

Causality of Childhood and Adult Body Mass Index on Sick Sinus Syndrome: A Mendelian Randomization Study

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Abstract

Background

The relationship between body mass index (BMI) and the risk of sick sinus syndrome (SSS) remains unclear. Clarifying the impact of BMI on SSS at different life stages is essential for advancing precision medicine and implementing effective prevention strategies to reduce the burden of SSS.

Methods

The causalities of childhood and adult BMI with SSS were investigated by univariate and multivariate Mendelian randomization. Reverse causalities were also explored to improve the accuracy of causality findings. Different sources of exposure data were used for replication analysis, and the effects of sample overlap were investigated using MRlap. The stability of the results was further enhanced through meta-analysis.

Results

There was a positive correlation of adult BMI with the risk of SSS in both the FinnGen (odds ratio (OR) = 1.17, 95% confidence interval (CI) 1.01-1.35, $P = 0.031$) and Integrative Epidemiology Unit (IEU) open genome-wide association study (GWAS) project (OR = 1.18, 95% CI 1.04-1.34, $P = 0.009$) databases. The causality remained valid after the correction of telomere length. There was no causality detected between childhood BMI and SSS, as determined by independent studies of the Early Growth Genetics (EGG) 2020 (OR = 1.06, 95% CI 0.89-1.27, $P = 0.513$) and EGG2015 (OR = 1.02, 95% CI 0.97-1.09, $P = 0.423$). Meta-analysis results further confirmed the reliability of the causal inference.

Conclusions

The findings indicate that elevated BMI in adults, particularly among middle-aged and elderly populations, increases the risk of developing SSS. In contrast, no causal relationship was observed between childhood BMI and SSS, suggesting that the influence of BMI on SSS susceptibility may predominantly emerge during later life stages. These results highlight the need for targeted public health interventions to address adult obesity as a modifiable risk factor for SSS.

Categories: Cardiology, Endocrinology/Diabetes/Metabolism, Epidemiology/Public Health

Keywords: body mass index, causality, life course epidemiology, mendelian randomization, sick sinus syndrome

Introduction

Sick sinus syndrome (SSS) collectively refers to diseases caused due to abnormal cardiac impulses and conduction that are clinically manifested as sinus bradycardia, sinus arrest, and other arrhythmias [1]. Owing to the complex etiology and pathogenesis of SSS, there are currently no effective long-term therapeutic strategies targeting the underlying pathways. With advancing age, the increase in comorbidities is associated with a poorer prognosis observed in studies of patients with SSS. Permanent pacemaker implantation is considered the only effective treatment among patients with irreversible etiology [2]. In the United States, new SSS cases are expected to rise from 172,000 patients per year by 2060, which will undoubtedly impose a tremendous burden on the healthcare system [3,4]. Therefore, it is worth exploring the risk factors of SSS to facilitate early disease management and prevent progression.

Studies have highlighted high body mass index (BMI), age, and low heart rate as risk factors for SSS [4]. In particular, age is considered as a major risk factor, as aging is accompanied by a gradual decline in the sinoatrial conduction time and high fibrosis [5,6]. Although the onset of SSS is predominately reported among the elderly population, SSS is regarded as a disease at all ages [7].

BMI is an indirect measure of body fat. Research findings have projected that more than half of the global population will be overweight (BMI ≥ 30 kg/m²) or obese (BMI ≥ 25 kg/m²) by 2030 [8]. Elevated BMI increases the risk of atrial fibrillation, ischemic stroke, and type 2 diabetes mellitus [9-11] and was found to significantly raise the worldwide disease burden [12]. To date, no randomized controlled trial has been performed to investigate the causality between BMI and SSS. Clarification of the relationship between BMI and SSS is essential for promoting early disease prevention strategies and precision treatment.

When observational studies are scarce, Mendelian randomization (MR) serves as an intuitive method for inferring causality. Considering the fact that genetic variation is already determined at the time of conception, MR equivalently assesses the relationship between exposure and the level of genetic prediction of the outcome. In addition, it avoids any interference from reverse causality and confounders in observational studies and provides researchers with valid etiological insight [13,14].

Materials And Methods

Study overview

This study is reported in accordance with the Strengthening of Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) statement [15]. This study explored the causalities of childhood and adult BMI on SSS. To enhance the robustness of the causal inference, replication analyses were conducted using different exposure data sources. The PhenoScanner database and multivariate Mendelian randomization (MVMR) were used to examine any interference from confounding factors. In addition, MR results were meta-merged. The study overview is shown in Figure 1. All analyses were performed using the "TwoSampleMR" package (0.6.5), "MendelianRandomization" package (0.10.0), "MVMR" package (0.4), and "meta" (8.0-1) in the R program (4.3.2; R Development Core Team, Vienna, Austria).

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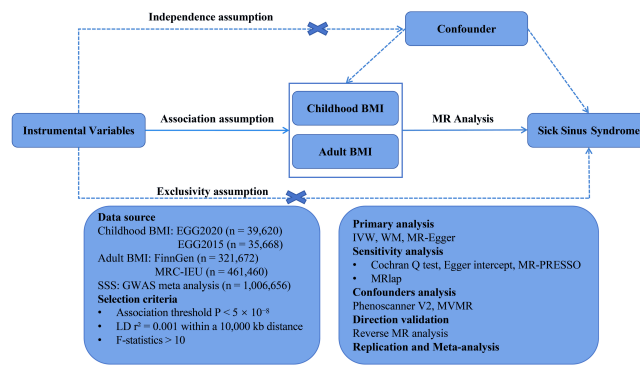


FIGURE 1: Overview of the Mendelian randomization study

The extraction of instrumental variables (IVs) adheres to three core assumptions: (1) the IVs are strongly associated with the exposure (relevance assumption), (2) the IVs are independent of confounders (independence assumption), and (3) the IVs have no direct effect on the outcome, influencing the outcome only through the exposure (exclusion restriction assumption).

BMI, body mass index; EGG, Early Growth Genetics; FinnGen, Finnish Health Research Environment for Genomic Research; GWAS, Genome-Wide Association Study; IVW, inverse-variance weighted; LD, linkage disequilibrium; MR, Mendelian randomization; MRC-IEU, Medical Research Council Integrated Epidemiology Unit; MR-PRESSO, Mendelian Randomization - Pleiotropy Residual Sum and Outlier; MVMR, multivariate Mendelian randomization; SSS, sick sinus syndrome; WM, weighted median

Data source

Childhood BMI data were derived from a meta-analysis of genome-wide association studies (GWAS) of BMI conducted among 39,620 children between two and 10 years of age from 26 studies and updated by the Early Growth Genetics (EGG) consortium [16]. Another meta-analysis of genome-wide association studies of BMI in 35,668 children of 2-10 years from earlier studies was included in the replication analysis [17].

The data on adult BMI were obtained from the FinnGen study where approximately 500,000 participants with a median age of 53 years old were enrolled [18]. The Integrative Epidemiology Unit (IEU) open GWAS database (IEU Open GWAS project (mrcieu.ac.uk) carrying genetic and health information from approximately 500,000 European individuals aged 40-69 years was employed for replication analysis [19]. While sample overlapping may have occurred between exposure and outcome in the replication analysis, efforts were taken to use non-overlapping samples in line with the STROBE statement recommendation. The direct calculation of the rate of sample overlap is challenging. We thus employed the MRlap method to correct for potential winner's curse and weak instrument bias. A detailed description of the MRlap method is provided in the subsequent section.

Telomere length (TL) has been incorporated into aging-related proxies, and telomere shortening has been observed during normal aging in humans and mice [20]. TL data were derived from the IEU OPEN GWAS database harboring genetic information of 472,174 European individuals.

SSS summary data were obtained from the largest meta-analysis available where SSS diagnoses were conducted in accordance with the International Classification of Diseases, 9th (ICD-9: 427.8) or 10th (ICD-10: I49.5) editions [6]. Table 1 shows specific information on data sources.

Phenotypes	Consortium	Ancestry	PMID	Sample size	Web source
Adult BMI	FinnGen	European	NA	321,672	https://r11.finnngen.fi/
Adult BMI	MRC-IEU	European	NA	461,460	https://gwas.mrcieu.ac.uk/datasets/ukb-b-19953/
Childhood BMI	EGG	European	33045005	39,620	http://egg-consortium.org/
Childhood BMI	EGG	European	26604143	35,668	http://egg-consortium.org/
SSS	The deCODE Genetics, UKB, the CHB-CVS/DBDS, the HUNT cohort	European	33580673	1,006,656 (6469 cases and 1,000,187 controls)	https://www.decode.com
TL	NA	European	NA	472,174	https://gwas.mrcieu.ac.uk/datasets/ieu-b-4879/

TABLE 1: Sources of GWAS data used in the MR study

BMI, body mass index; CHB-CVS, Copenhagen Hospital Biobank Cardiovascular Study; DBDS, Danish Blood Donor Study; EGG, Early Growth Genetics; FinnGen, Finnish Health Research Environment for Genomic Research; GWAS, genome-wide association studies; HUNT, Norwegian Nord-Trøndelag Health Study; MR, Mendelian randomization; MRC-IEU, Medical Research Council Integrated Epidemiology Unit; NA, not applicable; SSS, sick sinus syndrome; TL, telomere length; UKB, UK Biobank

Selection of instrumental variables (IVs)

The IVs were extracted in line with the assumptions of association, independence, and exclusivity in MR [21]. Single nucleotide polymorphisms (SNPs) were critically screened as follows. (a) To identify exposure-associated and independent SNPs, a threshold of $P < 5 \times 10^{-8}$ was set with the removal of SNPs that were in linkage disequilibrium (LD) ($r^2 = 0.001$, kb = 10,000). (b) Exposure-associated SNPs were extracted from the outcome dataset, and SNPs associated with the outcome phenotype were removed ($P < 5 \times 10^{-8}$). (c) Alleles were harmonized for exposure and outcome, and palindromic and incompatible SNPs were removed. (d) Building on previous findings that identified age-related ion channel disorders and idiopathic fibrosis as major risk factors for SSS [22-25], we employed univariate MR (UVMR) analysis to evaluate aging-related phenotypic SNPs through the PhenoScanner database [26]. (e) SNPs with $F < 10$ were eliminated, as they are in general considered to represent weak instrumental variables [27]. Additionally, statistical power for the estimates derived from the inverse variance weighted (IVW) method was calculated using an online

computational tool (<https://sb452.shinyapps.io/power/>). After the above screening steps, any potential horizontal pleiotropy outliers were determined by MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) [28]. The screened SNPs were finally used in the MR study.

UVMR analysis

In UVMR, the causality of childhood and adult BMI with SSS and the reverse causality of SSS with BMI were separately examined. The IVW method was employed for the main analysis and provided robust causal inference under the hypothesis that all IVs were valid [14]. A value of $P < 0.05$ in the IVW method indicated significant causality between exposure and outcome data. In addition, the weighted median method and the MR-Egger method served as supplements, wherein the former allowed for a more precise estimation if half of the IVs were valid [29]. Although the MR-Egger method had lower statistical performance, it alleviated the reliability of the causal inference when the direction of the MR-Egger estimate was consistent with that of the other methods.

During sensitivity analysis, a Cochran's Q test was employed for heterogeneity analysis. A value of $P < 0.05$ indicated the presence of heterogeneity. A random-effect IVW method analysis was performed to mitigate any effect of heterogeneity. In addition, horizontal pleiotropy was assessed using the MR-Egger intercept. An intercept value of $P < 0.05$ indicated potential pleiotropy in the results and weakened the validity of the causal inference conclusion.

MVMR analysis

MVMR, as an extension of UVMR, is more advantageous than UVMR when several relevant exposures have common genetic predictors. Based on previous studies, we included adult BMI, TL, and SSS in the MVMR model to differentiate the effects of confounding factors (TL) and to examine the independent causal relationship between adult BMI and SSS [25]. The shortening and damage of TL are recognized causes of aging and cellular senescence [30-32]. Epidemiological data on TL have demonstrated that shorter TL is associated with age [33]. In healthy newborns, median leukocyte TLs (LTLs) ranged from 8.5 to 13.5 kb. LTL was observed to shorten at an average annual rate of 30-35 bp, reaching about 5-6 kb in people over 60 years old [30]. Similarly, three complementary analysis methods, IVW, weighted median, and MR-Egger, were performed. Cochran's Q test was conducted for heterogeneity analysis, and random-effect IVW results were used for causal inference once heterogeneity was detected in MVMR.

MRlap

The MRlap method addresses the issues of weak IVs bias and winner's curse arising from sample overlap and is beneficial in situations where the use of overlapping samples is unavoidable. In particular, the method adjusts for causality estimates using linkage disequilibrium score regression and other techniques based on the hypothesis that the exposure adopts a spike-and-slab genomic structure. The effect estimates can be used as sensitivity analysis. Herein, we employed strict thresholds (MR threshold = 5×10^{-8} , MR pruning distribution = 10,000, MR pruning LD = 0.001). The bias did not affect the results for non-overlapping samples. In the case of sample overlapping, corrected results were used if they were statistically significant compared to the IVW results ($P < 0.05$) because the bias of the corrected results was small and unrelated to sample overlapping. In the absence of any significant difference ($P > 0.05$), the IVW-MR estimates were used [34,35].

Meta-analysis

In meta-analysis, MR estimates were combined using a fixed-effects meta-analysis. Heterogeneity across different data sources was assessed by the I^2 statistic, with I^2 values of $<25\%$, $25-75\%$, and $>75\%$, indicating low, moderate, and high heterogeneity, respectively. The meta-analysis of IVW methods in UVMR and MVMR results further increased the robustness and generalizability of causal inference.

Results

UVMR and meta-analysis

In the MR analysis, the causal relationship between childhood BMI and SSS was not supported (Figure 2). This was observed in both the analyses based on the EGG (2020) (odds ratio (OR) = 1.06, 95% confidence interval (CI) 0.89-1.27, $P = 0.513$) and the replication analyses using the EGG (2015) (OR = 1.02, 95% CI 0.97-1.09, $P = 0.423$). In reverse MR, no association was detected between SSS susceptibility and childhood BMI. No outliers, heterogeneity, or horizontal pleiotropy were recorded in all the above analyses. The meta-analysis found no evidence supporting a causal relationship between childhood BMI and the risk of SSS (OR = 1.02, 95% CI 0.97-1.08, $P = 0.405$).

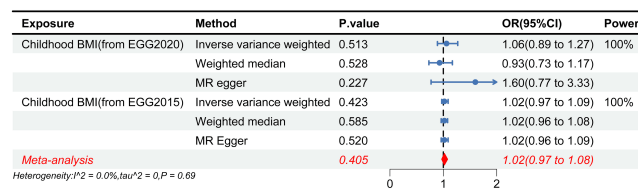


FIGURE 2: Forest plot of the MR causal estimates for childhood BMI and SSS

BMI, body mass index; CI, confidence interval; EGG, Early Growth Genetics; MR, Mendelian randomization; OR, odds ratio; SSS, sick sinus syndrome

Adult BMI showed a positive association with SSS, which demonstrated a consistent causal inference across different sources of the BMI database (Figure 3). During the analysis of FinnGen's adult BMI data, outliers were screened and eliminated by MR-PRESSO (rs914187). The results showed that adult BMI elevated the risk of SSS (OR = 1.17, 95% CI 1.01-1.35, $P = 0.031$) without any heterogeneity ($P_{\text{Cochran's Q}} = 0.13$) and horizontal pleiotropy ($P_{\text{intercept}} = 0.30$). As per reverse MR results, the identified causality was not affected by reverse causality (OR = 1.01, 95% CI 0.99-1.05, $P = 0.397$). In the replication analysis, we excluded the SNP (rs2870111) associated with aging. The causality conclusion was consistent in the adult BMI data of IEU OPEN GWAS (OR = 1.18, 95% CI 1.04-1.34, $P = 0.009$) and showed no heterogeneity ($P_{\text{Cochran's Q}} = 0.07$) and horizontal pleiotropy ($P_{\text{intercept}} = 0.74$). Similarly, causality was not affected by reverse causality (OR = 0.99, 95% CI 0.98-1.01, $P = 0.373$). MRlap analyses supported the causality between adult BMI and SSS. Sample overlapping did not affect MR results, while the difference between observed and corrected effects was statistically insignificant and in agreement with the findings of the IVW results. This observation further confirms that the causal inference was robust (Observed effect $p = 0.014$, Corrected effect $p = 0.029$, $P_{\text{difference}} = 0.667$). The meta-analysis further corroborated the causal relationship between elevated adult BMI and an increased risk of sick sinus syndrome SSS (OR = 1.18, 95% CI 1.07-1.29, $P = 0.0009$).

Exposure	Method	P-value	OR(95%CI)	Power
Adult BMI(from FinnGen)	Inverse variance weighted	0.031	1.17(1.01 to 1.35)	100%
	Weighted median	0.028	1.27(1.03 to 1.58)	
	MR Egger	0.084	1.42(0.96 to 2.11)	
Adult BMI(from MRC-IEU)	Inverse variance weighted	0.009	1.18(1.04 to 1.34)	100%
	Weighted median	0.960	1.01(0.82 to 1.24)	
	MR Egger	0.215	1.25(0.88 to 1.76)	
Meta-analysis		0.0009	1.18(1.07 to 1.29)	

Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0$, $P = 0.93$

FIGURE 3: Forest plot of the MR causal estimates for adult BMI and SSS

BMI, body mass index; CI, confidence interval; FinnGen, Finnish Health Research Environment for Genomic Research; MR, Mendelian randomization; OR, odds ratio; MRC-IEU, Medical Research Council Integrated Epidemiology Unit, SSS, sick sinus syndrome

The visualized scatterplot is shown in Figure 4, and the detailed results of IVs and MR analysis are described in Tables 2-11.

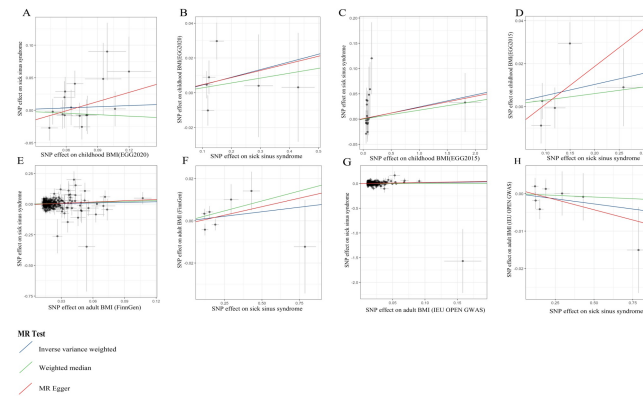


FIGURE 4: Scatter plot depicting causal associations between childhood/adult BMI and SSS

(A) Between childhood BMI (EGG2020) and SSS. (B) Between SSS and childhood BMI (EGG2020). (C) Between childhood BMI (EGG2015) and SSS. (D) Between SSS and childhood BMI (EGG2015). (E) Between adult BMI (FinnGen) and SSS. (F) Between SSS and adult BMI (FinnGen). (G) Between adult BMI (IEU OPEN GWAS) and SSS. (H) Between SSS and adult BMI (IEU OPEN GWAS).

BMI, body mass index; EGG, Early Growth Genetics; FinnGen, Finnish Health Research Environment for Genomic Research; IEU OPEN GWAS, Integrative Epidemiology Unit Open Genome-Wide Association Study; MR, Mendelian randomization; SNP, single nucleotide polymorphism; SSS, sick sinus syndrome

Exposure	Outcome	IVW		WM		MR-Egger		Power
		OR (95 % CI)	p	OR (95 % CI)	p	OR (95 % CI)	p	
SSS	Childhood BMI (EGG2020)	1.05 (0.97, 1.13)	0.266	1.03 (0.95, 1.11)	0.492	1.04 (0.81, 1.33)	0.762	3.3%
	Childhood BMI (EGG2015)	1.05 (0.96, 1.16)	0.294	1.03 (0.94, 1.14)	0.537	1.19 (0.88, 1.62)	0.340	3.2%
	Adult BMI (FinnGen)	1.01 (0.99, 1.03)	0.397	1.02 (1.00, 1.04)	0.080	1.02 (0.96, 1.07)	0.586	3.2%
	Adult BMI (IEU OPEN GWAS)	0.99 (0.98, 1.01)	0.373	1.00 (0.98, 1.01)	0.827	0.99 (0.96, 1.01)	0.434	3.4%

TABLE 2: The Reverse MR analysis does not support a causal relationship between SSS and BMI

BMI, body mass index; CI, confidence interval; EGG, Early Growth Genetics; FinnGen, Finnish Health Research Environment for Genomic Research; IEU OPEN GWAS, Integrative Epidemiology Unit Open Genome-Wide Association Study; IVW, inverse-variance weighted; MR, Mendelian randomization; OR, odds ratio; SSS, sick sinus syndrome; WM, weighted median

Exposure	Outcome	Heterogeneity		Pleiotropy		MR-PRESSO	
		Cochran Q	P	Intercept	P	Outlier-corrected	P
Childhood BMI (EGG2020)		16.58	0.34	-0.03	0.27	NA	0.33
Childhood BMI (EGG2015)		16.45	0.49	0.001	0.90	NA	0.627
Adult BMI (FinnGen)	SSS	311.48	0.13	-0.004	0.30	rs914187	0.048
Adult BMI (IEU OPEN GWAS)		416.15	0.07	-0.001	0.74	NA	0.06
	Childhood BMI (EGG2020)	8.38	0.14	0.001	0.98	NA	0.16
	Childhood BMI (EGG2015)	8.07	0.09	-0.02	0.46	NA	0.17
SSS	Adult BMI (FinnGen)	10.61	0.10	-0.001	0.78	NA	0.14
	Adult BMI (IEU OPEN GWAS)	5.07	0.54	0.001	0.65	NA	0.52

TABLE 3: Sensitivity analysis of the Mendelian randomization

BMI, body mass index; EGG, Early Growth Genetics; FinnGen, Finnish Health Research Environment for Genomic Research; IEU OPEN GWAS, Integrative Epidemiology Unit Open Genome-Wide Association Study; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; NA, not applicable; SSS, sick sinus syndrome

SNP	effect_allele.exposure	other_allele.exposure	effect_allele.outcome	other_allele.outcome	beta.exposure	beta.outcome	eaf.exposure	eaf.outcome	rval.outcome	se.outcome	samplesize.outcome	chr.exposure	pos.exposure	se.exposure	rval.exposure
rs114670539	T	C	T	C	0.0991	0.09019713	0.0487	NA	0.0411	0.0441	1006656	2	207064335	0.0179	3.16E-08
rs11676272	A	G	A	G	-0.075	0.02592044	0.5358	NA	0.184	0.0192	1006656	2	25141538	0.0079	2.37E-21
rs12042908	A	G	A	G	0.0586	-0.007699566	0.4523	NA	0.694	0.0197	1006656	1	74997762	0.0077	2.77E-14
rs12641981	T	C	T	C	0.044	-0.027104018	0.4185	NA	0.162	0.0194	1006656	4	45179883	0.008	4.19E-08
rs13107325	T	C	T	C	0.0953	0.048199514	0.0795	NA	0.383	0.0553	1006656	4	103188709	0.0173	3.51E-08
rs17817449	T	G	T	G	-0.0683	-0.040796394	0.5855	NA	0.0399	0.0199	1006656	16	53813367	0.008	1.69E-17
rs41279738	T	G	T	G	-0.1199	-0.059503994	0.9692	NA	0.266	0.0535	1006656	1	110082551	0.0211	1.30E-08
rs4477562	T	C	T	C	0.0802	-0.007095111	0.1103	NA	0.81	0.0293	1006656	13	54104968	0.0112	8.29E-13
rs543874	A	G	A	G	-0.0793	0.007598798	0.8131	NA	0.752	0.0241	1006656	1	177889480	0.0099	1.62E-15
rs56133711	A	G	A	G	0.0566	-0.006400439	0.2296	NA	0.77	0.022	1006656	11	27723334	0.0089	2.00E-10
rs571312	A	C	A	C	0.099	0.028601234	0.2396	NA	0.198	0.0223	1006656	18	57636709	0.0093	2.00E-10
rs61765651	T	C	T	C	-0.0584	-0.019998647	0.174	NA	0.416	0.0245	1006656	1	72754314	0.0102	9.50E-09
rs62009888	A	G	A	G	0.0472	-0.002097798	0.5408	NA	0.916	0.0197	1006656	8	28061823	0.0076	6.91E-10
rs7138803	A	G	A	G	0.0729	-0.008596847	0.338	NA	0.669	0.0201	1006656	12	50247468	0.008	7.12E-20
rs7199285	T	C	T	C	-0.0647	-0.004299228	0.171	NA	0.874	0.0272	1006656	16	19980931	0.0101	1.34E-10
rs939584	T	C	T	C	0.1066	0.002102208	0.83	NA	0.937	0.0266	1006656	2	621558	0.0102	8.85E-26
Summary	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

TABLE 4: Independent IVs in the causal analysis of childhood BMI (EGG2020) and SSS

BMI, body mass index; EGG, early growth genetics; IVs, instrumental variables; NA, not applicable; SNP: single nucleotide polymorphism; SSS, sick sinus syndrome

SNP	effect_allele.exposure	other_allele.exposure	effect_allele.outcome	other_allele.outcome	beta.exposure	beta.outcome	eaf.exposure	eaf.outcome	pval.outcome	se.outcome	samplesize.outcome	chr.exposure	pos.exposure	se.exposure	pval.exposure
rs11676272	A	G	A	G	-0.0769	0.02550244	0.0288	NA	0.184	0.0192	1006656	2	24995042	0.0078	8.55E-23
rs12041852	A	G	A	G	-0.0525	0.008203557	NA	NA	0.678	0.0197	1006656	1	74778088	0.0082	1.77E-10
rs12429545	A	G	A	G	0.0745	-0.009696863	NA	NA	0.738	0.0291	1006656	13	53002207	0.0113	3.66E-11
rs13107325	T	C	T	C	0.1022	0.049199514	NA	NA	0.383	0.0553	1006656	4	103407732	0.0179	1.19E-08
rs13130484	T	C	T	C	0.0506	-0.02899636	NA	NA	0.138	0.0195	1006656	4	44870448	0.0078	8.94E-11
rs13253111	A	G	A	G	0.0492	-0.0249688	NA	NA	0.9	0.0197	1006656	8	28117893	0.0084	4.13E-09
rs13387838	A	G	A	G	0.1507	0.120304299	NA	NA	0.091	0.0712	1006656	2	206988692	0.027	2.40E-08
rs1421085	T	C	T	C	-0.0734	-0.036302999	NA	NA	0.0673	0.0198	1006656	16	52358455	0.0082	3.20E-19
rs17309930	A	C	A	C	0.0529	-0.007004474	NA	NA	0.789	0.0239	1006656	11	27705069	0.0095	2.47E-06
rs2590942	T	G	T	G	0.0598	0.037701867	NA	NA	0.123	0.0244	1006656	1	72657869	0.0102	3.88E-09
rs4854349	T	C	T	C	-0.0974	-0.00030045	NA	NA	0.992	0.0323	1006656	2	637861	0.0104	6.00E-21
rs4870949	T	C	T	C	1.8167	0.032796274	NA	NA	0.572	0.0581	1006656	8	126704776	0.2887	3.13E-10
rs543874	A	G	A	G	-0.0819	0.007598798	NA	NA	0.752	0.0241	1006656	1	176156103	0.0097	2.38E-17
rs667180	T	C	T	C	-0.0649	-0.028704068	NA	NA	0.198	0.0223	1006656	18	55980115	0.0094	4.06E-12
rs7132908	A	G	A	G	0.0768	-0.002302649	NA	NA	0.908	0.02	1006656	12	48549415	0.0086	4.99E-19
rs7550711	T	C	T	C	0.12	0.059098752	NA	NA	0.269	0.0535	1006656	1	109884409	0.0212	1.50E-08
rs8046312	A	C	A	C	0.0668	0.006988558	NA	NA	0.82	0.027	1006656	16	19886835	0.0107	4.06E-10
rs987237	A	G	A	G	-0.0712	-0.001399021	NA	NA	0.956	0.0252	1006656	6	50911009	0.0098	3.81E-13
Summary	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

TABLE 5: Independent IVs in the causal analysis of childhood BMI (EGG2015) and SSS

BMI, body mass index; EGG, Early Growth Genetics; IVs, instrumental variables; NA, not applicable; SNP: single nucleotide polymorphism; SSS, sick sinus syndrome

SNP	effect_allele.exposure	other_allele.exposure	effect_allele.outcome	other_allele.outcome	beta.exposure	beta.outcome	eaf.exposure	eaf.outcome	chr.outcome	pos.outcome	se.outcome	pval.outcome	samplesize.outcome	pval.exposure	se.exposure
rs10149821	G	T	G	T	0.429799933	0.0031	NA	NA	14	23980080	0.0313	0.9215	35922	3.45E-14	0.0567
rs116307579	T	C	T	C	0.293698935	0.004	NA	NA	14	24534471	0.0295	0.8919	36235	2.79E-09	0.0494
rs11662320	T	C	T	C	0.119000073	-0.0102	NA	NA	18	67177899	0.0087	0.2386	39722	3.68E-08	0.0216
rs11711941	T	C	T	C	0.115103894	0.0046	NA	NA	3	38778540	0.0078	0.5558	38160	6.93E-09	0.0199
rs2106281	T	C	T	C	0.149703664	0.0297	NA	NA	16	73051620	0.0106	0.005114	35505	9.94E-10	0.0245
rs35813871	A	G	A	G	0.122898817	0.0089	NA	NA	2	179650408	0.0096	0.353	37034.9	2.64E-08	0.0221
Summary	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

TABLE 6: Independent IVs in the causal analysis of SSS and childhood BMI (EGG2020)

BMI, body mass index; EGG, Early Growth Genetics; IVs, instrumental variables; NA, not applicable; SNP, single nucleotide polymorphism; SSS, sick sinus syndrome

SNP	effect_allele.exposure	other_allele.exposure	effect_allele.outcome	other_allele.outcome	beta.exposure	beta.outcome	eaf.exposure	eaf.outcome	chr.outcome	pos.outcome	se.outcome	pval.outcome	samplesize.outcome	pval.exposure	se.exposure
rs1009380	C	T	C	T	-0.093201405	-0.0028	NA	NA	2	6512953	0.0084	0.754	30111	1.69E-06	0.0195
rs11662320	T	C	T	C	0.119000073	-6.00E-04	NA	NA	18	65328879	0.0095	0.9526	30106.8	3.68E-08	0.0216
rs13023947	T	C	T	C	-0.258705984	-0.009	NA	NA	2	129880524	0.0181	0.617	29990	1.51E-06	0.0538
rs1867785	A	G	A	G	0.090900471	-0.0088	NA	NA	2	46387842	0.0083	0.2903	29915	3.75E-06	0.0196
rs2106281	T	C	T	C	0.149703664	0.0294	NA	NA	16	71609121	0.0099	0.003091	35534	9.94E-10	0.0245
Summary	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

TABLE 7: Independent IVs in the causal analysis of SSS and childhood BMI (EGG2015)

BMI, body mass index; EGG, Early Growth Genetics; IVs, instrumental variables; NA, not applicable; SNP, single nucleotide polymorphism; SSS, sick sinus syndrome

SNP	effect_allele.exposure	other_allele.exposure	effect_allele.outcome	other_allele.outcome	beta.exposure	beta.outcome	eaf.exposure	eaf.outcome	pval.outcome	se.outcome	samplesize.outcome	pval.exposure	se.exposure	samplesize.exposure	R2
rs1000940	G	A	G	A	0.0155263	0.026797712	0.42681	NA	0.194	0.0207	1006656	4.01E-11	0.0023511	321672	0.000
rs10289783	A	G	A	G	0.0147676	-0.007004474	0.458426	NA	0.724	0.0198	1006656	2.02E-10	0.00232208	321672	0.000
rs10275348	C	T	C	T	-0.0137198	0.010900374	0.332516	NA	0.59	0.0202	1006656	2.51E-08	0.00246194	321672	9.65E
rs10404037	A	G	A	G	-0.0194287	-0.00950503	0.131998	NA	0.722	0.0266	1006656	1.34E-08	0.00341988	321672	0.000
rs10456701	T	C	T	C	0.0225431	0.021027782	0.283021	NA	0.289	0.0205	1006656	2.40E-18	0.00258023	321672	0.000

rs10757687	C	T	C	T	0.0178	-0.034105021	0.498315	NA	0.0803	0.0195	1006656	2.88E-14	0.00231447	321672	0.000
rs10769936	C	T	C	T	0.0162783	-0.015095488	0.74628	NA	0.5	0.0224	1006656	9.64E-10	0.00296189	321672	0.000
rs10787738	T	C	T	C	0.0166963	0.001598721	0.256679	NA	0.943	0.0227	1006656	3.33E-10	0.00265746	321672	0.000
rs10846920	T	C	T	C	0.0189662	-0.013902905	0.76721	NA	0.535	0.0224	1006656	5.47E-12	0.00275163	321672	0.000
rs10859055	T	C	T	C	-0.0149815	-0.011000282	0.384881	NA	0.582	0.02	1006656	4.77E-10	0.00240614	321672	0.000
rs10929925	A	C	A	C	-0.0195152	0.028295889	0.496719	NA	0.15	0.0197	1006656	3.69E-17	0.0023171	321672	0.000
rs10947793	G	A	G	A	-0.0131812	-0.012296278	0.388344	NA	0.543	0.0202	1006656	3.14E-08	0.00238222	321672	9.52E
rs10987749	C	A	C	A	-0.0145852	0.023104874	0.599461	NA	0.25	0.0201	1006656	4.38E-10	0.00233743	321672	0.000
rs11038839	G	A	G	A	0.0433566	0.07289724	0.0406188	NA	0.212	0.0584	1006656	2.31E-13	0.00591515	321672	0.000
rs1106236	C	T	C	T	-0.0133559	-0.046096296	0.401313	NA	0.0241	0.0204	1006656	1.84E-08	0.00237379	321672	9.84E
rs11086675	G	A	G	A	-0.0173683	-0.017997077	0.826396	NA	0.463	0.0246	1006656	1.31E-08	0.00305543	321672	0.000
rs11134425	A	G	A	G	-0.014844	0.011202515	0.412076	NA	0.563	0.0194	1006656	2.90E-10	0.00235478	321672	0.000
rs11150745	G	A	G	A	-0.0197904	0.001898197	0.281538	NA	0.927	0.0209	1006656	1.59E-14	0.00257682	321672	0.000
rs11159989	T	G	T	G	-0.0151418	0.053597637	0.289069	NA	0.00996	0.0208	1006656	3.07E-09	0.00255446	321672	0.000
rs11165493	A	G	A	G	0.0155747	-0.020600746	0.378985	NA	0.312	0.0204	1006656	7.29E-11	0.00239076	321672	0.000
rs11170433	T	C	T	C	-0.015324	0.027104018	0.562273	NA	0.177	0.0201	1006656	6.33E-11	0.00234462	321672	0.000
rs11185111	A	G	A	G	-0.0175914	-0.014798967	0.42458	NA	0.486	0.0212	1006656	7.47E-14	0.00235202	321672	0.000
rs11186668	G	A	G	A	-0.013075	-0.023696214	0.431816	NA	0.264	0.0212	1006656	2.35E-08	0.00234137	321672	9.69E
rs11192614	C	T	C	T	-0.0150153	0.013895783	0.353292	NA	0.506	0.0205	1006656	6.20E-10	0.0024276	321672	0.000
rs11229433	A	G	A	G	0.0223167	-0.02200024	0.192308	NA	0.417	0.0272	1006656	3.31E-14	0.00294198	321672	0.000
rs113931125	A	G	A	G	0.0133375	0.017299497	0.383681	NA	0.382	0.0198	1006656	2.27E-08	0.00238587	321672	9.71E
rs114497064	G	C	G	C	0.0262547	-0.282102692	0.0676099	0.15	0.0595	0.1391	1006656	1.49E-08	0.00463963	321672	9.97E
rs11545169	T	G	T	G	-0.021077	-0.031604193	0.190925	NA	0.248	0.0273	1006656	9.93E-13	0.00295549	321672	0.000
rs11601751	T	C	T	C	0.0194183	0.009603736	0.500439	NA	0.624	0.0196	1006656	5.30E-17	0.00231729	321672	0.000
rs11602411	A	G	A	G	-0.0197502	0.001099395	0.215868	NA	0.968	0.0274	1006656	2.48E-12	0.00281917	321672	0.000
rs11632852	C	T	C	T	0.0134144	0.014200349	0.493032	NA	0.468	0.0196	1006656	6.68E-09	0.00231313	321672	0.000
rs11640942	T	C	T	C	-0.0401737	-0.023698607	0.125364	NA	0.438	0.0305	1006656	2.08E-30	0.0035054	321672	0.000
rs11649885	G	A	G	A	-0.0127638	-0.015702644	0.566947	NA	0.421	0.0195	1006656	4.85E-08	0.0023391	321672	9.26E
rs116681793	A	G	A	G	-0.0332094	-0.007195628	0.0417894	NA	0.919	0.0704	1006656	1.63E-08	0.0058807	321672	9.91E
rs11671304	T	C	T	C	0.0209544	0.007296555	0.832872	NA	0.726	0.0208	1006656	2.77E-18	0.0024029	321672	0.000
rs11689962	T	C	T	C	0.0458364	-0.11079491	0.0266504	NA	0.102	0.0678	1006656	2.14E-10	0.00721758	321672	0.000
rs11694327	C	T	C	T	0.0153845	0.009603736	0.279609	NA	0.683	0.0235	1006656	3.08E-09	0.00259517	321672	0.000
rs1171148	C	T	C	T	-0.0147469	-0.010201862	0.325541	NA	0.604	0.0197	1006656	2.70E-09	0.00247987	321672	0.000
rs11738895	A	C	A	C	0.0146978	0.005002492	0.578926	NA	0.792	0.0191	1006656	3.68E-10	0.00234531	321672	0.000
rs117664796	T	G	T	G	0.0249402	0.048304332	0.0850525	NA	0.092	0.0287	1006656	1.98E-09	0.00415728	321672	0.000
rs11830128	A	G	A	G	-0.0223213	-0.01640381	0.10522	NA	0.656	0.0369	1006656	3.32E-09	0.00377379	321672	0.000
rs1184523	T	G	T	G	0.0171259	-0.010801454	0.575429	NA	0.603	0.0208	1006656	3.48E-13	0.00235423	321672	0.000
rs11907606	T	C	T	C	0.0194656	0.014297305	0.201946	NA	0.624	0.0291	1006656	1.80E-11	0.00289612	321672	0.000
rs11915638	G	A	G	A	0.0249349	0.006001952	0.183934	NA	0.798	0.0234	1006656	7.62E-17	0.00299069	321672	0.000
rs11959989	A	G	A	G	0.0134556	-0.015997277	0.448447	NA	0.43	0.0202	1006656	8.08E-09	0.00233326	321672	0.000
rs12001662	T	C	T	C	-0.0162864	-0.00020002	0.496448	NA	0.992	0.0197	1006656	2.39E-12	0.00232067	321672	0.000
rs12136024	T	C	T	C	0.0205244	-0.018204705	0.128113	NA	0.455	0.0244	1006656	3.64E-09	0.00347883	321672	0.000
rs12140153	T	G	T	G	-0.0429788	-0.025398863	0.078569	NA	0.421	0.0316	1006656	3.86E-23	0.00433799	321672	0.000
rs12184680	G	A	G	A	0.0154778	-0.001901807	0.233023	NA	0.937	0.0236	1006656	1.74E-08	0.00274918	321672	9.87E
rs12264040	T	C	T	C	-0.0126341	0.033701572	0.523193	NA	0.0857	0.0196	1006656	4.89E-08	0.00231593	321672	9.25E
rs12273461	C	T	C	T	-0.0146683	-0.026900682	0.353495	NA	0.187	0.0202	1006656	1.62E-09	0.00243173	321672	0.000
rs12281369	G	A	G	A	-0.0151582	-0.006501086	0.264101	NA	0.778	0.023	1006656	8.73E-09	0.00263452	321672	0.000
rs12476198	C	T	C	T	0.0637896	0.001100605	0.834505	NA	0.967	0.0265	1006656	1.66E-42	0.00312687	321672	0.001
rs12513212	C	A	C	A	0.0127732	0.012501529	0.496198	NA	0.527	0.0198	1006656	3.64E-08	0.00231924	321672	9.43E
rs12518987	G	A	G	A	0.0139809	-0.008697716	0.326193	NA	0.663	0.02	1006656	1.54E-08	0.00247136	321672	9.95E
rs12541615	C	T	C	T	0.018738	0.002696362	0.282469	NA	0.915	0.025	1006656	3.33E-13	0.00257378	321672	0.000
rs12599980	T	C	T	C	-0.0132011	-0.042698755	0.380195	NA	0.0309	0.0198	1006656	3.48E-08	0.0023936	321672	9.46E
rs12635614	A	G	A	G	0.0154249	-0.020204507	0.553936	NA	0.302	0.0196	1006656	3.67E-11	0.00233121	321672	0.000
rs12680237	T	C	T	C	0.0135778	0.021399391	0.504767	NA	0.279	0.0197	1006656	4.49E-09	0.00231504	321672	0.000
rs12756665	T	C	T	C	-0.0139594	-0.014200349	0.443965	NA	0.469	0.0197	1006656	2.25E-09	0.00233486	321672	0.000
rs12779865	C	T	C	T	0.0157137	0.001399021	0.31307	NA	0.945	0.0211	1006656	3.22E-10	0.00249905	321672	0.000
rs12858868	G	A	G	A	-0.013022	0.012001734	0.556854	NA	0.545	0.0198	1006656	2.55E-08	0.00233807	321672	9.64E

rs12887636	G	T	G	T	-0.0235024	-0.031304926	0.397602	NA	0.127	0.0205	1006656	3.33E-23	0.00236862	321672	0.000
rs13052235	G	A	G	A	-0.0185355	0.032699496	0.500539	NA	0.0981	0.0198	1006656	1.20E-15	0.00231557	321672	0.000
rs13100903	T	C	T	C	0.0237491	0.003902376	0.282111	NA	0.854	0.0211	1006656	4.67E-20	0.0025895	321672	0.000
rs13126805	C	T	C	T	0.0160845	0.02350166	0.247277	NA	0.272	0.0214	1006656	2.18E-09	0.00268797	321672	0.000
rs13130484	T	C	T	C	0.0351043	-0.0289636	0.472039	NA	0.138	0.0195	1006656	1.89E-51	0.00232636	321672	0.000
rs13133196	T	C	T	C	-0.0153118	0.019802627	0.350524	NA	0.338	0.0207	1006656	2.79E-10	0.00242658	321672	0.000
rs13206405	A	C	A	C	0.0157377	-0.002102208	0.263089	NA	0.928	0.0236	1006656	2.36E-09	0.00263569	321672	0.000
rs1333010	A	G	A	G	-0.0231355	0.017797439	0.515629	NA	0.374	0.02	1006656	2.20E-23	0.00232202	321672	0.000
rs13362819	G	A	G	A	0.0147505	0.008196318	0.377118	NA	0.687	0.0204	1006656	7.55E-10	0.00239883	321672	0.000
rs13399978	G	A	G	A	0.0138096	-0.004098387	0.519341	NA	0.836	0.0197	1006656	2.94E-09	0.00232981	321672	0.000
rs1372504	A	G	A	G	0.0136715	0.030897711	0.34566	NA	0.122	0.02	1006656	2.11E-08	0.00244018	321672	9.76E
rs138389194	A	G	A	G	0.026233	-0.019101273	0.0710467	NA	0.673	0.0453	1006656	9.20E-09	0.00456636	321672	0.000
rs139492988	A	G	A	G	-0.0486127	0.050902218	0.0209306	NA	0.576	0.0909	1006656	2.37E-09	0.0081428	321672	0.000
rs143264991	A	C	A	C	-0.0140539	0.02059643	0.293773	NA	0.503	0.0307	1006656	4.36E-08	0.00258654	321672	9.32E
rs1436351	T	G	T	G	0.0176996	0.03740077	0.788704	NA	0.107	0.0232	1006656	4.74E-10	0.00263736	321672	0.000
rs144285608	C	A	C	A	0.0492349	-0.056295257	0.0219858	NA	0.568	0.0985	1006656	5.76E-10	0.00794512	321672	0.000
rs1445796	A	G	A	G	0.015197	0.009000362	0.696952	NA	0.667	0.021	1006656	1.59E-09	0.00251807	321672	0.000
rs1478364	T	C	T	C	-0.0150391	-0.017604046	0.275536	NA	0.501	0.0262	1006656	8.17E-09	0.00260873	321672	0.000
rs148965592	A	G	A	G	0.0384257	0.078302733	0.0438551	NA	0.0592	0.0415	1006656	1.28E-11	0.00567495	321672	0.000
rs1517037	T	C	T	C	-0.0155785	-0.0389959	0.271571	NA	0.137	0.0249	1006656	2.34E-09	0.00260864	321672	0.000
rs1582931	A	G	A	G	-0.020703	-0.005203515	0.512146	NA	0.79	0.0196	1006656	4.42E-19	0.00231941	321672	0.000
rs1652348	T	C	T	C	-0.0201539	-0.03599882	0.506025	NA	0.0714	0.0194	1006656	3.27E-18	0.00231614	321672	0.000
rs16952520	G	A	G	A	-0.0523814	-0.107395919	0.0546274	NA	0.106	0.0665	1006656	1.43E-24	0.00511968	321672	0.000
rs17024258	T	C	T	C	0.0714812	0.059098752	0.058749	NA	0.253	0.0518	1006656	1.19E-47	0.00492931	321672	0.000
rs17147219	T	G	T	G	0.0185672	-0.001100605	0.279963	NA	0.964	0.0233	1006656	6.32E-13	0.00258116	321672	0.000
rs1773492	G	A	G	A	-0.0153002	-0.045898448	0.275026	NA	0.0273	0.0207	1006656	4.60E-09	0.00261046	321672	0.000
rs17789218	C	T	C	T	0.0185921	0.030403106	0.2079	NA	0.202	0.0238	1006656	8.04E-11	0.00268043	321672	0.000
rs17797972	G	T	G	T	-0.0206683	-0.008501086	0.131181	NA	0.827	0.0296	1006656	1.92E-09	0.00344221	321672	0.000
rs17821500	C	T	C	T	0.0209623	0.002796087	0.102036	NA	0.919	0.0281	1006656	4.19E-08	0.0038235	321672	9.34E
rs1800188	T	C	T	C	-0.0400045	0.03290272	0.0727345	NA	0.579	0.0593	1006656	3.97E-19	0.00447591	321672	0.000
rs183228384	C	G	C	G	-0.0540057	0.347499955	0.0217111	0.13	0.342	0.3658	1006656	1.42E-11	0.00799363	321672	0.000
rs1865719	G	A	G	A	0.024828	0.013095371	0.649162	NA	0.512	0.02	1006656	1.43E-24	0.00242853	321672	0.000
rs1927861	T	C	T	C	0.0289422	-0.011404788	0.140417	NA	0.691	0.0286	1006656	5.27E-18	0.00334693	321672	0.000
rs1937450	G	T	G	T	0.0144306	-0.017397777	0.567216	NA	0.375	0.0196	1006656	7.52E-10	0.00234462	321672	0.000
rs1962166	A	G	A	G	-0.0192926	-0.007898723	0.724877	NA	0.708	0.0211	1006656	1.08E-13	0.00259635	321672	0.000
rs1982441	T	G	T	G	0.0231105	-0.009000382	0.194822	NA	0.747	0.028	1006656	8.11E-15	0.00297993	321672	0.000
rs1995667	A	G	A	G	-0.0141567	0.042900835	0.342721	NA	0.0483	0.0215	1006656	6.53E-09	0.00244025	321672	0.000
rs2011077	T	C	T	C	-0.0191917	-0.018703831	0.216879	NA	0.414	0.0229	1006656	9.68E-12	0.00281756	321672	0.000
rs2012697	C	T	C	T	0.0277525	0.020898826	0.644585	NA	0.29	0.0197	1006656	2.47E-30	0.00242469	321672	0.000
rs2039667	C	T	C	T	0.0141921	0.015895669	0.563323	NA	0.43	0.0201	1006656	1.42E-09	0.0023446	321672	0.000
rs2076587	A	G	A	G	-0.0176183	-0.020600746	0.352097	NA	0.309	0.0203	1006656	4.40E-13	0.00243252	321672	0.000
rs208015	C	T	C	T	-0.0284433	-0.04449524	0.894061	NA	0.248	0.0385	1006656	4.01E-14	0.00376198	321672	0.000
rs2112708	A	G	A	G	0.0158396	-0.014996981	0.568977	NA	0.442	0.0195	1006656	1.35E-11	0.00234215	321672	0.000
rs2150854	T	G	T	G	0.0239363	0.016798118	0.374747	NA	0.421	0.0209	1006656	1.45E-23	0.0023925	321672	0.000
rs2161768	G	A	G	A	0.0184935	-0.010100842	0.1782	NA	0.673	0.0239	1006656	1.12E-09	0.00303637	321672	0.000
rs2198954	G	A	G	A	0.0161467	-0.005002492	0.3444	NA	0.813	0.021	1006656	4.10E-11	0.00244636	321672	0.000
rs2208938	T	C	T	C	-0.0136681	-0.010603583	0.554308	NA	0.594	0.0199	1006656	4.86E-09	0.00233561	321672	0.000
rs2209073	A	G	A	G	-0.0140254	-0.011997738	0.63086	NA	0.546	0.0199	1006656	4.47E-09	0.002391	321672	0.000
rs2236691	A	G	A	G	-0.020152	-0.016200523	0.259316	NA	0.49	0.0235	1006656	2.63E-14	0.00264619	321672	0.000
rs2239647	C	A	C	A	-0.0248566	-0.008404582	0.569754	NA	0.669	0.0196	1006656	2.44E-26	0.00234084	321672	0.000
rs2253032	G	A	G	A	-0.0360264	0.146402442	0.959997	NA	0.0828	0.0844	1006656	1.04E-09	0.0059033	321672	0.000
rs2270623	T	C	T	C	-0.0156298	0.024497632	0.506526	NA	0.2	0.0191	1006656	1.57E-11	0.00231854	321672	0.000
rs2275003	G	A	G	A	-0.0135648	-0.037295785	0.534861	NA	0.0503	0.0191	1006656	4.78E-09	0.00231692	321672	0.000
rs2297792	C	T	C	T	0.0233296	-0.00639948	0.615639	NA	0.752	0.0201	1006656	1.33E-22	0.00238476	321672	0.000
rs2307111	C	T	C	T	-0.0203098	-0.029796631	0.424404	NA	0.139	0.0202	1006656	4.77E-18	0.0023456	321672	0.000
rs2331416	C	T	C	T	0.012944	0.006200736	0.495088	NA	0.757	0.0199	1006656	4.00E-08	0.00235733	321672	9.37E
rs2465054	A	G	A	G	-0.0167116	-0.047395637	0.385764	NA	0.0213	0.0206	1006656	1.28E-11	0.00238844	321672	0.000

rs2567302	A	G	A	G	-0.0173444	-0.007898723	0.728319	NA	0.72	0.0221	1006656	2.56E-11	0.00260036	321672	0.000
rs281230	G	A	G	A	0.015389	-0.022797909	0.575928	NA	0.244	0.0195	1006656	5.12E-11	0.00234329	321672	0.000
rs266311	A	G	A	G	0.0190266	0.024302293	0.214192	NA	0.273	0.0222	1006656	1.37E-11	0.00281437	321672	0.000
rs2881584	A	C	A	C	-0.0151814	-0.020400488	0.860045	NA	0.327	0.0208	1006656	5.61E-10	0.00244819	321672	0.000
rs272611	C	T	C	T	-0.0303959	-0.028594967	0.0529313	NA	0.571	0.0505	1006656	5.39E-09	0.00520953	321672	0.000
rs2818417	T	C	T	C	-0.0149307	0.012801592	0.574609	NA	0.542	0.0209	1006656	1.88E-10	0.00234358	321672	0.000
rs2820314	C	A	C	A	0.0181126	-0.012599036	0.296351	NA	0.542	0.0206	1006656	9.66E-13	0.00253844	321672	0.000
rs28529403	C	T	C	T	-0.0241834	-0.018102873	0.436834	NA	0.364	0.0199	1006656	6.44E-25	0.00234594	321672	0.000
rs2881654	A	G	A	G	0.0224011	-0.036404682	0.170673	NA	0.214	0.0293	1006656	3.65E-13	0.00308216	321672	0.000
rs28865339	G	A	G	A	0.0214979	0.006101349	0.134284	NA	0.836	0.0296	1006656	3.45E-10	0.00342485	321672	0.000
rs2920926	G	A	G	A	0.0187998	-0.022798136	0.732371	NA	0.292	0.0216	1006656	7.19E-13	0.00261992	321672	0.000
rs300780	T	C	T	C	0.0140355	-0.003496104	0.530998	NA	0.86	0.0198	1006656	1.59E-09	0.00232553	321672	0.000
rs34142155	A	C	A	C	0.0309305	-0.029995398	0.129558	NA	0.311	0.0296	1006656	4.97E-19	0.00347032	321672	0.000
rs34517439	A	C	A	C	0.02715	0.031004359	0.128623	NA	0.284	0.0289	1006656	5.37E-15	0.00347275	321672	0.000
rs34621893	C	A	C	A	0.0183322	0.02180063	0.144228	NA	0.404	0.0262	1006656	2.66E-08	0.00329576	321672	9.62E
rs34755	T	G	T	G	0.0148197	0.01380485	0.526347	NA	0.478	0.0194	1006656	2.98E-10	0.00232074	321672	0.000
rs34811474	A	G	A	G	-0.025355	-0.017400515	0.229026	NA	0.451	0.023	1006656	4.55E-20	0.00276372	321672	0.000
rs35056791	T	C	T	C	0.0272478	-0.003295424	0.146946	NA	0.922	0.0336	1006656	9.49E-17	0.00327854	321672	0.000
rs35088240	G	A	G	A	-0.0557514	0.032498231	0.0148046	NA	0.618	0.0651	1006656	7.19E-09	0.00963489	321672	0.000
rs35209276	A	G	A	G	0.0386419	0.110395817	0.0318392	NA	0.152	0.0772	1006656	2.49E-08	0.00660975	321672	9.66E
rs35221880	C	T	C	T	-0.0205363	-0.026700352	0.813145	NA	0.212	0.0214	1006656	7.01E-12	0.00299471	321672	0.000
rs35378894	C	T	C	T	-0.0275525	-0.006501086	0.0572686	NA	0.823	0.0289	1006656	3.45E-08	0.00494433	321672	9.46E
rs38144	C	A	C	A	0.0162212	-0.003304534	0.66192	NA	0.871	0.0203	1006656	3.55E-11	0.00244975	321672	0.000
rs3747973	G	A	G	A	-0.0130488	0.008465989	0.613137	NA	0.668	0.0197	1006656	4.40E-08	0.00233837	321672	9.31E
rs3757589	A	G	A	G	-0.0128313	0.009999835	0.435855	NA	0.622	0.0203	1006656	4.22E-08	0.00234095	321672	9.34E
rs3786791	T	C	T	C	-0.0150168	0.013488484	0.246248	NA	0.573	0.0239	1006656	2.17E-08	0.00268276	321672	9.74E
rs3789220	A	G	A	G	0.0275396	0.055955527	0.0631943	NA	0.218	0.0451	1006656	6.75E-11	0.00421991	321672	0.000
rs3790076	T	G	T	G	0.0143404	-0.024204689	0.559458	NA	0.217	0.0196	1006656	8.73E-10	0.00233886	321672	0.000
rs3800227	G	A	G	A	0.0230512	0.024497632	0.680932	NA	0.28	0.0226	1006656	2.00E-20	0.00248871	321672	0.000
rs3813663	G	T	G	T	-0.0137985	-0.039000737	0.477909	NA	0.0494	0.0199	1006656	2.91E-09	0.00232436	321672	0.000
rs3814898	A	C	A	C	-0.0187708	0.023002542	0.778601	NA	0.34	0.0241	1006656	2.25E-11	0.00280637	321672	0.000
rs3935190	A	G	A	G	-0.0184631	-0.020096702	0.503279	NA	0.305	0.0196	1006656	1.78E-15	0.00232077	321672	0.000
rs4107635	G	A	G	A	-0.013951	0.02740203	0.665638	NA	0.19	0.0209	1006656	1.44E-08	0.00246103	321672	9.99E
rs41314513	A	G	A	G	0.0371765	0.074597138	0.0339871	NA	0.425	0.0935	1006656	7.32E-09	0.0064282	321672	0.000
rs4237769	A	G	A	G	-0.0130679	0.0009995	0.398623	NA	0.959	0.0202	1006656	3.42E-08	0.00236902	321672	9.47E
rs4287756	G	A	G	A	-0.0227542	0.033898103	0.755544	NA	0.123	0.0219	1006656	3.98E-17	0.00270454	321672	0.000
rs4319898	G	A	G	A	0.0181654	0.029099308	0.629264	NA	0.139	0.0197	1006656	3.93E-14	0.00240179	321672	0.000
rs4335979	G	A	G	A	0.0136827	0.040301297	0.538506	NA	0.0388	0.0195	1006656	4.15E-09	0.00232781	321672	0.000
rs437564	T	C	T	C	0.0316016	0.02399969	0.42642	NA	0.224	0.0197	1006656	1.09E-40	0.00236608	321672	0.000
rs4386268	A	G	A	G	-0.0155412	0.033695884	0.217084	NA	0.17	0.0245	1006656	3.31E-08	0.00281322	321672	9.49E
rs4397868	T	C	T	C	0.0179209	-0.01530232	0.808368	NA	0.537	0.0247	1006656	1.19E-09	0.00294676	321672	0.000
rs4414033	A	G	A	G	0.0140687	-0.021996298	0.570003	NA	0.273	0.0201	1006656	2.04E-09	0.00234689	321672	0.000
rs4462854	A	G	A	G	-0.0135249	0.001498876	0.408205	NA	0.943	0.0201	1006656	9.68E-09	0.00235779	321672	0.000
rs4488007	T	C	T	C	-0.0140687	0.018001051	0.578895	NA	0.361	0.0197	1006656	1.95E-09	0.0023436	321672	0.000
rs4474776	C	T	C	T	0.0196307	-0.006299802	0.385746	NA	0.759	0.0207	1006656	1.56E-16	0.00237897	321672	0.000
rs4554194	A	G	A	G	-0.0184583	0.005395419	0.367845	NA	0.797	0.021	1006656	1.70E-14	0.00240614	321672	0.000
rs45551238	T	C	T	C	-0.0735249	0.04449524	0.048684	0.629	0.615	0.0885	1006656	5.13E-42	0.00541344	321672	0.000
rs4596023	G	A	G	A	0.0147058	0.044903228	0.738194	NA	0.0448	0.0224	1006656	2.87E-08	0.00265011	321672	9.57E
rs4663210	G	A	G	A	-0.0150592	-0.011602431	0.735635	NA	0.613	0.023	1006656	1.05E-08	0.00263164	321672	0.000
rs4671328	G	T	G	T	-0.0223586	-0.008017144	0.599989	NA	0.738	0.0196	1006656	3.03E-21	0.00236304	321672	0.000
rs4678496	T	C	T	C	-0.0152172	-0.000499875	0.599665	NA	0.979	0.0195	1006656	1.37E-10	0.00237071	321672	0.000
rs4711634	A	G	A	G	-0.0266469	-0.032099262	0.417304	NA	0.101	0.0196	1006656	1.46E-29	0.00236015	321672	0.000
rs4771122	A	G	A	G	-0.018525	0.048003973	0.85979	NA	0.038	0.0231	1006656	4.25E-14	0.00245266	321672	0.000
rs4776375	A	G	A	G	-0.028657	-0.021203208	0.161776	NA	0.371	0.0238	1006656	7.14E-20	0.00314029	321672	0.000
rs4780852	G	T	G	T	0.0169023	0.0037972	0.735133	NA	0.877	0.0246	1006656	1.21E-10	0.00262522	321672	0.000
rs4832043	C	T	C	T	-0.0152219	-0.008899483	0.510011	NA	0.646	0.0194	1006656	5.88E-11	0.00232511	321672	0.000
rs4912844	C	A	C	A	-0.0152856	-0.005504821	0.726155	NA	0.805	0.0223	1006656	4.37E-09	0.00260419	321672	0.000

rs4926775	G	A	G	A	-0.0167321	-0.001099395	0.643518	NA	0.957	0.0205	1006656	5.35E-12	0.00242635	321672	0.000
rs4932493	C	A	C	A	0.0137728	-0.016896448	0.477375	NA	0.387	0.0196	1006656	3.61E-09	0.00233398	321672	0.000
rs4954552	A	G	A	G	-0.0246954	0.015597721	0.365531	NA	0.521	0.0243	1006656	2.56E-24	0.00242704	321672	0.000
rs509325	G	T	G	T	0.0478115	-0.011598986	0.181345	NA	0.632	0.0242	1006656	6.41E-57	0.00300715	321672	0.000
rs538656	T	G	T	G	0.0521373	0.029801491	0.180057	NA	0.18	0.0222	1006656	7.84E-49	0.00297345	321672	0.000
rs5668221	A	G	A	G	-0.0153855	0.002097798	0.257634	NA	0.918	0.0207	1006656	6.24E-09	0.00264805	321672	0.000
rs56915529	T	C	T	C	-0.0160635	-0.032955008	0.290468	NA	0.129	0.0215	1006656	4.72E-10	0.00257916	321672	0.000
rs57636386	C	T	C	T	-0.0305096	-0.02880079	0.0502816	NA	0.397	0.0341	1006656	9.04E-09	0.00530794	321672	0.000
rs577993	T	C	T	C	0.0142139	0.008102739	0.543555	NA	0.687	0.0201	1006656	1.05E-09	0.00232957	321672	0.000
rs58970950	C	A	C	A	-0.0192573	0.04580476	0.182108	NA	0.155	0.0322	1006656	1.59E-10	0.00301059	321672	0.000
rs59133600	C	A	C	A	-0.027638	0.017898855	0.0639282	NA	0.708	0.0478	1006656	5.77E-09	0.00474917	321672	0.000
rs59956089	C	T	C	T	0.0161914	0.024497472	0.247821	NA	0.312	0.0243	1006656	1.76E-09	0.00269011	321672	0.000
rs60264701	C	T	C	T	0.0699128	-0.015001969	0.0108838	NA	0.86	0.085	1006656	6.07E-10	0.0112969	321672	0.000
rs6044685	G	A	G	A	0.0145415	0.014602857	0.428392	NA	0.454	0.0195	1006656	4.71E-10	0.00233471	321672	0.000
rs6068144	G	A	G	A	-0.0216514	-0.037504587	0.227797	NA	0.0918	0.0222	1006656	4.66E-15	0.00276313	321672	0.000
rs612389	C	T	C	T	-0.0201715	0.033502472	0.155724	NA	0.219	0.0272	1006656	2.79E-10	0.00319886	321672	0.000
rs61579019	G	T	G	T	0.0171197	-0.014897481	0.317482	NA	0.477	0.0207	1006656	6.53E-12	0.00249285	321672	0.000
rs61937571	A	G	A	G	-0.0391603	-0.007598798	0.0352413	NA	0.904	0.063	1006656	6.20E-10	0.00633129	321672	0.000
rs61992671	G	A	G	A	-0.015245	-0.022103899	0.509746	NA	0.265	0.0199	1006656	8.04E-11	0.00234547	321672	0.000
rs62107281	C	T	C	T	-0.10732	-0.048602182	0.0199008	NA	0.326	0.0494	1006656	5.76E-38	0.00833168	321672	0.000
rs62171412	G	A	G	A	-0.0251408	-0.002402885	0.124275	NA	0.954	0.0425	1006656	9.23E-13	0.00352036	321672	0.000
rs62174267	C	T	C	T	0.0380966	0.030703778	0.0288067	NA	0.457	0.0412	1006656	4.60E-08	0.0069897	321672	9.29E
rs62294143	T	C	T	C	0.0194682	0.020802128	0.121119	NA	0.495	0.0305	1006656	4.41E-08	0.00355651	321672	9.31E
rs62430555	A	G	A	G	0.0188288	0.017702384	0.218444	NA	0.416	0.0217	1006656	2.33E-11	0.00281709	321672	0.000
rs6416742	T	C	T	C	0.0210287	-0.032595008	0.296539	NA	0.116	0.0207	1006656	1.56E-16	0.00254849	321672	0.000
rs6419384	C	T	C	T	-0.016219	0.010197825	0.31026	NA	0.647	0.0224	1006656	9.68E-11	0.00250099	321672	0.000
rs6444144	T	C	T	C	0.01323	-0.018802127	0.638135	NA	0.514	0.0288	1006656	4.02E-08	0.00240981	321672	9.37E
rs6471478	C	T	C	T	0.0187968	-0.012030394	0.651542	NA	0.537	0.02	1006656	1.23E-14	0.00243701	321672	0.000
rs652105	T	C	T	C	0.0134965	0.021800663	0.41911	NA	0.263	0.0195	1006656	9.40E-09	0.00235078	321672	0.000
rs6695685	A	G	A	G	0.0196489	-0.021795812	0.467361	NA	0.276	0.02	1006656	3.45E-17	0.0023308	321672	0.000
rs6705250	G	A	G	A	0.0211412	-0.033805005	0.122567	NA	0.266	0.0304	1006656	2.30E-09	0.00353817	321672	0.000
rs6746570	C	A	C	A	-0.0150999	-0.025799975	0.286227	NA	0.234	0.0217	1006656	5.03E-09	0.00255828	321672	0.000
rs6749170	G	A	G	A	0.0295204	-0.029202266	0.411895	NA	0.139	0.0197	1006656	6.86E-36	0.00236038	321672	0.000
rs680497	T	C	T	C	0.0136787	-0.003295424	0.329558	NA	0.888	0.0231	1006656	3.17E-08	0.00247272	321672	9.51E
rs680559	G	A	G	A	-0.0150787	-0.021795812	0.44903	NA	0.266	0.0196	1006656	1.01E-10	0.00233229	321672	0.000
rs6806706	A	C	A	C	0.0136892	0.034301632	0.625241	NA	0.0835	0.0198	1006656	1.10E-08	0.00230034	321672	0.000
rs6816991	C	T	C	T	-0.0146126	-0.029202266	0.280639	NA	0.155	0.0206	1006656	1.62E-08	0.00258708	321672	9.92E
rs6833262	A	C	A	C	0.0226279	0.008899483	0.833064	NA	0.723	0.0251	1006656	2.92E-13	0.00310062	321672	0.000
rs6913550	C	T	C	T	0.0220961	-0.011602431	0.707989	NA	0.628	0.0239	1006656	5.92E-18	0.00255918	321672	0.000
rs6955671	T	C	T	C	-0.0222247	-0.011197078	0.628324	NA	0.573	0.0199	1006656	2.52E-20	0.0024059	321672	0.000
rs6956986	C	T	C	T	-0.0385307	-0.054204054	0.804334	NA	0.0474	0.0274	1006656	1.10E-39	0.00292274	321672	0.000
rs7072873	T	C	T	C	-0.015047	0.004098387	0.515066	NA	0.636	0.0197	1006656	7.97E-11	0.00231453	321672	0.000
rs7102454	C	T	C	T	0.0165371	-0.045804245	0.287203	NA	0.026	0.0205	1006656	1.05E-10	0.00256007	321672	0.000
rs7132908	A	G	A	G	0.0279704	-0.002302649	0.382615	NA	0.908	0.02	1006656	1.07E-31	0.00238758	321672	0.000
rs7148887	A	G	A	G	0.0137337	-0.016902038	0.404736	NA	0.388	0.0196	1006656	5.67E-09	0.00235724	321672	0.000
rs7159126	C	T	C	T	-0.0173348	-0.024702613	0.276785	NA	0.269	0.0223	1006656	2.03E-11	0.00258572	321672	0.000
rs71627581	A	G	A	G	-0.0267146	0.003204859	0.171051	NA	0.917	0.0303	1006656	6.85E-18	0.00310011	321672	0.000
rs7200737	A	G	A	G	0.0174306	0.00449986	0.250946	NA	0.842	0.0223	1006656	7.45E-11	0.00267695	321672	0.000
rs7203844	G	A	G	A	0.0194812	0.042695439	0.149491	NA	0.194	0.0329	1006656	2.28E-09	0.00325966	321672	0.000
rs7259484	G	A	G	A	-0.0162593	0.027498429	0.227963	NA	0.238	0.0233	1006656	3.91E-09	0.00276149	321672	0.000
rs72634501	C	T	C	T	0.0153936	-0.060195964	0.22128	NA	0.00903	0.0231	1006656	4.39E-08	0.00281189	321672	9.32E
rs72654628	G	A	G	A	0.0193243	-0.023698607	0.266368	NA	0.36	0.0259	1006656	1.87E-13	0.00262638	321672	0.000
rs72733275	T	G	T	G	0.0286483	-0.010403934	0.078605	NA	0.822	0.0463	1006656	6.60E-11	0.00438716	321672	0.000
rs72734458	G	A	G	A	-0.0146259	-0.01899935	0.329342	NA	0.375	0.0214	1006656	3.54E-09	0.00247708	321672	0.000
rs72742731	G	A	G	A	0.021036	-0.0090032	0.274349	NA	0.977	0.0265	1006656	5.74E-16	0.00259871	321672	0.000
rs72759983	T	C	T	C	-0.036006	0.02940345	0.0376049	NA	0.573	0.0521	1006656	3.36E-09	0.00698922	321672	0.000
rs72811214	C	T	C	T	-0.0250905	0.024604804	0.090812	NA	0.537	0.0398	1006656	5.06E-10	0.00403564	321672	0.000

rs73082646	A	G	A	G	0.023245	0.08469954	0.0837369	NA	0.0476	0.0428	1006656	2.98E-08	0.00419401	321672	9.55E
rs73152535	A	G	A	G	0.0156425	-0.012204169	0.303444	NA	0.565	0.0213	1006656	5.24E-10	0.00251818	321672	0.000
rs73581567	T	C	T	C	-0.0222238	0.040700387	0.231091	NA	0.131	0.027	1006656	1.14E-14	0.00287777	321672	0.000
rs73614566	C	T	C	T	0.0383777	0.008702027	0.12056	NA	0.757	0.028	1006656	1.71E-24	0.00356142	321672	0.000
rs738140	G	A	G	A	-0.0176172	-0.017298765	0.323525	NA	0.408	0.021	1006656	1.04E-12	0.00247274	321672	0.000
rs7426145	A	G	A	G	-0.0242062	-0.03899599	0.0759484	NA	0.361	0.0405	1006656	4.26E-08	0.00441744	321672	9.33E
rs7434143	T	G	T	G	0.0173908	-0.004101577	0.684757	NA	0.842	0.0208	1006656	3.04E-12	0.00249299	321672	0.000
rs755555	T	C	T	C	0.022451	-0.017003748	0.307999	NA	0.416	0.0209	1006656	4.38E-19	0.00251481	321672	0.000
rs75634909	G	A	G	A	-0.0237829	0.004101577	0.0819434	NA	0.92	0.0406	1006656	2.18E-08	0.00424539	321672	9.74E
rs7563544	G	A	G	A	0.0134052	0.02968655	0.452453	NA	0.128	0.0196	1006656	8.54E-09	0.00232833	321672	0.000
rs7588732	A	G	A	G	-0.0133873	-0.002197584	0.543352	NA	0.911	0.0193	1006656	1.18E-08	0.00234432	321672	0.000
rs75947329	G	A	G	A	0.0486974	0.011701272	0.0210389	NA	0.878	0.075	1006656	3.68E-09	0.00625676	321672	0.000
rs7647305	C	T	C	T	0.0298999	0.030995434	0.817959	NA	0.194	0.0238	1006656	3.21E-23	0.00301225	321672	0.000
rs76569620	T	C	T	C	0.030548	-0.060100384	0.0462189	NA	0.225	0.0496	1006656	3.41E-08	0.00553509	321672	9.47E
rs76895963	G	T	G	T	0.0419681	0.19939988	0.0301208	NA	0.00328	0.0678	1006656	1.96E-09	0.00699298	321672	0.000
rs77159266	A	G	A	G	-0.022715	-0.053400777	0.125704	NA	0.0848	0.031	1006656	8.80E-11	0.00350205	321672	0.000
rs77479170	A	G	A	G	0.0157218	-0.016699779	0.489905	NA	0.391	0.0195	1006656	1.22E-11	0.00231953	321672	0.000
rs77505508	A	G	A	G	-0.06278	0.084396294	0.0210399	NA	0.191	0.0645	1006656	9.58E-15	0.00810614	321672	0.000
rs77669931	A	C	A	C	-0.0170119	-0.017096295	0.192026	NA	0.56	0.0293	1006656	9.00E-09	0.00299928	321672	0.000
rs7828742	G	A	G	A	0.0172232	0.015103486	0.530666	NA	0.452	0.0201	1006656	1.24E-13	0.00232369	321672	0.000
rs7860903	T	G	T	G	-0.0202718	-0.0009995	0.541401	NA	0.959	0.0196	1006656	3.17E-18	0.00232874	321672	0.000
rs7874346	C	T	C	T	0.0180998	-0.02898544	0.168513	NA	0.325	0.0273	1006656	5.64E-09	0.00310621	321672	0.000
rs78901918	A	G	A	G	0.0232993	0.017397777	0.117016	NA	0.687	0.0433	1006656	1.44E-10	0.00363411	321672	0.000
rs79027831	A	G	A	G	-0.0292904	-0.120203463	0.0655947	NA	0.00267	0.04	1006656	4.54E-10	0.00469825	321672	0.000
rs79565412	C	T	C	T	-0.029286	0.075404274	0.0827557	NA	0.0704	0.0417	1006656	4.01E-15	0.00419953	321672	0.000
rs80146384	G	A	G	A	-0.0175774	0.00809713	0.156992	NA	0.792	0.0309	1006656	3.57E-08	0.0031896	321672	9.44E
rs8022640	A	G	A	G	0.0146345	-0.050598799	0.32529	NA	0.0157	0.0209	1006656	3.69E-09	0.00248149	321672	0.000
rs80345943	A	C	A	C	0.0435029	0.153501898	0.0406849	NA	0.00557	0.0554	1006656	1.21E-13	0.005886	321672	0.000
rs8053333	G	T	G	T	-0.0150259	0.00079968	0.33531	NA	0.964	0.0171	1006656	1.03E-09	0.00246111	321672	0.000
rs8057911	T	C	T	C	0.0169455	-0.016902038	0.196804	NA	0.469	0.0233	1006656	6.49E-09	0.00291988	321672	0.000
rs8091425	C	T	C	T	-0.0147144	0.006598184	0.256797	NA	0.775	0.0232	1006656	3.03E-08	0.00265628	321672	9.54E
rs8095637	C	T	C	T	0.0192927	0.008395141	0.810989	NA	0.686	0.0208	1006656	4.69E-16	0.00237613	321672	0.000
rs807559	G	A	G	A	0.0206206	-0.004600566	0.332917	NA	0.847	0.024	1006656	6.96E-17	0.00246805	321672	0.000
rs807508	G	A	G	A	0.016717	-0.000299955	0.834484	NA	0.992	0.0301	1006656	4.10E-12	0.00241096	321672	0.000
rs809970	A	G	A	G	-0.0142125	-0.00039992	0.595319	NA	0.988	0.0195	1006656	1.92E-09	0.00236703	321672	0.000
rs80272339	G	A	G	A	-0.0153092	-0.00449986	0.70339	NA	0.814	0.0193	1006656	1.69E-09	0.00254858	321672	0.000
rs8024397	T	C	T	C	-0.0327221	-0.011802431	0.953762	NA	0.843	0.0589	1006656	3.33E-09	0.00555236	321672	0.000
rs8034935	A	G	A	G	0.014648	-0.027799975	0.688596	NA	0.162	0.0199	1006656	6.49E-09	0.002524	321672	0.000
rs80512706	C	A	C	A	0.0147377	-0.003304534	0.688528	NA	0.87	0.0205	1006656	3.82E-09	0.00250133	321672	0.000
rs80530843	C	A	C	A	-0.0170149	0.051500773	0.327123	NA	0.00837	0.0195	1006656	5.96E-12	0.00247288	321672	0.000
rs80549099	C	T	C	T	0.0183687	-0.012902885	0.32538	NA	0.558	0.022	1006656	1.12E-13	0.00247338	321672	0.000
rs80563548	G	A	G	A	-0.0209766	-0.009797842	0.272336	NA	0.661	0.0224	1006656	7.45E-16	0.00260162	321672	0.000
rs8054356	A	G	A	G	-0.0179408	0.013895783	0.214787	NA	0.534	0.0221	1006656	2.09E-10	0.00282334	321672	0.000
rs8013199	T	C	T	C	0.0136818	-0.01640381	0.528607	NA	0.403	0.0196	1006656	3.61E-09	0.00231859	321672	0.000
rs8041640	C	A	C	A	0.0236058	-0.04160355	0.0785832	NA	0.344	0.044	1006656	4.05E-08	0.00430077	321672	9.36E
rs809960	G	A	G	A	-0.016772	0.005897355	0.767559	NA	0.791	0.0224	1006656	1.04E-09	0.00274784	321672	0.000
rs802692	C	T	C	T	0.0172304	0.014602857	0.267095	NA	0.471	0.0203	1006656	4.92E-11	0.0026213	321672	0.000
rs8039020	C	T	C	T	0.0166072	0.017502275	0.539776	NA	0.378	0.0198	1006656	1.04E-12	0.00233101	321672	0.000
rs8047260	G	A	G	A	-0.0314128	0.040201002	0.0432808	NA	0.348	0.0428	1006656	3.96E-08	0.00571906	321672	9.38E
rs8066123	A	G	A	G	-0.0150171	-0.015895669	0.473977	NA	0.414	0.0195	1006656	1.21E-10	0.00233265	321672	0.000
rs808393	C	T	C	T	0.0142938	-0.001300846	0.299019	NA	0.951	0.0212	1006656	1.59E-08	0.00252932	321672	9.93E
rs8055276	T	C	T	C	0.024227	-0.010201862	0.17459	NA	0.709	0.0274	1006656	1.67E-15	0.00304218	321672	0.000
Summary	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.047

TABLE 8: Independent IVs in the causal analysis of adult BMI (FinnGen) and SSS

BMI, body mass index; FinnGen, Finnish Health Research Environment for Genomic Research; IVs, instrumental variables; NA, not applicable; SNP, single nucleotide polymorphism; SSS, sick sinus syndrome

SNP	effect_allele.exposure	other_allele.exposure	effect_allele.outcome	other_allele.outcome	beta.exposure	beta.outcome	esf.exposure	esf.outcome	pval.outcome	se.outcome	samplesize.outcome	se.exposure	pval.exposure	samplesize.exposure	R2
rs10063055	T	C	T	C	0.0136775	-0.011000282	0.253365	NA	0.628	0.0228	1006656	0.00226991	1.70E-09	461460	7.87E
rs10182416	G	A	G	A	0.0130378	0.001601281	0.512223	NA	0.934	0.0195	1006656	0.00197134	3.70E-11	461460	9.48E
rs10184537	T	C	T	C	-0.016303	-0.019998647	0.339341	NA	0.328	0.0204	1006656	0.00208355	5.10E-15	461460	0.000
rs10402950	C	T	C	T	0.0135545	0.008900275	0.289347	NA	0.672	0.0211	1006656	0.00218692	5.70E-10	461460	8.32E
rs10505836	C	A	C	A	0.0184851	0.012102946	0.860012	NA	0.66	0.0276	1006656	0.00287086	1.20E-10	461460	8.98E
rs10510025	T	C	T	C	0.0175843	0.001099395	0.247013	NA	0.96	0.0229	1006656	0.00229866	2.20E-14	461460	0.000
rs1084213	A	G	A	G	0.0149301	-0.025902594	0.478377	NA	0.188	0.0196	1006656	0.00197196	3.70E-14	461460	0.000
rs10742752	C	T	C	T	0.0117979	0.0010005	0.612239	NA	0.962	0.0201	1006656	0.00202961	6.10E-09	461460	7.32E
rs10760277	T	C	T	C	0.0138734	-0.007901132	0.385049	NA	0.69	0.0199	1006656	0.00203825	1.00E-11	461460	0.000
rs10771041	T	C	T	C	0.0213233	-0.000300045	0.116102	NA	0.992	0.0321	1006656	0.0030884	5.00E-12	461460	0.000
rs10780248	A	G	A	G	-0.0121232	0.022102047	0.559454	NA	0.265	0.0198	1006656	0.00199415	1.20E-09	461460	8.01E
rs1078141	T	C	T	C	0.0142239	0.015904449	0.383867	NA	0.428	0.02	1006656	0.00205862	4.90E-12	461460	0.000
rs10799778	G	T	G	T	-0.0182237	-0.034700899	0.833718	NA	0.202	0.0272	1006656	0.00264876	6.00E-12	461460	0.000
rs10824211	T	C	T	C	0.0207688	0.014297305	0.139491	NA	0.62	0.0288	1006656	0.00286631	4.30E-13	461460	0.000
rs10927006	C	T	C	T	-0.0168156	0.02810143	0.143704	NA	0.275	0.0257	1006656	0.00281467	2.30E-09	461460	7.73E
rs10960293	T	G	T	G	-0.0140984	0.0296855	0.333719	NA	0.149	0.0207	1006656	0.00210242	2.00E-11	461460	9.74E
rs10989067	A	G	A	G	0.0169514	-0.011000282	0.31593	NA	0.603	0.0212	1006656	0.00212349	1.40E-15	461460	0.000
rs11001863	T	C	T	C	0.0116794	-0.011404718	0.581338	NA	0.565	0.0198	1006656	0.00201921	7.30E-09	461460	7.25E
rs11009685	T	C	T	C	-0.0130834	-0.026800662	0.244096	NA	0.247	0.023	1006656	0.00230766	1.40E-08	461460	6.97E
rs11012732	G	A	G	A	0.0216425	0	0.331683	NA	1	0.0046	1006656	0.00210128	7.10E-25	461460	0.000
rs11057072	G	A	G	A	0.0128422	0.031101301	0.233706	NA	0.175	0.023	1006656	0.00233829	4.00E-08	461460	6.54E
rs11079849	T	C	T	C	-0.020093	-0.028697873	0.328531	NA	0.172	0.021	1006656	0.00211163	1.80E-21	461460	0.000
rs11099020	T	C	T	C	-0.0142038	-0.053597637	0.640609	NA	0.00839	0.0203	1006656	0.00206202	5.60E-12	461460	0.000
rs1115160	A	G	A	G	-0.0130768	0.020204507	0.237797	NA	0.368	0.0225	1006656	0.00233641	2.20E-08	461460	6.79E
rs11122450	G	T	G	T	-0.0116316	0.010201862	0.611739	NA	0.612	0.0201	1006656	0.00202425	9.10E-09	461460	7.15E
rs11134879	G	A	G	A	0.0182459	-0.002297359	0.884753	NA	0.916	0.0218	1006656	0.00213286	1.20E-17	461460	0.000
rs11150745	G	A	G	A	-0.0211611	0.001898197	0.317711	NA	0.927	0.0209	1006656	0.00212961	2.90E-23	461460	0.000
rs111598585	T	C	T	C	-0.0142245	0.01295195	0.208671	NA	0.589	0.024	1006656	0.00243798	5.40E-09	461460	7.38E
rs11165643	T	C	T	C	0.0193319	-0.0289839	0.590103	NA	0.146	0.0199	1006656	0.00200337	4.90E-22	461460	0.000
rs11218510	A	G	A	G	-0.0144616	0.016001294	0.40047	NA	0.421	0.0199	1006656	0.00202121	8.40E-13	461460	0.000
rs113079574	T	C	T	C	-0.0155896	-0.031098587	0.19279	NA	0.225	0.0256	1006656	0.00251598	5.80E-10	461460	8.32E
rs113603855	T	C	T	C	0.0186013	-0.075003758	0.21205	NA	0.00144	0.0235	1006656	0.00242689	1.80E-14	461460	0.000
rs113624107	A	G	A	G	0.0150461	-0.015205013	0.22586	NA	0.504	0.0228	1006656	0.00236876	2.10E-10	461460	8.74E
rs11525873	C	T	C	T	-0.0239781	0.023804413	0.097701	NA	0.486	0.0342	1006656	0.00333603	6.60E-13	461460	0.000
rs11607476	C	A	C	A	0.015712	0.009801805	0.486574	NA	0.604	0.0188	1006656	0.00199179	3.10E-15	461460	0.000
rs11608710	G	T	G	T	0.0248489	-0.033701572	0.062119	NA	0.409	0.0408	1006656	0.00415281	2.20E-09	461460	7.76E
rs11630647	A	G	A	G	-0.012674	0.019400586	0.251739	NA	0.384	0.0223	1006656	0.00228082	2.70E-08	461460	6.69E
rs116374395	A	G	A	G	0.0318817	-0.054804715	0.035444	NA	0.229	0.0455	1006656	0.00536236	2.80E-09	461460	7.66E
rs11642090	C	T	C	T	0.0114184	0.021399391	0.373536	NA	0.29	0.0202	1006656	0.00205925	2.90E-08	461460	6.66E
rs11656076	A	G	A	G	-0.0154285	-0.002102208	0.224774	NA	0.928	0.0235	1006656	0.00237054	7.60E-11	461460	9.18E
rs1167311	A	G	A	G	-0.0192949	0.01099161	0.681309	NA	0.601	0.0209	1006656	0.00213109	1.60E-19	461460	0.000
rs11691869	A	C	A	C	-0.0193158	0.014898405	0.362038	NA	0.464	0.0204	1006656	0.00205562	5.60E-21	461460	0.000
rs11699628	A	G	A	G	-0.0335418	-0.016495303	0.035832	NA	0.754	0.0526	1006656	0.00582677	8.60E-09	461460	7.16E
rs11709402	G	A	G	A	0.0228192	0.019802627	0.278732	NA	0.352	0.0213	1006656	0.00220796	4.90E-25	461460	0.000
rs11757278	C	T	C	T	-0.0146269	-0.030098448	0.303879	NA	0.147	0.0208	1006656	0.00214834	9.90E-12	461460	0.000
rs11778219	G	A	G	A	0.015796	0.047904057	0.163123	NA	0.0678	0.0262	1006656	0.00268674	4.20E-09	461460	7.49E
rs118136827	T	G	T	G	-0.0132582	-0.021795812	0.281086	NA	0.329	0.0223	1006656	0.0022019	1.70E-09	461460	7.86E
rs1191600	A	C	A	C	-0.0121197	0.016902038	0.593587	NA	0.384	0.0194	1006656	0.00202687	1.70E-09	461460	7.88E
rs12072739	G	A	G	A	0.0157008	0.028597175	0.224478	NA	0.201	0.0224	1006656	0.00236691	3.30E-11	461460	9.53E
rs12089815	A	G	A	G	-0.0123121	-0.005299562	0.54861	NA	0.787	0.0196	1006656	0.00198606	5.70E-10	461460	8.33E
rs12140153	T	G	T	G	-0.033075	-0.025399863	0.094252	NA	0.421	0.0316	1006656	0.0034589	1.20E-21	461460	0.000
rs12149660	A	G	A	G	-0.0227338	-0.041395075	0.114956	NA	0.14	0.0281	1006656	0.00311586	3.00E-13	461460	0.000
rs12259464	A	G	A	G	0.0130895	0.019498873	0.49447	NA	0.319	0.0195	1006656	0.00196986	4.50E-11	461460	9.40E
rs12273545	T	C	T	C	0.0249393	0.018399663	0.065605	NA	0.647	0.0403	1006656	0.00428551	6.80E-09	461460	7.28E
rs1229984	C	T	C	T	0.037357	-0.02580419	0.972775	NA	0.78	0.0921	1006656	0.00599385	4.60E-10	461460	8.42E

rs12340969	T	C	T	C	-0.0208868	-0.008495989	0.441399	NA	0.663	0.0195	1006656	0.0019941	1.10E-25	461460	0.000
rs12364470	G	T	G	T	0.0192705	-0.017604046	0.164556	NA	0.495	0.0257	1006656	0.0026658	4.90E-13	461460	0.000
rs12440603	T	C	T	C	0.0139285	0.016099701	0.433693	NA	0.409	0.0195	1006656	0.0020011	3.40E-12	461460	0.000
rs12462975	A	G	A	G	0.0195822	0.017496048	0.329692	NA	0.397	0.0207	1006656	0.00212071	2.60E-20	461460	0.000
rs12541408	C	T	C	T	-0.0143261	0.022504855	0.31742	NA	0.274	0.0205	1006656	0.00212723	1.60E-11	461460	9.83E
rs1263629	G	A	G	A	0.0176904	-0.018500076	0.143824	NA	0.504	0.0276	1006656	0.00282352	4.50E-10	461460	8.43E
rs1266874	G	A	G	A	0.0140966	0.02810143	0.349819	NA	0.179	0.0209	1006656	0.0020712	1.00E-11	461460	0.000
rs12681792	A	C	A	C	0.0148693	-0.008102739	0.1926	NA	0.733	0.0236	1006656	0.00251693	3.50E-09	461460	7.56E
rs12692596	T	C	T	C	0.0130872	-0.003696825	0.37185	NA	0.854	0.0203	1006656	0.00203738	1.30E-10	461460	8.94E
rs12696039	G	A	G	A	-0.0152802	0.034401427	0.149405	NA	0.198	0.0287	1006656	0.0027705	3.50E-08	461460	6.59E
rs12712767	A	G	A	G	0.0114221	0.003404199	0.370925	NA	0.866	0.0198	1006656	0.00204487	2.30E-08	461460	6.76E
rs12861629	G	A	G	A	0.0220748	0.038595518	0.08265	NA	0.274	0.0353	1006656	0.00358929	7.70E-10	461460	8.20E
rs12921986	G	A	G	A	0.0203237	-0.100196096	0.077984	NA	0.00715	0.0373	1006656	0.0036983	3.80E-08	461460	6.55E
rs12937411	T	C	T	C	-0.017187	0.00059982	0.408167	NA	0.977	0.0202	1006656	0.00201383	1.40E-17	461460	0.000
rs1296328	C	A	C	A	-0.018862	-0.004798469	0.559032	NA	0.808	0.0197	1006656	0.001999	3.90E-21	461460	0.000
rs12974458	T	C	T	C	0.0152466	-0.013597139	0.543175	NA	0.491	0.0197	1006656	0.00199717	2.30E-14	461460	0.000
rs13012070	A	G	A	G	-0.0136501	-0.03899341	0.228388	NA	0.0833	0.023	1006656	0.00234795	6.10E-09	461460	7.32E
rs13033310	A	G	A	G	0.012611	-0.015103486	0.25276	NA	0.5	0.0224	1006656	0.0022826	3.30E-08	461460	6.61E
rs13107325	T	C	T	C	0.0475799	0.048199514	0.07482	NA	0.383	0.0553	1006656	0.00375479	8.50E-37	461460	0.000
rs13176429	C	T	C	T	0.0141555	-0.005395419	0.887609	NA	0.792	0.0207	1006656	0.00213122	3.10E-11	461460	9.56E
rs1320251	T	C	T	C	-0.0180321	0.036100406	0.454791	NA	0.0646	0.0195	1006656	0.00199407	1.50E-19	461460	0.000
rs1322842	G	A	G	A	-0.0131292	-0.033959864	0.809274	NA	0.089	0.0198	1006656	0.00203539	1.10E-10	461460	9.02E
rs13248167	C	T	C	T	0.015784	0.006796849	0.268557	NA	0.761	0.0223	1006656	0.00224155	2.00E-12	461460	0.000
rs1327259	G	A	G	A	-0.0148532	-0.047301273	0.387722	NA	0.0194	0.0203	1006656	0.00203363	2.80E-13	461460	0.000
rs13291723	A	G	A	G	0.0110318	0.045499584	0.570683	NA	0.0217	0.0198	1006656	0.00199876	3.40E-08	461460	6.60E
rs13427822	G	A	G	A	-0.0181515	-0.001300846	0.271198	NA	0.95	0.0214	1006656	0.00224142	5.60E-16	461460	0.000
rs1346841	A	G	A	G	-0.013056	0.008801156	0.405041	NA	0.666	0.0205	1006656	0.0020172	9.70E-11	461460	9.08E
rs1380201	T	C	T	C	0.0130075	0.019898632	0.481546	NA	0.307	0.0195	1006656	0.00197747	4.80E-11	461460	9.38E
rs140159717	T	C	T	C	-0.0246882	0.066199841	0.082292	NA	0.0626	0.0355	1006656	0.00370967	2.80E-11	461460	9.60E
rs1411432	C	A	C	A	0.0214688	0.043796765	0.186225	NA	0.0979	0.0265	1006656	0.0025491	3.70E-17	461460	0.000
rs1441264	A	G	A	G	0.0179033	-0.027196792	0.593681	NA	0.17	0.0198	1006656	0.00205854	3.40E-18	461460	0.000
rs1451983	T	G	T	G	0.022201	-0.005002492	0.082266	NA	0.898	0.0387	1006656	0.00360585	7.40E-10	461460	8.21E
rs1458156	T	C	T	C	0.014075	-0.02059643	0.488431	NA	0.29	0.0195	1006656	0.00197951	1.20E-12	461460	0.000
rs145981104	G	A	G	A	0.022711	-0.00940408	0.063711	NA	0.82	0.0413	1006656	0.00404552	2.00E-08	461460	6.83E
rs146569428	A	G	A	G	0.0139633	0.021203606	0.200749	NA	0.378	0.0241	1006656	0.00248571	2.00E-08	461460	6.83E
rs1471093	A	G	A	G	0.0134819	0.002904213	0.818663	NA	0.888	0.0202	1006656	0.00203996	4.10E-11	461460	9.44E
rs147568678	C	T	C	T	-0.0133327	-0.058795047	0.23807	NA	0.0121	0.0234	1006656	0.00233034	1.10E-08	461460	7.09E
rs1477290	C	T	C	T	0.0337772	-0.002302649	0.136947	NA	0.939	0.0293	1006656	0.00289815	2.20E-31	461460	0.000
rs147730288	T	G	T	G	-0.0350799	-0.0037972	0.087243	NA	0.923	0.0389	1006656	0.00358357	1.30E-22	461460	0.000
rs1503526	C	T	C	T	0.0154308	0.006300113	0.480077	NA	0.745	0.0195	1006656	0.00197681	5.90E-15	461460	0.000
rs1582931	A	G	A	G	-0.0133419	-0.005203515	0.473242	NA	0.79	0.0196	1006656	0.0019956	2.30E-11	461460	9.69E
rs1609010	G	A	G	A	0.0209773	-0.006898184	0.565728	NA	0.734	0.0196	1006656	0.0019963	7.90E-26	461460	0.000
rs16965658	G	A	G	A	-0.0243736	0.020204507	0.060091	NA	0.609	0.0395	1006656	0.00418404	5.70E-09	461460	7.35E
rs17056301	C	T	C	T	0.0135831	1.00E-04	0.256425	NA	0.992	0.0104	1006656	0.0022897	2.20E-09	461460	7.76E
rs17146254	C	T	C	T	-0.0213507	-0.01400152	0.804854	NA	0.58	0.0254	1006656	0.00255804	7.00E-17	461460	0.000
rs17289010	G	A	G	A	-0.0134661	-0.009797842	0.32787	NA	0.643	0.0212	1006656	0.00210438	1.60E-10	461460	8.87E
rs17399739	G	A	G	A	0.0270713	0.061198575	0.068893	NA	0.0755	0.0344	1006656	0.00391006	4.40E-12	461460	0.000
rs17544384	C	T	C	T	0.0140981	0.004001981	0.210864	NA	0.87	0.0243	1006656	0.00241434	5.30E-09	461460	7.38E
rs17724992	G	A	G	A	-0.0171199	0.002197584	0.26777	NA	0.922	0.0227	1006656	0.00224218	1.70E-14	461460	0.000
rs17790336	T	C	T	C	0.0242931	0.017997077	0.322437	NA	0.391	0.021	1006656	0.00211161	1.30E-30	461460	0.000
rs1778830	A	G	A	G	0.0140775	0.003503854	0.362165	NA	0.861	0.0201	1006656	0.00205596	7.50E-12	461460	0.000
rs1788808	G	A	G	A	-0.020404	-0.035803359	0.49478	NA	0.0656	0.0195	1006656	0.00198255	7.70E-25	461460	0.000
rs1805123	G	T	G	T	-0.0167569	0.001598721	0.245301	NA	0.945	0.0234	1006656	0.00229711	3.00E-13	461460	0.000
rs1834144	A	C	A	C	-0.0140112	0.010999285	0.373192	NA	0.581	0.02	1006656	0.00205213	8.60E-12	461460	0.000
rs1861410	T	C	T	C	-0.0212558	-0.005299952	0.555423	NA	0.787	0.0197	1006656	0.00198918	1.20E-26	461460	0.000
rs1884897	G	A	G	A	0.020001	-0.006498837	0.827378	NA	0.747	0.0202	1006656	0.00205634	2.30E-22	461460	0.000
rs1919243	C	T	C	T	0.0116759	-0.00060018	0.487406	NA	0.975	0.0196	1006656	0.00200175	5.50E-09	461460	7.37E

rs1928708	A	G	A	G	-0.0119847	0.032502531	0.471082	NA	0.095	0.0195	1006656	0.00198846	1.70E-09	461460	7.87E
rs1934102	A	G	A	G	-0.0136682	-0.015997277	0.347583	NA	0.438	0.0206	1006656	0.00210374	8.20E-11	461460	9.15E
rs1967772	A	G	A	G	-0.0170434	-0.002402885	0.285117	NA	0.91	0.0212	1006656	0.00220377	1.00E-14	461460	0.000
rs1990662	C	A	C	A	0.0144775	0.004599406	0.192721	NA	0.86	0.0259	1006656	0.00251798	8.90E-09	461460	7.16E
rs2035936	T	G	T	G	0.0370963	0.030897711	0.055892	NA	0.491	0.0448	1006656	0.00435778	1.70E-17	461460	0.000
rs2051559	C	T	C	T	0.0204078	-0.012902885	0.13254	NA	0.649	0.0284	1006656	0.00291983	2.80E-12	461460	0.000
rs2102278	G	A	G	A	0.0118583	0.080304571	0.322486	NA	0.00383	0.0208	1006656	0.0021139	2.00E-08	461460	6.82E
rs213518	C	T	C	T	0.0157894	-0.017098295	0.145608	NA	0.542	0.0281	1006656	0.00280491	1.80E-08	461460	6.87E
rs2153740	G	A	G	A	-0.0112551	0.035695275	0.479914	NA	0.0672	0.0195	1006656	0.00199313	1.60E-08	461460	6.91E
rs215634	G	A	G	A	-0.0155223	-0.034804305	0.611879	NA	0.0875	0.0203	1006656	0.00203492	2.40E-14	461460	0.000
rs2172131	C	T	C	T	-0.0149382	0.013703485	0.578723	NA	0.491	0.0199	1006656	0.00200386	9.00E-14	461460	0.000
rs217672	C	A	C	A	0.0170155	-0.005897355	0.271741	NA	0.791	0.0222	1006656	0.00223046	2.40E-14	461460	0.000
rs2192158	G	A	G	A	-0.015012	0.006903776	0.553308	NA	0.724	0.0196	1006656	0.00198302	3.70E-14	461460	0.000
rs2216931	A	C	A	C	0.0169109	-0.004101577	0.661966	NA	0.837	0.0201	1006656	0.00208587	5.20E-16	461460	0.000
rs2234458	T	C	T	C	-0.0203841	0.039198313	0.639519	NA	0.0547	0.0204	1006656	0.00205579	3.60E-23	461460	0.000
rs2271189	A	G	A	G	-0.0163086	0.013902905	0.40272	NA	0.485	0.0199	1006656	0.00201869	6.50E-16	461460	0.000
rs2275003	G	A	G	A	-0.0119238	-0.037295785	0.520932	NA	0.0503	0.0191	1006656	0.00197803	1.70E-09	461460	7.87E
rs2289379	T	C	T	C	-0.0152765	-0.004701033	0.395648	NA	0.815	0.02	1006656	0.00202952	5.20E-14	461460	0.000
rs2307111	C	T	C	T	-0.0280042	-0.02979631	0.395025	NA	0.139	0.0202	1006656	0.00202203	1.30E-43	461460	0.000
rs2342892	G	T	G	T	-0.0126972	0.012902885	0.516212	NA	0.511	0.0196	1006656	0.00197715	1.30E-10	461460	8.94E
rs2381404	C	T	C	T	0.0139684	0.05399564	0.243837	NA	0.0162	0.0224	1006656	0.00229974	1.30E-09	461460	7.99E
rs2398861	G	A	G	A	0.0179952	-0.005002492	0.259169	NA	0.82	0.022	1006656	0.00226733	2.10E-15	461460	0.000
rs2425916	A	G	A	G	0.0122284	0.049199604	0.415111	NA	0.0126	0.0197	1006656	0.00201106	1.20E-09	461460	8.01E
rs2433733	A	G	A	G	-0.0171805	0.008395141	0.677659	NA	0.681	0.0204	1006656	0.00210907	3.80E-16	461460	0.000
rs2439823	G	A	G	A	0.0191998	0.022296735	0.545612	NA	0.261	0.0198	1006656	0.00199108	5.30E-22	461460	0.000
rs2482356	C	T	C	T	-0.0113511	-0.012599036	0.429018	NA	0.528	0.0199	1006656	0.00199506	1.30E-08	461460	7.01E
rs2512892	C	T	C	T	0.0129468	-0.007303266	0.568085	NA	0.71	0.0196	1006656	0.00199819	9.20E-11	461460	9.10E
rs252761	T	G	T	G	-0.0115046	0.00800193	0.587966	NA	0.684	0.0196	1006656	0.00201769	1.20E-08	461460	7.04E
rs2569958	A	G	A	G	0.0222928	0.015103486	0.603656	NA	0.444	0.0197	1006656	0.00201204	1.60E-28	461460	0.000
rs2569993	C	T	C	T	0.01267	0.045995787	0.320327	NA	0.0244	0.0205	1006656	0.00212202	2.40E-09	461460	7.72E
rs2606228	C	A	C	A	-0.0138791	-0.009802889	0.646368	NA	0.671	0.0201	1006656	0.00206379	2.70E-11	461460	9.61E
rs2616143	A	G	A	G	-0.0138738	-0.014789867	0.319862	NA	0.471	0.0206	1006656	0.00212547	6.70E-11	461460	9.23E
rs2676204	G	T	G	T	0.024161	-0.013896105	0.340162	NA	0.5	0.0206	1006656	0.00208158	3.80E-31	461460	0.000
rs2725371	G	A	G	A	-0.0160301	0.024096039	0.696115	NA	0.253	0.0211	1006656	0.00215845	1.10E-13	461460	0.000
rs2781668	T	C	T	C	0.0148965	0.022103899	0.165587	NA	0.38	0.0252	1006656	0.00265988	2.10E-08	461460	6.80E
rs2791643	T	C	T	C	-0.0133837	-0.010702523	0.761794	NA	0.646	0.0232	1006656	0.00231332	7.20E-09	461460	7.25E
rs28350	G	A	G	A	-0.0180335	-0.030199374	0.820684	NA	0.219	0.0245	1006656	0.00258234	2.90E-12	461460	0.000
rs28366156	C	T	C	T	-0.0264826	0.006001952	0.130595	NA	0.844	0.0307	1006656	0.00292978	1.60E-19	461460	0.000
rs2837996	C	T	C	T	0.0126847	-0.030500107	0.651408	NA	0.133	0.0203	1006656	0.00207859	1.10E-09	461460	8.04E
rs28404639	T	C	T	C	-0.0117129	0.009702775	0.386041	NA	0.638	0.0207	1006656	0.00205533	1.20E-08	461460	7.04E
rs28489620	A	G	A	G	-0.0153737	-0.01640381	0.290349	NA	0.442	0.0214	1006656	0.00220025	2.80E-12	461460	0.000
rs2861685	C	T	C	T	-0.0171274	-0.002803927	0.411984	NA	0.889	0.0201	1006656	0.00199763	1.00E-17	461460	0.000
rs28670671	C	T	C	T	-0.0124638	0.005803129	0.286024	NA	0.796	0.0223	1006656	0.00226426	3.70E-08	461460	6.57E
rs2896644	T	C	T	C	0.0149659	0.006995475	0.229995	NA	0.761	0.023	1006656	0.0023609	2.30E-10	461460	8.71E
rs2920503	T	C	T	C	-0.0140307	0.037199441	0.285413	NA	0.0744	0.0208	1006656	0.00219666	1.70E-10	461460	8.84E
rs2941452	G	A	G	A	0.0111622	-0.004798469	0.617751	NA	0.809	0.0198	1006656	0.00203237	4.00E-08	461460	6.54E
rs2962334	T	G	T	G	0.0432552	0.072999501	0.020065	NA	0.35	0.0781	1006656	0.00703547	7.80E-10	461460	8.19E
rs3212038	G	A	G	A	0.0149201	-0.01069701	0.328484	NA	0.606	0.0207	1006656	0.0021124	1.60E-12	461460	0.000
rs3213943	A	C	A	C	-0.0179406	0.034604305	0.131525	NA	0.278	0.0319	1006656	0.00288163	4.80E-10	461460	8.40E
rs329118	T	C	T	C	-0.0165734	0.022504855	0.419409	NA	0.252	0.0196	1006656	0.0020008	1.30E-16	461460	0.000
rs329651	T	G	T	G	0.0157218	-0.013902905	0.803977	NA	0.577	0.0249	1006656	0.00250202	3.30E-10	461460	8.56E
rs34045288	T	C	T	C	0.0234784	0.003404199	0.334435	NA	0.874	0.0212	1006656	0.00209371	3.50E-29	461460	0.000
rs34153025	C	T	C	T	-0.0389151	-0.030799472	0.022158	NA	0.715	0.0843	1006656	0.00678155	9.60E-09	461460	7.14E
rs34234296	A	G	A	G	-0.014947	0.010098835	0.392437	NA	0.617	0.0202	1006656	0.00204032	2.40E-13	461460	0.000
rs34481751	A	C	A	C	-0.0185029	-0.038397852	0.165329	NA	0.149	0.0266	1006656	0.00270404	7.80E-12	461460	0.000
rs34517439	A	C	A	C	0.038848	0.031004359	0.121787	NA	0.284	0.0289	1006656	0.00304983	3.60E-37	461460	0.000
rs34696181	C	T	C	T	0.0114345	-0.010403934	0.476084	NA	0.584	0.019	1006656	0.00198283	8.10E-09	461460	7.21E

rs34811474	A	G	A	G	-0.0285293	-0.017400515	0.230756	NA	0.451	0.023	1006656	0.00234269	4.10E-34	461460	0.000
rs349071	A	G	A	G	-0.0133062	0.025799975	0.500388	NA	0.176	0.0191	1006656	0.00198231	1.90E-11	461460	9.76E
rs35154326	G	A	G	A	-0.0130427	-0.01689865	0.274044	NA	0.444	0.0219	1006656	0.00223442	5.30E-09	461460	7.38E
rs35364449	T	C	T	C	0.0217069	-0.01680339	0.109739	NA	0.585	0.0307	1006656	0.00318335	9.20E-12	461460	0.000
rs35697587	A	G	A	G	-0.0164677	0.00940408	0.508121	NA	0.633	0.0197	1006656	0.00198067	9.20E-17	461460	0.000
rs35809007	A	G	A	G	-0.0171009	-0.04309541	0.383205	NA	0.0339	0.0203	1006656	0.00205627	9.10E-17	461460	0.000
rs35957544	T	G	T	G	-0.0196429	-0.023101103	0.574316	NA	0.243	0.0197	1006656	0.00200438	1.10E-22	461460	0.000
rs36007635	A	G	A	G	-0.021045	0.002197584	0.137898	NA	0.937	0.0278	1006656	0.00286788	2.20E-13	461460	0.000
rs36061954	T	C	T	C	0.0128445	0.019602627	0.398747	NA	0.319	0.0198	1006656	0.00201928	2.00E-10	461460	8.77E
rs3764625	G	T	G	T	-0.0117714	0.005796709	0.587594	NA	0.77	0.0197	1006656	0.00201523	5.20E-09	461460	7.39E
rs3766623	A	G	A	G	0.016056	-0.027802945	0.171196	NA	0.293	0.0284	1006656	0.0026141	8.10E-10	461460	8.17E
rs3784710	C	T	C	T	-0.0297067	-0.02880079	0.226602	NA	0.221	0.0235	1006656	0.00236042	2.50E-36	461460	0.000
rs3803286	G	A	G	A	-0.0186417	-0.012096541	0.666815	NA	0.557	0.0207	1006656	0.00209828	6.40E-19	461460	0.000
rs3807566	T	G	T	G	-0.0120727	-0.007095111	0.43832	NA	0.717	0.0195	1006656	0.00199583	1.50E-09	461460	7.93E
rs3814883	T	C	T	C	0.0240107	0.014996981	0.482402	NA	0.435	0.0193	1006656	0.00198424	1.00E-33	461460	0.000
rs3866805	A	C	A	C	0.0117835	-0.064495855	0.355683	NA	0.00172	0.0206	1006656	0.00206548	1.20E-08	461460	7.05E
rs3897102	T	C	T	C	0.0120838	-0.003997981	0.411157	NA	0.841	0.0198	1006656	0.00202716	2.50E-09	461460	7.70E
rs3901286	A	C	A	C	-0.0225553	0.022201708	0.15244	NA	0.418	0.0274	1006656	0.00275602	2.70E-16	461460	0.000
rs3902951	G	T	G	T	0.0141019	0.020302502	0.237151	NA	0.365	0.0224	1006656	0.00235267	2.00E-09	461460	7.79E
rs3935190	A	G	A	G	-0.0144864	-0.020096702	0.536784	NA	0.305	0.0196	1006656	0.00199701	4.00E-13	461460	0.000
rs394608	C	T	C	T	0.0186353	0.019804827	0.537697	NA	0.312	0.0195	1006656	0.00199484	9.50E-21	461460	0.000
rs40071	C	T	C	T	-0.0261666	0.01530232	0.179536	NA	0.556	0.0259	1006656	0.00258163	3.80E-24	461460	0.000
rs4017425	T	C	T	C	-0.0125817	0.021497269	0.470208	NA	0.271	0.0195	1006656	0.00198035	2.10E-10	461460	8.75E
rs4055791	T	C	T	C	-0.0178062	-0.039499952	0.416804	NA	0.0445	0.0197	1006656	0.00200801	7.40E-19	461460	0.000
rs41279738	G	T	G	T	0.0684263	0.059503994	0.025988	NA	0.266	0.0535	1006656	0.0062225	4.00E-28	461460	0.000
rs41315816	C	T	C	T	0.0254409	-0.0444954	0.056989	NA	0.33	0.0457	1006656	0.00419129	1.30E-09	461460	7.96E
rs4148155	G	A	G	A	-0.0229681	0.014602857	0.113268	NA	0.644	0.0316	1006656	0.00310659	1.40E-13	461460	0.000
rs4261944	G	T	G	T	0.0138553	-0.001300846	0.364935	NA	0.95	0.0203	1006656	0.00205652	1.60E-11	461460	9.84E
rs4284600	C	T	C	T	0.0119673	0.008495989	0.467122	NA	0.664	0.0196	1006656	0.00199508	2.00E-09	461460	7.80E
rs429343	G	A	G	A	-0.0173795	-0.01400152	0.576573	NA	0.478	0.0198	1006656	0.00199729	3.30E-18	461460	0.000
rs429358	C	T	C	T	-0.0266723	0.004897985	0.154166	NA	0.854	0.0284	1006656	0.00274373	2.40E-22	461460	0.000
rs4307239	G	A	G	A	0.0121413	-0.014098924	0.458941	NA	0.471	0.0196	1006656	0.00198816	1.00E-09	461460	8.08E
rs4456769	T	C	T	C	0.0146111	-0.002402885	0.333444	NA	0.908	0.0205	1006656	0.00210138	3.60E-12	461460	0.000
rs4477562	T	C	T	C	0.0296118	-0.007095111	0.129644	NA	0.81	0.0293	1006656	0.00296011	2.90E-23	461460	0.000
rs4482463	A	C	A	C	-0.0313175	0.046504778	0.923002	NA	0.204	0.0366	1006656	0.00370692	3.00E-17	461460	0.000
rs45486197	A	G	A	G	0.025706	-0.025207295	0.065685	NA	0.528	0.04	1006656	0.00403737	1.70E-10	461460	8.83E
rs4605363	C	A	C	A	0.0163638	0.025004759	0.341595	NA	0.223	0.0205	1006656	0.00207733	3.30E-15	461460	0.000
rs4625888	T	C	T	C	0.0117507	-0.014799939	0.557644	NA	0.449	0.0196	1006656	0.00198303	3.10E-09	461460	7.61E
rs4648450	A	C	A	C	-0.014837	-0.031397792	0.466824	NA	0.11	0.0197	1006656	0.00198775	8.40E-14	461460	0.000
rs4658403	T	C	T	C	-0.0188877	0.005697355	0.833659	NA	0.829	0.0273	1006656	0.00264997	1.00E-12	461460	0.000
rs4672338	T	C	T	C	0.0135646	0.000899595	0.336228	NA	0.963	0.0202	1006656	0.00208669	8.00E-11	461460	9.16E
rs4722398	T	C	T	C	0.0186993	-0.008102739	0.136137	NA	0.779	0.0288	1006656	0.00287545	7.90E-11	461460	9.16E
rs4764949	G	A	G	A	-0.0183924	0.007501791	0.325892	NA	0.715	0.0205	1006656	0.00211197	3.10E-18	461460	0.000
rs4790292	A	C	A	C	-0.0254509	-0.02290022	0.153693	NA	0.402	0.0273	1006656	0.00275603	2.60E-20	461460	0.000
rs4820410	G	A	G	A	-0.0177457	0.0036035	0.345317	NA	0.86	0.0201	1006656	0.00208527	1.70E-17	461460	0.000
rs4832298	T	C	T	C	-0.015985	-0.040901991	0.686142	NA	0.0463	0.0205	1006656	0.00212268	5.40E-14	461460	0.000
rs4858940	C	T	C	T	0.0229281	0.060302174	0.885569	NA	0.0515	0.031	1006656	0.00309976	1.40E-13	461460	0.000
rs4876611	G	A	G	A	0.0197549	0.035202397	0.720243	NA	0.101	0.0215	1006656	0.00220502	3.30E-19	461460	0.000
rs4892923	C	T	C	T	0.0189424	-0.019396496	0.645204	NA	0.349	0.0204	1006656	0.00206436	4.50E-20	461460	0.000
rs512121	C	T	C	T	-0.0159359	0.011602431	0.192054	NA	0.646	0.0253	1006656	0.00252176	2.60E-10	461460	8.65E
rs526200	G	A	G	A	0.0168965	-0.025297308	0.527829	NA	0.196	0.0195	1006656	0.0019785	1.30E-17	461460	0.000
rs539515	C	A	C	A	0.0495291	-0.006803089	0.204942	NA	0.779	0.0242	1006656	0.0024426	2.00E-01	461460	0.000
rs55707359	G	T	G	T	0.0531292	0.184997356	0.015432	NA	0.0382	0.0796	1006656	0.00812381	6.20E-11	461460	9.27E
rs55714539	C	A	C	A	0.0175719	-0.018703831	0.343587	NA	0.364	0.0207	1006656	0.00210043	6.00E-17	461460	0.000
rs55726687	A	G	A	G	0.02483	-0.023903424	0.209709	NA	0.331	0.0246	1006656	0.00242628	1.40E-24	461460	0.000
rs55769038	A	G	A	G	0.0160061	0.018102873	0.590384	NA	0.365	0.02	1006656	0.00201096	1.20E-15	461460	0.000
rs557951	G	T	G	T	0.0140534	-0.004801509	0.312937	NA	0.816	0.0208	1006656	0.00213387	4.50E-11	461460	9.40E

rs558887	G	A	G	A	-0.0129976	-0.0369599	0.307507	NA	0.0628	0.0213	1006656	0.00214881	1.50E-09	461460	7.93E
rs559231	T	G	T	G	0.0134907	-0.001801281	0.393053	NA	0.934	0.0199	1006656	0.00203562	3.40E-11	461460	9.52E
rs56038322	A	G	A	G	0.0139276	-0.005304042	0.31062	NA	0.804	0.0213	1006656	0.00214833	9.00E-11	461460	9.11E
rs561432307	G	T	G	T	0.0137622	-0.006400439	0.196875	NA	0.787	0.0238	1006656	0.00247385	2.70E-08	461460	6.71E
rs56143236	T	C	T	C	0.0126667	-0.045300759	0.256388	NA	0.0465	0.0227	1006656	0.00226533	2.30E-08	461460	6.77E
rs56203622	C	T	C	T	0.0179769	-0.008203557	0.145529	NA	0.77	0.0281	1006656	0.00280183	1.40E-10	461460	8.92E
rs56352336	C	T	C	T	-0.016327	0.001898197	0.154894	NA	0.946	0.0276	1006656	0.00275021	2.90E-09	461460	7.84E
rs56399737	T	C	T	C	-0.0161325	-0.014301785	0.449124	NA	0.464	0.0196	1006656	0.00199646	6.40E-16	461460	0.000
rs56858768	A	G	A	G	0.0159188	0.016798118	0.296861	NA	0.419	0.0208	1006656	0.00217378	2.40E-13	461460	0.000
rs56893062	G	T	G	T	0.0125141	-0.014900463	0.303342	NA	0.472	0.0208	1006656	0.00215383	6.20E-09	461460	7.31E
rs56930105	T	C	T	C	0.0157557	0.082795837	0.193295	NA	0.00307	0.028	1006656	0.00286187	3.70E-08	461460	6.57E
rs57636386	C	T	C	T	-0.0412553	-0.02880079	0.08383	NA	0.307	0.0341	1006656	0.00358326	1.10E-30	461460	0.000
rs57699773	C	T	C	T	0.0133488	0.025495804	0.244995	NA	0.269	0.024	1006656	0.00236315	1.60E-08	461460	6.91E
rs58862095	T	C	T	C	-0.0229877	0.00079968	0.419266	NA	0.972	0.023	1006656	0.00200786	2.40E-30	461460	0.000
rs59068084	T	G	T	G	0.0110552	0.008602889	0.410232	NA	0.663	0.0198	1006656	0.00201048	3.80E-08	461460	6.55E
rs59227842	G	A	G	A	0.0229675	-0.011900531	0.31149	NA	0.573	0.0211	1006656	0.00215313	1.50E-26	461460	0.000
rs594024	C	T	C	T	-0.0146771	0.000100005	0.554162	NA	1	0.0196	1006656	0.00199081	1.70E-13	461460	0.000
rs6023655	G	A	G	A	-0.0147348	-0.004698943	0.765741	NA	0.832	0.0223	1006656	0.00234997	3.60E-10	461460	8.52E
rs60764613	T	G	T	G	0.02099	-0.008395141	0.144883	NA	0.76	0.0273	1006656	0.00282688	1.10E-13	461460	0.000
rs61740468	A	G	A	G	-0.0135153	-0.015997277	0.237203	NA	0.494	0.0234	1006656	0.00231885	5.60E-09	461460	7.36E
rs61813324	T	C	T	C	0.0290259	-0.000904005	0.135728	NA	0.976	0.0286	1006656	0.00292038	2.80E-23	461460	0.000
rs61828641	A	G	A	G	0.0224585	0.012303994	0.10925	NA	0.708	0.0328	1006656	0.00315913	1.20E-12	461460	0.000
rs61871615	T	C	T	C	-0.0267159	0.033802213	0.091551	NA	0.313	0.0335	1006656	0.00359269	1.00E-13	461460	0.000
rs61903695	G	A	G	A	0.0166235	0.03299478	0.254964	NA	0.153	0.0231	1006656	0.00227115	2.50E-13	461460	0.000
rs61952671	G	A	G	A	-0.0161925	-0.022103899	0.49195	NA	0.265	0.0199	1006656	0.00206924	5.10E-15	461460	0.000
rs62007762	A	G	A	G	-0.0167007	-0.005002492	0.265091	NA	0.823	0.0224	1006656	0.00224215	9.40E-14	461460	0.000
rs62072006	C	A	C	A	0.0156492	0.03949952	0.144541	NA	0.163	0.0283	1006656	0.00282374	3.00E-08	461460	6.66E
rs62107261	C	T	C	T	-0.0911559	-0.048602182	0.048327	NA	0.326	0.0494	1006656	0.00460882	4.60E-87	461460	0.000
rs62241847	G	A	G	A	-0.0124263	0.020204507	0.314443	NA	0.32	0.0203	1006656	0.00212897	5.30E-09	461460	7.38E
rs62246311	A	G	A	G	0.0207539	0.011800104	0.102364	NA	0.724	0.0333	1006656	0.00325487	1.80E-10	461460	8.81E
rs62379271	G	T	G	T	0.0117237	-0.019302502	0.578511	NA	0.328	0.0197	1006656	0.00200557	5.00E-09	461460	7.40E
rs6265	T	C	T	C	-0.0399165	-0.019896032	0.188472	NA	0.436	0.0255	1006656	0.00252719	3.30E-06	461460	0.000
rs6430068	A	G	A	G	0.0186066	0.027303835	0.108559	NA	0.34	0.0286	1006656	0.0031862	5.30E-09	461460	7.36E
rs6444950	A	G	A	G	0.0158825	0.012600282	0.237474	NA	0.583	0.0229	1006656	0.00232007	8.30E-12	461460	0.000
rs6474856	T	C	T	C	-0.0122041	-0.007801039	0.64022	NA	0.711	0.0206	1006656	0.00207048	3.80E-09	461460	7.53E
rs6531639	A	G	A	G	-0.0136291	-0.021499466	0.247548	NA	0.345	0.0227	1006656	0.00233909	5.70E-09	461460	7.36E
rs6545714	A	G	A	G	-0.0205219	0.030201599	0.601448	NA	0.136	0.0202	1006656	0.00201573	2.40E-24	461460	0.000
rs6560906	C	T	C	T	-0.012198	0.000100005	0.691874	NA	1	0.0204	1006656	0.00214136	1.20E-08	461460	7.03E
rs6567160	C	T	C	T	0.0541723	0.028704068	0.232714	NA	0.198	0.0223	1006656	0.00234213	2.30E-118	461460	0.001
rs6575340	A	G	A	G	0.0207333	0.002904213	0.636038	NA	0.889	0.0208	1006656	0.00206189	8.70E-24	461460	0.000
rs66679256	T	C	T	C	0.0148864	0.019988687	0.445826	NA	0.309	0.0196	1006656	0.00198759	6.90E-14	461460	0.000
rs6681989	T	C	T	C	0.0171368	-0.024098039	0.401588	NA	0.227	0.0199	1006656	0.00201662	1.90E-17	461460	0.000
rs66869341	G	A	G	A	-0.0170287	-0.021301503	0.582679	NA	0.279	0.0197	1006656	0.0019986	1.60E-17	461460	0.000
rs6682438	C	T	C	T	0.0131586	-0.009098463	0.673061	NA	0.669	0.0212	1006656	0.00210047	3.70E-10	461460	6.50E
rs6705567	C	T	C	T	-0.0146168	0.028196654	0.37596	NA	0.157	0.02	1006656	0.00204919	9.80E-13	461460	0.000
rs6707827	G	A	G	A	0.0119437	-0.001698557	0.703627	NA	0.936	0.021	1006656	0.00217332	3.90E-08	461460	6.54E
rs6725931	T	C	T	C	0.0191046	0.013196695	0.847658	NA	0.635	0.0278	1006656	0.00274403	3.30E-12	461460	0.000
rs6744646	G	A	G	A	0.0554684	-0.00249688	0.828299	NA	0.924	0.0261	1006656	0.00261213	4.50E-100	461460	0.000
rs6752979	A	G	A	G	0.0125235	-0.025902594	0.31688	NA	0.221	0.0212	1006656	0.00211721	3.30E-09	461460	7.58E
rs67609008	C	T	C	T	0.0179863	-0.050903897	0.283614	NA	0.0234	0.0225	1006656	0.0022021	8.60E-15	461460	0.000
rs6831088	A	G	A	G	-0.0115222	0.012204169	0.640139	NA	0.549	0.0203	1006656	0.0020591	2.20E-08	461460	6.79E
rs6843852	T	C	T	C	0.0130897	0.04690267	0.507861	NA	0.0161	0.0195	1006656	0.00197607	3.50E-11	461460	9.51E
rs6909685	T	C	T	C	-0.014612	0.017004599	0.326809	NA	0.403	0.0203	1006656	0.00211352	4.70E-12	461460	0.000
rs6922607	G	A	G	A	0.0148848	-0.015294956	0.189847	NA	0.455	0.0259	1006656	0.00251479	3.20E-09	461460	7.59E
rs6938973	C	T	C	T	0.0182223	-0.001998003	0.601456	NA	0.918	0.0198	1006656	0.00201872	1.80E-19	461460	0.000
rs6950388	A	G	A	G	0.0155219	-0.022201708	0.795086	NA	0.341	0.0233	1006656	0.00244806	2.30E-10	461460	8.71E
rs6962980	C	A	C	A	-0.0159568	0.027802945	0.558019	NA	0.156	0.0196	1006656	0.00198814	1.00E-15	461460	0.000

rs698147	G	A	G	A	-0.0128512	0.006702411	0.543596	NA	0.734	0.0199	1006656	0.00198514	9.60E-11	461460	9.08E
rs698660	G	A	G	A	0.0125456	-0.004198803	0.452592	NA	0.834	0.0199	1006656	0.00198902	2.80E-10	461460	8.62E
rs7024334	G	T	G	T	-0.0138177	-0.014100124	0.77914	NA	0.555	0.0239	1006656	0.00238338	6.70E-09	461460	7.28E
rs7027304	T	C	T	C	0.0145492	0.003698825	0.652661	NA	0.847	0.0194	1006656	0.00208703	3.10E-12	461460	0.000
rs7034554	G	A	G	A	-0.0129826	-0.005897355	0.373825	NA	0.768	0.0199	1006656	0.00204252	2.10E-10	461460	8.75E
rs7038943	C	T	C	T	-0.0140202	-0.003395759	0.33879	NA	0.869	0.0204	1006656	0.00208641	1.80E-11	461460	9.78E
rs704061	C	T	C	T	0.0146374	-0.013399372	0.45505	NA	0.498	0.0197	1006656	0.00198552	1.70E-13	461460	0.000
rs705145	A	C	A	C	0.0139021	-0.008203557	0.34518	NA	0.685	0.0203	1006656	0.0020796	2.30E-11	461460	9.68E
rs7070670	T	C	T	C	-0.0123274	-0.010403934	0.327923	NA	0.622	0.021	1006656	0.00211928	6.00E-09	461460	7.33E
rs7081254	C	T	C	T	-0.0142516	0.010801454	0.205739	NA	0.654	0.024	1006656	0.00245216	6.20E-09	461460	7.32E
rs7124681	A	C	A	C	0.0256977	-0.034105021	0.408353	NA	0.0842	0.0198	1006656	0.0020063	1.50E-07	461460	0.000
rs7132908	A	G	A	G	0.0297904	-0.002302649	0.384458	NA	0.908	0.02	1006656	0.00203363	1.40E-08	461460	0.000
rs71495038	A	G	A	G	0.0277998	-0.026302908	0.076936	NA	0.475	0.0369	1006656	0.00370969	6.70E-14	461460	0.000
rs7201895	A	G	A	G	-0.0149781	0.013202463	0.354291	NA	0.515	0.0203	1006656	0.00207999	6.00E-13	461460	0.000
rs7218014	C	T	C	T	0.0189624	0.036804335	0.197305	NA	0.129	0.0243	1006656	0.00249216	2.90E-14	461460	0.000
rs7232171	T	G	T	G	0.0123404	0.057194885	0.58263	NA	0.00383	0.0198	1006656	0.00200821	8.00E-10	461460	8.18E
rs723672	T	C	T	C	0.0111273	-0.012700309	0.43151	NA	0.508	0.0192	1006656	0.00200698	3.00E-08	461460	6.66E
rs7259070	C	T	C	T	0.021869	-0.00019998	0.596062	NA	0.992	0.0211	1006656	0.00203628	6.60E-27	461460	0.000
rs72848373	C	T	C	T	0.0178062	-0.03910472	0.143188	NA	0.168	0.0282	1006656	0.00287805	6.10E-10	461460	8.29E
rs72873947	G	A	G	A	0.0218884	0.017004599	0.107031	NA	0.584	0.0311	1006656	0.00321496	9.90E-12	461460	0.000
rs72892910	T	G	T	G	0.0387798	-0.010100842	0.172232	NA	0.701	0.0262	1006656	0.00262053	1.50E-09	461460	0.000
rs72976986	A	G	A	G	-0.0232257	0.00079966	0.190123	NA	0.974	0.0239	1006656	0.00254712	7.60E-20	461460	0.000
rs73026725	A	C	A	C	-0.022318	0.019400586	0.153534	NA	0.483	0.0277	1006656	0.00275052	4.90E-16	461460	0.000
rs73052033	C	T	C	T	-0.0303929	-0.023698607	0.18493	NA	0.341	0.0249	1006656	0.00254634	7.70E-33	461460	0.000
rs7306534	A	G	A	G	-0.0112754	0.01440323	0.621712	NA	0.477	0.0203	1006656	0.00205437	4.10E-08	461460	6.53E
rs73124396	C	T	C	T	-0.0154472	-0.017604046	0.205144	NA	0.451	0.0234	1006656	0.0024548	3.10E-10	461460	8.58E
rs73142879	T	C	T	C	-0.0266936	-0.00359646	0.192297	NA	0.885	0.0245	1006656	0.00252257	3.60E-26	461460	0.000
rs73193736	G	A	G	A	-0.0177165	0.020302502	0.243934	NA	0.366	0.0225	1006656	0.00232002	2.20E-14	461460	0.000
rs7331420	A	G	A	G	-0.0143702	-0.02110107	0.286276	NA	0.327	0.0215	1006656	0.00220081	6.60E-11	461460	9.24E
rs7357754	G	A	G	A	0.0141146	0.012295278	0.500139	NA	0.531	0.0196	1006656	0.00198362	1.10E-12	461460	0.000
rs73601548	T	C	T	C	0.0177354	0.029102387	0.114527	NA	0.338	0.0304	1006656	0.00311639	1.30E-08	461460	7.02E
rs73965439	C	A	C	A	0.0136616	-0.003004509	0.307299	NA	0.889	0.0214	1006656	0.00214059	1.70E-10	461460	8.83E
rs745249	T	C	T	C	0.0176118	0.025297308	0.281945	NA	0.225	0.0209	1006656	0.00219724	1.10E-15	461460	0.000
rs74750262	C	T	C	T	-0.0196362	0.016503072	0.086623	NA	0.625	0.0338	1006656	0.00252561	2.50E-08	461460	6.72E
rs7498665	G	A	G	A	0.0268648	0.019302502	0.399659	NA	0.327	0.0197	1006656	0.00201997	2.30E-04	461460	0.000
rs7516554	T	C	T	C	0.0120066	0.051301294	0.399941	NA	0.00932	0.0197	1006656	0.00201565	2.60E-09	461460	7.69E
rs7519259	A	G	A	G	0.0140028	-0.010268605	0.52836	NA	0.596	0.0195	1006656	0.00198381	1.70E-12	461460	0.000
rs75499503	T	C	T	C	-0.0180331	-0.002302649	0.220101	NA	0.916	0.0217	1006656	0.00241845	8.90E-14	461460	0.000
rs7571496	G	A	G	A	-0.0158916	0.040796394	0.260545	NA	0.0691	0.0224	1006656	0.00225454	1.80E-12	461460	0.000
rs76183894	C	T	C	T	-0.0219584	0.021099908	0.080747	NA	0.552	0.0355	1006656	0.00364437	1.70E-09	461460	7.87E
rs7683836	A	G	A	G	-0.0122469	0.011799339	0.557215	NA	0.544	0.0195	1006656	0.00199427	8.20E-10	461460	8.17E
rs7706584	G	A	G	A	-0.0159321	0.003395759	0.572344	NA	0.863	0.0197	1006656	0.0019949	1.40E-15	461460	0.000
rs7762794	G	A	G	A	0.0149077	0.037295785	0.285408	NA	0.0754	0.021	1006656	0.00218606	9.10E-12	461460	0.000
rs7774	A	C	A	C	0.014988	0.041295482	0.310467	NA	0.0455	0.0207	1006656	0.00215169	3.30E-12	461460	0.000
rs7776021	A	G	A	G	0.0123701	0.057003957	0.287599	NA	0.00782	0.0214	1006656	0.00218251	1.40E-08	461460	6.96E
rs78012460	G	A	G	A	-0.0370628	0.10499945	0.022673	NA	0.183	0.0788	1006656	0.00666929	2.70E-08	461460	6.70E
rs7802342	G	T	G	T	0.0122748	0.003304534	0.288566	NA	0.879	0.0217	1006656	0.00218145	1.80E-08	461460	6.86E
rs7805441	T	C	T	C	0.0133747	0.019704583	0.502261	NA	0.303	0.0191	1006656	0.00198884	1.80E-11	461460	9.80E
rs784257	C	T	C	T	0.0179315	0.029397915	0.812541	NA	0.273	0.0268	1006656	0.00254968	2.00E-12	461460	0.000
rs78605811	C	A	C	A	-0.032737	-0.00250313	0.05405	NA	0.959	0.0477	1006656	0.00444673	1.80E-13	461460	0.000
rs78866584	G	A	G	A	0.0116661	-0.026703383	0.491021	NA	0.177	0.0197	1006656	0.0019948	5.00E-09	461460	7.41E
rs7893571	T	G	T	G	0.0140653	-0.012996541	0.665897	NA	0.56	0.0208	1006656	0.00210152	2.30E-11	461460	9.69E
rs7924036	T	G	T	G	-0.0142836	0.0037972	0.503265	NA	0.847	0.0196	1006656	0.0019778	5.10E-13	461460	0.000
rs7925100	A	G	A	G	0.014725	0.051500773	0.396117	NA	0.01	0.02	1006656	0.0020221	3.30E-13	461460	0.000
rs7944782	G	T	G	T	0.0157606	0.028296599	0.509784	NA	0.141	0.0192	1006656	0.00198748	2.20E-15	461460	0.000
rs7947143	A	G	A	G	-0.0162782	-0.011000282	0.163483	NA	0.688	0.0274	1006656	0.00267522	8.30E-12	461460	0.000
rs7975187	G	A	G	A	0.0151361	-0.012296278	0.213905	NA	0.608	0.024	1006656	0.00241251	3.50E-10	461460	8.53E

rs7976963	T	C	T	C	0.0236803	-0.034198147	0.077428	NA	0.339	0.0358	1006656	0.00389591	1.50E-10	461460	8.90E
rs7996639	A	G	A	G	0.0145559	-0.0006018	0.449354	NA	0.974	0.0199	1006656	0.00200245	3.60E-13	461460	0.000
rs8015400	A	C	A	C	0.0213422	0.04999094	0.677097	NA	0.0484	0.0208	1006656	0.00211709	6.70E-24	461460	0.000
rs8025516	G	T	G	T	-0.0146558	-0.040901991	0.645928	NA	0.04	0.0199	1006656	0.00207578	1.70E-12	461460	0.000
rs8047587	T	G	T	G	0.0676323	0.023804413	0.439435	NA	0.226	0.0197	1006656	0.00195438	1.00E-200	461460	0.000
rs8063946	T	C	T	C	-0.0251967	-0.060397773	0.05448	NA	0.206	0.0478	1006656	0.00436586	7.90E-09	461460	7.22E
rs8076689	C	T	C	T	0.0140681	0.014200349	0.561561	NA	0.467	0.0195	1006656	0.00199601	1.80E-12	461460	0.000
rs8112818	G	A	G	A	-0.020696	0.004997492	0.400329	NA	0.801	0.0199	1006656	0.00202712	1.80E-24	461460	0.000
rs8132491	A	G	A	G	-0.015375	0.012096541	0.313023	NA	0.559	0.0208	1006656	0.00219317	2.40E-12	461460	0.000
rs815163	C	T	C	T	-0.016485	0.010302893	0.563148	NA	0.604	0.0198	1006656	0.00198582	1.00E-16	461460	0.000
rs82042	G	A	G	A	-0.0131207	0.003395759	0.758575	NA	0.885	0.0236	1006656	0.00231309	1.40E-08	461460	6.97E
rs822320	T	C	T	C	-0.0231703	0.019596724	0.40965	NA	0.338	0.0204	1006656	0.00201345	1.20E-30	461460	0.000
rs879620	T	C	T	C	0.0241136	0.00800193	0.613237	NA	0.693	0.0203	1006656	0.00203595	2.30E-32	461460	0.000
rs909892	A	G	A	G	-0.0184105	0.009197572	0.134817	NA	0.757	0.0298	1006656	0.00291255	2.60E-10	461460	8.66E
rs923994	G	A	G	A	-0.0145761	-0.024804804	0.783195	NA	0.305	0.024	1006656	0.00240219	1.30E-09	461460	7.98E
rs9294260	A	G	A	G	0.014782	0.001798382	0.476559	NA	0.924	0.019	1006656	0.00198818	1.00E-13	461460	0.000
rs9349235	T	C	T	C	0.0118009	0.019704583	0.410635	NA	0.32	0.0199	1006656	0.00200924	2.60E-08	461460	6.71E
rs935166	A	G	A	G	-0.0181066	0.031101301	0.506805	NA	0.112	0.0196	1006656	0.00197292	3.20E-16	461460	0.000
rs9368863	C	T	C	T	-0.0285083	-0.03820963	0.671833	NA	0.069	0.021	1006656	0.00210043	5.80E-42	461460	0.000
rs9461887	T	C	T	C	0.0148892	-0.006702411	0.277069	NA	0.77	0.023	1006656	0.00220206	1.40E-11	461460	9.91E
rs9463175	T	C	T	C	-0.0115	0.028704068	0.338956	NA	0.16	0.0204	1006656	0.00210115	4.40E-08	461460	6.48E
rs9478496	C	T	C	T	0.0181836	-0.026795823	0.164225	NA	0.31	0.0264	1006656	0.00267493	1.10E-11	461460	0.000
rs9515446	G	A	G	A	0.0151051	-0.00549507	0.447709	NA	0.78	0.0196	1006656	0.00199052	3.20E-14	461460	0.000
rs9522180	T	C	T	C	-0.0141095	0.007296555	0.553392	NA	0.71	0.0196	1006656	0.00199325	1.50E-12	461460	0.000
rs9571687	A	C	A	C	-0.0135388	-0.003496104	0.329363	NA	0.871	0.0214	1006656	0.0021094	1.40E-10	461460	8.93E
rs9638713	G	A	G	A	-0.0061735	-0.046597285	0.97477	NA	0.465	0.0638	1006656	0.00635399	1.20E-08	461460	7.02E
rs9673839	G	A	G	A	0.0130337	0.028801234	0.490967	NA	0.134	0.0192	1006656	0.00198783	5.50E-11	461460	9.32E
rs9674487	G	C	G	C	0.158445	-1.56882394	0.001338	0.377	0.0152	0.646	1006656	0.0286171	3.10E-08	461460	6.84E
rs9830592	A	C	A	C	0.0154849	0.012700309	0.582421	NA	0.518	0.0197	1006656	0.00200184	1.00E-14	461460	0.000
rs9839081	A	G	A	G	-0.011701	0.019704583	0.325232	NA	0.344	0.0208	1006656	0.00214045	4.60E-08	461460	6.48E
rs9843653	C	T	C	T	0.0294509	-0.019600848	0.511652	NA	0.304	0.0191	1006656	0.00197538	2.90E-50	461460	0.000
rs9876664	T	G	T	G	-0.0180478	-0.017797439	0.375389	NA	0.373	0.02	1006656	0.00204174	9.60E-19	461460	0.000
rs9885533	T	C	T	C	0.0120038	-0.001099395	0.538079	NA	0.956	0.0197	1006656	0.0020182	2.70E-09	461460	7.67E
rs9926784	C	T	C	T	-0.023818	-0.00020002	0.194576	NA	0.992	0.0267	1006656	0.00254677	8.60E-21	461460	0.000
rs9951619	G	T	G	T	0.0144231	0.012902885	0.767369	NA	0.571	0.0227	1006656	0.00235777	9.50E-10	461460	8.11E
Summary	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.053

TABLE 9: Independent IVs in the causal analysis of adult BMI (IEU OPEN GWAS) and SSS

BMI, body mass index; IEU OPEN GWAS, Integrative Epidemiology Unit Open Genome-Wide Association Study; IVs, instrumental variables; NA, not applicable; SNP, single nucleotide polymorphism; SSS, sick sinus syndrome

SNP	effect_allele_exposure	other_allele_exposure	effect_allele_outcome	other_allele_outcome	beta_exposure	beta_outcome	esf_exposure	esf_outcome	pval_outcome	se_outcome	sample_size_outcome	pval_exposure	se_exposure	sample_size_exposure	R2
rs10149821	G	T	G	T	0.429799933	0.0141335	NA	0.0172529	0.120772	0.00910634	321672	3.45E-14	0.0967	1006656	5.71E
rs116307579	T	C	T	C	0.293989935	0.0100673	NA	0.0263378	0.166239	0.00727204	321672	2.78E-09	0.0494	1006656	3.51E
rs11662320	T	C	T	C	0.119000073	-0.00418987	NA	0.246742	0.119551	0.00209158	321672	3.68E-08	0.0216	1006656	3.02E
rs11715941	T	C	T	C	0.115103894	0.00337125	NA	0.465516	0.14772	0.0023288	321672	6.93E-09	0.0199	1006656	3.32E
rs2106261	T	C	T	C	0.149703664	0.00420746	NA	0.224326	0.129989	0.00277877	321672	9.94E-10	0.0245	1006656	3.71E
rs551862772	A	G	A	G	0.787101897	-0.012287	0.863	0.00298336	0.578393	0.0221095	321672	9.92E-27	0.0735	1006656	0.000
rs7689774	T	G	T	G	0.188303628	-0.00179769	NA	0.236827	0.508591	0.00271953	321672	2.28E-15	0.0238	1006656	6.22E
Summary	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.000

TABLE 10: Independent IVs in the causal analysis of SSS and adult BMI (FinnGen)

BMI, body mass index; FinnGen, Finnish Health Research Environment for Genomic Research; IVs, instrumental variables; NA, not applicable; SNP, single nucleotide polymorphism; SSS, sick sinus syndrome

SNP	effect_allele.exposure	other_allele.exposure	effect_allele.outcome	other_allele.outcome	beta.exposure	beta.outcome	esf.exposure	esf.outcome	se.outcome	pval.outcome	samplesize.outcome	pval.exposure	se.exposure	samplesize.exposure	R2
rs10149621	G	T	G	T	0.429799933	-0.000834236	NA	0.02829	0.00630369	0.889999986	461460	3.45E-14	0.0567	1006656	5.71E
rs116307579	T	C	T	C	0.293689835	5.43E-05	NA	0.029299	0.00588997	0.989999999	461460	2.78E-09	0.0494	1006656	3.51E
rs11662320	T	C	T	C	0.119000073	0.00198918	NA	0.264916	0.00225052	0.380000353	461460	3.68E-08	0.0216	1006656	3.02E
rs2106261	T	C	T	C	0.149703664	-0.00414536	NA	0.167612	0.00264284	0.119999932	461460	9.94E-10	0.0245	1006656	3.71E
rs35813871	A	G	A	G	0.122898817	-0.00182352	NA	0.242476	0.00229329	0.429999549	461460	2.64E-08	0.0221	1006656	3.07E
rs551962772	A	G	A	G	0.787101897	-0.0150544	0.863	0.008463	0.0114767	0.190000175	461460	9.92E-27	0.0735	1006656	0.000
rs7689774	T	G	T	G	0.188303628	0.00127801	NA	0.196754	0.00248707	0.610000232	461460	2.26E-15	0.0238	1006656	6.22E
Summary	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.000

TABLE 11: Independent IVs in the causal analysis of SSS and adult BMI (IEU OPEN GWAS)

BMI, body mass index; IEU OPEN GWAS, Integrative Epidemiology Unit Open Genome-Wide Association Study; IVs, instrumental variables; NA, not applicable; SNP, single nucleotide polymorphism; SSS, sick sinus syndrome

MVMR and meta-analysis

The MVMR analysis findings demonstrated independent effects of adult BMI on SSS after correction of TL. Analysis of the FinnGen BMI data in relation to SSS indicated a causal inference supporting the effect of increased adult BMI on SSS risk. Owing to the presence of heterogeneity ($P_{\text{Cochran's } Q} = 0.02$), we used the random-effects IVW results for causal inference (OR = 1.22, 95% CI 1.04-1.44, $P = 0.016$). A consistent causal inference was noted in the IEU OPEN GWAS BMI data (OR = 1.19, 95% CI 1.04-1.36, $P = 0.011$).

The results of the meta-analysis supported the causality between adult BMI and SSS (OR = 1.20, 95% CI 1.08-1.33, $P = 0.0005$). The results of MVMR and the meta-analysis are shown in Table 12 and Figure 5, respectively.

Exposure sources	Methods	nSNP	OR (95%CI)	P-value
FinnGen	MV-IVW	300	1.22 (1.04-1.44)	0.016
	MV- median		1.37 (1.09-1.71)	0.006
	MV- Egger		1.29 (0.95-1.76)	0.099
Cochrane's Q = 352.4 (P = 0.02); MR-Egger intercept (P = 0.66); F-statistic = 41.3				
IEU OPEN GWAS	MV-IVW	368	1.19 (1.04-1.36)	0.011
	MV-median		1.04 (0.80-1.35)	0.795
	MV-Egger		1.40 (1.06-1.85)	0.017
Cochrane's Q = 391.5(P = 0.17); MR-Egger intercept (P = 0.18); F-statistic = 55.6				

TABLE 12: MVMR results

CI, confidence interval; FinnGen, Finnish Health Research Environment for Genomic Research; IEU OPEN GWAS, Integrative Epidemiology Unit Open Genome-Wide Association Study; IVW, inverse variance weighted; MR, Mendelian randomization; OR, odds ratio

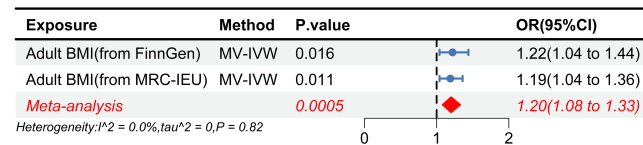


FIGURE 5: Forest plot of the MVMR causal estimates for adult BMI and SSS

BMI, body mass index; CI, confidence interval; FinnGen, Finnish Health Research Environment for Genomic Research; IVW, inverse-variance weighted; MRC-IEU, Medical Research Council Integrated Epidemiology Unit; MVMR, multivariate Mendelian randomization; OR, odds ratio; SSS, sick sinus syndrome

Discussion

Evidence generated from published epidemiological studies has highlighted the association of BMI with SSS, which contradicts the findings of Thorolfsdottir et al. who used the polygenic score to investigate the relationship between BMI and SSS [4,6]. This uncertainty in association and causality paves an opportunity for an MR study. Our study findings suggest a positive association of adult BMI with SSS, and the results of replication and meta-analysis further confirmed the causal inference that the risk of SSS is increased with adult BMI and that this effect is independent of reverse causality. Given the large median age of the adult BMI population enrolled in the study, the results suggest that the risk of SSS increases with an increase in BMI among the middle-aged and older populations.

The Centers for Disease Control and Prevention predicts that children or adolescents with high BMI percentiles on the BMI growth charts are at an increased risk of becoming overweight or obese as they age [36]. Although higher BMI during childhood was not associated with an increased risk of SSS in our study, the persistence of obesity in this population may lead to a higher risk of developing SSS as they grow older. The statistical power of our study to detect associations between childhood BMI and SSS was limited, which implies a reduced likelihood of identifying true effects. This limitation may be related to smaller sample sizes and effect sizes [37]. Although we incorporated studies from diverse sources to enhance the robustness of causal inferences, future GWAS studies with larger sample sizes are necessary to validate our findings.

BMI is a simple measure of obesity. In economically developed regions, the highest prevalence of obesity is

observed among individuals aged 60–69, while the upward trend in BMI among children and adolescents remains at a notably high level [38,39]. In patients with permanent pacemaker implantation, obesity is known to elevate cardiac mortality and reduce the opportunity for patients with SSS to receive optimal pacemaker therapy [40,41]. The total cost of permanent pacemaker implantation has already surged, and the growing obese population and the increase in the incidence of SSS will pose significant pressure on the healthcare economy [42].

The sinoatrial node (SN) is a heterogeneous pacemaker comprising a specialized population of cardiomyocytes. These clusters of cardiomyocytes generate action potentials spontaneously to maintain cardiac contraction [43,44]. A previous Polish study on aging and obesity in SN found that the SN of obese patients was enriched with connective tissue content, had reduced myocyte content, and showed alterations in cellular morphology as compared with the SN of non-obese patients. This observation implies that elevated SN fibrosis, apoptosis, and cellular hypertrophy in obese patients can contribute to the development of SSS. Microstructural manifestations of young obese right atrial (RA) muscle are more noteworthy than those of aging RA fibrosis [45]. In addition, the increased fat content can stimulate the release of inflammatory cytokines, which affect the SN via paracrine effects [45–47]. Studies in aged obese rats have reported SN cell hypertrophy and extracellular matrix remodeling, which are suggestive of the interaction between obesity and age that can cause SN dysfunction [45,48].

As the positive influence of weight loss on cardiovascular diseases such as heart failure and atrial fibrillation has been well documented [49–51], we anticipate that modulation of BMI could be effective for the prevention and treatment of SSS. However, there are no observational clinical studies to support this hypothesis, which may be limited by reasons such as time or costly expenses [52]. The present study offers several advantages as follows: (1) This, to the best of our knowledge, is the first comprehensive study to address the causalities between childhood and adult BMI and SSS through MR analysis. (2) The causal inference derived with SSS using a large, independent, high-quality BMI GWAS study may enhance the accuracy of the results. (3) Different methods were employed to eliminate confounders. The direction of the consistent effect estimates indicates that the causal inference findings are not by chance and that the use of reverse MR reduces the error in the causal inference [53,54]. (4) With respect to sample overlapping, which is unavoidable with the use of publicly available pooled data, the estimates were corrected using MRlap to increase the confidence of the causal inference. (5) The use of meta-analysis helped us synthesize the results of the studies, lower the possible errors in a single study, and increase the credibility of the causal interference.

The present study has some limitations: (1) There may be inconsistency in the degree of the effect of different ages on SSS, and as BMI is a continuous variable, we were unable to determine the effect of BMI on SSS at a specific age using MR. (2) To minimize bias, participants included in the MR analysis were of European descent. The causal relationships should be validated in more diverse populations to enhance the generalizability of the conclusions. (3) We cannot entirely exclude the possibility that the IVs in this study are associated with unmeasured confounders, a limitation inherent to most MR analyses. We evaluated the potential for risk factors to act as confounders in the BMI–SSS causal relationship by assessing whether they met the three key criteria for confounding. We also examined the associations between IVs and potential confounders using the Phenoscanner database. Although we cannot confirm that IVs are entirely independent of unmeasured confounders, this possibility is likely small. Additionally, the results from MVMR analyses strengthen confidence in our conclusions. (4) The potential for horizontal pleiotropy cannot be entirely excluded in this study – a methodological challenge inherent to MR analyses. Completely eliminating pleiotropic effects remains difficult, particularly for risk factors influenced by multiple genetic variants. Notably, the consistency of causal estimates across three MR approaches (IVW, MR–Egger, and weighted median) supports the robustness of our findings. (5) We cannot rule out potential influences of limited statistical power and weak instrument bias on the findings, particularly in the context of BMI reverse causation. Some results exhibited suboptimal statistical power (<80%), which may be attributed to the small sample size or effect values. Therefore, future studies with larger samples are warranted to validate these inferences. However, any bias from weak instruments is in the direction of the null, as we are considering the analyses in the two-sample setting [55].

Our findings provide MR evidence for researchers exploring the causal relationship between BMI and SSS. Specifically, focusing on adult BMI (middle-aged and older individuals), future studies should investigate the biological mechanisms underlying the association between BMI and SSS or develop targeted prevention and management strategies (e.g., weight management programs for middle-aged adults and obesity screening in primary care).

Conclusions

This study demonstrates that a higher BMI is associated with an increased risk of SSS, particularly among middle-aged and older adults. In contrast, no causal relationship was identified between childhood BMI and SSS, suggesting that the influence of BMI on SSS susceptibility may manifest predominantly in later life stages. These findings highlight the necessity of targeted public health strategies to address adult obesity as a modifiable risk factor for SSS. Future research should focus on elucidating the biological pathways connecting adult BMI to SSS and evaluating the efficacy of interventions, such as weight reduction and lifestyle modifications, in attenuating SSS risk among individuals with elevated BMI.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Guanzhen Xu, Zhuang Liu, Ping Hou

Acquisition, analysis, or interpretation of data: Guanzhen Xu

Drafting of the manuscript: Guanzhen Xu, Zhuang Liu

Critical review of the manuscript for important intellectual content: Guanzhen Xu, Zhuang Liu, Ping Hou

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Disclosures

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