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ORIGINAL RESEARCH

The Causal Relationship Between Body Mass Index and the Risk of Osteoarthritis

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Objective: The study aimed to explore the causal effect of body mass index (BMI) on osteoarthritis.

Methods: The genome-wide association data of BMI and osteoarthritis were obtained via the Mendelian randomization (MR)-base platform. Single nucleotide polymorphisms (SNPs) significantly associated with BMI were identified and used as instrumental variables, and the causal relationship between BMI and osteoarthritis was examined using the two-sample MR research method. Three statistical methods including inverse-variance weighted (IVW) method, weighted median estimator, and MR-Egger regression were employed.

Results: A total of 79 SNPs significantly associated with BMI were identified in the study ($P<5\times10^{-8}$; linkage disequilibrium $r^2<0.1$). Consistent association between BMI and osteoarthritis was observed when evaluated by different methods (IVW: odds ratio (OR) 1.028, 95% confidence interval (CI) 1.021–1.036; weighted median estimator: OR 1.028, 95% CI 1.019–1.037; MR-Egger regression: OR 1.028, 95% CI 1.009–1.046), which suggests that BMI is positively associated with increased risk of osteoarthritis. There was no evidence that the observed causal effect between BMI and the risk of osteoarthritis was affected by genetic pleiotropy (MR-Egger intercept 1.3×10^{-5}, P=0.959).

Conclusion: The MR analysis provided the strong evidence to indicate that BMI might be causally associated with the risk of osteoarthritis.

Keywords: osteoarthritis, body mass index, Mendelian randomization

Introduction

Osteoarthritis, a common disease of the musculoskeletal system, is an important cause of pain and disability in the elderly.[1] Although joint replacement is effective for treating end-stage osteoarthritis, problems such as poor joint function recovery and limited lifetime of artificial joint hinder further improvement in prognosis. Therefore, the management of the disease is shifting to the prevention and early treatment of osteoarthritis.[1,2] Overweight and obesity have been identified as risk factors of the occurrence and progression of osteoarthritis,[3–5] and relief of symptoms was observed in patients with osteoarthritis who had undergone diet and exercise therapy.[5,6] However, a causal effect of overweight or obesity on osteoarthritis cannot be convincingly established with evidence from observational studies, in which there is a lack of randomization of exposure factors and therefore confounding and reverse causality cannot be ruled out in the observed association. Traditional randomized clinical controlled trials are suitable from the viewpoint of methodology, but are not practicable due to ethical concern.

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Mendelian randomization (MR) is a method that used genetic variations as instrumental variables of exposure factors to infer the causal relationship between exposure factors and outcomes. Because genetic variations follow the law of Mendelian and are randomly distributed in the population, the influence of confounding factors are largely controlled.[7] With the popularity of genome-wide association study (GWAS) studies and GWAS meta-analysis, MR becomes an efficient and practicable method to investigate causal effect.[8] The two-sample MR is a method to estimate the causal effect of an exposure on an outcome using only summary statistics from GWAS, in which genetic variation-exposure factor association data and genetic variation-disease outcome association data from two independent samples with similar distribution characteristics were used. In the study, we used the two-sample MR method based on GWAS data to analyze whether there is a causal effect of body mass index (BMI) on the risk of osteoarthritis.

Materials and Methods

Genetic Variants Associated with BMI

Publicly accessible data for genetic variants associated with BMI were obtained from the Genetic Investigation of ANthropometric Traits (GIANT) Consortium.[9] The detail of studies and datasets was presented in Table 1. The consortium included 3,339,224 participants and the number of included single nucleotide polymorphism (SNP) was 2,555,511. To minimize the impact caused by linkage disequilibrium (LD), we set the threshold of statistical significance as "P $<5\times10^{-8}$; LD r^2 <0.1" to identify the SNPs associated with BMI. In total, there were 79 SNPs included in this study (rs1000940, rs10132280, rs1016287, rs10182181, rs10733682, rs10840100, rs11030104, rs11057405, rs11165643, rs11672660, rs1167827, rs11727676, rs12286929, rs12429545, rs12448257, rs12940622, rs12986742, rs13021737, rs13078960, rs13107325, rs13130484, rs13191362, rs13201877, rs13329567, rs1421085, rs1441264, rs1460676, rs14810, rs1516725, rs1528435, rs16851483, rs17001654, rs17066856, rs17094222, rs17203016, rs17381664, rs17724992, rs1928295, rs2033529, rs2060604, rs2112347, rs2176598, rs2183825, rs2365389, rs2820292, rs2836754, rs2890652, rs3736485, rs3800229, rs3817334, rs3849570, rs3888190, rs4740619, rs4889606, rs543874, rs6091540, rs6457796, rs6477694, rs6567160, rs657452, rs6713510, rs6804842, rs7138803, rs7144011, rs7531118, rs7550711, rs7599312, rs7715256, rs7899106, rs7903146, rs879620, rs891389, rs9304665, rs9374842, rs943005, rs9540493, rs9579083, rs977747, and rs9926784). The variation in the included SNPs was 2.7%. The F value was 5,529, which was larger than 10 and suggested the strength of the instrumental variable was not weak.[10] As a result, all these SNPs were included into the study.

Genetic Variants Associated with Osteoarthritis

The GWAS summary data for osteoarthritis were obtained from MRC Integrative Epidemiology Unit (MRC-IEU) consortium, which was published in 2018 and available through the UK Biobank.[11] The sample size was 462,933, with 38,472 cases and 424,461 participants in the control group. The number of SNP included in the study was 9,851,867. All the above SNPs associated with BMI were found in MRC-IEU consortium.

Estimation of the Causal Relationship Between BMI and Osteoarthritis

After data from the GWAS study or GWAS meta-analysis associated with BMI or osteoarthritis were obtained via MR-Base platform,[12] MR analysis was further carried out using the package "TwoSampleMR" of the R program (version 3.4.2). Three statistical methods including

Table 1 Details of Studies and Datasets Used in the Study

Exposure/ Outcomes	Web Source	Sample Size	SNP Size	First Author	Consortium	Year	Population Studied
BMI	https://pubmed.ncbi.nlm.nih.gov/25673413/	3339224	2555511	Locke AE	GIANT	2015	Mixed/Males and females
Osteoarthritis	Output from GWAS pipeline using Phesant derived variables from UKBiobank	462933	9851867	Ben Elsworth	MRCIEU	2018	European/Males and females

Abbreviations: BMI, body mass index; GIANT, ANthropometric Traits; GWAS, genome-wide association study; SNP, single nucleotide polymorphisms; MRCIEU, MRC Integrative Epidemiology Unit.

inverse-variance weighted (IVW) method, weighted median estimator, and MR-Egger regression were used to investigate the causal relationship between BMI and osteoarthritis.[12–15] The IVW method is the method to assess the causal relationship by the meta-analysis of every Wald ratio for the included SNPs.[12,13] Significantly, there is a premise for the IVW method that all the included SNPs must be valid variables. Unlike the IVW method, the MR-Egger regression can still function when all the SNPs are invalid.[15] The slope of MR-Egger indicates the effect of BMI on osteoarthritis when the intercept term is zero or without statistical significance.[12,15] The weighted median estimator was intermediate and the valid variables must be no less than 50%.[14] The result of the weighted median estimator was the median when the effect estimations of each single SNP are sorted in the order of weight values. The estimation of the causal relationship between BMI and osteoarthritis was expressed as odds ratio (OR) and its 95% confidence interval (CI). A P value less than 0.05 indicates that the difference is statistically significant.

Sensitivity Analysis

The method of leave-one-out method was utilized to investigate the sensitivity of the results. Similar to the meta-analysis, we removed the single SNP one by one and calculated the effect of the remaining SNPs by the IVW method.[16] In this way, we examined the effect of individual SNP on the causal inference.

Results

Detail Information of the Included SNPs

The details of each SNP were presented in Table 2, including the chromosome location, genes, effect allele (EA), and effect allele frequency (EAF). Estimations of the associations of each SNP with BMI and osteoarthritis including beta value, standard error (SE) and P value were also presented in Table 2. Among them, 17 SNPs, namely rs13107325 (β −0.0096; SE 0.0011; P<0.001), rs6457796 (β −0.0025; SE 0.0006; P<0.001), rs3736485 (β 0.0017; SE 0.0006; P<0.001), rs2836754 (β 0.0016; SE 0.0006; P 0.01), rs2820292 (β −0.0014; SE 0.0006; P 0.02), rs6477694 (β 0.0012; SE 0.0006; P 0.04), rs11030104 (β 0.0029; SE 0.0007; P <0.001), rs3849570 (β 0.0012; SE 0.0006; P 0.04), rs16851483 (β −0.0029; SE 0.0012; P 0.01), rs891389 (β −0.0012; SE 0.0006; P 0.05), rs1516725 (β −0.0023; SE 0.0008; P 0.01), rs10182181 (β −0.0013; SE 0.0006; P 0.02), rs13021737 (β −0.0026; SE 0.0008; P <0.001), rs7138803 (β −0.0013; SE 0.0006; P 0.03), rs7531118 (β −0.0012; SE 0.0006; P 0.04), rs6567160 (β 0.0017; SE 0.0007; P 0.01), and rs1421085 (β 0.0013; SE 0.0006; P 0.03), were significantly associated with both BMI and osteoarthritis.

Causal Effect of BMI on Osteoarthritis

As presented in Table 3, result of the IVW method suggested that there was a positive association between BMI with higher genetic predictability for the risk of osteoarthritis (OR 1.028, 95% CI 1.021–1.036). The weighted median estimator and MR-Egger method showed consistent results (the weighted median estimator: OR 1.028, 95% CI 1.019–1.037; MR-Egger Method: OR 1.028, 95% CI 1.009–1.046). These results could also be observed in the forest plot (Figure 1) and the scatter diagram (Figure 2).

Sensitivity Analysis

There was no evidence that the result was affected by genetic pleiotropy (MR-Egger regression intercept=1.3×10^{-5}, SE=0.00025, P=0.959). From the result of the Leave-one-out method, there was no single SNP playing a decisive role in the causal inference (Figure 3).

Discussion

Osteoarthritis is a chronic joint inflammatory disease with joint swelling, pain and dysfunction as the main clinical manifestations, which seriously affects the quality of life of patients and increases the economic burden of the family and society.[2] In recent years, with the gradual intensification of the aging trend in the population, the prevalence rate of osteoarthritis is also increasing year by year.[1,2] Age, sex, joint injury and obesity are important risk factors for osteoarthritis, among which overweight and obesity are easier to control and prevent than other risk factors. However, due to the influence of confounding factors, it is difficult for classical epidemiological studies to explain the causal sequence of exposure factors and disease results. The purpose of this study is to explore the relationship between BMI and the risk of osteoarthritis through a two-sample Mendelian randomized study based on GWAS. The result indicated that the causal relationship between BMI with the increased risk of osteoarthritis.

In this study, we explored the relationship between BMI and the risk of osteoarthritis through a two-sample

Table 2 Characteristics of the SNPs Associated with BMI and Their Associations with Osteoarthritis

SNPs	Chr	Gene	EA	EAF	BMI			Osteoarthritis		
					β	SE	P	β	SE	P
rs1000940	17:5379957	RABEP1	G	0.23	0.0184	0.0033	1.81E-08	0.0003	0.0006	0.61
rs10132280	14:25458973	STXBP6	A	0.33	−0.0221	0.0033	1.40E-11	−0.0009	0.0006	0.17
rs1016287	2:59078490	LINC01122	T	0.33	0.0228	0.0033	4.36E-12	0.0008	0.0006	0.18
rs10182181	2:24927427	ADCY3	A	0.50	−0.0309	0.0029	8.07E-26	−0.0013	0.0006	0.02
rs10733682	9:126698635	LMX1B	A	0.43	0.0188	0.0030	2.46E-10	0.0008	0.0006	0.20
rs10840100	11:8647890	TRIM66	G	0.73	0.0206	0.0030	6.67E-12	0.0011	0.0006	0.06
rs11030104	11:27662970	BDNF	A	0.80	0.0416	0.0037	6.66E-30	0.0029	0.0007	<0.001
rs11057405	12:122297350	CLIP1	A	0.09	−0.0304	0.0053	1.22E-08	−0.0009	0.0009	0.36
rs11165643	1:96458541	PTBP2	C	0.43	−0.0221	0.0030	1.43E-13	−0.0005	0.0006	0.40
rs11672660	19:45676926	GIPR, MIR642B	C	0.83	0.0339	0.0038	7.91E-19	0.0009	0.0007	0.19
rs1167827	7:75533848	HIP1	A	0.46	−0.0200	0.0031	1.98E-10	0.0000	0.0006	0.96
rs11727676	4:144737912	HHIP	C	0.08	−0.0365	0.0063	6.25E-09	0.0018	0.0010	0.07
rs12286929	11:115151684	CADM1	G	0.43	0.0211	0.0029	5.44E-13	−0.0001	0.0006	0.92
rs12429545	13:53528071	OLFM4	G	0.90	−0.0324	0.0044	3.15E-13	−0.0011	0.0009	0.19
rs12448257	16:3549655	NLRC3, LOC101929732	G	0.78	−0.0246	0.0037	3.90E-11	−0.0001	0.0007	0.93
rs12940622	17:80641771	RPTOR	A	0.46	−0.0183	0.0029	3.64E-10	−0.0002	0.0006	0.73
rs12986742	2:58748008	LINC01122	C	0.50	0.0207	0.0036	8.92E-09	0.0003	0.0006	0.63
rs13021737	2:632348	TMEM18	A	0.13	−0.0604	0.0039	5.44E-54	−0.0026	0.0008	<0.001
rs13078960	3:85758440	CADM2	T	0.82	−0.0290	0.0038	1.42E-14	−0.0010	0.0007	0.15
rs13107325	4:102267552	SLC39A8	C	0.88	−0.0472	0.0066	1.06E-12	−0.0096	0.0011	<0.001
rs13130484	4:45173674	/	C	0.57	−0.0398	0.0030	8.01E-41	−0.0011	0.0006	0.06
rs13191362	6:162612318	PRKN	A	0.80	0.0285	0.0047	1.09E-09	−0.0003	0.0009	0.70
rs13201877	6:137354404	LOC107986544	A	0.92	−0.0236	0.0043	4.29E-08	0.0005	0.0008	0.55
rs13329567	15:67812029	/	T	0.22	−0.0307	0.0035	1.53E-18	−0.0013	0.0007	0.06
rs1421085	16:53767042	FTO	C	0.45	0.0803	0.0030	2.17E-158	0.0013	0.0006	0.03
rs1441264	13:79006784	MR548A2	A	0.55	0.0172	0.0031	2.96E-08	−0.0001	0.0006	0.89
rs1460676	2:163711179	FIGN	T	0.78	−0.0209	0.0038	4.98E-08	−0.0006	0.0008	0.46
rs14810	19:33813998	KCTD15	C	0.33	−0.0183	0.0033	1.92E-08	−0.0011	0.0006	0.06
rs1516725	3:186106215	ETV5	T	0.09	−0.0448	0.0044	1.39E-24	−0.0023	0.0008	0.01
rs1528435	2:180686235	UBE2E3	T	0.58	0.0175	0.0030	4.77E-09	0.0006	0.0006	0.27
rs16851483	3:141556594	RASA2	G	0.91	−0.0478	0.0075	1.85E-10	−0.0029	0.0012	0.01
rs17001654	4:76208415	SCARB2	C	0.84	−0.0304	0.0052	5.03E-09	−0.0014	0.0008	0.08

(*Continued*)

Table 2 (Continued).

SNPs	Chr	Gene	EA	EAF	BMI			Osteoarthritis		
					β	SE	P	β	SE	P
rs17066856	18:60382423	/	C	0.13	−0.0371	0.0050	2.00E-13	0.0008	0.0010	0.42
rs17094222	10:100635683	HIF1AN	C	0.21	0.0249	0.0037	2.19E-11	0.0005	0.0007	0.49
rs17203016	2:207390794	CREB1;KLF7	G	0.20	0.0211	0.0038	3.41E-08	0.0004	0.0007	0.57
rs17381664	1:77582646	ZZZ3	C	0.43	0.0201	0.0031	4.57E-11	0.0006	0.0006	0.34
rs17724992	19:18344015	PGPEP1	A	0.69	0.0196	0.0034	7.79E-09	0.0006	0.0006	0.33
rs1928295	9:117616205	TLR4	C	0.43	−0.0182	0.0029	4.32E-10	−0.0007	0.0006	0.22
rs2033529	6:40380914	TDRG1;LRFN2	G	0.26	0.0183	0.0032	1.45E-08	0.0003	0.0006	0.58
rs2060604	8:75738099	/	T	0.56	0.0203	0.0030	9.46E-12	−0.0007	0.0006	0.25
rs2112347	5:75719417	POC5, LOC441087	G	0.38	−0.0254	0.0030	1.96E-17	0.0009	0.0006	0.14
rs2176598	11:43842728	HSD17B12	T	0.20	0.0185	0.0033	3.47E-08	0.0011	0.0007	0.08
rs2183825	9:28412377	LINGO2	C	0.29	0.0241	0.0032	2.22E-14	0.0010	0.0006	0.11
rs2365389	3:61250788	FHIT	C	0.66	0.0195	0.0030	1.35E-10	0.0005	0.0006	0.36
rs2820292	1:201815159	NAV1, IPO9AS1	A	0.49	−0.0181	0.0029	5.45E-10	−0.0014	0.0006	0.02
rs2836754	21:38919816	LOC400867	C	0.65	0.0169	0.0030	1.61E-08	0.0016	0.0006	0.01
rs2890652	2:142202362	/	T	0.88	−0.0279	0.0049	1.24E-08	0.0003	0.0008	0.73
rs3736485	15:51456413	DMXL2	A	0.43	0.0160	0.0029	4.52E-08	0.0017	0.0006	<0.001
rs3800229	6:108675760	FOXO3	T	0.69	0.0175	0.0032	4.95E-08	0.0006	0.0006	0.33
rs3817334	11:47629441	MTCH2	C	0.55	−0.0256	0.0030	1.17E-17	0.0003	0.0006	0.60
rs3849570	3:81742961	GBE1	A	0.37	0.0183	0.0033	1.93E-08	0.0012	0.0006	0.04
rs3888190	16:28878165	ATP2A1	A	0.36	0.0311	0.0030	3.45E-25	0.0007	0.0006	0.23
rs4740619	9:15634328	CCDC171	T	0.53	0.0170	0.0029	6.36E-09	0.0010	0.0006	0.08
rs4889606	16:30999862	STX1B	G	0.36	−0.0187	0.0030	6.58E-10	−0.0004	0.0006	0.54
rs543874	1:177920345	SEC16B	G	0.27	0.0497	0.0037	2.29E-40	0.0009	0.0007	0.19
rs6091540	20:52471323	LOC105372666, LOC105372667	C	0.73	0.0185	0.0033	2.14E-08	0.0009	0.0006	0.13
rs6457796	6:34860776	UHRF1BP1	T	0.74	−0.0209	0.0033	2.54E-10	−0.0025	0.0006	<0.001
rs6477694	9:109170062	EPB41L4B	C	0.36	0.0169	0.0030	1.71E-08	0.0012	0.0006	0.04
rs6567160	18:60161902	MC4R	C	0.28	0.0562	0.0035	6.68E-59	0.0017	0.0007	0.01
rs657452	1:49124175	AGBL4	A	0.42	0.0227	0.0031	2.12E-13	0.0004	0.0006	0.55
rs6713510	2:226169783	LOC646736	A	0.48	0.0164	0.0029	1.97E-08	−0.0007	0.0006	0.22
rs6804842	3:25064946	RARB	A	0.43	−0.0183	0.0030	8.02E-10	−0.0007	0.0006	0.25
rs7138803	12:49853685	BCDIN3D, FAIM2	G	0.56	−0.0320	0.0030	5.12E-26	−0.0013	0.0006	0.03
rs7144011	14:79474040	NRXN3	T	0.28	0.0274	0.0035	6.05E-15	0.0008	0.0007	0.26

(*Continued*)

Table 2 (Continued).

SNPs	Chr	Gene	EA	EAF	BMI			Osteoarthritis		
					β	SE	P	β	SE	P
rs7531118	1:72371556	LOC105378797	T	0.39	−0.0331	0.0030	1.88E-28	−0.0012	0.0006	0.04
rs7550711	1:109540264	GPR61	T	0.03	0.0659	0.0087	5.06E-14	0.0003	0.0018	0.85
rs7599312	2:212548507	LOC107985979	G	0.71	0.0214	0.0033	4.73E-11	0.0001	0.0007	0.88
rs7715256	5:154158333	GALNT10	G	0.45	0.0168	0.0029	8.85E-09	−0.0001	0.0006	0.80
rs7899106	10:85651147	GRID1	A	0.95	−0.0379	0.0067	1.27E-08	0.0001	0.0013	0.92
rs7903146	10:112998590	TCF7L2	T	0.25	−0.0235	0.0033	1.10E-12	−0.0004	0.0006	0.49
rs879620	16:3965728	ADCY9	C	0.41	−0.0244	0.0039	3.94E-10	0.0006	0.0006	0.30
rs891389	18:23507567	NPC1, RMC1	C	0.68	−0.0209	0.0037	1.62E-08	−0.0012	0.0006	0.05
rs9304665	19:47099320	ZC3H4	A	0.70	0.0243	0.0043	1.59E-08	0.0003	0.0007	0.66
rs9374842	6:119864519	LOC285762	T	0.74	0.0196	0.0034	7.20E-09	0.0010	0.0007	0.16
rs943005	6:50898107	/	T	0.10	0.0444	0.0038	4.52E-31	0.0006	0.0008	0.43
rs9540493	13:65631572	MIR548X2, PCDH9	G	0.55	−0.0182	0.0031	3.95E-09	0.0001	0.0006	0.93
rs9579083	13:27443133	MTIF3	G	0.77	−0.0295	0.0046	1.43E-10	0.0002	0.0007	0.79
rs977747	1:47219005	TAL1	T	0.47	0.0168	0.0030	2.18E-08	0.0005	0.0006	0.43
rs9926784	16:19930646	/	T	0.79	0.0249	0.0038	8.55E-11	0.0009	0.0007	0.23

Abbreviations: BMI, body mass index; EA, effect allele; EAF, effect allele frequency; SE, standard error; SNP, single-nucleotide polymorphism.

MR study based on GWAS. 79 SNPs significantly related to BMI were selected as tool variables. When using the IVW method, weighted median estimator, and MR-Egger MR method with data from the GWAS study of osteoarthritis, it was found that there was a causal relationship between high BMI and the increased risk of osteoarthritis. The main implication of our findings is that it supports weight control as a intervention for the prevention and management of osteoarthritis.

Table 3 Causal Associations Between Genetically Determined BMI and Osteoarthritis

	β	SE	OR (95% CI)	P
IVW	0.02778	0.0037	1.028(1.021–1.036)	1.253e-13
Weighted median	0.02739	0.0044	1.028(1.019–1.037)	5.848e-10
MR-Egger	0.02735	0.0092	1.028(1.009–1.046)	0.009

Abbreviations: CI, confidence interval; IVW, inverse variance weighted; OR, odds ratio; SE, standard error; SNP, single-nucleotide polymorphism.

Overweight and obesity are modifiable and easier to manage than other risk factors of osteoarthritis (such as age, sex, and joint injury), and therefore it becomes a promising target for management of osteoarthritis if overweight and obesity do casually increase the risk of the occurrence and/or progress of osteoarthritis. The association between overweight and osteoarthritis has been reported in several studies. Raud et al[17] found that there was a dose-response relation between BMI and the knee of osteoarthritis. A Spanish research demonstrated that the osteoarthritis risk both in hip and knee was increased in being overweight.[18] However, due to the potential influence of confounding factors and reverse causality, it is difficult for conventional observational studies to establish the causal relationship between BMI and osteoarthritis, while the MR method is a promising tool for such an investigation, since it uses genetic variations as instrumental variables of exposure factors to infer the causal relationship between exposure factors and outcomes. There were a few available studies that used the MR method to investigate the relationship between BMI and

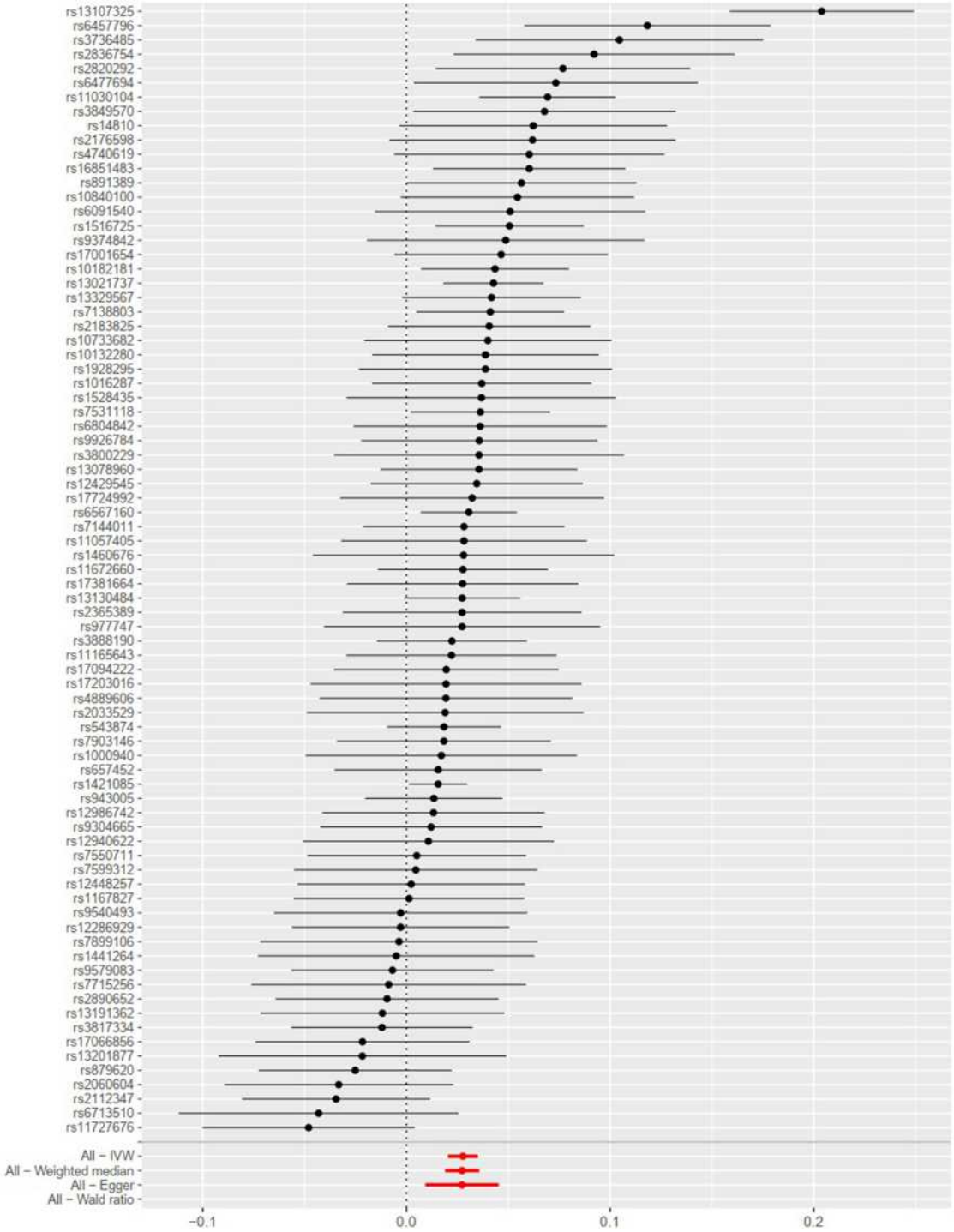

Figure 1 Forest plot of single nucleotide polymorphisms (SNPs) associated with body mass index (BMI) and the risk of osteoarthritis. Black points represent the log odds ratio (OR) for osteoarthritis per standard deviation (SD) increase in BMI, which is produced by using each SNP selected as a separate instrument (rs1000940, rs10132280, rs1016287, rs10182181, rs10733682, rs10840100, rs11030104, rs11057405, rs11165643, rs11672660, rs1167827, rs11727676, rs12286929, rs12429545, rs12448257, rs12940622, rs12986742, rs13021737, rs13078960, rs13107325, rs13130484, rs13191362, rs13201877, rs13329567, rs1421085, rs1441264, rs1460676, rs14810, rs1516725, rs1528435, rs16851483, rs17001654, rs17066856, rs17094222, rs17203016, rs17381664, rs17724992, rs1928295, rs2033529, rs2060604, rs2112347, rs2176598, rs2183825, rs2365389, rs2820292, rs2836754, rs2890652, rs3736485, rs3800229, rs3817334, rs3849570, rs3888190, rs4740619, rs4889606, rs543874, rs6091540, rs6457796, rs6477694, rs6567160, rs657452, rs6713510, rs6804842, rs7138803, rs7144011, rs7531118, rs7550711, rs7599312, rs7715256, rs7899106, rs7903146, rs879620, rs891389, rs9304665, rs9374842, rs943005, rs9540493, rs9579083, rs977747, and rs9926784). Red points show the combined causal estimate using all SNPs together as a single instrument, using the three different methods (the inverse-variance weighted (IVW) method, weighted median estimator, and MR-Egger). Horizontal line segments denote 95% confidence intervals of the estimate.

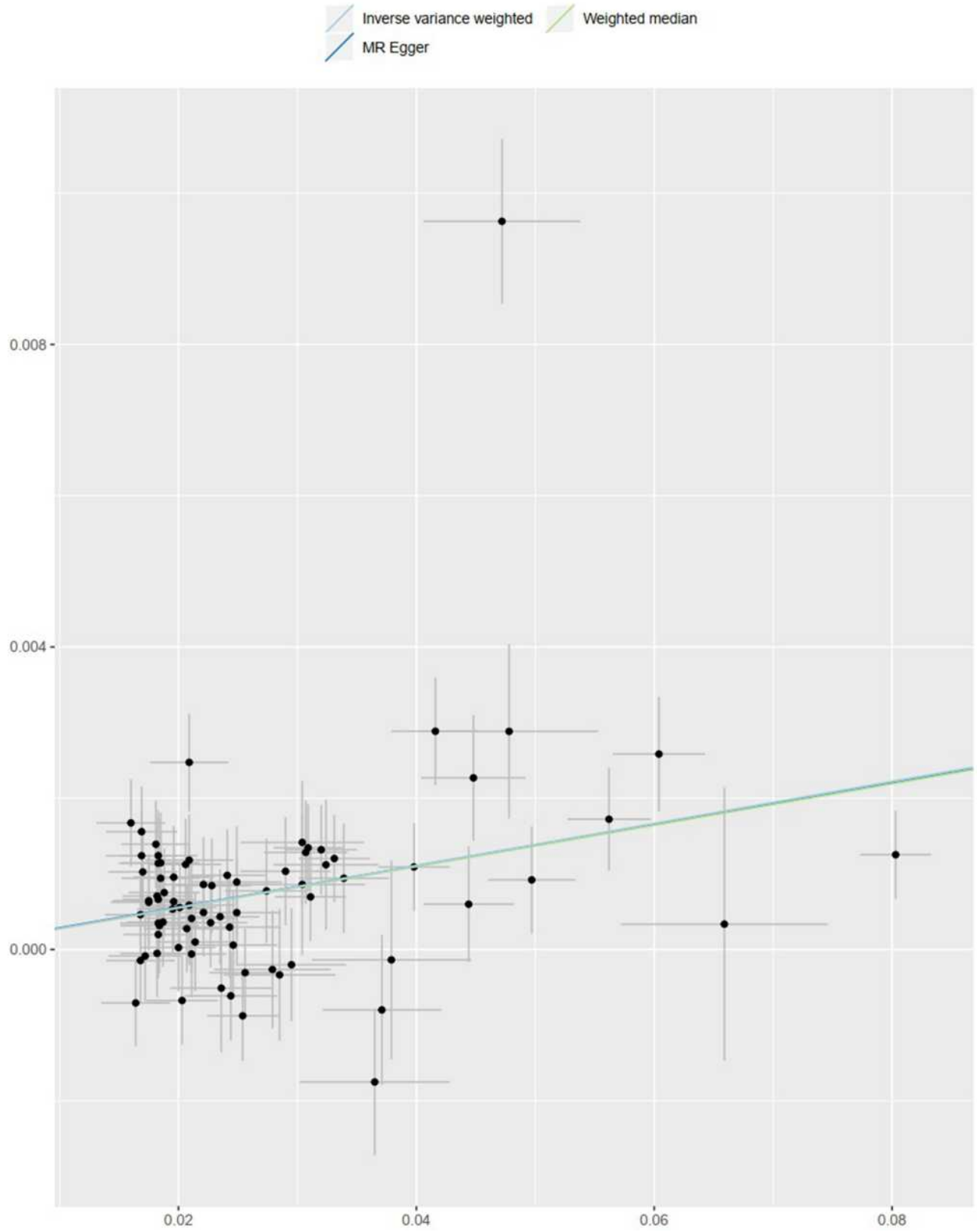

Figure 2 Scatter plot of SNPs associated with BMI and the risk of osteoarthritis. The plot presents the effect sizes of the SNP-BMI association (x-axis, SD units) and the SNP-osteoarthritis association (y-axis, log (OR)) with 95% confidence intervals. The regression slopes of the lines correspond to causal estimates using the three Mendelian randomization (MR) methods (the IVW method, weighted median estimator, and MR-Egger).

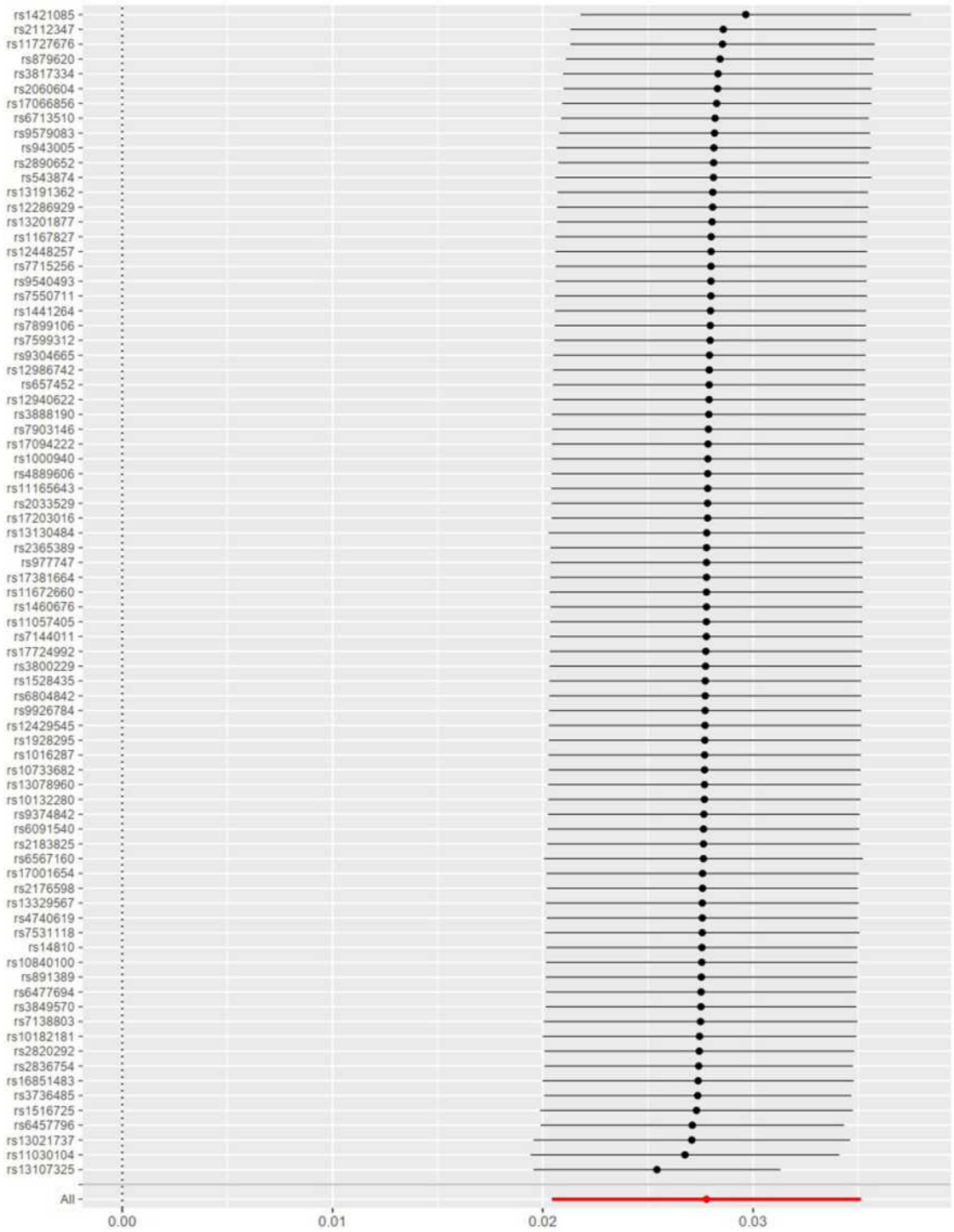

Figure 3 Leave-one-out of SNPs associated with BMI and their risk of osteoarthritis. Each black point represents result of the IVW MR method applied to estimate the causal effect of BMI on osteoarthritis excluding particular SNP (rs1000940, rs10132280, rs1016287, rs10182181, rs10733682, rs10840100, rs11030104, rs11057405, rs11165643, rs11672660, rs1167827, rs11727676, rs12286929, rs12429545, rs12448257, rs12940622, rs12986742, rs13021737, rs13078960, rs13107325, rs13130484, rs13191362, rs13201877, rs13329567, rs1421085, rs1441264, rs1460676, rs14810, rs1516725, rs1528435, rs16851483, rs17001654, rs17066856, rs17094222, rs17203016, rs17381664, rs17724992, rs1928295, rs2033529, rs2060604, rs2112347, rs2176598, rs2183825, rs2365389, rs2820292, rs2836754, rs2890652, rs3736485, rs3800229, rs3817334, rs3849570, rs3888190, rs4740619, rs4889606, rs543874, rs6091540, rs6457796, rs6477694, rs6567160, rs657452, rs6713510, rs6804842, rs7138803, rs7144011, rs7531118, rs7550711, rs7599312, rs7715256, rs7899106, rs7903146, rs879620, rs891389, rs9304665, rs9374842, rs943005, rs9540493, rs9579083, rs977747, and rs9926784) from the analysis. Each red point depicts the IVW estimate using all SNPs. No single SNP is strongly driving the overall effect of BMI on osteoarthritis in this leave-one-out sensitivity analysis.

osteoarthritis.[19,20] Hindy et al[19] used methods including independent sample traditional and multivariate MR, and two sample traditional and multivariate MR methods to explore the causal relationship between BMI and osteoarthritis. Their results showed that there was a causal relationship between high BMI and low LDL and osteoarthritis. However, the study population they investigated was mainly from Malmö Diet and Cancer Study, which contained 4,226 cases and 23,456 controls in 1991 to 1996. Instead, we used the GWAS data released in 2018, with 38,472 cases and 424,461 controls. The updated data and increased sample sizes increased the strengths of our study, which had more practical significance and statistical power to confirm the investigated causal relationship. Funck-Brentano et al[20] also found a causal relationship between high BMI and knee arthritis and hip arthritis through MR method, but not with hand arthritis. The conclusion of our study was similar to these two studies, but in addition to the use of updated data and a larger sample size, the methods we used for investigation were more rigorous since a sensitivity analysis using the method of leave-one-out was conducted and consistent results were observed.

The etiology of the causal effect of BMI on osteoarthritis is not completely clear. Some studies have suggested that individuals with high BMI might be with increased joint load and therefore it accelerates the aging of the articular surface, leading to the occurrence and aggravation of osteoarthritis.[21] In addition, obesity can induce the development of inflammation by increasing the intermediates produced by lipid metabolism, leading to osteoarthritis.[22] However, more researches are need for further study.

Our study had some strengths. First, the MR method was used in the study, and therefore confounding factors and reverse causality were well controlled, at least to a great extent. Second, the study was based on data from published GWAS researches and GWAS meta-analyses, with a large sample size and genetic variations. However, the study also had some limitations. First, genetic polymorphisms are difficult to validate, and even if we used the MR-Egger method, misclassification in genetic polymorphisms cannot be completely ruled out. Second, the GWAS dataset of BMI used in this study was based on a mixed population, while the population from which the data of osteoarthritis was derived was European. This might lead to the bias from population stratification, and it remains unknown whether the result can be directly applied to other populations, which warrants further investigations. Third, there might be over-identification in the two-sample MR study, which may overestimate the association between SNP and exposure.[23]

Conclusion

This study indicated that high BMI might be causally associated with increased risk of osteoarthritis, which supports the importance of weight control for the prevention and treatment of osteoarthritis. Further researches are needed to explore the underlying mechanisms of this causal relationship.

Compliance with Ethical Guidelines

This article does not contain any studies with human participants or animals performed by any of the authors.

Disclosure

The authors declare that they have no competing interests.

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