

AMP-DCC Data Analysis Report

BioMe

Complications Phase 2

03/16/2020 (18:37)

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This document was generated using Loamstream [10] and the AMP-DCC Data Analysis Pipeline [11]

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1 Data

In order to run the data we received through our analysis pipeline in an efficient manner, the genotype arrays were each given a short code name; EX, ILL, and AFFY. In Table 1, we list the corresponding filename of the data set we received, the format of the file set (*note: 'bfile' refers to binary Plink format [1]*), and a liftOver [2] chain file if it was required to remap the variants to GRCh37 / hg19 coordinates.

See Figures 1 and 2 for intersection counts of samples and variants available for analysis. The counts for each genotype array have been broken down by inferred ancestry as well.

Table 1: Genotype array information

ID	Filename	Format	LiftOver
EX	BioMe_EXOMECHIP	bfile	N/A
ILL	BioMe_ILLUMINA	bfile	N/A
AFFY	BioMe_AFFY	bfile	N/A

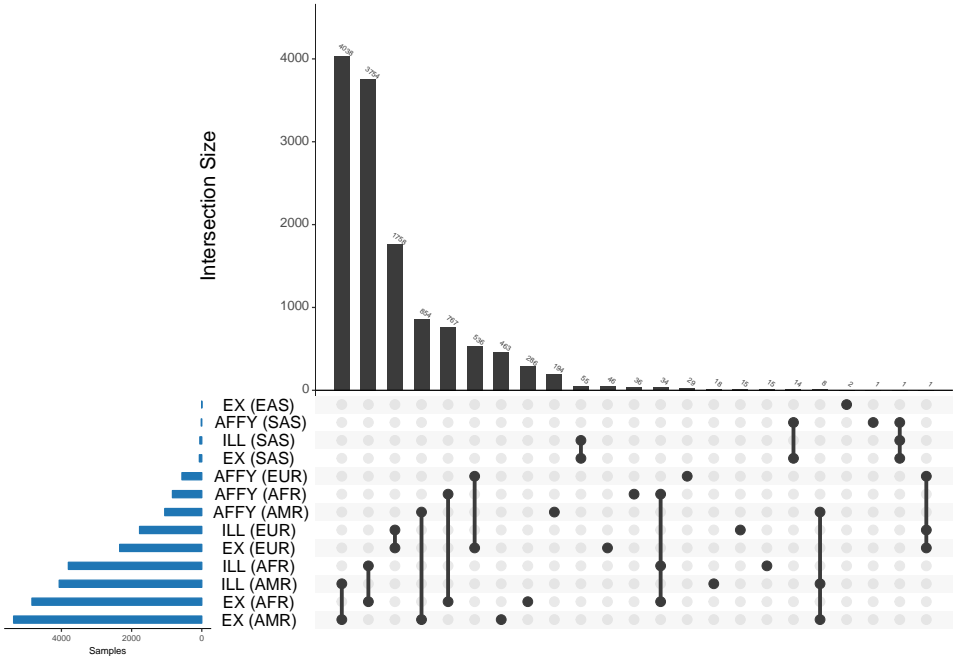


Figure 1: Samples remaining for analysis after quality control

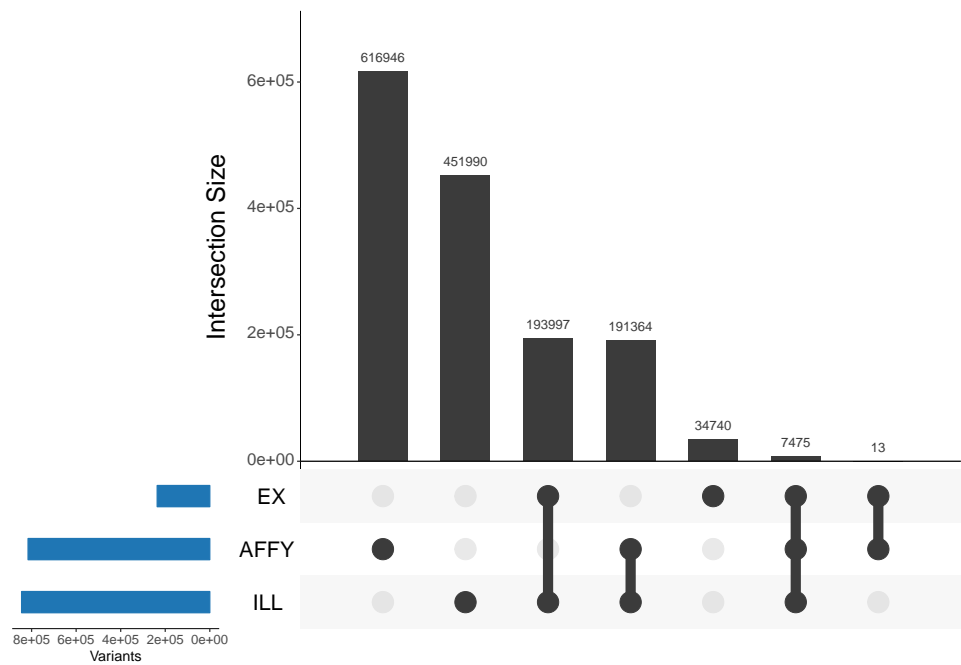


Figure 2: Variants remaining for analysis after quality control

2 Strategy

2.1 Sample structure and pipeline

The strategy we used to perform association testing can be found below. The 'ID' columns are the names used to identify each set of association test results in this document. The 'Report' columns indicate whether or not that particular set of association results will be presented in the tables and plots of the proceeding sections.

2.1.1 Cohort-level analysis

In Table 2, all of the cohorts available for analysis are defined. Each cohort was defined by a single array and one or more ancestral populations.

Table 2: Cohort-level analysis

ID	Array	Ancestry	Report
EX_EUR	EX	EUR	NO
EX_AFR	EX	AFR	NO
EX_AMR	EX	AMR	NO
ILL_EUR	ILL	EUR	NO
ILL_AFR	ILL	AFR	NO
ILL_AMR	ILL	AMR	NO
AFFY_EUR	AFFY	EUR	NO
AFFY_AFR	AFFY	AFR	NO
AFFY_AMR	AFFY	AMR	NO

2.1.2 Meta-analysis

Table 3 defines any meta-analyses performed on the cohorts. Each cohort that was included is detailed along with the number of samples removed prior to cohort-level association testing. In order to identify samples that needed to be removed due to relatedness across cohorts, the cohorts genotypes were first merged on common variants. Then, autosomal variants with $MAF \geq 0.01$ and $callrate \geq 0.98$ were extracted and kinship values were calculated using King [4] with the '--kinship' flag. The reference cohort, the first one listed, maintained all of its samples. Starting from the last listed cohort, any samples shown to have some relation ($kinship \geq 0.0884$) to a sample from any preceding cohort was removed. This was continued until all cohorts subsequent to the reference cohort had been processed.

Table 3: Meta-analysis

ID	Cohort	KinshipRemove	Report
META_EX	EX_EUR	0	NO
	EX_AFR	0	
	EX_AMR	49	
META_GWAS	ILL_EUR	0	NO
	ILL_AFR	0	
	ILL_AMR	0	
	AFFY_EUR	8	
	AFFY_AFR	143	
	AFFY_AMR	188	

2.1.3 Merged results

In order to present results in a comprehensive way, we identified a single reference set of results as the default and merged in results from other arrays where either the variant failed to provide a p -value or did not exist in the reference set. Table 4 describes the merges performed. The '>' symbol in the 'Cohorts/Metas' column implies the strategy used to combine the results. The left-most results set was kept as reference, while variants from the following set were merged in where applicable. This merge was repeated (ie. additively) for all sets listed from left to right.

Table 4: Merged results

ID	Cohorts/Metas	Report
MERGE	META_EX>META_GWAS	YES

2.2 Ancestry Adjustment and Outlier Removal

Adjusting the statistical models for underlying ancestry is often crucial to reduce or eliminate Type 1 error. Often analysts include principal components of ancestry as covariates in their models as a matter of convention. In our case, we undertook a more nuanced approach. First, the top 10 PC's were calculated for each cohort using the PC-AiR method [3]. Then, the phenotype of interest was regressed on the covariates to be used in the model

and all of the PC's. If the N th PC exhibited a statistically significant p -value ($p \leq 0.05$), we selected PC's $1 - N$ to be included in association testing. Once determined, any sample lying outside 6 standard deviations from the mean on any of the N PC's was marked as an outlier and removed from the sample set. This process was repeated up to a maximum of ten times until no outliers were found, resulting in more homogeneous sample sets for each particular analysis. For this project, a hard minimum of 0 PC's to be included in analysis was set by the analyst.

3 Coronary Artery Disease in samples with T2D (CADinT2Dcases)

3.1 Summary

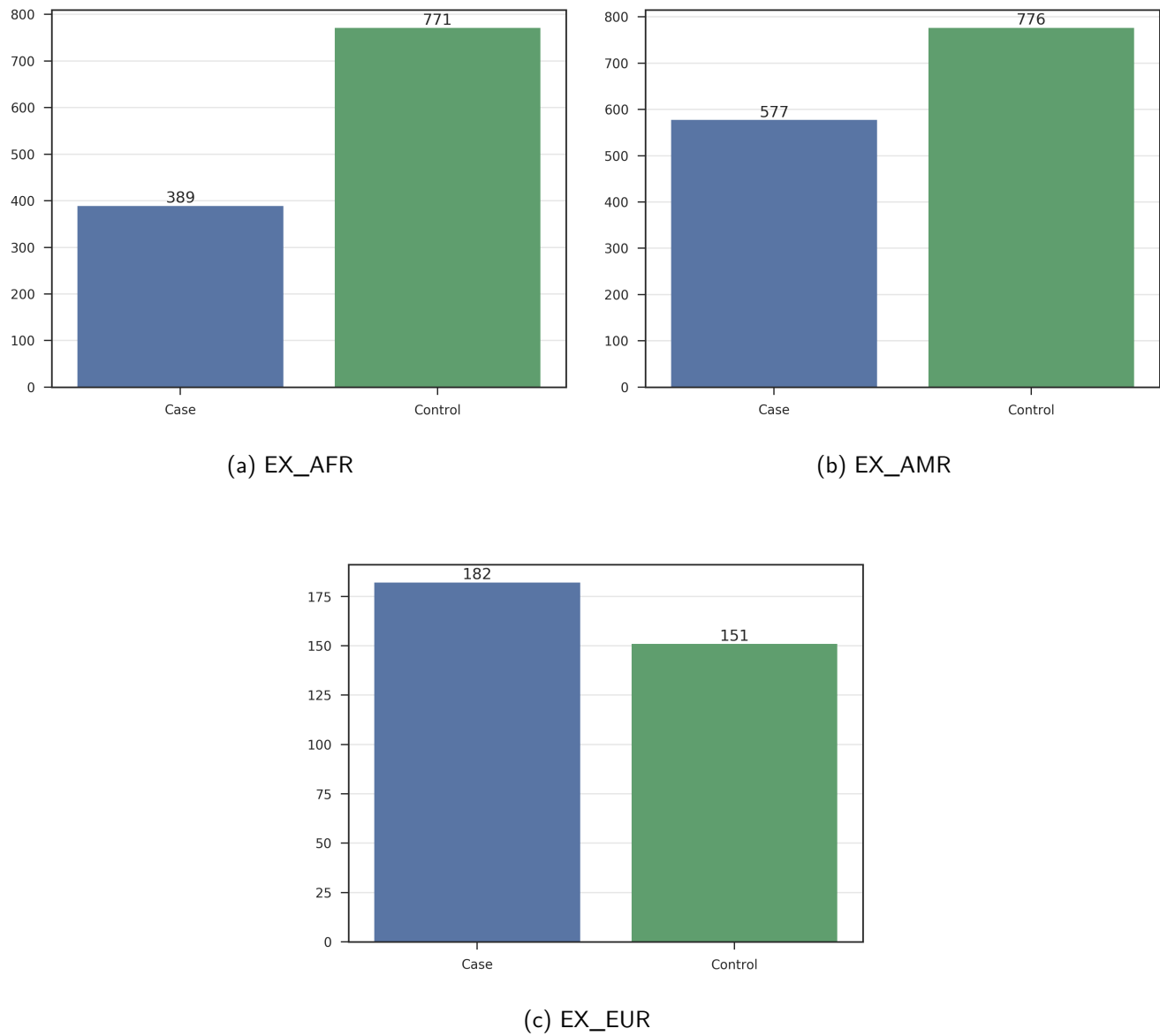
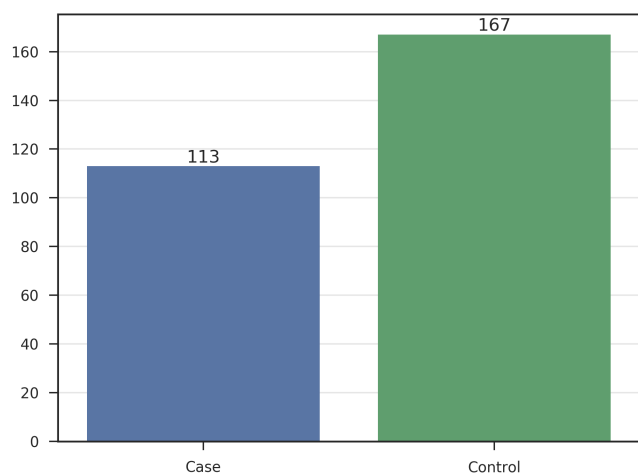
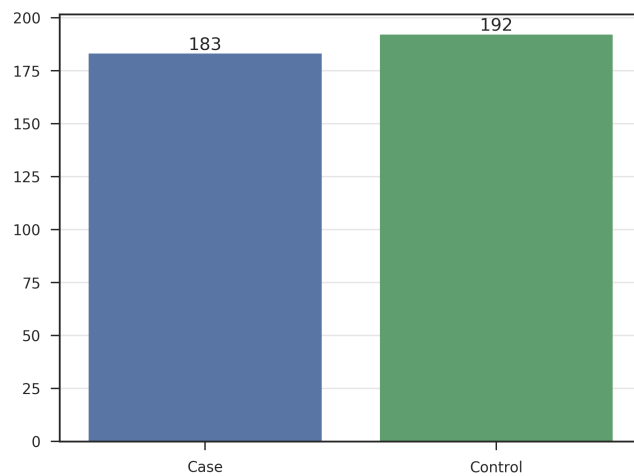


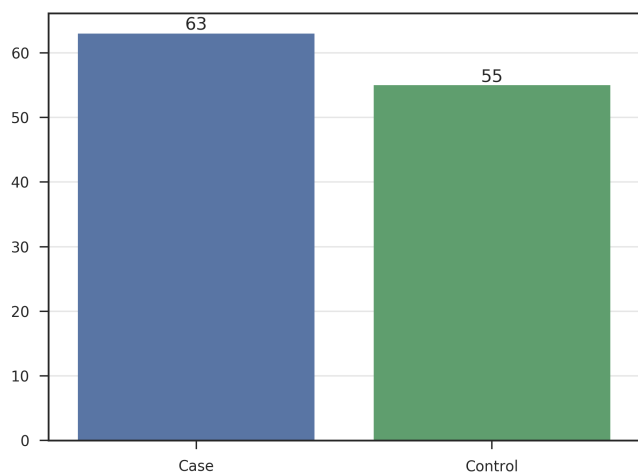
Figure 3: Distribution of CADinT2Dcases in META_EX by cohort



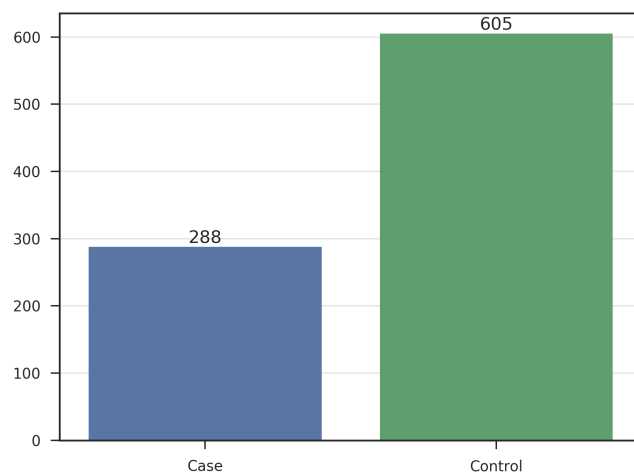
(a) AFFY_AFR



(b) AFFY_AMR



(c) AFFY_EUR



(d) ILL_AFR

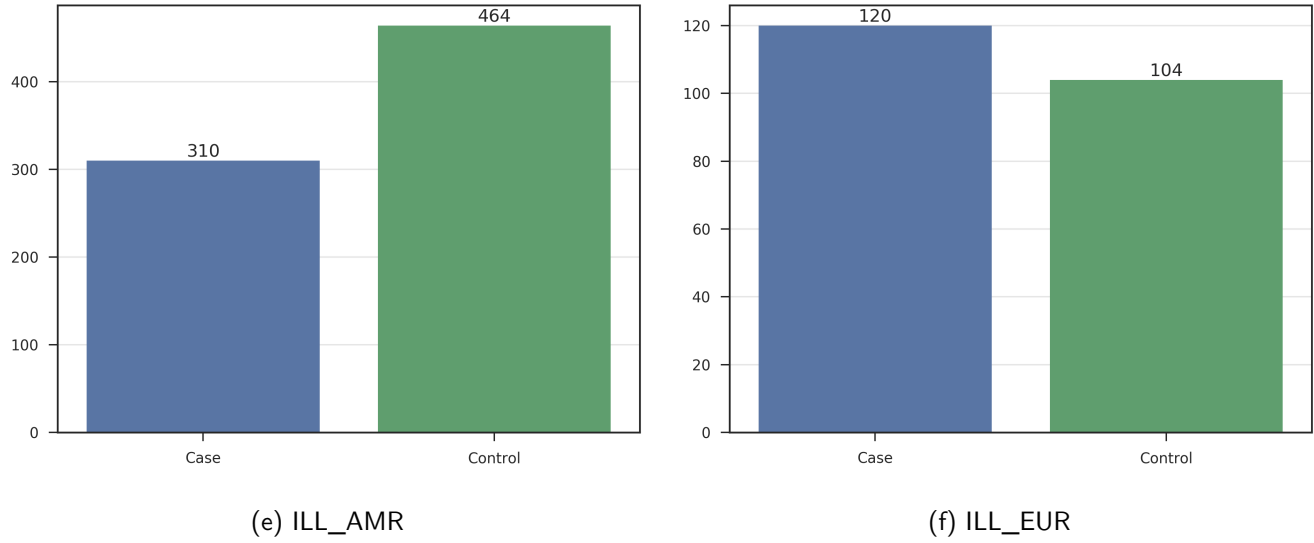


Figure 4: Distribution of CADinT2Dcases in META_GWAS by cohort

Table 5: Summary of samples removed from Coronary Artery Disease in samples with T2D analysis by cohort and model

	Cohort	Array	Ancestry	Trans	Covars	Total	-SampleQc	-KinshipCrossArray	-KinshipArray	-missObs	-PcOutlier	
	META_EX	EX_AFR	EX	AFR	-	SEX	4892	53	0	323	3447	11
	META_EX	EX_AMR	EX	AMR	-	SEX	5425	65	49	492	3586	0
	META_EX	EX_EUR	EX	EUR	-	SEX	2379	38	0	9	1999	0
	META_GWAS	AFFY_AFR	AFFY	AFR	-	SEX	853	16	141	7	415	0
	META_GWAS	AFFY_AMR	AFFY	AMR	-	SEX	1078	22	184	26	469	0
	META_GWAS	AFFY_EUR	AFFY	EUR	-	SEX	578	12	7	2	450	0
	META_GWAS	ILL_AFR	ILL	AFR	-	SEX	3853	51	0	2	3027	10
	META_GWAS	ILL_AMR	ILL	AMR	-	SEX	4111	49	0	0	3172	0
	META_GWAS	ILL_EUR	ILL	EUR	-	SEX	1796	22	0	0	1545	7

Table 6: Summary of samples remaining for Coronary Artery Disease in samples with T2D analysis by cohort and model

	Cohort	Array	Ancestry	Trans	Covars	PCs	N	Male	Female	Case	Ctrl	
	META_EX	EX_AFR	EX	AFR	-	SEX	1	1058	370	688	355	703
	META_EX	EX_AMR	EX	AMR	-	SEX	10	1233	535	698	526	707
	META_EX	EX_EUR	EX	EUR	-	SEX	2	333	264	69	182	151
	META_GWAS	AFFY_AFR	AFFY	AFR	-	SEX	0	274	105	169	113	161
	META_GWAS	AFFY_AMR	AFFY	AMR	-	SEX	0	377	169	208	179	198
	META_GWAS	AFFY_EUR	AFFY	EUR	-	SEX	0	107	90	17	59	48
	META_GWAS	ILL_AFR	ILL	AFR	-	SEX	5	763	267	496	234	529
	META_GWAS	ILL_AMR	ILL	AMR	-	SEX	3	890	374	516	359	531
	META_GWAS	ILL_EUR	ILL	EUR	-	SEX	0	222	170	52	117	105

3.2 Calibration

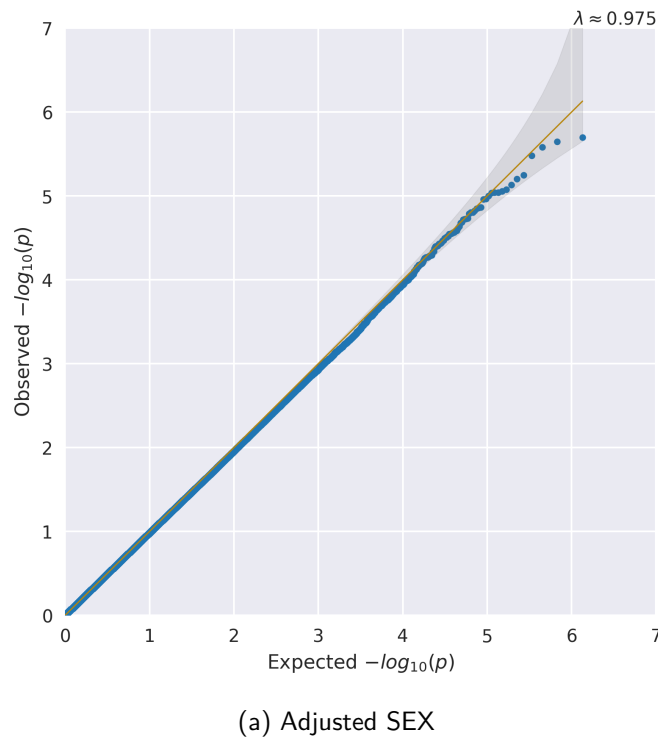
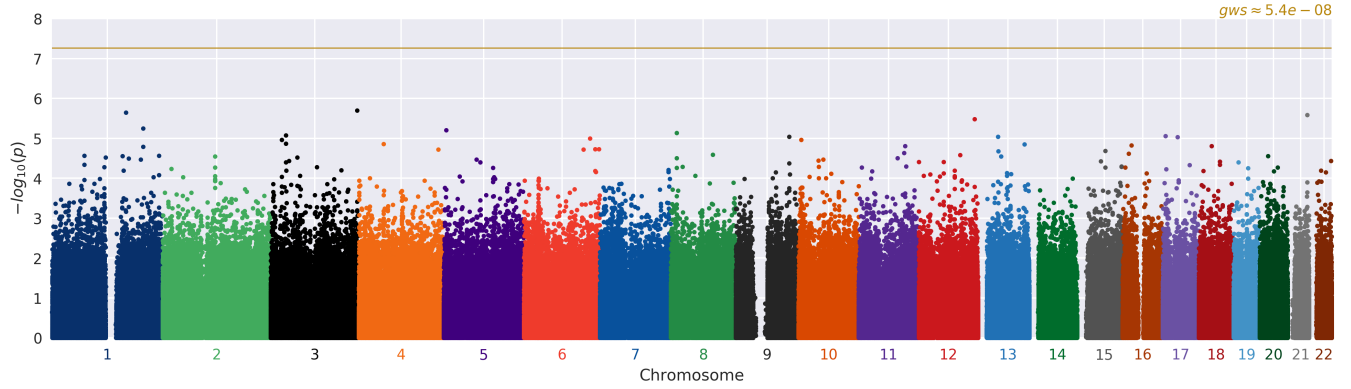


Figure 5: QQ plots for CADinT2Dcases in the MERGE analysis



(a) Adjusted SEX

Figure 6: Manhattan plots for CADinT2Dcases in the MERGE analysis

3.3 Top associations

Table 7: Top variants in the MERGE Adjusted SEX model (**bold** variants indicate previously identified associations)

CHR	POS	ID	EA	OA	GENE _{CLOSEST}	COHORT	DIR	N	MALE	FEMALE	CASE	CTRL	FREQ _{AVG}	FREQ _{MIN}	FREQ _{MAX}	EFFECT	STDERR	OR	ZSCORE	P
3	194105706	rs6793930	A	G	GP5	META_GWAS	xxx+++	756	363	393	349	407	0.243	0.148	0.403	0.616	0.13	1.852	-4.754	$2 \cdot 10^{-6}$
1	166640635	rs472293	T	C	POGK	META_GWAS	+++xxx	1,875	811	1,064	710	1,165	0.286	0.137	0.396	0.376	$7.95 \cdot 10^{-2}$	1.456	-4.73	$2.25 \cdot 10^{-6}$
21	44072377	rs8134355	A	C	PDE9A	META_GWAS	+++xxx	1,873	811	1,062	710	1,163	0.327	0.267	0.406	0.351	$7.47 \cdot 10^{-2}$	1.42	4.699	$2.61 \cdot 10^{-6}$
12	125438336	rs7299198	A	G	DHX37	META_GWAS	xxx+++	758	364	394	351	407	0.548	0.464	0.659	0.481	0.103	1.618	4.65	$3.32 \cdot 10^{-6}$
1	205048616	rs16855053	C	G	CNTN2	META_GWAS	xxx+++	758	364	394	351	407	0.196	0.135	0.239	0.626	0.138	1.871	-4.538	$5.68 \cdot 10^{-6}$
5	5566987	rs2652701	A	G	ICE1	META_GWAS	+++xxx	1,875	811	1,064	710	1,165	0.143	$6.62 \cdot 10^{-2}$	0.197	0.453	0.1	1.574	4.517	$6.28 \cdot 10^{-6}$
8	13257778	rs1454957	T	C	DLC1	META_GWAS	+++xxx	1,875	811	1,064	710	1,165	0.213	0.11	0.32	0.378	$8.43 \cdot 10^{-2}$	1.459	4.483	$7.37 \cdot 10^{-6}$
3	34001190	rs4599247	T	A	PDCD6IP	META_GWAS	xxx+++	757	364	393	350	407	0.673	0.533	0.804	0.504	0.113	1.655	-4.454	$8.41 \cdot 10^{-6}$
17	6311556	rs1567838	C	A	AIP1	META_GWAS	xxx+++	758	364	394	351	407	0.594	0.416	0.748	0.493	0.111	1.637	4.446	$8.77 \cdot 10^{-6}$
13	44585837	rs4942266	G	T	LACC1	META_GWAS	xxx+++	757	364	393	350	407	0.791	0.734	0.819	0.581	0.131	1.788	4.437	$9.12 \cdot 10^{-6}$
9	119891290	rs4838237	A	G	ASTN2	META_GWAS	xxx+++	758	364	394	351	407	0.606	0.505	0.639	0.465	0.105	1.592	-4.437	$9.13 \cdot 10^{-6}$
17	33592621	rs2291189	T	C	SLFN5	META_EX	+++	2,624	1,169	1,455	1,063	1,561	0.134	$7.51 \cdot 10^{-2}$	0.147	0.366	$8.25 \cdot 10^{-2}$	1.442	4.435	$9.22 \cdot 10^{-6}$
6	148569472	rs10872613	C	T	SASH1	META_GWAS	xxx+++	758	364	394	351	407	0.307	0.299	0.318	0.503	0.114	1.654	-4.418	$9.97 \cdot 10^{-6}$
10	6459414	rs4750422	T	C	PRKCQ	META_GWAS	+++xxx	1,873	810	1,063	710	1,163	0.908	0.893	0.921	0.547	0.124	1.727	4.4	$1.08 \cdot 10^{-5}$
3	25008333	rs4858671	G	C	RARB	META_GWAS	xxx++	757	364	393	350	407	0.557	0.549	0.568	0.458	0.104	1.581	-4.398	$1.09 \cdot 10^{-5}$
4	55714886	rs9312653	A	G	KIT	META_GWAS	xxx++	758	364	394	351	407	0.904	0.776	0.973	0.787	0.181	2.197	-4.347	$1.38 \cdot 10^{-5}$
13	103833647	rs17292284	C	T	SLC10A2	META_GWAS	++++++	2,632	1,174	1,458	1,060	1,572	0.182	0.136	0.235	0.322	$7.43 \cdot 10^{-2}$	1.38	4.341	$1.42 \cdot 10^{-5}$
16	20141365	rs4238574	T	C	GPR139	META_GWAS	+++xxx	1,875	811	1,064	710	1,165	0.692	0.651	0.797	0.327	$7.56 \cdot 10^{-2}$	1.387	4.329	$1.5 \cdot 10^{-5}$
18	29009409	rs12961029	G	A	DSG4	META_GWAS	+++xxx	1,866	810	1,056	709	1,157	$3.83 \cdot 10^{-2}$	$1.19 \cdot 10^{-2}$	$6.53 \cdot 10^{-2}$	0.746	0.173	2.109	4.319	$1.57 \cdot 10^{-5}$
11	104202484	rs17102337	G	T	PDGFD	META_GWAS	xxxx++	650	274	376	292	358	0.131	$6.65 \cdot 10^{-2}$	0.219	0.727	0.168	2.07	4.318	$1.57 \cdot 10^{-5}$

3.4 Previously identified risk loci

Table 8 shows statistics from the MERGE cohort for 19 loci that were shown to be significantly associated with Coronary Artery Disease in samples with T2D in the 2011 Nature Genetics paper by Schunkert et al [8]. Where a previously reported variant was not genotyped in the study (indicated by $\bar{R}^2 < 1$), if available, a tagging variant in LD with the reported variant ($\bar{R}^2 \geq 0.7$ and within 250kb) was provided. Tags were identified using 1000 Genomes data. There are 1 variants that show at least nominal significance ($p < 0.05$) in this study. Out of the 18 variants in both studies, 11 exhibit the same direction of effect with the known result (binomial test $p = 0.24$).

Table 8: Top known loci in MERGE model Adjusted SEX (**bold** variants indicate matching direction of effect)

CHR	POS	ID	EA	OA	N	CASE	CTRL	FREQ _{AVG}	FREQ _{MIN}	FREQ _{MAX}	OR	P	DIR	COHORT	GENE _{CLOSEST}	R ²	ID _{KNOWN}	N _{KNOWN}	CASE _{KNOWN}	CTRL _{KNOWN}	OR _{KNOWN}	P _{KNOWN}
9	22003223	rs3217992	C	T	2,623	1,063	1,560	0.265	0.14	0.452	1.026	0.699	---	META_EX	CDKN2B	1	rs3217992	86,995	22,233	64,762	1.175	$1.58 \cdot 10^{-27}$
2	203880992	rs2351524	T	C	2,623	1,063	1,560	0.911	0.866	0.948	1.145	0.176	+++	META_EX	NBEAL1	1	rs2351524	86,995	22,233	64,762	0.87	$1.76 \cdot 10^{-11}$
6	12901441	rs9369640	C	A	2,623	1,063	1,560	0.463	0.333	0.566	1.025	0.67	---	META_EX	PHACTR1	1	rs9369640	86,995	22,233	64,762	1.101	$2.53 \cdot 10^{-11}$
2	203734365	rs3845800	T	A	752	348	404	$7.58 \cdot 10^{-2}$	$2.77 \cdot 10^{-2}$	0.148	1.205	0.336	xxx+++	META_GWAS	ICAIL	1	rs3845800	86,995	22,233	64,762	1.147	$4.13 \cdot 10^{-11}$
2	203753072	rs7582720	C	T	1,875	710	1,165	$7.31 \cdot 10^{-2}$	$3.21 \cdot 10^{-2}$	0.128	1.169	0.23	+++xxx	META_GWAS	WDR12	1	rs7582720	86,995	22,233	64,762	0.875	$1.9 \cdot 10^{-10}$
1	109822166	rs599839	A	G	2,622	1,062	1,560	0.495	0.246	0.814	1.094	0.172	+++	META_EX	PSRC1	1	rs599839	86,995	22,233	64,762	0.899	$2.89 \cdot 10^{-10}$
21	35599128	rs9982601	C	T	2,622	1,062	1,560	0.178	0.117	0.243	1.034	0.66	---	META_EX	MRP56	1	rs9982601	86,995	22,233	64,762	1.178	$4.22 \cdot 10^{-10}$
1	109818306	rs629301	T	G	2,623	1,063	1,560	0.701	0.629	0.817	1.174	$1.22 \cdot 10^{-2}$	+++	META_EX	CELSR2	1	rs629301	86,995	22,233	64,762	0.9	$6.13 \cdot 10^{-10}$
11	116648917	rs964184	G	C	2,621	1,063	1,558	0.796	0.787	0.829	1.037	0.613	+++	META_EX	ZPR1	1	rs964184	86,995	22,233	64,762	0.882	$8.02 \cdot 10^{-10}$
19	11163601	rs1122608	T	G	2,623	1,063	1,560	0.124	$5.01 \cdot 10^{-2}$	0.269	1.038	0.677	---	META_EX	SMARCA4	1	rs1122608	86,995	22,233	64,762	1.136	$9.73 \cdot 10^{-10}$
11	107600570	rs7127880	T	C	757	350	407	0.153	0.112	0.221	1.214	0.181	xxx+++	META_GWAS	AP002353	1	rs7127880	86,995	22,233	64,762	1.269	$1.05 \cdot 10^{-9}$
15	79019578	rs899997	T	G	1,875	710	1,165	0.454	0.265	0.721	1.007	0.922	---xxx	META_GWAS	ADAMTS7	1	rs899997	86,995	22,233	64,762	1.103	$2.05 \cdot 10^{-9}$
7	129663496	rs11556924	T	C	2,623	1,063	1,560	0.189	$6 \cdot 10^{-2}$	0.375	1.033	0.67	---	META_EX	ZC3HC1	1	rs11556924	86,995	22,233	64,762	1.095	$2.22 \cdot 10^{-9}$
1	56963821	rs17114036	A	G	2,621	1,063	1,558	0.133	$9.61 \cdot 10^{-2}$	0.179	1.015	0.864	---	META_EX	PLPP3	1	rs17114036	86,995	22,233	64,762	0.865	$1.43 \cdot 10^{-8}$
3	15648004	rs7651039	T	C	2,623	1,063	1,560	0.733	0.535	0.849	1.005	0.94	---	META_EX	BTD	1	rs7651039	86,995	22,233	64,762	1.153	$1.85 \cdot 10^{-8}$
6	72193707	rs9351814	C	A	1,875	710	1,165	0.328	0.251	0.391	1.071	0.353	++-xxx	META_GWAS	OGFRL1	1	rs9351814	86,995	22,233	64,762	1.083	$2.02 \cdot 10^{-8}$
3	138119952	rs2306374	C	T	2,623	1,063	1,560	$7.97 \cdot 10^{-2}$	$6.43 \cdot 10^{-2}$	0.128	1.073	0.502	---	META_EX	MRAS	1	rs2306374	86,995	22,233	64,762	0.897	$3.34 \cdot 10^{-8}$
6	134198175	rs1967917	A	G	758	351	407	0.373	0.313	0.387	1.018	0.869	xxx---	META_GWAS	TCF21	1	rs1967917	86,995	22,233	64,762	1.089	$3.55 \cdot 10^{-8}$
9	22003223	rs3217992	C	T	2,623	1,063	1,560	0.265	0.14	0.452	1.026	0.699	---	META_EX	CDKN2A	0.871	rs3218020	86,995	22,233	64,762	1.185	$3.07 \cdot 10^{-27}$

4 Stroke in samples with T2D (STROKEinT2Dcases)

4.1 Summary

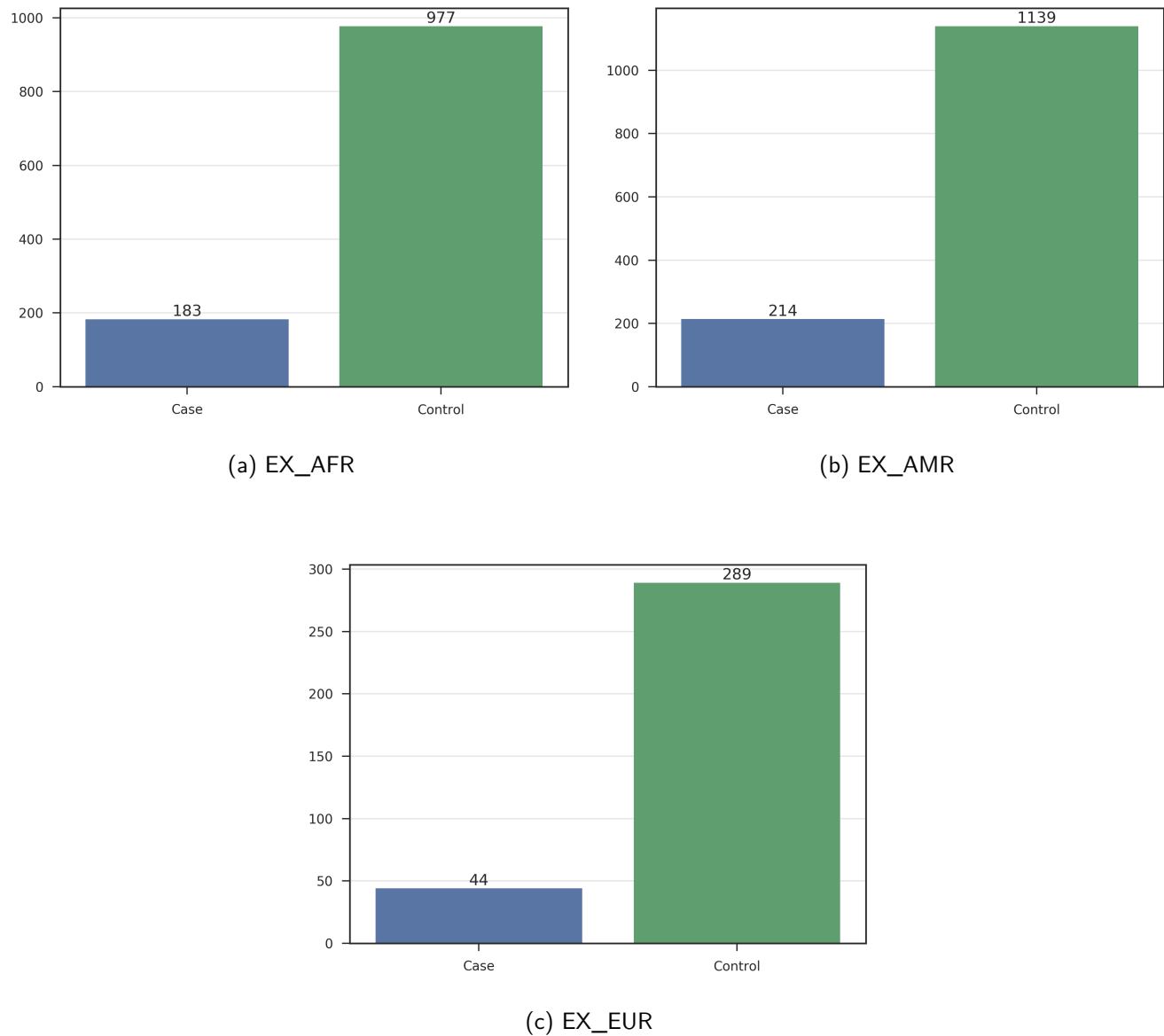
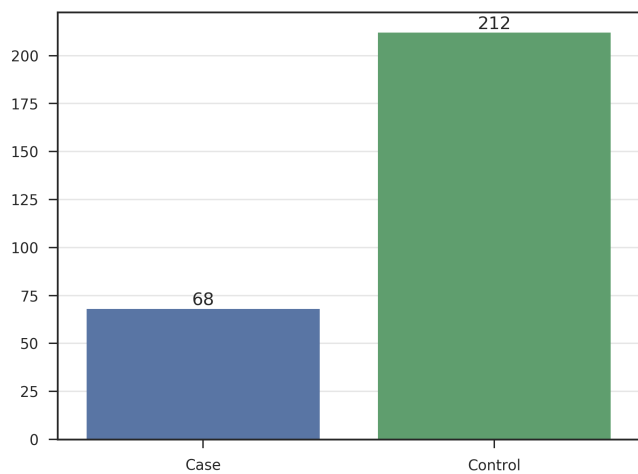
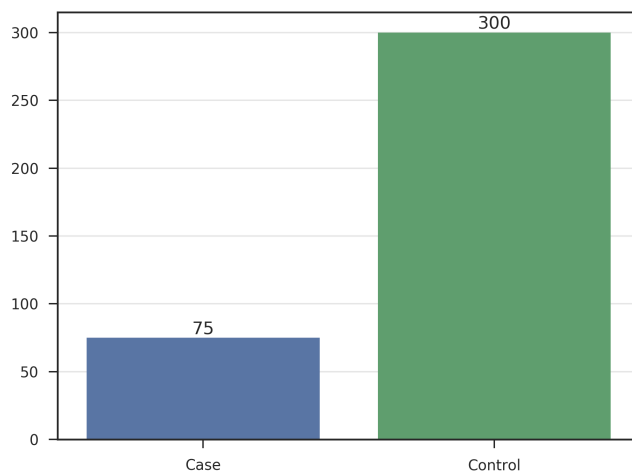


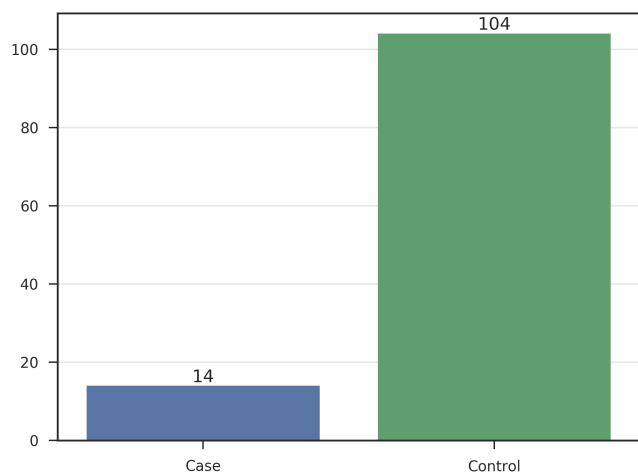
Figure 7: Distribution of STROKEinT2Dcases in META_EX by cohort



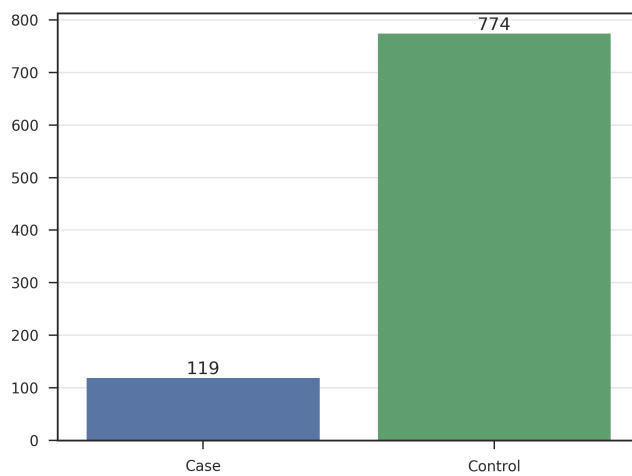
(a) AFFY_AFR



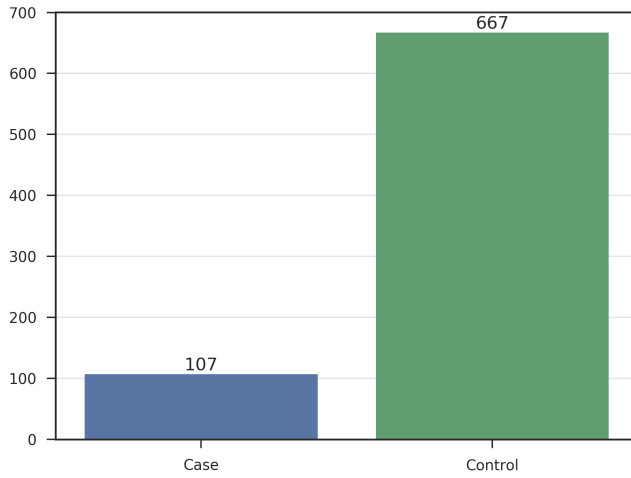
(b) AFFY_AMR



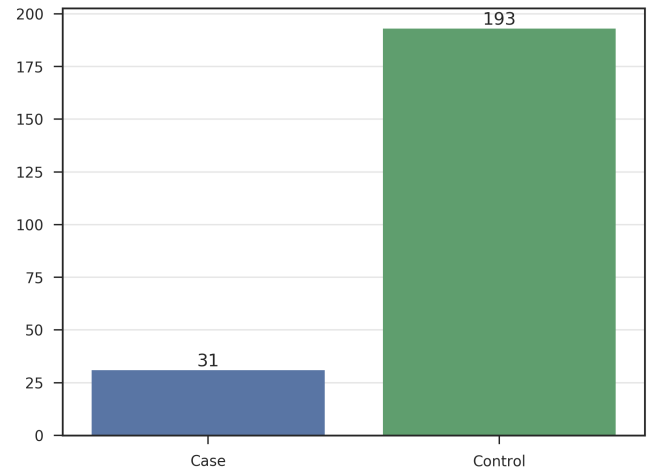
(c) AFFY_EUR



(d) ILL_AFR



(e) ILL_AMR



(f) ILL_EUR

Figure 8: Distribution of STROKEinT2Dcases in META_GWAS by cohort

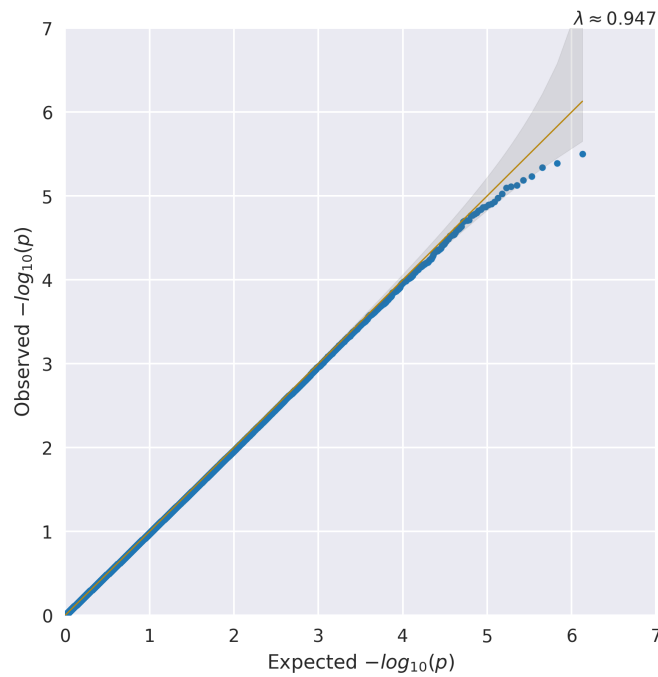
Table 9: Summary of samples removed from Stroke in samples with T2D analysis by cohort and model

	Cohort	Array	Ancestry	Trans	Covars	Total	-SampleQc	-KinshipCrossArray	-KinshipArray	-missObs	-PcOutlier
META_EX	EX_AFR	EX	AFR	-	SEX	4892	53	0	324	3446	11
META_EX	EX_AMR	EX	AMR	-	SEX	5425	65	49	492	3588	0
META_EX	EX_EUR	EX	EUR	-	SEX	2379	38	0	9	1999	1
META_GWAS	AFFY_AFR	AFFY	AFR	-	SEX	853	16	141	7	415	0
META_GWAS	AFFY_AMR	AFFY	AMR	-	SEX	1078	22	184	26	469	11
META_GWAS	AFFY_EUR	AFFY	EUR	-	SEX	578	12	7	2	450	0
META_GWAS	ILL_AFR	ILL	AFR	-	SEX	3853	51	0	2	3027	10
META_GWAS	ILL_AMR	ILL	AMR	-	SEX	4111	49	0	0	3172	0
META_GWAS	ILL_EUR	ILL	EUR	-	SEX	1796	22	0	0	1545	3

Table 10: Summary of samples remaining for Stroke in samples with T2D analysis by cohort and model

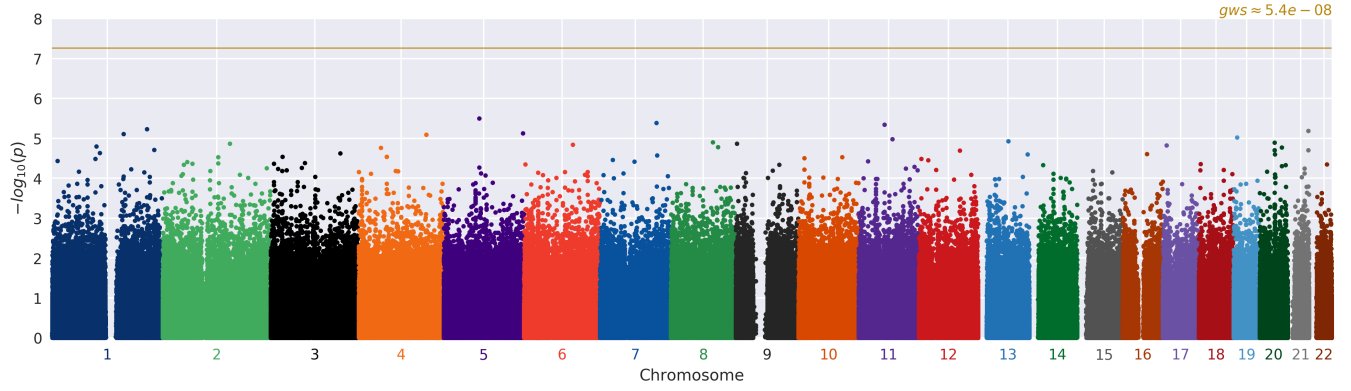
	Cohort	Array	Ancestry	Trans	Covars	PCs	N	Male	Female	Case	Ctrl	
	META_EX	EX_AFR	EX	AFR	-	SEX	10	1058	370	688	162	896
	META_EX	EX_AMR	EX	AMR	-	SEX	5	1231	533	698	189	1042
	META_EX	EX_EUR	EX	EUR	-	SEX	8	332	263	69	43	289
	META_GWAS	AFFY_AFR	AFFY	AFR	-	SEX	0	274	105	169	61	213
	META_GWAS	AFFY_AMR	AFFY	AMR	-	SEX	1	366	164	202	74	292
	META_GWAS	AFFY_EUR	AFFY	EUR	-	SEX	0	107	90	17	13	94
	META_GWAS	ILL_AFR	ILL	AFR	-	SEX	0	763	267	496	100	663
	META_GWAS	ILL_AMR	ILL	AMR	-	SEX	6	890	374	516	122	768
	META_GWAS	ILL_EUR	ILL	EUR	-	SEX	0	226	172	54	30	196

4.2 Calibration



(a) Adjusted SEX

Figure 9: QQ plots for STROKEinT2Dcases in the MERGE analysis



(a) Adjusted SEX

Figure 10: Manhattan plots for STROKEinT2Dcases in the MERGE analysis

4.3 Top associations

Table 11: Top variants in the MERGE Adjusted SEX model (**bold** variants indicate previously identified associations)

CHR	POS	ID	EA	OA	GENE _{CLOSEST}	COHORT	DIR	N	MALE	FEMALE	CASE	CTRL	FREQ _{AVG}	FREQ _{MIN}	FREQ _{MAX}	EFFECT	STDERR	OR	ZSCORE	P
5	80228327	rs4704691	G	A	RASGRF2	META_GWAS	+++++	2,626	1,172	1,454	400	2,226	0.506	0.336	0.662	0.372	$7.97 \cdot 10^{-2}$	1.45	-4.66	$3.16 \cdot 10^{-6}$
7	126659702	rs17869216	G	A	GRM8	META_GWAS	x++xxx	1,653	641	1,012	222	1,431	$3.02 \cdot 10^{-2}$	$1.63 \cdot 10^{-2}$	$4.65 \cdot 10^{-2}$	1.098	0.238	2.999	4.606	$4.1 \cdot 10^{-6}$
11	58111700	rs11229371	A	G	OR5B17	META_GWAS	xxx+++	747	359	388	148	599	0.21	0.168	0.23	0.829	0.181	2.291	-4.584	$4.56 \cdot 10^{-6}$
1	213679087	rs6666874	T	C	RPS6KC1	META_GWAS	+++xxx	1,879	813	1,066	252	1,627	0.108	$1.33 \cdot 10^{-2}$	0.193	0.837	0.185	2.309	-4.532	$5.84 \cdot 10^{-6}$
21	46181564	rs885657	C	A	UBE2G2	META_GWAS	xxx+++	746	359	387	148	598	0.266	0.186	0.341	0.656	0.145	1.926	4.511	$6.45 \cdot 10^{-6}$
5	178604465	rs6862563	A	G	ADAMTS2	META_GWAS	+++xxx	1,879	813	1,066	252	1,627	$6.76 \cdot 10^{-2}$	$3.6 \cdot 10^{-2}$	0.124	0.759	0.169	2.137	4.481	$7.42 \cdot 10^{-6}$
1	160846284	rs1333062	G	T	ITLN1	META_GWAS	+++xxx	1,879	813	1,066	252	1,627	0.507	0.325	0.715	0.449	0.1	1.567	4.473	$7.7 \cdot 10^{-6}$
4	151822085	rs13117608	A	G	LRBA	META_GWAS	xxx++	744	359	385	148	596	$6.45 \cdot 10^{-2}$	$1.47 \cdot 10^{-2}$	0.123	1.135	0.254	3.111	4.464	$8.03 \cdot 10^{-6}$
19	8321969	rs36248	T	C	CERS4	META_GWAS	+++xxx	1,879	813	1,066	252	1,627	0.164	0.106	0.209	0.532	0.12	1.702	4.43	$9.41 \cdot 10^{-6}$
11	75428971	rs34643721	A	G	MOGAT2	META_EX	x++	2,289	903	1,386	351	1,938	$8.3 \cdot 10^{-3}$	$3.25 \cdot 10^{-3}$	$1.42 \cdot 10^{-2}$	1.555	0.353	4.736	4.405	$1.06 \cdot 10^{-5}$
13	67849764	rs2985928	A	G	PCDH9	META_GWAS	-+++	2,622	1,170	1,452	399	2,223	0.395	0.254	0.513	0.357	$8.14 \cdot 10^{-2}$	1.428	4.383	$1.17 \cdot 10^{-5}$
8	94573456	rs7005045	A	G	FAM92A1	META_GWAS	-++xxx	1,879	813	1,066	252	1,627	0.788	0.715	0.881	0.5	0.114	1.649	-4.369	$1.25 \cdot 10^{-5}$
20	33405227	rs6120739	G	A	NCOA6	META_GWAS	xxx+++	747	359	388	148	599	0.592	0.545	0.651	0.602	0.138	1.826	4.364	$1.28 \cdot 10^{-5}$
9	2304143	rs10117864	C	G	SMARCA2	META_GWAS	xxx+++	747	359	388	148	599	0.924	0.889	0.945	0.906	0.208	2.475	-4.351	$1.35 \cdot 10^{-5}$
2	151311055	rs16828194	G	A	RND3	META_GWAS	+++xxx	1,878	813	1,065	252	1,626	0.234	0.157	0.313	0.53	0.122	1.7	-4.349	$1.37 \cdot 10^{-5}$
6	109781800	rs9487114	T	C	MICAL1	META_GWAS	x++xxx	1,653	641	1,012	222	1,431	$3.6 \cdot 10^{-2}$	$1.91 \cdot 10^{-2}$	$5.57 \cdot 10^{-2}$	1.888	0.435	6.608	-4.336	$1.45 \cdot 10^{-5}$
17	8272627	rs370752	A	G	KRBA2	META_EX	x++	2,289	903	1,386	351	1,938	$2.42 \cdot 10^{-2}$	$9.34 \cdot 10^{-3}$	$4.16 \cdot 10^{-2}$	0.952	0.22	2.59	4.33	$1.49 \cdot 10^{-5}$
1	99745415	rs17399618	A	G	PLPPR4	META_GWAS	xxx+++	743	358	385	145	598	$4.91 \cdot 10^{-2}$	$3.68 \cdot 10^{-2}$	$6.54 \cdot 10^{-2}$	1.104	0.256	3.016	4.316	$1.59 \cdot 10^{-5}$
8	106207444	rs13262572	C	T	ZFPF2	META_GWAS	-++xxx	1,879	813	1,066	252	1,627	$8.94 \cdot 10^{-2}$	$3.28 \cdot 10^{-2}$	0.215	0.661	0.153	1.936	4.308	$1.65 \cdot 10^{-5}$
20	49939743	rs1555235	A	G	NFATC2	META_GWAS	+++xxx	1,878	813	1,065	251	1,627	0.734	0.584	0.811	0.463	0.108	1.588	-4.301	$1.7 \cdot 10^{-5}$

4.4 Previously identified risk loci

Table 12 shows statistics from the MERGE cohort for 22 loci that were shown to be significantly associated with Stroke in samples with T2D in the 2018 Nature Genetics paper by Malik et al [7]. Where a previously reported variant was not genotyped in the study (indicated by $\bar{R}^2 < 1$), if available, a tagging variant in LD with the reported variant ($\bar{R}^2 \geq 0.7$ and within 250kb) was provided. Tags were identified using 1000 Genomes data. None of the variants shows even nominal significance ($p < 0.05$) in this study. Out of the 16 variants in both studies, 6 exhibit the same direction of effect with the known result (binomial test $p = 0.895$).

Table 12: Top known loci in MERGE model Adjusted SEX (**bold** variants indicate matching direction of effect)

CHR	POS	ID	EA	OA	N	CASE	CTRL	FREQ _{AVG}	FREQ _{MIN}	FREQ _{MAX}	OR	P	DIR	COHORT	GENE _{CLOSEST}	R ²	ID _{KNOWN}	N _{KNOWN}	CASE _{KNOWN}	CTRL _{KNOWN}	OR _{KNOWN}	P _{KNOWN}
4	111688752	rs2723334	C	T	2,626	400	2,226	0.573	0.471	0.723	1.021	0.792	----	META_GWAS	PITX2	1	rs2723334	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	0.92	9.46 · 10 ⁻¹⁴
1	156169610	rs2072499	A	G	1,876	252	1,624	0.515	0.302	0.668	1.056	0.587	---+xxx	META_GWAS	SLC25A44	1	rs2072499	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	1.068	3.23 · 10 ⁻¹²
12	111884608	rs3184504	C	T	2,624	395	2,229	0.766	0.467	0.935	1.078	0.459	++	META_EX	SH2B3	1	rs3184504	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	0.938	5.89 · 10 ⁻¹²
1	156182710	rs2241107	C	T	747	148	599	0.502	0.36	0.661	1.27	8.46 · 10 ⁻²	xxx+++	META_GWAS	PMF1-BGLAP	1	rs2241107	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	0.938	1.41 · 10 ⁻¹¹
1	156204047	rs2251847	A	G	1,878	252	1,626	0.415	0.299	0.487	1.041	0.676	+++xxx	META_GWAS	PMF1	1	rs2251847	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	0.939	2.22 · 10 ⁻¹¹
7	19049388	rs2107595	A	G	1,879	252	1,627	0.199	0.175	0.219	1.081	0.513	---+xxx	META_GWAS	HDAC9	1	rs2107595	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	1.084	3.59 · 10 ⁻¹¹
12	112007756	rs653178	T	C	2,624	395	2,229	0.765	0.467	0.935	1.083	0.431	++	META_EX	ATXN2	1	rs653178	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	0.939	4.4 · 10 ⁻¹¹
12	112072424	rs11065987	A	G	2,623	395	2,228	0.212	5.72 · 10 ⁻²	0.498	1.122	0.27	+++	META_EX	BRAP	1	rs11065987	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	0.943	5.23 · 10 ⁻¹⁰
12	112906415	rs11066320	G	A	1,879	252	1,627	0.787	0.489	0.944	1.217	0.134	+++xxx	META_GWAS	PTPN11	1	rs11066320	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	0.946	1.79 · 10 ⁻⁹
12	112486818	rs17696736	A	G	2,624	395	2,229	0.216	5.9 · 10 ⁻²	0.514	1.181	0.112	+++	META_EX	NAA25	1	rs17696736	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	0.946	3.34 · 10 ⁻⁹
6	1350834	rs6912034	T	C	747	148	599	8.37 · 10 ⁻²	5.47 · 10 ⁻²	0.117	1.336	0.193	xxx+++	META_GWAS	FOXQ1	1	rs6912034	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	1.08	3.52 · 10 ⁻⁹
13	47201874	rs1570620	T	C	747	148	599	0.892	0.762	0.945	1.038	0.867	xxx+++	META_GWAS	LRCH1	1	rs1570620	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	1.065	3.53 · 10 ⁻⁹
9	22125347	rs1333048	A	C	2,624	395	2,229	0.414	0.295	0.556	1.031	0.709	++	META_EX	CDKN2B	1	rs1333048	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	0.948	1.98 · 10 ⁻⁸
11	102700360	rs473238	T	C	743	147	596	0.927	0.818	0.991	1.377	0.222	xxx++	META_GWAS	MMP3	1	rs473238	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	1.077	3.04 · 10 ⁻⁸
6	1350834	rs6912034	T	C	747	148	599	8.37 · 10 ⁻²	5.47 · 10 ⁻²	0.117	1.336	0.193	xxx+++	META_GWAS	FOXF2	1	rs4959130	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	1.083	1.13 · 10 ⁻⁹
11	102691419	rs564018	A	G	747	148	599	0.925	0.813	0.991	1.284	0.332	xxx++	META_GWAS	MMP1	1	rs470928	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	0.927	3.06 · 10 ⁻⁸
12	112211833	rs2238151	C	T	2,624	395	2,229	0.646	0.301	0.896	1.134	0.178	+++	META_EX	ACAD10	0.996	rs47892	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	1.055	3.28 · 10 ⁻⁸
12	112072424	rs11065987	A	G	2,623	395	2,228	0.212	5.72 · 10 ⁻²	0.498	1.122	0.27	+++	META_EX	ALDH2	0.971	rs2013002	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	1.061	1.03 · 10 ⁻⁹
12	112871372	rs11066301	A	G	2,621	394	2,227	0.213	5.78 · 10 ⁻²	0.508	1.183	0.111	+++	META_EX	RPL6	0.952	rs11066283	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	0.933	2.36 · 10 ⁻¹¹
12	112072424	rs11065987	A	G	2,623	395	2,228	0.212	5.72 · 10 ⁻²	0.498	1.122	0.27	+++	META_EX	MAPKAPK5	0.934	rs11513729	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	1.059	5.65 · 10 ⁻⁹
12	112486818	rs17696736	A	G	2,624	395	2,229	0.216	5.9 · 10 ⁻²	0.514	1.181	0.112	+++	META_EX	TRAFD1	0.922	rs17630235	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	1.06	4.23 · 10 ⁻¹⁰
12	112486818	rs17696736	A	G	2,624	395	2,229	0.216	5.9 · 10 ⁻²	0.514	1.181	0.112	+++	META_EX	HECTD4	0.913	rs11066188	4.47 · 10 ⁵	40,585	4.06 · 10 ⁵	1.062	1.28 · 10 ⁻¹⁰

5 Hypertension in samples with T2D (HYPERTENSIONinT2Dcases)

5.1 Summary

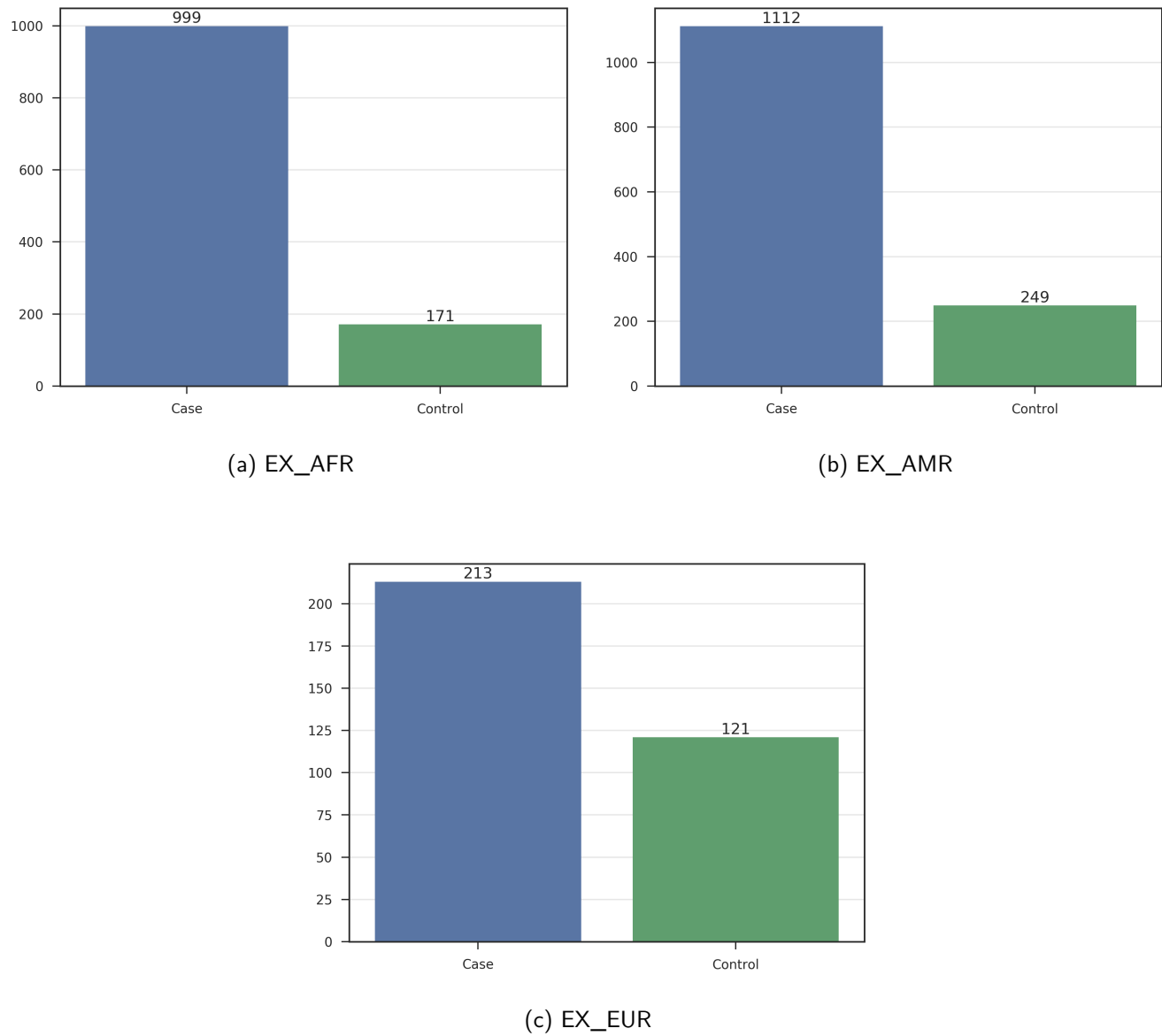
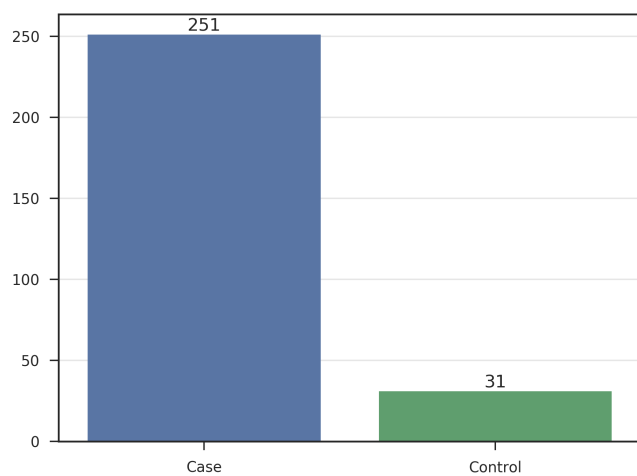
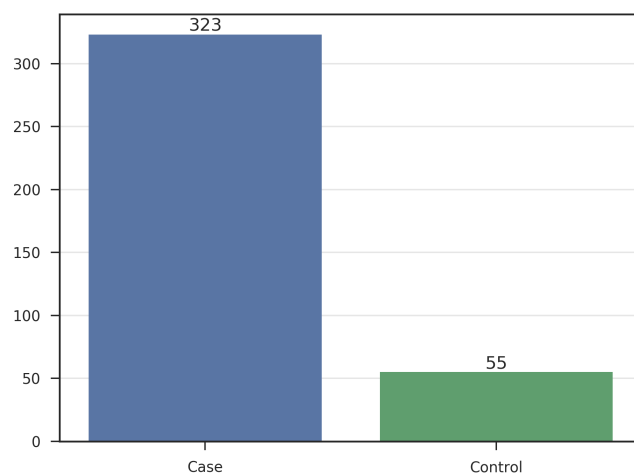


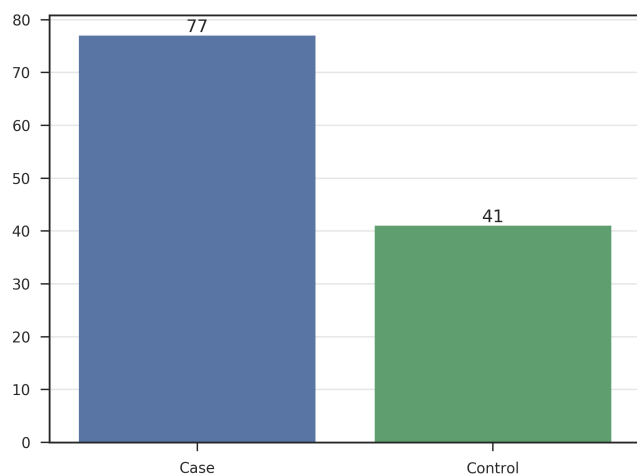
Figure 11: Distribution of HYPERTENSIONinT2Dcases in META_EX by cohort



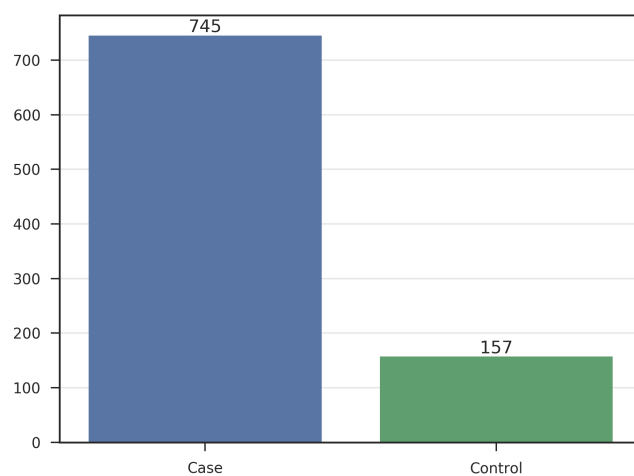
(a) AFFY_AFR



(b) AFFY_AMR



(c) AFFY_EUR



(d) ILL_AFR

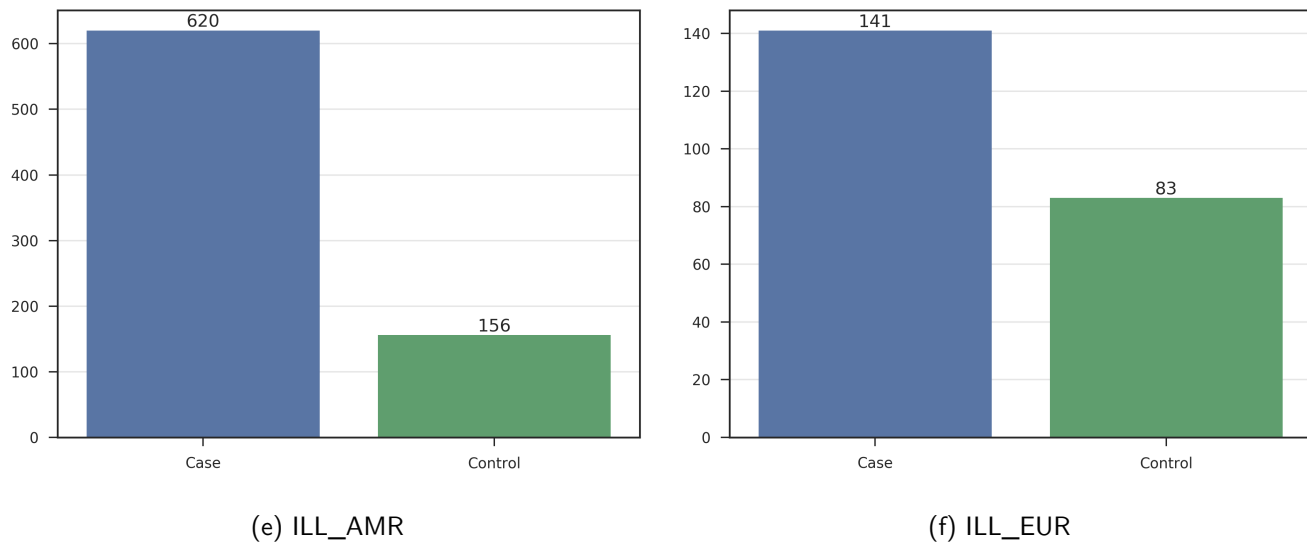


Figure 12: Distribution of HYPERTENSIONinT2Dcases in META_GWAS by cohort

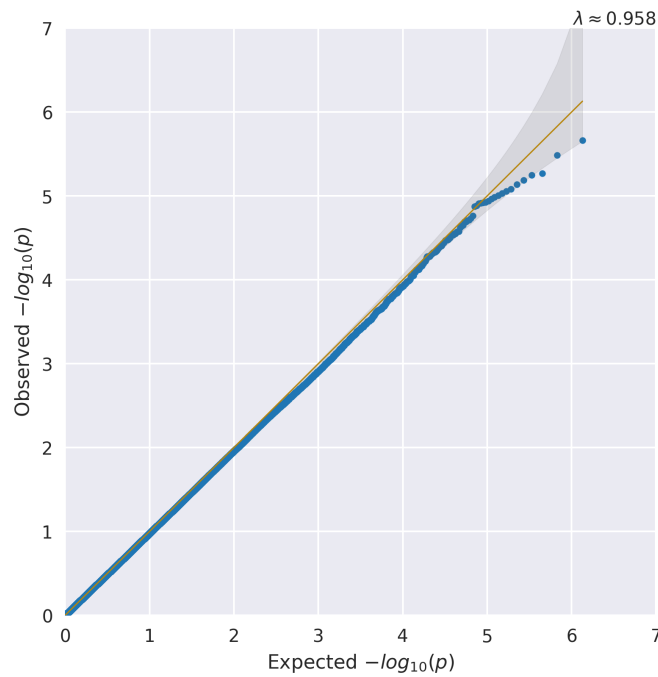
Table 13: Summary of samples removed from Hypertension in samples with T2D analysis by cohort and model

	Cohort	Array	Ancestry	Trans	Covars	Total	-SampleQc	-KinshipCrossArray	-KinshipArray	-missObs	-PcOutlier
	META_EX EX_AFR	EX	AFR	-	SEX	4892	53	0	323	3436	11
	META_EX EX_AMR	EX	AMR	-	SEX	5425	65	49	492	3580	0
	META_EX EX_EUR	EX	EUR	-	SEX	2379	38	0	9	1998	0
	META_GWAS AFFY_AFR	AFFY	AFR	-	SEX	853	16	141	7	413	0
	META_GWAS AFFY_AMR	AFFY	AMR	-	SEX	1078	22	184	26	466	5
	META_GWAS AFFY_EUR	AFFY	EUR	-	SEX	578	12	7	2	450	8
	META_GWAS ILL_AFR	ILL	AFR	-	SEX	3853	51	0	2	3019	10
	META_GWAS ILL_AMR	ILL	AMR	-	SEX	4111	49	0	0	3169	0
	META_GWAS ILL_EUR	ILL	EUR	-	SEX	1796	22	0	0	1545	0

Table 14: Summary of samples remaining for Hypertension in samples with T2D analysis by cohort and model

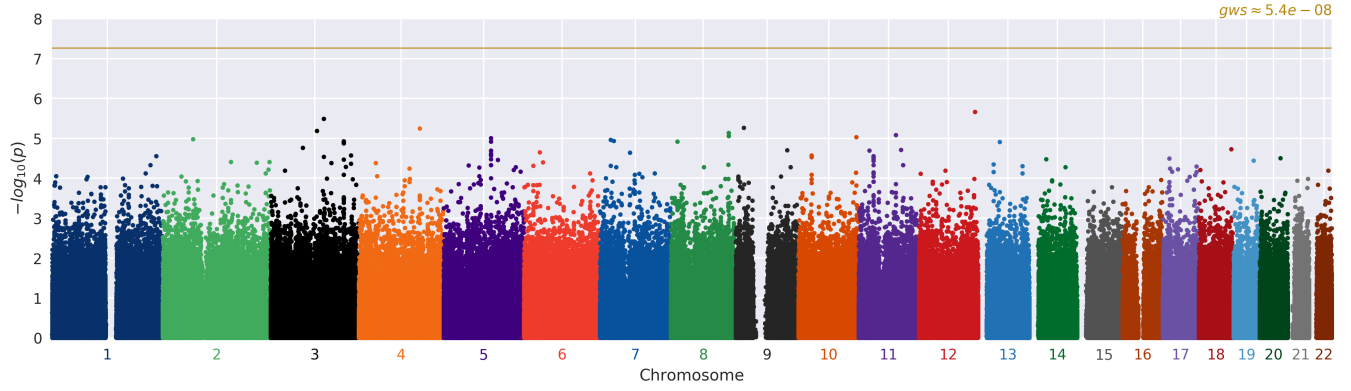
	Cohort	Array	Ancestry	Trans	Covars	PCs	N	Male	Female	Case	Ctrl	
	META_EX	EX_AFR	EX	AFR	-	SEX	3	1069	375	694	906	163
	META_EX	EX_AMR	EX	AMR	-	SEX	3	1239	536	703	1000	239
	META_EX	EX_EUR	EX	EUR	-	SEX	1	334	264	70	213	121
	META_GWAS	AFFY_AFR	AFFY	AFR	-	SEX	0	276	106	170	244	32
	META_GWAS	AFFY_AMR	AFFY	AMR	-	SEX	0	375	169	206	322	53
	META_GWAS	AFFY_EUR	AFFY	EUR	-	SEX	1	99	85	14	60	39
	META_GWAS	ILL_AFR	ILL	AFR	-	SEX	10	771	269	502	641	130
	META_GWAS	ILL_AMR	ILL	AMR	-	SEX	0	893	376	517	710	183
	META_GWAS	ILL_EUR	ILL	EUR	-	SEX	2	229	173	56	146	83

5.2 Calibration



(a) Adjusted SEX

Figure 13: QQ plots for HYPERTENSIONinT2Dcases in the MERGE analysis



(a) Adjusted SEX

Figure 14: Manhattan plots for HYPERTENSIONinT2Dcases in the MERGE analysis

5.3 Top associations

Table 15: Top variants in the MERGE Adjusted SEX model (**bold** variants indicate previously identified associations)

CHR	POS	ID	EA	OA	GENE _{CLOSEST}	COHORT	DIR	N	MALE	FEMALE	CASE	CTRL	FREQ _{AVG}	FREQ _{MIN}	FREQ _{MAX}	EFFECT	STDERR	OR	ZSCORE	P
12	126836267	rs16920540	A	G	RP4-809F18	META_GWAS	+++xxx	2,544	1,093	1,451	2,063	481	$9.26 \cdot 10^{-2}$	$4.37 \cdot 10^{-3}$	0.174	0.732	0.155	2.08	4.736	$2.18 \cdot 10^{-6}$
3	119051568	rs16829700	A	G	ARHGAP31	META_GWAS	xxx+++	747	359	388	624	123	0.169	0.111	0.254	0.893	0.192	2.442	-4.654	$3.25 \cdot 10^{-6}$
9	18231265	rs1944752	A	G	ADAMTSL1	META_GWAS	+++xxx	1,893	818	1,075	1,497	396	0.519	0.473	0.629	0.373	$8.2 \cdot 10^{-2}$	1.452	-4.549	$5.38 \cdot 10^{-6}$
4	136962217	rs10015316	T	C	PCDH18	META_GWAS	xxx+++	749	360	389	625	124	0.703	0.515	0.839	0.805	0.177	2.237	-4.538	$5.67 \cdot 10^{-6}$
3	103412597	rs7618237	G	T	ZPLD1	META_GWAS	x++x++	2,308	917	1,391	1,913	395	$4.22 \cdot 10^{-2}$	$1.63 \cdot 10^{-2}$	$7.36 \cdot 10^{-2}$	0.791	0.176	2.207	-4.509	$6.51 \cdot 10^{-6}$
8	129902395	rs10956450	C	T	GSDMC	META_GWAS	xxx+++	750	360	390	626	124	0.206	0.167	0.24	0.755	0.168	2.128	-4.485	$7.28 \cdot 10^{-6}$
11	83262562	rs1367986	A	G	DLG2	META_GWAS	+++xxx	1,893	818	1,075	1,497	396	0.169	0.136	0.218	0.461	0.103	1.586	-4.458	$8.29 \cdot 10^{-6}$
10	130122697	rs12772143	T	C	MKI67	META_GWAS	+++xxx	1,893	818	1,075	1,497	396	0.128	$8.63 \cdot 10^{-2}$	0.172	0.507	0.114	1.66	-4.433	$9.28 \cdot 10^{-6}$
5	106553396	rs1159078	G	A	EFNA5	META_GWAS	+++xxx	1,892	818	1,074	1,496	396	0.484	0.46	0.505	0.363	$8.2 \cdot 10^{-2}$	1.437	4.421	$9.83 \cdot 10^{-6}$
2	68540378	rs10169617	C	T	CNRIP1	META_EX	+++	2,642	1,175	1,467	2,119	523	0.484	0.368	0.556	0.313	$7.1 \cdot 10^{-2}$	1.368	4.409	$1.04 \cdot 10^{-5}$
7	24376379	rs17376624	G	A	NPY	META_GWAS	xxx+++	750	360	390	626	124	$4.47 \cdot 10^{-2}$	$1.09 \cdot 10^{-2}$	0.101	1.279	0.291	3.592	-4.399	$1.09 \cdot 10^{-5}$
7	30989577	rs4507663	C	T	GHRHR	META_GWAS	++++++	2,640	1,176	1,464	2,121	519	0.676	0.36	0.877	0.35	$7.98 \cdot 10^{-2}$	1.419	4.386	$1.15 \cdot 10^{-5}$
3	164141692	rs7340644	C	G	SI	META_GWAS	xxx+++	750	360	390	626	124	0.572	0.515	0.583	0.651	0.149	1.917	4.381	$1.18 \cdot 10^{-5}$
8	15036046	rs268352	T	G	SGCZ	META_GWAS	xxx+++	750	360	390	626	124	0.179	0.148	0.225	0.789	0.18	2.202	-4.378	$1.2 \cdot 10^{-5}$
13	48004741	rs9591046	C	T	SUCLA2	META_GWAS	xxx+++	651	275	376	566	85	$5.15 \cdot 10^{-2}$	$2.53 \cdot 10^{-2}$	$8.7 \cdot 10^{-2}$	1.338	0.306	3.81	-4.372	$1.23 \cdot 10^{-5}$
3	72315956	rs4532099	C	T	PROK2	META_GWAS	++++++	2,643	1,178	1,465	2,123	520	0.848	0.723	0.933	0.409	$9.51 \cdot 10^{-2}$	1.505	4.299	$1.71 \cdot 10^{-5}$
18	72794781	rs7231943	C	T	ZNF407	META_GWAS	x++xxx	1,664	645	1,019	1,351	313	$5.23 \cdot 10^{-2}$	$2.69 \cdot 10^{-2}$	$8.17 \cdot 10^{-2}$	1.088	0.254	2.969	4.281	$1.86 \cdot 10^{-5}$
11	94825823	rs628606	A	G	ENDOD1	META_GWAS	++++++	2,643	1,178	1,465	2,123	520	0.852	0.772	0.965	0.441	0.103	1.554	4.271	$1.95 \cdot 10^{-5}$
9	115259011	rs3849132	A	G	KIAA1958	META_GWAS	xxx+++	747	359	388	623	124	0.954	0.934	0.964	1.313	0.308	3.715	4.268	$1.97 \cdot 10^{-5}$
11	24247743	rs7131490	T	G	LUZP2	META_GWAS	xxx+++	649	273	376	564	85	$3 \cdot 10^{-2}$	$1.73 \cdot 10^{-2}$	$4.74 \cdot 10^{-2}$	1.671	0.392	5.316	-4.262	$2.03 \cdot 10^{-5}$

6 Peripheral Vascular Disease in samples with T2D (PVDinT2Dcases)

6.1 Summary

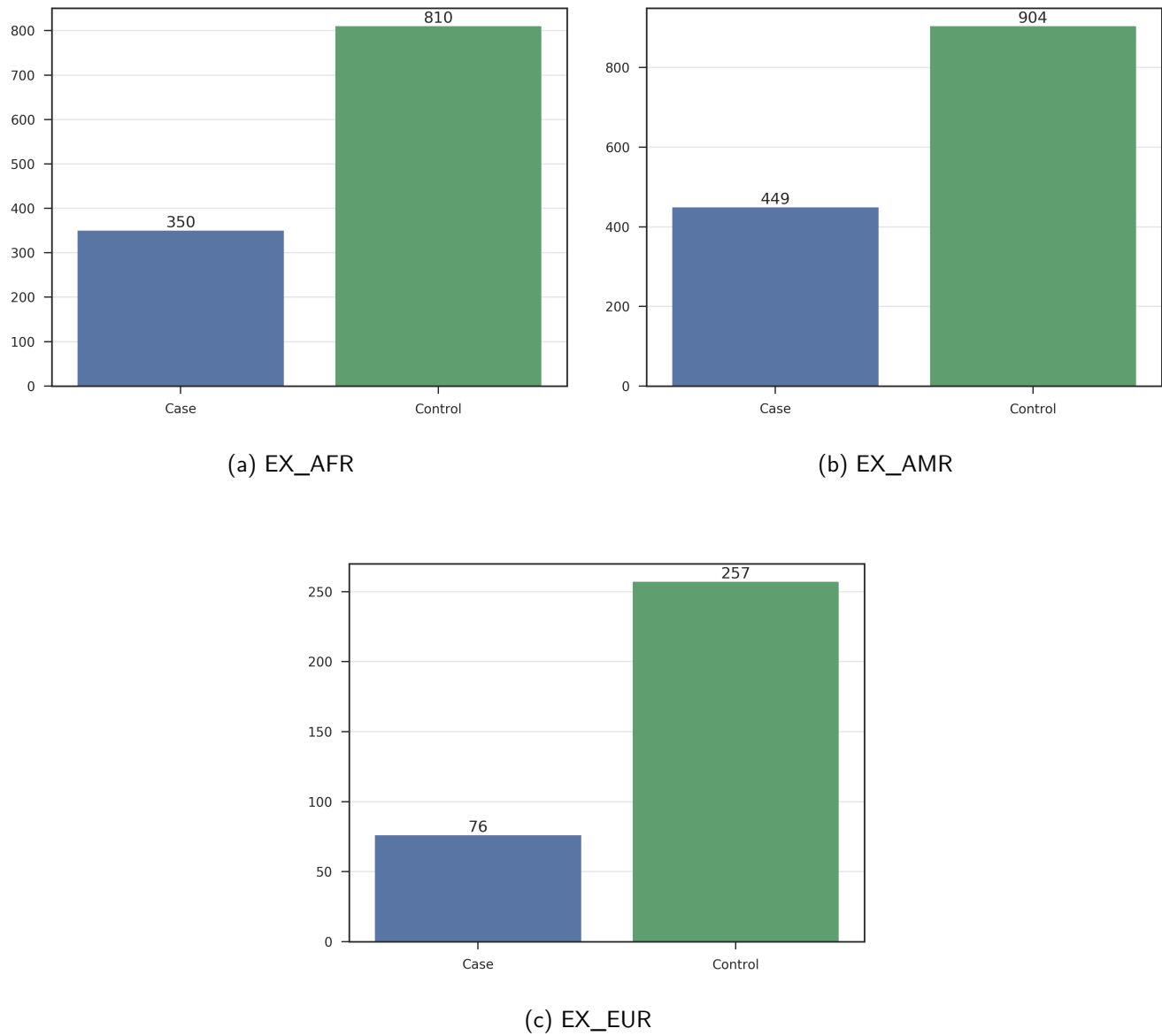
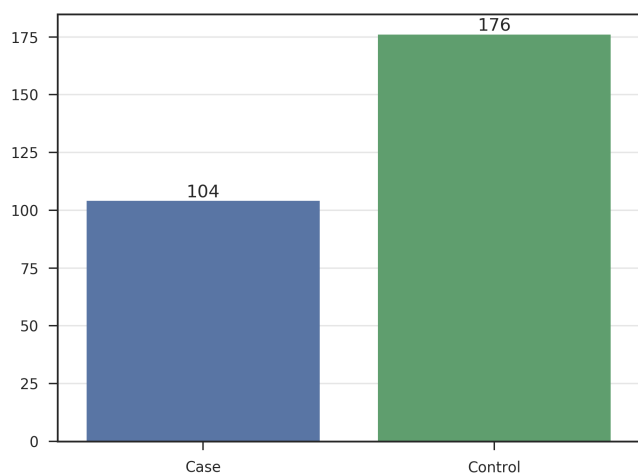
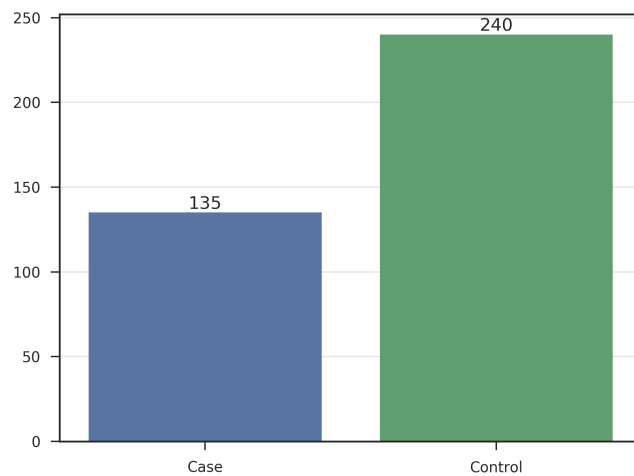


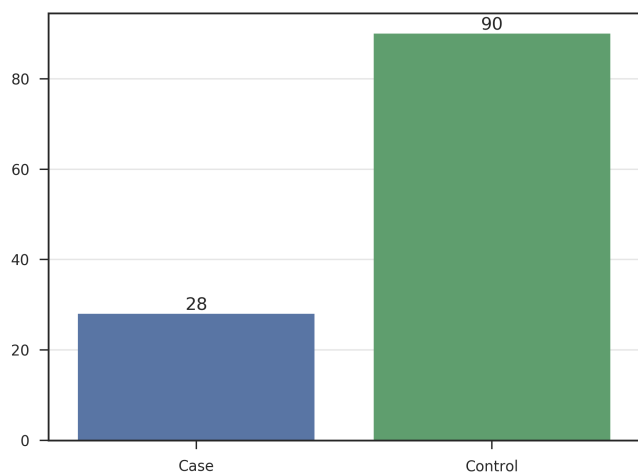
Figure 15: Distribution of PVDinT2Dcases in META_EX by cohort



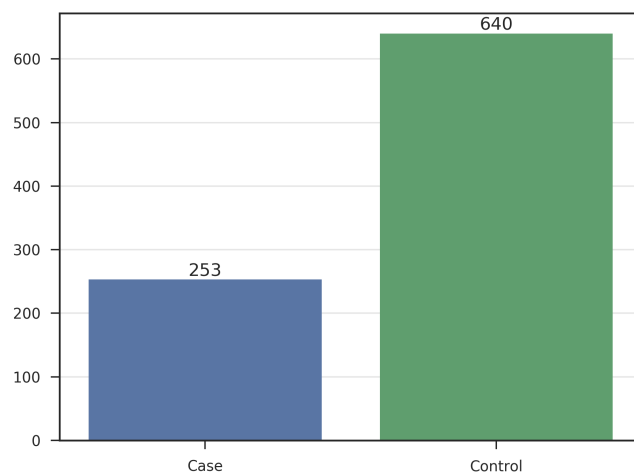
(a) AFFY_AFR



(b) AFFY_AMR



(c) AFFY_EUR



(d) ILL_AFR

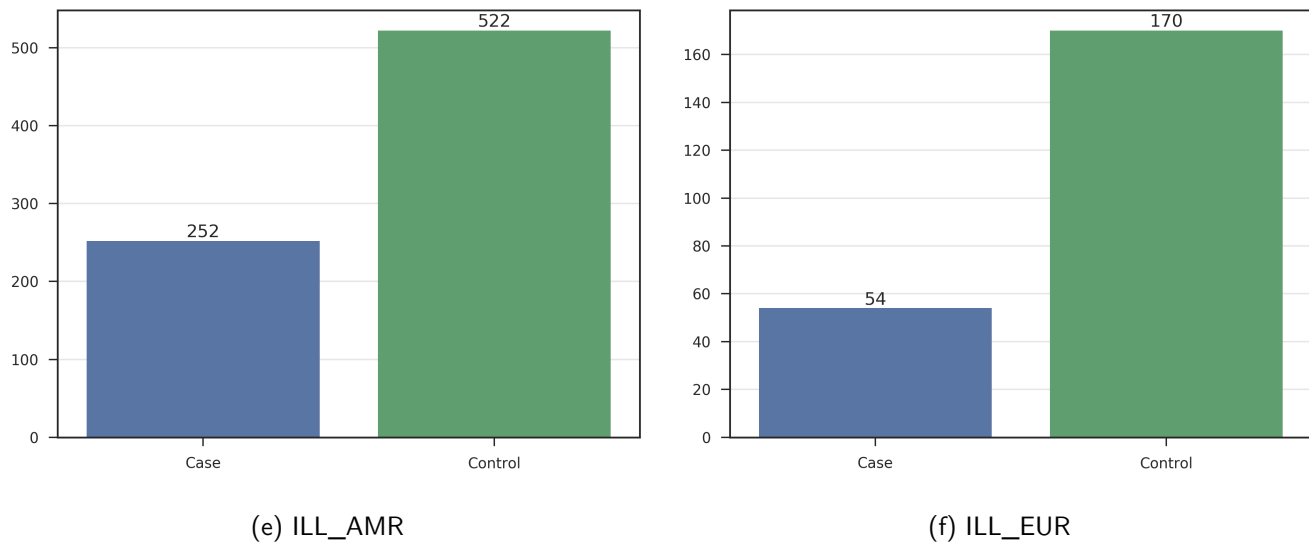


Figure 16: Distribution of PVDinT2Dcases in META_GWAS by cohort

Table 16: Summary of samples removed from Peripheral Vascular Disease in samples with T2D analysis by cohort and model

	Cohort	Array	Ancestry	Trans	Covars	Total	-SampleQc	-KinshipCrossArray	-KinshipArray	-missObs	-PcOutlier
META_EX	EX_AFR	EX	AFR	-	SEX	4892	53	0	323	3447	0
META_EX	EX_AMR	EX	AMR	-	SEX	5425	65	49	491	3588	0
META_EX	EX_EUR	EX	EUR	-	SEX	2379	38	0	9	1999	1
META_GWAS	AFFY_AFR	AFFY	AFR	-	SEX	853	16	141	7	415	0
META_GWAS	AFFY_AMR	AFFY	AMR	-	SEX	1078	22	184	26	469	20
META_GWAS	AFFY_EUR	AFFY	EUR	-	SEX	578	12	7	2	450	0
META_GWAS	ILL_AFR	ILL	AFR	-	SEX	3853	51	0	2	3027	10
META_GWAS	ILL_AMR	ILL	AMR	-	SEX	4111	49	0	0	3172	0
META_GWAS	ILL_EUR	ILL	EUR	-	SEX	1796	22	0	0	1545	7

Table 17: Summary of samples remaining for Peripheral Vascular Disease in samples with T2D analysis by cohort and model

	Cohort	Array	Ancestry	Trans	Covars	PCs	N	Male	Female	Case	Ctrl	
	META_EX	EX_AFR	EX	AFR	-	SEX	0	1069	373	696	324	745
	META_EX	EX_AMR	EX	AMR	-	SEX	8	1232	535	697	417	815
	META_EX	EX_EUR	EX	EUR	-	SEX	9	332	263	69	76	256
	META_GWAS	AFFY_AFR	AFFY	AFR	-	SEX	0	274	105	169	101	173
	META_GWAS	AFFY_AMR	AFFY	AMR	-	SEX	4	357	159	198	131	226
	META_GWAS	AFFY_EUR	AFFY	EUR	-	SEX	0	107	90	17	22	85
	META_GWAS	ILL_AFR	ILL	AFR	-	SEX	9	763	267	496	214	549
	META_GWAS	ILL_AMR	ILL	AMR	-	SEX	5	890	374	516	287	603
	META_GWAS	ILL_EUR	ILL	EUR	-	SEX	2	222	170	52	53	169

6.2 Calibration

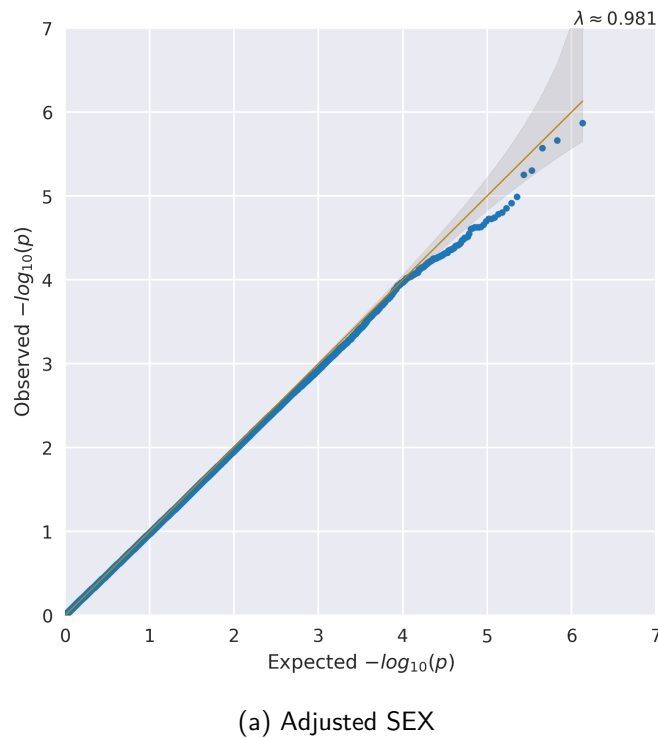
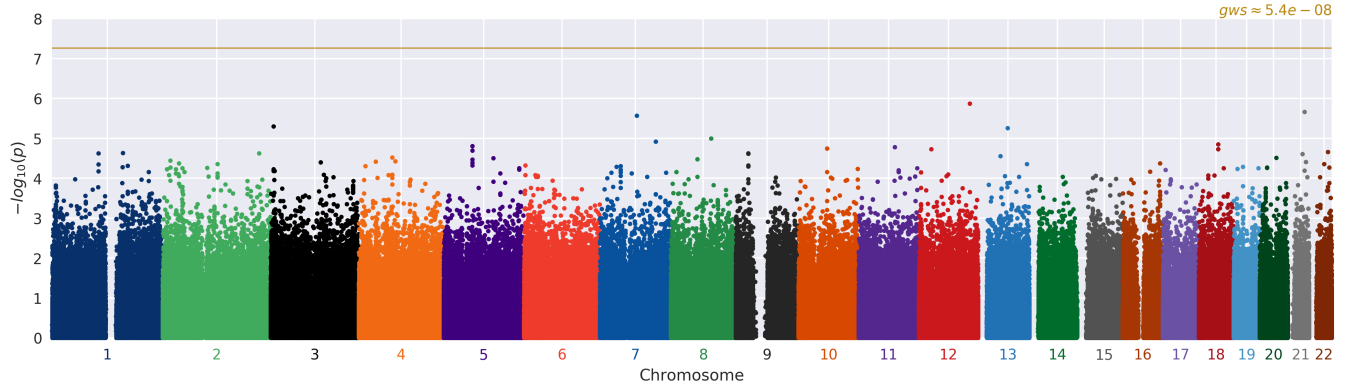


Figure 17: QQ plots for PVDinT2Dcases in the MERGE analysis



(a) Adjusted SEX

Figure 18: Manhattan plots for PVDinT2Dcases in the MERGE analysis

6.3 Top associations

Table 18: Top variants in the MERGE Adjusted SEX model (**bold** variants indicate previously identified associations)

CHR	POS	ID	EA	OA	GENE_CLODEST	COHORT	DIR	N	MALE	FEMALE	CASE	CTRL	FREQ_AVG	FREQ_MIN	FREQ_MAX	EFFECT	STDERR	OR	ZSCORE	P
12	114816360	rs4113925	T	C	TBX5	META_GWAS	++++xxx	1,875	811	1,064	554	1,321	0.324	0.253	0.417	0.373	$7.71 \cdot 10^{-2}$	1.452	4.832	$1.35 \cdot 10^{-6}$
21	37985104	rs1023368	T	G	CLDN14	META_GWAS	++++xxx	1,875	811	1,064	554	1,321	0.884	0.874	0.91	0.524	0.111	1.689	-4.735	$2.19 \cdot 10^{-6}$
7	83191317	rs17157829	G	C	SEMA3E	META_GWAS	xxx+++	631	264	367	232	399	$6.02 \cdot 10^{-2}$	$2.8 \cdot 10^{-2}$	0.102	1.199	0.255	3.316	4.693	$2.69 \cdot 10^{-6}$
3	5826383	rs6442990	G	T	EDEM1	META_GWAS	++++xxx	1,875	811	1,064	554	1,321	0.579	0.387	0.818	0.359	$7.86 \cdot 10^{-2}$	1.432	-4.566	$4.97 \cdot 10^{-6}$
13	66181960	rs1417218	A	C	PCDH9	META_GWAS	++++xxx	1,875	811	1,064	554	1,321	0.297	0.194	0.406	0.374	$8.24 \cdot 10^{-2}$	1.454	-4.543	$5.55 \cdot 10^{-6}$
8	90656988	rs160441	C	T	RIPK2	META_EX	+++	2,632	1,170	1,462	816	1,816	0.532	0.473	0.605	0.266	$6.04 \cdot 10^{-2}$	1.305	4.414	$1.02 \cdot 10^{-5}$
7	125508794	rs9649018	A	C	GRM8	META_GWAS	++++xxx	1,865	805	1,060	552	1,313	0.368	0.342	0.459	0.334	$7.64 \cdot 10^{-2}$	1.397	-4.375	$1.21 \cdot 10^{-5}$
18	43958173	rs1470324	G	A	RNF165	META_GWAS	+++++	2,613	1,165	1,448	808	1,805	0.563	0.507	0.667	0.267	$6.14 \cdot 10^{-2}$	1.306	-4.343	$1.4 \cdot 10^{-5}$
5	64699702	rs10065799	C	G	CENPK	META_GWAS	xxx+++	734	352	382	253	481	0.668	0.443	0.86	0.557	0.129	1.745	-4.319	$1.56 \cdot 10^{-5}$
11	80975989	rs2514486	C	T	FAM181B	META_GWAS	++++xxx	1,875	811	1,064	554	1,321	0.273	$7.8 \cdot 10^{-2}$	0.471	0.386	$8.95 \cdot 10^{-2}$	1.47	-4.307	$1.65 \cdot 10^{-5}$
10	64148125	rs3852424	C	A	ZNF365	META_GWAS	xxx+++	631	264	367	232	399	0.891	0.834	0.934	0.821	0.191	2.273	-4.289	$1.8 \cdot 10^{-5}$
12	27863792	rs35475802	C	A	MRPS35	META_EX	x++	2,301	908	1,393	741	1,560	$5.5 \cdot 10^{-2}$	$2.23 \cdot 10^{-2}$	$9.26 \cdot 10^{-2}$	0.663	0.155	1.94	-4.281	$1.86 \cdot 10^{-5}$
18	43303089	rs10460032	A	G	SLC14A1	META_GWAS	++++xxx	1,874	810	1,064	554	1,320	0.608	0.434	0.863	0.33	$7.71 \cdot 10^{-2}$	1.391	-4.279	$1.87 \cdot 10^{-5}$
22	42622915	rs5996132	C	T	TCF20	META_GWAS	xxx+++	631	264	367	232	399	0.151	$6.72 \cdot 10^{-2}$	0.261	0.74	0.174	2.096	4.243	$2.2 \cdot 10^{-5}$
1	159815940	rs2501353	G	T	C1orf204	META_GWAS	+++++	2,613	1,165	1,448	808	1,805	0.88	0.788	0.943	0.397	$9.38 \cdot 10^{-2}$	1.487	-4.23	$2.34 \cdot 10^{-5}$
1	104887259	rs10785866	A	G	AMY1C	META_GWAS	++++xxx	1,875	811	1,064	554	1,321	0.797	0.642	0.872	0.402	$9.52 \cdot 10^{-2}$	1.495	4.228	$2.36 \cdot 10^{-5}$
9	27949504	rs145458168	A	C	LINGO2	META_EX	x++	2,301	908	1,393	741	1,560	$7.61 \cdot 10^{-3}$	$6.09 \cdot 10^{-3}$	$9.35 \cdot 10^{-3}$	1.444	0.342	4.239	4.228	$2.36 \cdot 10^{-5}$
2	216486673	rs1519016	C	A	FN1	META_GWAS	+++++	2,613	1,165	1,448	808	1,805	0.371	0.223	0.489	0.267	$6.32 \cdot 10^{-2}$	1.306	4.227	$2.37 \cdot 10^{-5}$
21	32914173	rs7278455	G	A	TIAM1	META_GWAS	xxx+++	737	353	384	254	483	0.305	0.23	0.423	0.525	0.124	1.69	-4.216	$2.48 \cdot 10^{-5}$
13	49796038	rs7326106	C	T	MLNR	META_GWAS	x++++	1,653	641	1,012	501	1,152	$3.42 \cdot 10^{-2}$	$2.19 \cdot 10^{-2}$	$4.85 \cdot 10^{-2}$	0.85	0.203	2.339	4.189	$2.8 \cdot 10^{-5}$

7 Myocardial Infarction in samples with T2D (MlinT2Dcases)

7.1 Summary

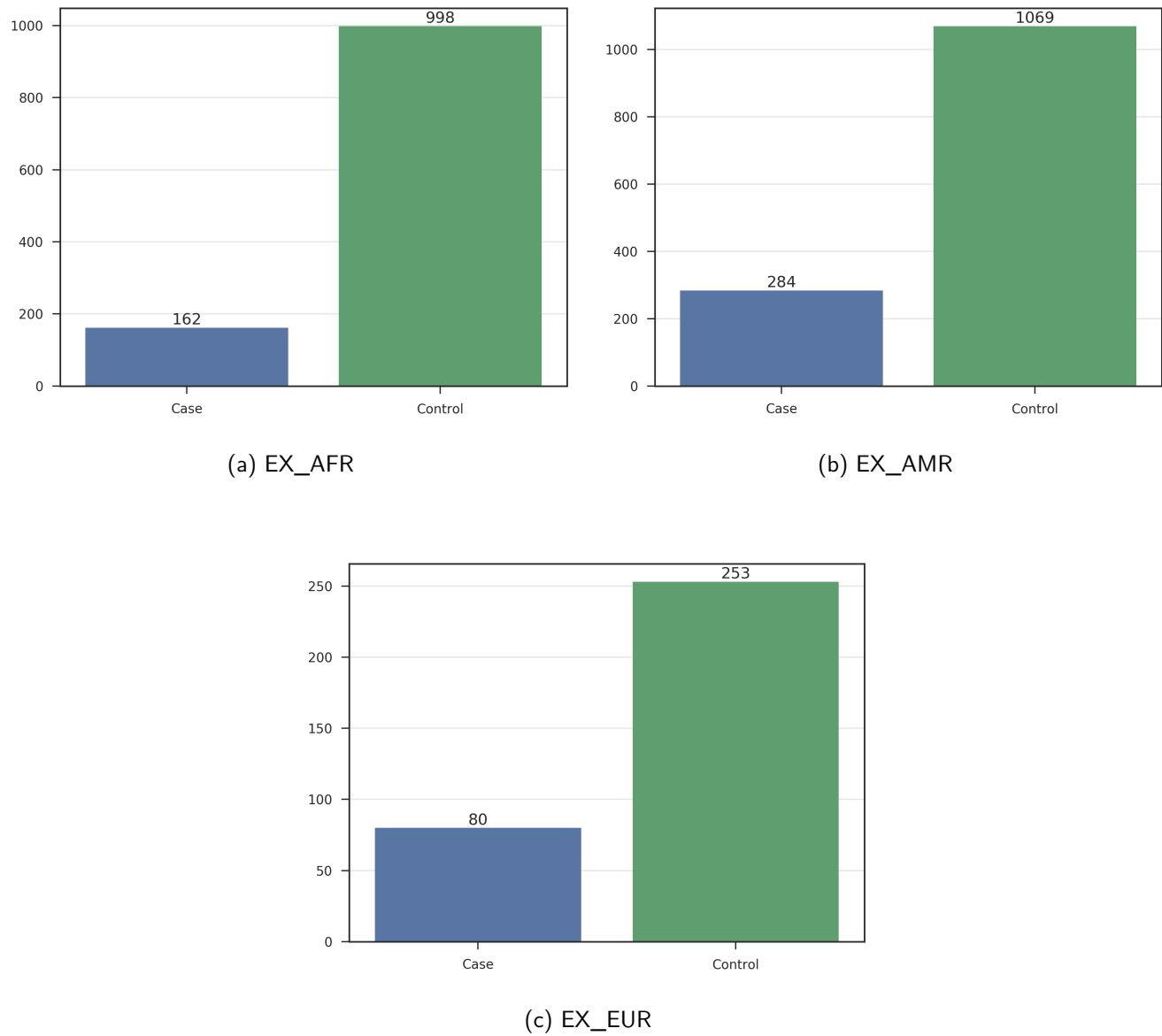
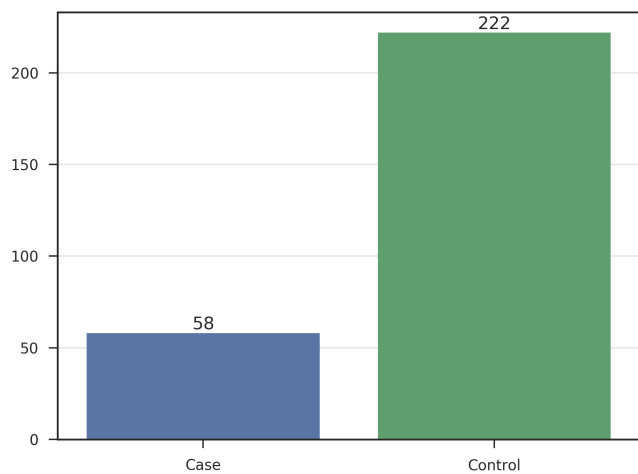
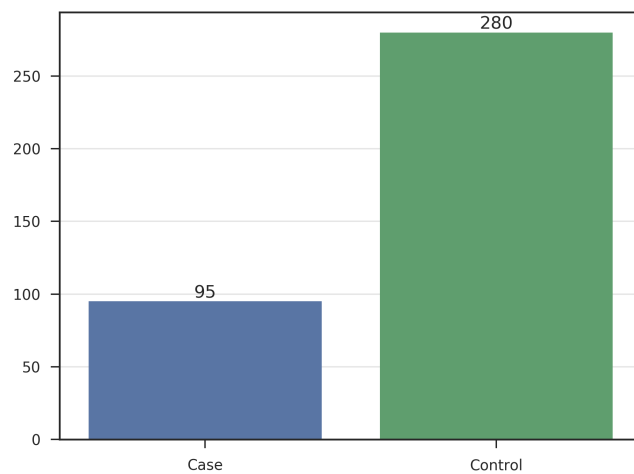


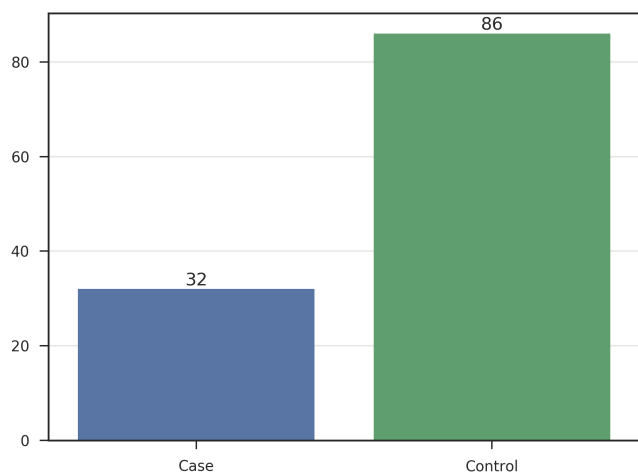
Figure 19: Distribution of MlinT2Dcases in META_EX by cohort



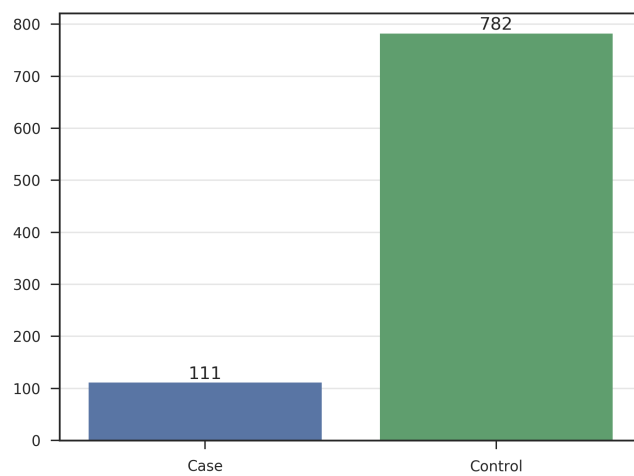
(a) AFFY_AFR



(b) AFFY_AMR



(c) AFFY_EUR



(d) ILL_AFR

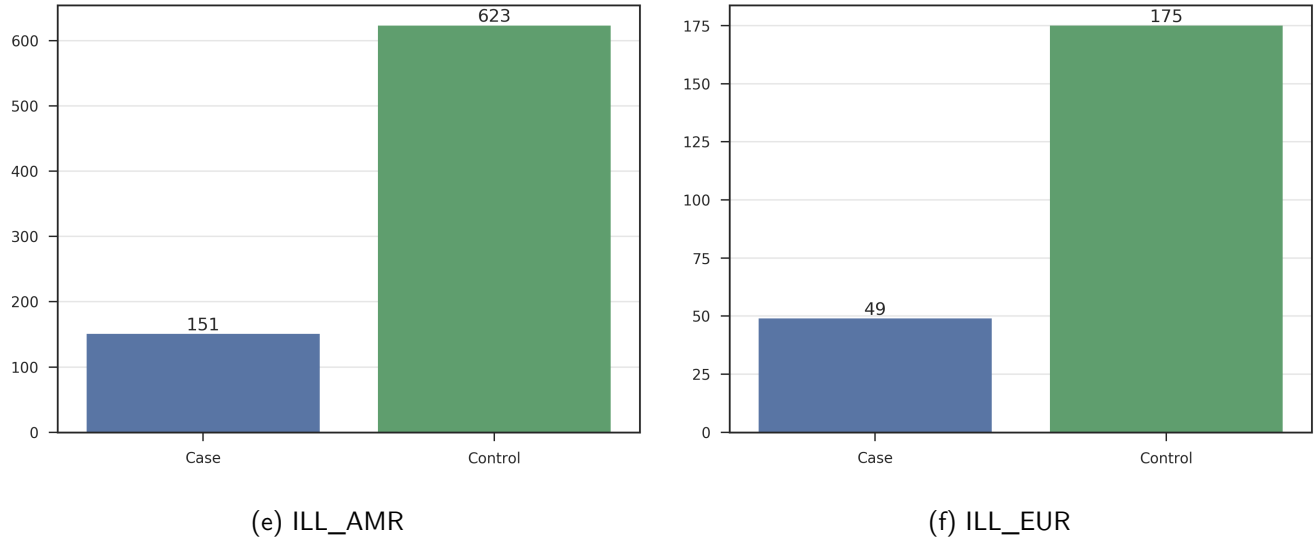


Figure 20: Distribution of MlinT2Dcases in META_GWAS by cohort

Table 19: Summary of samples removed from Myocardial Infarction in samples with T2D analysis by cohort and model

	Cohort	Array	Ancestry	Trans	Covars	Total	-SampleQc	-KinshipCrossArray	-KinshipArray	-missObs	-PcOutlier
META_EX	EX_AFR	EX	AFR	-	SEX	4892	53	0	324	3445	1
META_EX	EX_AMR	EX	AMR	-	SEX	5425	65	49	491	3586	0
META_EX	EX_EUR	EX	EUR	-	SEX	2379	38	0	9	1999	0
META_GWAS	AFFY_AFR	AFFY	AFR	-	SEX	853	16	141	7	415	4
META_GWAS	AFFY_AMR	AFFY	AMR	-	SEX	1078	22	184	26	469	0
META_GWAS	AFFY_EUR	AFFY	EUR	-	SEX	578	12	7	2	450	0
META_GWAS	ILL_AFR	ILL	AFR	-	SEX	3853	51	0	2	3027	10
META_GWAS	ILL_AMR	ILL	AMR	-	SEX	4111	49	0	0	3172	0
META_GWAS	ILL_EUR	ILL	EUR	-	SEX	1796	22	0	0	1545	0

Table 20: Summary of samples remaining for Myocardial Infarction in samples with T2D analysis by cohort and model

	Cohort	Array	Ancestry	Trans	Covars	PCs	N	Male	Female	Case	Ctrl	
	META_EX	EX_AFR	EX	AFR	-	SEX	1	1069	373	696	147	922
	META_EX	EX_AMR	EX	AMR	-	SEX	9	1234	536	698	266	968
	META_EX	EX_EUR	EX	EUR	-	SEX	0	333	264	69	80	253
	META_GWAS	AFFY_AFR	AFFY	AFR	-	SEX	0	270	102	168	56	214
	META_GWAS	AFFY_AMR	AFFY	AMR	-	SEX	0	377	169	208	93	284
	META_GWAS	AFFY_EUR	AFFY	EUR	-	SEX	0	107	90	17	29	78
	META_GWAS	ILL_AFR	ILL	AFR	-	SEX	9	763	267	496	87	676
	META_GWAS	ILL_AMR	ILL	AMR	-	SEX	5	890	374	516	172	718
	META_GWAS	ILL_EUR	ILL	EUR	-	SEX	0	229	173	56	51	178

7.2 Calibration

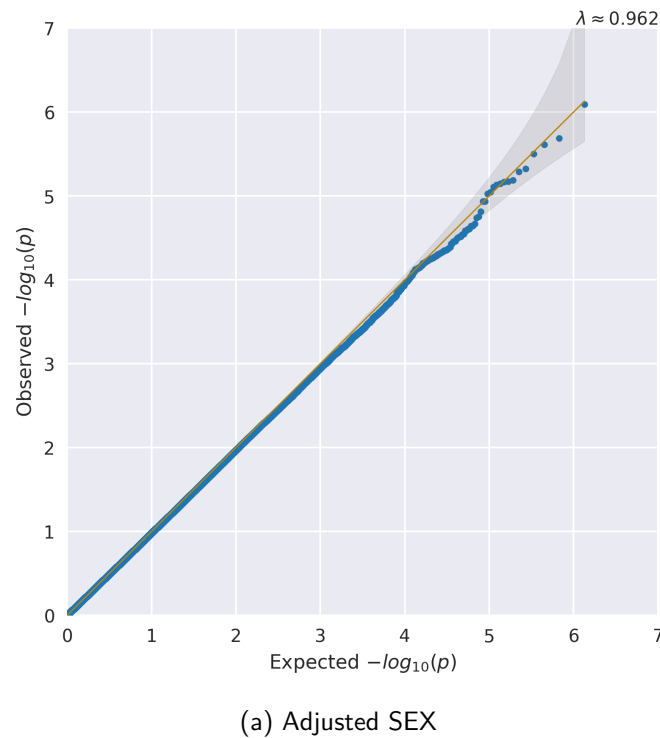
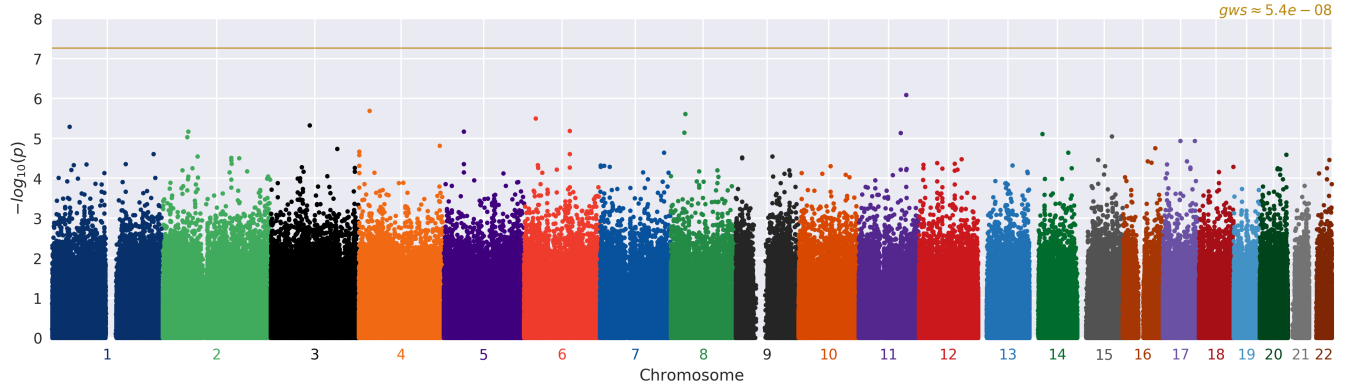


Figure 21: QQ plots for MlinT2Dcases in the MERGE analysis



(a) Adjusted SEX

Figure 22: Manhattan plots for MlinT2Dcases in the MERGE analysis

7.3 Top associations

Table 21: Top variants in the MERGE Adjusted SEX model (**bold** variants indicate previously identified associations)

CHR	POS	ID	EA	OA	GENE _{CLOSEST}	COHORT	DIR	N	MALE	FEMALE	CASE	CTRL	FREQ _{AVG}	FREQ _{MIN}	FREQ _{MAX}	EFFECT	STDERR	OR	ZSCORE	P
11	106941553	rs1840572	G	A	GUCY1A2	META_GWAS	+++++	2,636	1,175	1,461	488	2,148	0.12	$6.29 \cdot 10^{-2}$	0.172	0.58	0.117	1.785	-4.932	$8.12 \cdot 10^{-7}$
4	23994155	rs6833157	A	G	PPARGC1A	META_GWAS	+++xxx	1,881	813	1,068	310	1,571	0.215	0.205	0.224	0.566	0.119	1.761	-4.747	$2.06 \cdot 10^{-6}$
8	32587074	rs7845747	C	T	NRG1	META_GWAS	xxx+++	754	361	393	178	576	$6.43 \cdot 10^{-2}$	$5.61 \cdot 10^{-2}$	$7.78 \cdot 10^{-2}$	1.068	0.227	2.909	4.712	$2.46 \cdot 10^{-6}$
6	26456280	rs9348718	A	G	BTN2A1	META_GWAS	xxx+++	754	361	393	178	576	0.175	$7.94 \cdot 10^{-2}$	0.289	0.845	0.181	2.327	-4.66	$3.16 \cdot 10^{-6}$
3	87200635	rs1844097	C	G	CHMP2B	META_GWAS	xxx+++	754	361	393	178	576	0.237	$9.07 \cdot 10^{-2}$	0.43	0.724	0.158	2.064	-4.577	$4.72 \cdot 10^{-6}$
1	40030823	rs121217094	T	C	PABPC4	META_GWAS	+++xxx	1,881	814	1,067	310	1,571	$4.36 \cdot 10^{-2}$	$1.51 \cdot 10^{-2}$	$7.89 \cdot 10^{-2}$	0.828	0.182	2.289	4.559	$5.13 \cdot 10^{-6}$
6	103225137	rs6900311	G	T	GRIK2	META_EX	+++	2,636	1,173	1,463	493	2,143	0.38	0.293	0.467	0.329	$7.3 \cdot 10^{-2}$	1.39	4.509	$6.52 \cdot 10^{-6}$
2	57155524	rs17048511	G	C	CCDC85A	META_GWAS	xxx+++	647	271	376	149	498	$5.1 \cdot 10^{-2}$	$2.79 \cdot 10^{-2}$	$8.33 \cdot 10^{-2}$	1.246	0.277	3.477	4.503	$6.71 \cdot 10^{-6}$
5	45298611	rs6864928	G	C	HCN1	META_GWAS	xxx+++	749	359	390	178	571	0.421	0.114	0.634	0.608	0.135	1.837	-4.5	$6.79 \cdot 10^{-6}$
8	30809614	rs11990181	T	C	PURG	META_GWAS	+++xxx	1,881	813	1,068	310	1,571	0.537	0.253	0.791	0.464	0.103	1.591	-4.49	$7.14 \cdot 10^{-6}$
11	94060134	rs11601246	T	C	IZUMO1R	META_GWAS	+++xxx	1,882	814	1,068	310	1,572	$9.51 \cdot 10^{-2}$	$5.31 \cdot 10^{-2}$	0.151	0.604	0.135	1.83	4.483	$7.34 \cdot 10^{-6}$
14	29213100	rs17145596	T	C	FOXG1	META_GWAS	xxx+++	754	361	393	178	576	$8.95 \cdot 10^{-2}$	$7.01 \cdot 10^{-2}$	0.122	0.86	0.192	2.364	4.471	$7.78 \cdot 10^{-6}$
15	78581938	rs16969675	A	C	WDR61	META_GWAS	+++xxx	1,882	814	1,068	310	1,572	0.648	0.624	0.672	0.43	$9.68 \cdot 10^{-2}$	1.537	4.441	$8.95 \cdot 10^{-6}$
2	55134309	rs4671992	T	C	EML6	META_GWAS	+++xxx	1,882	814	1,068	310	1,572	0.53	0.493	0.551	0.397	$8.97 \cdot 10^{-2}$	1.488	4.431	$9.37 \cdot 10^{-6}$
17	71926893	rs7223619	T	C	RPL38	META_GWAS	xxx+++	754	361	393	178	576	0.66	0.486	0.78	0.599	0.137	1.821	4.385	$1.16 \cdot 10^{-5}$
17	39969369	rs202017366	A	G	FKBP10	META_EX	xx+	1,234	536	698	266	968	$1.66 \cdot 10^{-2}$	$1.66 \cdot 10^{-2}$	$1.66 \cdot 10^{-2}$	1.46	0.333	4.305	4.384	$1.16 \cdot 10^{-5}$
4	181748293	rs17070115	T	C	TENM3	META_GWAS	xxx+++	647	271	376	149	498	$1.16 \cdot 10^{-2}$	$5.31 \cdot 10^{-3}$	$2.04 \cdot 10^{-2}$	2.243	0.519	9.417	4.324	$1.54 \cdot 10^{-5}$
16	73438386	rs41325148	C	G	ZFX3	META_GWAS	xxx+++	754	361	393	178	576	$9.55 \cdot 10^{-2}$	$7.29 \cdot 10^{-2}$	0.135	1.094	0.255	2.985	-4.294	$1.76 \cdot 10^{-5}$
3	149242016	rs17195624	G	A	WWTR1	META_GWAS	+++xxx	1,882	814	1,068	310	1,572	0.167	0.163	0.17	0.483	0.113	1.621	4.285	$1.83 \cdot 10^{-5}$
4	1174861	rs4974641	G	A	SPON2	META_GWAS	xxx+++	647	271	376	149	498	0.905	0.852	0.943	0.927	0.218	2.526	-4.249	$2.14 \cdot 10^{-5}$

7.4 Previously identified risk loci

Table 22 shows statistics from the MERGE cohort for 34 loci that were shown to be significantly associated with Myocardial Infarction in samples with T2D in the 2017 Journal of the American College of Cardiology paper by Webb et al [9]. Where a previously reported variant was not genotyped in the study (indicated by $\bar{R}^2 < 1$), if available, a tagging variant in LD with the reported variant ($\bar{R}^2 \geq 0.7$ and within 250kb) was provided. Tags were identified using 1000 Genomes data. There are 3 variants that show at least nominal significance ($p < 0.05$) in this study. Out of the 34 variants in both studies, 22 exhibit the same direction of effect with the known result (binomial test $p = 0.0607$).

Table 22: Top known loci in MERGE model Adjusted SEX (**bold** variants indicate matching direction of effect)

CHR	POS	ID	EA	OA	N	CASE	CTRL	FREQ _{AVG}	FREQ _{MIN}	FREQ _{MAX}	OR	P	DIR	COHORT	GENE _{CLOSEST}	R ²	ID _{KNOWN}	N _{KNOWN}	CASE _{KNOWN}	CTRL _{KNOWN}	OR _{KNOWN}	P _{KNOWN}
9	22125503	rs1333049	C	G	2,636	493	2,143	0.376	0.244	0.523	1.04	0.601	+-	META_EX	CDKN2B	1	rs1333049	1.21 · 10 ⁵	42,335	78,240	1.187	5.69 · 10 ⁻⁷⁴
6	12903957	rs9349379	A	G	2,636	493	2,143	0.223	6.41 · 10 ⁻²	0.374	1.032	0.719	+-	META_EX	PHACTR1	1	rs9349379	1.21 · 10 ⁵	42,335	78,240	0.888	8.61 · 10 ⁻³⁶
1	109817590	rs12740374	G	T	2,636	493	2,143	0.227	0.182	0.241	1.201	3.72 · 10 ⁻²	+++	META_EX	CELSR2	1	rs12740374	1.21 · 10 ⁵	42,335	78,240	1.122	1.13 · 10 ⁻²³
6	160863532	rs2048327	T	C	2,637	493	2,144	0.232	7.76 · 10 ⁻²	0.349	1.003	0.975	+++	META_EX	SLC22A3	1	rs2048327	1.21 · 10 ⁵	42,335	78,240	0.913	8.11 · 10 ⁻²¹
1	109822166	rs599839	A	G	2,636	492	2,144	0.494	0.245	0.814	1.097	0.261	+++	META_EX	PSRC1	1	rs599839	1.21 · 10 ⁵	42,335	78,240	1.114	8.47 · 10 ⁻²¹
19	11202306	rs6511720	T	G	2,637	493	2,144	0.126	0.106	0.155	1.056	0.61	+++	META_EX	LDLR	1	rs6511720	1.21 · 10 ⁵	42,335	78,240	0.874	2.28 · 10 ⁻¹⁹
9	136149399	rs507666	A	G	2,637	493	2,144	0.129	9.68 · 10 ⁻²	0.182	1.005	0.959	+-	META_EX	ABO	1	rs507666	1.21 · 10 ⁵	42,335	78,240	1.101	9.31 · 10 ⁻¹⁷
10	91004886	rs2246942	G	A	2,636	493	2,143	0.42	0.338	0.433	1.036	0.633	---	META_EX	LIPA	1	rs2246942	1.21 · 10 ⁵	42,335	78,240	1.093	3.04 · 10 ⁻¹⁶
2	203880992	rs2351524	T	C	2,637	493	2,144	0.911	0.866	0.948	1.329	1.52 · 10 ⁻²	+++	META_EX	NBEAL1	1	rs2351524	1.21 · 10 ⁵	42,335	78,240	1.115	2.26 · 10 ⁻¹⁵
1	222823529	rs17465637	C	A	2,636	493	2,143	0.43	0.261	0.751	1.15	6.37 · 10 ⁻²	+++	META_EX	MIA3	1	rs17465637	1.21 · 10 ⁵	42,335	78,240	1.085	1.22 · 10 ⁻¹⁴
12	112007756	rs653178	T	C	2,637	493	2,144	0.767	0.467	0.937	1.078	0.391	+++	META_EX	ATXN2	1	rs653178	1.21 · 10 ⁵	42,335	78,240	0.931	2.5 · 10 ⁻¹³
2	216304384	rs1250229	C	T	2,637	493	2,144	0.793	0.737	0.802	1.002	0.982	+-	META_EX	FN1	1	rs1250229	1.21 · 10 ⁵	42,335	78,240	0.928	1.22 · 10 ⁻¹²
10	44753867	rs501120	T	C	2,636	493	2,143	0.338	0.179	0.459	1.037	0.648	+++	META_EX	C10orf142	1	rs501120	1.21 · 10 ⁵	42,335	78,240	1.097	1.99 · 10 ⁻¹¹
6	160681393	rs3127573	A	G	2,637	493	2,144	0.115	6.91 · 10 ⁻²	0.155	1.3	3.13 · 10 ⁻²	+++	META_EX	SLC22A2	1	rs3127573	1.21 · 10 ⁵	42,335	78,240	0.911	2.09 · 10 ⁻¹¹
8	126507389	rs2954038	C	A	2,637	493	2,144	0.806	0.61	0.891	1.126	0.174	---	META_EX	TRIB1	1	rs2954038	1.21 · 10 ⁵	42,335	78,240	1.069	3.18 · 10 ⁻¹¹
11	10360567	rs974819	T	C	2,635	493	2,142	0.596	0.5	0.663	1.045	0.568	---	META_EX	PDGFD	1	rs974819	1.21 · 10 ⁵	42,335	78,240	1.07	4.1 · 10 ⁻¹¹
19	11163601	rs1122608	G	T	2,637	493	2,144	0.124	4.96 · 10 ⁻²	0.269	1.01	0.926	+++	META_EX	SMARCA4	1	rs1122608	1.21 · 10 ⁵	42,335	78,240	1.073	1.02 · 10 ⁻¹⁰
6	161143608	rs4252120	C	T	2,637	493	2,144	0.211	0.186	0.29	1.064	0.469	+-	META_EX	PLG	1	rs4252120	1.21 · 10 ⁵	42,335	78,240	0.937	2.62 · 10 ⁻¹⁰
12	125307053	rs11057830	A	G	2,637	493	2,144	0.177	0.164	0.191	1.007	0.939	++	META_EX	SCARB1	1	rs11057830	1.21 · 10 ⁵	42,335	78,240	1.085	3.69 · 10 ⁻¹⁰
1	56965664	rs9970807	T	C	2,637	493	2,144	0.14	9.61 · 10 ⁻²	0.181	1.018	0.864	++	META_EX	PLPP3	1	rs9970807	1.21 · 10 ⁵	42,335	78,240	0.901	4.55 · 10 ⁻¹⁰
12	112072424	rs11065987	A	G	2,636	493	2,143	0.211	5.57 · 10 ⁻²	0.499	1.134	0.16	+++	META_EX	BRAP	1	rs11065987	1.21 · 10 ⁵	42,335	78,240	0.942	1.73 · 10 ⁻⁹
21	35599128	rs9982601	T	C	2,636	493	2,143	0.178	0.117	0.243	1.064	0.511	++	META_EX	MRP56	1	rs9982601	1.21 · 10 ⁵	42,335	78,240	1.084	3.51 · 10 ⁻⁹
12	112486818	rs17696736	A	G	2,637	493	2,144	0.215	5.75 · 10 ⁻²	0.514	1.137	0.152	+++	META_EX	NAA25	1	rs17696736	1.21 · 10 ⁵	42,335	78,240	0.945	8.2 · 10 ⁻⁹
2	44074431	rs4245791	C	T	2,637	493	2,144	0.802	0.691	0.871	1.073	0.426	---	META_EX	ABCG8	1	rs4245791	1.21 · 10 ⁵	42,335	78,240	1.058	1.69 · 10 ⁻⁸
1	55496039	rs11206510	T	C	2,637	493	2,144	0.135	0.118	0.186	1.021	0.842	+++	META_EX	PCSK9	1	rs11206510	1.21 · 10 ⁵	42,335	78,240	1.071	1.7 · 10 ⁻⁸
12	57527283	rs11172113	C	T	2,637	493	2,144	0.454	0.398	0.47	1.059	0.419	+++	META_EX	LRP1	1	rs11172113	1.21 · 10 ⁵	42,335	78,240	1.055	1.78 · 10 ⁻⁸
15	79111093	rs4380028	T	C	2,636	493	2,143	0.323	0.22	0.407	1.077	0.334	+++	META_EX	MORF4L1	1	rs4380028	1.21 · 10 ⁵	42,335	78,240	0.947	1.81 · 10 ⁻⁸
3	138119952	rs2306374	C	T	2,637	493	2,144	7.96 · 10 ⁻²	6.41 · 10 ⁻²	0.128	1.118	0.383	---	META_EX	MRAS	1	rs2306374	1.21 · 10 ⁵	42,335	78,240	1.074	1.83 · 10 ⁻⁸
10	104652323	rs11191447	C	T	2,637	493	2,144	8.27 · 10 ⁻²	5.85 · 10 ⁻²	0.101	1.182	0.199	++	META_EX	BORCS7-ASMT	1	rs11191447	1.21 · 10 ⁵	42,335	78,240	1.099	2.16 · 10 ⁻⁸
16	56995236	rs1800775	A	C	2,637	493	2,144	0.522	0.464	0.569	1.028	0.702	---	META_EX	CETP	1	rs1800775	1.21 · 10 ⁵	42,335	78,240	0.946	2.21 · 10 ⁻⁸
10	104906211	rs11191580	T	C	2,632	493	2,139	6.31 · 10 ⁻²	1.88 · 10 ⁻²	0.101	1.249	0.127	+++	META_EX	NT5C2	1	rs11191580	1.21 · 10 ⁵	42,335	78,240	1.099	2.78 · 10 ⁻⁸
10	30335122	rs2505083	C	T	2,637	493	2,144	0.248	8.79 · 10 ⁻²	0.398	1.08	0.355	+++	META_EX	KIAA1462	1	rs2505083	1.21 · 10 ⁵	42,335	78,240	1.054	2.91 · 10 ⁻⁸
11	10745394	rs11042937	T	G	2,637	493	2,144	0.666	0.489	0.718	1.112	0.165	---	META_EX	CTR9	1	rs11042937	1.21 · 10 ⁵	42,335	78,240	1.053	3.21 · 10 ⁻⁸
10	104719096	rs12413409	G	A	2,637	493	2,144	8 · 10 ⁻²	5.57 · 10 ⁻²	0.101	1.173	0.226	++	META_EX	CNNM2	1	rs12413409	1.21 · 10 ⁵	42,335	78,240	1.097	4.46 · 10 ⁻⁸

8 Claudication in samples with T2D (CLAUDICATIONinT2Dcases)

8.1 Summary

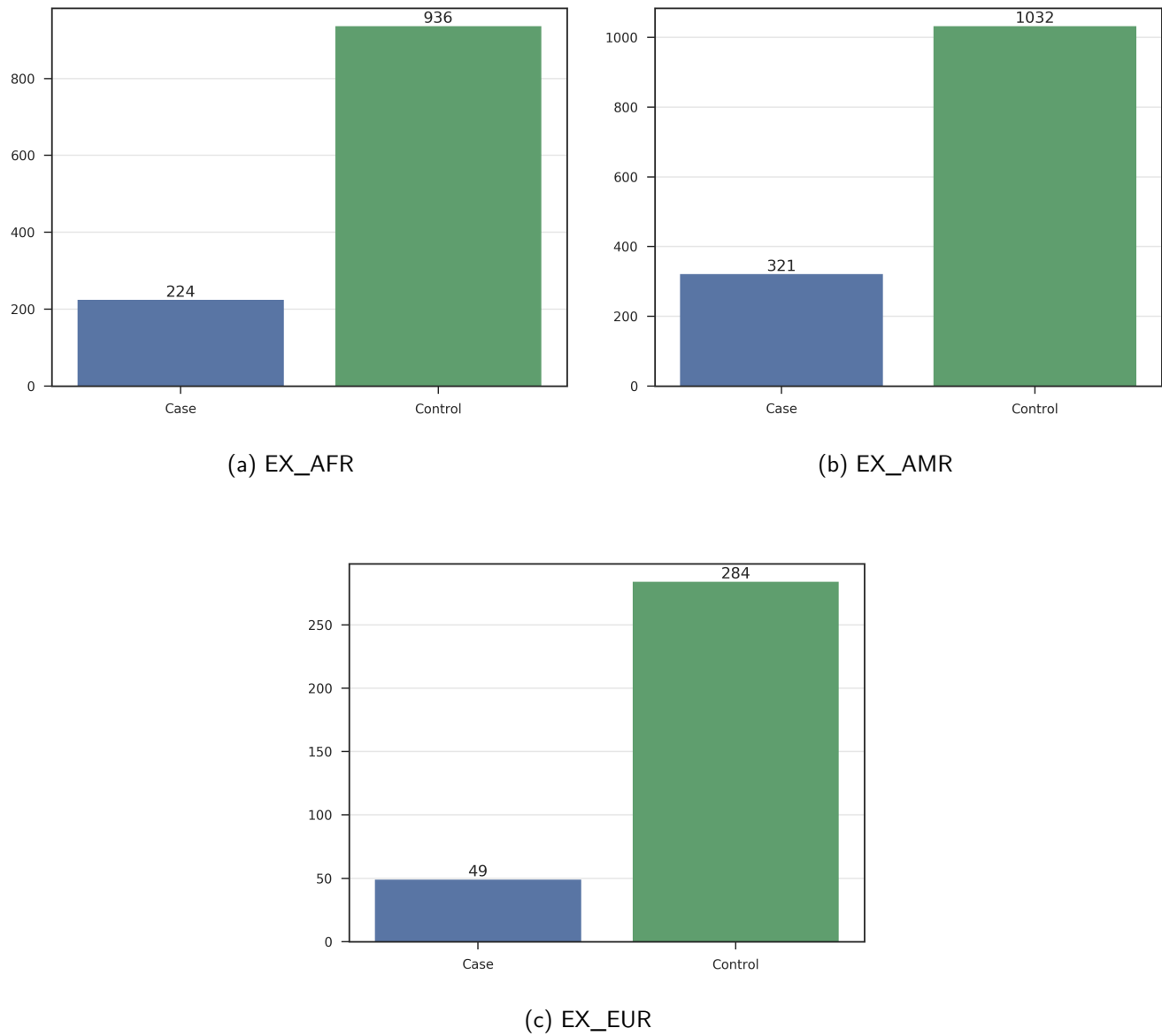
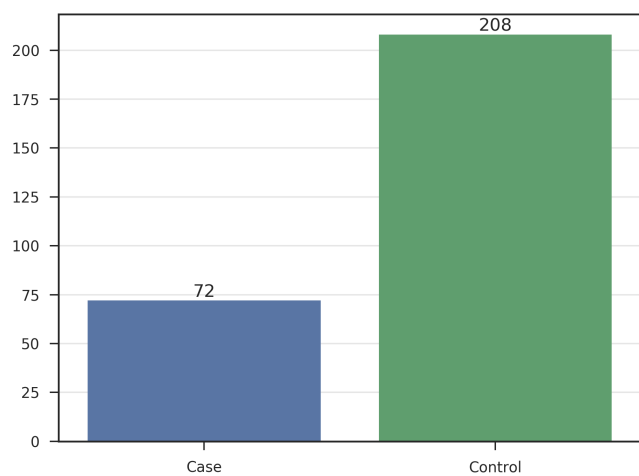
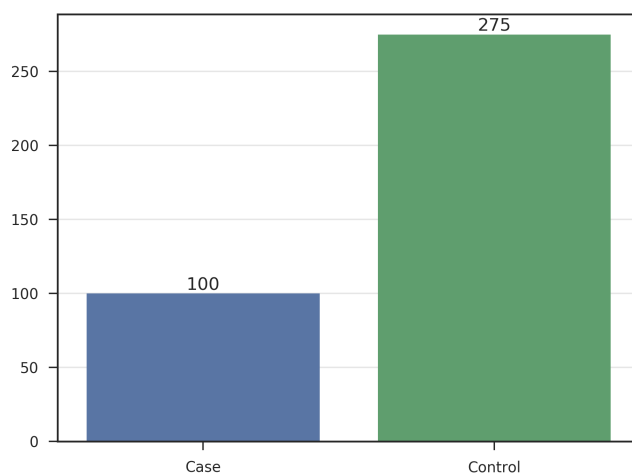


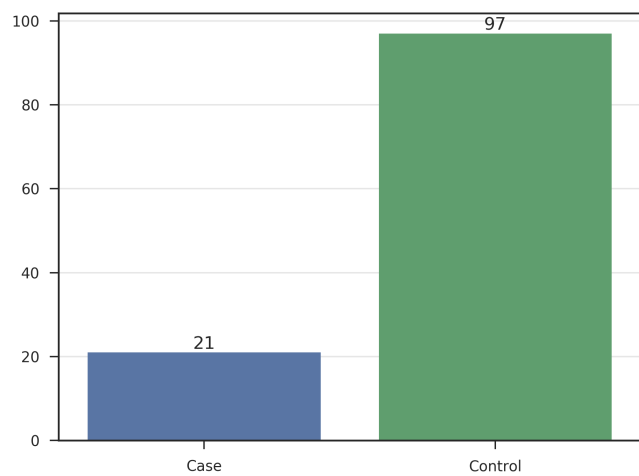
Figure 23: Distribution of CLAUDICATIONinT2Dcases in META_EX by cohort



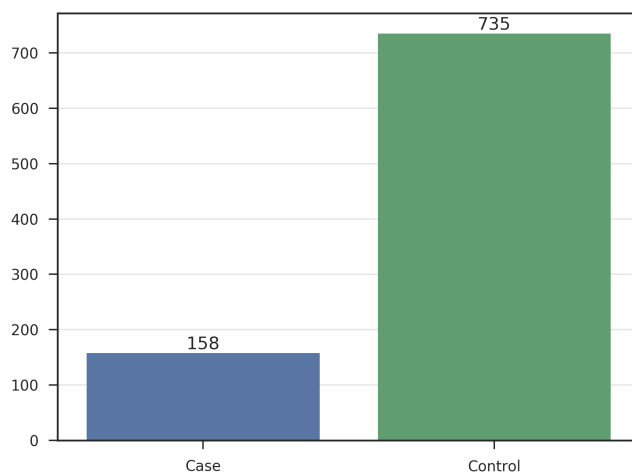
(a) AFFY_AFR



(b) AFFY_AMR



(c) AFFY_EUR



(d) ILL_AFR

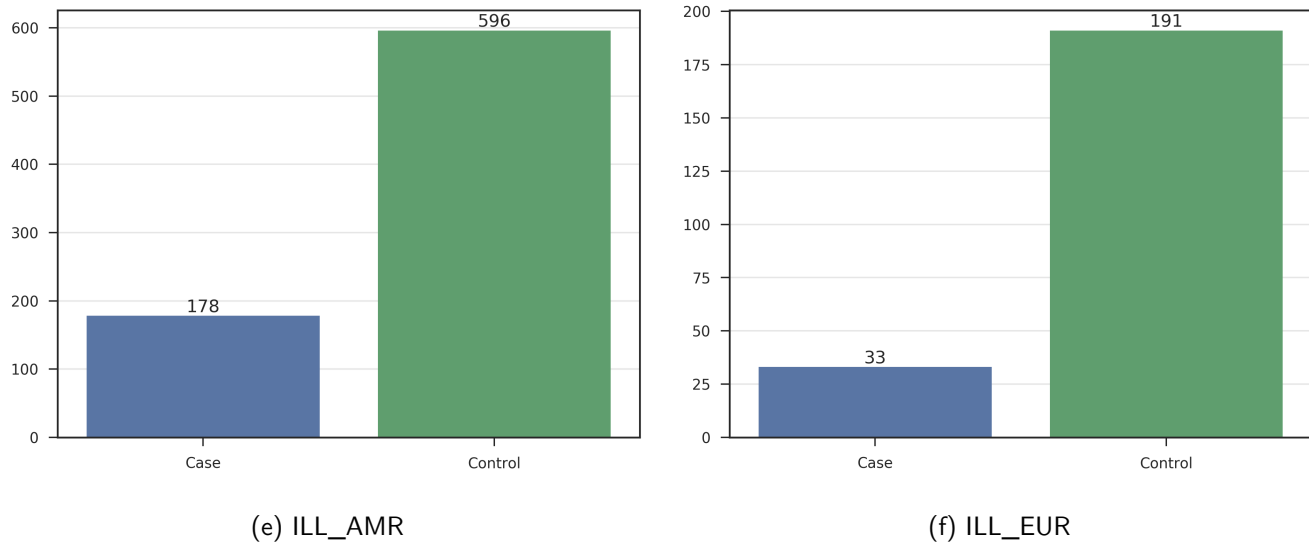


Figure 24: Distribution of CLAUDICATIONinT2Dcases in META_GWAS by cohort

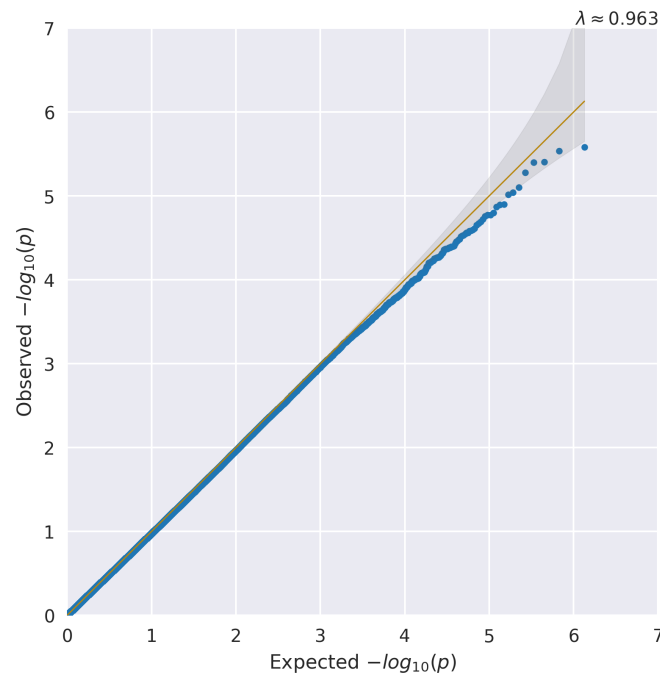
Table 23: Summary of samples removed from Claudication in samples with T2D analysis by cohort and model

	Cohort	Array	Ancestry	Trans	Covars	Total	-SampleQc	-KinshipCrossArray	-KinshipArray	-missObs	-PcOutlier
META_EX	EX_AFR	EX	AFR	-	SEX	4892	53	0	323	3446	0
META_EX	EX_AMR	EX	AMR	-	SEX	5425	65	49	491	3589	0
META_EX	EX_EUR	EX	EUR	-	SEX	2379	38	0	9	1999	1
META_GWAS	AFFY_AFR	AFFY	AFR	-	SEX	853	16	141	7	415	0
META_GWAS	AFFY_AMR	AFFY	AMR	-	SEX	1078	22	184	26	469	22
META_GWAS	AFFY_EUR	AFFY	EUR	-	SEX	578	12	7	2	450	0
META_GWAS	ILL_AFR	ILL	AFR	-	SEX	3853	51	0	2	3027	0
META_GWAS	ILL_AMR	ILL	AMR	-	SEX	4111	49	0	0	3172	0
META_GWAS	ILL_EUR	ILL	EUR	-	SEX	1796	22	0	0	1545	0

Table 24: Summary of samples remaining for Claudication in samples with T2D analysis by cohort and model

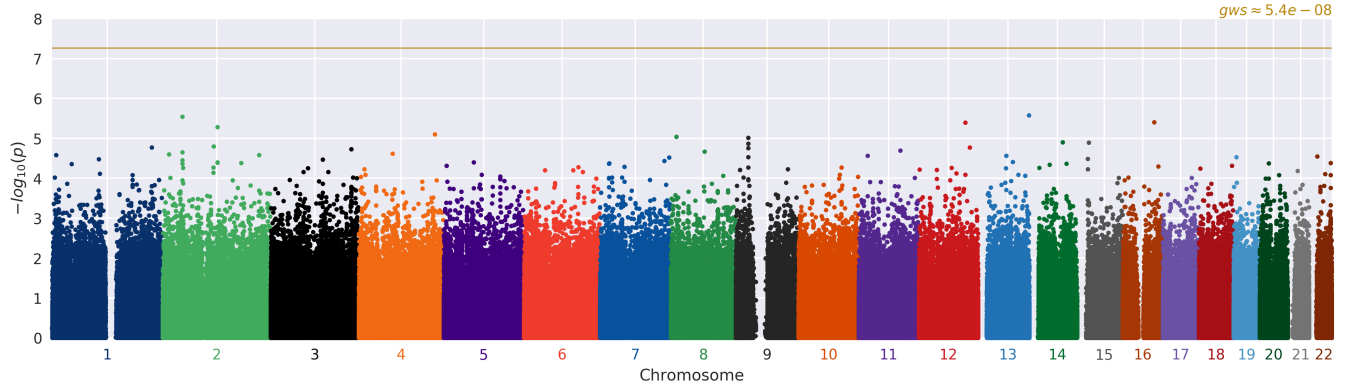
	Cohort	Array	Ancestry	Trans	Covars	PCs	N	Male	Female	Case	Ctrl
	META_EX EX_AFR	EX	AFR	-	SEX	0	1070	374	696	205	865
	META_EX EX_AMR	EX	AMR	-	SEX	8	1231	532	699	305	926
	META_EX EX_EUR	EX	EUR	-	SEX	5	332	263	69	49	283
	META_GWAS AFFY_AFR	AFFY	AFR	-	SEX	0	274	105	169	70	204
	META_GWAS AFFY_AMR	AFFY	AMR	-	SEX	4	355	157	198	96	259
	META_GWAS AFFY_EUR	AFFY	EUR	-	SEX	0	107	90	17	17	90
	META_GWAS ILL_AFR	ILL	AFR	-	SEX	0	773	269	504	133	640
	META_GWAS ILL_AMR	ILL	AMR	-	SEX	5	890	374	516	202	688
	META_GWAS ILL_EUR	ILL	EUR	-	SEX	0	229	173	56	34	195

8.2 Calibration



(a) Adjusted SEX

Figure 25: QQ plots for CLAUDICATIONinT2Dcases in the MERGE analysis



(a) Adjusted SEX

Figure 26: Manhattan plots for CLAUDICATIONinT2Dcases in the MERGE analysis

8.3 Top associations

Table 25: Top variants in the MERGE Adjusted SEX model (**bold** variants indicate previously identified associations)

CHR	POS	ID	EA	OA	GENE _{CLOSEST}	COHORT	DIR	N	MALE	FEMALE	CASE	CTRL	FREQ _{AVG}	FREQ _{MIN}	FREQ _{MAX}	EFFECT	STDERR	OR	ZSCORE	P
13	113811478	rs3024700	A	G	PROZ	META_GWAS	xxxx++	627	262	365	166	461	$2.23 \cdot 10^{-2}$	$5.63 \cdot 10^{-3}$	$4.41 \cdot 10^{-2}$	1.829	0.389	6.225	4.698	$2.62 \cdot 10^{-6}$
2	44187829	rs10190161	A	C	LRPPRC	META_GWAS	++++++	2,627	1,167	1,460	552	2,075	0.715	0.674	0.783	0.344	$7.35 \cdot 10^{-2}$	1.41	-4.678	$2.89 \cdot 10^{-6}$
16	70778742	rs16970476	T	C	VAC14	META_GWAS	xxxx++	629	262	367	166	463	$2.7 \cdot 10^{-2}$	$1.13 \cdot 10^{-2}$	$4.74 \cdot 10^{-2}$	1.669	0.362	5.308	4.615	$3.93 \cdot 10^{-6}$
12	104943853	rs12581832	C	T	CHST11	META_GWAS	+++xxx	1,892	816	1,076	369	1,523	$2.3 \cdot 10^{-2}$	$4.37 \cdot 10^{-3}$	$4.38 \cdot 10^{-2}$	1.124	0.244	3.077	4.612	$3.99 \cdot 10^{-6}$
2	122966970	rs1432303	C	A	TSN	META_GWAS	+++xxx	1,892	816	1,076	369	1,523	0.138	0.105	0.179	0.613	0.135	1.846	-4.554	$5.25 \cdot 10^{-6}$
4	170834427	rs4634183	A	G	MFAP3L	META_GWAS	+++xxx	1,888	815	1,073	368	1,520	0.579	0.544	0.611	0.371	$8.31 \cdot 10^{-2}$	1.449	4.467	$7.95 \cdot 10^{-6}$
8	12733321	rs2977171	T	C	KIAA1456	META_GWAS	++xxx	1,891	815	1,076	368	1,523	$9.57 \cdot 10^{-2}$	$2.78 \cdot 10^{-2}$	0.178	0.605	0.136	1.832	4.439	$9.06 \cdot 10^{-6}$
9	28395585	rs10812802	G	A	LINGO2	META_GWAS	+++xxx	1,892	816	1,076	369	1,523	0.367	0.321	0.406	0.375	$8.47 \cdot 10^{-2}$	1.455	4.425	$9.66 \cdot 10^{-6}$
14	74835298	rs10131983	C	T	VRTN	META_GWAS	+++xxx	1,892	816	1,076	369	1,523	0.148	$6.33 \cdot 10^{-2}$	0.208	0.492	0.113	1.635	4.366	$1.26 \cdot 10^{-5}$
15	26356400	rs8036922	T	C	ATP10A	META_GWAS	++++++	2,628	1,168	1,460	552	2,076	0.325	0.28	0.374	0.317	$7.27 \cdot 10^{-2}$	1.374	4.365	$1.27 \cdot 10^{-5}$
2	114918233	rs6754886	C	A	ACTR3	META_GWAS	+++xxx	1,891	816	1,075	369	1,522	0.155	0.144	0.168	0.471	0.109	1.601	4.317	$1.58 \cdot 10^{-5}$
12	114816360	rs4113925	T	C	TBX5	META_GWAS	+++xxx	1,892	816	1,076	369	1,523	0.324	0.256	0.41	0.374	$8.68 \cdot 10^{-2}$	1.453	4.304	$1.68 \cdot 10^{-5}$
1	224427171	rs10799551	G	T	NVL	META_GWAS	+++xxx	1,892	816	1,076	369	1,523	0.825	0.808	0.86	0.498	0.116	1.645	4.302	$1.69 \cdot 10^{-5}$
3	180904082	rs11716918	A	C	DNAJC19	META_GWAS	+++xxx	1,892	816	1,076	369	1,523	0.173	0.125	0.24	0.454	0.106	1.574	4.278	$1.88 \cdot 10^{-5}$
11	93517464	rs16919375	C	A	MED17	META_GWAS	++xxx++	2,292	905	1,387	501	1,791	$3.62 \cdot 10^{-2}$	$1.83 \cdot 10^{-2}$	$6.02 \cdot 10^{-2}$	0.76	0.178	2.138	4.262	$2.03 \cdot 10^{-5}$
8	76326793	rs114809191	C	T	HNFA4G	META_GWAS	+++xxx	1,889	815	1,074	369	1,520	$4 \cdot 10^{-2}$	$6.55 \cdot 10^{-3}$	$5.25 \cdot 10^{-2}$	0.794	0.187	2.212	4.251	$2.13 \cdot 10^{-5}$
4	75723973	rs17186071	T	C	BTC	META_GWAS	xxx+++	735	352	383	182	553	$7.69 \cdot 10^{-2}$	$4.74 \cdot 10^{-2}$	0.1	0.929	0.22	2.532	4.221	$2.43 \cdot 10^{-5}$
2	14316914	rs14448971	T	C	FAM84A	META_GWAS	++++++	2,624	1,166	1,458	552	2,072	0.201	$9.81 \cdot 10^{-2}$	0.283	0.378	$8.98 \cdot 10^{-2}$	1.46	-4.211	$2.54 \cdot 10^{-5}$
1	9129945	rs770041	A	G	SLC2A5	META_GWAS	++xxx	1,891	815	1,076	369	1,522	0.78	0.623	0.854	0.406	$9.64 \cdot 10^{-2}$	1.5	-4.206	$2.6 \cdot 10^{-5}$
2	216489977	rs2678270	A	G	FN1	META_GWAS	xxx+++	736	352	384	183	553	0.36	0.224	0.469	0.535	0.127	1.707	4.203	$2.63 \cdot 10^{-5}$

9 Acknowledgements

We would like to acknowledge the following people for their contributions to this work.

Ryan Koesterer

Maria Costanzo

Lizz Caulkins

Noel Burt

Jason Flannick

Miriam Udler

Alisa Manning

Jose Florez

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