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ARTICLE

Genetics and Genomics

Identifying causality, genetic correlation, priority and pathways of large-scale complex exposures of breast and ovarian cancers

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BACKGROUND: Genetic correlations, causalities and pathways between large-scale complex exposures and ovarian and breast cancers need systematic exploration.
METHODS: Mendelian randomisation (MR) and genetic correlation (GC) were used to identify causal biomarkers from 95 cancer-related exposures for risk of breast cancer [BC: oestrogen receptor-positive (ER + BC) and oestrogen receptor-negative (ER − BC) subtypes] and ovarian cancer [OC: high-grade serous (HGSOC), low-grade serous, invasive mucinous (IMOC), endometrioid (EOC) and clear cell (CCOC) subtypes].
RESULTS: Of 31 identified robust risk factors, 16 were new causal biomarkers for BC and OC. Body mass index (BMI), body fat mass (BFM), comparative body size at age 10 (CBS-10), waist circumference (WC) and education attainment were shared risk factors for overall BC and OC. Childhood obesity, BMI, CBS-10, WC, schizophrenia and age at menopause were significantly associated with ER + BC and ER − BC. Omega-6:omega-3 fatty acids, body fat-free mass and basal metabolic rate were positively associated with CCOC and EOC; BFM, linoleic acid, omega-6 fatty acids, CBS-10 and birth weight were significantly associated with IMOC; and body fat percentage, BFM and adiponectin were significantly associated with HGSOC. Both GC and MR identified 13 shared factors. Factors were stratified into five priority levels, and visual causal networks were constructed for future interventions.
CONCLUSIONS: With analysis of large-scale exposures for breast and ovarian cancers, causalities, genetic correlations, shared or specific factors, risk factor priority and causal pathways and networks were identified.

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BACKGROUND

Cancer is an important cause of worldwide morbidity and mortality. Breast cancer (BC) accounted for approximately one in four cancer cases among women in 2018 [1], and ovarian cancer (OC) is the second most common form and leading cause of death due to cancer in the female reproductive system [2]. Although hereditary factors can explain 5–10% of the risk for breast or ovarian cancer [1], non-hereditary factors remain the major drivers. One-third to two-fifths of new cancer cases could be avoided by eliminating or reducing exposure to known risk factors [1, 3–5]. Thus, primary preventive measures that can reduce risk of BC and OC by targeting intervention on complex causal biomarkers or pathways are of increasing interest.

Unobserved confounding and reverse causality limit the ability of epidemiological observational studies to identify causalities. Observational studies are also often limited in acquiring large-scale exposure measurements, whereas randomised clinical trials are not widely available because of ethical concerns, high cost and long duration [6]. Recently, thousands of summary-level statistics from genome-wide association studies (GWASs) have provided great opportunities to support wide-range causal findings. Mendelian randomisation (MR) uses genome-wide significant genetic variants as instrumental variables (IVs) that can accurately assess the causal effect and direction of one exposure on a specific outcome after ruling out unobserved confounders in theory ("causal" represents the causality in statistics). Genetic correlation (GC) analysis can identify the common genetic risk between two specific traits [7]. Identifying GCs can provide useful etiological insights and help prioritise likely causal relationships [7]. Combining GC with MR can be used to identify direct causal relations and shared genetic risks for an exposure–outcome pair.

To date, MR has been used to explore the effects of alcohol consumption and glycemic, lipids and obesity traits on ovarian and breast cancers [6, 8–11]. Although many causal biomarkers have been identified, focusing on a specific exposure can provide only limited evidence for primary prevention, compared with focusing on a wide range of potential biomarkers. In addition, genome-wide correlations between BC and OC and complex exposures remain unclear. There is intense interest identifying these associations because the shared genetic architecture and

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causal associations can provide valuable references for joint, precise and priority intervention targets. Although information has been obtained on many risk factors, prioritising these factors remains essential. Complex network pathways may also occur that lead from extensive exposures to the occurrence of cancer, which may involve mediators as potential targets. Si et al. used network-MR to study biomarkers and complex metabolic pathways [12]. With a network, upstream or downstream targets for a specific risk factor can be identified and also contribute to primary prevention.

In this study, large-scale genomic summary-level statistics were used in a comprehensive analysis to gain insight into the complex relations of 95 cancer-related factors and nine cancer types. The aim of the research was to screen for robust causal biomarkers of BC and OC and then identify shared or distinct risk factors, stratify risks by priority and construct visual causal networks to guide prevention measures.

METHODS

Determination of exposures

Risk factors associated with human cancers were hypothesised to also have potential carcinogenic mechanisms in the occurrence of breast and ovarian cancers. To determine candidate exposures, all MR analyses (Supplementary Table S1) were reviewed for any cancer types, and only the factors with available summary-level datasets were used in this research. Details about the process are described in Supplementary Text 1. Ultimately, 95 complex traits were included in the study. Except for the established birth length (BIRL), birth weight (BIRW) and age at menarche (AAM), most factors could be modified. Data sources of the 95 exposures are listed in Supplementary Table S2.

Among the factors, literature review showed that only 32 factors had been explored for association with both BC and OC, only 18 for BC and only 1 for OC. The other 44 exposures have not been studied previously in BC and OC (Supplementary Table S2). Previous MR studies have not explored GCs, risk stratification and network pathways for these risk factors on BC or OC. Because of the lack of information, the exposures were examined as candidate factors for BC and OC in this research [13–48]. The 95 factors were further divided into the following categories: anthropometry traits (16), blood biochemistry traits (8), disease traits (5), lifestyle traits (14), lipids/glycemic traits (11), metabolites (13), nutrients (23) and sex-related traits (5) (see Supplementary Text 1 for details).

Data sources of breast and ovarian cancers

Summary statistics for 122,977 cases of breast cancer and 105,974 controls of European ancestry were acquired from a combined study including the Breast Cancer Association Consortium (BCAC), Discovery, Biology and Risk of Inherited Variants in Breast Cancer Consortium (DRIVE), Collaborative Oncological Gene-environment Study (iCOGS) and several other GWAS meta-analyses [49]. Summary statistics of two BC subtypes, oestrogen receptor-positive (ER + BC, 69,501 cases) and oestrogen receptor-negative (ER − BC, 21,468 cases), were also included.

Genetic associations with OC were obtained from the Ovarian Cancer Association Consortium using an Illumina Custom Infinium array (OncoArray) including 25,509 epithelial OC cases and 40,941 controls [50]. The OC cases were further divided into five major invasive histotypes: high-grade serous OC (HGSOC, 13,037 cases), low-grade serous OC (LGSOC, 1012 cases), invasive mucinous OC (IMOC, 1417 cases), endometrioid OC (EOC, 2810 cases) and clear cell OC (CCOC, 1366 cases). Detailed information about BC and OC research populations and sample sizes can be found in Supplementary Text 2 and Supplementary Table S3, as well as the original publications [49, 50].

Statistical analysis

Two-sample Mendelian randomization. The study graph model and flowchart are shown in Fig. 1. The univariate two-sample MR method was used to determine the causal effect of each exposure on a target outcome (Fig. 1a). In the MR analysis, genome-wide significant genetic variants were used as instrumental variables (IVs) to examine causal associations of exposures with OC or BC. The MR approach assumes that IVs (1) are associated with the candidate exposure, (2) are not associated with confounders (upper red cross) and (3) are associated with the outcome only through the candidate exposure but not through other pathways (lower red cross) [51].

Candidate IVs associated with a specific risk factor were determined at the standard threshold of genome-wide significance ($P < 5 \times 10^{-8}$). Furthermore, candidate IVs within the threshold of linkage disequilibrium (LD, $r^2 < 0.01$) were pruned to keep nearly independent IVs. The proportion of variance in the exposure explained by the IVs (R^2) was calculated as $2\beta^2 \times MAF \times (1 - MAF)$, where β is the association of single-nucleotide polymorphisms (SNP) with the exposure and MAF is the minor allele frequency. The F statistic was calculated from the R^2 statistic as $F = [(N - K - 1) / K] \times [R^2 / (1 - R^2)]$, where N is the sample size and K is the number of IVs [52]. Generally, an F value > 10 indicated a strong IV [12, 53].

To acquire the causal estimator, first, the Wald ratio (WRO) was used to estimate causal effects for each SNP. Then, the conventional inverse variance weighted (IVW) MR method was used to aggregate causal estimators of all SNPs for the principal analyses in this research [54]. Furthermore, the weighted median estimator (WME) method was applied simultaneously as one of the sensitivity analyses to assess the robustness of causal findings. The method produces robust estimates in the presence of some invalid genetic instruments (when the number of invalid IVs < 50%) [55]. For those exposures with one IV, only WRO results were reported. Additionally, testing for the intercept of the MR-Egger regression was used to assess horizontal pleiotropy. Significant results in both IVW and WME analysis were viewed as robust associations in this research.

Pairwise multivariate Mendelian randomization. The multivariable MR (MVMR) approach [56] is designed to assess the robustness of causality under the possible horizontal pleiotropy and acquire the direct effects of the interested exposure on the outcome. Currently, a consistent standard for covariates selection from large-scale exposures has not been determined. Because adjusting more covariates causes a sharp decline in the number of IVs, and to avoid unknown bias caused by overadjustment, the causal effect of a specific exposure was assessed by adjusting other exposures one by one (here, pairwise MVMR) (Fig. 1b). The exposures (or covariates) that were selected from the above univariate MR analysis were significant for BC, OC or their subtypes. Adjusted effects of the exposures were estimated by the standard IVW–MVMR method [56]. The pairwise MVMR adjusted for a wide range of covariates was also considered a sensitivity analysis in this research.

Genetic correlation. Cross-trait linkage disequilibrium score regression (LDSC) is a useful epidemiological tool to estimate the GC of two traits (Fig. 1c) [7, 57]. An LDSC analysis can rapidly screen for correlations among a diverse set of traits, without needing to measure multiple traits on the same individuals [7]. Genetic variants used in LDSC usually required whole genome-wide SNPs. To keep a consistent number of SNPs for traits from different consortiums, they were matched with a common SNP list that was used in previous work [58]. The SNP list was a file called "w_hm3.noMHC.snplist" that included ~1.2 million SNPs based on the HapMap 3 reference panel stored in "ldsc" software. It can also be download from the LD Hub website (http://ldsc.broadinstitute.org). In addition, LD Hub website also recommend using this SNP list to reduce the number of SNPs to improve computing performance. In this research, genetic variants of the candidate traits were extracted from the MR Base (https://www.mrbase.org/) or the corresponding consortiums based on the SNP list to retain the common 1.2 million recommended SNPs. Then, the direction of effect values (Z-values) of each SNP across all traits was adjusted to ensure they corresponded to consistent-effect alleles. In GC analysis, the genetic dataset of Europeans from 1000 Genomes was used as a reference to compute LD scores. The genetic correlation coefficient was termed rg, which ranged from −1 to 1. Details about this method are introduced elsewhere [7].

Network Mendelian randomization. Network-MR was used to investigate the intermediate phenotypes in causal pathways to help to construct causal networks from the detected risk factors to outcomes (Fig. 1d) [59]. Network-MR was based on the univariate MR approach to achieve point-by-point analyses for each component (exposure, mediator and outcome), which were robust biomarkers (also include the results of WRO for biomarkers with only one IV) in the principal MR analysis. The initial network-MR framework was composed of three separate two-sample MRs that included pairwise analysis of one trait on another trait, as described elsewhere [12]. The network was organised according to the following steps: (1) keep all significant factors (robust association) of BC and OC (or subtypes) from the univariate MR analysis, (2) perform MR analysis for these factors with one another, (3) select the robust associations (both IVW

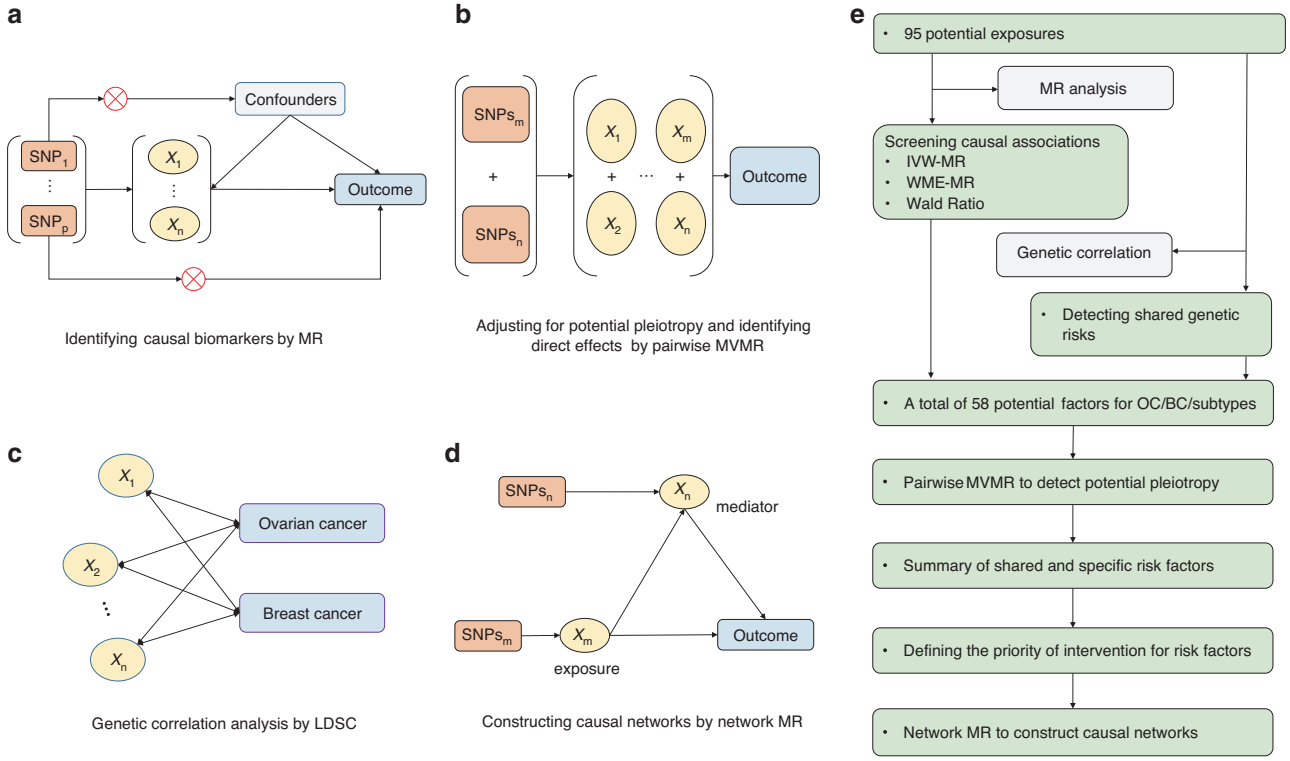


Fig. 1 Study design and framework of this research. Panel **a** was the causal graph of Mendelian randomization (MR), this method should satisfy three assumptions: (1) the IV is associated with the exposure, (2) the IV affects outcome only through the exposure (lower red cross), (3) the IV is not associated with the confounders (upper red cross). Panel **b** was a framework of multivariable MR, which used a pairwise design to measure exposure X_m–X_n pair on the risk of the outcome. The causal effects of candidate exposure X_n on outcome were calculated in turns. Panel **c** showed the framework of genetic correlation, the correlation between factors (X_n) and ovarian/breast cancer was measured. Panel **d** indicated a network-MR framework. This framework utilised the IVs of X_m to acquire the effect of X_m on X_n (potential mediator) and outcome, then, the IVs of X_n were utilised to acquire the effect of X_n on the outcome. Panel **e** was the flowchart of these analyses. LDSC trait linkage disequilibrium score regression, OC ovarian cancer, BC breast cancer, MR Mendelian randomization, IVW inverse variance weighted, WME weighted median estimator, MVMR multivariable Mendelian randomization.

and WME, or WRO) among the factors and (4) connect the significant exposure–exposure pairs and the previous exposure–outcome pairs to construct the final network.

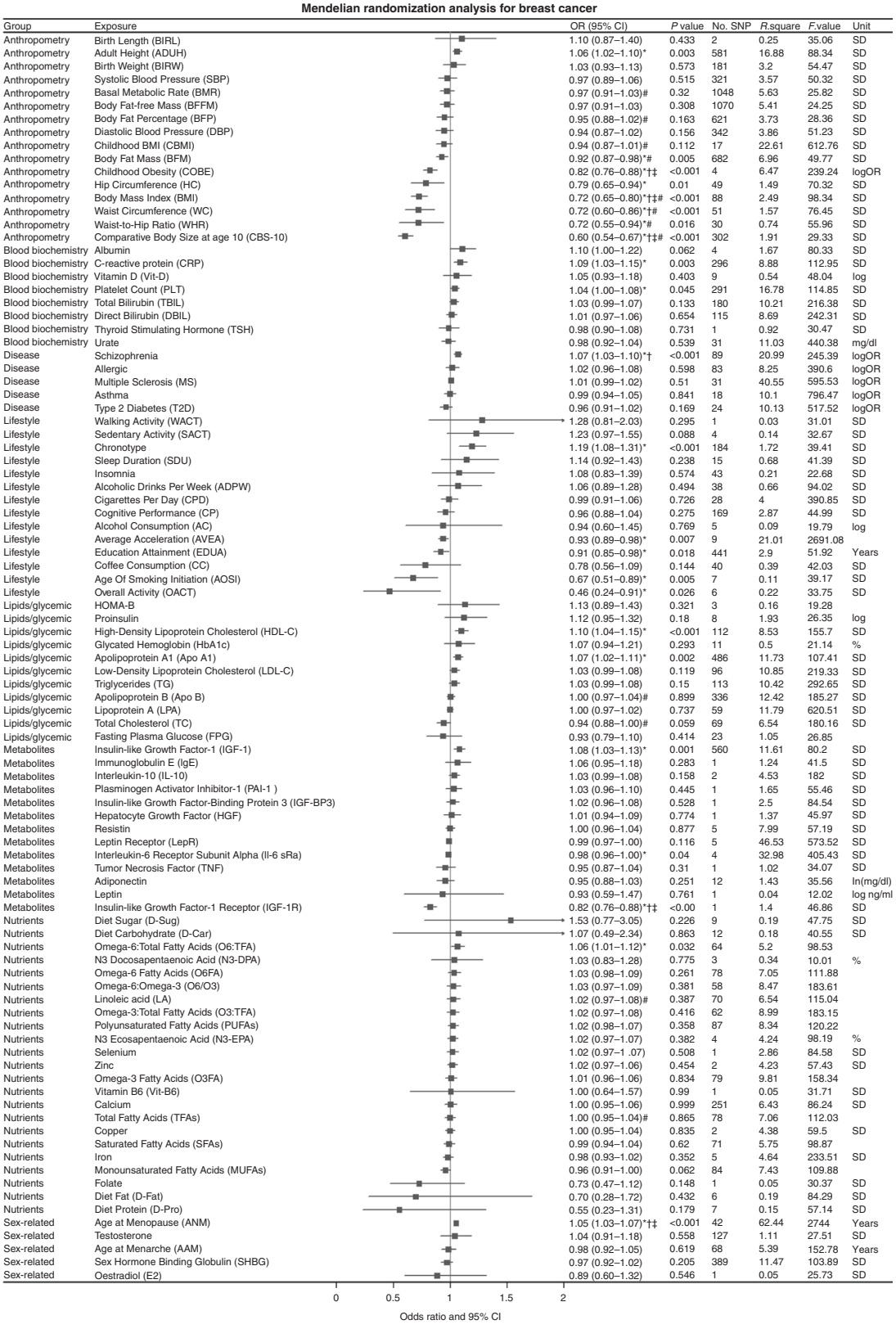
Study procedures. The study flowchart is shown in Fig. 1e. First, the univariable MR method (including IVW, WME and WRO methods) was used to determine the causal effect of each exposure on a target outcome. Simultaneously, cross-trait LDSC was used to measure GCs across OC, BC and large-scale exposures. Then, pairwise MVMR was used to detect potential pleiotropy. Furthermore, the shared and specific risk factors for the outcomes were summarised, and the priority and rank of risk factors were defined. Finally, according to the network-MR design, causal networks for different outcomes were constructed to guide prevention practice.

Risk factors were prioritised at five levels: (1) level 1, robust MR evidence for both BC and OC plus GC evidence; (2) level 2, only robust MR results for both BC and OC; (3) level 3, robust MR evidence plus GC evidence for either BC or OC; (4) level 4, factors only robustly associated with BC or OC but without GC and (5) level 5, remaining MR evidence (only significant in one method), which was suggestive. In addition, a score was defined for each factor to indicate its importance, and then, all significant factors were ranked according to their importance. The score was acquired by adding the number of times a specific exposure was significant for the nine outcomes in the three univariate MR methods and the GC evidence. The level of a factor and its rank indicated the degree of robustness and universality, respectively.

All MR results were reported as odds ratios (ORs) and 95% confidence intervals (CIs) for genetically predicted per standard deviation or per unit increment of each risk factor. Bonferroni-corrected *P*-values (two-tailed) were used to show the significance of multiple testing. Two Bonferroni thresholds were used. The "moderate" one was $P < 5.26 \times 10^{-4}$ (0.05/95), which considered only the number of candidate exposures, whereas the "strict" one was $P < 5.85 \times 10^{-5}$ (0.05/855), which considered both the number of exposures and cancer subtypes. We picked the strict one for standard multiply testing. *P*-values that exceeded the strict Bonferroni threshold but were less than 0.05 indicated a suggestive association. All statistical analyses for MR were performed in the R software v 3.6.2. R package "TwoSampleMR" was used for two-sample MR analysis. Large-scale LDSC analyses were performed using the 'ldsc' software with the Linux system.

RESULTS

Figure 2 shows the associations of 95 genetically determined risk factors with BC in the IVW method or WRO analysis. Twenty-three exposures were significantly associated with overall BC. Positive associations [OR (95% CIs)] were with adult height (ADUH) [1.06 (1.02–1.10)], C-reactive protein (CRP) [1.09 (1.03–1.15)], platelet count (PLT) [1.04 (1.00–1.08)], schizophrenia [1.07 (1.03–1.10)], chronotype [1.19 (1.08–1.31)], high-density lipoprotein cholesterol (HDL-C) [1.10 (1.04–1.15)], apolipoprotein A1 (Apo A1) [1.07 (1.02–1.11)], insulin-like growth factor-1 (IGF-1) [1.08 (1.03–1.13)], omega-6:total fatty acids (O6:TFA) [1.06 (1.01–1.12)] and age at menopause (ANM) [1.05 (1.03–1.07)]. Negative associations were with body fat mass (BFM) [0.92 (0.87–0.98)], childhood obesity (COBE) [0.82 (0.76–0.88)], hip circumference (HC) [0.79 (0.65–0.94)], body mass index (BMI) [0.72 (0.65–0.80)], waist circumference (WC) [0.72 (0.60–0.86)], waist-to-hip ratio (WHR) [0.72 (0.55–0.94)], comparative body size at age 10 (CBS-10) [0.60 (0.54–0.67)], average acceleration (AVEA) [0.93 (0.89–0.98)], education attainment (EDUA) [0.91 (0.85–0.98)], age of smoking initiation (AOSI) [0.67 (0.51–0.89)], overall activity (OACT) [0.46 (0.24–0.91)],



Group	Exposure	OR (95% CI)	*P* value	No. SNP	*R*.square	*F*.value	Unit
Anthropometry	Birth Length (BIRL)	1.10 (0.87–1.40)	0.433	2	0.25	35.06	SD
Anthropometry	Adult Height (ADUH)	1.06 (1.02–1.10)*	0.003	581	16.88	88.34	SD
Anthropometry	Birth Weight (BIRW)	1.03 (0.93–1.13)	0.573	181	3.2	54.47	SD
Anthropometry	Systolic Blood Pressure (SBP)	0.97 (0.89–1.06)	0.515	321	3.57	50.32	SD
Anthropometry	Basal Metabolic Rate (BMR)	0.97 (0.91–1.03)#	0.32	1048	5.63	25.82	SD
Anthropometry	Body Fat-free Mass (BFFM)	0.97 (0.91–1.03)	0.308	1070	5.41	24.25	SD
Anthropometry	Body Fat Percentage (BFP)	0.95 (0.88–1.02)#	0.163	621	3.73	28.36	SD
Anthropometry	Diastolic Blood Pressure (DBP)	0.94 (0.87–1.02)	0.156	342	3.86	51.23	SD
Anthropometry	Childhood BMI (CBMI)	0.94 (0.87–1.01)#	0.112	17	22.61	612.76	SD
Anthropometry	Body Fat Mass (BFM)	0.92 (0.87–0.98)*#	0.005	682	6.96	49.77	SD
Anthropometry	Childhood Obesity (COBE)	0.82 (0.76–0.88)*†‡	<0.001	4	6.47	239.24	logOR
Anthropometry	Hip Circumference (HC)	0.79 (0.65–0.94)*	0.01	49	1.49	70.32	SD
Anthropometry	Body Mass Index (BMI)	0.72 (0.65–0.80)*†‡#	<0.001	88	2.49	98.34	SD
Anthropometry	Waist Circumference (WC)	0.72 (0.60–0.86)*†#	<0.001	51	1.57	76.45	SD
Anthropometry	Waist-to-Hip Ratio (WHR)	0.72 (0.55–0.94)*#	0.016	30	0.74	55.96	SD
Anthropometry	Comparative Body Size at age 10 (CBS-10)	0.60 (0.54–0.67)*†‡#	<0.001	302	1.91	29.33	SD
Blood biochemistry	Albumin	1.10 (1.00–1.22)	0.062	4	1.67	80.33	SD
Blood biochemistry	C-reactive protein (CRP)	1.09 (1.03–1.15)*	0.003	296	8.88	112.95	SD
Blood biochemistry	Vitamin D (Vit-D)	1.05 (0.93–1.18)	0.403	9	0.54	48.04	log
Blood biochemistry	Platelet Count (PLT)	1.04 (1.00–1.08)*	0.045	291	16.78	114.85	SD
Blood biochemistry	Total Bilirubin (TBIL)	1.03 (0.99–1.07)	0.133	180	10.21	216.38	SD
Blood biochemistry	Direct Bilirubin (DBIL)	1.01 (0.97–1.06)	0.654	115	8.69	242.31	SD
Blood biochemistry	Thyroid Stimulating Hormone (TSH)	0.98 (0.90–1.08)	0.731	1	0.92	30.47	SD
Blood biochemistry	Urate	0.98 (0.92–1.04)	0.539	31	11.03	440.38	mg/dl
Disease	Schizophrenia	1.07 (1.03–1.10)*†	<0.001	89	20.99	245.39	logOR
Disease	Allergic	1.02 (0.96–1.08)	0.598	83	8.25	390.6	logOR
Disease	Multiple Sclerosis (MS)	1.01 (0.99–1.02)	0.51	31	40.55	595.53	logOR
Disease	Asthma	0.99 (0.94–1.05)	0.841	18	10.1	796.47	logOR
Disease	Type 2 Diabetes (T2D)	0.96 (0.91–1.02)	0.169	24	10.13	517.52	logOR
Lifestyle	Walking Activity (WACT)	1.28 (0.81–2.03)	0.295	1	0.03	31.01	SD
Lifestyle	Sedentary Activity (SACT)	1.23 (0.97–1.55)	0.088	4	0.14	32.67	SD
Lifestyle	Chronotype	1.19 (1.08–1.31)*	<0.001	184	1.72	39.41	SD
Lifestyle	Sleep Duration (SDU)	1.14 (0.92–1.43)	0.238	15	0.68	41.39	SD
Lifestyle	Insomnia	1.08 (0.83–1.39)	0.574	43	0.21	22.68	SD
Lifestyle	Alcoholic Drinks Per Week (ADPW)	1.06 (0.89–1.28)	0.494	38	0.66	94.02	SD
Lifestyle	Cigarettes Per Day (CPD)	0.99 (0.91–1.06)	0.726	28	4	390.85	SD
Lifestyle	Cognitive Performance (CP)	0.96 (0.88–1.04)	0.275	169	2.87	44.99	SD
Lifestyle	Alcohol Consumption (AC)	0.94 (0.60–1.45)	0.769	5	0.09	19.79	log
Lifestyle	Average Acceleration (AVEA)	0.93 (0.89–0.98)*	0.007	9	21.01	2691.08	
Lifestyle	Education Attainment (EDUA)	0.91 (0.85–0.98)*	0.018	441	2.9	51.92	Years
Lifestyle	Coffee Consumption (CC)	0.78 (0.56–1.09)	0.144	40	0.39	42.03	SD
Lifestyle	Age Of Smoking Initiation (AOSI)	0.67 (0.51–0.89)*	0.005	7	0.11	39.17	SD
Lifestyle	Overall Activity (OACT)	0.46 (0.24–0.91)*	0.026	6	0.22	33.75	SD
Lipids/glycemic	HOMA-B	1.13 (0.89–1.43)	0.321	3	0.16	19.28	
Lipids/glycemic	Proinsulin	1.12 (0.95–1.32)	0.18	8	1.93	26.35	log
Lipids/glycemic	High-Density Lipoprotein Cholesterol (HDL-C)	1.10 (1.04–1.15)*	<0.001	112	8.53	155.7	SD
Lipids/glycemic	Glycated Hemoglobin (HbA1c)	1.07 (0.94–1.21)	0.293	11	0.5	21.14	%
Lipids/glycemic	Apolipoprotein A1 (Apo A1)	1.07 (1.02–1.11)*	0.002	486	11.73	107.41	SD
Lipids/glycemic	Low-Density Lipoprotein Cholesterol (LDL-C)	1.03 (0.99–1.08)	0.119	96	10.85	219.33	SD
Lipids/glycemic	Triglycerides (TG)	1.03 (0.99–1.08)	0.15	113	10.42	292.65	SD
Lipids/glycemic	Apolipoprotein B (Apo B)	1.00 (0.97–1.04)#	0.899	336	12.42	185.27	SD
Lipids/glycemic	Lipoprotein A (LPA)	1.00 (0.97–1.02)	0.737	59	11.79	620.51	SD
Lipids/glycemic	Total Cholesterol (TC)	0.94 (0.88–1.00)#	0.059	69	6.54	180.16	SD
Lipids/glycemic	Fasting Plasma Glucose (FPG)	0.93 (0.79–1.10)	0.414	23	1.05	26.85	
Metabolites	Insulin-like Growth Factor-1 (IGF-1)	1.08 (1.03–1.13)*	0.001	560	11.61	80.2	SD
Metabolites	Immunoglobulin E (IgE)	1.06 (0.95–1.18)	0.283	1	1.24	41.5	SD
Metabolites	Interleukin-10 (IL-10)	1.03 (0.99–1.08)	0.158	2	4.53	182	SD
Metabolites	Plasminogen Activator Inhibitor-1 (PAI-1)	1.03 (0.96–1.10)	0.445	1	1.65	55.46	SD
Metabolites	Insulin-like Growth Factor-Binding Protein 3 (IGF-BP3)	1.02 (0.96–1.08)	0.528	1	2.5	84.54	SD
Metabolites	Hepatocyte Growth Factor (HGF)	1.01 (0.94–1.09)	0.774	1	1.37	45.97	SD
Metabolites	Resistin	1.00 (0.96–1.04)	0.877	5	7.99	57.19	SD
Metabolites	Leptin Receptor (LepR)	0.99 (0.97–1.00)	0.116	5	46.53	573.52	SD
Metabolites	Interleukin-6 Receptor Subunit Alpha (Il-6 sRa)	0.98 (0.96–1.00)*	0.04	4	32.98	405.43	SD
Metabolites	Tumor Necrosis Factor (TNF)	0.95 (0.87–1.04)	0.31	1	1.02	34.07	SD
Metabolites	Adiponectin	0.95 (0.88–1.03)	0.251	12	1.43	35.56	ln(mg/dl)
Metabolites	Leptin	0.93 (0.59–1.47)	0.761	1	0.04	12.02	log ng/ml
Metabolites	Insulin-like Growth Factor-1 Receptor (IGF-1R)	0.82 (0.76–0.88)*†‡	<0.00	1	1.4	46.86	SD
Nutrients	Diet Sugar (D-Sug)	1.53 (0.77–3.05)	0.226	9	0.19	47.75	SD
Nutrients	Diet Carbohydrate (D-Car)	1.07 (0.49–2.34)	0.863	12	0.18	40.55	SD
Nutrients	Omega-6:Total Fatty Acids (O6:TFA)	1.06 (1.01–1.12)*	0.032	64	5.2	98.53	
Nutrients	N3 Docosapentaenoic Acid (N3-DPA)	1.03 (0.83–1.28)	0.775	3	0.34	10.01	%
Nutrients	Omega-6 Fatty Acids (O6FA)	1.03 (0.98–1.09)	0.261	78	7.05	111.88	
Nutrients	Omega-6:Omega-3 (O6/O3)	1.03 (0.97–1.09)	0.381	58	8.47	183.61	
Nutrients	Linoleic acid (LA)	1.02 (0.97–1.08)#	0.387	70	6.54	115.04	
Nutrients	Omega-3:Total Fatty Acids (O3:TFA)	1.02 (0.97–1.08)	0.416	62	8.99	183.15	
Nutrients	Polyunsaturated Fatty Acids (PUFAs)	1.02 (0.98–1.07)	0.358	87	8.34	120.22	
Nutrients	N3 Ecosapentaenoic Acid (N3-EPA)	1.02 (0.97–1.07)	0.382	4	4.24	98.19	%
Nutrients	Selenium	1.02 (0.97–1 .07)	0.508	1	2.86	84.58	SD
Nutrients	Zinc	1.02 (0.97–1.06)	0.454	2	4.23	57.43	SD
Nutrients	Omega-3 Fatty Acids (O3FA)	1.01 (0.96–1.06)	0.834	79	9.81	158.34	
Nutrients	Vitamin B6 (Vit-B6)	1.00 (0.64–1.57)	0.99	1	0.05	31.71	SD
Nutrients	Calcium	1.00 (0.95–1.06)	0.999	251	6.43	86.24	SD
Nutrients	Total Fatty Acids (TFAs)	1.00 (0.95–1.04)#	0.865	78	7.06	112.03	
Nutrients	Copper	1.00 (0.95–1.04)	0.835	2	4.38	59.5	SD
Nutrients	Saturated Fatty Acids (SFAs)	0.99 (0.94–1.04)	0.62	71	5.75	98.87	
Nutrients	Iron	0.98 (0.93–1.02)	0.352	5	4.64	233.51	SD
Nutrients	Monounsaturated Fatty Acids (MUFAs)	0.96 (0.91–1.00)	0.062	84	7.43	109.88	
Nutrients	Folate	0.73 (0.47–1.12)	0.148	1	0.05	30.37	SD
Nutrients	Diet Fat (D-Fat)	0.70 (0.28–1.72)	0.432	6	0.19	84.29	SD
Nutrients	Diet Protein (D-Pro)	0.55 (0.23–1.31)	0.179	7	0.15	57.14	SD
Sex-related	Age at Menopause (ANM)	1.05 (1.03–1.07)*†‡	<0.001	42	62.44	2744	Years
Sex-related	Testosterone	1.04 (0.91–1.18)	0.558	127	1.11	27.51	SD
Sex-related	Age at Menarche (AAM)	0.98 (0.92–1.05)	0.619	68	5.39	152.78	Years
Sex-related	Sex Hormone Binding Globulin (SHBG)	0.97 (0.92–1.02)	0.205	389	11.47	103.89	SD
Sex-related	Oestradiol (E2)	0.89 (0.60–1.32)	0.546	1	0.05	25.73	SD

Fig. 2 Association of 95 genetically determined risk factors with breast cancer. The odds ratio (OR) represented the effect of genetically predicted per unit increase in the risk factor. The majority of units were standard deviation (SD) and part of them were original units since the SD values were not available. Several R^2 and F statistics were calculated by using the effect allele frequency in the outcome dataset since the missing allele frequency of exposure. For the number of SNP more than 1, the results were from the inverse variance weighted (IVW) Mendelian randomization; for the number of SNP equal to 1, the results were from the Wald ratio. * denotes $P < 0.05$, † denotes $P < 5.26 \times 10^{-4}$ (0.05/95), ‡ denotes $P < 5.85 \times 10^{-5}$ (0.05/855), # denotes potential pleiotropy in testing for the intercept of MR-Egger regression.

interleukin-6 receptor subunit alpha (IL-6 sRa) [0.98 (0.96–1.00)] and IGF-1 receptor (IGF-1R) [0.82 (0.76–0.88)]. Of the significant factors, COBE, BMI, CBS-10, IGF-1R and ANM passed the strict Bonferroni correction, whereas WC and schizophrenia also passed the correction when only considering the number of exposures. Supplementary Figures S1 and S2 show the results for ER + BC and ER − BC.

The relations between 95 traits and overall OC in the IVW method or WRO analysis are shown in Fig. 3. Fourteen exposures were significantly associated with overall OC. Positive associations [OR (95% CIs)] were with HC [1.24 (1.07–1.44)], WC [1.24 (1.05–1.46)], CBS-10 [1.20 (1.04–1.39)], BMI [1.19 (1.05–1.35)], body fat percentage (BFP) [1.18 (1.06–1.31)], BFM [1.14 (1.06–1.24)], basal metabolic rate (BMR) [1.13 (1.03–1.23)], body fat-free mass (BFFM) [1.12 (1.02–1.23)], schizophrenia [1.07 (1.02–1.12)] and omega-6:omega-3 fatty acids (O6/O3) [1.12 (1.02–1.24)]. Negative associations were with thyroid-stimulating hormone (TSH) [0.82 (0.67–0.99)], EDUA [0.83 (0.73–0.94)], adiponectin [0.87 (0.76–0.99)] and IGF-1R [0.64 (0.55–0.74)]. Of the factors, IGF-1R passed the Bonferroni correction. Supplementary Figures S3 to S7 show results for OC subtypes.

Forty-eight factors were significant for at least one cancer type in the IVW method or WRO analysis. Supplementary Figures S8 and S9 show the results of pairwise MVMR for BC and OC and the 48 factors. Overall, the associations were relatively robust after adjusting for other potential pleiotropy factors in turn. Effects of OACT, diet fat (D-Fat), folate and N3 docosapentaenoic acid (N3-DPA) could change to some extent when adjusted for other factors, which suggested potential horizontal pleiotropy.

Figure 4 summarises the robust associations (significant in both IVW and WME methods) for BC, OC and their subtypes. In general, 16 factors were identified as robust traits for overall BC, including chronotype, HDL-C, IGF-1, Apo A1, schizophrenia, O6:TFA, ANM, PLT, AVEA, BFM, EDUA, COBE, HC, BMI, WC and CBS-10 (Fig. 4a). In addition, CRP, O6:TFA, Apo A1, ADUH, IGF-1, schizophrenia, ANM, monounsaturated fatty acids (MUFAs), BFM, AVEA, COBE, WC, BMI, WHR and CBS-10 were robustly associated with ER + BC (Fig. 4b). Associated with ER − BC were HDL-C, schizophrenia, ANM, BMR, cognitive performance (CP), BFFM, COBE, EDUA, HC, BMI, WC and CBS-10 (Fig. 4c). For ER + BC, ANM, BFM, WC, BMI and CBS-10 passed the strict multiple testing, as did COBE, EDUA, BMI, WC and CBS-10 for ER − BC. For overall OC, WC, CBS-10, BMI, BFP, BFM, O6/O3 and EDUA remained significant after the sensitivity analysis by the WME method (Fig. 4d). For OC subtypes, CBS-10, linoleic acid (LA), O6FA, BFM, zinc and BIRW had robust associations with IMOC. Causally associated with EOC were HC, BMR, BFFM, O6/O3, BFM, ANM, BIRW and N3-DPA. The factors BMR and BFFM also passed multiple testing when considering the number of exposures. In addition, the BFP, BFM and adiponectin were robustly associated with HGSOC, and the BFFM, BMR, sex hormone-binding globulin (SHBG) and O6/O3 were also robust factors for CCOC.

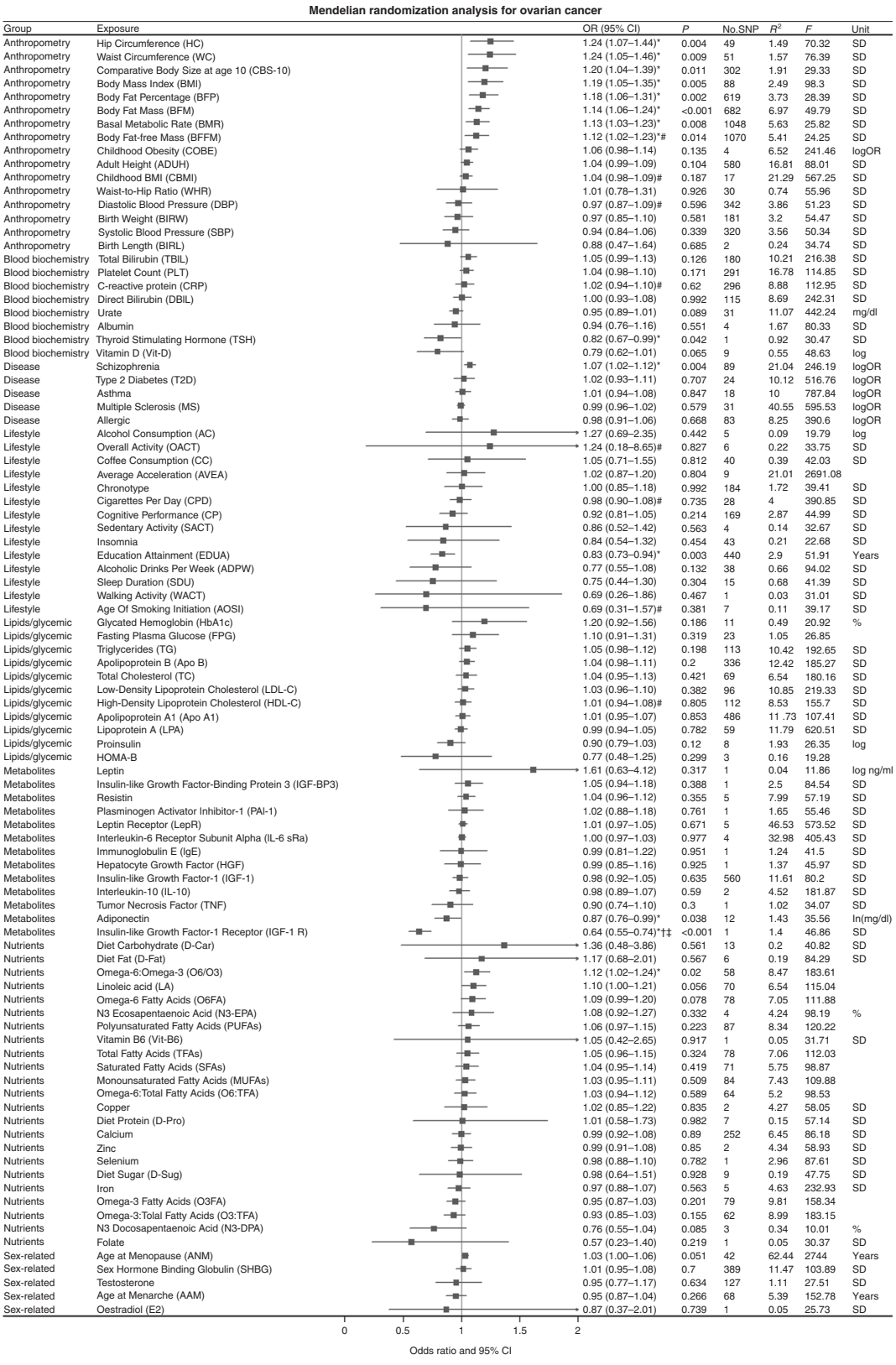
Figure 5 summarises results for MR, GC and levels and rank of risk factors. Fifty-eight risk factors were significant for at least one type of cancer with at least one MR method (IVW, WRO or WME) (Fig. 5a). Thirty-one of the risk factors were robust factors for at least one BC/OC type (dark red). Moreover, many traits were shared risk factors across BC, OC and their subtypes. For example, BMI, BFM, CBS-10, HC, WC, schizophrenia, EDUA and IGF-1R were shared risk factors for overall BC and OC. In addition, 13 factors that shared genetic risk with these outcomes were also combined in the heat map, including OACT, COBE, BMI, BFFM, BMR, AVEA, CBS-10, schizophrenia, ANM, ADUA, CP, EDUA and insomnia (solid triangle). All significant results of GC analysis are shown in Fig. 5b. According to the results of MR and GC, five levels of risk factors were defined for BC and OC (Fig. 5c). Level 1 represented the robust MR plus the GC evidence for both BC and OC, which included only EDUA. Level 2 comprised only the robust MR results for both BC and OC, which included BMI, CBS-10, WC and BFM. In level 3, only COBE, AVEA, ANM, and schizophrenia were robustly associated with BC, and no factors were associated with OC. The above OACT, D-Fat, folate and N3-DPA, which showed potential horizontal pleiotropy in MVMR analysis, were mainly classified into level 5. Factors in level 5 were relatively unimportant compared with factors in other levels. Figure 5d shows the rank of the 58 significant factors according to their number of significant results (scores). The top 10 factors in order were CBS-10, EDUA, schizophrenia, BFM, BMI, ANM, WC, COBE, HC and O6/O3.

Causal pathways and networks were developed from identified risk factors to BC (Fig. 6a) and to OC (Fig. 6b). In the networks, HC, WC, O6:TFA, IGF-1R, BFM, CBS-10, chronotype, ANM, IGF-1, Apo A1, PLT, AVEA, COBE, EDUA and BMI had both direct and indirect effects on BC, whereas BFM, CBS-10, BFP, O6/O3, EDUA, BMI, WC, IGF-1R and TSH affected the risk of OC through their respective pathways. For example, CBS-10 could affect the risk of OC by acting on BFM, WC, BMI and BFP (yellow pathways), suggesting that early-life body status could act on later-stage stature and lead to the risk of OC. In addition, the effect of EDUA on OC could also be mediated by obesity-related traits (grey pathways), indicating education could drive health-related behaviour to control obesity and ultimately modify the risk of OC. Causal pathways of BC and OC subtypes are shown in Supplementary Figs. S10 and S11. Causal estimators of exposure–outcome pairs between each node in the causal network diagrams are shown in Supplementary Table S4. The other independent factors were not shown in networks because they had no identifiable mediators that could be explained as having only direct causal effects on cancer.

DISCUSSION

In this study, genetic statistical methods were used to identify the relations between large-scale cancer-related exposures and breast and ovarian cancers. Thirty-one exposures were robust risk factors for at least one type of BC or OC. Among them, BMI, BFM, CBS-10, WC and EDUA were shared robust risk factors for overall BC and OC, which implied potential joint intervention targets. In addition, 13 shared factors were detected in both GC and MR analyses, including OACT, COBE, BMI, BFFM, BMR, AVEA, CBS-10, schizophrenia, ANM, ADUA, CP, EDUA and insomnia. Furthermore, risk factors were stratified into five levels and ranked in order to prioritise future intervention measurements. Finally, visual causal networks were constructed that showed potential causal pathways from identified large-scale exposures to target outcomes to guide primary prevention practices.

Of the 31 putative robust factors from MR analysis, 16 factors were new causal biomarkers, including WC, BMR, BFP, BFFM, HC, COBE, BFM, PLT, CP, Apo A1, O6FA, O6:TFA, O6/O3, LA, MUFAs and N3-DPA. The other 15 factors, including BMI, WHR, ADUH, CBS-10, BIRW, CRP, schizophrenia, AVEA, EDUA, chronotype, HDL-C, adiponectin, IGF-1, ANM and SHBG, have been previously reported to be causal biomarkers. [8, 9, 11, 60–73] Consistent with previous studies, in this study, AUDH, schizophrenia, HDL-C, and IGF-1 were positively associated with BC and BMI and schizophrenia were positively associated with OC [8, 60, 63, 65, 67, 69]. In addition, BMI, CBS-10, AVEA and EDUA were negatively associated with BC, also consistent with previous studies [11, 62, 70, 73]. Same with previous studies [9, 61, 65, 68, 69], significant causal associations of BIRW and adiponectin with BC and WHR, ADUH, BIRW, CRP, adiponectin, IGF-1, ANM and SHBG with OC were not detected in this study. However, additional negative associations were detected, including WHR with BC and ER + BC, BIRW with IMOC and EOC and adiponectin with ER − BC, OC and HGSOC. Additional positive associations included ADUH with CCOC; CRP with BC and ER + BC; ANM with BC, ER + BC, ER − BC, and EOC and SHBG with CCOC, although some associations were only significant in the IVW method.



Group	Exposure	OR (95% CI)	P	No.SNP	R^2	F	Unit
Anthropometry	Hip Circumference (HC)	1.24 (1.07–1.44)*	0.004	49	1.49	70.32	SD
Anthropometry	Waist Circumference (WC)	1.24 (1.05–1.46)*	0.009	51	1.57	76.39	SD
Anthropometry	Comparative Body Size at age 10 (CBS-10)	1.20 (1.04–1.39)*	0.011	302	1.91	29.33	SD
Anthropometry	Body Mass Index (BMI)	1.19 (1.05–1.35)*	0.005	88	2.49	98.3	SD
Anthropometry	Body Fat Percentage (BFP)	1.18 (1.06–1.31)*	0.002	619	3.73	28.39	SD
Anthropometry	Body Fat Mass (BFM)	1.14 (1.06–1.24)*	<0.001	682	6.97	49.79	SD
Anthropometry	Basal Metabolic Rate (BMR)	1.13 (1.03–1.23)*	0.008	1048	5.63	25.82	SD
Anthropometry	Body Fat-free Mass (BFFM)	1.12 (1.02–1.23)*#	0.014	1070	5.41	24.25	SD
Anthropometry	Childhood Obesity (COBE)	1.06 (0.98–1.14)	0.135	4	6.52	241.46	logOR
Anthropometry	Adult Height (ADUH)	1.04 (0.99–1.09)	0.104	580	16.81	88.01	SD
Anthropometry	Childhood BMI (CBMI)	1.04 (0.98–1.09)#	0.187	17	21.29	567.25	SD
Anthropometry	Waist-to-Hip Ratio (WHR)	1.01 (0.78–1.31)	0.926	30	0.74	55.96	SD
Anthropometry	Diastolic Blood Pressure (DBP)	0.97 (0.87–1.09)#	0.596	342	3.86	51.23	SD
Anthropometry	Birth Weight (BIRW)	0.97 (0.85–1.10)	0.581	181	3.2	54.47	SD
Anthropometry	Systolic Blood Pressure (SBP)	0.94 (0.84–1.06)	0.339	320	3.56	50.34	SD
Anthropometry	Birth Length (BIRL)	0.88 (0.47–1.64)	0.685	2	0.24	34.74	SD
Blood biochemistry	Total Bilirubin (TBIL)	1.05 (0.99–1.13)	0.126	180	10.21	216.38	SD
Blood biochemistry	Platelet Count (PLT)	1.04 (0.98–1.10)	0.171	291	16.78	114.85	SD
Blood biochemistry	C-reactive protein (CRP)	1.02 (0.94–1.10)#	0.62	296	8.88	112.95	SD
Blood biochemistry	Direct Bilirubin (DBIL)	1.00 (0.93–1.08)	0.992	115	8.69	242.31	SD
Blood biochemistry	Urate	0.95 (0.89–1.01)	0.089	31	11.07	442.24	mg/dl
Blood biochemistry	Albumin	0.94 (0.76–1.16)	0.551	4	1.67	80.33	SD
Blood biochemistry	Thyroid Stimulating Hormone (TSH)	0.82 (0.67–0.99)*	0.042	1	0.92	30.47	SD
Blood biochemistry	Vitamin D (Vit-D)	0.79 (0.62–1.01)	0.065	9	0.55	48.63	log
Disease	Schizophrenia	1.07 (1.02–1.12)*	0.004	89	21.04	246.19	logOR
Disease	Type 2 Diabetes (T2D)	1.02 (0.93–1.11)	0.707	24	10.12	516.76	logOR
Disease	Asthma	1.01 (0.94–1.08)	0.847	18	10	787.84	logOR
Disease	Multiple Sclerosis (MS)	0.99 (0.96–1.02)	0.579	31	40.55	595.53	logOR
Disease	Allergic	0.98 (0.91–1.06)	0.668	83	8.25	390.6	logOR
Lifestyle	Alcohol Consumption (AC)	1.27 (0.69–2.35)	0.442	5	0.09	19.79	log
Lifestyle	Overall Activity (OACT)	1.24 (0.18–8.65)#	0.827	6	0.22	33.75	SD
Lifestyle	Coffee Consumption (CC)	1.05 (0.71–1.55)	0.812	40	0.39	42.03	SD
Lifestyle	Average Acceleration (AVEA)	1.02 (0.87–1.20)	0.804	9	21.01	2691.08	
Lifestyle	Chronotype	1.00 (0.85–1.18)	0.992	184	1.72	39.41	SD
Lifestyle	Cigarettes Per Day (CPD)	0.98 (0.90–1.08)#	0.735	28	4	390.85	SD
Lifestyle	Cognitive Performance (CP)	0.92 (0.81–1.05)	0.214	169	2.87	44.99	SD
Lifestyle	Sedentary Activity (SACT)	0.86 (0.52–1.42)	0.563	4	0.14	32.67	SD
Lifestyle	Insomnia	0.84 (0.54–1.32)	0.454	43	0.21	22.68	SD
Lifestyle	Education Attainment (EDUA)	0.83 (0.73–0.94)*	0.003	440	2.9	51.91	Years
Lifestyle	Alcoholic Drinks Per Week (ADPW)	0.77 (0.55–1.08)	0.132	38	0.66	94.02	SD
Lifestyle	Sleep Duration (SDU)	0.75 (0.44–1.30)	0.304	15	0.68	41.39	SD
Lifestyle	Walking Activity (WACT)	0.69 (0.26–1.86)	0.467	1	0.03	31.01	SD
Lifestyle	Age Of Smoking Initiation (AOSI)	0.69 (0.31–1.57)#	0.381	7	0.11	39.17	SD
Lipids/glycemic	Glycated Hemoglobin (HbA1c)	1.20 (0.92–1.56)	0.186	11	0.49	20.92	%
Lipids/glycemic	Fasting Plasma Glucose (FPG)	1.10 (0.91–1.31)	0.319	23	1.05	26.85	
Lipids/glycemic	Triglycerides (TG)	1.05 (0.98–1.12)	0.198	113	10.42	192.65	SD
Lipids/glycemic	Apolipoprotein B (Apo B)	1.04 (0.98–1.11)	0.2	336	12.42	185.27	SD
Lipids/glycemic	Total Cholesterol (TC)	1.04 (0.95–1.13)	0.421	69	6.54	180.16	SD
Lipids/glycemic	Low-Density Lipoprotein Cholesterol (LDL-C)	1.03 (0.96–1.10)	0.382	96	10.85	219.33	SD
Lipids/glycemic	High-Density Lipoprotein Cholesterol (HDL-C)	1.01 (0.94–1.08)#	0.805	112	8.53	155.7	SD
Lipids/glycemic	Apolipoprotein A1 (Apo A1)	1.01 (0.95–1.07)	0.853	486	11 .73	107.41	SD
Lipids/glycemic	Lipoprotein A (LPA)	0.99 (0.94–1.05)	0.782	59	11.79	620.51	SD
Lipids/glycemic	Proinsulin	0.90 (0.79–1.03)	0.12	8	1.93	26.35	log
Lipids/glycemic	HOMA-B	0.77 (0.48–1.25)	0.299	3	0.16	19.28	
Metabolites	Leptin	1.61 (0.63–4.12)	0.317	1	0.04	11.86	log ng/ml
Metabolites	Insulin-like Growth Factor-Binding Protein 3 (IGF-BP3)	1.05 (0.94–1.18)	0.388	1	2.5	84.54	SD
Metabolites	Resistin	1.04 (0.96–1.12)	0.355	5	7.99	57.19	SD
Metabolites	Plasminogen Activator Inhibitor-1 (PAI-1)	1.02 (0.88–1.18)	0.761	1	1.65	55.46	SD
Metabolites	Leptin Receptor (LepR)	1.01 (0.97–1.05)	0.671	5	46.53	573.52	SD
Metabolites	Interleukin-6 Receptor Subunit Alpha (IL-6 sRa)	1.00 (0.97–1.03)	0.977	4	32.98	405.43	SD
Metabolites	Immunoglobulin E (IgE)	0.99 (0.81–1.22)	0.951	1	1.24	41.5	SD
Metabolites	Hepatocyte Growth Factor (HGF)	0.99 (0.85–1.16)	0.925	1	1.37	45.97	SD
Metabolites	Insulin-like Growth Factor-1 (IGF-1)	0.98 (0.92–1.05)	0.635	560	11.61	80.2	SD
Metabolites	Interleukin-10 (IL-10)	0.98 (0.89–1.07)	0.59	2	4.52	181.87	SD
Metabolites	Tumor Necrosis Factor (TNF)	0.90 (0.74–1.10)	0.3	1	1.02	34.07	SD
Metabolites	Adiponectin	0.87 (0.76–0.99)*	0.038	12	1.43	35.56	ln(mg/dl)
Metabolites	Insulin-like Growth Factor-1 Receptor (IGF-1 R)	0.64 (0.55–0.74)*†‡	<0.001	1	1.4	46.86	SD
Nutrients	Diet Carbohydrate (D-Car)	1.36 (0.48–3.86)	0.561	13	0.2	40.82	SD
Nutrients	Diet Fat (D-Fat)	1.17 (0.68–2.01)	0.567	6	0.19	84.29	SD
Nutrients	Omega-6:Omega-3 (O6/O3)	1.12 (1.02–1.24)*	0.02	58	8.47	183.61	
Nutrients	Linoleic acid (LA)	1.10 (1.00–1.21)	0.056	70	6.54	115.04	
Nutrients	Omega-6 Fatty Acids (O6FA)	1.09 (0.99–1.20)	0.078	78	7.05	111.88	
Nutrients	N3 Ecosapentaenoic Acid (N3-EPA)	1.08 (0.92–1.27)	0.332	4	4.24	98.19	%
Nutrients	Polyunsaturated Fatty Acids (PUFAs)	1.06 (0.97–1.15)	0.223	87	8.34	120.22	
Nutrients	Vitamin B6 (Vit-B6)	1.05 (0.42–2.65)	0.917	1	0.05	31.71	SD
Nutrients	Total Fatty Acids (TFAs)	1.05 (0.96–1.15)	0.324	78	7.06	112.03	
Nutrients	Saturated Fatty Acids (SFAs)	1.04 (0.95–1.14)	0.419	71	5.75	98.87	
Nutrients	Monounsaturated Fatty Acids (MUFAs)	1.03 (0.95–1.11)	0.509	84	7.43	109.88	
Nutrients	Omega-6:Total Fatty Acids (O6:TFA)	1.03 (0.94–1.12)	0.589	64	5.2	98.53	
Nutrients	Copper	1.02 (0.85–1.22)	0.835	2	4.27	58.05	SD
Nutrients	Diet Protein (D-Pro)	1.01 (0.58–1.73)	0.982	7	0.15	57.14	SD
Nutrients	Calcium	0.99 (0.92–1.08)	0.89	252	6.45	86.18	SD
Nutrients	Zinc	0.99 (0.91–1.08)	0.85	2	4.34	58.93	SD
Nutrients	Selenium	0.98 (0.88–1.10)	0.782	1	2.96	87.61	SD
Nutrients	Diet Sugar (D-Sug)	0.98 (0.64–1.51)	0.928	9	0.19	47.75	SD
Nutrients	Iron	0.97 (0.88–1.07)	0.563	5	4.63	232.93	SD
Nutrients	Omega-3 Fatty Acids (O3FA)	0.95 (0.87–1.03)	0.201	79	9.81	158.34	
Nutrients	Omega-3:Tolal Fatty Acids (O3:TFA)	0.93 (0.85–1.03)	0.155	62	8.99	183.15	
Nutrients	N3 Docosapentaenoic Acid (N3-DPA)	0.76 (0.55–1.04)	0.085	3	0.34	10.01	%
Nutrients	Folate	0.57 (0.23–1.40)	0.219	1	0.05	30.37	SD
Sex-related	Age at Menopause (ANM)	1.03 (1.00–1.06)	0.051	42	62.44	2744	Years
Sex-related	Sex Hormone Binding Globulin (SHBG)	1.01 (0.95–1.08)	0.7	389	11.47	103.89	SD
Sex-related	Testosterone	0.95 (0.77–1.17)	0.634	127	1.11	27.51	SD
Sex-related	Age at Menarche (AAM)	0.95 (0.87–1.04)	0.266	68	5.39	152.78	Years
Sex-related	Oestradiol (E2)	0.87 (0.37–2.01)	0.739	1	0.05	25.73	SD

Fig. 3 Association of 95 genetically determined risk factors with ovarian cancer. The odds ratio (OR) represented the effect of genetically predicted per unit increase in the risk factor. The majority of units were standard deviation (SD) and part of them were original units since the SD values were not available. Several R^2 and F statistics were calculated by using the effect allele frequency in the outcome dataset since the missing allele frequency of exposure. For the number of SNP more than 1, the results were from the inverse variance weighted (IVW) Mendelian randomization; for the number of SNP equal to 1, the results were from the Wald ratio. * denotes $P < 0.05$, † denotes $P < 5.26 \times 10^{-4}$ (0.05/95), ‡ denotes $P < 5.85 \times 10^{-5}$ (0.05/855), # denotes potential pleiotropy in testing for the intercept of MR-Egger regression.

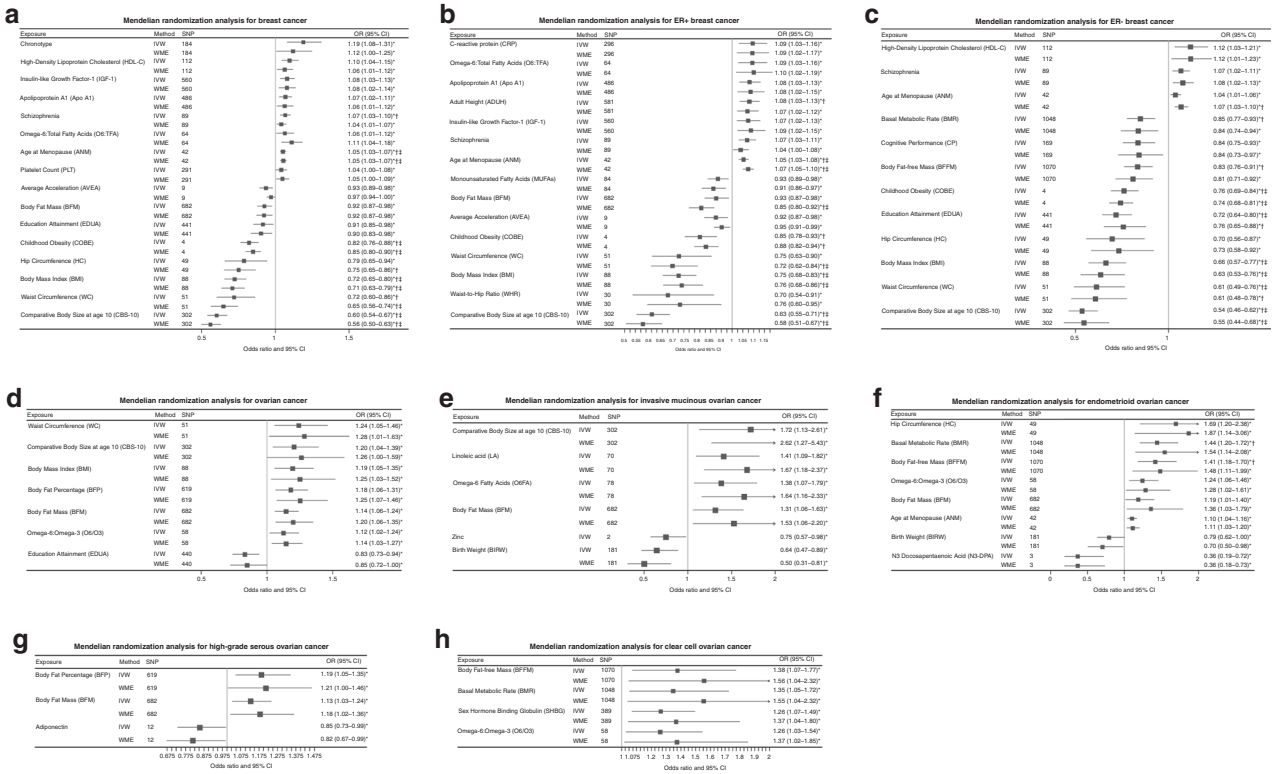
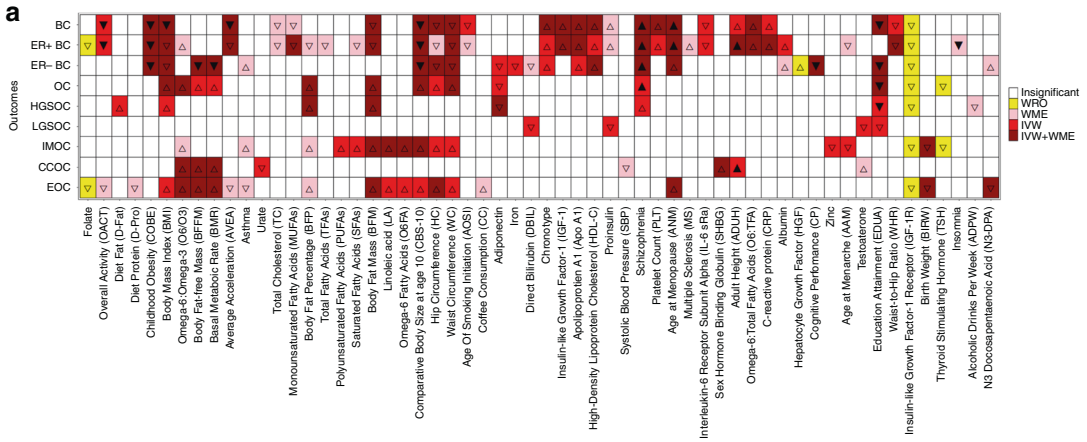


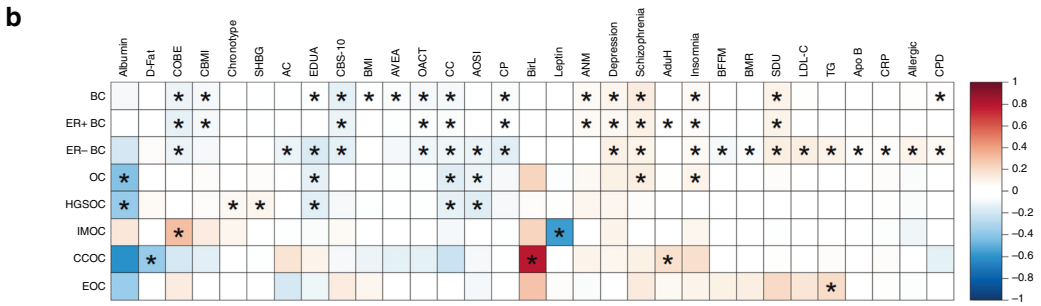
Fig. 4 Summarised robust associations for overall BC, OC and their subtypes. The odds ratio (OR) represented the effect of genetically predicted per unit increase in the risk factor. Only factors both significant in IVW and WME method could be shown. The panel **a**-**h** showed the results of overall BC, ER+ BC, ER- BC, overall OC, IMOC, EOC, HGSOC, and CCOC, respectively. The results for low-grade serous ovarian cancer were not shown since no robust risk factors were detected. * denotes $P < 0.05$, † denotes $P < 5.26 \times 10^{-4}$ (0.05/95), ‡ denotes $P < 5.85 \times 10^{-5}$ (0.05/855). IVW inverse variance weighted, WME weighted median estimator.

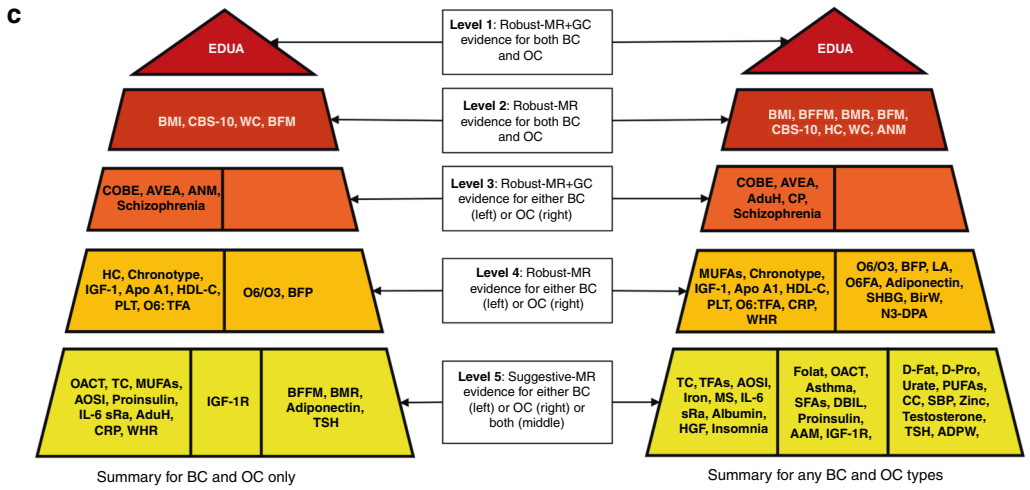
Of the robust risk factors, COBE, BMI, BFFM, BMR, AVEA, CBS-10, schizophrenia, ANM, ADUA, CP and EDUA also showed significant GCs, which suggested a higher level of causal evidence for which they could be stratified as priority intervention targets (all of these factors were classified into levels 1, 2 and 3). A factor that has a GC with cancer is more worthy of attention because it shares genetic risks with the outcome, and thus, an individual with such a trait would have a higher cancer risk than other people at the genetic level, even if it was not a causal risk factor. For a causal risk factor with GC, a comprehensive intervention should be implemented that intervenes not only with the particular factor but also with other risk factors (including those upstream, downstream and in other pathways in a network). For example, schizophrenia was a causal risk factor and had strong GC with BC (Fig. 5a), indicating that an individual with schizophrenia was at a genetically higher risk of BC. In this situation, intervention for only schizophrenia could not rule out additional genetic risk of BC, compared with other conventional risk factors. Therefore, a comprehensive intervention should target alternative pathways, such as BMI, AVEA, IGF-1, WC, HC and O6:TFA et al (Fig. 6). Moreover, although GC analysis showed significant results for coffee consumption (CC), childhood BMI (CBMI), alcohol consumption (AC), BIRL, Apo B, allergies, cigarettes per day (CPD), low-density lipoprotein cholesterol (LDL-C), sleep duration (SDU), triglycerides (TG) and depression with several outcomes, MR studies did not support a significant causal effect of those factors. Therefore, they were not included as intervention targets. Although GC could increase the priority of a causal risk factor, intervention could fail to decrease cancer risk because the factor did not have a causal effect.

The newly identified risk factors O6FA, O6:TFA, O6/O3 and MUFAs had a strong causal effect on OC, BC or several subtypes. These results suggested an adverse effect of O6FA and a potential protective effect of omega-3 fatty acids (O3FA). Causal evidence of fatty acids on cancer risk is limited, but in their review, Saini et al. [74] noted that O3FA and O6FA suppressed and induced inflammation, respectively. Diets enriched in O6FA are associated with inflammation, which provides an ideal tumour microenvironment and is linked to cancer risk and metastasis [74]. By contrast, O3FA help to resolve inflammation and alter the function of vascular and carcinogen biomarkers and thus reduce cancer risk [74, 75]. These differences may explain why different fatty acids can increase or decrease BC or OC risks. In addition, the results in study are consistent with the previous opinion that the ratio of O6FA to O3FA is more crucial than the absolute amounts [74].

Notably, there was dimorphism in obesity-related traits for OC and BC risks. This causal evidence suggests double-sided effects of obesity traits for different female cancers and indicates the importance of maintaining a moderate body shape. The factor CBS-10 reflects the early-life status of an individual and also had strong causality and GC with cancer (ranked No. 1 among the factors), indicating early childhood intervention is key. The protective effect of education on lung cancer has been previously verified [76], and the results of this study further extend the protective effect of education to OC and BC. A relatively high level of education is more likely to drive positive health-related behaviours and thus reduce the risk of cancer. The robust inverse associations combined with the extensive GCs with both BC and OC indicate education is one of the top factors to be addressed in intervention. The protective effect of IGF-1R may be due to negative feedback regulation of IGF-1, which has been reported as a risk factor for breast cancer [64]. The risk of Apo A1 for BC was consistent with the reported positive effect of HDL-C [8], likely because Apo A1 is a transporter of HDL-C.







d

Rank	Exposures	Score	Rank	Exposures	Score	Rank	Exposures	Score	Rank	Exposures	Score	Rank	Exposures	Score	Rank	Exposures	Score
1	CBS-10	14	11	BFFM	8	21	Adiponectin	4	31	MUFAs	3	41	TSH	2	51	Urate	1
2	EDUA	12	12	BMR	8	22	O6:TFA	4	32	O6FA	3	42	Folate	2	52	Zinc	1
3	Schizophrenia	12	13	IGF-1R	7	23	Chronotype	4	33	N3-DPA	3	43	Insomnia	2	53	ADPW	1
4	BFM	12	14	BFP	7	24	IGF-1	4	34	CRP	3	44	DBIL	2	54	PUFAs	1
5	BMI	11	15	AVEA	6	25	Proinsulin	3	35	AAM	2	45	SHBG	2	55	TFAs	1
6	ANM	10	16	AduH	6	26	PLT	3	36	TC	2	46	Testosterone	2	56	HGF	1
7	WC	10	17	Apo A1	5	27	CP	3	37	AOSI	2	47	D-Fat	1	57	SBP	1
8	COBE	9	18	HDL-C	5	28	Asthma	3	38	Albumin	2	48	D-Pro	1	58	CC	1
9	HC	9	19	OACT	5	29	WHR	3	39	SFAs	2	49	MS	1			
10	O6/O3	8	20	BirW	4	30	LA	3	40	IL-6 sRa	2	50	Iron	1			

Some important results that are not consistent with those of other studies should also be noted. For example, with AAM, whereas negative associations with ER + BC and IMOC were indicated, the association was not significant with BC. By contrast, Day et al. [77] reported a strong negative relation with BC after removing or adjusting BMI-related SNPs. To attempt to reproduce that result, additional analyses were conducted by using different AAM datasets (versions 2014 and 2017), different BC datasets (Oncoarray, iCOGS, GWAS and combined), different LD thresholds (0.01 and 0.001), and different methods (IVW, WME and BMI-

Fig. 5 Summarised results for MR, GC and the levels of identified risk factors. Panel **a** was the heat map of MR results. The coloured region represented the significant result in different methods including the IVW, WME and IVW + WME, while the white represented insignificant results. The direction of the triangle represents the direction of causal estimators where the upward triangle indicates positive association and the downward triangle indicates negative association. The solid triangle indicates a significant genetic correlation. Panel **b** was the result of genetic correlation (GC) analysis. The GC was quantified by the statistic of genetic correlation coefficient *r*, ranged from −1 to 1, and presented from blue to red colour. GC more than 0 represented a positive association and smaller than 0 represented a negative association. The asterisks (*) in the figure represent statistically significant results ($P < 0.05$). The results of low-grade serous ovarian cancer were not shown in GC analysis because the ldsc software failed to perform GC analysis on account of low h^2 statistics or a small sample size. The insignificant factors for any outcomes were also not shown in this heat map. Panel **c** was the stratification of putative risk factors according to our criteria. The left one showed the factors for overall BC and OC only. The right one showed the factor for any BC and OC types. Panel **d** was the rank of these putative causal risk factors according to their scores defined by our criteria in the methods. The full annotation of the abbreviations in this Figure could be found in panel **a** or supplement Table S2.

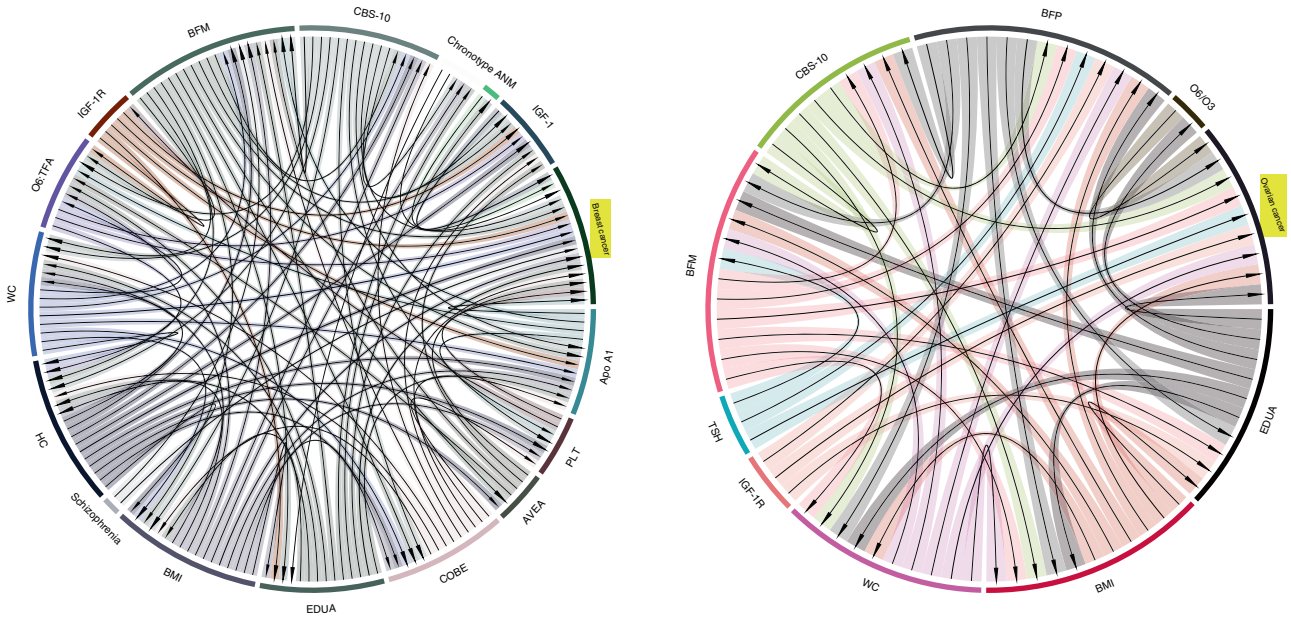


Fig. 6 Causal pathways and networks of identified risk factors for breast and ovarian cancer. The left panel was the network for breast cancer and the right one was for ovarian cancer. The arrows represented the direction of causal effect from one causal biomarker to another one, and finally, to ovarian/breast cancer (yellow highlight) from the network-MR analysis. This network only showed the factors with identifiable mediators. Each arrow represents a significant IVW-MR result.

adjusted and BMI-excluded SNPs) (Supplementary Fig. S12). Several results in only specific conditions were consistent the conclusion of Day et al. The possible difference in conclusions could be because the BMI GWAS dataset could not be acquired that, together with the reported AMM 61 BMI-related SNPs (AAM increasing/BMI decreasing) produced the strong positive association with BC. However, the results in this study are consistent with their unadjusted results and are also consistent with those of another MR study by Qi et al. [78]. Therefore, future research should focus on the mechanism by which AAM combined with BMI affects the risk of BC and distinguish the data sources in MR studies.

Finally, based on the above evidence, risk factors were stratified and ranked in order to provide a reference for future primary prevention targets. A complex network for BC, OC and each subtype was constructed based on network-MR analysis. This study was the first to summarise and stratify causal biomarkers and construct causal networks for BC and OC using biostatistics and data-driven evidence. When using a network, stratified risk factors can be referenced to identify more important targets. For each factor, primary prevention interventions can be directed not only at direct effects but also to interrupt its pathway in other related nodes. For example, CBS-10 could be altered in childhood, which would benefit downstream adult BMI and ultimately decrease the risk of OC (Fig. 6). Furthermore, when a risk factor cannot be easily modified, such as lower EDUA for risk of BC, alternative downstream targets (e.g. Apo A1 and obesity-related traits) can be identified to implement primary prevention interventions.

Compared with previous studies, this study had the advantage of examining large-scale factors (the largest to our knowledge) associated with OC and BC under a comprehensive framework in order to detect causalities, genetic correlations, and shared or distinct factors and to prioritise risk factors and develop causal networks. The study also had limitations that should be noted. First, some of the candidate factors did not have enough IVs and might suffer bias from that weakness. Second, pleiotropy is a dilemma in MR. Fortunately, the WME was more robust to IV assumptions, and the pairwise MVMR design found that few of the identified risk factors were affected by pleiotropy. Third, in large-scale exploratory research of observational datasets, there are natural limitations to detailed exploration of mechanisms of each factor, as in most similar studies. Further research is required to determine biological mechanisms of the risk factors newly identified in this research, as well as to explore the suggestive evidence. The practical value of risk stratification and a causal network needs to be verified in further public health intervention practices.

CONCLUSIONS

Sixteen new factors associated with OC or BC were identified, including WC, BMR, BFP, BFFM, HC, COBE, BFM, PLT, CP, Apo A1,

O6FA, O6:TFA, O6/O3, LA, MUFAs and N3-DPA. In addition, BMI, BFM, CBS-10, WC and EDUA were shared robust risk factors for overall BC and OC. Thirteen factors were significant in both GC and MR analyses, including OACT, COBE, BMI, BFFM, BMR, AVEA, CBS-10, schizophrenia, ANM, ADUA, CP, EDUA and insomnia. The risk factors were stratified into five levels and ranked to prioritise for future intervention measurements. Causal networks were developed that show pathways from putative factors to cancer in order to guide primary prevention.

DATA AVAILABILITY

Researchers may have access to this data from the original researches shown in the supplement material.

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AUTHOR CONTRIBUTIONS

SS and FX have the conception. SS did the statistical analyses and drafted the initial manuscript. MAT completed the revision of English grammar. All authors participated in the interpretation of the results, edited and reviewed the manuscript.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Our research is only based on publicly available summarised data and no individual data were involved. These genome-wide association studies (including the GIANT, EGG, MRC-IEU, GUGC, Neale Lab, DIAGRAM, IMSGC, PGC, SSGAC, UK Biobank, GSCAN, GLGC, MAGIC, ADIPOGen, GIS, CHARGE and ReproGen consortium, and the individual research by Astle WJ et al, Jiang X et al, Sun BB et al, Kettunen et al, T-K Clarke et al, Aiden Doherty et al, Ferreira MA et al, Demenais F et al, Klimentidis YC et al, Strawbridge RJ et al, Manning AK et al, Dupuis J et al, Evans et al and Borges CM et al) had declared the ethic approval from the relevant institutional review board and in accordance with the declaration of Helsinki, or other (see reference [15–50]). This

secondary analysis is based on summary-level statistics that are not applicable for the clauses of ethics, the Ethics Committee of the School of Public Health of Shandong University ruled that ethics approval was not required in this particular case.

CONSENT FOR PUBLICATION

Not applicable

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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