Genetic risk score Mendelian randomization shows obesity measured as body mass index, but not waist:hip ratio, is causal for endometrial cancer.

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Abstract

Background: The strongest known risk factor for endometrial cancer (EC) is obesity. To determine whether single nucleotide polymorphisms (SNPs) associated with increased body mass index (BMI) or waist-hip ratio (WHR) are associated with EC risk, independent of measured BMI, we investigated relationships between 77 BMI and 47 WHR SNPs and EC in 6,609 cases and 37,926 country-matched controls.

Methods: Logistic regression analysis and fixed-effects meta-analysis were used to test for associations between EC risk and (i) individual BMI or WHR SNPs, (ii) a combined weighted genetic risk score (wGRS) for BMI or WHR. Causality of BMI for EC was assessed using Mendelian randomization, with BMIwGRS as instrumental variable.

Results: The BMIwGRS was significantly associated with EC risk (P=3.4x10^{-17}). Scaling the effect of the BMIwGRS on EC risk by its effect on BMI, the EC odds ratio (OR) per 5kg/m^2 of genetically predicted BMI was 2.06 (95% confidence interval (CI)=1.89-2.21), larger than the observed effect of BMI on EC risk (OR=1.55, 95% CI 1.44-1.68, per 5kg/m^2). The association attenuated but remained significant after adjusting for BMI (OR=1.22, 95% CI=1.10-1.39, P=5.3x10^{-4}). There was evidence of directional pleiotropy (P=1.5x10^{-4}). BMI SNP rs2075650 was associated with EC at study-wide significance (P<4.0x10^{-4}), independent of BMI. EC was not significantly associated with individual WHR SNPs or the WHRwGRS.

Conclusions: BMI, but not WHR, is causally associated with EC risk, with evidence that some BMI-associated SNPs alter EC risk via mechanisms other than measurable BMI.

Impact: The causal association between BMI SNPs and EC has possible implications for EC risk modeling.

Introduction

Endometrial cancer (EC: cancer of the lining of the uterine corpus) is the fourth most diagnosed cancer in European and North American women (1). Endometrial tumors are typically classified into two etiological types (2): hormonally driven Type 1, usually low grade endometrioid histology with 'good' prognosis (~80% of cases), and Type 2, non-endometrioid, largely serous or clear cell histologies with poorer prognosis. Overall, the strongest known risk factor is obesity (3), with every 5kg/m^2 increase in body mass index (BMI) increasing EC risk by up to 60% (4). Women with a BMI ≥30 kg/m^2 have a ~3-fold overall increased EC risk compared to non-obese women (BMI <25), increasing to an 8-fold risk in women with BMI ≥40 (5). Obesity is most commonly associated with endometrioid EC, and may also modestly increase the risk of non-endometrioid tumors (3, 6). Body fat distribution, measured as waist-hip ratio (WHR) or waist circumference (WC), may influence EC risk but the evidence is weaker (4, 7). Additionally, whether the WHR/WC associations are independent of BMI remains to be clarified.

Association studies assessing cancer risk with variants proven to be associated with obesity may inform our understanding of the biological relationship between obesity and cancer risk, and also identify variants/genetic loci that play a direct role in the etiology of obesity-associated cancers. Genome-wide association studies (GWAS) have now identified 97 loci associated with BMI and another 49 loci independently associated with WHR adjusted for BMI (8-11). Of these, a SNP in the *FTO* gene, in high linkage disequilibrium with obesity SNP rs1558902, is associated with a significantly increased risk of breast cancer (12), while combinations of BMI-associated variants summarised by a genetic risk score (GRS) have been associated with prostate and colorectal cancers (13, 14). A recent study of 3,376 European-ancestry EC cases and 3,867 controls found an association between a 97-SNP BMI

GRS and EC which disappeared after adjusting for BMI (15). However, a 26-SNP BMI GRS was found to be significantly associated with EC in Chinese cases and controls independently of measured BMI (16). The relationship between WHR-associated SNPs and EC is as yet unknown for any population.

We have investigated whether SNPs known to influence BMI (N=77) or WHR adjusted for BMI (N=47) in Europeans, are also associated with the risk of EC using a large sample of 6,609 EC cases and 37,926 controls. We present the results of our association analyses for each SNP individually, and combined as a weighted genetic risk score (wGRS) (17) for each adiposity measure. Further, we investigated possibly pleiotropy of BMI risk SNPs using a Mendelian Randomization approach with a test for heterogeneity among the causal estimates from the different SNPs.

Material and Methods

Datasets

We analyzed four datasets from separate studies contributing to the Endometrial Cancer Association Consortium (ECAC), as detailed previously (18, 19), and as summarized in **Supplementary Table 1**). The first three comprised GWAS datasets genotyped using Illumina genotyping arrays, from Australia (“ANECS/QIMR/HCS”: 606 cases, 3,083 controls), and the UK (“SEARCH/WTCCC”, 681 cases, 5,190 controls (18, 20)); “NSECG/CORGI”, 919 cases, 894 controls(19, 21)). The fourth dataset (“iCOGS”) was genotyped using the ‘iCOGs’ custom Illumina Infinium iSelect genotyping array comprising 211,155 SNPs chosen for follow-up and fine-mapping of hormonal cancer GWAS hits, and included 4,402 cases recruited from 11 separate studies from 7 countries, and 28,758 controls from the same countries.

BMI information was available for subsets of cases and controls from the ANECS, SEARCH and iCOGS datasets (**Table 1, Supplementary Table 2**). Analyses that did not include BMI as a covariate included 6,609 cases and 37,296 controls; analyses including BMI as a covariate included 4,088 cases and 15,986 controls. The association between BMI and EC risk was assessed by meta-analysis of the ANECS, SEARCH and iCOGS datasets. There was modest evidence for heterogeneity (P_{trend} All cases I^2=73.4, *P*=0.02), driven by a lower estimate for the SEARCH dataset, with little difference between a fixed effects and random effects model (presented in Table 1).

WHR information was available only for a subset of WTCCC controls (the 1958 Birth Cohort, N=1259); the association between WHR wGRS and WHR was confirmed in this subset of individuals. Analyses assessing the association between WHR wGRS and EC risk included all cases and controls.

BMI and WHR SNP genotype imputation

Our analyses included 77 SNPs recently validated as associated with BMI at a genome-wide level of significance ($P<5.0\text{x}10^{-8}$) in a large-scale meta-analysis including 339,224 individuals of European ancestry from 125 separate studies conducted by the Genetic Investigation of Anthropomorphic Traits (GIANT) consortium (8, 9). Only SNPs significant in the primary analysis were included (*i.e.* we did not include SNPs significant only in secondary or conditional analyses, or in the analysis including other ancestries). Using the same criteria, we included 47 SNPs associated with WHR after adjustment for BMI (WHRadjBMI) in a GIANT meta-analysis including 210,088 individuals from 101 studies (10, 11); 34 of these WHR SNPs had also reached genome-wide significance in analyses including only women (11). The BMI and WHR SNPs were non-overlapping. SNPs that were not directly genotyped on either the Illumina or iCOGS platforms were imputed to the 1000 Genomes dataset v3 (April 2012 release) using IMPUTE v2 (22) as described in (19). All target SNPs had imputation information scores >0.85 across datasets and minor allele frequencies >0.05.

Association of EC with individual BMI or WHR SNPs

The four datasets were analysed separately using unconditional logistic regression with a per-allele (1 degree of freedom) model using SNPTEST v2 (23), adjusting for principal components of the genomic kinship matrix as described previously (18, 19). The GWAS datasets were each analysed as a single stratum, the iCOGS dataset was adjusted for eight strata (six defined by country, while the large UK dataset was divided into 'SEARCH' and 'NSECG'). Given no indication for heterogeneity between studies, betas and their standard errors for each dataset were combined using standard fixed-effects meta-analyses across studies in METAL (24). All statistical tests were 2-sided. *P*-values $<4.0 \times 10^{-4}$ (where $P=0.05/124$) were considered significant.

Association of EC with genetic risk scores for BMI and WHR

We next tested for associations between EC and the wGRS for BMI and WHR. For each individual in the study, the number of trait-increasing alleles at each SNP (between 0 and 2) was weighted by the reported effect size in the GIANT consortium meta-analysis (per-allele regression coefficient) on the relevant phenotype and then summed across SNPs (**Supplementary Text**) (8-11). As most WHR-associated SNPs showed a significant difference in effect between the sexes, we calculated the WHRwGRS using the effect size as reported for women (11). The weighted contributions from all SNPs were summed to give a BMIwGRS and two different WHRwGRS for each individual (a 34-SNP WHRwGRS including only SNPs reaching genome-wide significance in women, and a 47 SNP WHRwGRS including all WHR-associated SNPs for which we had data).

Associations between the BMIwGRS and BMI and the WHRwGRS and WHR were determined by linear regression, and associations between the BMIwGRS, WHRwGRS and case-control status by logistic regression. These analyses were performed separately for each study, and results combined using random effects meta-analysis. Associations between each wGRS and EC were performed per GRS unit (continuous) and after stratifying into quartiles based on the distribution in controls. All wGRS analyses were performed using the R software package (**http://www.r-project.org/**) with two-sided *P*-values <0.05 considered significant.

Finally, we used Mendelian Randomization (MR), with BMIwGRS as the instrumental variable, to assess the causality of BMI for EC. We genetically predicted the effect of a 5kg/m^2 increase in BMI on EC risk by scaling the natural logarithm of the OR of EC per unit increase in the BMIwGRS on BMI. Using the MR approach, if BMI is causal for EC then the observed BMI OR for EC should be consistent with that predicted using the scaled BMIwGRS. A larger observed than predicted OR would suggest that at least part of the observed BMI-EC association is attributable to bias or confounding inflating the observed estimates. Conversely, a larger predicted than observed OR might indicate pleiotropy or bias or confounding that has reduced the observed estimate towards the null. To formally test the MR assumption of no pleiotropy, we used the MR adaptation of Egger's test – a method originally developed for assessing small-study bias in meta-analysis (25). In this setting each point on the funnel plot represents the causal estimate derived from one BMI SNP, and we are testing whether the causal estimates from weaker SNPs (those less strongly associated with BMI) are skewed towards either high or low values, compared with stronger variants. We used Cochran's Q-test as a further test for heterogeneity in the causal estimates of the individual SNPs (where the analysis is over the 77 SNPs rather than over multiple studies, as would be more usual in a meta-analysis context), and used the result of this test to guide whether the best estimate of the causal effect of BMI on EC is the combined estimate from the fixed-effects or from the random-effects inverse-variance weighted meta-analysis of the per-SNP causal estimates.

Results

There was evidence of association between EC and one BMI-associated SNP at $P<4.0\times10^{-4}$; SNP rs2075650 located within *TOMM40* on chromosome 19 (per allele OR=1.13, 95% CI 1.05-1.21, $P=2.4\times10^{-4}$) (**Supplementary Table 3**). The signal was similar in the subset of samples with BMI information (OR=1.18, 95% CI 1.10-1.26; $P=2.0\times10^{-4}$), and remained significant after including BMI as a covariate (OR=1.16, 95% CI 1.07-1.24, $P=3.7\times10^{-4}$). For the individual SNPs, there was a very modest positive correlation between the published effect on BMI and the estimated effect on EC risk (Pearson R=0.26, P=0.02), which was attenuated when only samples with BMI information were included (Pearson R=0.19, P=0.09), and disappeared completely after conditioning on BMI (Pearson R=0.004, *P*=0.96) (**Supplementary Figure 1**).

There was also evidence for association with one WHR SNP, rs10842707 at the *ITPR2-SSPN* locus on chromosome 12 (OR=1.09, 95% CI 1.05-1.13, *P*=$3.7x10^{-4}$) (**Supplementary Table 4**), although this signal fell below our study-wide significance threshold after adjusting for BMI (OR=1.08, 95% CI 1.01-1.14, *P*=$1.1x10^{-2}$; unadjusted OR for the subset with BMI information was 1.07, 95% CI 1.01-1.13, *P*=$2.4x10^{-2}$). There was no obvious correlation between published effect sizes for WHR SNPs and EC risk (Pearson R=-0.19, *P*=0.09; **Supplementary Figure 2**).

As expected, self-reported BMI was highly significantly associated with EC risk overall, with an OR=1.55 (95% CI 1.44-1.68, per $5kg/m^2$, *P*=$1.8x10^{-26}$) for every $5kg/m^2$ increase in BMI (**Table 1**): ORs were somewhat greater for endometrioid (OR=1.56, 95% CI 1.42-1.72) HERE than non-endometrioid/mixed (OR=1.50, 95% CI 1.43-1.57) histologies. The association between BMI and the BMIwGRS was significant in both cases and controls (**Supplementary Figure 3**); overall each weighted allele (*i.e.* each unit increase in the BMIwGRS) was associated with a $4.83kg/m^2$ increase in BMI, 95% CI 4.33-5.32, *P*=$1.2x10^{-81}$, indicating the suitability of this score as an instrumental variable for BMI in our dataset (F statistic on a pooled analysis adjusting for study 587.7).

The BMIwGRS was significantly associated with EC risk in the entire dataset, with a per weighted allele OR=2.11 (95% CI 1.94-2.28, *P*=$3.4x10^{-17}$: **Table 2**). Scaling according to the magnitude of the effect of the score on BMI (β=$4.83kg/m^2$), we find the EC OR per $5kg/m^2$ of genetically predicted BMI to be 2.06 (95% CI 1.89-2.21) (**Figure 1**). This effect is apparently driven by an association with endometrioid disease (scaled OR=2.21, 95% CI 2.03-2.38, *P*=$6.6x10^{-12}$). The overall association was similar for the subset with BMI information (scaled OR=2.18, 95% CI 1.96-2.41, $P=4.2 \times 10^{-12}$), and attenuated but remained significant after including BMI as a covariate in the model (scaled OR=1.22, 95% CI 1.12-1.34, $P=5.3 \times 10^{-4}$).

According to the Ptest, there was no significant evidence of directional pleiotropy ($P=0.53$), despite some possible asymmetry in the funnel plot **(Supplementary Figure 4)**. However, Cochran's Q-test did show some significant heterogeneity in the causal estimates from the individual SNPs ($P=1.5 \times 10^{-4}$), hence the causal effect of BMI on EC would be more appropriately estimated from the inverse-variance weighted random effects meta-analysis of the 77 BMI SNPs ($P=1.8 \times 10^{-9}$). Unfortunately, this effect estimate cannot be interpreted since the SNP-BMI regression coefficients presented by the GIANT consortium are for an inverse-normalised transformation of BMI, from which effects on the kg/m^2 scale cannot be derived. Nevertheless, we note that the causal lnOR estimate from the random-effects analysis of individual SNPs is ~10% higher than that from the equivalent fixed-effects analysis **(Supplementary Figure 4),** thus we infer that the true causal effect of BMI on EC is slightly larger than our best estimate under the assumption of no directional pleiotropy i.e. OR >2.06 per $5kg/m^2$as predicted in our dataset. This is somewhat larger than the observed OR=1.55 (95% CI 1.44-1.68) per $5kg/m^2$ of reported BMI in this dataset, and also larger than previously published estimates of the effect of reported BMI on EC in epidemiological studies (e.g. OR 1.54, 95% CI 1.47-1.61, per $5kg/m^2$ (4); OR=1.57, 95% CI 1.54-1.61, per $5kg/m^2$ for "Type1" largely endometrioid EC (3)).

Both WHRwGRS were significantly associated with WHR in the WTCCC control group (34-SNP WHRwGRS β=0.05, 95% CI 0.02-0.08, $P=2.2 \times 10^{-3}$; 47-SNP WHRwGRS β=0.05, 95% CI 0.03-0.08, $P=1.8 \times 10^{-4}$). As expected, neither WHRwGRS was associated with BMI (P=>0.80). The results for the 34-SNP WHRwGRS were very similar to those from secondary analyses using all 47 WHR SNPs, neither of which were significantly associated with EC risk (OR=1.02, 95% CI 0.99-1.04, *P*=0.09 and OR=0.97, 95% CI 0.63-1.31, *P*=0.86, respectively) (**Table 3**), or with risk stratified by histology (data not shown).

Discussion

In this study we assessed whether SNPs associated with increased BMI or WHR are also associated with increased EC risk, either individually or in combination, and whether these genetic associations are independent of BMI. While BMI is clearly recognized as a major risk factor for EC, the role of WHR, independent of BMI, is less clear. Most studies including WHR have reported evidence for an association with EC (4, 26-32) but only four presented analyses adjusting for BMI, suggesting the WHR-EC risk association was attenuated in Caucasians (29-31), but not in Asians (32).

Combined as a wGRS, the 77 BMI-associated SNPs were highly significantly associated with BMI, even though the BMIwGRS explained only ~1% of the variance in BMI in our sample (less than the estimated 2.7% of the variance in BMI explained by 97 BMI-associated SNPs across ancestries in the discovery dataset (9)). The BMIwGRS was also significantly associated with EC, explaining ~0.1% of the variance in risk and confirming the causal nature of the association between BMI and EC. Indeed, the association between genetically-predicted BMI (based on the 77 SNP BMIwGRS) and EC risk was somewhat larger than that between observed BMI (i.e. that calculated from self-reported height and weight) and EC risk, and we identified significant heterogeneity in the per-SNP causal estimates, both of which suggest some modest degree of directional pleiotropy. Furthermore, the overall association signal attenuated but did not disappear when adjusting for BMI (OR=1.22 *vs* 2.06 per 5kg/m^2 genetically predicted BMI), which also suggests that these SNPs mainly, but not entirely, operate to increase EC risk via BMI. In particular, we note that one BMI SNP, rs2075650, was found to be associated with EC risk independent of BMI in our dataset.

Our result could also (or instead) suggest that the aspect of body composition most relevant for EC risk is only partially captured by BMI; although BMI is widely used as a convenient proxy measure for adiposity, it is by no means a perfect measure (33). One would expect that the SNPs identified to date in GWAS of BMI, at least on aggregate, are more strongly associated with adiposity than with its proxy, BMI. Hence the combined effect of the 77 BMI SNPs might be a better predictor of risk due to adiposity than BMI self-reported at a single time point (which could be subject to regression dilution). The effect of BMI on EC risk has been reported to be attenuated among ever users of hormone replacement therapy (HRT), as compared to never users (34). Although we were unable to stratify our analyses according to HRT use, we are confident that the difference between the effects of observed and genetically-predicted BMI on EC risk seen in our study is not attributable to an interaction between BMI and HRT use, since both analyses were based on the same set of women, and so will necessarily have included the same proportions of current, previous and never HRT users. However, the discrepancy between the observed and predicted effects of BMI on EC could theoretically point to negative confounding between measured BMI and EC, via HRT use and some other factor (e.g. socioeconomic status) associated with both higher BMI and less frequent HRT use.

The evidence for modest pleiotropy for BMI SNPs and EC risk has been reported previously in a study of Chinese women. A study of 26 SNPs then reported as (nominally) associated with different measures of obesity in GWAS datasets (35) identified a GRS-EC association in Chinese women (16), which attenuated but remained significant after adjusting for BMI. Direct comparison to our findings is difficult, due to differences in SNP selection and overlap, and also because the relationship between BMI and percentage body fat differs among ethnic groups (36). However, the results from our European-ancestry study contrast with those from another recent analysis of 3,376 European-ancestry EC cases and 3,867 controls from the E2C2 consortium (15); neither cases nor controls from the E2C2 analysis overlap with those presented here. While the E2C2 analysis also identified a significant association between a 97-SNP GRS and EC risk (*P*=0.002), this association ablated after adjustment for BMI (*P*=0.78). The differences in findings between the two European studies may possibly reflect the BMI profiles of the two studies; while the mean BMI of the controls did not differ between the two studies (*P*=0.11), the mean BMI of cases in the E2C2 study was greater than that for cases in our study (*P*=0.017, mean difference of 0.43kg/m2). However, the differences are more likely to reflect the increased power of our larger study to detect modest effects. This is particularly pertinent to the single SNP findings. Although BMI SNP rs2075650 was found to be significantly associated with EC risk independent of BMI in our dataset (per allele OR of 1.13, 95% CI=1.05-1.21), this same SNP was not significantly associated with EC risk in the E2C2 analysis (15) ($OR_{BMI\text{-}adjusted}$= 1.00, 95% CI=0.90-1.10), although there was some overlap between the 95% CIs. We note also that we find no evidence in support of the E2C2 tentative finding of a protective effect on EC of the subset of five BMI-risk alleles at loci known to be involved in Monogenic Obesity Syndromes, with OR point estimates above unity observed for the four loci we investigated in our study (rs6567160, *MC4R*, OR 1.02 (0.98-1.06), *P*=0.3; rs11030104, *BDNF*, OR 1.05 (1.01-1.09), *P*=0.05; rs10182181, *POMC/ADCY3*, OR 1.02 (0.98-1.06), *P*=0.4; **Supplementary Table 3**).

We also, for the first time, used a genetic approach to assess the influence of body fat distribution on EC risk, an epidemiological association which is less clear than that of adiposity as measured by BMI. Combined as a wGRS, 34 SNPs reported as significantly associated with WHR in women (11) were not significantly associated with EC in our sample. We focused on the 34-SNP WHRwGRS due to the marked sexual dimorphism amongst WHR-associated loci (11), however, the results did not differ when 47 SNPs were included in the WHRwGRS. Together, the 49 SNPs now reported as associated with WHR explain ~2.4% of the variance in WHR in women (~1.4% in both sexes combined) (11). As this is similar to the proportion of variation in BMI explained by currently known BMI-associated SNPs, it seems most likely that the lack of association between the WHRwGRS and EC is due to a true lack of association between WHR and EC, rather than the smaller number of SNPs included in the WHRwGRS, particularly as the WHR-EC association seen in epidemiological studies seems to be accounted for by BMI (4). Rather than WHR, waist circumference (WC) may be a more relevant measure of central adiposity, with evidence that the association between WC and EC is independent of BMI (4). However, analysis of the genetic association between WC and EC awaits the discovery of additional WC-associated SNPs, as only six have been reported to date (four in Caucasians), none of which reached genome-wide significance in women only (11).

In summary, our combined results from weighted genetic risk scores and Mendelian Randomization analysis provide a further line of evidence that increasing BMI has a direct effect on EC risk, and thus that interventions aimed at weight loss should reduce that risk (5). We also found that SNP alleles associated with increased BMI have an aggregate effect on EC risk that is over and above that predicted by their effects on BMI. This suggests a possible degree of pleiotropy in SNP functions, indicating that these SNPs, and potentially other BMI-associated SNPs yet to be discovered, would be more useful components in an EC risk prediction model than BMI itself. In contrast, our genetic findings indicate that WHR is not independently associated with EC risk. These findings support the value of genetic approaches to verify causal relationships between epidemiological risk factors and cancer risk.

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Table 1. Association between body mass index (BMI) and endometrial cancer risk overall, and for endometrioid and non-endometrioid histologies[1]

	Controls	**All cases**		**Endometrioid cases**		**Non-endometrioid cases**	
BMI[2] Category	N (%)	N (%)	OR (95% CIs)	N (%)	OR (95% CIs)	N (%)	OR (95% CIs)
<25kg/m^2	7146 (45%)	1159 (28%)	Reference	964 (28%)	Reference	195 (32%)	Reference
25-29.9	5628 (35%)	1252 (31%)	1.06 (0.65-1.70)	1053 (30%)	1.05 (0.64-1.72)	199 (33%)	1.27 (1.07-1.48)
30-34.9	2213 (14%)	795 (19%)	1.60 (0.95-2.71)	684 (20%)	1.62 (0.94-2.80)	111 (18%)	1.88 (1.64-2.12)
35-39.9	693 (4%)	472 (12%)	3.522(2.35-4.43)	413 (12%)	3.26 (2.31-4.61)	59 (10%)	3.16 (2.85-3.48)
≥40	294 (2%)	409 (10%)	6.10 (3.67-10.17)	366 (10%)	6.26 (3.55-11.06)	43 (7%)	5.92 (5.56-6.27)
Ptrend[3]			1.8×10^{-26}		1.7×10^{-17}		1.42×10^{-27}
Per 5kg/m^2 increase in EC risk			1.55 (1.44-1.68)		1.56 (1.42-1.72)		1.50 (1.43-1.57)

[1]Random effects model.
[2]BMI range: Overall 15.24-75.00 (mean 27.18, SD 5.72); Cases 15.24-75.00 (mean 29.86, SD 7.45)' Controls 15.94-67.90 (mean 26.52, SD 4.99).
[3]Tests for heterogeneity: All cases I^2=73.4%, Q=7.53, *P*=0.02; Endometrioid cases I^2=81.1%, Q=10.57, *P*=0.005. Non-endometrioid cases are from the iCOGs dataset only and were not meta-analyzed.

Table 2. Association of the 77 SNP body mass index weighted genetic risk score (BMIwGRS) with endometrial cancer risk

	Total dataset		Dataset with BMI information		BMI-adjusted	
BMIwGRS[1] Quartiles	**Odds Ratio (95% CI)**	***P*-value**	**Odds Ratio (95% CI)**	***P*-value**	**Odds Ratio (95% CI)**	***P*-value**
All cases	(6609 cases; 37926 controls)		(4062 cases; 15974 controls)			
Q1	Reference		Reference		Reference	
Q2	1.06 (0.98-1.15)	$1.1x10^{-2}$	1.03 (0.93-1.14)	$5.0x10^{-1}$	0.98 (0.88-1.09)	$8.0x10^{-1}$
Q3	1.20 (1.12-1.28)	$4.0x10^{-6}$	1.23 (1.13-1.33)	$6.7x10^{-5}$	1.10 (1.00-1.21)	$6.2x10^{-2}$
Q4	1.34 (1.27-1.42)	$2.3x10^{-14}$	1.38 (1.28-1.48)	$3.0x10^{-10}$	1.16 (1.06-1.26)	$3.7x10^{-3}$
Per wGRS quartile increase in EC risk	1.02 (0.01-1.03)	$9.2x10^{-8}$	1.06 (1.04-1.07)	$1.1x10^{-10}$	1.03 (1.02-1.05)	$1.3x10^{-4}$
wGRS as a continuous variable	2.11 (1.94-2.28)	$3.4x10^{-17}$	2.24 (2.01-2.48)	$4.2x10^{-12}$	1.23 (1.12-1.36)	$5.3x10^{-4}$
Endometrioid	(5612 cases; 37926 controls)		(3484 cases; 15974 controls)			
Q1	Reference		Reference		Reference	
Q2	1.09 (1.00-1.17)	$5.6x10^{-2}$	1.05 (0.94-1.17)	$3.5x10^{-1}$	1.00 (0.88-1.11)	$9.8x10^{-1}$
Q3	1.22 (1.13-1.30)	$4.1x10^{-6}$	1.28 (1.17-1.39)	$8.0x10^{-6}$	1.14 (1.03-1.26)	$1.8x10^{-2}$
Q4	1.38 (1.30-1.46)	$1.7x10^{-14}$	1.43 (1.32-1.54)	$5.3x10^{-11}$	1.20 (1.09-1.31)	$1.2x10^{-3}$
Per wGRS quartile increase in EC risk	1.02 (0.01-1.03)	$2.1x10^{-7}$	1.06 (1.04-1.07)	$1.0x10^{-10}$	1.03 (1.02-1.05)	$7.8x10^{-5}$
wGRS as a continuous variable	2.27 (2.08-2.45)	$6.6x10^{-12}$	2.51 (2.30-2.72)	$3.3x10^{-17}$	1.26 (1.13-1.38)	$2.2x10^{-4}$

[1] BMIwGRS range: Overall 1.19-2.57 (mean 1.85, SD 0.17); Cases 1.21-2.53 (mean 1.87, SD 0.17); Controls 1.19-2.57 (mean 1.85, SD 0.17).

Table 3. Association of the 34- and 47-SNP waist-hip ratio weighted genetic risk score (WHRwGRS) with endometrial cancer risk

	34-SNP wGRS		47-SNP wGRS	
WHRwGRS[1] Quartiles	**Odds Ratio (95% CI)**	***P*-value**	**Odds Ratio (95% CI)**	***P*-value**
Q1	Reference		Reference	
Q2	1.00 (0.96-1.03)	$9.5x10^{-1}$	0.99 (0.96-1.02)	$4.5x10^{-1}$
Q3	0.98 (0.96-0.01)	$7.0x10^{-2}$	098 (0.94-0.01)	$2.6x10^{-1}$
Q4	0.99 (0.97-0.01)	$3.2x10^{-1}$	0.98 (0.95-0.01)	$1.3x10^{-1}$
Per wGRS quartile increase in EC risk	0.99 (0.99-1.00)	$1.7x10^{-1}$	0.99 (0.99-1.00)	$2.4x10^{-1}$
wGRS as a continuous variable	1.02 (0.99-1.04)	$9.0x10^{-2}$	0.97 (0.63-1.31)	$8.6x10^{-1}$

[1] Range 34 SNP WHRwGRS: Overall 0.53-1.52 (mean 0.98, SD 0.12); Cases 0.57-1.36 (mean 0.98, SD 0.12); Controls 0.53-1.52 (mean 0.98, SD 0.12). Range 47 SNP WHRwGRS: Overall 0.67-1.76 (mean 1.21, SD 0.14): Cases 0.67-1.69 (mean 1.22, SD 0.14); Controls 0.68-1.76 (mean 1.20, SD 0.14).

Figure Legend

Figure 1. Observed and predicted risks of increasing BMI on endometrial cancer. The predicted effect of a 5kg/m^2 increase in BMI on EC risk was estimated by scaling the effect of the per weighted allele increase in the BMIwGRS on BMI (4.83 kg/m^2) by the effect of the per weighted allele increase in the BMIwGRS on EC (OR 2.11) in our dataset (exp[(4.83/5)*ln(2.11)]). The predicted effect (grey arrow) of a per 5kg/m^2 increase in BMI on endometrial cancer risk (OR 2.06) is larger than that observed in our study (OR 1.55).

Supplementary Text for:

Genetic risk score Mendelian randomization shows obesity measured as body mass index, but not waist:hip ratio, is causal for endometrial cancer

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INDEX

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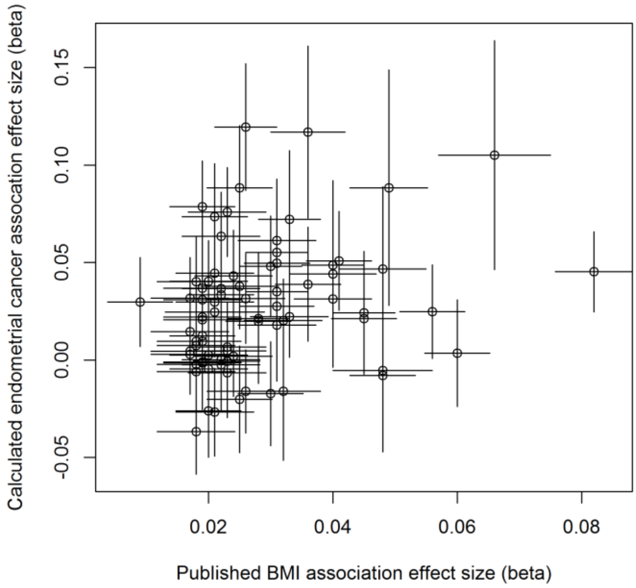
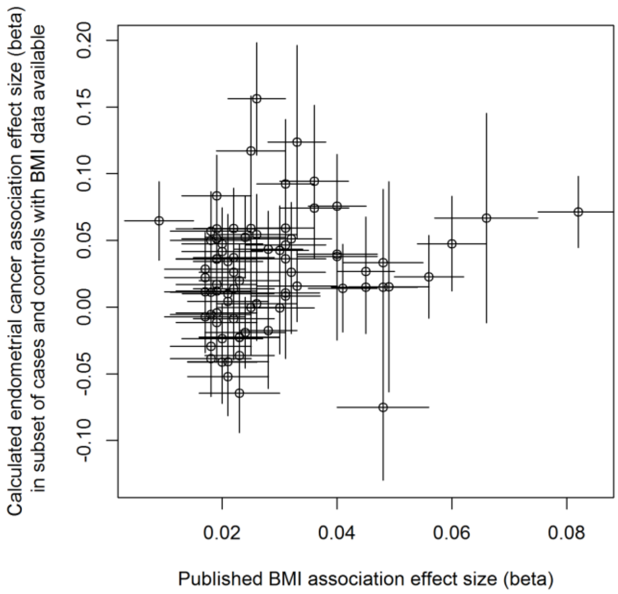
D. Supplementary Figure 1: Relationship between endometrial cancer association effect size (this study) and published BMI effect size for 77 BMI-associated SNPs (1). **A.** Overall endometrial cancer association effect size; **B.** Endometrial cancer association effect size including only cases and controls with BMI data; **C.** Endometrial cancer association effect size including only cases and controls with BMI data conditioning on BMI.

A.



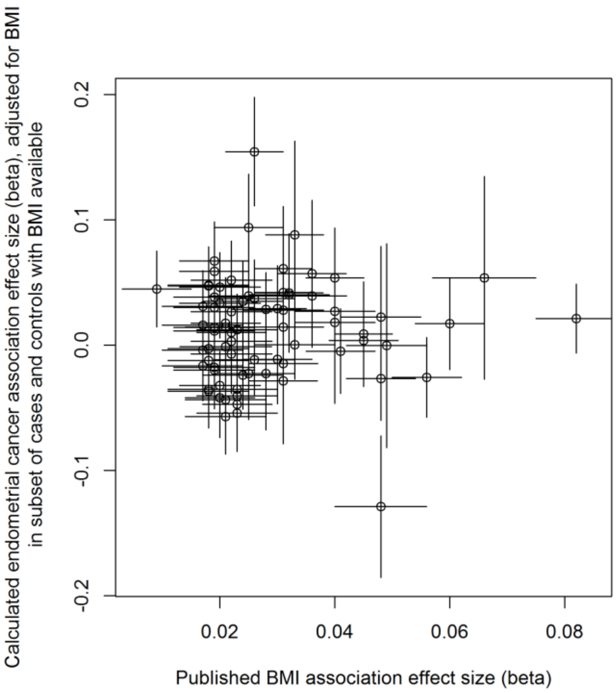
Pearson R for correlation between effect sizes=0.26, N=77, *P*-value=0.02

B.



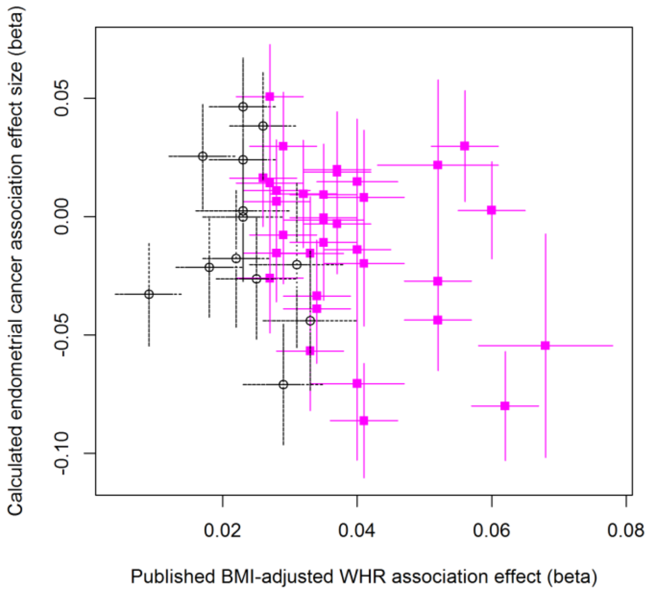
Pearson R for correlation between effect sizes=0.19, N=77, *P*-value=0.09

C.



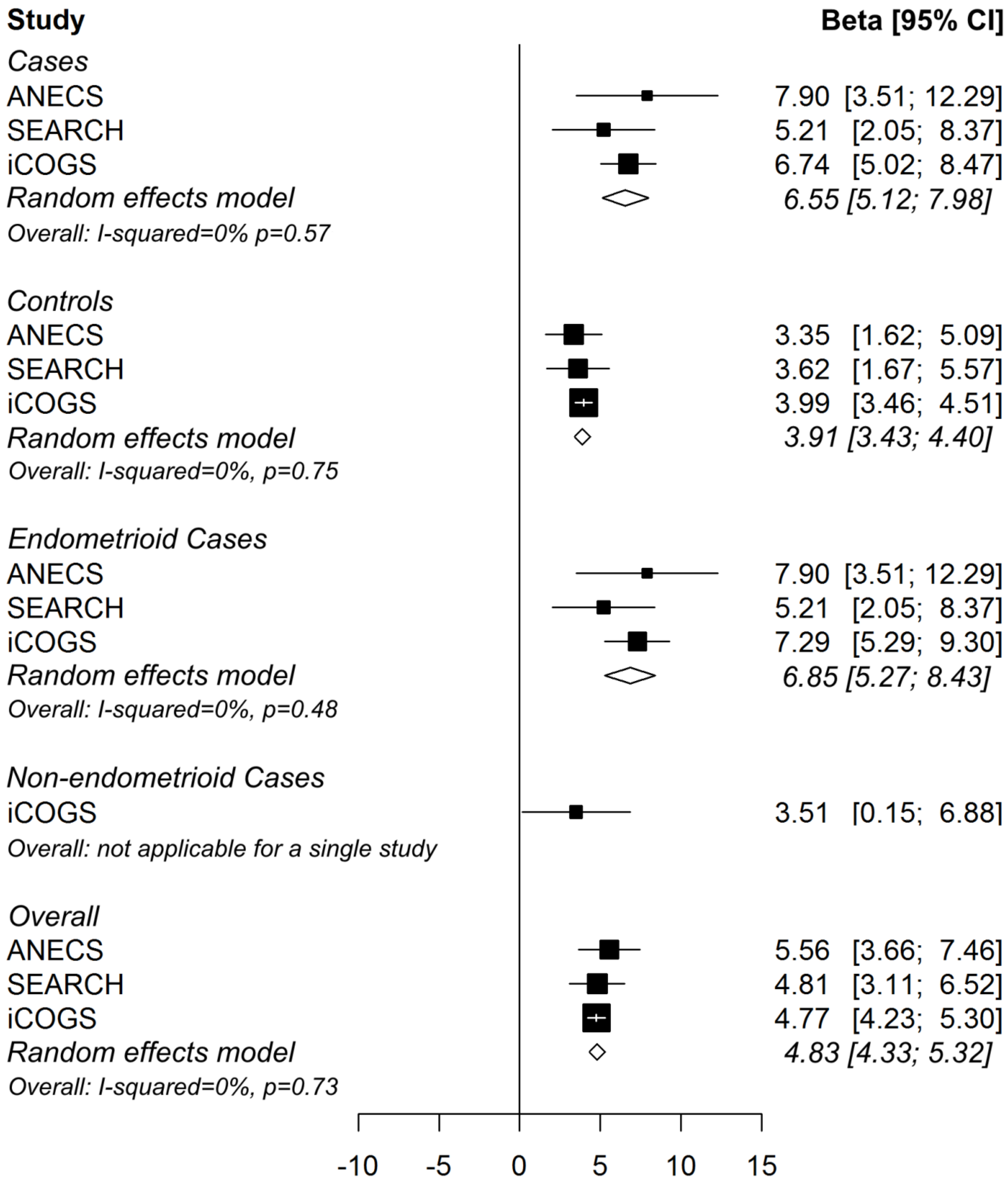
Pearson R for correlation between effect sizes=0.004, N=77, *P*-value=0.96

E. Supplementary Figure 2. Relationship between endometrial cancer association effect size (this study) and published WHR effect size for 47 WHR-associated SNPs (2). SNPs reaching genome-wide significant association with WHR in analyses including women only are shown in pink, while SNPs reaching genome-wide significant association with WHR only in sex-combined analyses are shown in black.



Pearson R for correlation between effect sizes=0.19, N=47, *P*-value=0.09

F: Supplementary Figure 3: Forest plot of effect sizes for the association between the 77 SNP BMIwGRS and BMI across three endometrial cancer datasets and endometrioid and non-endometrioid histologies.



G. Supplementary Figure 4. Funnel plot of minor allele frequency corrected SNP associations with BMI, against the BMI-EC causal estimates. Each dot indicates one of the 77 BMI SNPs. The darker grey vertical line represents the random effects combined causal estimate (95% CI limits shown by lighter grey vertical lines).

<u>Meta-analysis of the causal estimates* from each of the 77 BMI SNPs:</u>

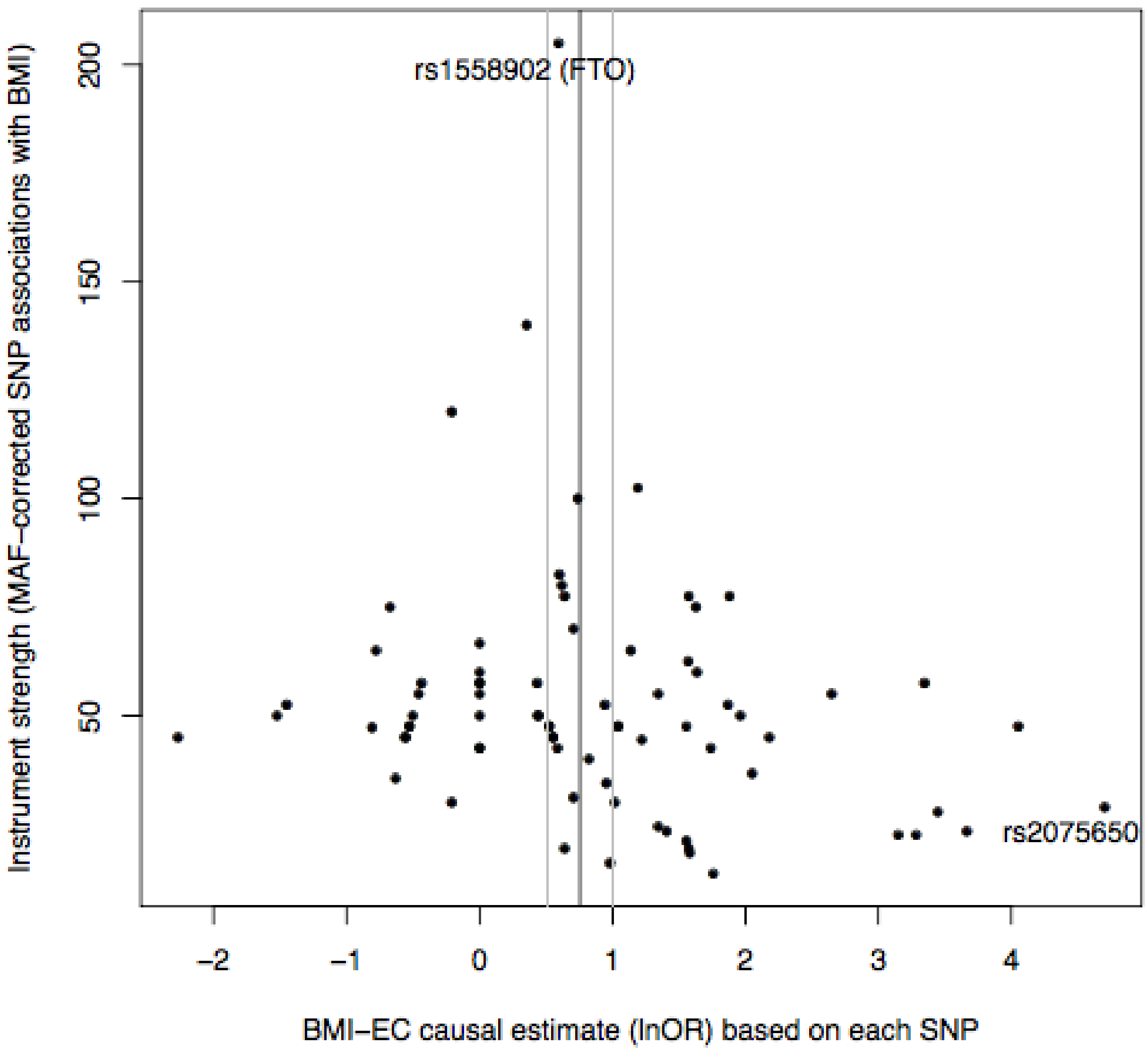
Fixed effects: OR=1.98 (95% CI 1.67-2.36) $P=1.1\times10^{-14}$

Random effects: OR=2.13 (95% CI 1.67-2.72) $P=1.8\times10^{-9}$

Heterogeneity I^2=41%
$P_{\text{Cochran's Q}} = 1.5\times10^{-4}$

*Note: OR cannot be interpreted in terms of kg/m^2 because the BMI regression coefficients from the GIANT consortium were derived using an inverse normalised transformation of BMI.

Supplementary Figure 4



H. References

1. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature 2015;518:197-206

2. Shungin D, Winkler TW, Croteau-Chonka DC, Ferreira T, Locke AE, Magi R, et al. New genetic loci link adipose and insulin biology to body fat distribution. Nature 2015;518:187-196

Supplemental Table 1. Details of cases and controls included in the endometrial cancer analyses*

Study	Acronym	Description	Cases	Controls	Genotyping platform
Genome-wide association studies					
Australian National Endometrial Cancer Study	ANECS	Australia; population based case-control study	606	-	Illumina 610K
Queensland Institute of Medical Research	QIMR	Australia; parents of participants in adolescent twin study	-	1,846	Illumina 610K
Hunter Community Study	HCS	Australia; population-based cohort	-	1,237	Illumina 610K
Study of Epidemiology and Risk Factors in Cancer Heredity	SEARCH	England; population based case-control study	681	-	Illumina 610K
Wellcome Trust Case-Control Consortium	WTCCC	United Kingdom; sample from 1958 Birth Cohort and UK Blood Donors from NBS	-	5,190	Illumina 1.2M
National Study of the Genetics of Endometrial Cancer	NSECG	United Kingdom; population based case-control study	919	-	Illumina 660K
Colorectal Tumour Gene Identification	CORGI	United Kingdom; cancer-free spouse/partner controls for colorectal cancer study	-	894	Illumina Hap550
iCOGS Sample Sets**					
Australian National Endometrial Cancer Study	ANECS	Australia; population-based case-control study	439	-	Custom Illumina Infinium iSelect array
Newcastle Endometrial Cancer Study	NECS	Newcastle, Australia; hospital-based cases	182	-	Custom Illumina Infinium iSelect array
Australian Breast Cancer Family Study	ABCFS	Melbourne/Sydney Australia; from electoral rolls	-	550	Custom Illumina Infinium iSelect array
Australian Ovarian Cancer Study	AOCS	Australia; population-based, from electoral rolls	-	896	Custom Illumina Infinium iSelect array
Melbourne Collaborative Cohort Study	MCCS	Melbourne, Australia; random sample from initial cohort	-	510	Custom Illumina Infinium iSelect array
Study of Epidemiology and Risk Factors in Cancer Heredity	SEARCH	England; population based case-control study	829	8,045	Custom Illumina Infinium iSelect array
National Study of the Genetics of Endometrial Cancer	NSECG	UK; population based case-control study	797	-	Custom Illumina Infinium iSelect array
British Breast Cancer Study	BBCS	UK; friend, sister-in-law, daughter-in-law or other non-blood relative of breast cancer case	-	1395	Custom Illumina Infinium iSelect array
Sheffield Breast Cancer Study	SBCS	Sheffield, UK; women attending Sheffield Mammography Screening, with no breast lesion	-	848	Custom Illumina Infinium iSelect array
UK Breakthrough Generations Study	UKBGS	UK; women without breast cancer selected from BGS cohort	-	471	Custom Illumina Infinium iSelect array
Mayo Endometrial Cancer Study	MECS	Mayo Clinic, USA. Hospital based case-control study.	236	-	Custom Illumina Infinium iSelect array
Mayo Clinic Breast Cancer Study	MCBCS	Mayo Clinic, USA. Cancer-free women presenting for general medical examination	-	1928	Custom Illumina Infinium iSelect array
Mayo Clinic Ovarian Cancer Case-Control Study	MCOCCCS	Mayo Clinic, USA. Cancer-free women presenting for general medical examination	-	656	Custom Illumina Infinium iSelect array
Leuven Endometrial Cancer Study	LES	Leuven, Belgium; hospital based case-control study	327	-	Custom Illumina Infinium iSelect array
Leuven Multidisciplinary Breast Centre	LMBC	Leuven, Belgium; blood donors.	-	1387	Custom Illumina Infinium iSelect array
Bavarian Endometrial Cancer Study/Hannover-Jena Endometrial Cancer Study	BECS/HJECS	Germany; hospital-based/population-based case-control study	139	-	Custom Illumina Infinium iSelect array
Bavarian Breast Cancer Cases and Controls	BBCC	Bavaria, Germany; healthy women >55yrs from newspaper advertisement	-	458	Custom Illumina Infinium iSelect array
Breast Cancer Study of the University Clinic Heidelberg	BSUCH	Mannheim, Germany; female blood donors	-	953	Custom Illumina Infinium iSelect array
ESTHER Breast Cancer Study	ESTHER	Saarland, Germany; random sample from routine health check-up	-	502	Custom Illumina Infinium iSelect array
German Consortium for Hereditary Breast & Ovarian Cancer	GC-HBOC	Augsburg, Germany; KORA study	-	139	Custom Illumina Infinium iSelect array
Gene Environment Interaction and Breast Cancer in Germany	GENICA	Bonn area, Germany; random address sample	-	427	Custom Illumina Infinium iSelect array
Mammary Carcinoma Risk Factor Investigation	MARIE	Hamburg/Rhein-Neckar-Karlsruhe, Germany; randomly drawn from population registries	-	1777	Custom Illumina Infinium iSelect array
Molecular Markers in Treatment of Endometrial Cancer	MoMaTEC	Norway; population based case-control study	637	183	Custom Illumina Infinium iSelect array
Norwegian Breast Cancer Study	NBCS	Tromso/Bergen, Norway; attendees at Norwegian Breast Cancer Screening Program	-	70	Custom Illumina Infinium iSelect array
Cancer Hormone Replacement Epidemiology in Sweden	CAHRES	Sweden; population based case-control study	554	1374	Custom Illumina Infinium iSelect array
Registry of Endometrial Cancer in Sweden	RENDOCAS	Stockholm, Sweden; hospital based study	262	-	Custom Illumina Infinium iSelect array
Karolinska Breast Cancer Study	KARBAC	Stockholm, Sweden; blood donors	-	660	Custom Illumina Infinium iSelect array
Karolinska Mammography Project for Risk Prediction of Breast Cancer	pKARMA	Helsingborg/Stockholm, Sweden; cancer-free participants in KARMA mammographic screening program	-	5529	Custom Illumina Infinium iSelect array
TOTAL			***6,608***	***37,925***	

* For further details of substudies, please see Painter et al Hum Mol Genet. (2015) 24:1478-92.
The number of cases and controls represents the maximum number of genotypes from cases and controls of reported Caucasian ethnicity, following exclusions

**For the iCOGS sample sets, studies which are grouped together in the table were analysed as a single strata.

Supplemental Table 2. Average BMIs in the ANECS, SEARCH and iCOGS endometria

	Range	Mean (SD)	Pdiff*	N
ANECS				
Cases	18.8-75.0	32.1 (8.9)	2.7×10^{-17}	585
Controls	16.5-47.4	28.7 (4.7)		631
SEARCH				
Cases	16.1-60.8	29.1 (6.5)	2.4×10^{-16}	644
Controls	17.2-54.2	26.7 (5.3)		1259
iCOGs				
All cases	15.2-66.7	29.5 (7.3)	4.3×10^{-105}	2864
Endometrioid-only	16.4-66.7	29.8 (7.5)	6.9×10^{-93}	2256
Non-endometrioid	15.2-54.2	28.6 (6.5)	1.9×10^{-16}	578
Controls	15.4-67.9	26.3 (4.9)		14098

*: *P* -value for a 2-tailed Student's t-test of unequal variances between cases and controls

ıl cancer datasets.

Supplementary Table 3. Association of 77 body mass index (BMI) SNPs with endometrial cancer risk and BMI in the endometrial cancer dataset

The single SNP passing the study-wide signficance threshold for significant association with endometrial cancer risk $(0.05/124)=4.0\times10^{-4}$) is shown in bold.

							Association with endometrial cancer risk				**Association with BMI in this dataset**			
SNP[1]	**CHR**	**Build 19 Position**	**Notable Genes**[2]	**BMI effect size**[3]	**Effect allele**	**Other allele**	***P*-value**	**OR (SE)**	**Q**	**I**	***P*-value**	**Beta SE)**	**Q**	**I**
rs657452	1	49589847	*AGBL4*	0.023	A	G	8.2×10^{-1}	1.00 (0.02)	0.79	0	2.1×10^{-1}	0.01 (0.01)	0.268	24.1
rs11583200	1	50559820	*ELAVL4*	0.018	C	T	9.4×10^{-2}	0.96 (0.02)	0.33	12.81	8.8×10^{-1}	0.00 (0.01)	0.433	0
rs3101336	1	72751185	*NEGR1*	0.033	C	T	2.9×10^{-1}	1.02 (0.02)	0.48	0	4.3×10^{-3}	0.03 (0.01)	0.251	27.7
rs12566985	1	75002193	*FPGT-TNN13K*	0.024	G	A	9.3×10^{-1}	1.00 (0.02)	0.2	35.23	3.8×10^{-1}	0.01 (0.01)	0.179	41.9
rs12401738	1	78446761	*FUBP1, USP33*	0.021	A	G	2.3×10^{-1}	0.97 (0.02)	0.95	0	6.6×10^{-1}	0.00 (0.01)	0.944	0
rs11165643	1	96924097	*PTBP2*	0.022	T	C	1.2×10^{-1}	1.03 (0.02)	0.89	0	9.4×10^{-2}	0.02 (0.01)	0.151	47.2
rs17024393	1	110154688	*GNAT2, AMPD2*	0.066	C	T	7.4×10^{-2}	1.11 (0.06)	0.09	54.09	2.4×10^{-1}	0.03 (0.03)	0.084	59.6
rs543874	1	177889480	*SEC16B*	0.048	G	A	7.5×10^{-1}	0.99 (0.02)	0.67	0	2.4×10^{-8}	0.07 (0.01)	0.4	0
rs2820292	1	201784287	*NAV1*	0.02	C	A	5.5×10^{-2}	1.04 (0.02)	0.35	9.32	1.5×10^{-2}	0.02 (0.01)	0.086	59.2
rs13021737	2	632348	*TMEM18*	0.06	G	A	9.0×10^{-1}	1.00 (0.03)	0.5	0	2.4×10^{-4}	0.05 (0.01)	0.381	0
rs10182181	2	25150296	*ADCY3, POMC, NCOA1*	0.031	G	A	4.5×10^{-1}	1.02 (0.02)	0.96	0	1.8×10^{-3}	0.04 (0.01)	0.072	62
rs11126666	2	26928811	*KCNK3*	0.021	A	G	2.9×10^{-1}	1.03 (0.03)	0.12	48.53	7.2×10^{-1}	0.01 (0.01)	0.132	50.5
rs1016287	2	59305625	*LINC01122*	0.023	T	C	7.7×10^{-1}	1.01 (0.02)	0.38	1.36	1.6×10^{-2}	0.03 (0.01)	0.936	0
rs11688816	2	63053048	*EHBP1*	0.017	G	A	8.9×10^{-1}	1.00 (0.02)	0.99	0	2.0×10^{-2}	0.02 (0.01)	0.541	0
rs2121279	2	143043285	*LRP1B*	0.025	T	C	5.6×10^{-3}	1.09 (0.03)	0.33	12.28	3.9×10^{-3}	0.05 (0.01)	0.631	0
rs1528435	2	181550962	*UBE2E3*	0.018	T	C	9.2×10^{-1}	0.99 (0.02)	0.34	10.57	2.4×10^{-1}	0.01 (0.01)	0.736	0
rs7599312	2	213413231	*ERBB4*	0.022	G	A	9.2×10^{-1}	0.99 (0.02)	0.24	28.64	8.7×10^{-1}	0.00 (0.01)	0.762	0
rs6804842	3	25106437	*RARB*	0.019	G	A	9.6×10^{-1}	0.99 (0.02)	0.05	62.17	4.0×10^{-1}	0.01 (0.01)	0.776	0
rs2365389	3	61236462	*FHIT*	0.02	C	T	9.2×10^{-1}	1.00 (0.02)	0.16	41.12	3.5×10^{-1}	0.01 (0.01)	0.128	51.3
rs3849570	3	81792112	*GBE1*	0.019	A	C	3.7×10^{-1}	1.02 (0.02)	0.82	0	2.3×10^{-1}	0.01 (0.01)	0.724	0
rs13078960	3	85807590	*CADM2*	0.03	G	T	5.2×10^{-1}	0.98 (0.02)	0.07	57.63	5.0×10^{-1}	0.01 (0.01)	0.718	0
rs16851483	3	141275436	*RASA2*	0.048	T	G	9.0×10^{-1}	0.99 (0.04)	0.55	0	2.3×10^{-4}	0.08 (0.02)	0.757	0

rs1516725	3	185824004	*ETV5*	0.045	C	T	4.4×10^{-1}	1.02 (0.03)	0.95	0	2.7×10^{-2}	0.03 (0.01)	0.791	0
rs10938397	4	45182527	*GNPDA2, GABRG1*	0.04	G	A	1.3×10^{-1}	1.03 (0.02)	0.86	0	2.4×10^{-3}	0.03 (0.01)	0.249	28.2
rs17001654	4	77129568	*SCARB2*	0.031	G	C	2.6×10^{-1}	1.03 (0.03)	0.14	45.44	4.4×10^{-2}	0.03 (0.01)	0.004	82
rs13107325	4	103188709	*SLC39A8*	0.048	T	C	2.7×10^{-1}	1.05 (0.04)	0.89	0	5.7×10^{-2}	0.04 (0.02)	0.986	0
rs11727676	4	145659064	*HHIP*	0.036	T	C	8.1×10^{-3}	1.12 (0.04)	0.5	0	1.5×10^{-3}	0.07 (0.02)	0.875	0
rs2112347	5	75015242	*POC5, HMGCR, COL4A3BP*	0.026	T	G	4.5×10^{-1}	0.98 (0.02)	0.39	0	2.7×10^{-2}	0.02 (0.01)	0.291	19.1
rs205262	6	34563164	*C6orf106, SNRPC*	0.009	G	A	1.9×10^{-1}	1.03 (0.02)	0.61	0	1.2×10^{-4}	0.04 (0.01)	0.447	0
rs2033529	6	40348653	*TDRG1*	0.019	G	A	2.7×10^{-1}	1.03 (0.03)	0.95	0	2.2×10^{-2}	0.03 (0.01)	0.363	1.41
rs2207139	6	50845490	*TFAP2B*	0.045	G	A	4.3×10^{-1}	1.02 (0.03)	0.67	0	1.5×10^{-2}	0.03 (0.01)	0.947	0
rs9400239	6	108977663	*FOXO3*	0.019	C	T	9.5×10^{-1}	0.99 (0.02)	0.17	39.5	1.1×10^{-2}	0.03 (0.01)	0.444	0
rs13191362	6	163033350	*PARK2*	0.028	A	G	5.2×10^{-1}	1.02 (0.03)	0.04	63.73	6.0×10^{-1}	0.01 (0.01)	0.084	59.6
rs1167827	7	75163169	*HIP1*	0.02	G	A	8.3×10^{-1}	0.99 (0.02)	0.25	27.55	2.9×10^{-1}	0.01 (0.01)	0.474	0
rs2245368	7	76608143	*PMS2L11*	0.032	C	T	6.5×10^{-1}	0.98 (0.03)	0.93	0	3.9×10^{-1}	-0.02 (0.02)	0.258	26.1
rs17405819	8	76806584	*HNF4G*	0.022	T	C	4.9×10^{-3}	1.06 (0.02)	0.48	0	2.1×10^{-2}	0.02 (0.01)	0.676	0
rs2033732	8	85079709	*RALYL*	0.019	C	T	6.4×10^{-1}	1.01 (0.02)	0.82	0	2.5×10^{-1}	-0.02 (0.01)	0.349	5.05
rs4740619	9	15634326	*C9orf93*	0.018	T	C	7.2×10^{-1}	1.01 (0.02)	0.83	0	2.0×10^{-1}	0.01 (0.01)	0.65	0
rs10968576	9	28414339	*LINGO2*	0.025	G	A	8.3×10^{-2}	1.04 (0.02)	0.81	0	1.5×10^{-4}	0.04 (0.01)	0.367	0.18

rs6477694	9	111932342	*EPB41L4B*	0.017	C	T	$8.3x10^{-1}$	1.00 (0.02)	0.81	0	$7.1x10^{-1}$	0.00 (0.01)	0.02	74.5
rs1928295	9	120378483	*TLR4*	0.019	T	C	$6.5x10^{-1}$	1.01 (0.02)	0.85	0	$7.0x10^{-1}$	0.00 (0.01)	0.582	0
rs10733682	9	129460914	*LMX1*	0.017	A	G	$5.0x10^{-1}$	1.01 (0.02)	0.7	0	$5.3x10^{-1}$	0.01 (0.01)	0.479	0
rs7899106	10	87410904	*GRID1*	0.04	G	A	$3.6x10^{-1}$	1.04 (0.05)	0.66	0	$2.5x10^{-1}$	0.03 (0.02)	0.53	0
rs17094222	10	102395440	*HIF1AN*	0.025	C	T	$4.6x10^{-1}$	0.98 (0.02)	0.38	1.52	$1.2x10^{-2}$	0.03 (0.01)	0.175	42.6
rs11191560	10	104869038	*NT5C2*	0.031	C	T	$1.4x10^{-1}$	1.05 (0.04)	0.62	0	$4.1x10^{-3}$	0.05 (0.02)	0.813	0
rs7903146	10	115022404	*TCF7*	0.023	C	T	$9.0x10^{-4}$	1.08 (0.02)	0.24	28.21	$1.4x10^{-1}$	0.02 (0.01)	0.729	0
rs4256980	11	8673939	*TRIM66, TUB*	0.021	G	C	$3.9x10^{-2}$	1.04 (0.02)	0.7	0	$4.9x10^{-1}$	0.99 (0.01)	0.026	72.7
rs11030104	11	27684517	*BDNF*	0.041	A	G	$4.5x10^{-2}$	1.05 (0.02)	0.28	32.61	$2.3x10^{-2}$	0.03 (0.01)	0.179	42
rs2176598	11	43864278	*HSD17B12*	0.02	T	C	$2.7x10^{-1}$	0.97 (0.02)	0.26	24.52	$9.9x10^{-1}$	0.00 (0.01)	0.306	15.6
rs3817334	11	47650993	*MTCH2, C1QTNF4, SPI1, CELF1*	0.026	T	C	$1.7x10^{-1}$	1.03 (0.02)	0.99	0	$2.7x10^{-3}$	0.03 (0.01)	0.205	36.9
rs12286929	11	115022404	*CADM1*	0.022	G	A	$1.0x10^{-1}$	1.00 (0.02)	0.55	0	$9.7x10^{-2}$	0.02 (0.01)	0.556	0
rs7138803	12	50247468	*BCDIN, FAIM*	0.032	A	G	$3.4x10^{-1}$	1.02 (0.02)	0.47	0	$3.0x10^{-3}$	0.03 (0.01)	0.456	0
rs11057405	12	122781897	*CLIP1*	0.031	G	A	$4.7x10^{-1}$	1.02 (0.04)	0.62	0	$4.3x10^{-3}$	0.05 (0.02)	0.181	41.6
rs9581854[4]	13	28017782	*MTIF3, GTF3A*	0.03	T	C	$6.4x10^{-2}$	1.05 (0.02)	0.25	26.73	$2.8x10^{-2}$	0.03 (0.01)	0.396	0
rs12429545	13	54102206	*OLFM4*	0.033	A	G	$4.2x10^{-2}$	1.07 (0.03)	0.69	0	$1.3x10^{-2}$	0.09 (0.03)	0.633	0
rs10132280	14	25928179	*STXBP6*	0.023	C	A	$7.8x10^{-1}$	0.99 (0.02)	0.78	0	$1.6x10^{-1}$	0.01 (0.01)	0.639	0
rs12885454	14	29736838	*FOXG1, PRKD1*	0.021	C	A	$2.5x10^{-1}$	1.02 (0.02)	0.94	0	$4.3x10^{-2}$	0.02 (0.01)	0.893	0
rs11847697	14	30515112	*PRKD1*	0.049	T	C	$1.4x10^{-1}$	1.09 (0.06)	0.75	0	$3.2x10^{-1}$	0.03 (0.03)	0.261	25.6
rs7141420	14	79899454	*NRXN3*	0.024	T	C	$6.6x10^{-2}$	1.04 (0.02)	0.26	25.36	$1.7x10^{-3}$	0.04 (0.01)	0.121	52.7
rs3736485	15	51748610	*DMXL2*	0.018	A	G	$7.8x10^{-1}$	0.99 (0.02)	0.47	0	$1.5x10^{-1}$	0.01 (0.01)	0.897	0
rs16951275	15	68077168	*MAP2K5, LBXCOR*	0.031	T	C	$4.4x10^{-2}$	1.05 (0.02)	0.74	0	$2.6x10^{-3}$	0.04 (0.01)	0.026	72.6
rs758747	16	3627358	*NLRC3*	0.023	T	C	$9.8x10^{-1}$	1.00 (0.02)	0.8	0	$8.7x10^{-3}$	0.03 (0.01)	0.171	43.4
rs12446632	16	19935389	*GPRC5B, IQCK*	0.04	G	A	$1.0x10^{-1}$	1.05 (0.03)	0.19	36.75	$2.7x10^{-3}$	0.04 (0.01)	0.53	0

rs2650492	16	28333411	*SBK1*	0.021	A	G	$6.7x10^{-3}$	1.08 (0.03)	0.94	0	$8.4x10^{-2}$	0.02 (0.01)	0.343	6.52
rs3888190	16	28889486	*ATXN2, SBK1, SULTA2, TUFM*	0.031	A	C	$3.1x10^{-3}$	1.06 (0.02)	0.32	13.27	$7.3x10^{-4}$	0.03 (0.01)	0.474	0
rs9925964	16	31129895	*KAT8*	0.019	A	G	$8.3x10^{-2}$	1.03 (0.02)	0.67	0	$5.7x10^{-2}$	0.02 (0.01)	0.088	59
rs1558902	16	53803574		0.082	A	T	$2.8x10^{-2}$	1.05 (0.02)	0.04	64.35	$2.0x10^{-18}$	0.09 (0.01)	0.447	0
rs1000940	17	5283252	*RABEP*	0.019	G	A	$3.2x10^{-1}$	1.02 (0.02)	0.95	0	$1.5x10^{-1}$	0.01 (0.01)	0.589	0
rs12940622	17	78615571	*RPTOR*	0.018	G	A	$8.0x10^{-2}$	1.04 (0.02)	0.45	0	$1.1x10^{-1}$	0.02 (0.01)	0.445	0
rs1808579	18	21104888	*NPC1, C18orf8*	0.017	C	T	$1.3x10^{-1}$	1.03 (0.02)	0.83	0	$3.2x10^{-2}$	0.02 (0.01)	0.635	0
rs7243357	18	56883319	*GRP*	0.022	T	G	$2.3x10^{-1}$	1.03 (0.03)	0.74	0	$2.5x10^{-2}$	0.03 (0.01)	0.324	11.3
rs6567160	18	57829135	*MC4R*	0.056	C	T	$3.0x10^{-1}$	1.02 (0.02)	0.08	54.86	$8.1x10^{-11}$	0.08 (0.01)	0.829	0
rs17724992	19	18454825	*PGPEP1*	0.019	A	G	$8.3x10^{-4}$	1.08 (0.02)	0.29	19.86	$1.0x10^{-2}$	0.03 (0.01)	0.844	0
rs29941	19	34309532	KCTD1	0.018	G	A	$6.6x10^{-1}$	1.01 (0.02)	0.36	7.08	$1.8x10^{-2}$	0.02 (0.01)	0.356	3.27
rs2075650	**19**	**45395619**	***TOMM40, APOE, APOC1***	**0.026**	**A**	**G**	$\mathbf{2.4x10^{-4}}$	**1.13 (0.03)**	**0.25**	**26.82**	$2.9x10^{-1}$	0.02 (0.01)	0.503	0
rs2287019	19	46202172	*QPCTL, GIPR*	0.036	C	T	$1.8x10^{-1}$	1.03 (0.03)	0.35	8.06	$9.8x10^{-4}$	0.05 (0.01)	0.555	0
rs3810291	19	47569003	*ZC3H4*	0.028	A	G	$3.7x10^{-1}$	1.02 (0.02)	0.06	58.58	$2.3x10^{-2}$	0.02 (0.01)	0.929	0

[1] All SNPs had reached genome-wide significance in the primary BMI analysis by Locke et al., 2015 (2) *i.e* . SNPs significantly associated with BMI in secondary or conditional analyses, or analyses including other ancestries were not included her

[2] Genes notable for biological relevance as reported in Locke et al., 2015 (2).

[3] SNP-BMI regression coefficients as presented by the GIANT consortium (Locke et al., 2015) (2), for an inverse-normalised transformation of BMI; the effects on the kg/m2 scale cannot be derived.

[4] Perfect proxy (r^2 =1) for BMI SNP rs12016871.

Supplementary Table 4. Association of 47 waist-hip ratio (WHR) SNPs with endometrial cancer risk
The single SNP passing the study-wide signficance threshold for significant association with endomet

SNP[1]	CHR	Build19 Position	Nearest Gene	Combined effect size[2]	Effect size in women only[2]
SNPs associated with WHR at a genome-wide level of significance in women					
rs2645294	1	119574587	*TBX15-WARS2*	0.031	0.035
rs905938	1	154991389	*DCST2*	0.025	0.034
rs10919388	1	170372503	*GORAB*	0.024	0.033
rs714515	1	172352990	*DNM3-PIGC*	0.027	0.029
rs2820443	1	219753509	*LYPLAL1*	0.035	0.062
rs10195252	2	165513091	*GRB14-COBLL1*	0.027	0.052
rs17819328	3	12489342	*PPARG*	0.021	0.035
rs2276824	3	52637486	*PBRM1*	0.024	0.028
rs2371767	3	64718258	*ADAMTS9*	0.036	0.056
rs10804591	3	129334233	*PLXND1*	0.025	0.04
rs3805389	4	56482750	*NMU*	0.012	0.027
rs9991328	4	89713121	*FAM13A*	0.019	0.028
rs9687846	5	55861894	*MAP3K1*	0.024	0.041
rs1045241	5	118729286	*TNFAIP8-HSD17B4*	0.019	0.035
rs7705502	5	173320815	*CPEB4*	0.027	0.027
rs1294410	6	6738752	*LY86*	0.031	0.037
rs1776897	6	34195011	*BTNL2*	0.03	0.052
rs1358980	6	43764551	*VEGFA*	0.039	0.06
rs1936805	6	127452116	*RSPO3*	0.043	0.052
rs10245353	7	25858614	*NFE2L3*	0.035	0.041
rs7830933	8	23603324	*NKX2-6*	0.022	0.037
rs12679556	8	72514228	*MSC*	0.027	0.033
rs10991437	9	107735920	*ABCA1*	0.031	0.04
rs7917772	10	104487443	*SFXN2*	0.014	0.027
rs11231693	11	63862612	*MACROD1-VEGFB*	0.041	0.068
rs10842707	**12**	**26471364**	***ITPR2-SSPN***	**0.032**	**0.041**
rs1443512	12	54342684	*HOXC13*	0.028	0.04
rs4765219	12	124440110	*CCDC92*	0.028	0.037
rs2925979	16	81534790	*CMIP*	0.018	0.032
rs4646404	17	17420199	*PEMT*	0.027	0.034
rs8066985	17	68453345	*KCNJ2*	0.018	0.026
rs12454712	18	60845884	*BCL2*	0.016	0.035
rs6090583	20	45558831	*EYA2*	0.022	0.029
rs2294239	22	29449477	*ZNRF3*	0.025	0.028

Additional WHR-associated SNPs GWS in sex-combined analyses

SNP[1]	CHR	Build19 Position	Nearest Gene	Combined effect size[2]	Effect size in women only[2]
rs1385167	2	66200648	*MEIS1*	0.029	0.023
rs1569135	2	188115398	*CALCRL*	0.021	0.023
rs17451107	3	156797609	*LEKR1*	0.026	0.023
rs303084	4	124066948	*SPATA5-FGF2*	0.023	0.029
rs6556301	5	176527577	*FGFR4*	0.022	0.018
rs7801581	7	27223771	*HOXA11*	0.027	0.025
rs8042543	15	31708263	*KLF13*	0.026	0.023
rs8030605	15	56504598	*RFX7*	0.03	0.031
rs1440372	15	67033151	*SMAD6*	0.024	0.022
rs12608504	19	18389135	*JUND*	0.022	0.017
rs4081724	19	33824946	*CEBPA*	0.035	0.033
rs979012	20	6623374	*BMP2*	0.027	0.026
rs224333	20	34023962	*GDF5*	0.02	0.009

[1] All SNPs had reached genome-wide significance in the primary WHR analysis by Shungin et al. (20

[2] Effect size overall and in women as reported in Shungin et al. (2015) (2).

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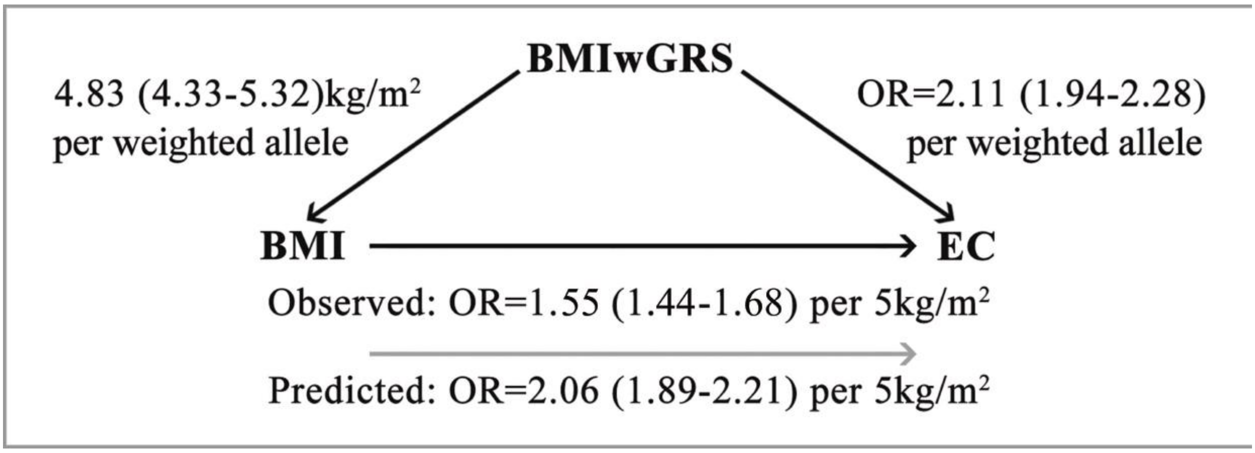
rial cancer risk (0.05/124)=4.0x10^{-4}) is shown in bold.

Effect allele	Other allele	*P*-value	OR (SE)	Q	I
T	C	9.8x10^{-1}	1.00 (0.00)	0.8214	0
T	C	1.5x10^{-1}	0.97 (0.02)	0.9711	0
C	A	2.4x10^{-2}	1.06 (0.03)	0.8649	0
G	A	7.0x10^{-1}	1.01 (0.03)	0.2838	21.07
T	C	5.0x10^{-4}	0.92 (0.02)	0.9872	0
T	C	1.9x10^{-1}	0.97 (0.02)	0.956	0
G	T	6.7x10^{-1}	0.99 (0.02)	0.7251	0
C	T	6.1x10^{-1}	1.01 (0.02)	0.8992	0
G	T	2.1x10^{-1}	1.03 (0.02)	0.4872	0
A	C	5.8x10^{-1}	1.01 (0.02)	0.691	0
A	G	2.6x10^{-1}	0.97 (0.03)	0.1325	46.48
T	C	7.6x10^{-1}	1.01 (0.03)	0.1946	36.26
A	G	7.8x10^{-1}	1.01 (0.04)	0.9855	0
C	T	6.5x10^{-1}	1.01 (0.02)	0.3147	15.43
A	G	2.2x10^{-2}	1.05 (0.02)	0.243	28.17
C	G	8.8x10^{-1}	0.99 (0.02)	0.6998	0
G	T	5.5x10^{-1}	0.98 (0.03)	0.47	0
T	C	9.0x10^{-1}	0.99 (0.02)	0.4741	0
T	C	4.0x10^{-2}	0.96 (0.02)	0.2482	27.29
A	G	4.5x10^{-1}	0.98 (0.03)	0.4852	0
A	G	4.3x10^{-1}	1.02 (0.03)	0.5918	0
G	T	5.2x10^{-1}	1.02 (0.03)	0.2768	22.32
A	C	2.9x10^{-2}	0.93 (0.03)	0.5853	0
A	G	5.1x10^{-1}	1.01 (0.02)	0.389	0.57
A	G	2.5x10^{-1}	0.95 (0.04)	0.7827	0
T	**C**	**3.7x10^{-4}**	**1.09 (0.02)**	**0.6478**	**0**
A	G	6.1x10^{-1}	1.01 (0.02)	0.5473	0
C	A	4.2x10^{-1}	0.98 (0.02)	0.7768	0
T	C	6.7x10^{-1}	1.01 (0.02)	0.1047	51.19
G	A	9.2x10^{-2}	1.04 (0.02)	0.6372	0
A	G	6.1x10^{-1}	1.01 (0.02)	0.6208	0
T	C	9.3x10^{-1}	0.99 (0.02)	0.4566	0
A	G	2.0x10^{-1}	1.03 (0.02)	0.2281	30.69
A	G	4.5x10^{-1}	1.02 (0.02)	0.7895	0

Effect allele	Other allele	*P* -value	OR (SE)	Q	I
G	A	$9.3x10^{-1}$	1.00 (0.02)	0.658	0
A	G	$2.3x10^{-2}$	1.05 (0.02)	0.1328	46.43
T	C	$2.6x10^{-1}$	1.02 (0.02)	0.8886	0
A	G	$5.4x10^{-3}$	0.93 (0.03)	0.3866	1.09
T	G	$3.1x10^{-1}$	0.98 (0.02)	0.0804	55.54
T	C	$3.0x10^{-1}$	0.97 (0.02)	0.0123	72.45
C	T	$9.9x10^{-1}$	1.00 (0.00)	0.014	71.75
A	G	$5.6x10^{-1}$	0.98 (0.03)	0.9006	0
C	T	$5.4x10^{-1}$	1.02 (0.03)	0.7011	0
A	G	$2.6x10^{-1}$	1.02 (0.03)	0.4026	0
G	A	$1.3x10^{-1}$	1.04 (0.03)	0.8044	0
T	C	$9.2x10^{-2}$	1.04 (0.02)	0.7525	0
G	A	$1.3x10^{-1}$	1.03 (0.01)	0.5973	0

15) (2) *i.e* . SNPs significantly associated with WHR in secondary or conditional analyses, or analyses

including other ancestries were not included here.


BMIwGRS
4.83 (4.33-5.32)kg/m2
per weighted allele
OR=2.11 (1.94-2.28)
per weighted allele
BMI
EC
Observed: OR=1.55 (1.44-1.68) per 5kg/m2
Predicted: OR=2.06 (1.89-2.21) per 5kg/m2