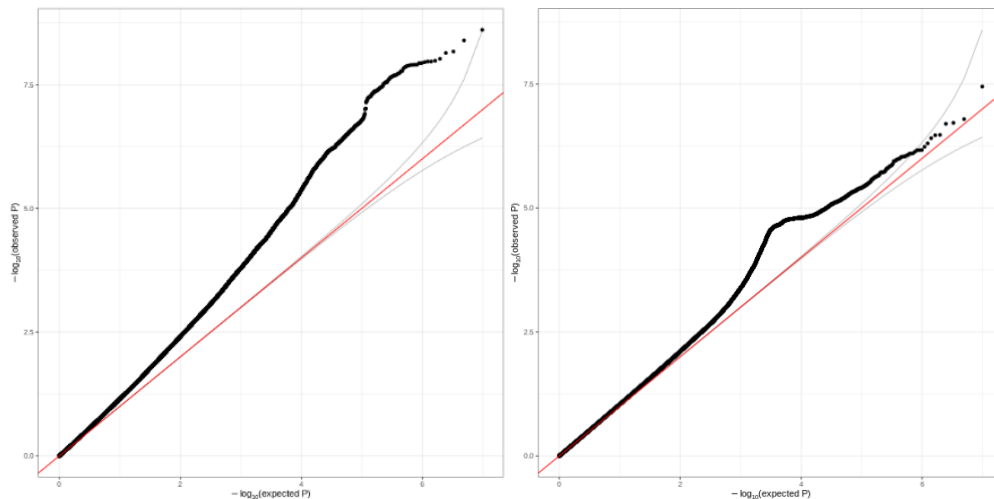
Primary studies: UK Biobank

European-ancestry population

Supplementary Figure 1. Mirrored Manhattan plot showing genetic associations with short sleep duration (top) and long sleep duration (bottom) in European UK Biobank participants. Loci reaching a nominal threshold of 1×10^{-5} highlighted in green, and the red line indicating genome-wide significance threshold of 5×10^{-8} .

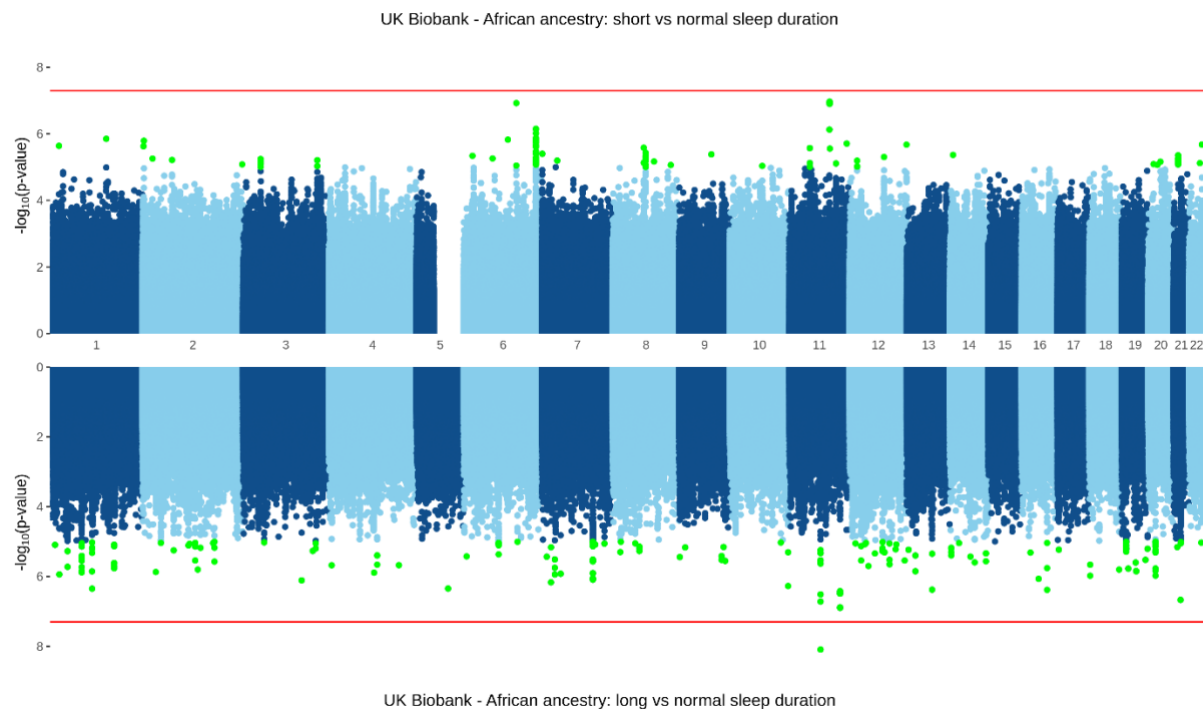


Supplementary Figure 2. Quantile-quantile plot for short sleep duration (left) and long sleep duration (right) in the European UK Biobank sample.

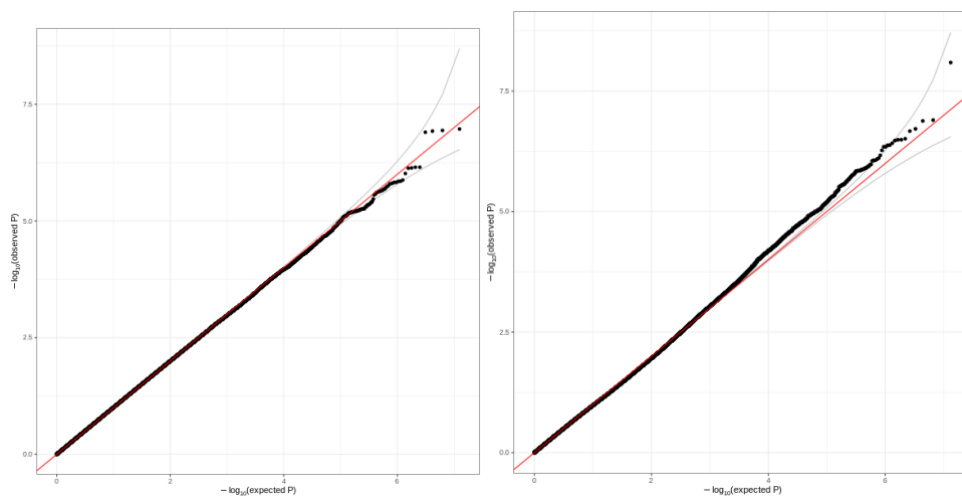


African-ancestry population

Supplementary Figure 3. Mirrored Manhattan plot showing genetic associations with short sleep duration (top) and long sleep duration (bottom) in African UK Biobank participants. Loci reaching a nominal threshold of 1×10^{-5} highlighted in green, and the red line indicating genome-wide significance threshold of 5×10^{-8} .

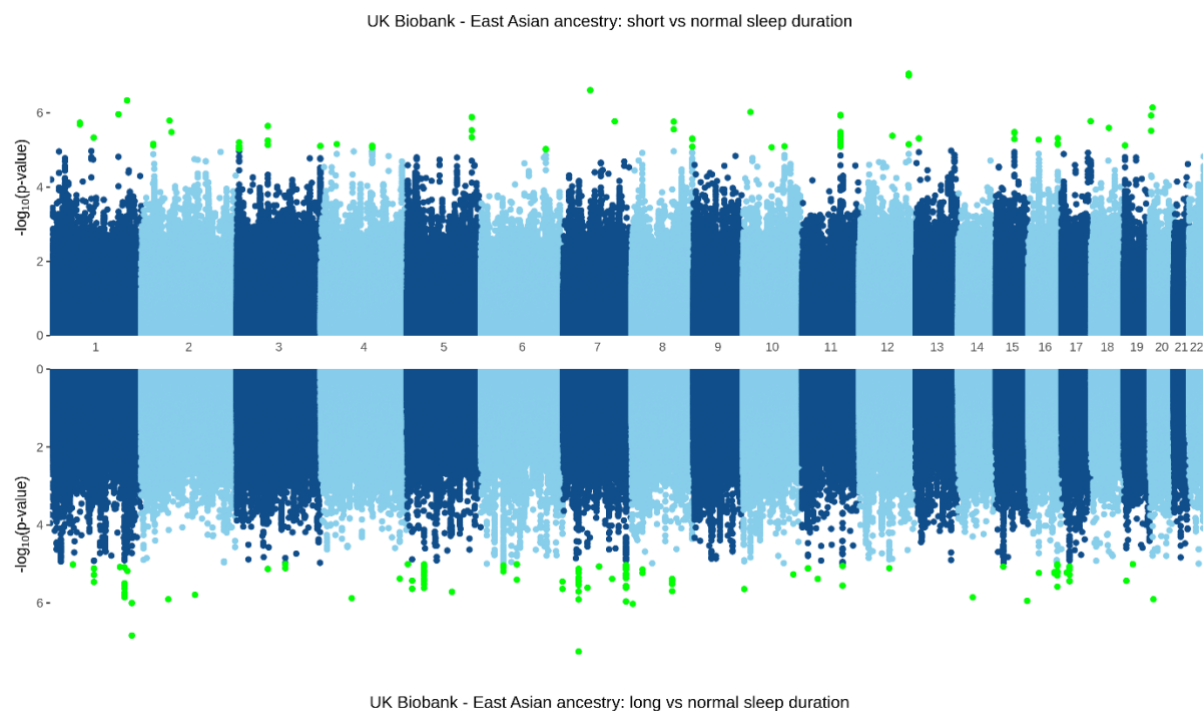


Supplementary Figure 4. Quantile-quantile plot for short sleep duration (left) and long sleep duration (right) in African UK Biobank participants.

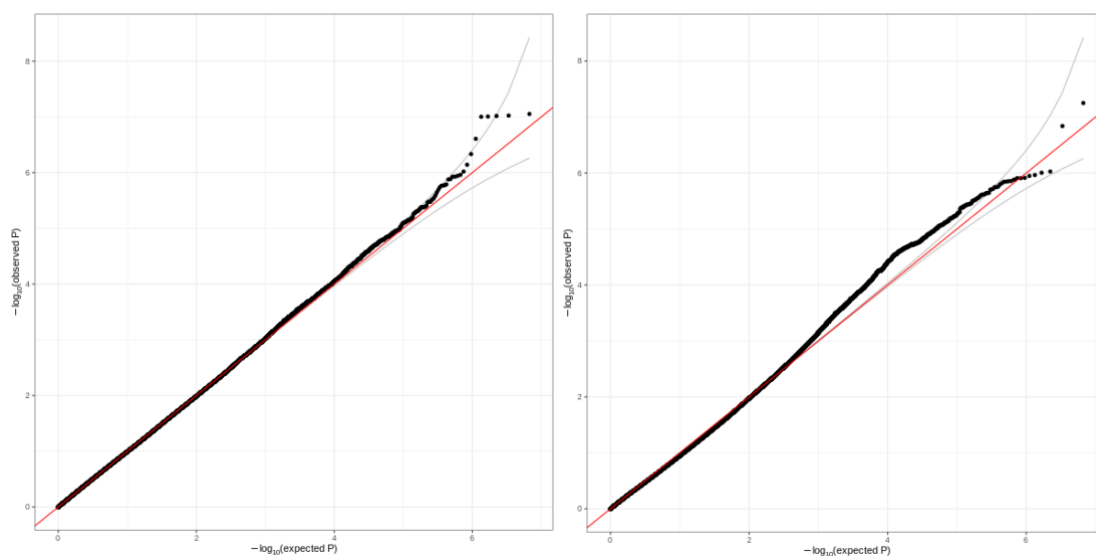


East Asian-ancestry population

Supplementary Figure 5. Mirrored Manhattan plot showing genetic associations with short sleep duration (top) and long sleep duration (bottom) in East Asian UK Biobank participants. Loci reaching a nominal threshold of 1×10^{-5} highlighted in green, and the red line indicating genome-wide significance threshold of 5×10^{-8} .

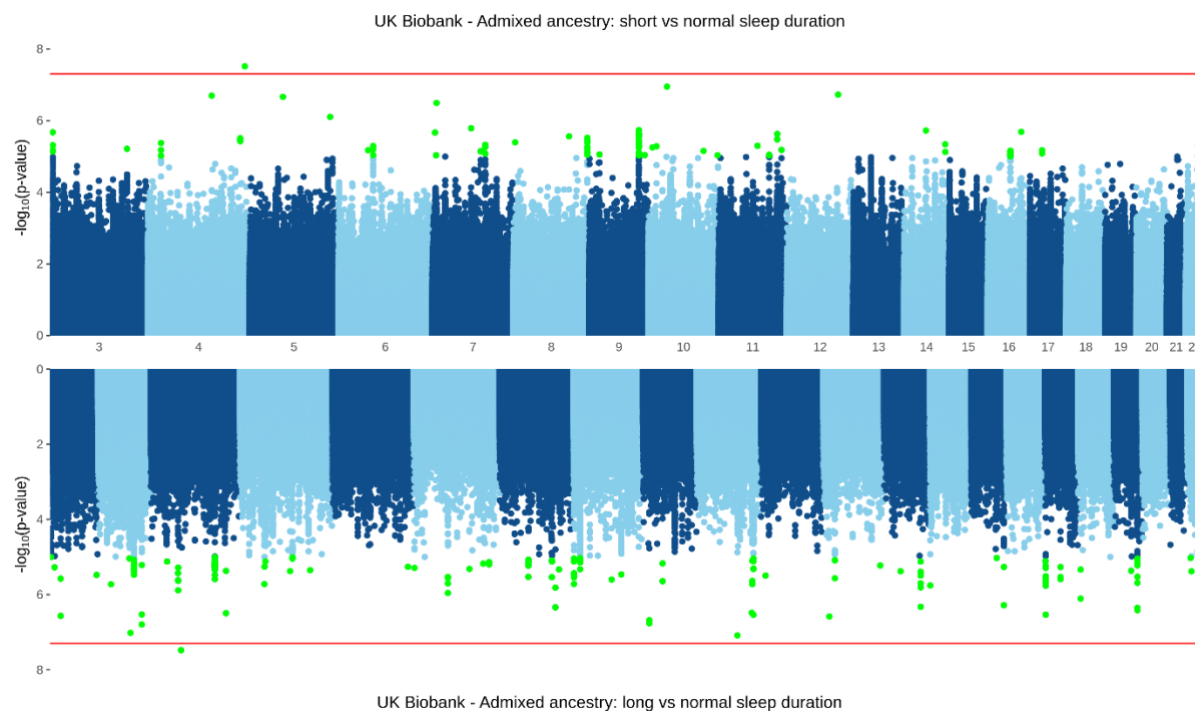


Supplementary Figure 6. Quantile-quantile plot for short sleep duration (left) and long sleep duration (right) in East Asian UK Biobank participants.

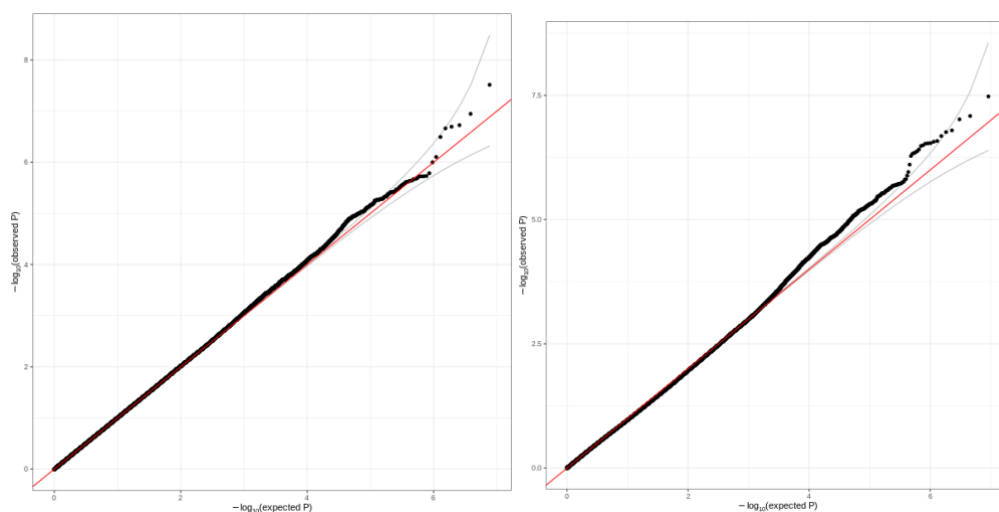


Admixed American population

Supplementary Figure 7. Mirrored Manhattan plot showing genetic associations with short sleep duration (top) and long sleep duration (bottom) in Admixed UK Biobank participants. Loci reaching a nominal threshold of 1×10^{-5} highlighted in green, and the red line indicating genome-wide significance threshold of 5×10^{-8} .



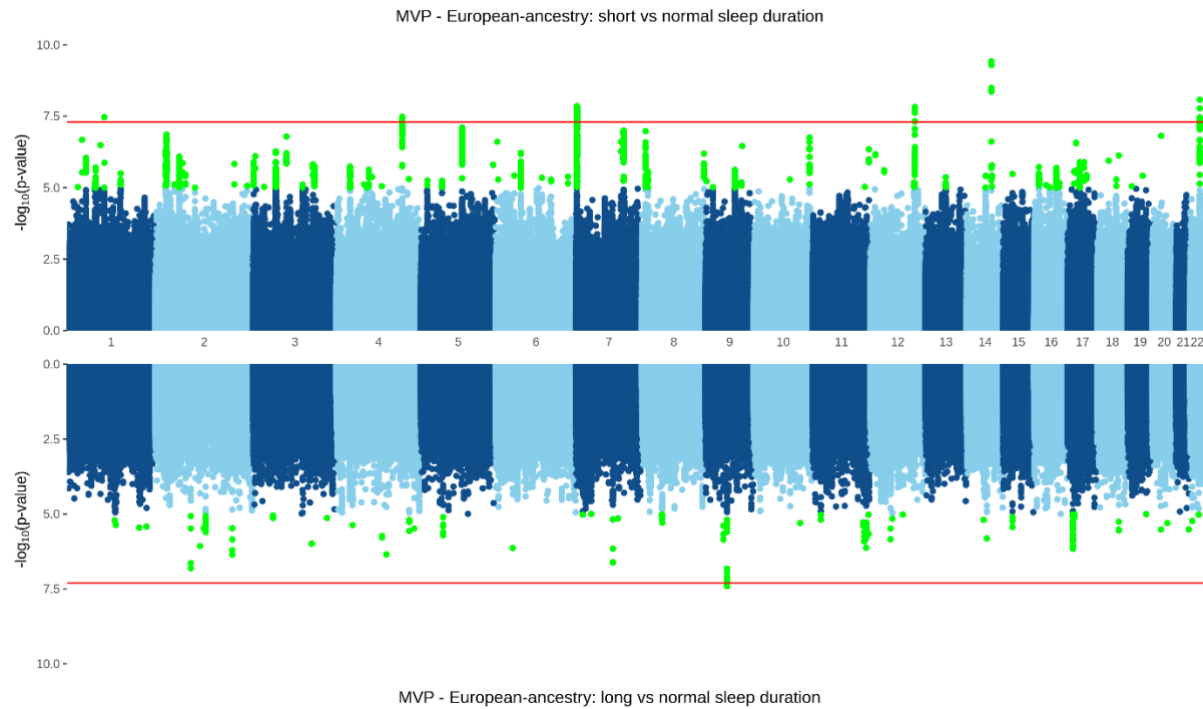
Supplementary Figure 8. Quantile-quantile plot for short sleep duration (left) and long sleep duration (right) in Admixed UK Biobank participants.



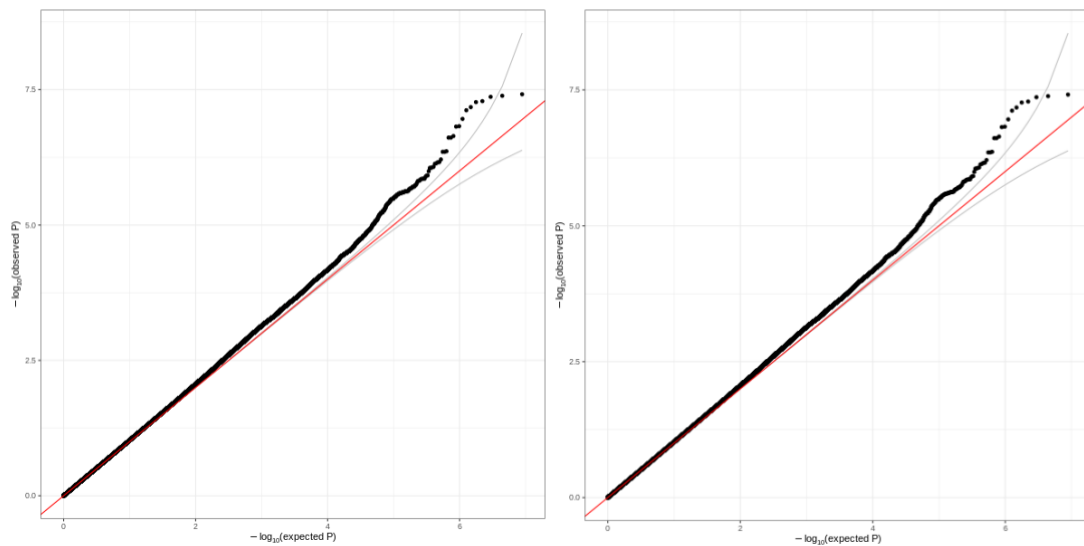
Primary studies: MVP

European-ancestry population

Supplementary Figure 9. Mirrored Manhattan plot showing genetic associations with short sleep duration (top) and long sleep duration (bottom) in European MVP participants. Loci reaching a nominal threshold of 1×10^{-5} highlighted in green, and the red line indicating genome-wide significance threshold of 5×10^{-8} .

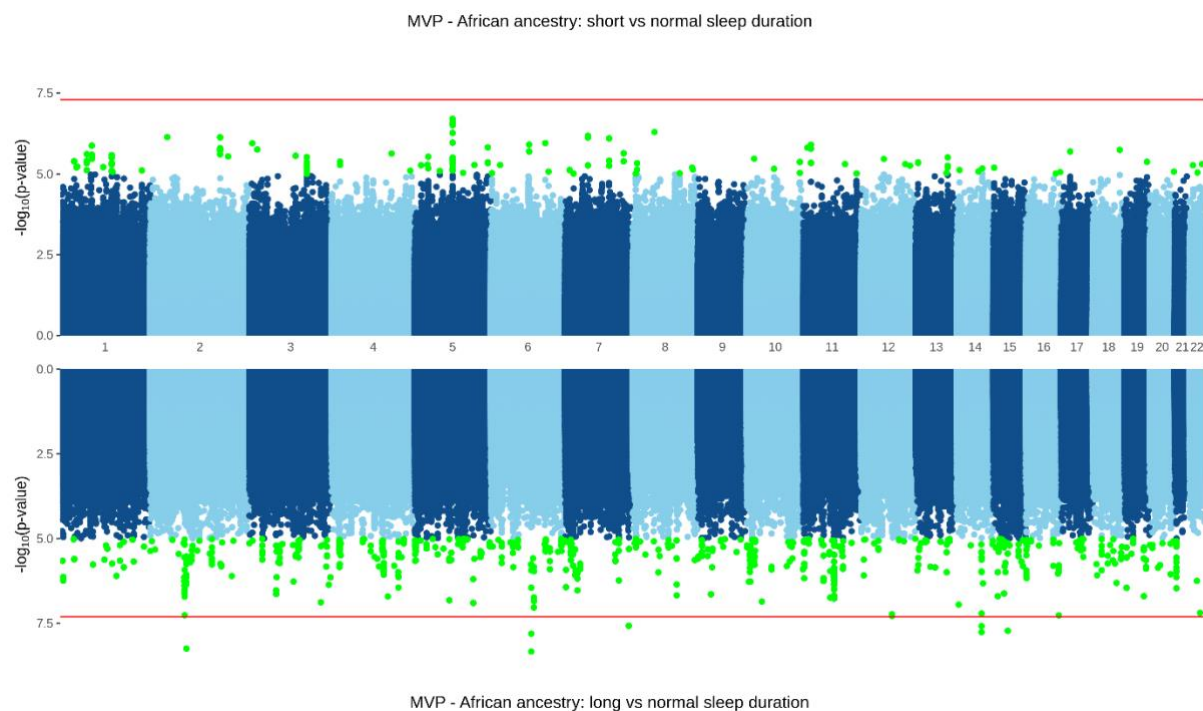


Supplementary Figure 10. Quantile-quantile plot for short sleep duration (left) and long sleep duration (right) in European MVP participants.

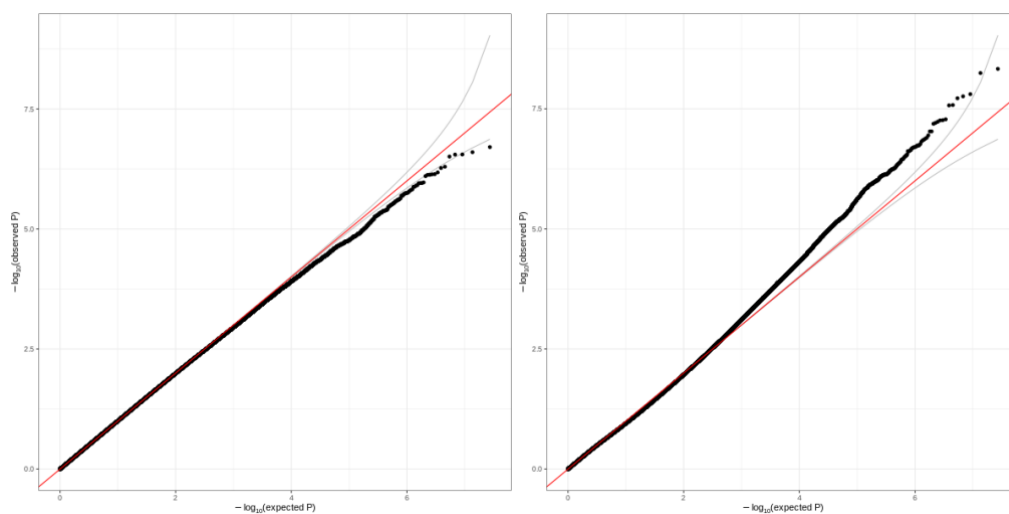


African-ancestry population

Supplementary Figure 11. Mirrored Manhattan plot showing genetic associations with short sleep duration (top) and long sleep duration (bottom) in African MVP participants. Loci reaching a nominal threshold of 1×10^{-5} highlighted in green, and the red line indicating genome-wide significance threshold of 5×10^{-8} .

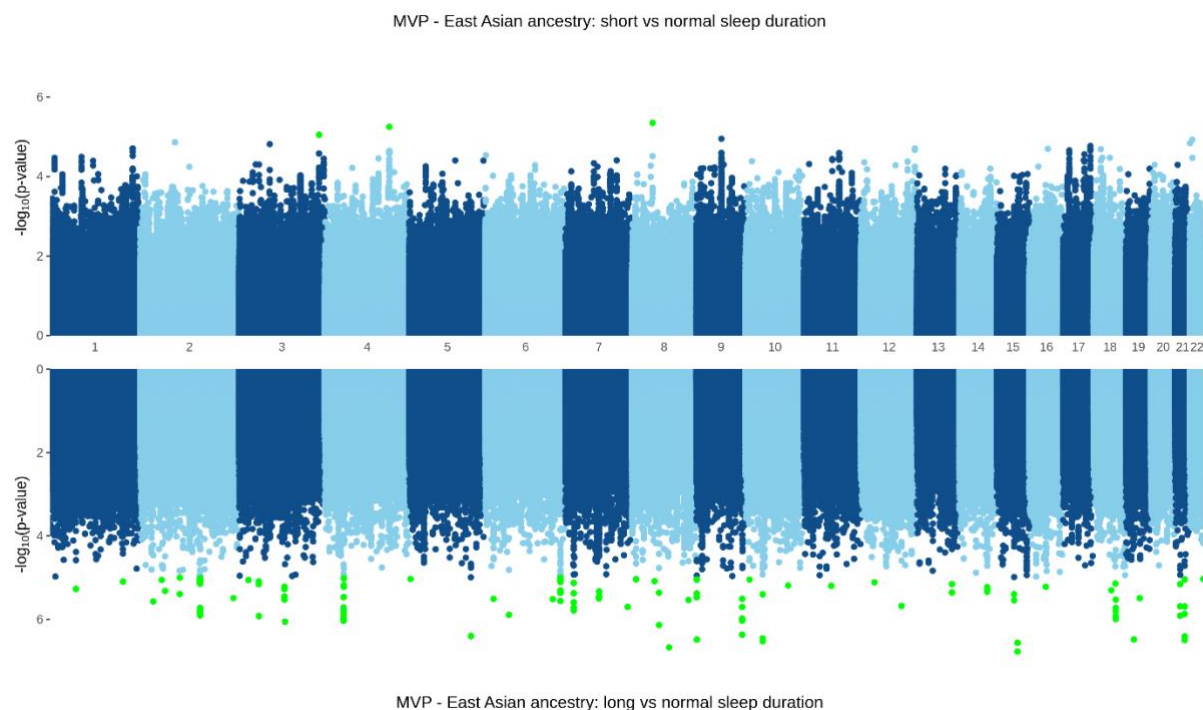


Supplementary Figure 12. Quantile-quantile plot for short sleep duration (left) and long sleep duration (right) in African MVP participants.

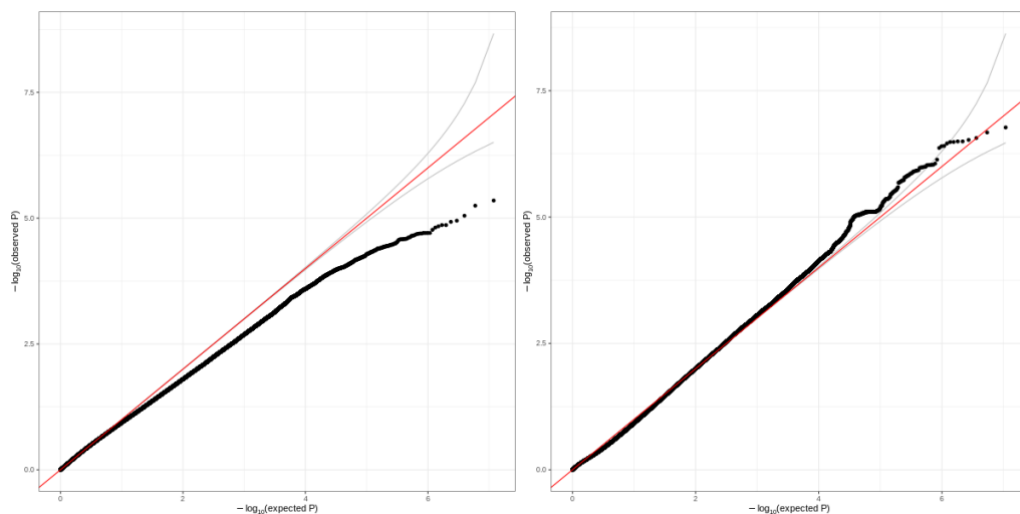


East Asian-ancestry population

Supplementary Figure 13. Mirrored Manhattan plot showing genetic associations with short sleep duration (top) and long sleep duration (bottom) in East Asian MVP participants. Loci reaching a nominal threshold of 1×10^{-5} highlighted in green.

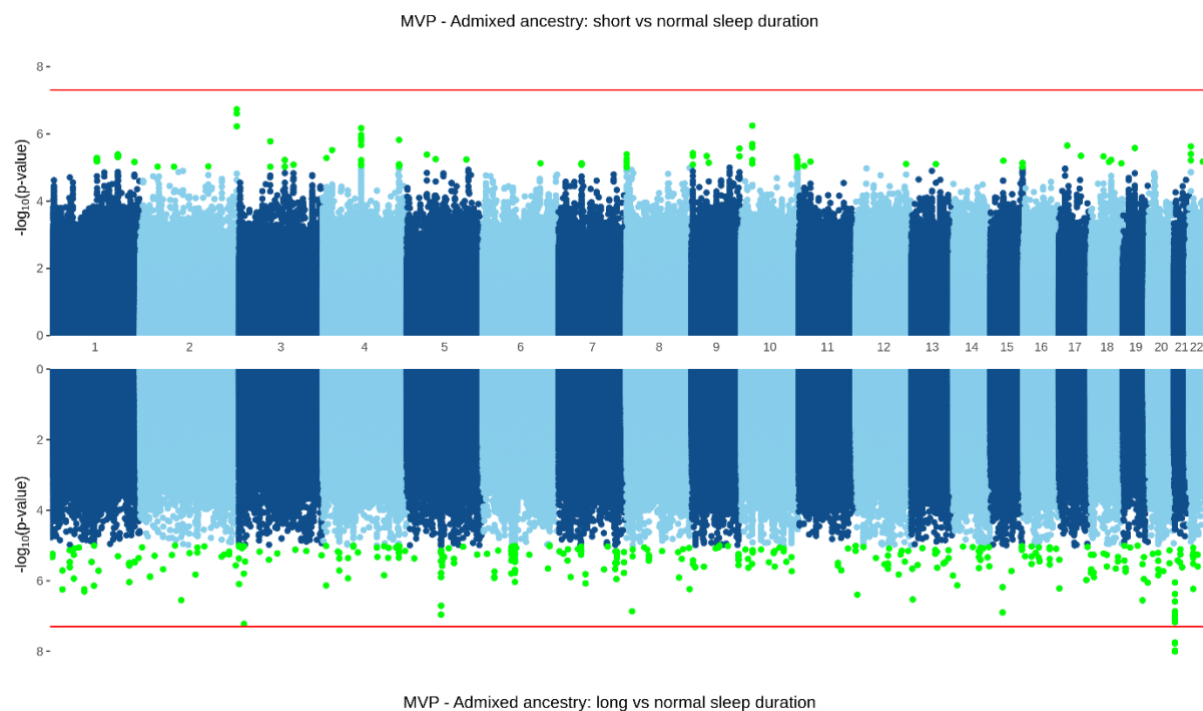


Supplementary Figure 14. Quantile-quantile plot for short sleep duration (left) and long sleep duration (right) in East Asian MVP participants.

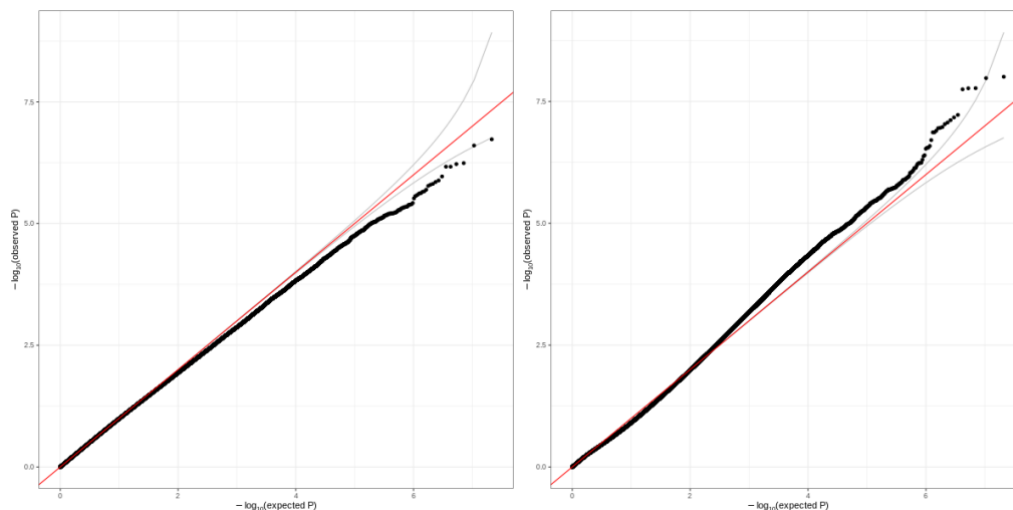


Admixed American population

Supplementary Figure 15. Mirrored Manhattan plot showing genetic associations with short sleep duration (top) and long sleep duration (bottom) in the East admixed-American MVP participants. Loci reaching a nominal threshold of 1×10^{-5} highlighted in green, and the red line indicating genome-wide significance threshold of 5×10^{-8} .



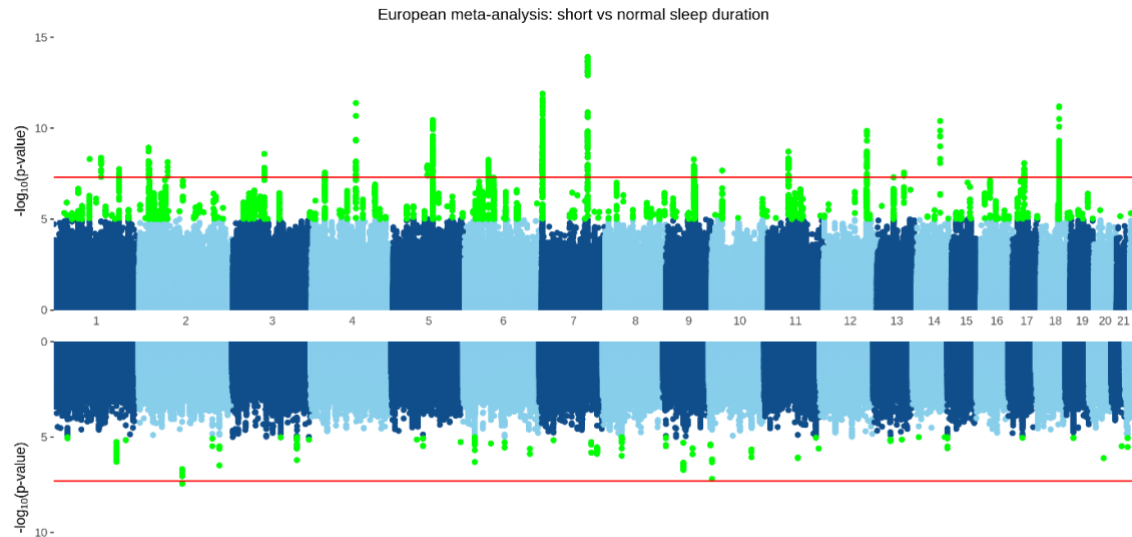
Supplementary Figure 16. Quantile-quantile plot for short sleep duration (left) and long sleep duration (right) in admixed-American MVP participants.



Ancestry-specific meta-analyses

European-ancestry population

Supplementary Figure 17 Mirrored Manhattan plot showing results of a meta-analysis in EUR groups in the UK Biobank and MVP cohorts. TOP: short (<6 hours, n=47,180) versus normal (7-8 hours, n=384,594), with 46 independent genetic-risk loci reaching genome-wide significance highlighted in green. BOTTOM: long (>9 hours, n=15,995) versus normal with one genome wide significant locus. All variants reaching a suggestive threshold of 1×10^{-5} are highlighted in green.



Supplementary Figure 18 Gene-based test for short (top) and long (bottom) sleep duration in EUR from UK Biobank and MVP cohorts. Bonferroni-adjusted significance threshold $P < 2.7 \times 10^{-6}$

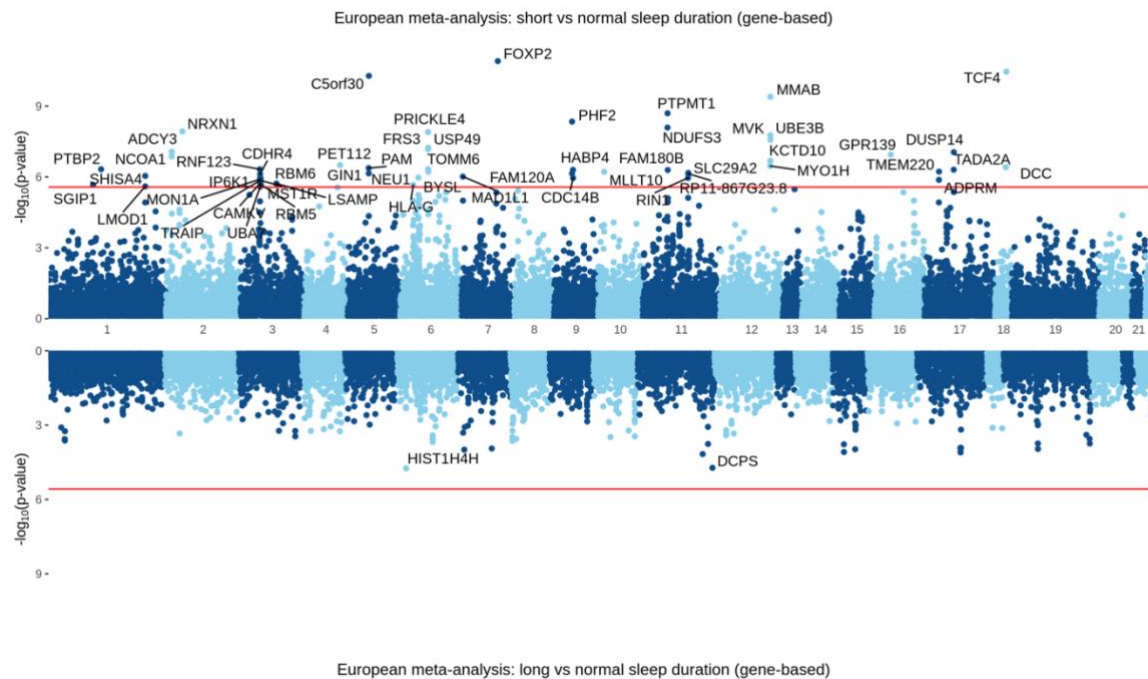
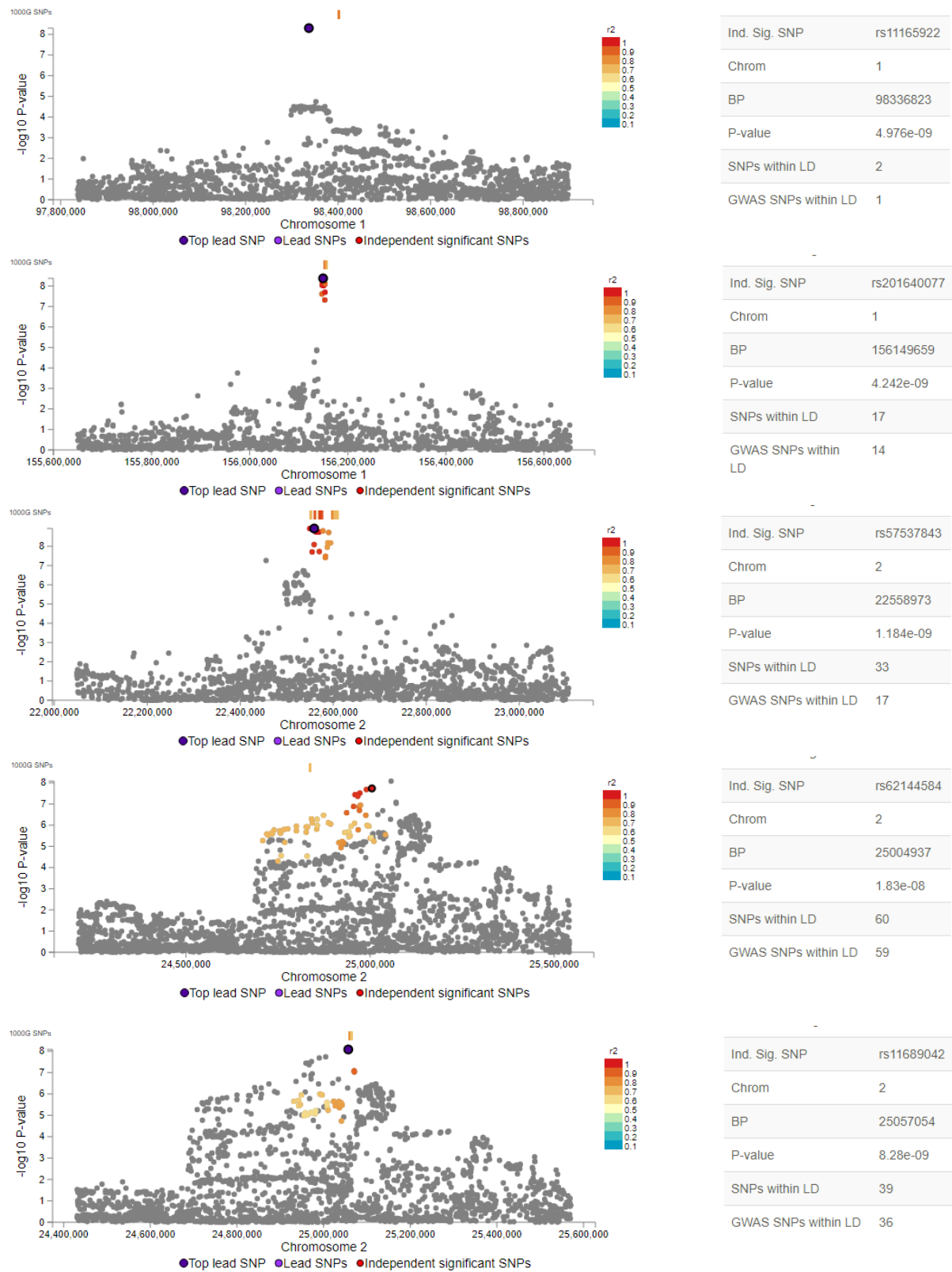
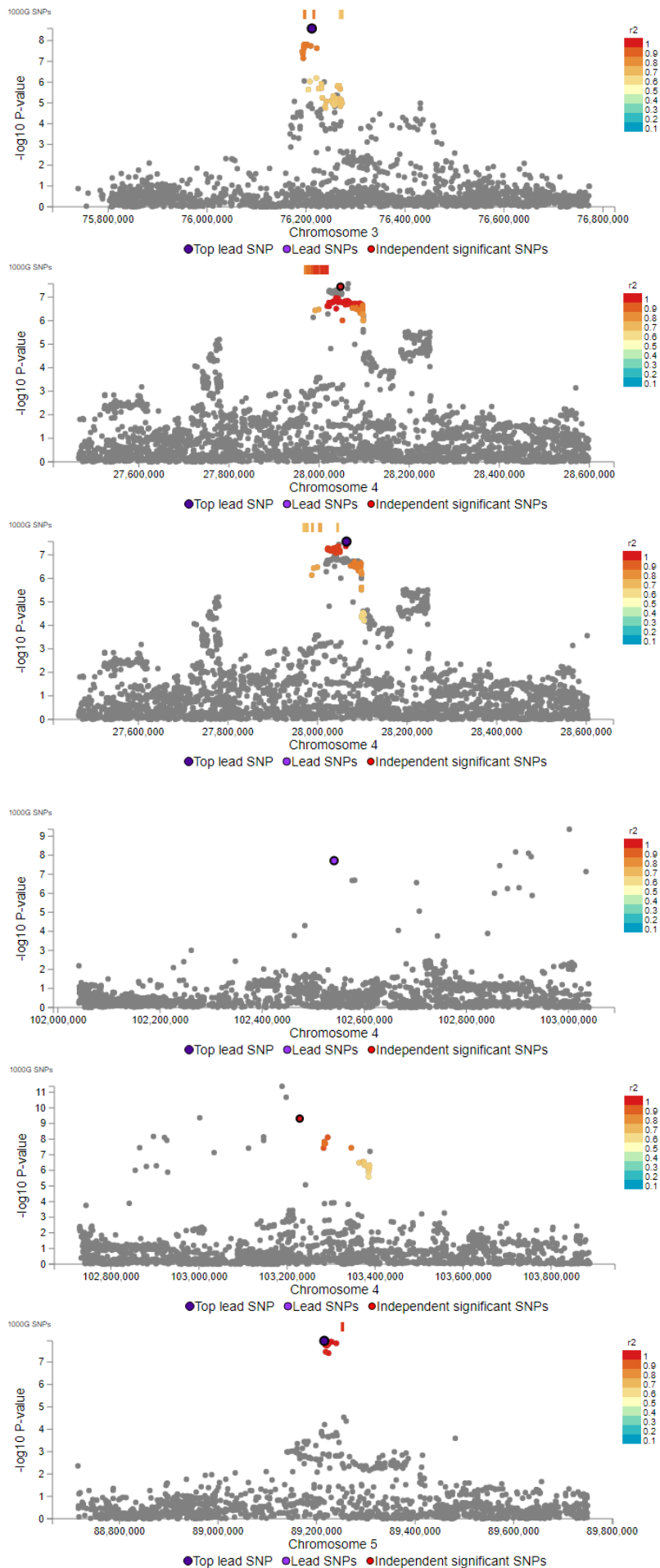


Figure 19 Regional plots showing novel loci for EUR short sleep analysis. Images generated by FUMA.





Ind. Sig. SNP	rs11128505
Chrom	3
BP	76211681
P-value	2.614e-09
SNPs within LD	54
GWAS SNPs within LD	48

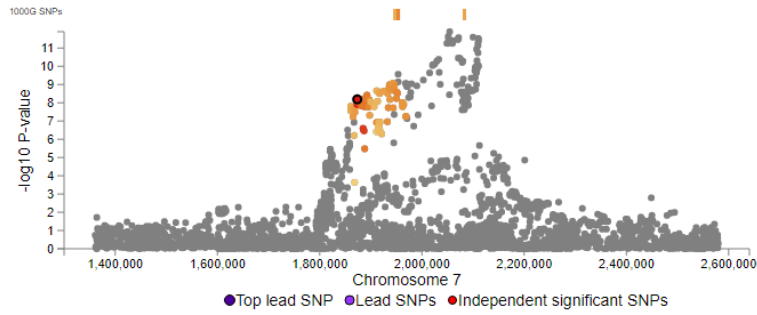
Ind. Sig. SNP	rs796217750
Chrom	4
BP	28047538
P-value	3.594e-08
SNPs within LD	164
GWAS SNPs within LD	119

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Chrom	4
BP	28064697
P-value	2.719e-08
SNPs within LD	158
GWAS SNPs within LD	140

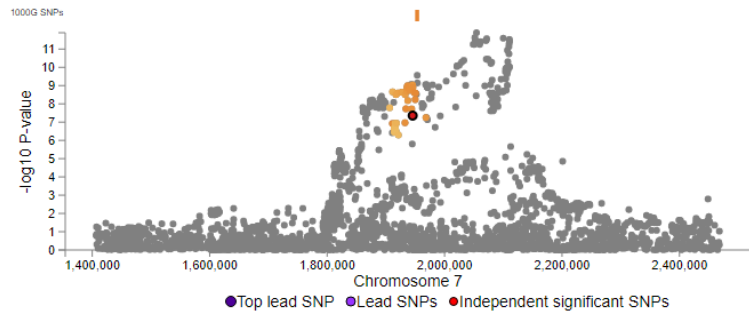
Ind. Sig. SNP	rs71614699
Chrom	4
BP	102540919
P-value	1.932e-08
SNPs within LD	1
GWAS SNPs within LD	1

Ind. Sig. SNP	rs13105581
Chrom	4
BP	103228830
P-value	4.867e-10
SNPs within LD	19
GWAS SNPs within LD	19

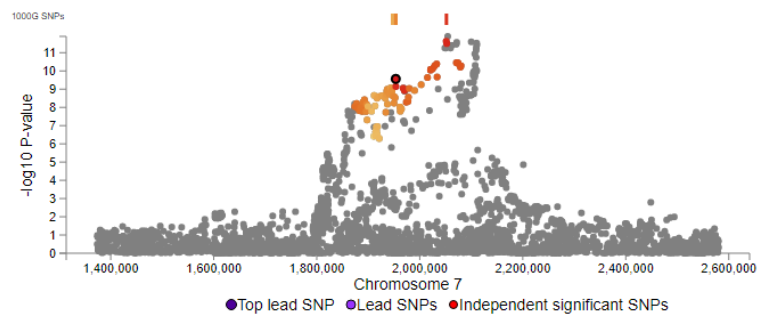
Ind. Sig. SNP	rs10079421
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P-value	1.124e-08
SNPs within LD	13
GWAS SNPs within LD	10



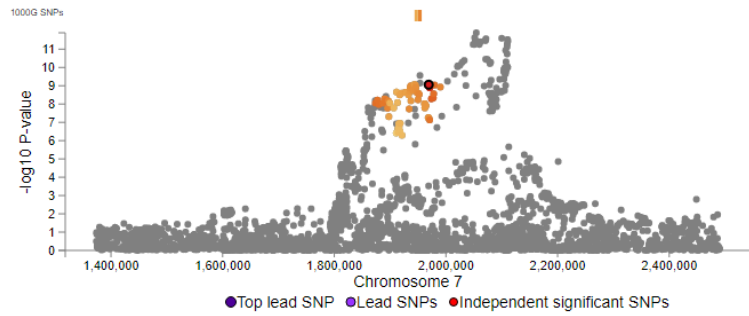
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Chrom	7
BP	1873406
P-value	6.478e-09
SNPs within LD	90
GWAS SNPs within LD	85



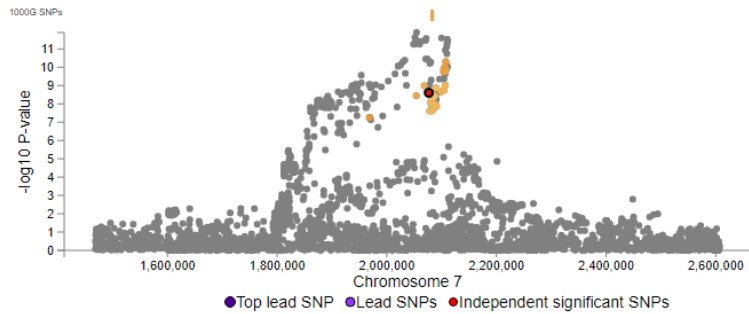
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Chrom	7
BP	1945685
P-value	4.399e-08
SNPs within LD	41
GWAS SNPs within LD	39



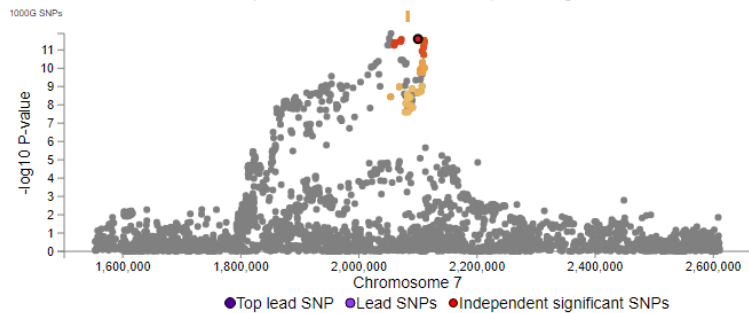
Ind. Sig. SNP	rs62442903
Chrom	7
BP	1953416
P-value	2.734e-10
SNPs within LD	90
GWAS SNPs within LD	86



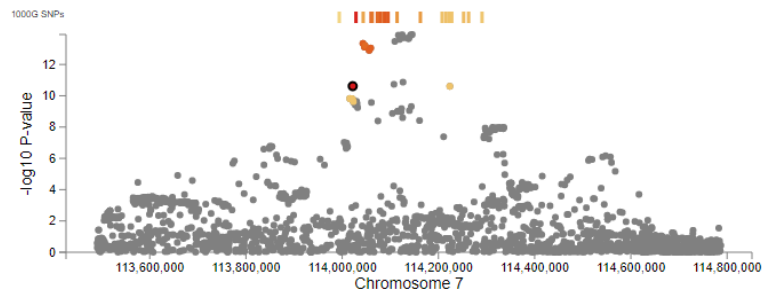
Ind. Sig. SNP	rs62442910
Chrom	7
BP	1969133
P-value	8.757e-10
SNPs within LD	69
GWAS SNPs within LD	66



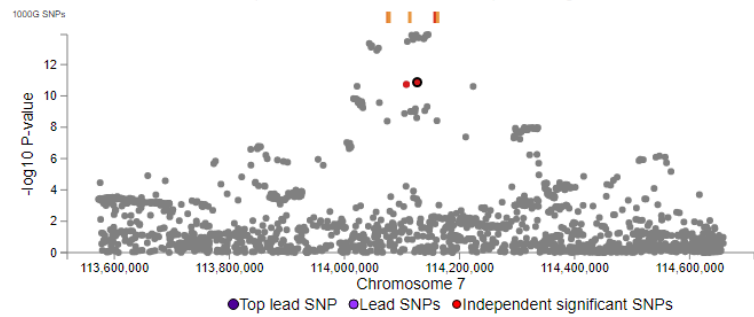
Ind. Sig. SNP	rs6948912
Chrom	7
BP	2076701
P-value	2.482e-09
SNPs within LD	32
GWAS SNPs within LD	30



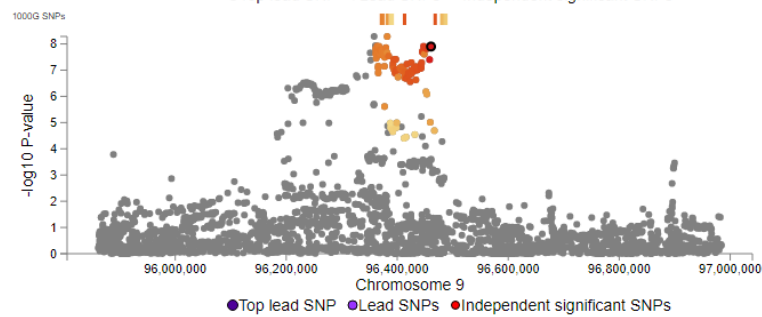
Ind. Sig. SNP	rs111595851
Chrom	7
BP	2099924
P-value	2.539e-12
SNPs within LD	46
GWAS SNPs within LD	44



Ind. Sig. SNP	rs66571810
Chrom	7
BP	114021870
P-value	2.433e-11
SNPs within LD	33
GWAS SNPs within LD	13



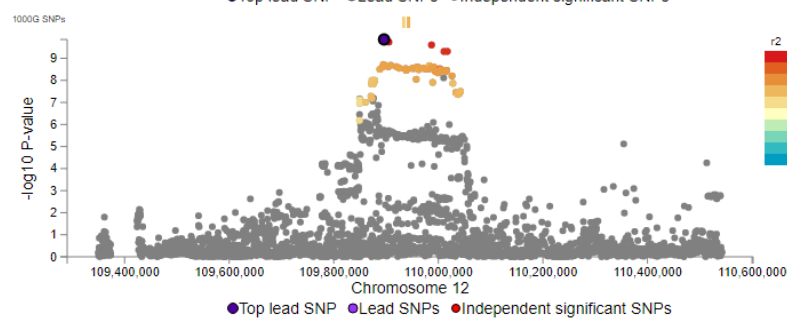
Ind. Sig. SNP	rs2079070
Chrom	7
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P-value	1.347e-11
SNPs within LD	7
GWAS SNPs within LD	2



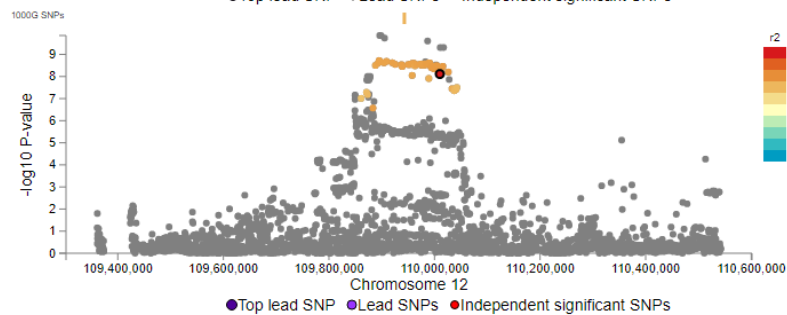
Ind. Sig. SNP	rs765110298
Chrom	9
BP	96460883
P-value	1.258e-08
SNPs within LD	128
GWAS SNPs within LD	111



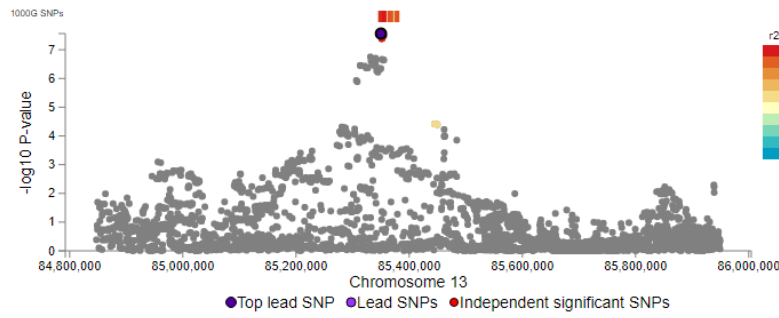
Ind. Sig. SNP	rs1243197
Chrom	10
BP	21970077
P-value	2.152e-08
SNPs within LD	17
GWAS SNPs within LD	2



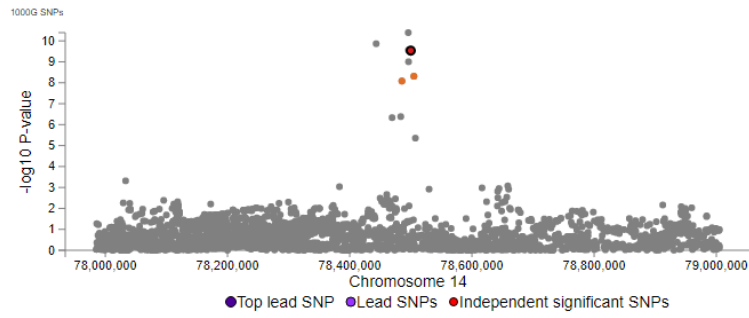
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Chrom	12
BP	109896165
P-value	1.394e-10
SNPs within LD	79
GWAS SNPs within LD	77



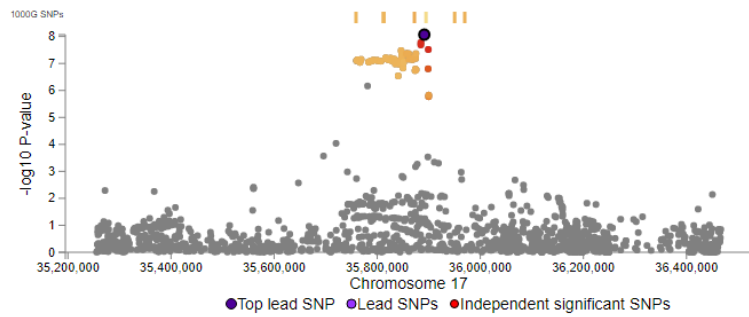
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Chrom	12
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P-value	7.725e-09
SNPs within LD	58
GWAS SNPs within LD	57



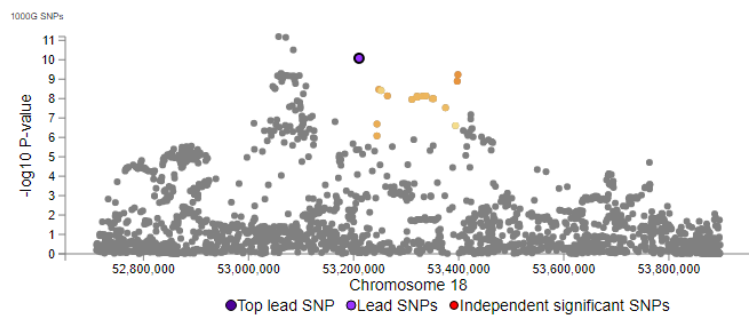
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Chrom	13
BP	85350099
P-value	2.737e-08
SNPs within LD	29
GWAS SNPs within LD	12



Ind. Sig. SNP	rs76251410
Chrom	14
BP	78499897
P-value	2.922e-10
SNPs within LD	3
GWAS SNPs within LD	3

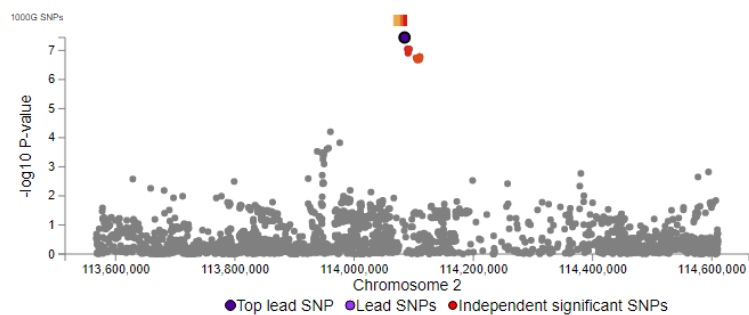


Ind. Sig. SNP	rs3110628
Chrom	17
BP	35891384
P-value	8.524e-09
SNPs within LD	73
GWAS SNPs within LD	65



Ind. Sig. SNP	rs613872
Chrom	18
BP	53210302
P-value	8.35e-11
SNPs within LD	17
GWAS SNPs within LD	17

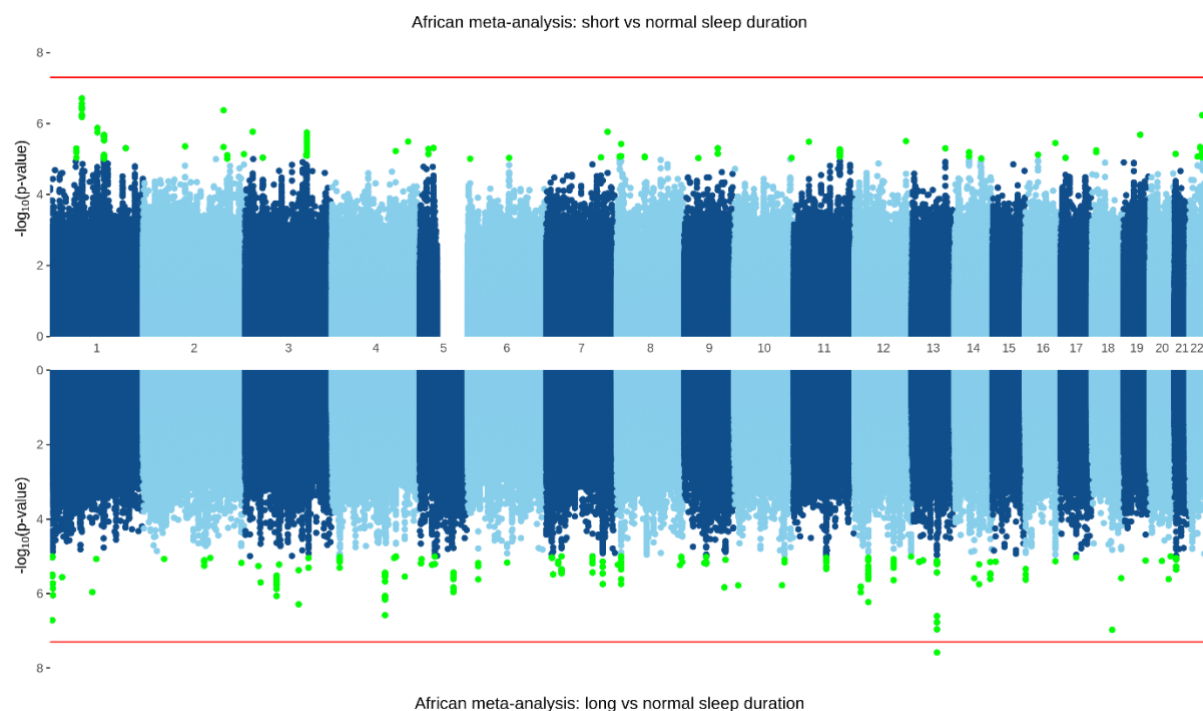
Figure 20 Regional plot for rs62158206, a genome-wide significant association with long sleep in EUR-only meta-analysis of UKBB and MVP. Image generated using FUMA.



Ind. Sig. SNP	rs62158206
Chrom	2
BP	114084596
P-value	3.589e-08
SNPs within LD	24
GWAS SNPs within LD	10

African-ancestry population

Supplementary Figure 21 Mirrored Manhattan plot showing results of a meta-analysis in AFR in the UK Biobank and MVP cohorts. TOP: short (<6 hours, n=11,352) versus normal (7-8 hours, n=15,305), with no genome-wide significance loci. BOTTOM: long (>9 hours, n=1,128) versus normal with one genome-wide significant locus. All variants reaching a suggestive threshold of 1×10^{-5} are highlighted in green.



Supplementary Figure 22 Gene-based test for short (top) and long (bottom) sleep duration in African participants from UK Biobank and MVP cohorts, with top associations labelled.

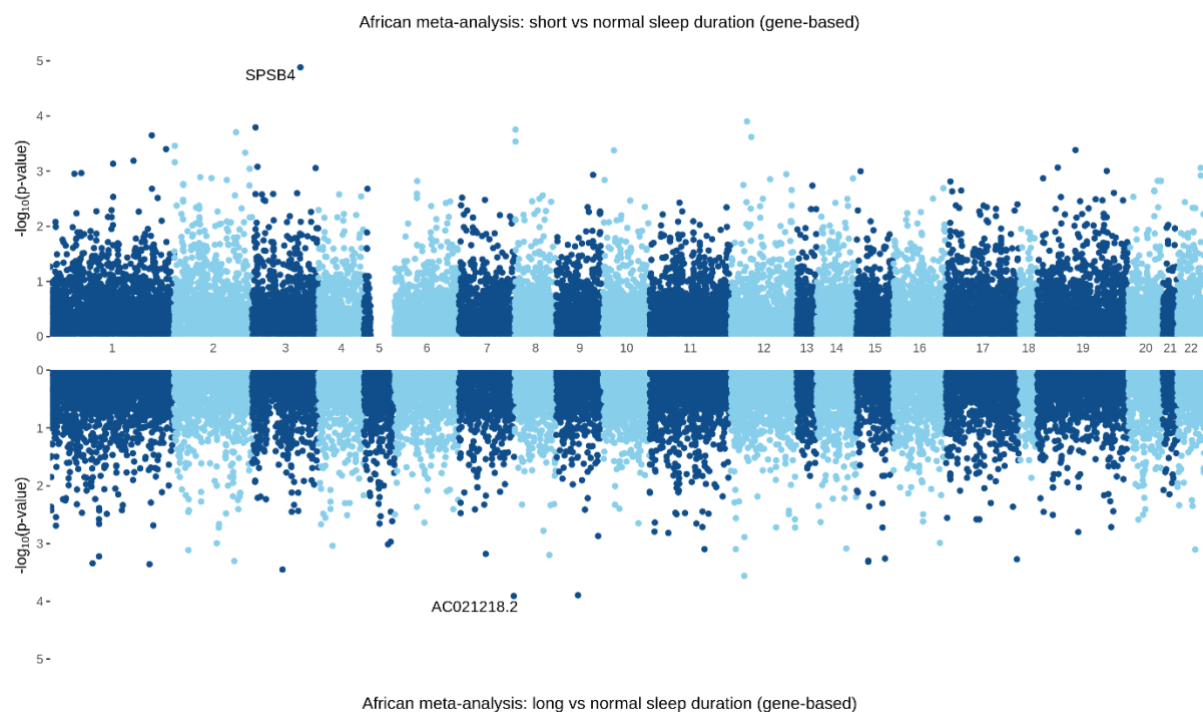


Figure 23 Regional plot for rs1412139, the strongest association for short sleep in an AFR meta-analysis of UKBB and MVP. Image generated using FUMA.

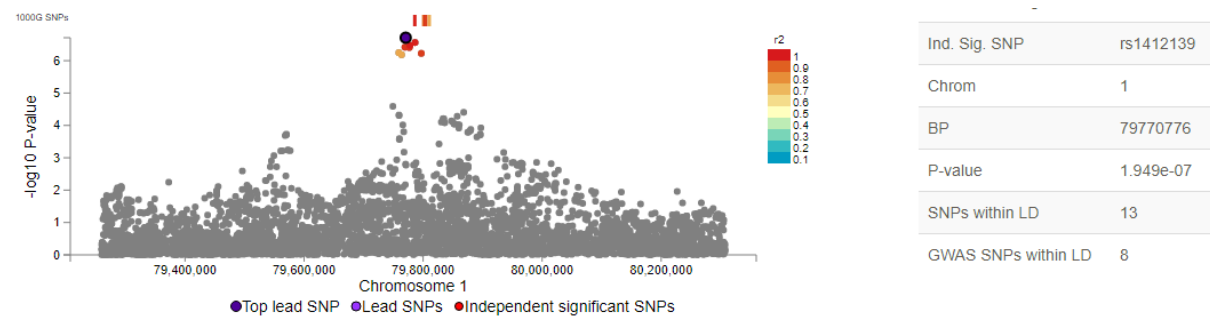
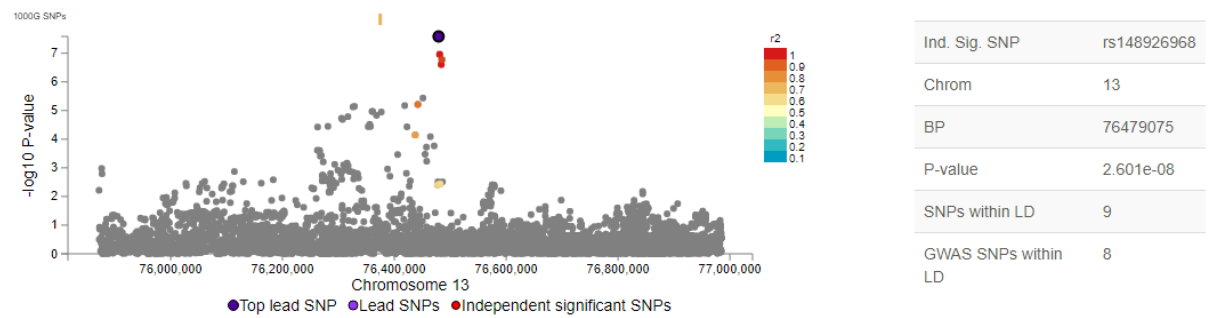


Figure 24 Regional plot for rs148926698, genome-wide significant association for long sleep in an AFR meta-analysis of UKBB and MVP. Image generated using FUMA.



2. Case-case analysis

We conducted a case-case analysis, comparing the short versus long sleep duration in the EUR sample of UK Biobank and MVP. This analysis revealed two independent genome-wide significant loci on chromosome 2. Firstly, rs62158206, which was genome-wide significant in the EUR meta-analyses of both short and long sleep duration (with opposite directions of effect). Secondly, rs4618068, which was a sub-threshold association in the EUR meta-analyses of both short ($p=5.67 \times 10^{-7}$) and long ($p=2.05 \times 10^{-7}$), again with contrasting effect directions. See supplementary table 27 and

Supplementary Figure 27 for further details

Figure 25 Manhattan plot showing results of a short (<6 hours, N=47,180) versus long (>9 hours, N=15,995) meta-analysis in EUR in the UK Biobank and MVP cohorts.

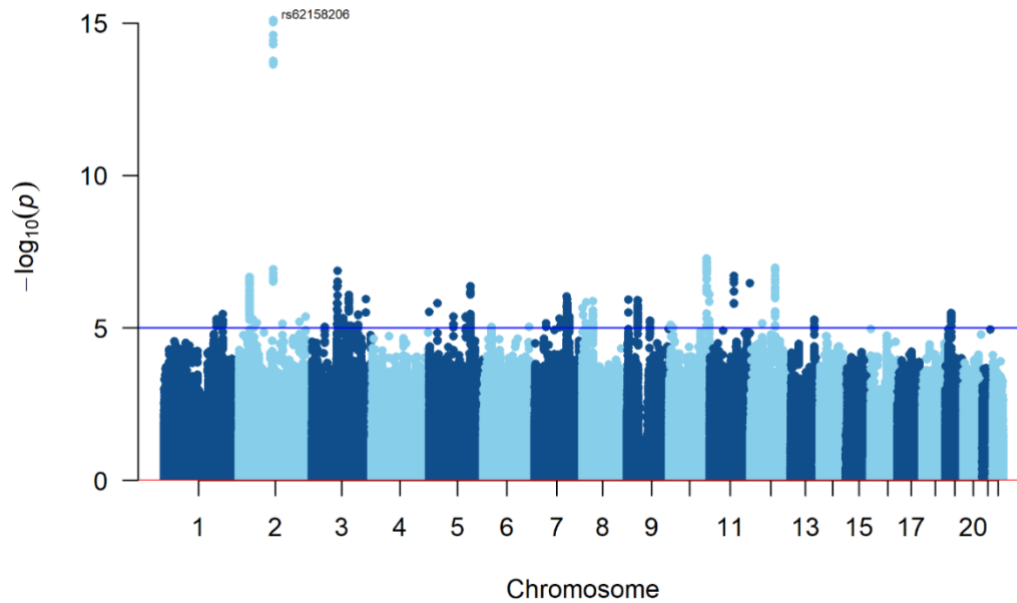
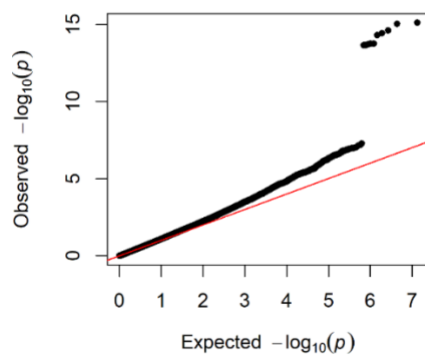
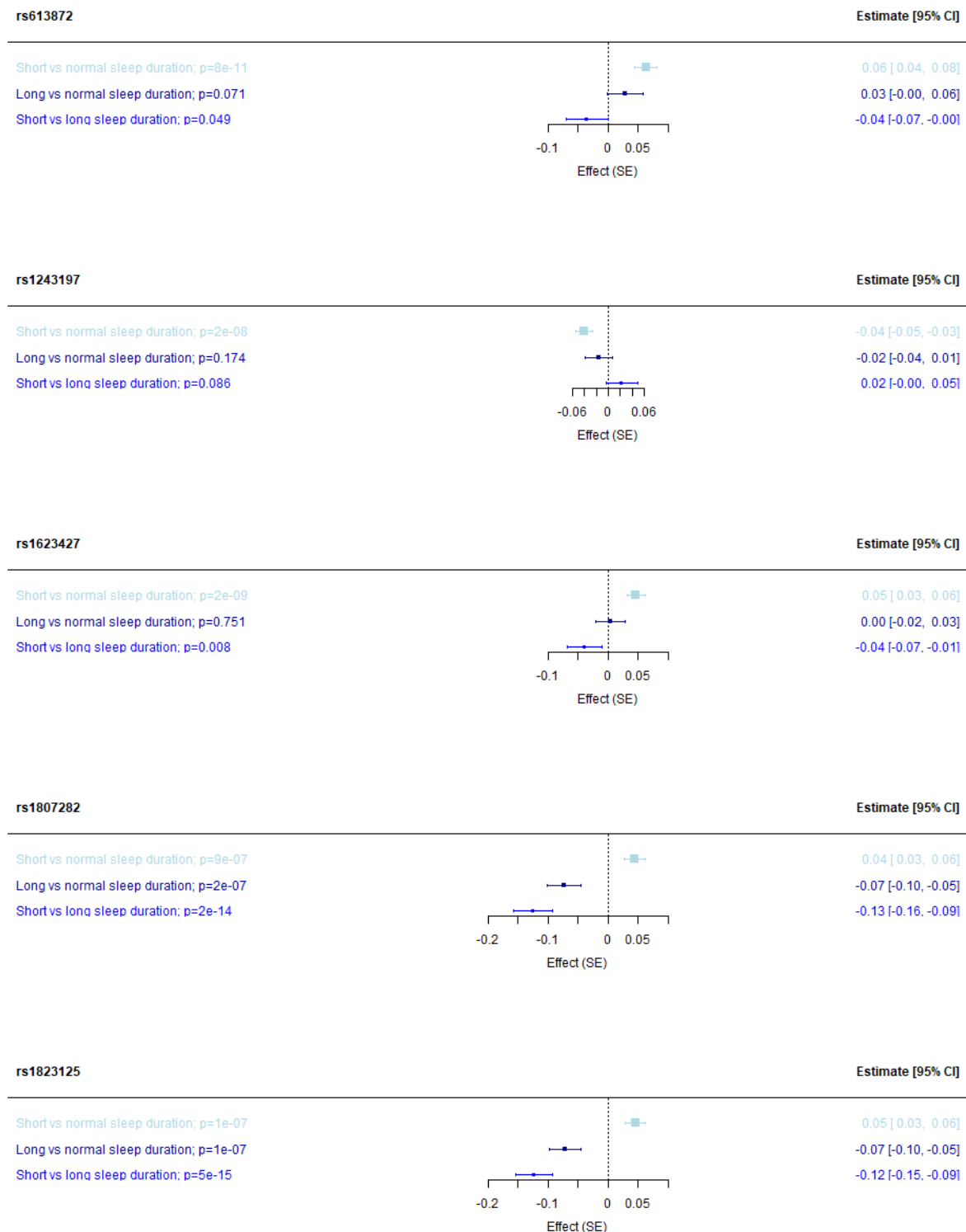
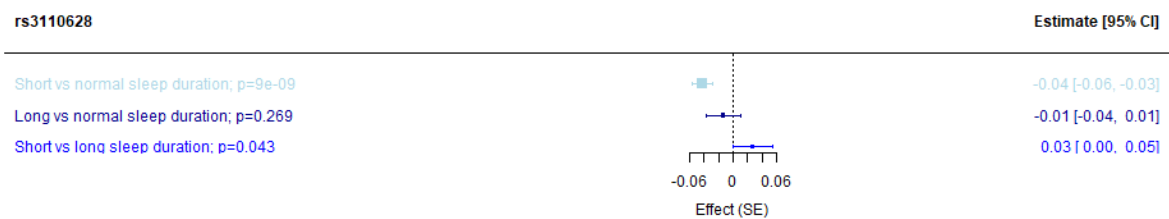
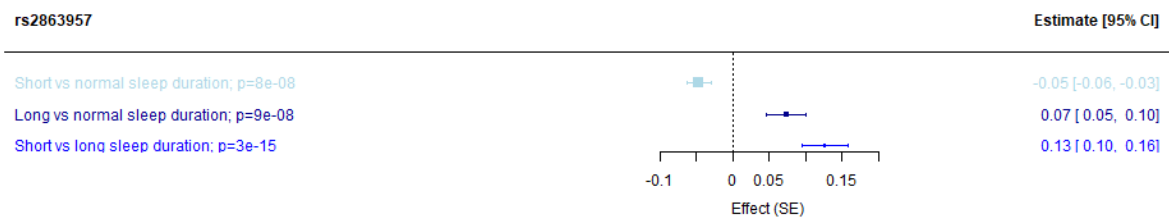
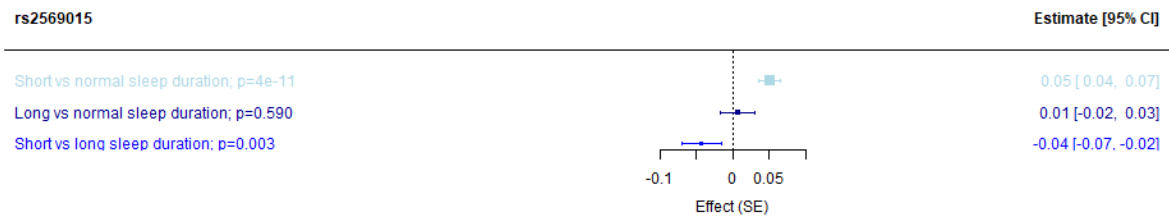
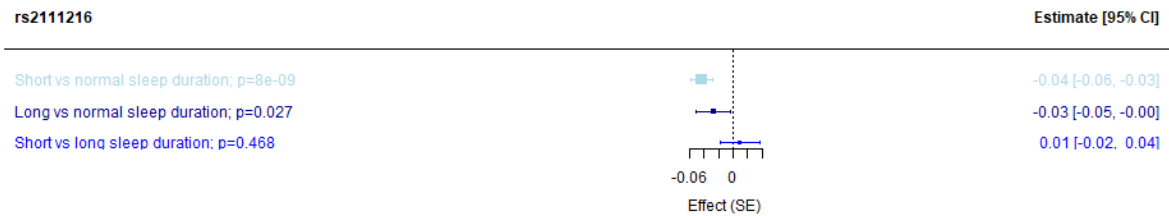
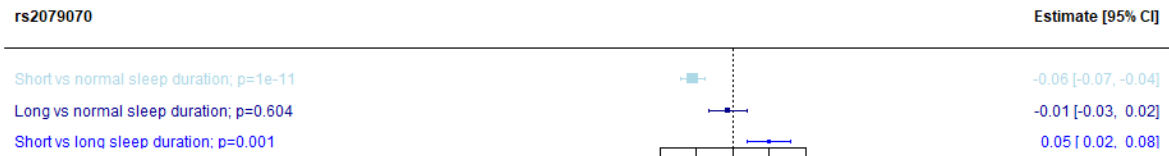


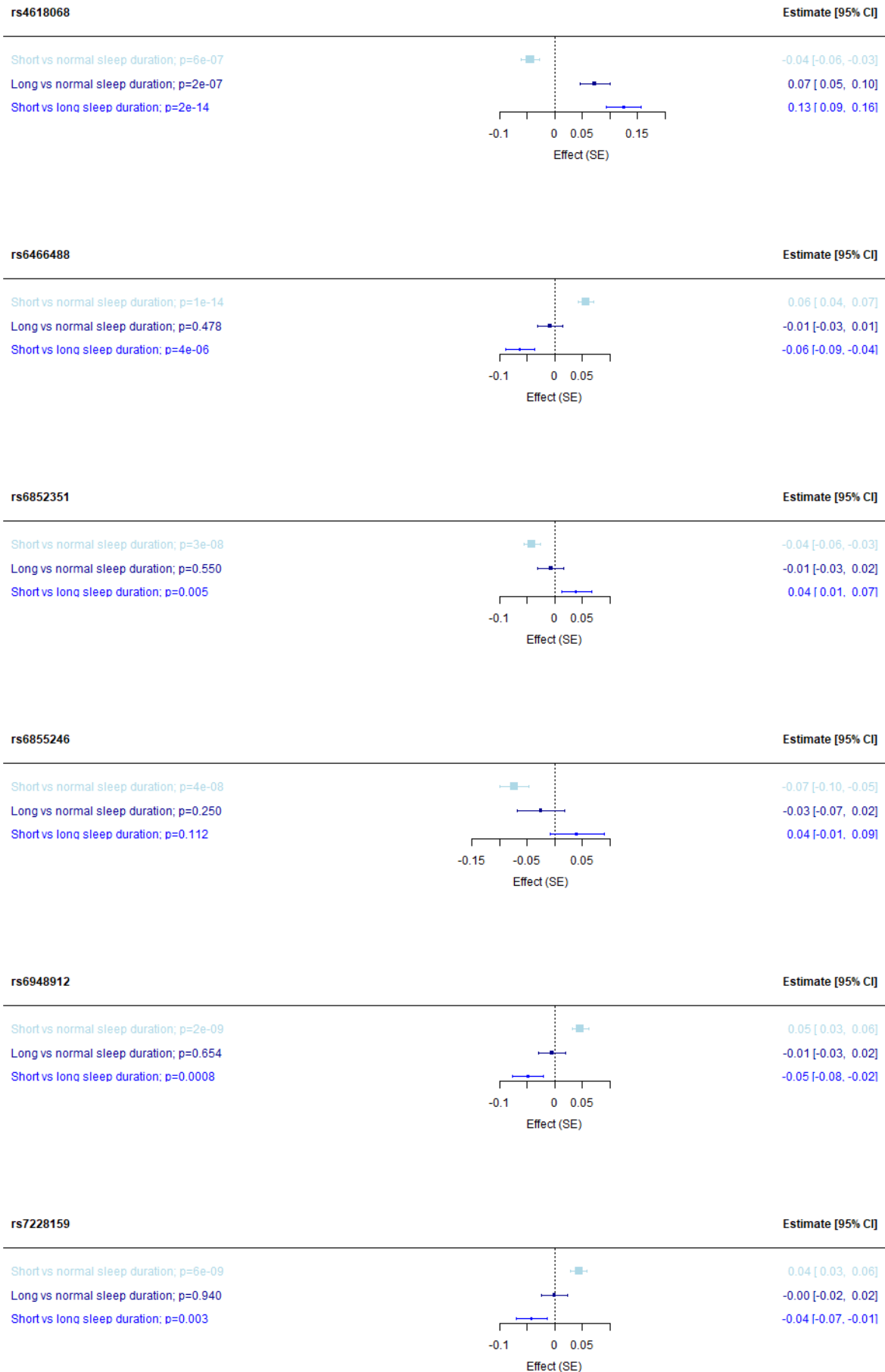
Figure 26 Quantile-quantile plot for short versus long sleep duration in EUR participants from the UKBB and MVP cohorts.



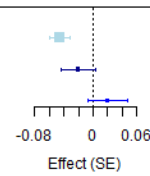
Supplementary Figure 27 Forest plots showing top associations in the short vs normal, long vs normal and short vs long analyses (EUR-only meta-analyses). Forest plots show the beta-coefficient and standard error for each SNP.



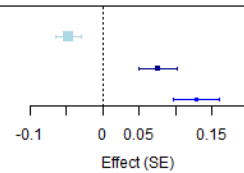




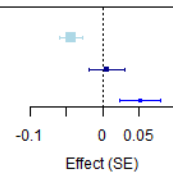
rs7313797	Estimate [95% CI]
Short vs normal sleep duration; $p=1e-10$	-0.05 [-0.06, -0.03]
Long vs normal sleep duration; $p=0.087$	-0.02 [-0.04, 0.00]
Short vs long sleep duration; $p=0.129$	0.02 [-0.01, 0.05]



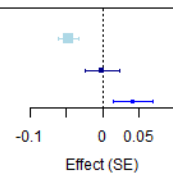
rs7556815	Estimate [95% CI]
Short vs normal sleep duration; $p=8e-08$	-0.05 [-0.06, -0.03]
Long vs normal sleep duration; $p=4e-08$	0.08 [0.05, 0.10]
Short vs long sleep duration; $p=9e-16$	0.13 [0.10, 0.16]



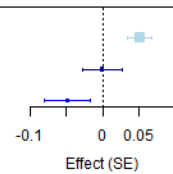
rs10079421	Estimate [95% CI]
Short vs normal sleep duration; $p=1e-08$	-0.04 [-0.06, -0.03]
Long vs normal sleep duration; $p=0.690$	0.00 [-0.02, 0.03]
Short vs long sleep duration; $p=0.0003$	0.05 [0.02, 0.08]



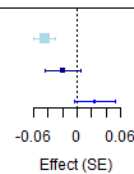
rs10228350	Estimate [95% CI]
Short vs normal sleep duration; $p=3e-10$	-0.05 [-0.06, -0.03]
Long vs normal sleep duration; $p=0.899$	-0.00 [-0.03, 0.02]
Short vs long sleep duration; $p=0.003$	0.04 [0.01, 0.07]

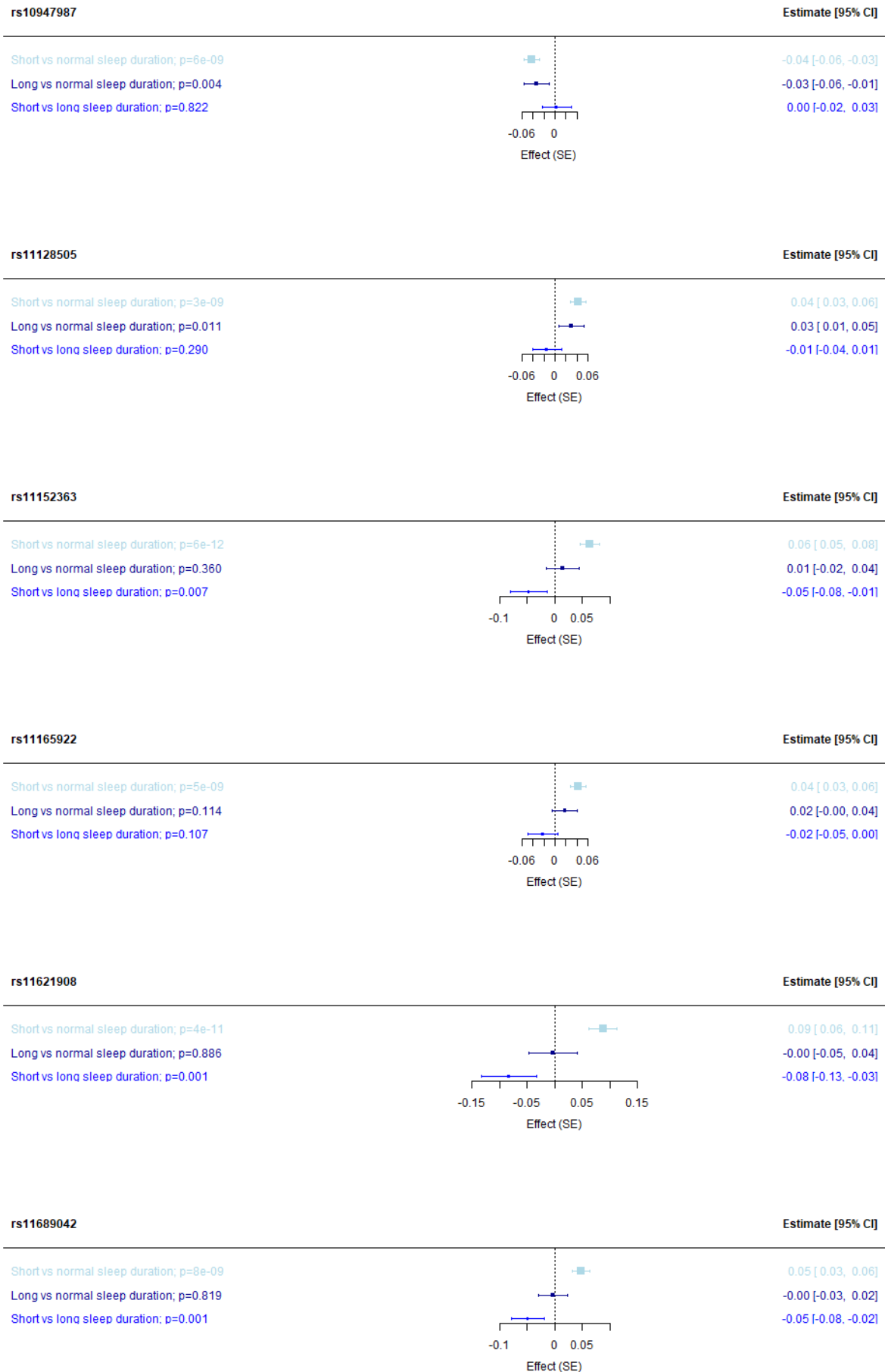


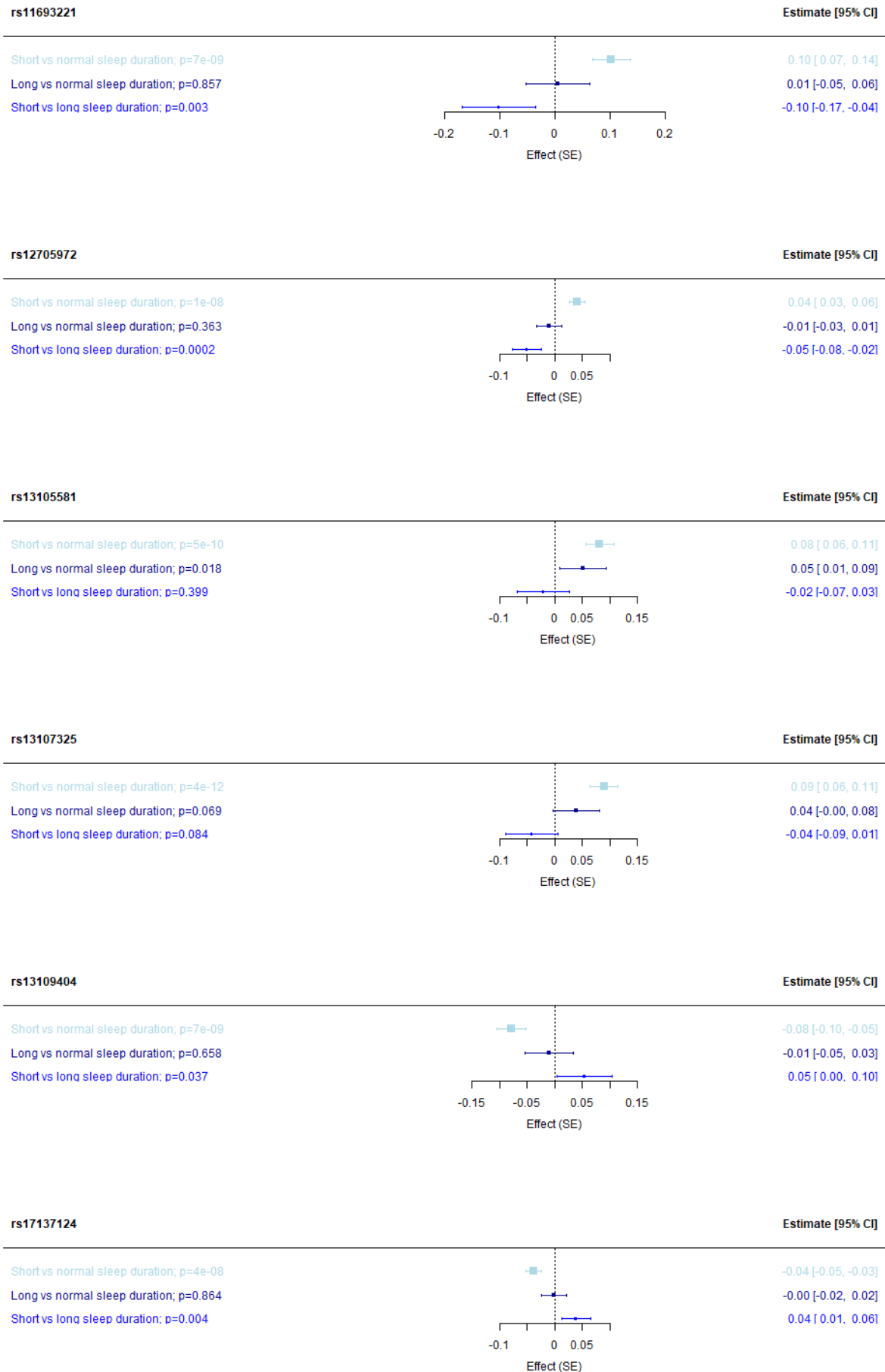
rs10268294	Estimate [95% CI]
Short vs normal sleep duration; $p=6e-09$	0.05 [0.03, 0.07]
Long vs normal sleep duration; $p=0.954$	-0.00 [-0.03, 0.03]
Short vs long sleep duration; $p=0.003$	-0.05 [-0.08, -0.02]



rs10821168	Estimate [95% CI]
Short vs normal sleep duration; $p=5e-09$	-0.04 [-0.06, -0.03]
Long vs normal sleep duration; $p=0.115$	-0.02 [-0.04, 0.00]
Short vs long sleep duration; $p=0.080$	0.02 [-0.00, 0.05]

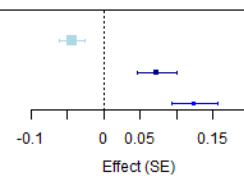






rs56093896 Estimate [95% CI]

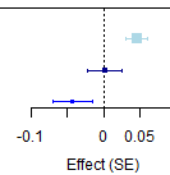
Short vs normal sleep duration; $p=6e-07$
 Long vs normal sleep duration; $p=2e-07$
 Short vs long sleep duration; $p=2e-14$



-0.04 [-0.06, -0.03]
 0.07 [0.05, 0.10]
 0.12 [0.09, 0.16]

rs57537843 Estimate [95% CI]

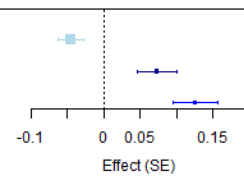
Short vs normal sleep duration; $p=1e-09$
 Long vs normal sleep duration; $p=0.911$
 Short vs long sleep duration; $p=0.002$



0.05 [0.03, 0.06]
 0.00 [-0.02, 0.03]
 -0.04 [-0.07, -0.02]

rs60873293 Estimate [95% CI]

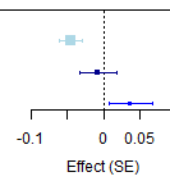
Short vs normal sleep duration; $p=2e-07$
 Long vs normal sleep duration; $p=9e-08$
 Short vs long sleep duration; $p=4e-15$



-0.05 [-0.06, -0.03]
 0.07 [0.05, 0.10]
 0.13 [0.09, 0.16]

rs62144584 Estimate [95% CI]

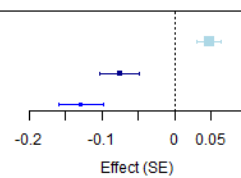
Short vs normal sleep duration; $p=2e-08$
 Long vs normal sleep duration; $p=0.512$
 Short vs long sleep duration; $p=0.014$



-0.04 [-0.06, -0.03]
 -0.01 [-0.03, 0.02]
 0.04 [0.01, 0.07]

rs62158206 Estimate [95% CI]

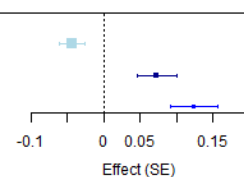
Short vs normal sleep duration; $p=8e-08$
 Long vs normal sleep duration; $p=4e-08$
 Short vs long sleep duration; $p=8e-16$



0.05 [0.03, 0.06]
 -0.08 [-0.10, -0.05]
 -0.13 [-0.16, -0.10]

rs62158211 Estimate [95% CI]

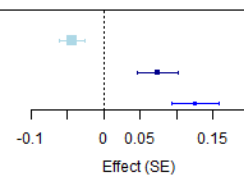
Short vs normal sleep duration; $p=7e-07$
 Long vs normal sleep duration; $p=2e-07$
 Short vs long sleep duration; $p=2e-14$



-0.04 [-0.06, -0.03]
 0.07 [0.05, 0.10]
 0.12 [0.09, 0.16]

rs62158213 Estimate [95% CI]

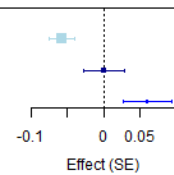
Short vs normal sleep duration; $p=1e-06$
 Long vs normal sleep duration; $p=2e-07$
 Short vs long sleep duration; $p=2e-14$



-0.04 [-0.06, -0.03]
 0.07 [0.05, 0.10]
 0.13 [0.09, 0.16]

rs62442903 Estimate [95% CI]

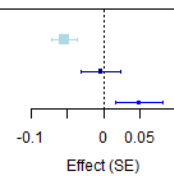
Short vs normal sleep duration; $p=3e-10$
 Long vs normal sleep duration; $p=0.978$
 Short vs long sleep duration; $p=0.0004$



-0.06 [-0.08, -0.04]
 0.00 [-0.03, 0.03]
 0.06 [0.03, 0.09]

rs62442910 Estimate [95% CI]

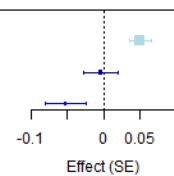
Short vs normal sleep duration; $p=9e-10$
 Long vs normal sleep duration; $p=0.761$
 Short vs long sleep duration; $p=0.003$



-0.05 [-0.07, -0.04]
 -0.00 [-0.03, 0.02]
 0.05 [0.02, 0.08]

rs66571810 Estimate [95% CI]

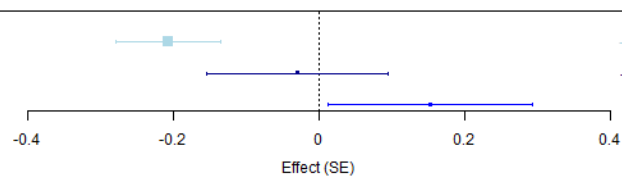
Short vs normal sleep duration; $p=2e-11$
 Long vs normal sleep duration; $p=0.743$
 Short vs long sleep duration; $p=0.0002$



0.05 [0.04, 0.06]
 -0.00 [-0.03, 0.02]
 -0.05 [-0.08, -0.03]

rs71614699 Estimate [95% CI]

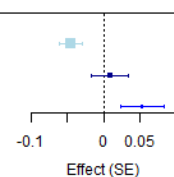
Short vs normal sleep duration; $p=2e-08$
 Long vs normal sleep duration; $p=0.646$
 Short vs long sleep duration; $p=0.033$



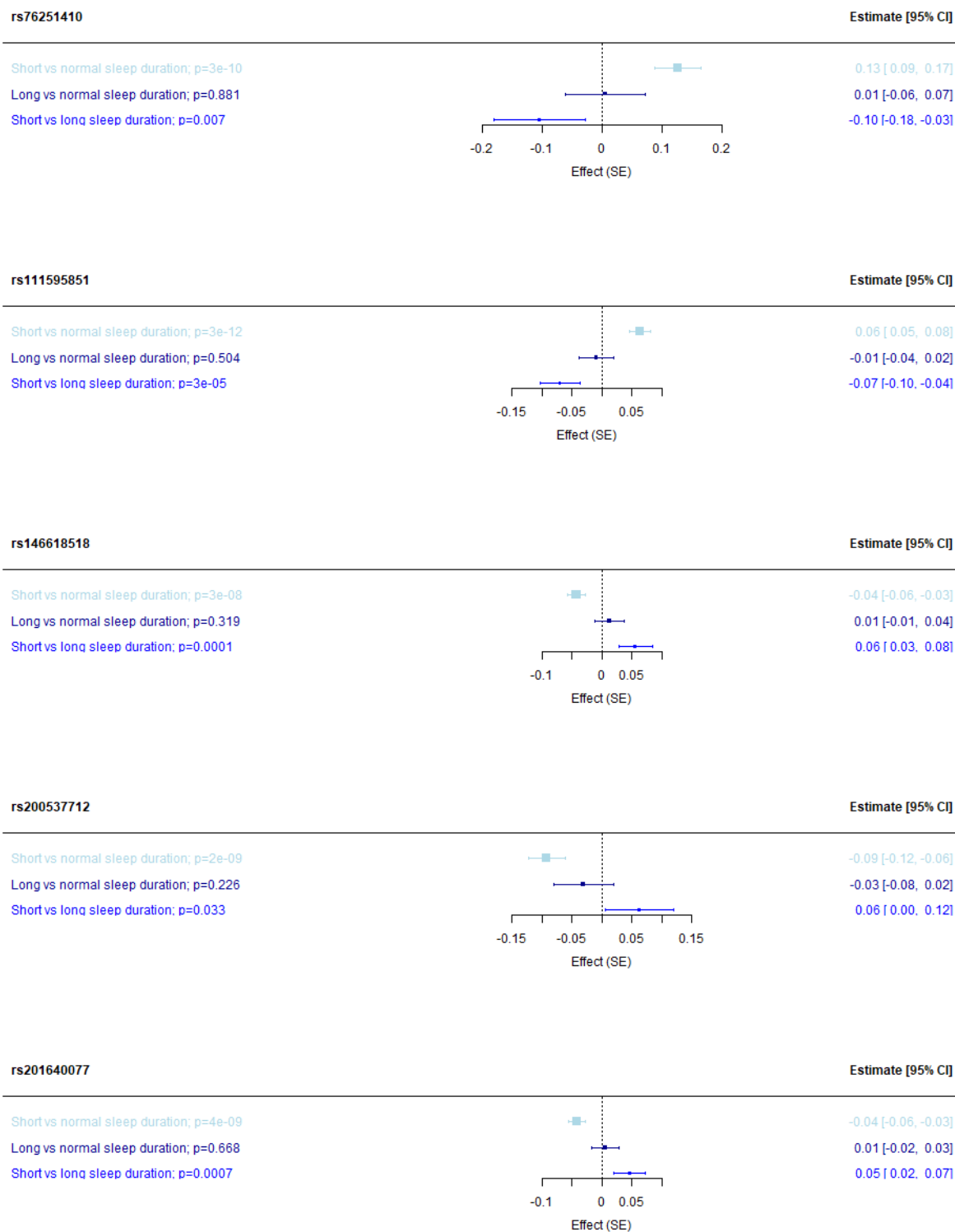
-0.21 [-0.28, -0.13]
 -0.03 [-0.15, 0.10]
 0.15 [0.01, 0.29]

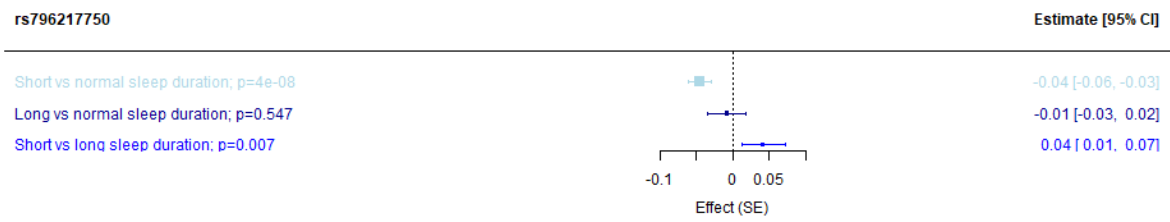
rs72629492 Estimate [95% CI]

Short vs normal sleep duration; $p=3e-08$
 Long vs normal sleep duration; $p=0.490$
 Short vs long sleep duration; $p=0.0004$



-0.04 [-0.06, -0.03]
 0.01 [-0.02, 0.03]
 0.05 [0.02, 0.08]



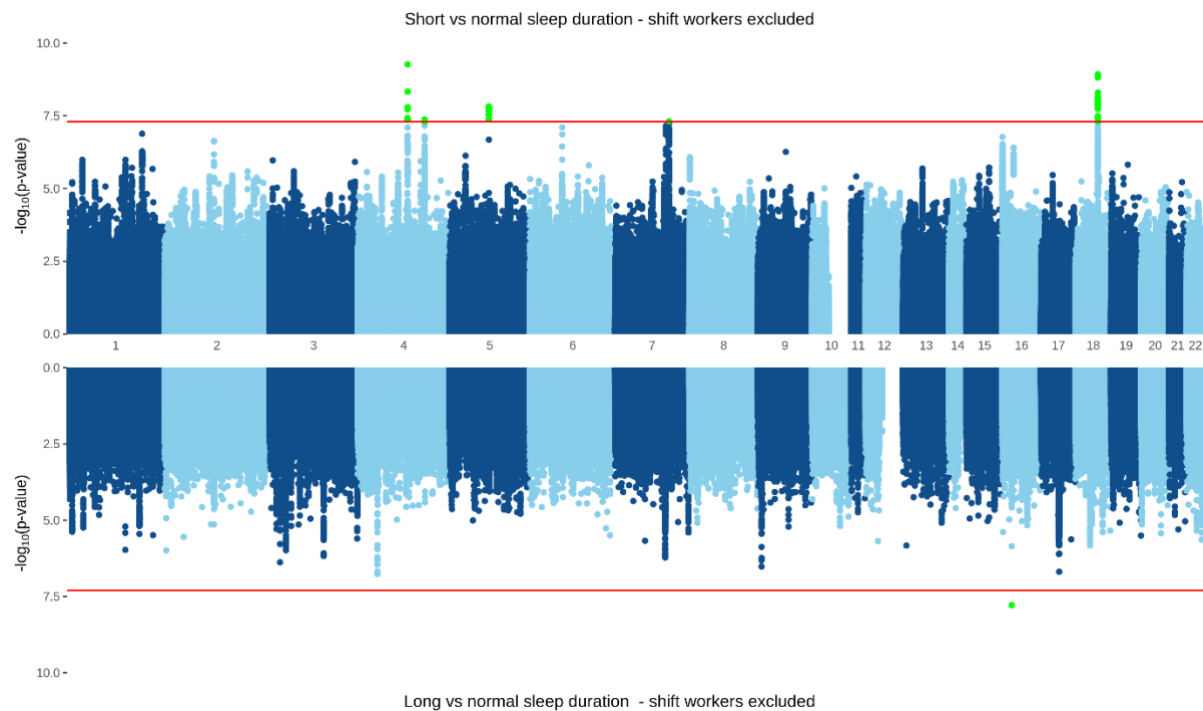


3. Analysis with nightshift workers excluded

We extracted information on all those participants who responded ‘Usually’ or ‘Always’ to the question “Does your work involve night shifts?” (data field 3426; question asked to 51,930 participants who indicated that their work involved shift patterns at least occasionally). A total of 11,087 individuals indicated that their job usually or always involved night shift work, and we re-ran our main analyses on short versus normal and long versus normal sleep duration with these participants excluded. This resulted in a total of N=18,284 short sleep cases, N= 6,445 long sleep cases and N= 250,079 controls. The mirrored Manhattan plots for short (top) and long (bottom) are below (Supplementary Figure 28).

We calculated the genetic correlation (r_g) between our primary analyses and these sub-analyses and found the r_g to be very close to 1 in both cases (r_g short sleep with and without night shift workers = 0.99, SE 0.008, $p=0$; r_g long sleep with and without night shift workers = 1.02, SE 0.0012, $p=0$ (Supplementary Figure 31). The correlation between long and short sleep duration in this subpopulation was 0.23 (SE=0.060, $p=0.0001$, as compared to r_g 0.24 (SE 0.060, $p=4.74 \times 10^{-5}$ between long and short sleep in the main UK Biobank analysis). Given this near perfect genetic correlation. And considering additional challenges in accessing the necessary phenotype data in the MVP sample, we have conducted this sub-analysis in the UK Biobank cohort only.

Supplementary Figure 28 Mirrored Manhattan plot showing genetic associations with short sleep duration (top) and long sleep duration (bottom) in EUR UK Biobank participants, with participants who report working nightshifts excluded. Loci reaching genome-wide significance threshold of 5×10^{-8} highlighted in green.



4. Sex-stratified analysis

We conducted further sub-analyses in male only and female only populations. In the UK Biobank only analysis, both sex-stratified analyses were underpowered (female short sleep cases = 10,662, female long sleep cases = 3,565, female controls = 136,242; male short sleep cases = 8,379, male long sleep cases = 2,989, and male controls = 117,978) (Supplementary Figure 29) and revealed no genome-wide significant associations. The genetic correlation for between these sex-stratified analyses and the main analyses were over 0.97 in all cases (Supplementary Figure 31).

Supplementary Figure 29 Mirrored Manhattan plot showing genetic associations with short sleep duration (top) and long sleep duration (bottom) in female only EUR UK Biobank participants. Loci reaching genome-wide significance threshold of 5×10^{-8} highlighted in green.

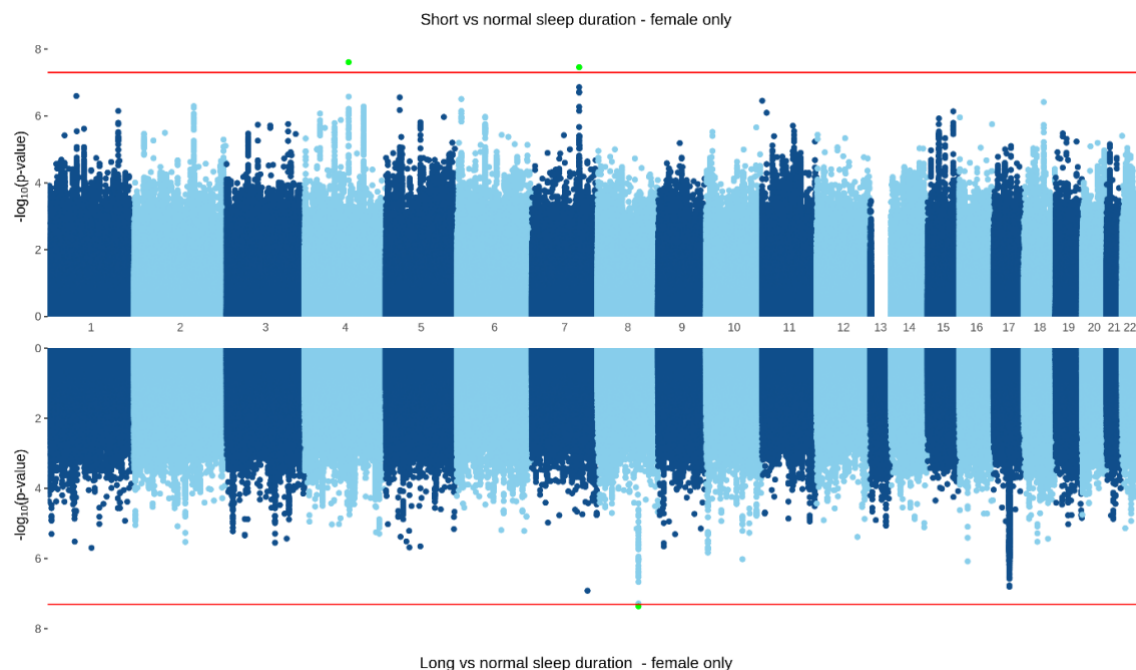
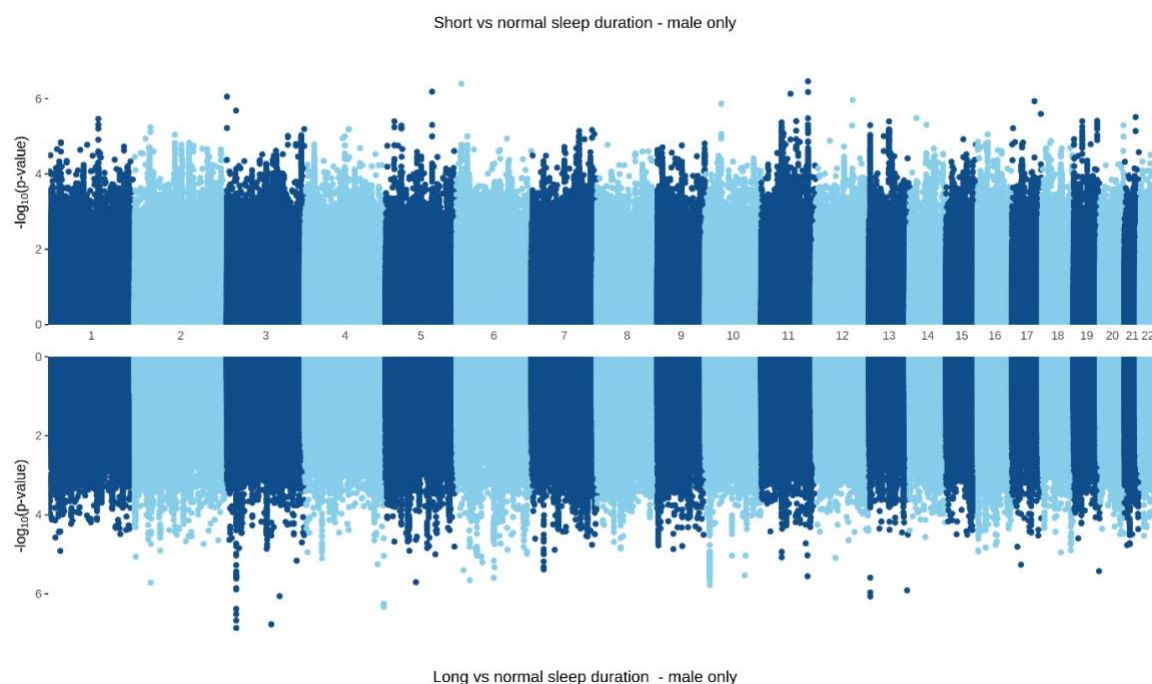


Figure 30 Mirrored Manhattan plot showing genetic associations with short sleep duration (top) and long sleep duration (bottom) in male only EUR UK Biobank participants.



5. Comparison of results between primary EUR analyses and sensitivity analyses

Genetic correlation between main analyses

We calculated the genetic correlation between our main analyses, and the analyses excluding shift workers and stratified by sex. Across all comparisons, the patterns of genetic correlation are very similar. The genetic correlation between all analyses of short sleep is 0.98 or greater. The genetic correlation between all analyses of long sleep is 0.90 or greater. This lower score of 0.90 is between male and female long sleepers.

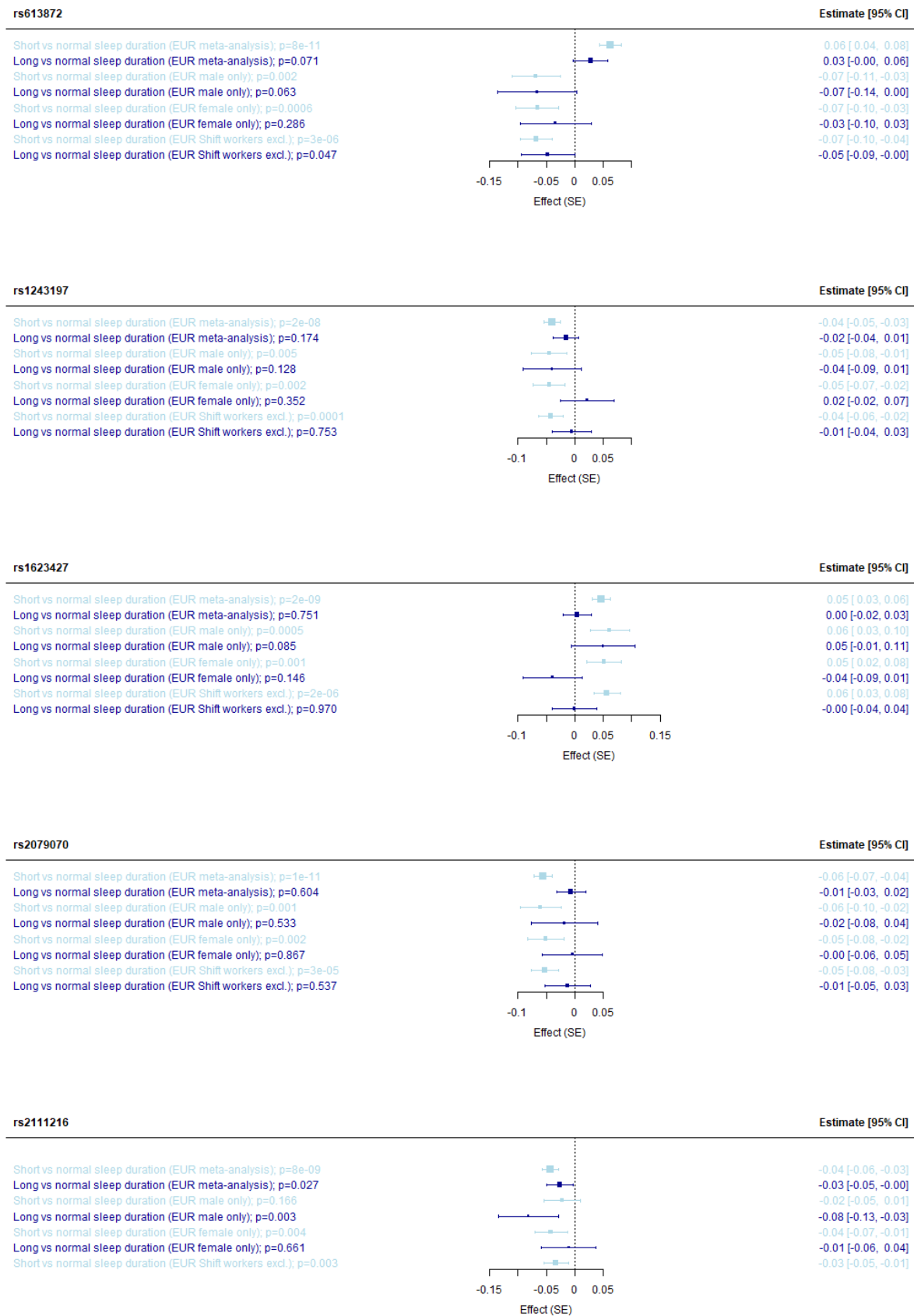
Similarly, the patterns of genetic correlation between long and short sleep are consistent across all groups, being 0.24 (SE=0.06) in the main analysis, 0.23 (SE=0.06) in the shift worker excluded analysis, 0.32 (SE=0.12) in the male only analysis and 0.26 (SE=0.11) in the female only analysis.

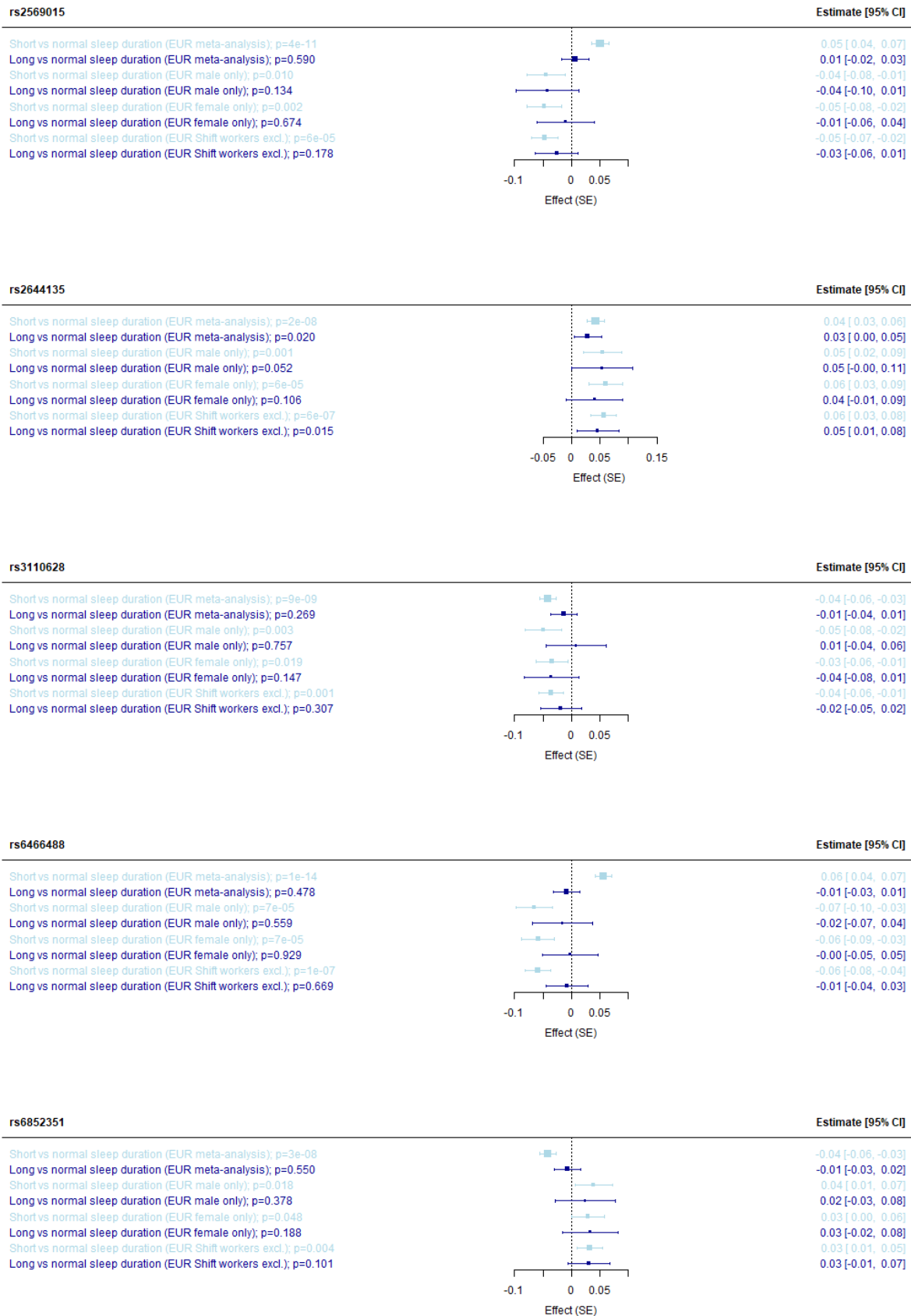
These findings indicate that the genetic architecture of both long and short sleep duration is independent from sex.

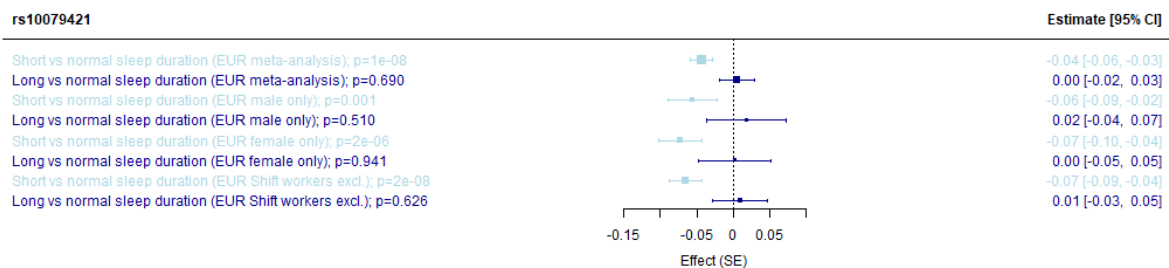
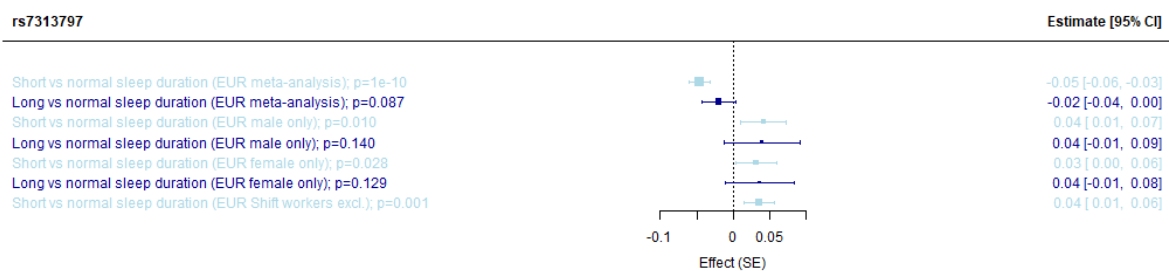
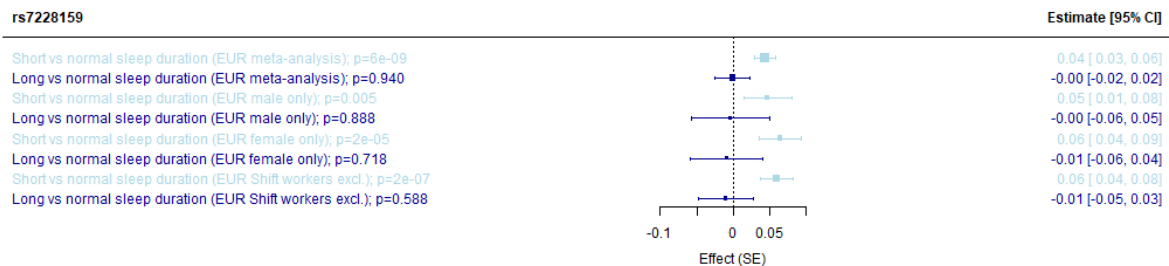
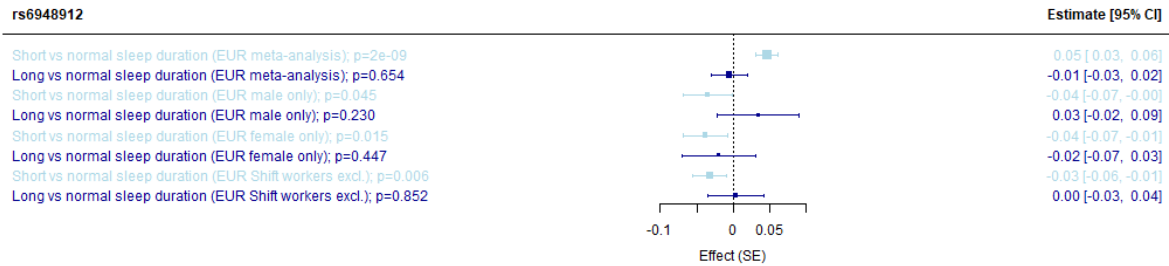
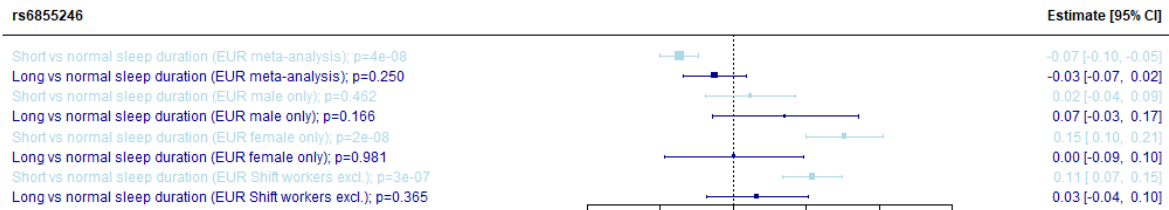
Supplementary Figure 31 Genetic correlation analysis between primary analyses of short and long sleep duration and sensitivity analyses of a) shift workers excluded and b) stratified by sex. Darker shades indicate stronger correlation.

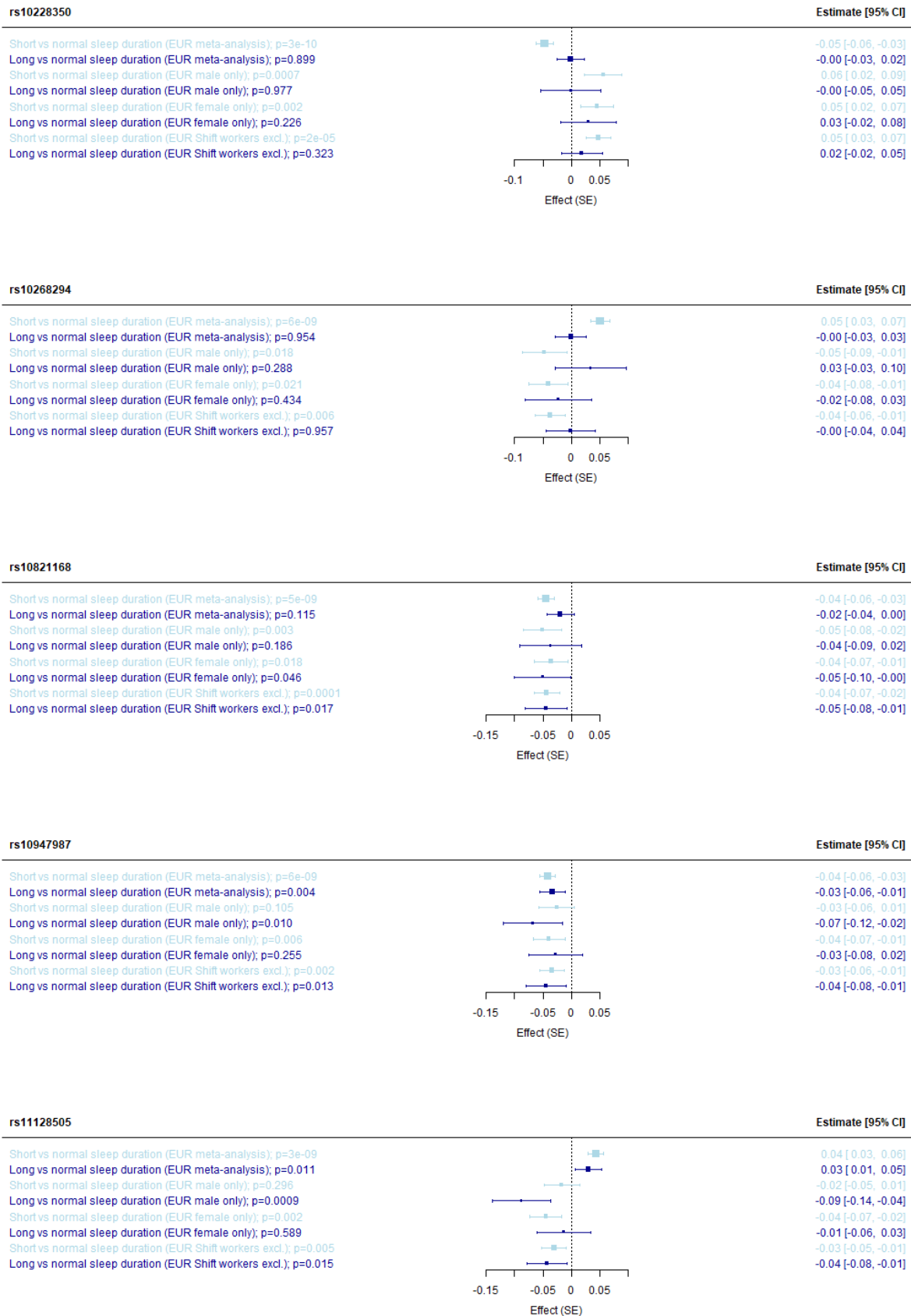
	Short sleep - main analysis	Short sleep - shift workers excluded	Short sleep - male only	Short sleep - female only	Long sleep - main analysis	Long sleep - shift workers excluded	Long sleep - male only	Long sleep - female only
Short sleep - main analysis		1.00 (0.0008); p=0	0.99 (0.022); p=0	1.00 (0.013); p=0	0.24 (0.060); p=4.74e-05	0.22 (0.067); p=0.0008	0.22 (0.09); p=0.0194	0.25 (0.078); p=0.0014
Short sleep - shift workers excluded	1.00 (0.0008); p=0		1.00 (0.026); p=0	1.01 (0.013); p=0	0.26 (0.067); p=0.0001	0.23 (0.060); p=0.0001	0.28 (0.096); p=0.0041	0.23 (0.086); p=0.0077
Short sleep - male only	0.99 (0.022); p=0	1.00 (0.026); p=0		0.98 (0.067); p=7.83e-48	0.27 (0.09); p=0.0026	0.26 (0.094); p=0.0051	0.32 (0.12); p=0.0093	0.22 (0.13); p=0.073
Short sleep - female only	1.00 (0.013); p=0	1.01 (0.013); p=0	0.98 (0.067); p=7.83e-48		0.24 (0.078); p=0.0019	0.21 (0.086); p=0.015	0.20 (0.11); p=0.078	0.26 (0.11); p=0.014
Long sleep - main analysis	0.24 (0.060); p=4.74e-05	0.26 (0.067); p=0.0001	0.27 (0.09); p=0.0026	0.24 (0.078); p=0.0019		1.00 (0.0012); p=0	0.98 (0.068); p=1.77e-47	0.97 (0.049); p=2.24e-87
Long sleep - shift workers excluded	0.22 (0.067); p=0.0008	0.23 (0.060); p=0.0001	0.26 (0.094); p=0.0051	0.21 (0.086); p=0.015	1.00 (0.0012); p=0		1.01 (0.079); p=4.48e-38	0.99 (0.06); p=1.051e-60
Long sleep - male only	0.22 (0.09); p=0.0194	0.28 (0.096); p=0.0041	0.32 (0.12); p=0.0093	0.20 (0.11); p=0.078	0.98 (0.068); p=1.77e-47	1.01 (0.079); p=4.48e-38		0.90 (0.22); p=6.13e-05
Long sleep - female only	0.25 (0.078); p=0.0014	0.23 (0.086); p=0.0077	0.22 (0.13); p=0.073	0.26 (0.11); p=0.014	0.97 (0.049); p=2.24e-87	0.99 (0.06); p=1.051e-60	0.90 (0.22); p=6.13e-05	

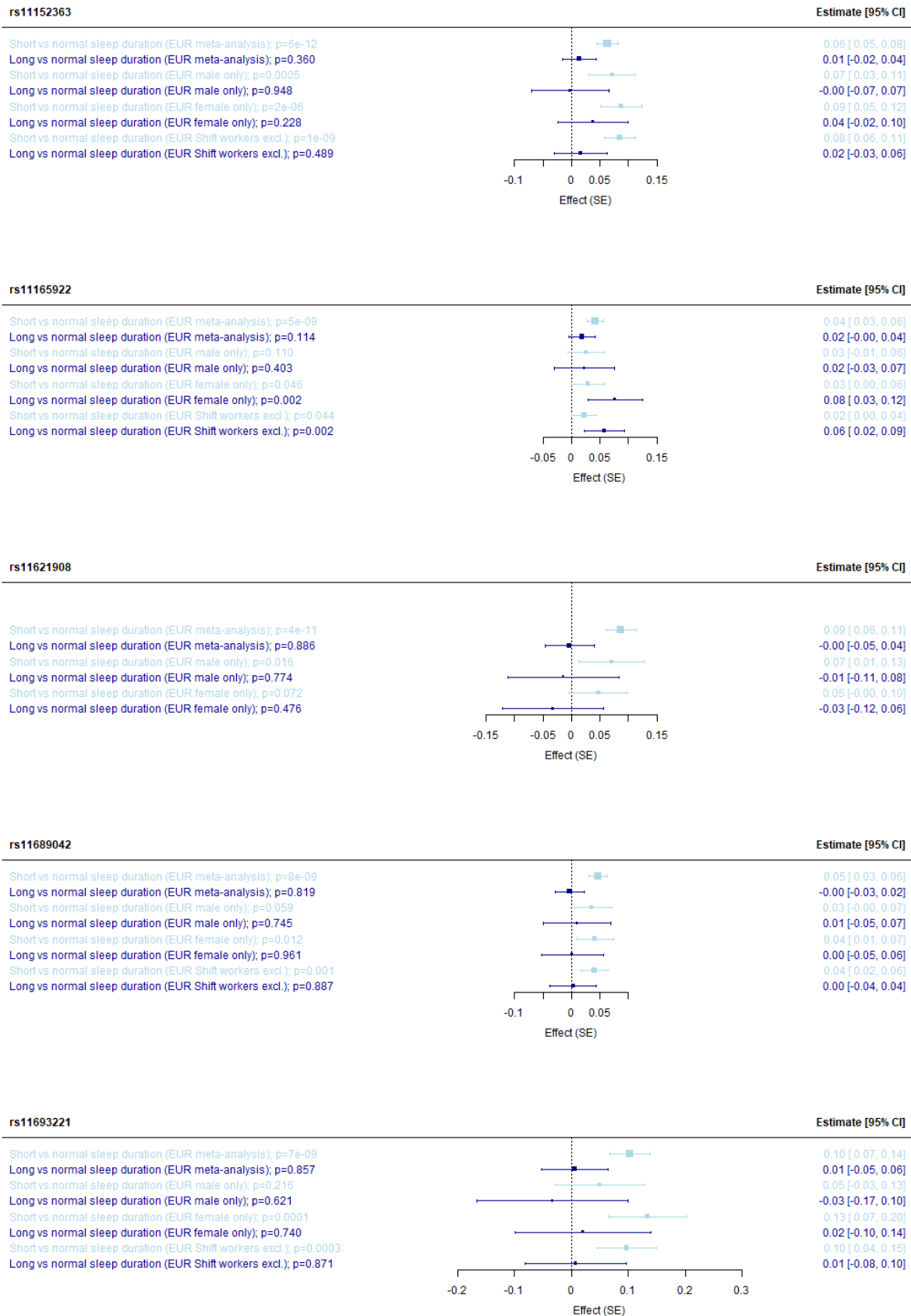
Figure 32 Forest plots for genome-wide significant associations from EUR meta-analysis of short vs normal and long vs normal sleep duration in MVP and UKBB samples, and the same association in the UKBB only sensitivity analyses (shift-workers excluded and sex-stratified). Forest plots show the beta-coefficient and standard error for each SNP.

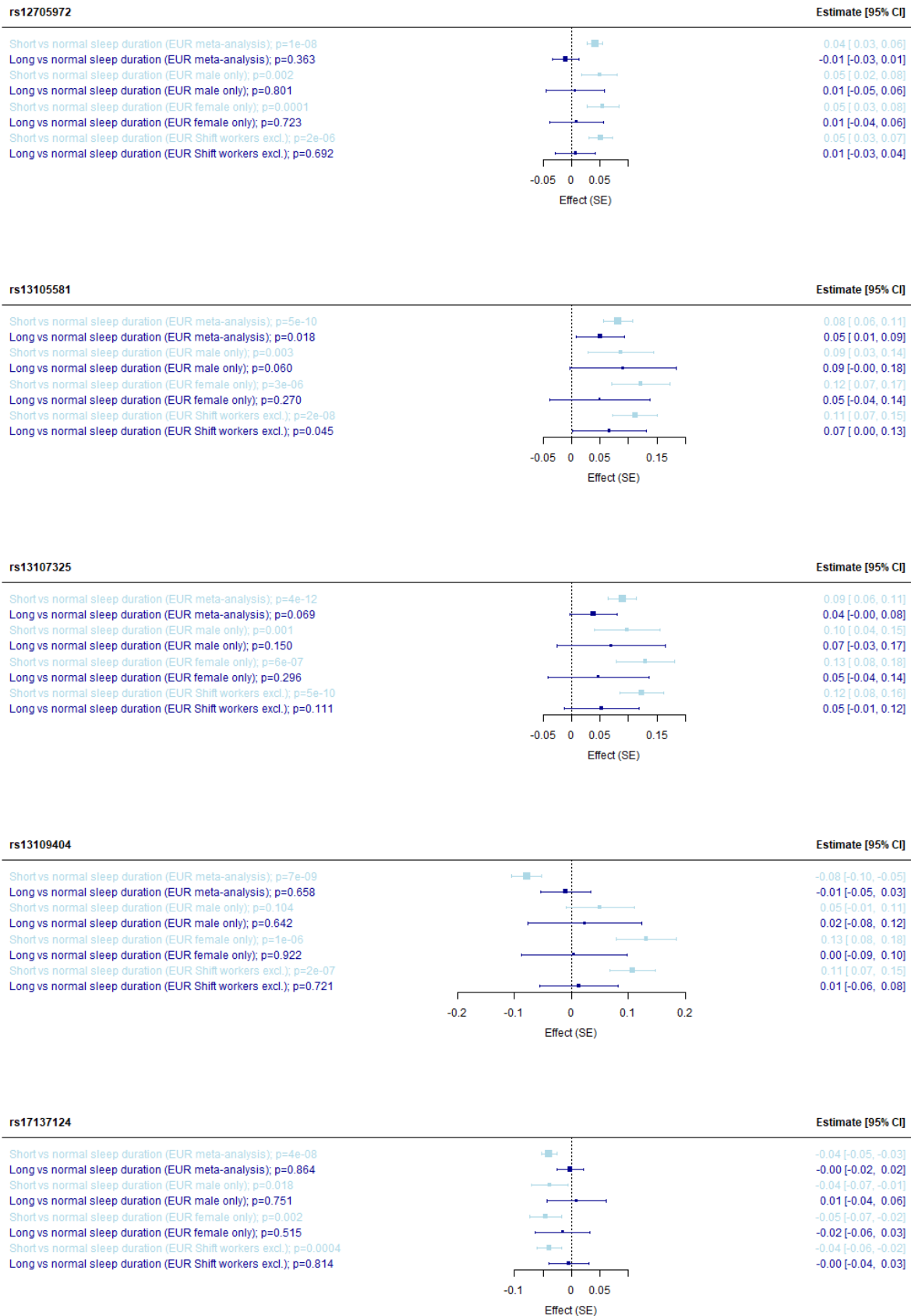


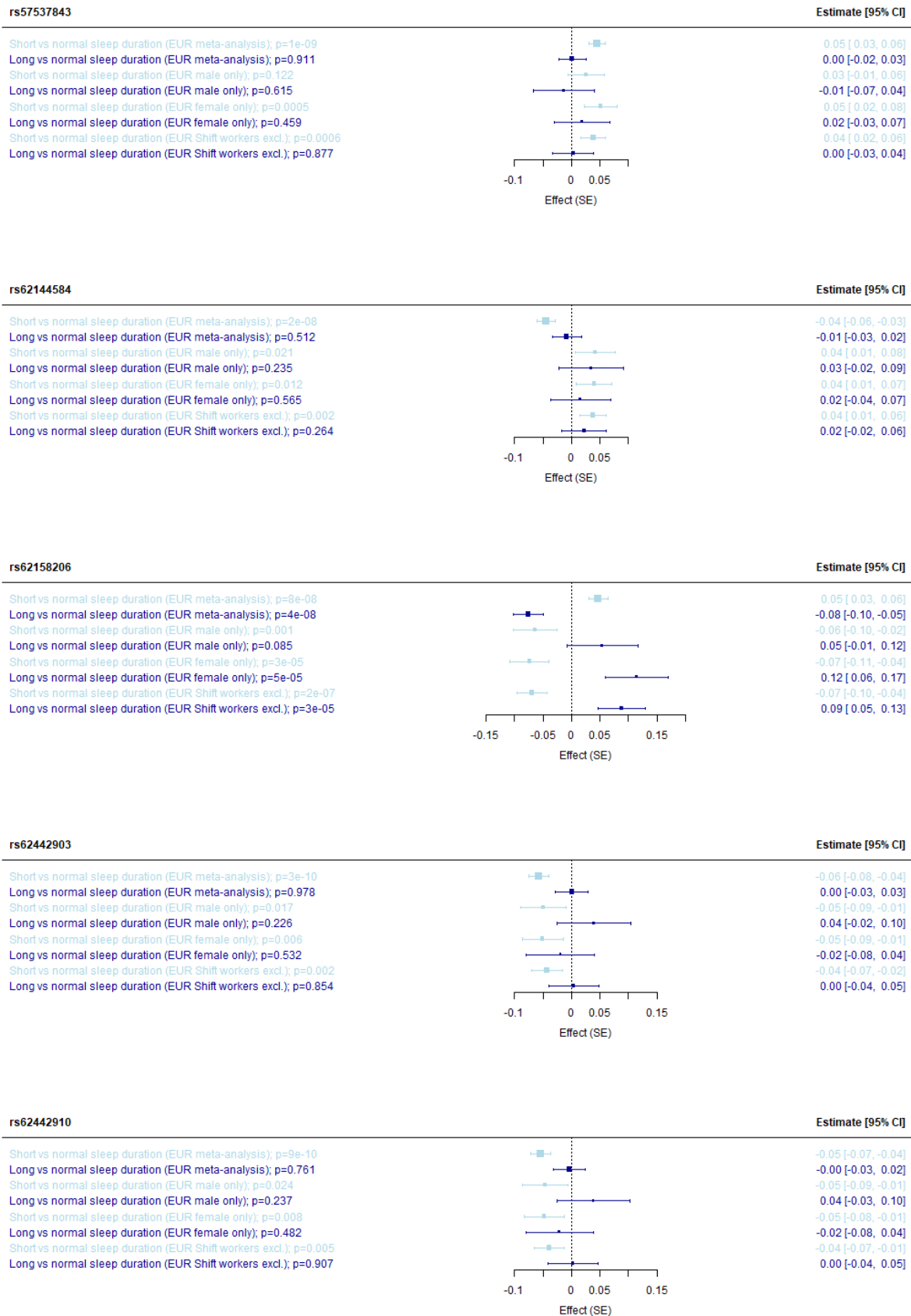


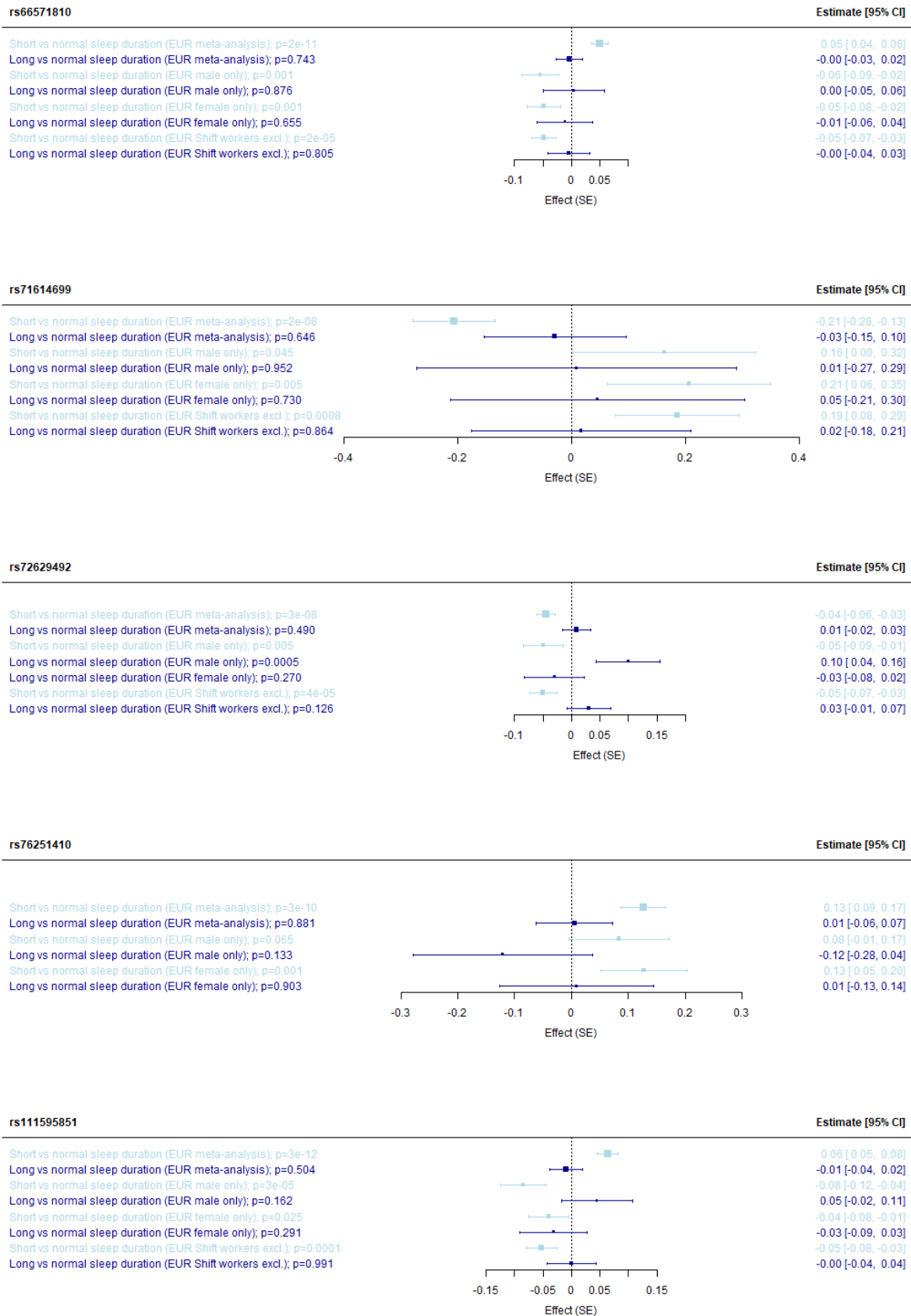


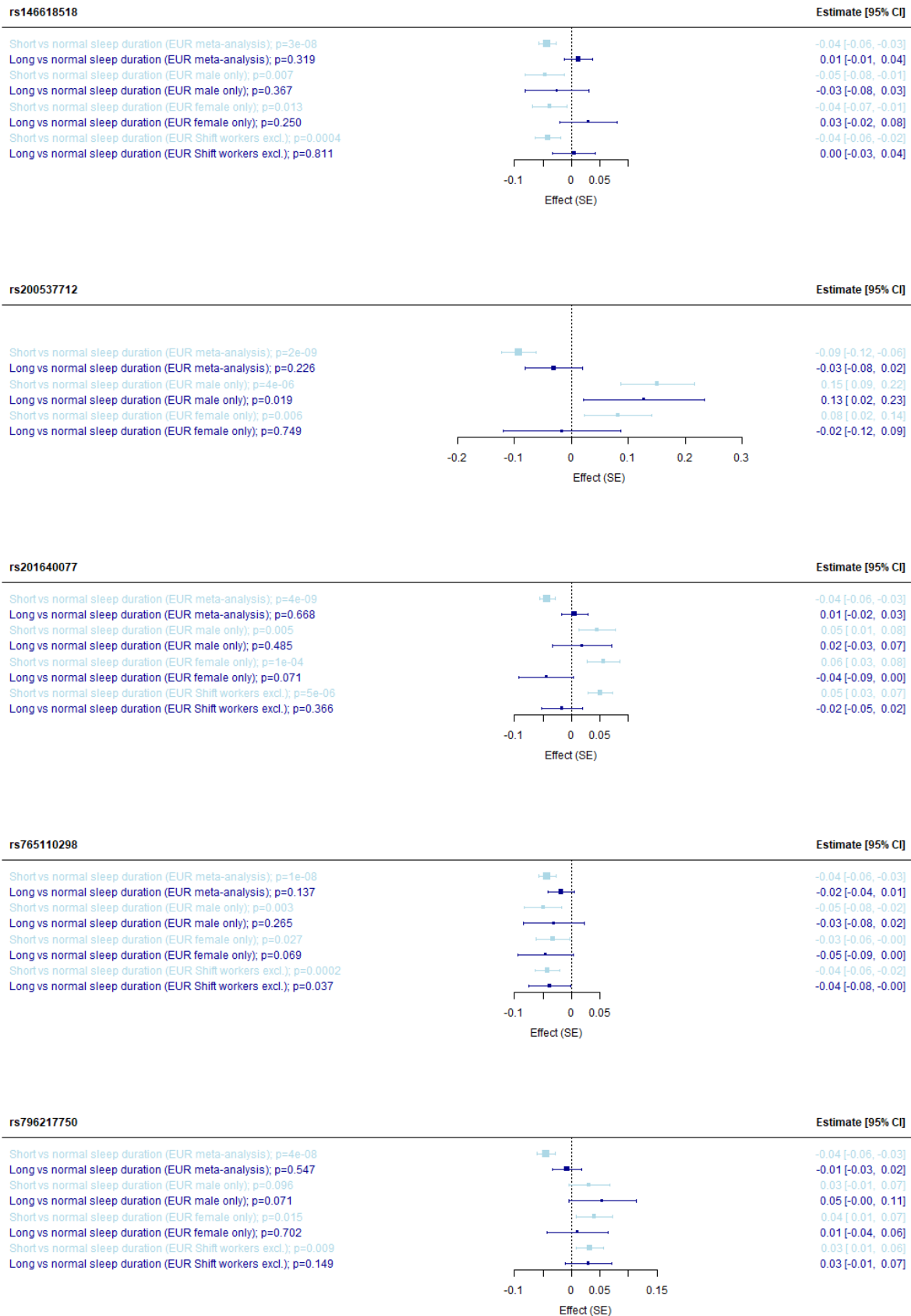












6. Ingenuity Pathways Analysis: Results

The top significantly enriched canonical pathway for short sleep was DNA Methylation and Transcriptional Repression Signaling, followed by the Complement System, molecular mechanisms of cancer, caveolar-mediated endocytosis signaling and synaptogenesis signaling pathway. For long sleep the top findings were reelin signaling in neurons, semaphoring neuronal repulsive signaling pathway, breast cancer regulation by stathmin 1, cAMP-mediated signaling, and glutaryl-CoA degradation (supplementary table 28).

7. Replication of previously published significant associations in the MVP sample.

A previously published GWAS of sleep duration in European UK Biobank sample revealed several GWS risk loci for short sleep (<7 hours; 27 significant loci), long sleep (>8 hours; 8 significant loci) and sleep as a quantitative trait (from 0-24 hours) (78 significant loci) (14). Note that the definitions of short and long sleep differ slightly from our own. As noted in the main text, we did not assess the sleep data from MVP as a continuous trait. We used the European MVP-only GWAS to provide an independent replication sample for previously published GWAS assessing self-reported sleep duration as both a binary and quantitative trait in 446,118 European UK Biobank subjects¹ (7). For this analysis, we considered a locus replicated if it reached a nominal significance threshold of $p < 0.05$ in the MVP GWAS. Where SNPs were not present in MVP, we investigated SNPs in high LD ($r^2 > 0.8$) for replication, using 1000 Genomes Project European population as a reference panel. Where the primary study investigated sleep as a continuous trait, we considered a locus as replicated in our sample where the odds ratio was in the opposite direction for short sleep, and a consistent direction for long sleep.

Of the 27 significant loci for short sleep duration, 17 were present in our study. We were able to identify reliable LD proxies for seven additional SNPs, leaving a total of three that could not be assessed in our data. A total of 10 reach a significance threshold of at least $p < 0.05$ in an independent sample of 158,222 EUR subjects from the MVP GWAS for short sleep duration (with a more stringent definition of <6 hours sleep) with same effect direction. In addition, two loci were significantly associated with long sleep in our MVP data, with an opposite direction of effect to that observed in the primary study of short sleep duration (see supplementary tables 17 and 18).

Of the eight loci significant associated with long sleep in (14), five are present in our MVP data, and we were able to identify a reliable LD proxy for a further two. One locus, rs549961083 on chromosome five, could not be assessed. None of these seven loci were replicated in our study of long sleep duration. However, two of these loci (rs4585442 on chromosome 5, and rs1229762 on chromosome 7) are significantly associated with short sleep duration in the MVP sample, with an opposite direction of effect to that reported in the original study of long sleep (see supplementary tables 19 and 20)

In addition to considering long and short sleep as binary traits, Dashti *et al* (14) conducted a GWAS of sleep as a quantitative continuous measure, for which they identify 78 GWS loci. A total of 58 of these loci were present in our MVP data, and we identified reliable LD proxies for further 12. Eight of these loci could not be assessed in our data. Of those 78 significant associations with continuous sleep duration, we replicate a total of 18 of these associations in our MVP GWAS on short sleep, and three in our MVP GWAS on long sleep (see supplementary tables 21 and 22).

¹ Dashti HS, Jones SE, Wood AR, Lane JM, van Hees VT, Wang H, et al. Genome-wide association study identifies genetic loci for self-reported habitual sleep duration supported by accelerometer-derived estimates. Nat Commun. 2019;10(1):1100.

