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ORIGINAL ARTICLE

Genetic Obesity Variants and Risk of Conventional Adenomas and Serrated Polyps

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Abstract

Background Higher body mass index (BMI) is associated with increased risk of colorectal cancer. How genetically predicted BMI may be associated with colorectal cancer precursors is unknown.

Aims Our objective was to quantify the association of genetically predicted and measured BMI with risk of colorectal cancer precursors.

Methods We evaluated the association of genetically predicted and measured BMI with risk of conventional adenomas, serrated polyps, and synchronous polyps among 27,426 participants who had undergone at least one lower gastrointestinal endoscopy in the Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-up Study. Genetic risk score was derived from 97 BMI-related single nucleotide polymorphisms. Multivariable logistic regression evaluated each polyp subtype compared to non-polyps.

Results For conventional adenomas, the OR per 2-kg/m^2 increase was 1.03 (95% CI, 1.01–1.04) for measured BMI and 0.98 (95% CI, 0.88–1.10) for genetically predicted BMI; for serrated polyps, the OR was 1.06 (95% CI, 1.04–1.08) and 1.04 (95% CI, 0.90–1.20), respectively; for synchronous polyps, the OR was 1.10 (95% CI, 1.07–1.13) and 1.09 (95% CI, 0.89–1.34), respectively. Genetically predicted BMI was associated with synchronous polyps in women (OR = 1.37, 95% CI: 1.05–1.79).

Conclusion Genetically predicted BMI was not associated with colorectal cancer precursor lesions. The confidence intervals were wide and encompassed those for measured BMI, indicating that null findings may be due to insufficient power.

Keywords Colorectal cancer · Conventional adenoma · Serrated polyp · Body mass index (BMI) · Mendelian randomization

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Introduction

Colorectal cancer (CRC) is the third most common cancer in the United States and is associated with risk factors including physical inactivity dietary patterns, and increased body mass index (BMI) [1]. Although the observed association between increased BMI and CRC risk has been fairly consistent in prospective cohort studies, the association may vary among CRC subtypes and by biological sex. For example, in observational studies, BMI appears to be more strongly associated with CRC risk in men than women [1–3]. Recently, distinct subtypes of CRC have been established, and these subtypes are thought to arise from distinct precursor lesions: conventional adenomas and serrated polyps. In one study, BMI showed a much stronger association with serrated polyps than with conventional adenomas [4]. Other studies suggest that BMI is more strongly associated with microsatellite-instable CRC (compared to microsatellite-stable), which is more likely to develop from serrated polyps than conventional adenomas [5].

Evidence for the association between increased BMI and polyp subtypes is limited to observational studies. Mendelian randomization provides insight on disentangling the effects of predisposed obesity versus acquired obesity on CRC risk. We previously reported that genetic risk of obesity, derived from 97 established adult BMI-associated variants, correlated with BMI across all ages [6]. Genetic risk of BMI has been associated with risk of CRC using Mendelian randomization [7]. When stratified by sex, genetic risk of BMI was associated with CRC in women only, in contrast to studies of measured BMI [7]. The association between genetic risk of adulthood obesity and CRC precursor lesions has not yet been assessed and has the potential to improve the understanding of the influence of increased adiposity on heterogeneous CRC pathways.

The objective of this study was to evaluate the relationship between genetically predicted BMI and two distinct CRC precursor lesions (conventional adenomas and serrated polyps). We created a genetic risk score (GRS) using 97 previously identified SNPs that were associated with adult BMI. The association between GRS and risk of conventional adenomas or serrated polyps was evaluated among participants with genetic data in three large cohort studies: Nurses' Health Study (NHS), Nurses' Health Study II (NHS2), and Health Professionals Follow-up Study (HPFS). For comparison, we also assessed the associations for measured BMI in the same set of samples. To test for potential sex difference, we also performed the analysis in men and women separately.

Materials and Methods

Study Population

The NHS enrolled 121,700 registered female nurses, aged 30–55 (at enrollment), in 1976; the NHS2 enrolled 116,686 registered female nurses, aged 25–42, in 1989; and the HPFS enrolled 51,529 male health professionals, aged 40–75, in 1986. A subset of participants provided blood specimens: 32,826 NHS participants, between 1989 and 1990; 29,611 NHS2 participants, between 1996 and 1999; and 18,225 HPFS participants, between 1993 and 1995. Blood specimens were returned on ice packs by overnight courier.

The present study was limited to 37,661 participants with genetic information available from previous, nested genome-wide association studies (NHS, 18,498; NHS2, 8,274; HPFS, 10,889). After excluding participants who were of non-European origin; had a history of cancer (except non-melanoma skin cancer), colorectal polyps, or inflammatory bowel disease; or who had no reported endoscopies of the lower GI tract; a total of 27,436 participants (NHS, 13,103; NHS2, 6,494; HPFS, 7,839) were included in the present analysis.

The collection of detailed histological information on colorectal polyps began in 1992 for the NHS and HPFS, and 1991 for the NHS2; these years were used as baseline for the present study. Eligible participants were followed until first colorectal polyp diagnosis, death, or end of follow-up for the present study: June 1, 2012 for NHS, June 1, 2011 for NHS2, and January 1, 2010 for the HPFS.

Computation of GRS

Genotype data were derived from various nested studies within the NHS, NHS2, and HPFS studies. Details of genotyping and imputation of SNPs included in the GRS have been described elsewhere in detail [8]. Weighted GRS was calculated from 97 SNPs and relative effect size (β coefficient) identified as associated with adult BMI in the most recent genome-wide association study (GWAS) [9]. GRS was calculated using established methods, with an assigned value of 0, 1, or 2 for the number of risk alleles and the following equation: $\mathrm{GRS}=\left(\sum_{i=1}^{97}\beta_i * SNP_i\right) * \left(97/\sum_{i=1}^{97}\beta_i\right)$, where β_i is the regression coefficient identified in the GWAS. Sex-specific GRS was calculated using the sex-specific β_i [9].

Assessment of Exposure Variables

Measured BMI was calculated as the cumulative average of BMI based on self-reported height at baseline and self-reported weight from enrollment to polyp diagnosis or end of follow-up. Weight reported on the NHS questionnaires was validated among 140 NHS participants; self-reported and measured weights were highly correlated ($r = 0.97$), indicating that self-reported weight measurements are reasonably valid. Lifestyle characteristics were assessed by questionnaire at baseline and biennially via follow-up questionnaires. Food frequency questionnaires were administered every four years to assess dietary risk factors. Missing data for covariates during follow-up questionnaires were carried forward from the most recent available data.

Assessment of Outcomes

Every two years via follow-up questionnaire, participants reported whether they had undergone a colonoscopy or sigmoidoscopy, and whether any colorectal polyps had been diagnosed, during that two-year period. If a polyp diagnosis was reported, we requested permission to obtain the endoscopy and pathology reports. Investigators who were blinded to participants' exposures and genetic data reviewed the medical records and confirmed polyp diagnoses. Relevant clinical and pathological data were also extracted from the medical records [4].

In the present study, conventional adenomas included tubular, tubulovillous, and villous adenomas and adenomas with high-grade dysplasia. Serrated polyps included hyperplastic polyps and mixed/serrated adenomas. Mixed/serrated adenomas consisted of both mixed polyps (those with both adenomatous and hyperplastic changes in histology) and polyps with any serrated diagnosis (e.g., serrated adenomas, serrated polyps, and sessile serrated adenoma/polyp). Diagnosis of serrated polyp and conventional adenoma at the same endoscopy was considered a synchronous polyp.

Statistical Analyses

All analyses were conducted using three pooled cohorts and repeated separately in women (NHS, NHS2) and men (HPFS) to assess potential differences in the relationship between BMI and CRC risk by biologic sex. We evaluated measured BMI and genetically predicted BMI in relation to risk of polyp type (non-polyps, conventional adenoma only, serrated polyp only, and synchronous polyps). GRS was regressed on measured BMI to derive the change in GRS associated with a 2 kg/m^2 change in measured BMI.

Multivariable logistic regression was used to evaluate the risk of conventional, serrated, or synchronous polyps in relation to genetically predicted and measured BMI, compared to non-polyps. We also modeled the risk of conventional adenoma subtypes (non-advanced or advanced) and serrated polyp subtypes (small, < 10 mm; large, ≥ 10 mm) compared to non-polyps. Advanced conventional adenomas were defined as having at least 1 conventional adenoma of 10 mm or greater in diameter or with advanced histology (tubulovillous/villous histologic features or high-grade or severe dysplasia).

Effect modification by biologic sex (i.e., study cohort) was evaluated using Wald test for the product term. Heterogeneity among the polyp subtypes was assessed using multivariate regression in case-only analyses. To account for multiple records per participant and to handle time-varying covariates efficiently, we used an Andersen-Gill data structure with a new record for each 2-year follow-up period during which a participant underwent an endoscopy.

In a secondary analysis, the models were repeated with conventional adenomas, serrated polyps, and their subtypes with the inclusion of synchronous polyps in each subtype grouping. We also modeled the risk of polyp location (proximal colon, distal colon, or rectum) for conventional adenomas and serrated polyps. Polyps were classified as proximal if they were removed from the cecum to the transverse colon, distal if they were removed from the splenic flexure to the sigmoid colon, and rectal if they were removed from the rectosigmoid junction to the anal canal (excluding anal squamous cell carcinoma). Groupings by polyp location were not mutually exclusive; for example, one participant could have contributed both a proximal and distal conventional adenoma, or a proximal conventional adenoma and distal serrated polyp. In another secondary analysis, we assessed the polyp associations for each of the 97 individual SNPs included in the GRS. Bonferroni correction for multiple testing (adjusted $\alpha = 0.05/97 = 5.2 \times 10^{-4}$) was applied in this analysis.

Genetically predicted BMI models were adjusted for the following characteristics: age, study cohort (NHS, NHS2, HPFS; in pooled models only), time period of endoscopy (in 2-year intervals), reason for endoscopy (screening or symptoms), number of previous endoscopies, time in years since most recent endoscopy, and top three principal components for population structure (in order to account for systematic ancestry differences) [10]. Measured BMI models were adjusted for age, study cohort, time period of endoscopy, reason for endoscopy, number of previous endoscopies, time in years since most recent endoscopy, family history of colorectal cancer (yes or no), height, alcohol intake, regular aspirin use (yes or no), and physical activity. All covariates were treated as continuous variables unless otherwise noted.

Results

Among 27,436 participants with genetic data and outcomes available, there were a total of 2,952 participants with conventional adenomas only, 1,589 with serrated polyps only, and 790 with synchronous polyps. Genetically predicted BMI, measured BMI, and endoscopy-related characteristics are shown in Table 1. Participants with serrated polyps were more likely to be women. Serrated polyps and synchronous polyps both tracked with higher measured BMI. Participants with no polyps had a higher average number of endoscopies, longer time since most recent previous period endoscopy, and were less likely to report symptoms as the reason for endoscopy.

The median measured BMI was 1.7 kg/m^2 greater at the highest vs. lowest quintile of BMI genetic risk score (26.3 kg/m^2 compared to 24.6 kg/m^2), with a wide interval of measured BMI at each quintile (Fig. 1). An 18-unit increase in GRS was correlated with 2 kg/m^2 increase in measured BMI (R-squared = 0.02).

Measured BMI was significantly associated with risk of conventional adenomas (OR per 2 kg/m^2 increase = 1.03, 95% CI: 1.01–1.04), serrated polyps (OR = 1.06, 95% CI: 1.04–1.08), and synchronous polyps (OR = 1.10, 95% CI: 1.07–1.13) (Fig. 2, Online Resource 1). Among conventional

Table 1 BMI and endoscopy characteristics of pooled study participants from three cohort studies (NHS, NHS2, HPFS) by polyp diagnosis

	Polyp Type			
	Non-Polyps (n = 22 105)	Conventional Adenoma Only (n = 2952)	Serrated Polyp Only (n = 1589)	Synchronous Conventional Adenoma and Serrated Polyp (n = 790)
Adult BMI, genetic risk score	87.8 (6.2)[a]	87.8 (6.2)	87.9 (6.2)	88.0 (6.1)
Adult BMI, measured, kg/m^2	26.1 (4.7)[b]	26.3 (4.3)	26.7 (4.8)	27.1 (4.8)
Number of prior endoscopies	3.2 (2.0)	2.2 (1.6)	2.1 (1.5)	2.1 (1.6)
Time since most recent previous period endoscopy, years	3.0 (3.2)	2.6 (3.7)	2.4 (3.3)	2.2 (3.4)
Reason for endoscopy is symptoms, %	26.0	31.2	32.4	30.5
Female, %	73.8	56.8	72.8	57.5

BMI: body mass index, NHS: Nurses' Health Study, NHS2: Nurses' Health Study II, HPFS: Health Professionals Follow-up Study

[a]Values are mean (SD) for continuous variables, percentages for categorical variables

[b]n = 20 participants missing BMI, all non-polyps

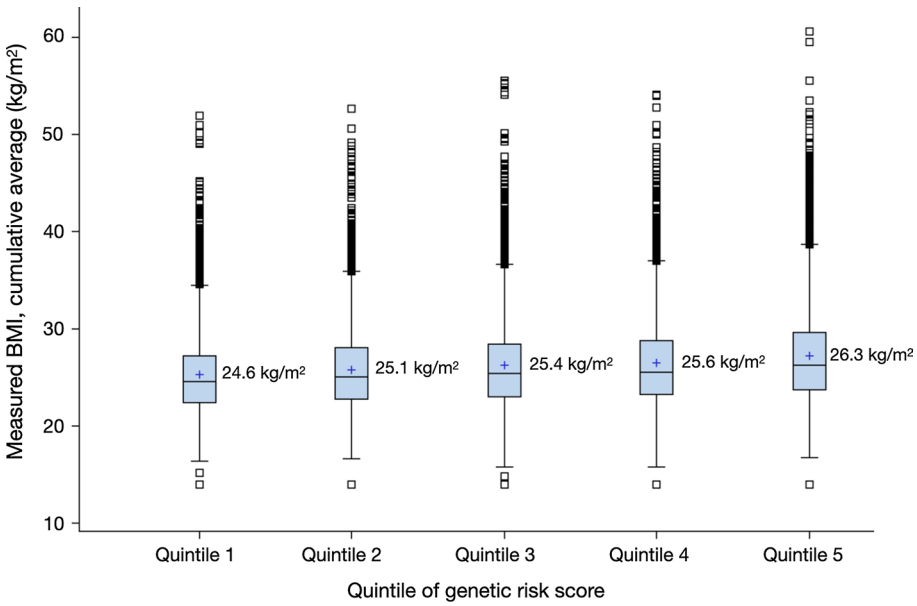

Fig. 1 Distribution of measured BMI according to quintiles of genetic risk score in three cohorts (NHS, NHS2, HPFS). Median value of measured BMI for each quintile is shown. BMI: body mass index, NHS: Nurses' Health Study, NHS2: Nurses' Health Study II, HPFS: Health Professionals Follow-up Study

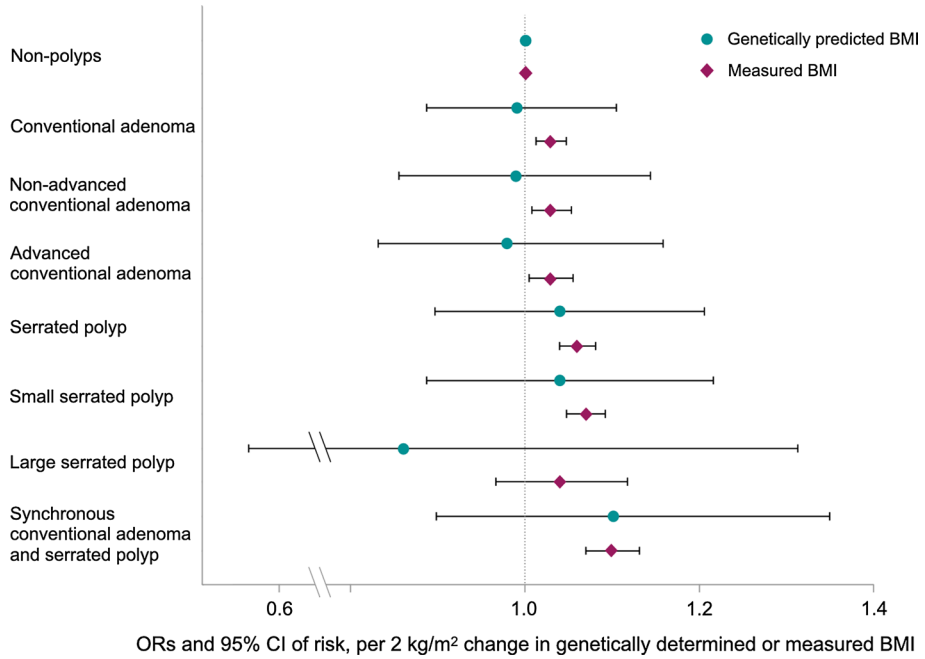

Fig. 2 Association between genetically predicted [a,b] or measured BMI [c] and risk of colorectal polyp subtypes in three cohort studies (NHS, NHS2, HPFS). BMI: body mass index, NHS: Nurses' Health Study, NHS2: Nurses' Health Study II, HPFS: Health Professionals Follow-up Study. [a] An 18-unit change in genetic risk score is equivalent to a 2 kg/m^2 change in measured BMI, per regression analysis. [b] Genetically predicted BMI multivariable logistic regression model adjusted for age, study cohort (NHS, NHS2, HPFS), time period of endoscopy (in 2-year intervals), reason for endoscopy (screening or symptoms), number of previous endoscopies, time in years since most recent endoscopy, and top three principal components for population structure. All covariates were treated as continuous variables unless otherwise noted. [c] Measured BMI multivariable logistic regression model adjusted for age, study cohort (NHS, NHS2, HPFS), time period of endoscopy (in 2-year intervals), reason for endoscopy (screening or symptoms), number of previous endoscopies, time in years since most recent endoscopy, family history of colorectal cancer (yes or no), height, alcohol intake, regular aspirin use (yes or no), and physical activity. All covariates were treated as continuous variables unless otherwise noted

adenoma subtypes, measured BMI was associated with increased risk of non-advanced adenomas (OR = 1.03, 95% CI: 1.01–1.05) and advanced adenomas (OR = 1.02, 95% CI: 0.99–1.04). Among serrated polyp subtypes, measured BMI was associated with increased risk of small polyps (OR = 1.06, 95% CI: 1.04–1.08) and large polyps (OR = 1.03, 95% CI: 0.96–1.11), although the large serrated polyps group had a smaller sample size and confidence interval included unity (Online Resource 1).

The association between genetically predicted BMI and polyp risk in the pooled cohorts was the same as measured BMI for serrated polyps (OR per 18 unit [equivalent to 2 kg/m^2] increase = 1.04, 95% CI: 0.90, 1.20) and synchronous polyps (OR = 1.09, 95% CI: 0.89, 1.34), although confidence intervals were wide and included unity (Fig. 2 and Online Resource 1). Test for heterogeneity showed that measured BMI was associated with a significantly higher risk of serrated polyps compared to conventional adenomas and significantly higher risk of synchronous polyps compared to conventional adenomas or serrated polyps alone. All other tests for heterogeneity were null. Including synchronous polyps in the conventional adenoma and serrated polyp groups did not change the association with genetically predicted or measured BMI (Online Resource 2).

Table 2 shows the association between genetically predicted BMI or measured BMI and risk of colorectal polyp subtypes by polyp location, in the three pooled cohorts (NHS, NHS2, HPFS). Measured BMI was associated with increased risk of conventional adenomas and serrated polyps at all locations. Of the subtypes and locations, measured BMI was associated with serrated polyps of the proximal colon (OR = 1.07, CI: 1.04–1.10), distal colon (OR per 2 kg/m^2 increase = 1.07, 95% CI: 1.05–1.10), and rectum (OR = 1.08, 95% CI: 1.05–1.11). Genetically predicted BMI was also associated with increased risk of serrated polyps of the distal colon (OR per 18 unit [equivalent to 2 kg/m^2] increase = 1.07, CI: 0.90–1.28) and rectum (OR = 1.10, 95% CI: 0.91–1.34), although the confidence intervals were wide and included unity. All tests for heterogeneity were null.

No differences were found between men and women, with the exception of genetically predicted BMI and risk of synchronous polyps (P value for interaction = 0.04). Both genetically predicted BMI and measured BMI were associated with increased risk of synchronous polyps in women

Table 2 Association between genetically predicted or measured BMI and risk of colorectal polyps, by location, in three cohort studies (NHS, NHS2, HPFS)

	Genetically predicted BMI, per 2 kg/m^2 increase [a,b]	Measured BMI, per 2 kg/m^2 increase [c]
Conventional Adenoma		
Proximal Colon		
n	1921	1921
Mean (GRS or BMI)	87.8	26.6
OR (95% CI)	1.00 (0.88–1.15)	1.05 (1.03–1.07)
Distal Colon		
n	1843	1843
Mean (GRS or BMI)	87.7	26.5
OR (95% CI)	0.96 (0.84–1.11)	1.05 (1.03–1.07)
Rectum		
n	668	668
Mean (GRS or BMI)	87.9	26.4
OR (95% CI)	1.04 (0.83–1.30)	1.04 (1.01–1.08)
Serrated Polyp		
Proximal Colon		
n	762	762
Mean (GRS or BMI)	87.7	26.8
OR (95% CI)	0.95 (0.77–1.18)	1.07 (1.04–1.10)
Distal Colon		
n	1086	1086
Mean (GRS or BMI)	88.0	26.9
OR (95% CI)	1.07 (0.90–1.28)	1.07 (1.05–1.10)
Rectum		
n	855	855
Mean (GRS or BMI)	88.0	27.0
OR (95% CI)	1.10 (0.91–1.34)	1.08 (1.05–1.11)

BMI: body mass index, NHS: Nurses' Health Study, NHS2: Nurses' Health Study II, HPFS: Health Professionals Follow-up Study, GRS: genetic risk score,

[a] An 18-unit change in GRS is equivalent to a 2 kg/m^2 change in measured BMI, per regression analysis

[b] Genetically predicted BMI multivariable logistic regression model adjusted for age, study cohort (NHS, NHS2, HPFS), time period of endoscopy (in 2-year intervals), reason for endoscopy (screening or symptoms), number of previous endoscopies, time in years since most recent endoscopy, and top three principal components for population structure. All covariates were treated as continuous variables unless otherwise noted

[c] Measured BMI multivariable logistic regression model adjusted for age, study cohort (NHS, NHS2, HPFS), time period of endoscopy (in 2-year intervals), reason for endoscopy (screening or symptoms), number of previous endoscopies, time in years since most recent endoscopy, family history of colorectal cancer (yes or no), height, alcohol intake, regular aspirin use (yes or no), and physical activity. All covariates were treated as continuous variables unless otherwise noted

(genetically predicted BMI, OR per 18 unit [equivalent to 2 kg/m^2] increase = 1.37, 95% CI: 1.05–1.79; measured BMI, OR = 1.11, 95% CI: 1.07–1.14). Measured BMI, but not genetically predicted BMI, was associated with increased risk of synchronous polyps in men (genetically predicted BMI, OR = 0.88, 95% CI: 0.65–1.20; measured BMI, OR = 1.09, 95% CI: 1.03–1.16).

Tests for association between individual SNPs and risk of polyp subtypes at the adjusted α level revealed two SNPs that were inversely associated with synchronous polyp: rs11727676 (OR per 1-allele = 0.72, 95% CI: 0.61–0.84) and rs10132280 (OR = 0.83, 95% CI: 0.74–0.92). No individual SNPs were significantly associated with risk of conventional adenomas or serrated polyps. There were no significant associations between individual SNPs and polyps in men or women separately.

Discussion

In three cohorts of men and women, genetically predicted BMI was correlated with measured adulthood BMI. Measured BMI showed a positive association with risk of conventional adenoma, serrated polyp, and synchronous polyps. These associations tended to be stronger for serrated polyp and synchronous polyps compared to conventional adenoma. Genetically predicted BMI showed similar positive associations with risk of serrated and synchronous polyps; however, confidence intervals for genetically predicted BMI were wide and included unity. When stratified by sex, genetically predicted BMI was associated with increased risk of synchronous polyps in women only.

This is the first study to our knowledge to assess risk of CRC polyp subtypes in relation to BMI genetic risk score; thus, it is difficult to put these findings in the context of the literature. Several studies analyzed genetic BMI in relation to CRC diagnosis: all three found that genetic BMI was associated with increased risk of CRC overall [11, 12] and in women only, when stratified by sex [7]. Our finding that genetically predicted BMI was not significantly associated with CRC precursor lesions could be due to limited power in the present study, given that these other studies investigating CRC risk included 9,254 to 51,537 cases. It is not possible to draw conclusions from the present study regarding whether genetically predicted BMI is more strongly associated with CRC than CRC precursor lesions.

Our finding that measured BMI was associated most strongly with risk of serrated polyp and synchronous polyps is consistent with one other large study which analyzed measured BMI in relation to polyp subtypes in the same three cohorts (NHS, NHS2, HPFS), and found that BMI was most strongly associated with synchronous polyps compared to serrated polyp or conventional adenoma [4]. Prior studies have demonstrated an association between BMI and conventional adenoma and serrated polyp independently, but no other studies to our knowledge have compared the association between BMI and various polyp

subtypes [13, 14]. The association between increased BMI and serrated polyp risk is reasonable given that serrated polyps tend to be associated with other environmental factors related to inflammation, including smoking and alcohol consumption [4]. Inflammatory cytokines, which are increased in a state of excess adiposity, are hypothesized to contribute to the development of microsatellite-instable colorectal cancer [15, 16]. These microsatellite-instable cancers are more commonly developed in serrated polyps and more commonly found in women; thus, the inflammatory state of obesity may explain the association of increased adiposity with serrated as well as synchronous polyps, especially in women [5].

The significance of the relationship between BMI and synchronous polyps is unclear. Synchronous polyps were not associated with greater risk of progression to CRC, compared to conventional adenoma only, in a previous study, suggesting that synchronous polyp diagnosis is not necessarily predictive of a more advanced lesion [17]. In contrast to observational studies, which found increased CRC risk in association with BMI in men only, but consistent with Mendelian randomization studies, which found increased CRC risk in association with BMI in women only, we observed an association between genetically predicted BMI and synchronous polyps in women only [3, 12]. Genetically predicted BMI has been associated with adiposity across the lifespan, particularly in early life and therefore may capture the influence of early life adiposity [6, 18]. Interestingly, early life body fatness has been associated with higher CRC risk in women but not in men [19].

Our analysis of individual obesity-related SNPs showed no statistically significant associations of individual SNPs and conventional adenoma or serrated polyp. Another study evaluated the association between five individual *FTO* gene polymorphisms and colorectal neoplasia, and found no significant associations in Caucasians, consistent with our findings for individual BMI alleles in relation to serrated polyp or conventional adenoma [20]. Interestingly, we identified two SNPs which were inversely related to synchronous polyp risk: rs11727676 and rs10132280. SNP rs11727676 is associated with the *HHIP* (Hedgehog interacting protein) gene, which is hypothesized to be associated with increased subcutaneous fat with more favorable metabolic markers [9]. SNP rs10132280 is related to the *STXBP6* (syntaxin-binding protein 6) gene, which has previously been shown to be negatively correlated with lung adenocarcinoma [21]. No other studies to our knowledge have investigated individual obesity-related SNPs in relation to CRC precursor lesions or CRC risk.

The strengths of this study include the large cohort with prospective assessment of lifestyle factors, polyp documentation, and detailed histopathological information, which allowed for stratification of CRC precursor lesions by histology and location. We used a genetic risk score derived from 97 SNPs that have been associated with adult BMI to date. Despite the large sample size, the number of polyp cases was still relatively small for a Mendelian randomization study, and the non-significant findings for genetically predicted BMI and polyp subtypes may have been due to limited power.

In conclusion, in three large prospective cohorts of men and women, we found similar associations between measured or genetic BMI and CRC precursor lesions. Associations tended to be stronger for serrated and synchronous polyps, compared to conventional adenoma, in congruence with previous studies. Larger cohorts and meta-analyses would be helpful in elucidating the relationship between genetic risk of BMI and distinct CRC precursor lesions.

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Declarations

Conflict of interests All authors report no competing interests and/or relevant financial interests in this manuscript.

Ethics approval The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required.

Consent to participate Informed consent was obtained from all individual participants included in the study.

References

1. Johnson CM, Wei C, Ensor JE et al. Meta-analyses of Colorectal Cancer Risk Factors. *Cancer Causes Control* 2013;24:1207–1222.
2. Kobiela J, Wieszczy P, Reguła J et al. Association of obesity with colonic findings in screening colonoscopy in a large population-based study. *United European Gastroenterology Journal* 2018;6:1538–1546.

3. Frezza EE, Wachtel MS, Chiriva-Internati M. Influence of obesity on the risk of developing colon cancer. *Gut* 2006;55:285–291.
4. He X, Wu K, Ogino S et al. Association Between Risk Factors for Colorectal Cancer and Risk of Serrated Polyps and Conventional Adenomas. *Gastroenterology* 2018;155:355-373.e18.
5. Hoffmeister M, Blaker H, Kloor M et al. Body Mass Index and Microsatellite Instability in Colorectal Cancer: A Population-based Study. *Cancer Epidemiology Biomarkers & Prevention* 2013;22:2303–2311.
6. Song M, Zheng Y, Qi L et al. Longitudinal Analysis of Genetic Susceptibility and BMI Throughout Adult Life. *Diabetes* 2018;67:248–255.
7. Thrift AP, Gong J, Peters U et al. Mendelian Randomization Study of Body Mass Index and Colorectal Cancer Risk. *Cancer Epidemiology Biomarkers & Prevention* 2015;24:1024–1031.
8. Hunter DJ, Kraft P, Jacobs KB et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. *Nat Genet* 2007;39:870–874.
9. Locke AE, Kahali B, Berndt SI et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015;518:197–206.
10. Price AL, Patterson NJ, Plenge RM et al. Principal components analysis corrects for stratification in genome-wide association studies. *Nature Genetics* 2006;38:904–909.
11. Gao C, Patel CJ, Michailidou K et al. Mendelian randomization study of adiposity-related traits and risk of breast, ovarian, prostate, lung and colorectal cancer. *Int J Epidemiol* 2016;45:896–908.
12. Jarvis D, Mitchell JS, Law PJ et al. Mendelian randomisation analysis strongly implicates adiposity with risk of developing colorectal cancer. *British Journal of Cancer* 2016;115:266–272.
13. Ben Q, An W, Jiang Y et al. Body Mass Index Increases Risk for Colorectal Adenomas Based on Meta-analysis. *Gastroenterology* 2012;142:762–772.
14. Bailie L, Loughrey MB, Coleman HG. Lifestyle Risk Factors for Serrated Colorectal Polyps: A Systematic Review and Meta-analysis. *Gastroenterology* 2017;152:92–104.
15. Colotta F, Allavena P, Sica A et al. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 2009;30:1073–1081.
16. Schmidt FM, Weschenfelder J, Sander C, et al. Inflammatory Cytokines in General and Central Obesity and Modulating Effects of Physical Activity. *PLoS One*; 10. Epub ahead of print 17 March 2015. https://doi.org/10.1371/journal.pone.0121971.
17. He X, Hang D, Wu K, et al. Long-term Risk of Colorectal Cancer After Removal of Conventional Adenomas and Serrated Polyps. *Gastroenterology*. Epub ahead of print July 2019. https://doi.org/10.1053/j.gastro.2019.06.039.
18. Garcia H, Song M. Early-life obesity and adulthood colorectal cancer risk: a meta-analysis. *Rev Panam Salud Publica*; 43. Epub ahead of print 4 January 2019. https://doi.org/10.26633/RPSP.2019.3.
19. Zhang X, Wu K, Giovannucci EL, et al. Early Life Body Fatness and Risk of Colorectal Cancer in U.S. Women and Men--Results from Two Large Cohort Studies. *Cancer Epidemiology Biomarkers & Prevention* 2015; 24: 690–697.
20. Nock NL, Plummer SJ, Thompson CL et al. FTO polymorphisms are associated with adult body mass index (BMI) and colorectal adenomas in African-Americans. *Carcinogenesis* 2011;32:748–756.
21. Lenka G, Tsai M-H, Lin H-C, et al. Identification of Methylation-Driven, Differentially Expressed STXBP6 as a Novel Biomarker in Lung Adenocarcinoma. *Sci Rep*; 7. Epub ahead of print 15 February 2017. https://doi.org/10.1038/srep42573.