







ORIGINAL ARTICLE

Body mass index and colorectal cancer risk: A Mendelian randomization study

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Abbreviations: BBJ, Biobank Japan; BMI, body mass index; CRC, colorectal cancer; GWAS, genome-wide association study; HERPACC, Hospital-based Epidemiologic Research Program at Aichi Cancer Centre; IVW, inverse-variance weighted; J-CGE, Japanese Consortium of Genetic Epidemiology studies; J-MICC, Japan Multi-Institutional Collaborative Cohort Study; JPHC, Japan Public Health Centre-based Prospective Study; MR, Mendelian randomization; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; NAGANO, NAGANO hospital-based study; SNP, single nucleotide polymorphism.

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Abstract

Traditional observational studies have reported a positive association between higher body mass index (BMI) and the risk of colorectal cancer (CRC). However, evidence from other approaches to pursue the causal relationship between BMI and CRC is sparse. A two-sample Mendelian randomization (MR) study was undertaken using 68 single nucleotide polymorphisms (SNPs) from the Japanese genome-wide association study (GWAS) and 654 SNPs from the GWAS catalogue for BMI as sets of instrumental variables. For the analysis of SNP-BMI associations, we undertook a meta-analysis with 36 303 participants in the Japanese Consortium of Genetic Epidemiology studies (J-CGE), comprising normal populations. For the analysis of SNP-CRC associations, we utilized 7636 CRC cases and 37 141 controls from five studies in Japan, and undertook a meta-analysis. Mendelian randomization analysis of inverse-variance weighted method indicated that a one-unit (kg/m^2) increase in genetically predicted BMI was associated with an odds ratio of 1.13 (95% confidence interval, 1.06-1.20; P value $<.001$) for CRC using the set of 68 SNPs, and an odds ratio of 1.07 (1.03-1.11, 0.001) for CRC using the set of 654 SNPs. Sensitivity analyses robustly showed increased odds ratios for CRC for every one-unit increase in genetically predicted BMI. Our MR analyses strongly support the evidence that higher BMI influences the risk of CRC. Although Asians are generally leaner than Europeans and North Americans, avoiding higher BMI seems to be important for the prevention of CRC in Asian populations.

KEYWORDS

Asia, body mass index, colorectal cancer, epidemiology, Mendelian randomization

1 | INTRODUCTION

According to a 2018 worldwide report, CRC represents 10.2% of cancer incidence and 9.2% of cancer mortality.¹ The GLOBOCAN database² shows that the number of new cases and deaths from CRC are increasing rapidly, such that it is predicted to exceed 2.2 million new cases and 1.1 million deaths by 2030.³ To control this increasing disease burden, it is essential to explore approaches for the prevention of CRC.

To date, numerous observational studies have reported an association between higher BMI and increased CRC risk.⁴ However, these traditional observational studies possess certain inherent limitations like reverse causality and residual confounding. For example, early life environments,⁵ which could influence both adult BMI and CRC risk, were not adjusted in any of these studies, possibly

leading to residual confounding. Moreover, even with information on confounders, observational studies might yield biased results, as covariate adjustments need to be done with considerable caution. Although socioeconomic status and smoking behavior would be confounders of the BMI and CRC association, they could also act as mediators in the association; higher BMI could influence CRC through employment status⁶ or through smoking behavior.⁷ In such a case, adjusting for both factors fails to estimate the total effect of BMI on CRC.

To overcome these limitations, we used the MR analysis, which is currently gaining popularity. Mendelian randomization analysis regards gene variants as instrumental variables and exploits Mendel's second law or the law of independent assortment.⁸ The random allocation of genotypes at conception mimics natural, randomized, controlled study conditions, thus allowing observational studies to

overcome biases such as residual confounding and reverse causality.⁹ Although BMI is time-dependent and could decrease during the early stages of cancer,⁴ the use of BMI-associated gene variants as a proxy for BMI can help reflect the typical lifetime BMI and counteract reverse causality and misclassification issues arising from one-time point measurements.

Recent MR studies have suggested a positive association between BMI and CRC in Europeans.^{10,11} However, it is unclear if this association can be applied to other ethnicities like Asians, because the allele frequencies of SNPs vary widely across ethnicities,¹² and the prevalence and features of obesity are different across countries. Generally, Asians are leaner than Europeans and North Americans.¹³ However, they possess higher body fat for given body weight compared to White populations.¹⁴ Furthermore, Asians tend to develop diabetes at lower BMI values compared to Europeans.¹⁵ This could be attributed to their stronger glucose intolerance for a given BMI compared to other populations.¹⁶ Therefore, the interpretation of each BMI value and the biological mechanisms of obesity might not be the same across all populations. These heterogeneities between ethnicities warrant the need for an Asian population-specific MR study to evaluate the association between BMI and CRC.

We recently established the J-CGE, comprising normal Japanese populations. By using the data obtained from this large consortium and combining it with publicly available summary statistics-level data,¹⁷ we undertook the two-sample MR analyses and examined whether a genetically predicted higher BMI increased the CRC risk in Japanese populations.

2 | MATERIALS AND METHODS

Using two sets of instrumental variables, we carried out two-sample MR analyses. In the two-sample approach, SNPs of

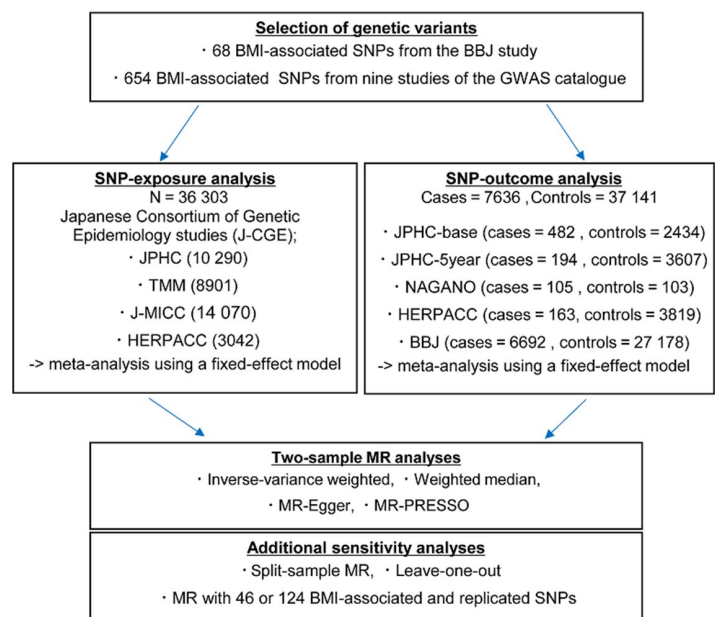
instrumental variables associated with exposure are examined in one dataset, and the associations of these SNPs with CRC are investigated in a separate dataset. The study design is depicted in Figure 1.

The MR analysis is a method that uses genetic variables, like SNPs, as instrumental variables. To obtain unbiased results, the instrumental variables used in the analysis must satisfy three assumptions: (a) the instrumental variable must be associated with the exposure (the relevance assumption), (b) the instrumental variable must not be associated with any confounder of the exposure-outcome association (the independent assumption) and, (c) given the exposure and confounders, the instrumental variable must be conditionally independent of the outcome (the exclusion restriction assumption).^{8,18} Concisely, the second and third assumptions indicate that no horizontal pleiotropy must occur. Pleiotropy is the phenomenon in which a single SNP affects multiple phenotypes.¹⁹ In the MR framework, pleiotropy includes two types, vertical and horizontal.^{18,20} In vertical pleiotropy, a single SNP influences the exposure and the other phenotypes in the pathway through exposure to the outcome (eg biomarkers); it is generally not problematic. In contrast, in horizontal pleiotropy, a single SNP not only influences the exposure but also influences phenotypes in other pathways without exposure to the outcome; it is a violation of the second and third assumptions. As the ability of SNPs to cause pleiotropy is not verifiable, we used several MR methods to relax these assumptions and assess the robustness.

2.1 | Data source for the selection of BMI-associated SNPs

In this study, we used two sets of SNPs as instrumental variables. First, we selected BMI-associated SNPs from a previous Japanese GWAS reported by the BBJ project.^{21,22} Among the

FIGURE 1 Study design. BBJ, Biobank Japan; BMI, body mass index; J-MICC, Japan Multi-Institutional Collaborative Cohort Study; JPHC, Japan Public Health Centre-based Prospective Study; JPHC-5 year, participants who did not respond to the baseline survey but responded to the 5-year follow-up survey in JPHC; JPHC-base, responders to the baseline survey in JPHC; MR, Mendelian randomization; NAGANO, NAGANO hospital-based study; SNP, single nucleotide polymorphism; TMM, Tohoku Medical Megabank Community-Based Cohort Study



SNPs reported, we identified 68 SNPs that had a P value of less than 5.0×10^{-8} at the discovery GWAS in the Japanese population (Table S1).

Second, on 29 July 2019, we undertook a search for the BMI-associated SNPs in the GWAS catalogue (<https://www.ebi.ac.uk/gwas/>) comprising all ethnic populations in strict criteria. Details of this selection is provided in Figure S1. Finally, we identified 654 SNPs (Table S2) from nine studies (Table S3), and used them in our study.

The coefficients (effect size of the SNP on BMI) of all selected SNPs were obtained from previous studies and compared with our coefficients. We encountered certain studies where all the obtained data were not reported in the manuscript. In such cases, we extracted the data that was publicly available on their websites. Furthermore, regardless of the statistical significance of the SNP-BMI associations in the J-CGE, all selected SNPs were included in sets of instrumental variables to overcome biases from false negatives arising from insufficient power²⁰ and from overfitting.²³

2.2 | Data source for the estimations of SNP effect on exposure

For the analysis of SNP-BMI associations, we used study data from the J-CGE and undertook a meta-analysis with 36 303 subjects. The J-CGE consisted of Japanese population-based and hospital-based studies: the Tohoku Medical Megabank Community-Based Cohort (TMM) Study ($n = 8901$), the JPHC Study ($n = 10\ 290$), the J-MICC Study ($n = 14\ 070$), and the HERPACC ($n = 3042$). The data obtained from these studies are summarized below the same protocol. In each study, the BMI was assessed at baseline through health check-ups (83%) or self-administered questionnaires. Although the question style differed in each study, the BMI was calculated as follows: weight (in kilograms) divided by the square of the height (in meters). All studies were approved by the respective institutional review boards. The characteristics of each study are described in Table S4.

2.3 | Data source for the estimations of SNP effect on outcome

For the analysis of SNP-CRC associations, we used individual-level data from the JPHC study, the NAGANO study, and the HERPACC study, and publicly available summary statistics-level data from a previous GWAS reported by the BBJ project.¹⁷ Briefly, these studies were all based on individuals of Japanese ancestry and included cases and controls from the JPHC case-cohort study-base (JPHC-base; 482 cases and 2434 controls), the JPHC case-cohort study-5 year (JPHC-5 year; 194 cases and 3607 controls), the NAGANO study (105 cases and 103 controls), the HERPACC study (163 cases and 3819 controls), and the BBJ study (6692 cases and 27 178 controls). All studies were approved by the respective institutional

review boards. For each study, the characteristics and ascertainment of CRC are described in Table S5.

2.4 | Statistical analysis

Meta-analysis was carried out on the study-level data and publicly available summary statistics-level data using the IVW method in a fixed-effect model, using META (version 1.7) or METAL,²⁴ and the overall SNP-exposure or SNP-outcome effect (coefficient) was calculated. Methods of association analysis and information on DNA-typing based on individual-level data are listed in Table S6.

We undertook the two-sample MR analyses to assess the association between BMI and CRC risk, using the MR-Base platform.²⁵ We used the IVW method as the main analysis to combine the ratio estimates of all BMI-associated SNPs on CRC, based on a fixed-effects model.²⁶ As our sets of instrumental variables consist of many SNPs, certain invalid SNPs that may not meet the MR assumption might have also been included in them. Therefore, to assess the robustness and to relax the assumptions, we used several MR methods: the funnel plot analysis, the leave-one-out analysis, and three other MR methods including weighted median,²⁷ MR-Egger,²⁸ and MR-PRESSO.²⁹ The weighted median method provides robust results even when the instruments include 50% invalid SNPs. The MR-Egger and MR-PRESSO methods examine the violation of the assumptions by testing the intercept of regression or the outlier SNPs.

Additionally, we also carried out split-sample MR analyses using the aforementioned methods for sensitivity analyses. Generally, two-sample MR analysis identifies SNPs associated with exposure in one dataset and investigates the association of these SNPs with the outcome in a separate dataset, to reduce the bias toward conventional observational analysis results^{30,31}; however, our exposure and outcome datasets showed slight overlap of samples. Therefore, we used the split-sample MR analyses as the sensitivity analyses to remove sample overlap bias.^{32,33} Our split-sample MR design is depicted in Figure S2.

Furthermore, for additional sensitivity analyses, we excluded the unreplicated SNPs from the set of 68 or 654 selected SNPs and conducted MR analyses using 46 or 124 replicated SNPs. We did not utilize estimates from previous GWAS reports of BMI-associated SNPs because there is a possibility of the overestimation of SNP-BMI associations (called winner's curse) in the GWAS discovery stage, which could lead to the underestimation of MR results.^{34,35} However, analysis of the SNP effect on BMI in the normal Japanese populations of J-CGE revealed that some of the SNPs used as instrumental variables were not significant. Therefore, we carried out analyses with the replication criteria, using the same directions of SNP-exposure effects between the J-CGE and previous studies, and P value less than .05 in the J-CGE.

Power calculations for MR analysis are presented in Table S7, suggesting that this study possessed the power to detect the association. Thresholds for nominal significance were set at a P value less than .05. Statistical analyses were carried out using SAS (version 9.4) or R (version 3.5.2), with the TwoSampleMR and MR-PRESSO packages.

TABLE 1 Mendelian randomization (MR) analyses of body mass index (BMI) and colorectal cancer (CRC) risk

MR methods	68 SNPs						654 SNPs					
	Two-sample MR			Split-sample MR			Two-sample MR			Split-sample MR		
	OR ^a	(95% CI)	P value	OR ^a	(95% CI)	P value	OR ^a	(95% CI)	P value	OR ^a	(95% CI)	P value
IVW	1.13	(1.06-1.20)	<.001	1.10	(1.04-1.17)	.001	1.07	(1.03-1.11)	.001	1.06	(1.02-1.09)	.001
MR-Egger	1.11	(0.99-1.24)	.07	1.13	(1.03-1.25)	.012	1.08	(1.02-1.15)	.013	1.04	(0.99-1.09)	.157
Weighted median	1.17	(1.07-1.28)	<.001	1.16	(1.07-1.26)	<.001	1.11	(1.04-1.18)	.001	1.09	(1.04-1.14)	<.001
MR-PRESSO	1.13	(1.06-1.20)	<.001	NA			1.07	(1.03-1.11)	.001	NA		
MR-Egger test	Intercept (95% CI)		P value	Intercept (95% CI)		P value	Intercept (95% CI)		P value	Intercept (95% CI)		P value
Intercept test	0.002	(-0.009-0.012)	.72	-0.004	(-0.014-0.006)	.45	-0.001	(-0.004-0.002)	.68	0.002	(-0.001-0.005)	.27

Abbreviations: CI, confidence interval; IVW, inverse variance weighted; MR-Egger, Mendelian randomization-Egger; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; NA, not applicable; SNP, single nucleotide polymorphism.

^aOdds ratio (OR) are shown per a one-unit (kg/m²) increase in BMI.

3 | RESULTS

3.1 | Participant characteristics

The characteristics of the 36 303 participants of the J-CGE used in the SNP-exposure analysis are reported in Table S8. The proportion of female participants and the mean age ranged from 50.6% to 65.8% and 52.1 to 60.7 years, respectively. The mean BMI was between 22.7 and 23.8 kg/m².

The characteristics of the participants from the five studies included in the SNP-outcome analysis are reported in Table S9. There were 37 141 controls and 7636 CRC cases. The proportion of female participants and the mean age ranged from 37.0% to 62.3% and 52.1 to 66.9 years, respectively. Except for the data obtained from the publicly available summary statistics, the mean BMI was between 22.7 and 23.8 kg/m² in cases and 22.7 and 23.7 kg/m² in controls.

3.2 | Associations of SNP-BMI and SNP-CRC

Of the 68 BMI-associated SNPs selected from a previous Japanese GWAS, seven SNPs replicated at genome-wide significance levels (*P* value less than 5.0×10^{-8}), 19 SNPs reached the Bonferroni-corrected significance level (*P* value less than 7.35×10^{-4}), and 46 SNPs reached nominal significance association levels in our SNP-exposure analysis of the J-CGE (Table S10). Comparison of the direction of effect of our SNP-exposure analysis and the previous GWAS revealed a consistency in the effect direction for almost all SNPs (Figure S3).

Of the 654 BMI-associated SNPs from the GWAS catalogue of all ethnic populations, seven SNPs replicated at genome-wide significant levels, 18 SNPs attained the Bonferroni-corrected significance level (*P* value less than 7.64×10^{-5}), and 131 SNPs attained nominal significant levels in our SNP-exposure analysis of the J-CGE (Table S11). Comparison of the direction of effect of our SNP-exposure analysis and the GWAS catalogue revealed a high consistency between them (Figure S4).

In the J-CGE, the total explained variance in BMI was approximately 2.0% on a set of 68 SNPs and approximately 5.0% on the set of 654 SNPs (Tables S1 and S2).

The SNP-CRC associations estimated by using a fixed-effect meta-analysis of five studies are shown in Tables S10 and S11.

3.3 | Association between BMI and CRC in the MR framework

In the main MR analysis using the IVW method on 68 SNPs, a one-unit (kg/m²) increase in BMI was associated with an odds ratio of 1.13 (95% confidence interval, 1.06-1.20) for CRC (Table 1 and Figure 2). Sensitivity analyses consistently showed increased odds ratios for CRC for every one-unit (kg/m²) increase in BMI (Table 1

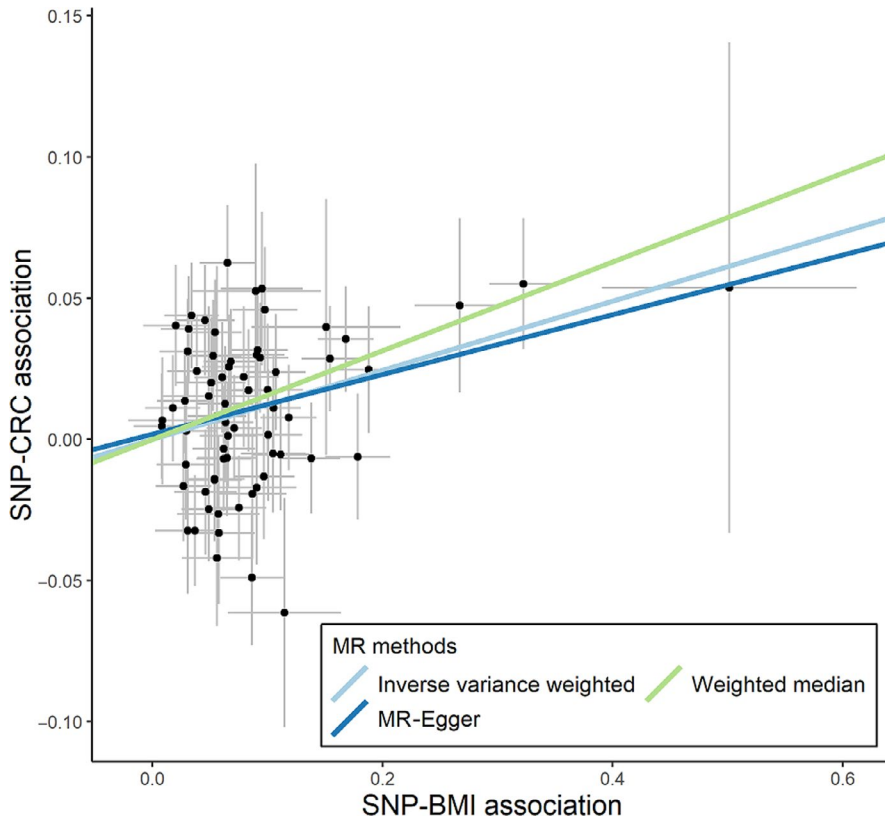


FIGURE 2 Scatter plot of single nucleotide polymorphism (SNP)-body mass index (BMI) associations against SNP-colorectal cancer (CRC) associations using 68 SNPs. MR, Mendelian randomization

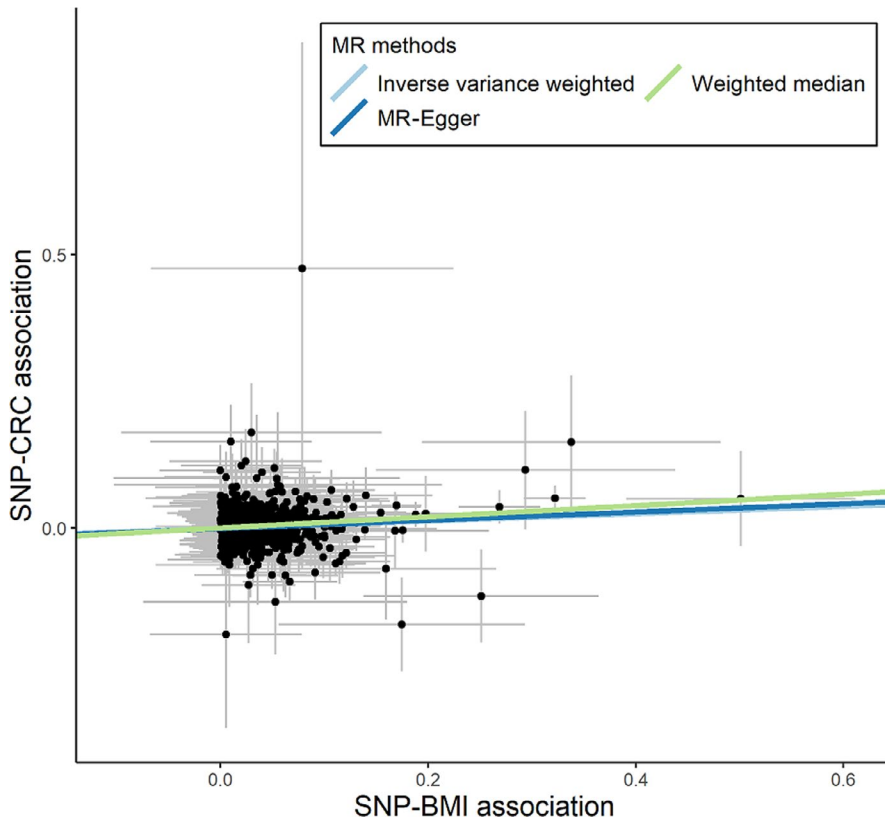


FIGURE 3 Scatter plot of single nucleotide polymorphism (SNP)-body mass index (BMI) associations against SNP-colorectal cancer (CRC) associations using 654 SNPs. MR, Mendelian randomization

and Figure 2). The odds ratios from the MR-Egger and weighted median were 1.11 (0.99-1.24) and 1.17 (1.07-1.28), respectively. The MR-Egger intercept *P* value was .72. Additionally, no outlier was

detected while using the MR-PRESSO method (Table S12), thus suggesting the absence of pleiotropic effect. Moreover, this symmetrical funnel plot of one divided by the standard error of the MR effects

against the MR effects of 68 individual SNPs indicated the absence of heterogeneity between the MR effects of each SNP and balanced pleiotropy (Figure S5).

Mendelian randomization analyses of 654 SNPs showed a slightly weaker association between BMI and CRC (IVW, 1.07 [1.03-1.11]; MR-Egger, 1.08 [1.02-1.15]; Egger-intercept *P* value, .68; weighted median, 1.11 [1.04-1.18]; MR-PRESSO, 1.07 [1.03-1.11]; Tables 1 and S12, Figure 3). The funnel plot showed a roughly symmetrical distribution (Figure S5), suggesting little evidence of estimates biased by pleiotropy.

Similar results were observed in the split-sample MR analyses, which were used to avoid sample overlap between the exposure and outcome datasets (Tables 1 and S13-S16). As the split-sample analyses yielded almost identical results, sample overlap bias was not a concern in this study. Furthermore, the application of restrictions to 46 or 124 replicated SNPs also showed similar results (Table S17 and Figure S6).

Finally, we assessed the impact of a potential outlier SNP using the leave-one-out analysis. We excluded one SNP from the instrument variables and applied the IVW method in turn. All analyses on the 68 SNPs and 654 SNPs showed consistent results (Tables S18 and S19).

4 | DISCUSSION

In this MR study, we showed that genetically predicted higher BMI was associated with an increased risk of CRC, using individual-level, study-level, and publicly available summary statistics-level data in Japanese populations. The results remained consistent despite strict variant selection, and across a variety of sensitivity analyses. To our best knowledge, this is the first study to provide evidence of a link between BMI and CRC risk using the MR framework in an Asian population. Importantly, the identified positive association between higher BMI and CRC risk is in line with the findings of previous MR studies in Europeans.^{10,11} In contrast to the differences in the distributions of SNPs¹² and BMI³⁶ across ethnicities, our findings seem to suggest that the MR estimates for the BMI-CRC association remain consistent across different ethnicities. Moreover, as this association was observed in a population of relatively low mean BMI, current findings could be important for the prevention of CRC.

The largest systematic review of seven million participants showed that the relative risk of a one-unit increase in BMI was 1.03 (95% confidence interval, 1.03-1.04).³⁷ With respect to the Asian populations, a prospective observational study of 300 000 Japanese participants reported that the adjusted hazard ratio for a one-unit increase in BMI was 1.03 (1.02-1.04) for male participants and 1.02 (1.00-1.03) for female participants.³⁸ Nevertheless, conventional observational studies have inherent limitations, such as residual confounding and reverse causation. Additionally, evidence from other approaches to pursue the causal relationship between BMI and CRC is sparse. Here, to evaluate that higher BMI influences increased risk of CRC, we undertook an MR study, which resulted in the positive

association. The magnitude of the association, identified through our MR study (odds ratio 1.13), was larger than that observed in conventional observational studies (odds ratio 1.03).³⁷ This difference of magnitude could be explained by the fact that genetically determined BMI is likely to reflect lifelong exposure.^{39,40} In fact, there is empirical evidence showing that the magnitude of the association for lifelong exposure to the risk of disease estimated by the MR approach is larger than that for the short-term exposure beginning later in life estimated by the randomized controlled trial.⁴¹ Considering the differences in the timing and duration of the exposure between the MR approach and other study designs, our MR estimates might have been inflated, to some extent, compared with the real-world effects. Although we believe our sets of instrumental variables satisfy three MR assumptions, another possibility is an overestimation due to the violation of the assumptions.

For the relevance assumption, only a part of the SNPs used as instrumental variables reached significant levels. However, as the explained variance in BMI in the study population was 2.0% and 5.0% on a set of 68 and 654 SNPs, respectively, we realized that our sets of SNPs were related to the BMI. For the independent assumption, the population structure could be a confounding factor in the association between BMI and CRC.⁹ Nevertheless, as the subjects were restricted to the Japanese population and our SNP-BMI and SNP-CRC analyses were adjusted for it using principal components, the population structure is unlikely to distort the results. For the exclusion restriction assumption, multiple BMI-associated SNPs affect other traits, a condition termed as horizontal pleiotropy. However, the results of MR-PRESSO and the weighted median method consistently showed the association. Furthermore, MR-Egger, the intercept of which could indicate the overall pleiotropy in the same way as small study bias in meta-analysis,²⁸ did not detect pleiotropy. Although each SNP might show a pleiotropy effect, in our sets of instrumental variables, the overall pleiotropy could be balanced and not introduce any bias on our estimates.^{28,42} In addition, the symmetrical distribution in the funnel plot supported balanced pleiotropy (Figure S5). For the study design, although the bias arising from slight sample overlap between the analyses of SNP-BMI and SNP-CRC associations could lead to overestimation,³¹ our results were robust for biases arising from the violation of the MR assumption or design.

A previous MR study from Europe showed the odds ratio of 1.50 (1.13-2.01) for every five-unit increase in BMI corresponding to the odds ratio of 1.08 (1.02-1.15) for every one-unit increase in BMI.¹⁰ Another European study showed an odds ratio of 1.26 (1.10-1.44) for every one-unit increase in BMI.¹¹ Apart from ethnicity, certain other differences also exist between the aforementioned studies and the current study. The current study has progressed one step ahead of the aforementioned MR studies. Neither of the previous studies considered sample overlap between SNP-BMI and SNP-CRC analyses, resulting in bias toward to non-null.³¹ In contrast, we used the split-sample analyses, a more robust method compared to the previously mentioned analysis methods, to evaluate the association between BMI and CRC. Second, we utilized two sets of instrumental variables for BMI. One was limited to the SNPs identified in

the Japanese population, which explained 2.0% (68 SNPs) in BMI variance. The other covered all SNPs identified in any ethnicity in order to obtain more precise estimates, which explained 5.0% (654 SNPs) of the variance. The latter explained variance was higher than the studies by Thrift et al (1.2%; 77 SNPs)¹⁰ or Jarvis et al (3.0%; 76 SNPs).¹¹

The strengths of the study include the harmonization of the MR framework and the identification of two sets of instrumental variables. For the SNP-BMI analysis, we used a common protocol and undertook a meta-analysis on normal Japanese populations. For SNP-CRC analyses, we used individual-level and publicly available summary statistics-level data of Japanese populations to obtain a relatively large sample size of non-Europeans. In addition, we systematically identified instrumental variables from multiple GWAS. We believe that this selection of a comprehensive set of SNPs makes our estimates precise.

Our study has also several limitations. First, similar to previous MR studies, we failed to exclude the possibility of violation of assumptions by the SNPs used as instrumental variables. Second, as we used the two-sample MR framework and assumed that BMI had a linear effect on CRC risk, we could not investigate whether the effect of BMI on CRC risk varies across the BMI range. Third, we could not access information on the histological and molecular subtype of the CRC. To assess complex pathological processes from adiposity to CRC,¹³ further epidemiological research is warranted. Finally, as Japanese populations possess different allele frequencies for the SNPs¹² compared to South Asians, the extrapolation of the study findings to other Asians populations might be limited. Further MR study is required for other populations as well.

Our findings add to the current body of evidence that obesity strongly influences the development of CRC. Many observational studies have reported the association between higher BMI and CRC. However, repeating the study by the same method is not enough to pursue the truth. To present the evidence confidently, the concept of triangulation, which is the practice of using multiple approaches to address one question, is useful. Each approach uses different unrelated assumptions that are likely to cause bias.^{43,44} As the development of CRC occurs over a period of time in obese individuals, randomized controlled studies are not feasible. Therefore, we undertook an MR study using genetically predicted BMI to improve the quality of evidence. However, the biological functions of many SNPs used as instrumental variables are not clear. Previous GWAS have reported that SNPs might play a role in the central nervous systems,^{21,45} whereas traditional studies have proposed three hormonal mechanisms—sex hormone hypothesis, insulin-IGF hypothesis, and inflammatory mediators and adipokine hypothesis—to explain the association between adiposity and cancer risk.^{46,47} Therefore, further experimental research is needed to elucidate the underlying mechanisms. This is essential to strengthen the confidence of the evidence.

In addition, this is the first MR study that evaluated the association between BMI and CRC among an Asian population. Of note, in recent years, the proportion of obesity^{36,48} and CRC incidence^{3,49}

is on the rise in Asian populations. Although Asians are leaner than Europeans and North Americans, Asians possess higher body fat for a given body weight compared to matched Caucasians.¹⁴ Moreover, they also have stronger tendency towards predominance of insulin resistance than other populations,^{16,50,51} thereby suggesting that Asians could be more likely to develop obesity-related diseases. Therefore, it is critical to reveal the association between BMI and CRC, and implement preventive strategies to avert obesity in Asians.

In conclusion, we found the positive association between genetically predicted BMI and CRC risk in an Asian population. This MR study strongly supports the role of higher BMI in the development of CRC. Although generally Asians are leaner than Europeans and North Americans, averting higher BMI could be important for the prevention of CRC in Asian populations.

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DISCLOSURE

All authors declare no conflict of interest.

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