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Full title - Adult Body Mass Index and Risk of Ovarian Cancer by Subtype:**A Mendelian Randomization Study****Short title - BMI and Ovarian Cancer Risk by Subtype**

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Abstract

Background: Observational studies have reported a positive association between body mass index (BMI) and ovarian cancer risk. However, questions remain as to whether this represents a causal effect, or holds for all histologic subtypes. The lack of association observed for serous cancers may for instance be due to disease-associated weight loss. Mendelian randomization (MR) uses genetic markers as proxies for risk factors to overcome limitations of observational studies. We used MR to elucidate the relationship between BMI and ovarian cancer, hypothesising that genetically-predicted BMI would be associated with increased risk of non-high grade serous ovarian cancers (non-HGSC) but not HGSC.

Methods: We pooled data from 39 studies (14 047 cases, 23 003 controls) in the Ovarian Cancer Association Consortium. We constructed a weighted genetic risk score (GRS, partial F-statistic=172) summing alleles at 87 single nucleotide polymorphisms previously associated with BMI, weighting by their published strength of association with BMI. Applying two-stage predictor-substitution MR, we used logistic regression to estimate study-specific odds ratios (OR) and 95% confidence intervals (CI) for the association between genetically-predicted BMI and risk, and pooled these using random-effects meta-analysis.

Results: Higher genetically-predicted BMI was associated with increased risk of non-HGSC (pooled-OR=1.29, 95%CI 1.03-1.61 per 5 units BMI) but not HGSC (pooled-OR=1.06, 95%CI 0.88-1.27). Secondary analyses stratified by behaviour/subtype suggested that, consistent with observational data, the association was strongest for low-grade/borderline serous cancers (OR=1.93, 95%CI 1.33-2.81).

Conclusions: Our data suggest that higher BMI increases risk of non-HGSC, but not the more common and aggressive HGSC subtype, confirming the observational evidence.

KEY WORDS (MEDICAL SUBJECT HEADINGS): Body mass index; Obesity; Ovarian neoplasms; Mendelian randomization analysis.

Key Messages

- Observational studies had reported a positive association between BMI and overall risk of ovarian cancer, but it was unclear whether the observed differences by subtype—no association for serous cancers but an association for the other subtypes—were meaningful, and whether the observed associations represent a causal effect.
- We used Mendelian randomization to clarify the relationship between BMI and risk of ovarian cancer.
- Our study provides the clearest evidence to date that obesity increases risk of non-high grade serous ovarian cancer (non-HGSC) for women of European ancestry.
- Our results also support the absence of a relationship between BMI and risk of the more aggressive high-grade serous ovarian cancers (HGSC), confirming evidence from previous observational studies.
- This study confirms the clinical relevance of elevated BMI to risk of some subtypes of ovarian cancer, thus interventions to reduce obesity may alleviate the worldwide burden from non-HGSC.

Introduction

Observational studies including two recent large pooled analyses have reported a positive association between body mass index (BMI) and risk of ovarian cancer.^{1,2} In both, the association was observed only for non-serous cancers. However, although the subtype-specific estimates reported by the two pooled analyses were very similar,^{1,2} the authors reached different conclusions about whether the differences by subtype were meaningful. Potentially, the lack of association seen for invasive serous ovarian cancer, the most aggressive subtype accounting for 62% of adenocarcinomas,³ could result from reverse causality because of disease-associated weight loss before diagnosis. Furthermore, given the potential for biases and confounding in observational studies, the observed association with non-serous ovarian cancer might not reflect a causal effect. Mendelian randomization (MR) has the potential to overcome these limitations by using genetic markers as proxies (instrumental variables [IVs]) for conventionally-measured traits in observational studies.⁴ We used MR to clarify the relationship between BMI and risk of ovarian cancer, using data from the international Ovarian Cancer Association Consortium (OCAC). Based on existing data and the current understanding that low- and high-grade serous ovarian cancers (HGSC) represent distinct entities,⁵ our *a priori* hypothesis was that genetically-predicted BMI would be associated with increased risk of non-HGSC but not HGSC.

Methods

Study population and data available

We pooled data from 39 OCAC studies⁶ which included 14 047 cases and 23 003 controls, all of whom had >90% European ancestry and were genotyped via the Collaborative Oncological Gene-Environment Study.⁷ Twenty-two studies were population-based and 17 were clinic- or family registry-based. Nine case-only studies were grouped with case-control studies in the same region (Table 1; Supplementary Table S1). Cases included women with primary ovarian, fallopian tube or peritoneal cancer. All studies provided demographic data and tumour characteristics (site, behaviour, grade, FIGO (Fédération Internationale de Gynécologie Obstétrique)/SEER (Surveillance, Epidemiology and End Results program) stage, and histology). A subset provided lifestyle data for >50% of their participants, including usual weight one or five years before diagnosis (cases) or interview (controls), adult height, parity, oral contraceptive (OC) use, family history of cancer, education, smoking, menopausal status, and hormone replacement therapy (HRT) use.

(Table 1 here)

Outcome variables

For primary analysis, we classified cases as invasive HGSC, invasive non-HGSC, and borderline (low malignant potential). The HGSC group (n=7933) included all invasive serous cancers except low-grade (G1) (n=469). We classified invasive serous cancers of unknown grade (n=1452) and primary peritoneal cancers of unknown behaviour (n=44) as HGSC because in both instances the majority would be HGSC. The non-HGSC-group (n=4434) included G1 serous cancers and all invasive mucinous, endometrioid, and clear cell cancers. The third group included borderline tumours (n=1680) of any histology.

For secondary analysis by cancer site, we subdivided HGSC into ovarian/fallopian tube and primary peritoneal cancers. Two studies (AUS, SRO), where <20% of women with peritoneal tumours were genotyped, were excluded from peritoneal analyses. For secondary analysis by histologic subtype/behaviour, we divided the non-HGSC and borderline groups into four sub-categories: invasive low-grade and borderline serous cancers; invasive and borderline mucinous cancers; invasive endometrioid cancers; and invasive clear cell carcinomas.

Genetic risk score

Samples were genotyped using a custom-designed Illumina genotyping array (iCOGS) comprising over 200 000 single nucleotide polymorphisms (SNPs).⁷ Genotyped SNPs that were not in Hardy-Weinberg equilibrium, or with discordant duplicate samples or call rates <95 or 99% (depending on SNP minor allele frequencies [MAF]), were excluded.⁷ Approximately fifteen million additional SNPs were imputed from measured genotypes using 1000 Genome Project data.^{7,8}

We used 87 of 97 loci reported to be associated with BMI in a meta-analysis of genome-wide association studies conducted by the Genetic Investigation of ANthropometric Traits (GIANT) Consortium (Supplementary Table S2).⁹ We excluded three loci which were associated with BMI only among men in the GIANT analysis, and seven loci where the GIANT SNP was not genotyped on iCOGS, and was imputed with a quality score (estimated correlation between imputed and true genotype, r^2) of <0.6 in our data. Overall, 12 selected SNPs were genotyped and 75 imputed. We used imputed genotype probabilities where genotyped values were missing (<0.7%, all genotyped SNPs). We constructed a weighted genetic risk score (GRS) for BMI by summing alleles associated with higher BMI across the 87 SNPs, assuming additive effects based on evidence from GIANT.⁹ We weighted alleles by β -coefficients for their association with BMI reported by GIANT investigators. All MAFs were >5% in controls (except for two SNPs with MAFs of 4.7% and 2.8%), and were consistent with GIANT data.

Statistical analysis

We examined associations between the GRS and potential confounders of the BMI-ovarian cancer relationship using chi-square statistics or analysis of variance, stratified by study. In a two-stage predictor-substitution MR approach using individual-level data,^{10,11} we used multivariable logistic regression to model case-control status on BMI predicted by the GRS within each study. First, we predicted BMI from the GRS by using linear regression in 10 085 controls from 16 studies with BMI data available for >50% of women. The model regressed BMI on the GRS, adjusting for age and the first five principal components from a principal-components analysis in European-ancestry OCAC participants.⁷ We applied the results of this model to predict BMI from the GRS for the whole study population (14 047 cases and 23 003 controls). In the second stage, we used logistic regression to determine the association between case-control status and this genetically-predicted BMI, adjusted for age and the principal components. As MR is relatively new with multiple approaches proposed, we also tested alternative methods including the control function estimator (adjusting for residual variation in BMI not predicted by the GRS),^{10,12} the sub-sample estimator,¹³ and inverse-variance weighted and likelihood-based MR (combining summary data across SNPs).¹⁴ The resulting odds ratios (ORs) and 95% confidence intervals (CI) were very similar to those from our primary analysis, and so are not reported here. The robust standard errors obtained using seemingly unrelated regression and the delta method¹³ were identical to those estimated in our primary analysis.

For the primary analyses, study-specific IV-estimates per 5-unit increase in genetically-predicted BMI were pooled to generate odds ratios (pOR) and 95% CI using random-effects meta-analysis.^{15,16} We also compared HGSC and non-HGSC directly in a single pooled model comparing HGSC vs. non-HGSC cases, stratified by study. We examined inter-study heterogeneity of the association between the GRS and ovarian cancer risk by inspecting Cochran's I^2 and p -values for heterogeneity.¹⁷

We conducted sensitivity analyses including: removing two studies where MAFs for 27 or more SNPs (>30%) exceeded two standard deviations from the mean; restricting the GRS to 56 SNPs with imputation quality scores ≥ 0.9 ; using a single-SNP instrument in the locus explaining most variation (*FTO*); and weighting the GRS using published β -coefficients for SNP associations with BMI in women.⁹ We also conducted MR-Egger regression¹⁸ to assess the robustness of our findings to pleiotropy.

Secondary analyses by tumour site and behaviour/histology were conducted using single models stratified by study, to maximise power. Similarly, we explored whether menopausal status or HRT use modified the relationship by conducting stratified models (women grouped as: pre-/peri-menopausal; postmenopausal without HRT; postmenopausal with HRT). Information on menopausal status and HRT use was available for 21 938 women (59.2%) from 19 studies. Among 16 studies with BMI and confounder data, we conducted traditional epidemiologic analysis modelling case-control status on

BMI, adjusted for age, parity, OC use, HRT use, and family history of ovarian or breast cancer, stratified by study, for comparison with IV-estimates among the same women.

Analyses were conducted using SAS9.2 (SAS Institute Inc., Cary, NC) and STATA13.0 (StataCorp LP, College Station, TX) software. This analysis and each contributing study received approval from the appropriate institutional review board or equivalent committee. All participants provided written informed consent.

Results

Population characteristics

The 39 studies were conducted in Europe, North America, and Australia (Table 1) and included 12 367 women with invasive cancer, 1680 with borderline tumours (from 20 studies), and 23 003 control women. The median diagnosis year was 2003, with 74.4% of cases diagnosed after 2000. Participants were aged between 18 and 92 (median 57) years. Median BMI ranged from 23.6 to 27.4 kg/m² across 16 studies with these data, and was 25.0 (interquartile range 22.3-29.1) kg/m² for controls and 25.4 (22.4-29.8) kg/m² for cases ($p<0.001$). Mean age varied by histologic subtype: women with HGSC were older, and women with low-grade or borderline serous cancers younger, than controls (Supplementary Table S3). Compared with controls, a higher proportion of cases (all subtypes combined) was obese (BMI>30kg/m², $p<0.001$).

Characteristics of the genetic risk score

The GRS was normally distributed among OCAC controls. GRS values ranged from 9.11 to 15.88 (median 12.62; interquartile range 12.01-13.23). Alone, the GRS explained 1.6% of variance in BMI among OCAC controls. After adjusting for age and principal components, the GRS explained 3.0% (partial R²=1.7%) (first-stage regression partial F-statistic=172.0, $p<0.001$). A 1-unit increase in GRS was associated with a 0.8 kg/m² increase in BMI. Average BMI was 1.9 kg/m² higher in the highest GRS quartile than the lowest.

There was no evidence of inter-study heterogeneity ($I^2=32%$, p -heterogeneity=0.11) in the relationship between the 87-SNP GRS and BMI among controls, nor for the simplified 56-SNP ($I^2=28%$, p -heterogeneity=0.14) GRS, or *FTO* ($I^2=21%$, p -heterogeneity=0.22) (Supplementary Figure S1). While BMI was associated with potential confounders of the BMI-ovarian cancer association (including parity, OC use, and menopausal status, all $p<0.001$), the GRS was not (all $p>0.10$) (Supplementary Table S4). We also saw no substantial variation in GRS values by levels of potential confounders within individual studies.

The ORs (95%CI) for ovarian cancer per 1-unit increase in the GRS were 1.04 (1.01-1.08) for non-HGSC, 1.01 (0.98-1.04) for HGSC, and 1.05 (0.99-1.11) for borderline tumours.

Association between genetically-predicted BMI and primary outcomes

Higher genetically-predicted BMI was associated with increased risk of non-HGSC (pOR=1.29, 95%CI 1.03-1.61 per 5-unit predicted-BMI increase) but not HGSC (pOR=1.06, 95%CI 0.88-1.27) (Figure 1A and B; Table 2). The same pattern was seen for the simplified GRS comprising 56 SNPs (pOR=1.33 vs. 1.10 for non-HGSC and HGSC, respectively), and for *FTO* (pOR=1.51 vs. 0.88). Tests for heterogeneity between HGSC and non-HGSC gave $p=0.24$ and $p=0.23$ using the 87- and 56-SNP GRSs, respectively, and $p=0.046$ when we predicted BMI from *FTO* alone. The pooled-OR for borderline tumours was 1.28 (95%CI 0.86-1.90) (Figure 1C; Table 2).

(Table 2 here)

There was little evidence of inter-study heterogeneity in the association between genetically-predicted BMI and ovarian cancer risk (Figure 1A, B, C). Results were similar when we used female-specific weights (β -coefficients) published by GIANT,⁹ when we removed two SNPs with MAF <5%, and when we excluded two studies (HMO, HOC) with extreme MAFs for ≥ 27 SNPs. The association between BMI and non-HGSC, but not HGSC, was seen when we excluded family registry-based studies or case-only studies. Excluding eight studies with tumour grade unknown for >50% of invasive serous cases made little difference to HGSC results (pOR=1.04, 95%CI 0.86-1.27). The results from an MR-Egger test suggested no bias from pleiotropy ($p=0.9$ and $p=0.2$ comparing traditional MR and MR-Egger results for HGSC and non-HGSC, respectively).

For women with GRS, BMI, and confounder data, results of the conventional BMI analysis (Supplementary Table S5) and IV analysis (Table 2) were similar, although the association with non-HGSC was weaker (adjusted-OR=1.18, 95%CI 1.13-1.23 per 5 kg/m²) in the former, suggesting the true association might be stronger than that seen in conventional epidemiologic analyses.

Secondary outcomes

Secondary analyses stratifying HGSC by cancer site and subtype suggested that the lack of association with BMI might hold only for HGSC of the ovary and fallopian tube (Table 2). The estimate for HGSC of the peritoneum was elevated, but the CI was wide and crossed null (OR=1.77, 95%CI 0.91-3.43) (Table 2). For non-HGSC sub-categories, the strongest association was seen for invasive low-grade and borderline serous cancers (OR=1.93, 95%CI 1.33-2.81) and the weakest for endometrioid (OR=1.17, 95%CI 0.87-1.59) and mucinous (OR=1.18, 95%CI 0.84-1.67) cancers (Table 2) but the relatively small numbers (in the MR context) led to wide and overlapping confidence intervals.

The associations with HGSC and non-HGSC did not vary substantially by menopausal status or combined menopausal status/HRT use. The association between genetically-predicted BMI and non-HGSC was slightly stronger for premenopausal women (OR=1.62, 95% CI 0.88-3.01) compared to postmenopausal HRT users (OR=1.26, 95% CI 0.57-2.82) and non-users (OR=1.17, 95% CI 0.61-2.24).

Discussion

Having established the GRS as an appropriate instrument for BMI in our sample, we used this to assess the relationship between BMI and ovarian cancer risk for women of European ancestry. Our data suggest a likely causal effect of BMI on risk of non-HGSC, but do not support an association with the more common HGSC subtype. Secondary analyses had limited power so CI were wide, however they suggested that the association was strongest for low-grade/borderline serous cancers, that higher BMI might increase risk of HGSC of the peritoneum, and that the association with non-HGSC might be stronger for premenopausal women.

Ovarian cancer is a heterogeneous disease: the separate histologic subtypes display distinct molecular profiles and have different risk factors.^{19,20} Our primary findings for genetically-predicted BMI are consistent with results of the two large pooled analyses (one including 11 OCAC studies)^{1,2} which investigated conventionally-measured BMI and ovarian cancer risk by histologic subtype, although our data suggest the association with non-HGSC may be somewhat stronger than previously reported. Overall, our results suggest that the previously-reported relationship with non-HGSC is probably not due to bias or confounding, and the lack of association with HGSC is unlikely to arise from reverse causality. We observed a positive association with BMI and risk of endometrioid tumours of the same magnitude (pOR=1.17 per 5 kg/m²) seen in the previous OCAC study,¹ but the 95% CI around our estimate (0.87-1.59) is wide. Similarly, we observed odds ratios for borderline tumours and for low-grade/borderline serous cancers which were comparable with findings from the previous OCAC study.¹ Few studies have investigated an association between BMI and primary peritoneal cancers, but if a causal effect exists, rising obesity prevalence would result in increasing incidence of these cancers, which has been observed.²¹

Obesity has been associated with increased cancer risk at multiple body sites.²² Mechanisms hypothesised to explain this involve lipid signalling, inflammatory and adipokine pathways, and insulin-like growth factor influencing cell proliferation.²³ If adiposity affects ovarian cancer risk via a disrupted endocrine environment,^{23,24} then hormonal levels may modify this risk. Results by menopausal status and HRT use from previous studies have been inconsistent. In one pooled analysis, the BMI association was restricted to non-users of HRT,² while another reported that the association for non-serous invasive cancers did not differ by menopausal status or HRT use.¹ Our findings do not resolve this controversy.

The advantage of MR is that it allows non-causal explanations that might affect epidemiological studies (bias, confounding, and reverse causality) to be excluded, provided several underlying assumptions are met.²⁵ We satisfied the first assumption by using SNPs most strongly associated with BMI in a large external study, and confirming the association between GRS and BMI in OCAC. The F-statistic also exceeded the threshold below which weak-instrument bias is likely.²⁶ To support the second MR assumption²⁵ we confirmed that the GRS was not associated with potential confounders of the BMI-ovarian cancer association. Our analysis has a number of other strengths. The variance in BMI explained by the GRS was consistent with GIANT results,⁹ and only modest inter-study heterogeneity was observed in the association between the GRS and BMI. Our primary results were consistent across multiple GRS versions, different sub-groups of the study population, various MR methods, and when using female-specific weights. The weaker association with non-HGSC risk for conventional BMI than genetically-predicted BMI may arise from measurement error or residual confounding in observational studies.

The chief concerns regarding the validity of MR studies are: an absence of appropriate variants, including due to canalisation (developmental compensation for the effects of the SNPs); population structure influencing both SNP frequency and risk; and pleiotropy or linkage disequilibrium whereby the IV might influence risk via a non-BMI pathway.^{4,12,25} Canalisation can weaken the association between the IV and risk factor, but this effect, if present in our sample, did not prevent the GRS from being an adequate instrument for BMI. Population structure and/or pleiotropy may violate the third MR assumption (that the IV influences the outcome only via the risk factor).²⁵ A limitation of MR studies is that this assumption cannot be tested directly. However, our IV estimates are likely to represent BMI-outcome effects for the following reasons. We restricted our analysis to an ethnically-homogeneous analysis sample and adjusted models for principal components of population substructure. Using multiple independent variants can minimise potential bias from pleiotropy,²⁷ and the biological effect of this IV is becoming more fully understood. The SNPs do not show much evidence of pleiotropy in genome-wide association studies, and none have been identified as, or are in linkage disequilibrium with, ovarian cancer susceptibility SNPs. In addition, MR-Egger regression results suggested a lack of bias from pleiotropy.

The significance of this study lies in the clear evidence it provides that obesity increases risk of non-HGSC for women of European ancestry. Our results do not support an association between obesity and risk of the more common and more aggressive HGSC subtype. This study also provides reassurance that the results of the large pooled epidemiological studies were not seriously biased. As the fifth most common cancer and the sixth most common cause of cancer death for women in more developed regions, ovarian cancer is responsible for a substantial health burden.²⁸ The major risk factors identified to-date, low parity and non-use or short-duration use of OCs, have barriers to their modification, especially at older ages. Given the high and increasing prevalence of overweight and

obesity,²⁹ our findings suggest that intervening on obesity may reduce the worldwide burden from these subtypes of ovarian cancer. This study adds to the body of evidence suggesting that maintaining healthy weight is important. Continued efforts should be made to develop effective interventions to reduce BMI, and to identify women who would benefit most from these. Our results also suggest that we should pursue other avenues for prevention of HGSC. Further work is required to replicate these findings, to investigate the effects of adipose tissue distribution and to explore the mechanisms underlying the different associations for non-HGSC and HGSC.

Supplementary Data

Supplementary data are available online.

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Table 1. Characteristics of 39 OCAC studies and 37 050 participants of European ancestry included in the Mendelian randomisation analysis

Type of study	Study acronym ^{a b c}	Country	Diagnosis (years)	Median (range) age at diagnosis	Invasive HGSC (N)	Invasive non-HGSC (N) ^d	Borderline cases (N)	Median (interquartile range) BMI ^e
Population-based	AUS	Australia	2002-06	58 (19-80)	508	224	1	25.9 (22.7-29.7)
	DOV	USA	2002-09	57 (35-74)	510	255	327	25.1 (22.2-29.5)
	GER	Germany	1993-98	57 (21-75)	81	62	24	--
	HAW	USA	1993-2008	56 (27-87)	36	22	20	24.4 (22.0-28.8)
	HOC	Finland	1975-99	46 (18-86)	106	76	8	--
	HOP	USA	2003-09	58 (25-94)	338	167	71	27.4 (23.6-32.2)
	MAL	Denmark	1994-99	57 (31-80)	197	204	138	23.6 (21.5-26.1)
	MCC	Australia	1990-2008	65 (45-79)	31	23	0	26.6 (23.2-29.0)
	NCO	USA	1999-2008	57 (20-75)	373	255	171	26.1 (22.8-30.5)
	NEC	USA	1992-2003	52 (21-78)	367	243	232	24.7 (22.0-28.6)
	NJO	USA	2002-09	60 (25-88)	92	62	0	25.9 (22.3-30.4)
	NOR	Norway	2001-10	51 (18-86)	123	64	12	--
	NTH	Netherlands	1997-2008	55 (18-83)	94	139	3	24.5 (22.2-27.0)
	OVA	Canada	2002-09	58 (19-80)	344	186	161	--
	POL	Poland	2000-04	56 (24-74)	101	69	0	23.8 (22.0-26.4)
	SEA	UK	1998-2011	57 (19-78)	643	599	76	--
	SOC	UK	1993-98	62 (22-92)	91	116	20	--
	SRO	Scotland	1999-2001	59 (34-84)	89	31	0	--
	STA	USA	1997-2002	50 (20-64)	141	81	10	--
	TOR	Canada	1995-2007	58 (26-85)	339	205	0	25.7 (23.1-29.1)
UCI	USA	1993-2005	56 (18-86)	154	102	141	24.9 (21.9-29.1)	
USC	USA	1992-2010	57 (22-82)	418	187	152	24.2 (21.7-28.1)	
Clinic-based	BAV	Germany	2002-08	58 (24-83)	42	41	5	25.4 (22.7-28.7)
	BEL	Belgium	2007-10	46 (19-87)	188	74	0	--
	HJO	Germany	2007-11	54 (18-88)	136	43	13	--
	HMO	Belarus	2006-11	45 (22-76)	50	20	0	--
	HSK	Germany	2000-07	58 (18-81)	103	21	9	--
	LAX	USA	1989-2008	58 (31-88)	213	43	0	--
	MAY	USA	2000-2010	61 (20-93)	516	154	79	26.1 (23.0-30.3)
	MDA	USA	1997-2009	62 (23-88)	190	59	0	--
	MSK	USA	1997-2010	57 (18-89)	354	50	0	--
	ORE	USA	2007-11	58 (22-86)	40	11	9	--

Type of study	Study acronym ^{a b c}	Country	Diagnosis (years)	Median (range) age at diagnosis	Invasive HGSC (N)	Invasive non-HGSC (N) ^d	Borderline cases (N)	Median (interquartile range) BMI ^e
	POC	Poland	1998-2008	55 (23-82)	200	81	0	--
	PVD	Denmark	2004-09	63 (30-88)	121	39	0	--
	RMH	UK	1993-96	52 (26-73)	49	60	7	--
	UKO	UK	2006-10	63 (19-89)	329	277	0	--
	WOC	Poland	1997-2010	44 (20-81)	131	45	2	--
Familial registry	GRR	USA	1981-2012	48 (21-83)	72	33	0	--
	UKR	UK	1991-2009	54 (24-77)	23	11	0	--

BMI, body mass index; HGSC, high-grade serous ovarian cancer; OCAC, Ovarian Cancer Association Consortium.

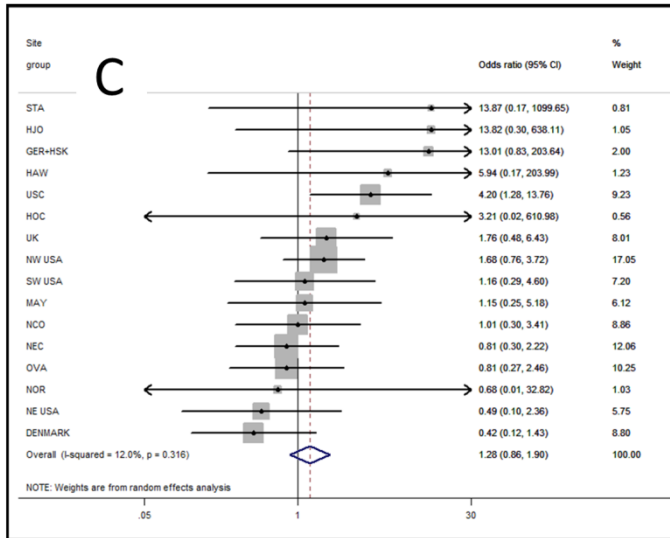
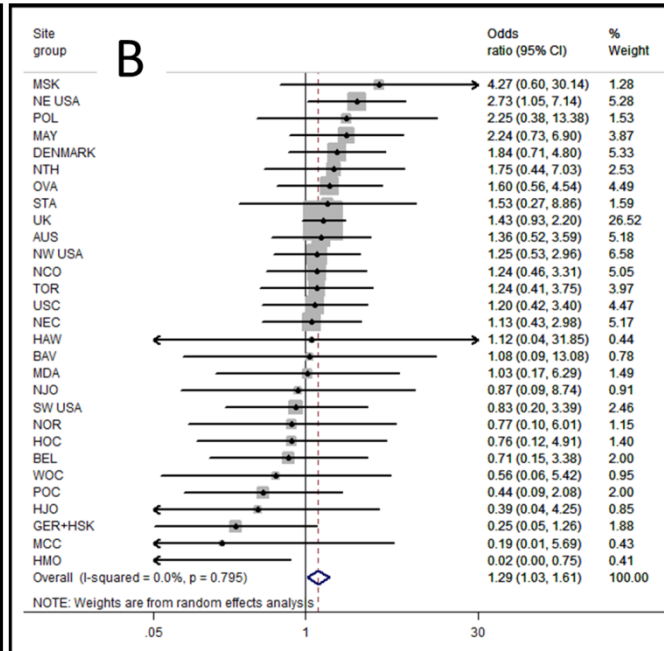
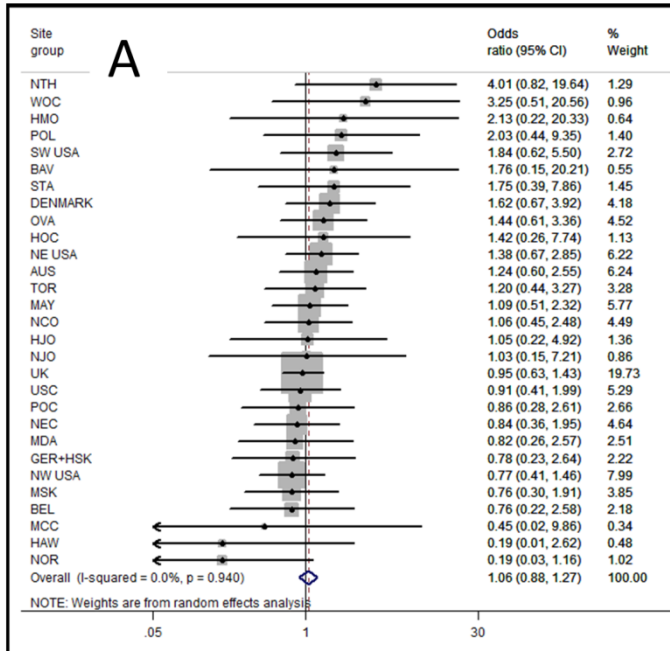
- a. See Supplementary Table S1 for study names and references.
- b. For analysis, we combined case-only with case-control sites: HSK combined with GER; GRR with HOP; PVD with MAL; RMH, SOC, SRO, UKR with SEA and UKO; ORE with DOV; LAX with UCI.
- c. Nineteen studies (AUS, BAV, DOV, GER, HAW, HOP, MAL, MAY, NEC, NJO, NTH, POL, PVD, SEA, STA, TOR, UCI, UKO, USC) were used in menopausal/hormonal replacement therapy analyses as they provided these data for >50% of participants.
- d. Histologic subtypes other than serous, mucinous, endometrioid, and clear cell carcinoma are not included.
- e. Recent BMI (1-5 years prior to diagnosis). BMI is summarised for 16 studies where >50% participants had data available. These 16 studies were also used in conventional BMI analyses, as they provided data on potential confounders (parity, use of oral contraceptives and hormone replacement therapy, and family history of ovarian or breast cancer) for >50% of participants.

Table 2. Association between increasing BMI (per 5 units) - predicted by a weighted^a 87-locus genetic risk score - and risk of ovarian cancer by histologic subtype, stratified by study

Histologic subtype	N studies	N controls	N cases	Odds Ratios (95% CI) ^b
Primary outcomes				
High-grade serous	39	23 003	7933	1.06 (0.88-1.27)
Non-high grade serous	39	23 003	4434	1.29 (1.03-1.61)
Borderline	20	16 463	1680	1.28 (0.86-1.90)
Secondary outcomes				
Serous				
High-grade ovary/tubal	39	23 003	7466	1.06 (0.89-1.27)
High-grade peritoneal ^c	37	22 026	447	1.77 (0.91-3.43)
Invasive low-grade & borderline	39	23 003	1411	1.93 (1.33-2.81)
Mucinous (invasive & borderline)	39	23 003	1563	1.18 (0.84-1.67)
Endometrioid	39	23 003	2059	1.17 (0.87-1.59)
Clear cell	39	23 003	962	1.27 (0.83-1.96)

BMI, body mass index; CI, confidence interval.

- a. Weights applied were β -coefficients for the relationship between each SNP and BMI as reported in a large meta-analysis of genome-wide association studies.
- b. Pooled odds ratios are reported for primary outcomes.
- c. Excludes two studies (AUS and SRO) where <20% of women with primary peritoneal cancers were genotyped.



Supplementary Material

Adult Body Mass Index and Risk of Ovarian Cancer by Subtype: A Mendelian Randomization Study

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Table S1. Studies included in the analysis

Acronym	Study name	Reference
AUS	Australian Ovarian Cancer Study/Australian Cancer Study (Ovarian Cancer)	1
BAV	Bavarian Ovarian Cancer Cases and Controls	2
BEL	Belgian Ovarium Cancer Study	2
DOV	Diseases of the Ovary and their Evaluation	3
GER	German Ovarian Cancer Study	4
GRR	Gilda Radner Familial Ovarian Cancer Registry	5,6
HAW	Hawaii Ovarian Cancer Case-Control Study	7
HJO	Hannover-Jena Ovarian Cancer Study	2
HMO	Hannover-Minsk Ovarian Cancer Study	8
HOC	Helsinki Ovarian Cancer Study	9
HOP	Novel Risk Factors and Potential Early Detection Markers for Ovarian Cancer	10
HSK	Dr Horst Schmidt Kliniken	11,12
LAX	Women's Cancer Program at the Samuel Oschin Comprehensive Cancer Institute	13
MAL	MALignant OVarian cancer	14-16
MAY	Mayo Clinic Ovarian Cancer Case-Control Study	17,18
MCC	Melbourne Collaborative Cohort Study	19
MDA	MD Anderson Cancer Center	13
MSK	Memorial Sloan-Kettering Cancer Center	13
NCO	North Carolina Ovarian Cancer Study	20,21
NEC	New England Case Control Study	22,23
NJO	New Jersey Ovarian Cancer Study	24,25
NOR	University of Bergen, Haukeland University Hospital, Norway	26,27
NTH	Nijmegen Ovarian Cancer Study	28,29
ORE	Oregon Ovarian Cancer Registry	30,31
OVA	Ovarian Cancer in Alberta and British Columbia	32
POC	Polish Ovarian Cancer Study	13
POL	Polish Ovarian Cancer Case Control Study	33
PVD	Danish Pelvic Mass Study	34,35
RMH	Royal Marsden Hospital Ovarian Cancer Study	36
SEA	Study of Epidemiology and Risk Factors in Cancer Heredity	37
SOC	Southampton Ovarian Cancer Study	38,39
SRO	Scottish Randomised Trial in Ovarian Cancer	40,41
STA	Family Registry for Ovarian Cancer, and Genetic Epidemiology of Ovarian Cancer	42
TOR	Familial Ovarian Tumour Study, and Health Watch	43
UCI	University California Irvine Ovarian Study	44
UKO	United Kingdom Ovarian cancer Population Study	45
UKR	UK Familial Ovarian Cancer Registry	46
USC	Los Angeles County Case-Control Studies of Ovarian Cancer	47-49
WOC	Warsaw Ovarian Cancer Study	50

Table S2. Eighty-seven single nucleotide polymorphisms included in the genetic risk score for body mass index

Chromosome	Nearest gene	GIANT SNP	SNP in GRS^a	BMI-increasing allele	Other allele	Frequency of BMI-increasing allele (controls)	Approximate per allele effect (increase (kg/m²) in BMI per one BMI-increasing allele)^b
1	PTBP2	rs11165643	rs11165643	T	C	0.59	0.13
1	ELAVL4	rs11583200	rs11583200	C	T	0.38	0.10
1	FUBP1	rs12401738	rs12401738	A	G	0.37	0.12
1	FPGT-TNNI3K	rs12566985	rs12566985	G	A	0.44	0.14
1	GNAT2	rs17024393	rs17024393	C	T	0.03	0.39
1	NAV1	rs2820292	rs2820292	C	A	0.55	0.11
1	NEGR1	rs3101336	rs3101336	C	T	0.62	0.20
1	SEC16B	rs543874	rs543874	G	A	0.19	0.28
1	AGBL4	rs657452	rs657452	A	G	0.37	0.13
1	TAL1	rs977747	rs977747	T	G	0.40	0.10
2	LINC01122	rs1016287	rs1016287	T	C	0.29	0.13
2	ADCY3	rs10182181	rs10182181	G	A	0.46	0.18
2	EHBP1	rs11688816	rs11688816	G	A	0.53	0.10
2	TMEM18	rs13021737	rs13021737	G	A	0.82	0.35
2	FIGN	rs1460676	rs1460676	C	T	0.16	0.12
2	UBE2E3	rs1528435	rs1528435	T	C	0.62	0.10
2	CREB1	rs17203016	rs17203016	G	A	0.20	0.12
2	LRP1B	rs2121279	rs2121279	T	C	0.13	0.14
2	ERBB4	rs7599312	rs7599312	G	A	0.72	0.13
3	CADM2	rs13078960	rs13078960	G	T	0.19	0.17
3	ETV5	rs1516725	rs1516725	C	T	0.86	0.26
3	RASA2	rs16851483	rs16851483	T	G	0.06	0.28
3	FHIT	rs2365389	rs2365389	C	T	0.59	0.12
3	GBE1	rs3849570	rs3849570	A	C	0.32	0.11
3	RARB	rs6804842	rs6804842	G	A	0.59	0.11
4	GNPDA2	rs10938397	rs10938397	G	A	0.44	0.24

Chromosome	Nearest gene	GIANT SNP	SNP in GRS ^a	BMI-increasing allele	Other allele	Frequency of BMI-increasing allele (controls)	Approximate per allele effect (increase (kg/m ²) in BMI per one BMI-increasing allele) ^b
4	HHIP	rs11727676	rs11727676	T	C	0.90	0.21
4	SLC39A8	rs13107325	rs13107325	T	C	0.08	0.28
4	SCARB2	rs17001654	rs17001654	G	C	0.16	0.18
5	POC5	rs2112347	rs2112347	T	G	0.64	0.15
5	GALNT10	rs7715256	rs7715256	G	T	0.42	0.10
6	PARK2	rs13191362	rs13191362	A	G	0.88	0.16
6	TDRG1	rs2033529	rs2033529	G	A	0.30	0.11
6	C6orf106	rs205262	rs205262	G	A	0.28	0.13
6	TFAP2B	rs2207139	rs2207139	G	A	0.17	0.26
6	LOC285762	rs9374842	rs9374842	T	C	0.76	0.11
6	FOXO3	rs9400239	rs9400239	C	T	0.69	0.11
7	HIP1	rs1167827	rs1167827	G	A	0.57	0.12
7	ASB4	rs6465468	rs6465468	T	G	0.27	0.10
7	CALCR	rs9641123	rs9641123	C	G	0.41	0.11
8	HNF4G	rs17405819	rs17405819	T	C	0.69	0.13
8	RALYL	rs2033732	rs2033732	C	T	0.75	0.11
9	LMX1B	rs10733682	rs10733682	A	G	0.48	0.10
9	LINGO2	rs10968576	rs10968576	G	A	0.31	0.15
9	TLR4	rs1928295	rs1928295	T	C	0.56	0.11
9	C9orf93	rs4740619	rs4740619	T	C	0.54	0.11
9	EPB41L4B	rs6477694	rs6477694	C	T	0.36	0.10
10	NT5C2	rs11191560	rs11191560	C	T	0.09	0.18
10	HIF1AN	rs17094222	rs17094222	C	T	0.22	0.15
10	GRID1	rs7899106	rs7899106	G	A	0.05	0.23
10	TCF7L2	rs7903146	rs7903146	C	T	0.71	0.14
11	BDNF	rs11030104	rs11030104	A	G	0.79	0.24
11	CADM1	rs12286929	rs12286929	G	A	0.51	0.13
11	HSD17B12	rs2176598	rs2176598	T	C	0.25	0.12

Chromosome	Nearest gene	GIANT SNP	SNP in GRS ^a	BMI-increasing allele	Other allele	Frequency of BMI-increasing allele (controls)	Approximate per allele effect (increase (kg/m ²) in BMI per one BMI-increasing allele) ^b
11	MTCH2	rs3817334	rs3817334	T	C	0.41	0.15
11	TRIM66	rs4256980	rs4256980	G	C	0.64	0.12
12	CLIP1	rs11057405	rs11057405	G	A	0.90	0.18
12	BCDIN3D	rs7138803	rs7138803	A	G	0.39	0.18
13	MTIF3	rs12016871	rs9581854	T	C	0.19	0.17
13	MIR548X2	rs9540493	rs9540493	A	G	0.44	0.10
14	STXBP6	rs10132280	rs10132280	C	A	0.69	0.13
14	PRKD1	rs12885454	rs12885454	C	A	0.65	0.12
14	NRXN3	rs7141420	rs7141420	T	C	0.50	0.14
15	MAP2K5	rs16951275	rs16951275	T	C	0.77	0.18
15	DMXL2	rs3736485	rs3736485	A	G	0.47	0.10
15	LOC100287559	rs7164727	rs7164727	T	C	0.66	0.11
16	GPRC5B	rs12446632	rs12446632	G	A	0.86	0.24
16	FTO	rs1558902	rs1558902	A	T	0.41	0.48
16	CBLN1	rs2080454	rs2080454	C	A	0.42	0.10
16	ATP2A1	rs3888190	rs3888190	A	C	0.39	0.18
16	INO80E	rs4787491	rs4787491	G	A	0.53	0.09
16	NLRC3	rs758747	rs758747	T	C	0.27	0.13
16	KAT8	rs9925964	rs9925964	A	G	0.63	0.11
17	RABEP1	rs1000940	rs1000940	G	A	0.30	0.11
17	RPTOR	rs12940622	rs12940622	G	A	0.58	0.11
17	SMG6	rs9914578	rs9914578	G	C	0.20	0.12
18	C18orf8	rs1808579	rs1808579	C	T	0.53	0.10
18	MC4R	rs6567160	rs6567160	C	T	0.23	0.33
18	LOC284260	rs7239883	rs7239883	G	A	0.40	0.10
18	GRP	rs7243357	rs7243357	T	G	0.83	0.13
19	PGPEP1	rs17724992	rs17724992	A	G	0.74	0.11
19	TOMM40	rs2075650	rs2075650	A	G	0.85	0.15

Chromosome	Nearest gene	GIANT SNP	SNP in GRS^a	BMI-increasing allele	Other allele	Frequency of BMI-increasing allele (controls)	Approximate per allele effect (increase (kg/m²) in BMI per one BMI-increasing allele)^b
19	QPCTL	rs2287019	rs2287019	C	T	0.79	0.21
19	KCTD15	rs29941	rs29941	G	A	0.68	0.11
19	ZC3H4	rs3810291	rs3810291	A	G	0.67	0.17
20	ZFP64	rs6091540	rs6091540	C	T	0.71	0.11
21	ETS2	rs2836754	rs2836754	C	T	0.63	0.10

BMI, body mass index; GIANT, Genetic Investigation of ANthropometric Traits consortium; SNP, single nucleotide polymorphism.

- a. The GIANT SNP was used at all loci except MTIF3, where the SNP reported in the GIANT analysis (rs12016871) has been renamed rs9581854 in the National Center for Biotechnology Information Database of SNPs (dbSNP).
- b. Derived by multiplying betas (per standard deviation of BMI) from the GIANT consortium analysis by the standard deviation of measured BMI in controls in this analysis (5.867 kg/m²).

Table S3. Characteristics of the analysis population (14 047 cases and 23 003 controls)

Characteristic	Controls N=23 003		Cases N=14 047 ^a				P-value Controls vs all Cases combined
	High grade serous N=7933	Low grade invasive & borderline serous N=1411	Mucinous (Invasive & borderline) N=1563	Endometrioid N=2059	Clear-cell N=962		
Age at diagnosis (mean [SD])	55.5 (11.9)	59.5 (10.7)	51.8 (12.9)	52.4 (13.3)	55.9 (11.0)	56.3 (10.0)	<0.001
Attained education							
High school or lower	5297 (45.5)	2209 (53.1)	444 (44.1)	537 (53.5)	663 (50.5)	318 (52.6)	
Trade/college/higher education	6351 (54.5)	1952 (46.9)	564 (55.9)	467 (46.5)	649 (49.5)	287 (47.4)	<0.001
Number of full-term pregnancies ^b							
0	2627 (14.7)	993 (18.7)	344 (28.7)	323 (27.5)	456 (30.6)	264 (37.1)	
1	2492 (13.9)	781 (14.7)	223 (18.6)	193 (16.5)	247 (16.6)	121 (17.0)	
2	7017 (39.2)	1826 (34.3)	348 (29.0)	370 (31.5)	447 (30.0)	205 (28.8)	
≥3	5777 (32.3)	1723 (32.4)	284 (23.7)	287 (24.5)	339 (22.8)	121 (17.0)	<0.001
Oral contraceptive use							
Never	6303 (35.5)	2376 (43.9)	384 (32.2)	390 (33.1)	679 (44.2)	317 (43.0)	
Ever	11430 (64.5)	3036 (56.1)	809 (67.8)	789 (66.9)	859 (55.8)	420 (57.0)	<0.001
<5 years	4866 (28.2)	1653 (31.3)	438 (37.2)	361 (31.3)	428 (28.6)	225 (31.1)	
≥5 years	6081 (35.3)	1259 (23.8)	354 (30.1)	404 (35.0)	391 (26.1)	181 (25.0)	<0.001
Menopausal status and HRT use							
Pre/Peri	4586 (30.3)	1440 (28.9)	582 (53.4)	561 (50.1)	638 (45.0)	235 (36.4)	
Post – no HRT use	5587 (36.9)	1822 (36.5)	241 (22.1)	343 (30.6)	440 (31.0)	271 (42.0)	
Post + HRT use	4968 (32.8)	1724 (34.6)	266 (24.4)	216 (19.3)	340 (24.0)	139 (21.6)	<0.001
Smoking							
Never	6270 (53.0)	2198 (52.1)	504 (49.8)	459 (45.1)	743 (56.3)	356 (58.1)	
Ex	3782 (32.0)	1463 (34.7)	335 (33.1)	302 (29.7)	425 (32.2)	179 (29.2)	
Current	1782 (15.1)	558 (13.2)	173 (17.1)	256 (25.2)	151 (11.5)	78 (12.7)	0.2

Characteristic	Controls N=23 003		Cases N=14 047^a				P-value Controls vs all Cases combined
	High grade serous N=7933	Low grade invasive & borderline serous N=1411	Mucinous (Invasive & borderline) N=1563	Endometrioid N=2059	Clear-cell N=962		
Body mass index (kg/m ²) (recent) ^c							
<18.5	186 (1.8)	73 (1.9)	16 (1.5)	30 (3.5)	24 (2.2)	6 (1.3)	
18.5-24.9	4809 (47.7)	1807 (46.7)	436 (42.0)	393 (46.1)	451 (40.5)	206 (44.0)	
25-29.9	2997 (29.7)	1151 (29.8)	276 (26.6)	245 (28.7)	335 (30.1)	137 (29.3)	
30-34.9	1277 (12.7)	516 (13.3)	171 (16.5)	108 (12.7)	166 (14.9)	66 (14.1)	
≥35	816 (8.1)	320 (8.3)	140 (13.5)	77 (9.0)	138 (12.4)	53 (11.3)	<0.001

HRT, hormone replacement therapy; SD, standard deviation.

- N=119 cases (other histologic subtypes) not presented.
- Defined as longer than 6 months.
- Self-reported recent body mass index (1-5 years prior to diagnosis), restricted to 16 studies where >50% participants had data available.

Figure S1. Association between three genetic risk score (GRS) versions and BMI, by study

(A) GRS comprising 87 BMI SNPs. (B) GRS comprising 56 SNPs with imputation quality scores ≥ 0.9 . (C) *FTO*.

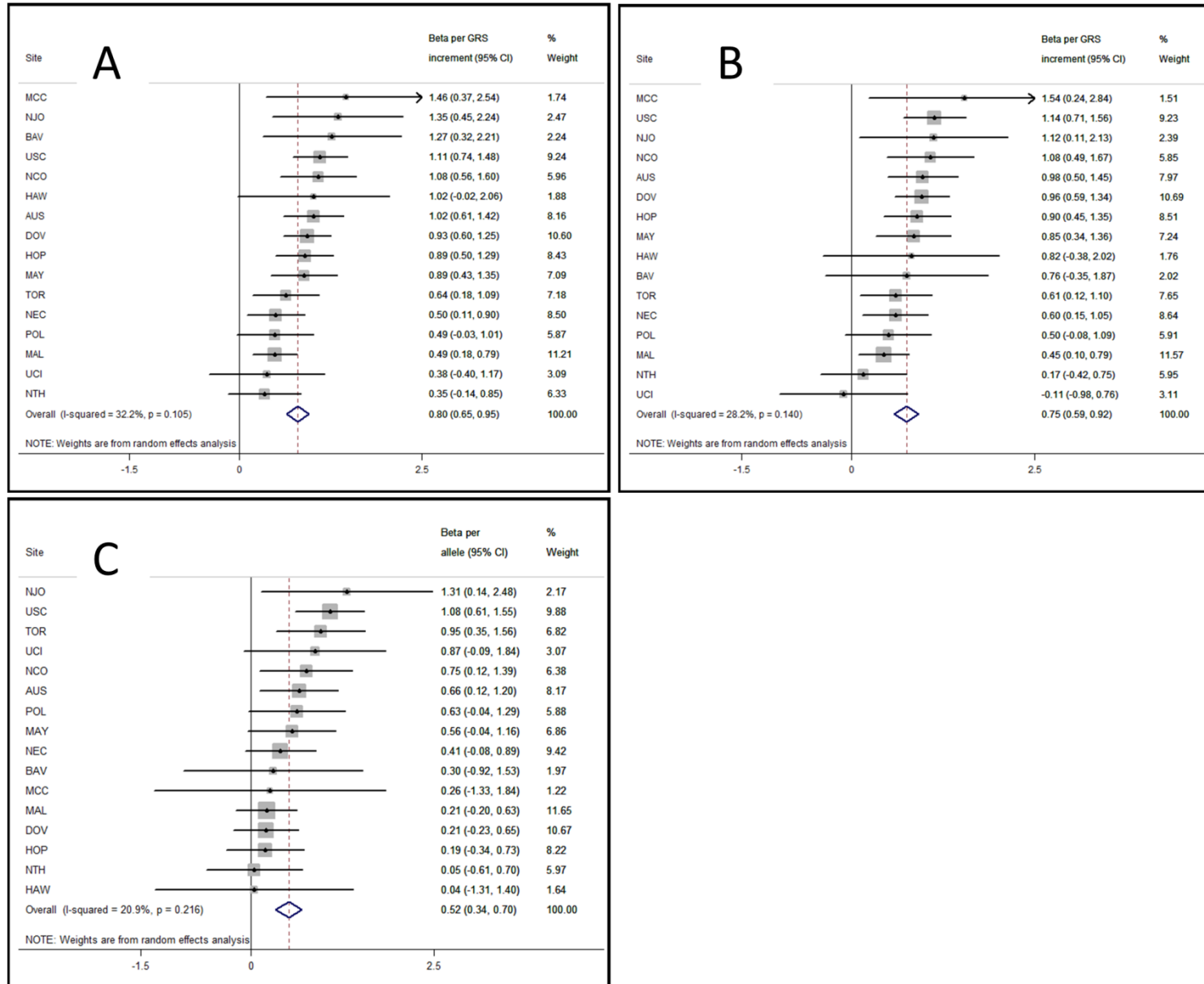


Table S4. Association of potential confounders with recent BMI and with the BMI genetic risk score, and the association of BMI with the genetic risk score, among controls ^a

Characteristic	Recent BMI (Median [Q1-Q3])	<i>P</i>-value ^b	Unweighted GRS Mean (SD)	<i>P</i>-value ^b	Weighted GRS Mean (SD)	<i>P</i>-value ^b
Age at diagnosis						
<40	23.5 (21.2-27.4)		84.3 (5.7)		12.6 (0.9)	
40-49	24.1 (21.6-28.1)		84.2 (5.7)		12.6 (0.9)	
50-59	25.5 (22.6-29.4)		84.5 (5.6)		12.6 (0.9)	
60-69	25.7 (23.0-29.7)		84.4 (5.6)		12.6 (0.9)	
≥70	25.6 (22.5-29.0)	<0.001	84.0 (5.7)	0.2	12.6 (0.9)	0.1
Attained education						
High school or lower	25.6 (22.6-29.7)		84.2 (5.7)		12.6 (0.9)	
Trade/college/higher education	24.9 (22.1-28.9)	<0.001	84.3 (5.6)	0.4	12.6 (0.9)	0.2
Number of full-term pregnancies ^c						
0	24.3 (21.6-28.8)		84.3 (5.7)		12.6 (0.9)	
≥1	25.1 (22.4-29.1)	<0.001	84.3 (5.6)	0.6	12.6 (0.9)	0.6
Oral contraceptive use						
Never	25.4 (22.6-29.2)		84.3 (5.7)		12.6 (0.9)	
Ever	25.0 (22.2-29.0)	<0.001	84.3 (5.6)	1.0	12.6 (0.9)	0.7
<5 years	25.2 (22.2-29.4)		84.3 (5.7)		12.6 (0.9)	
≥5 years	24.7 (22.1-28.4)	<0.001	84.4 (5.6)	1.0	12.6 (0.9)	0.9
Menopausal status and HRT use						
Pre/Peri	24.2 (21.6-28.0)		84.3 (5.6)		12.6 (0.9)	
Post – no HRT use	25.8 (22.7-29.8)		84.4 (5.6)		12.6 (0.9)	
Post + HRT use	25.0 (22.3-28.8)	<0.001	84.2 (5.6)	0.1	12.6 (0.9)	0.1
Body mass index (kg/m ²) (recent)						
<18.5	NA		83.3 (5.7)		12.4 (0.9)	
18.5-24.9	NA		83.7 (5.7)		12.5 (0.9)	
25-29.9	NA		84.6 (5.6)		12.7 (0.9)	
30-34.9	NA		85.0 (5.5)		12.7 (0.9)	
≥35	NA	NA	85.4 (5.8)	<0.001	12.8 (0.9)	<0.001

BMI, body mass index; GRS, genetic risk score; HRT, hormone replacement therapy; NA, not applicable; Q1, quartile 1; Q3, quartile 3; SD, standard deviation.

- a. Data are summarised for studies where >50% participants had data available. BMI data are for 16 studies; GRS data are for all studies.
- b. *P*-values are from comparisons adjusting for study.
- c. Defined as longer than 6 months.

Table S5. Association between increasing BMI (measured/self-reported) per 5 kg/m², and risk of ovarian cancer by histologic subtype, stratified by study, among women with BMI and confounder data

Histologic subtype	N studies	N controls	N cases	Odds Ratios (95% CI)^a
Primary outcomes				
High-grade serous	16	9802	3761	1.00 (0.96-1.03)
Non-high grade serous	16	9802	2150	1.18 (1.13-1.23)
Borderline	9	7599	1258	1.21 (1.14-1.27)
Secondary outcomes				
Serous				
High-grade ovary/tubal	16	9802	3475	0.98 (0.95-1.02)
High-grade peritoneal ^b	5	4868	286	1.16 (1.05-1.29)
Invasive low-grade & borderline	14	9314	1010	1.25 (1.18-1.33)
Mucinous (invasive & borderline)	16	9802	812	1.12 (1.05-1.20)
Endometrioid	16	9802	1061	1.21 (1.15-1.28)
Clear cell	16	9802	451	1.09 (1.00-1.19)

BMI, body mass index; CI, confidence intervals.

- a. Adjusted for oral contraceptive use, parity, and family history of ovarian/breast cancer, and stratified by 5-year age groups and study.
- b. Excludes one study (AUS) where <10% of women with primary peritoneal cancers were genotyped.

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