Supplementary material

Multi-trait body shape phenotypes and breast cancer risk in postmenopausal women: a causal mediation analysis in the UK Biobank cohort

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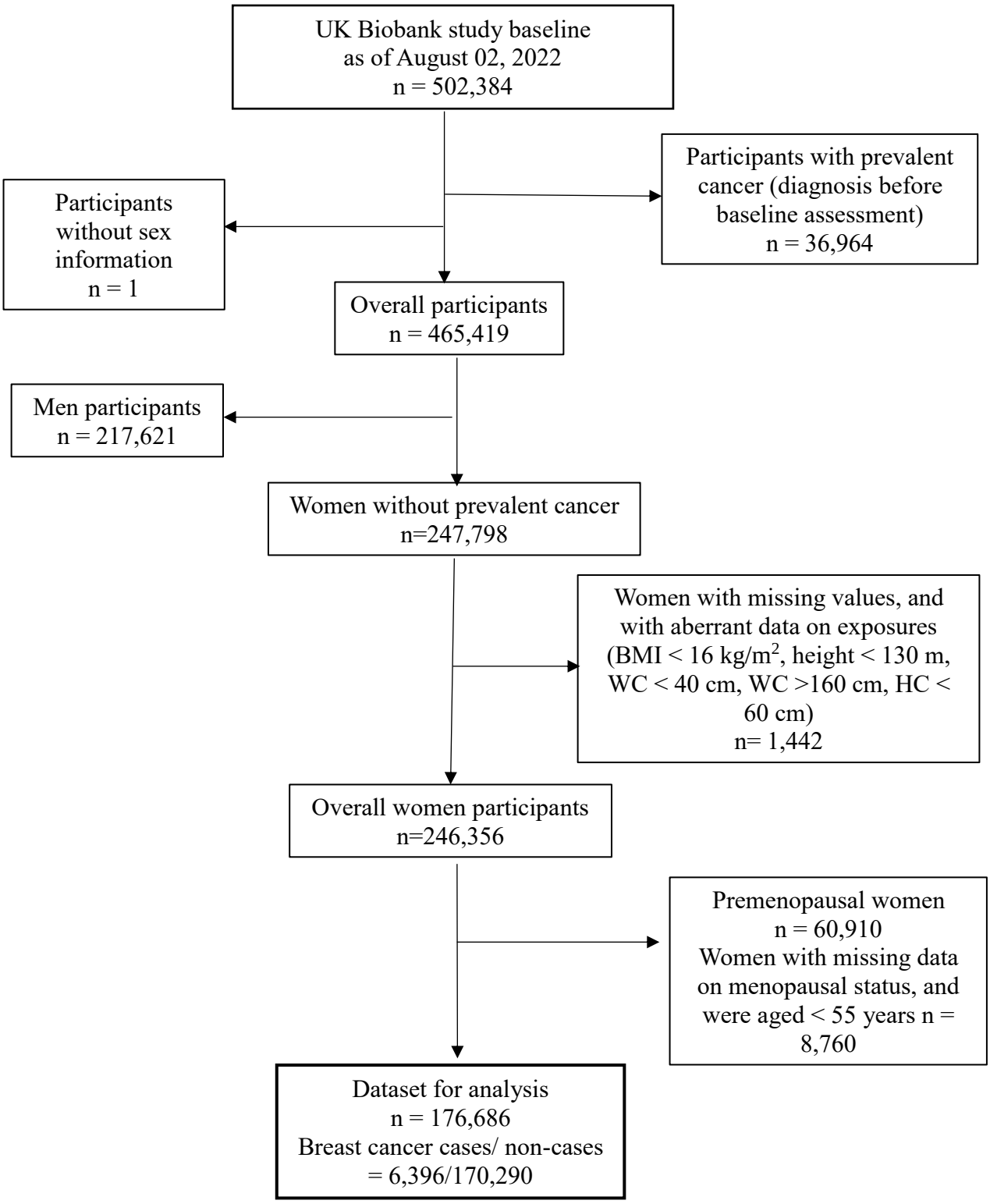
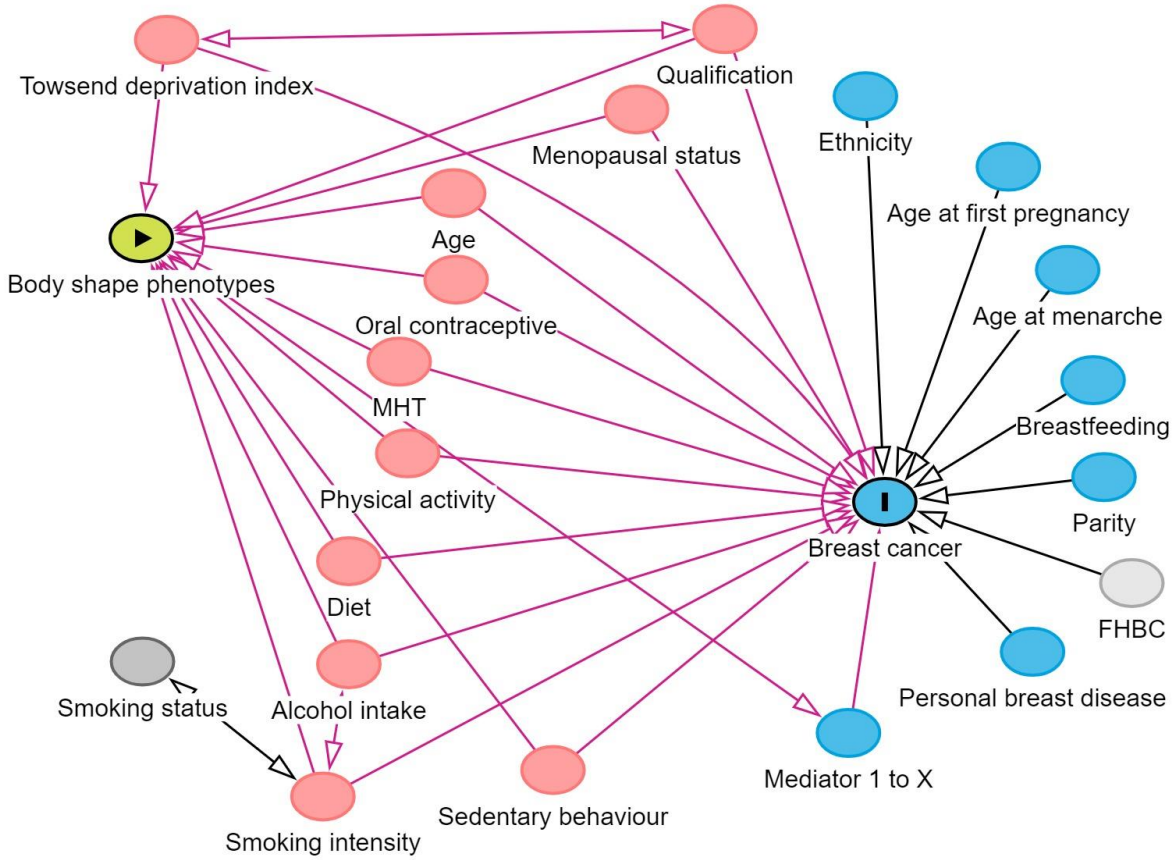


Supplementary Figure 1: Flowchart of the selection of the study participants.
BMI: body mass index, WC: waist circumference, HC: hip circumference.



Supplementary Figure 2: Directed Acyclic Graph showing the relationship between potential confounders in the association between body shape phenotypes and breast cancer risk.

MHT: use of menopausal hormone treatment, FHBC: family history of breast cancer.

Supplementary Table 1: Baseline characteristics of postmenopausal women by breast cancer status from the UK Biobank cohort study

Characteristics	Cases (n = 6,396)	Non cases (n = 170,290)
Age at recruitment (years), mean (SD)	61.0 (5.3)	60.4 (5.7)
Age at menarche (years), mean (SD)	12.9 (1.6)	12.9 (1.6)
Townsend deprivation index, mean (SD)	-1.5 (2.9)	-1.4 (2.9)
Sedentary behaviour, mean (SD)	4.51 (2.1)	4.47 (2.1)
BMI (kg/m²), mean (SD)	27.7 (5.1)	27.3 (5.1)
Weight (kg), mean (SD)	73.2 (13.7)	71.4 (13.8)
Height(m), mean (SD)	1.63 (0.1)	1.62 (0.1)
WHR, mean (SD)	0.83 (0.1)	0.82 (0.1)
Waist circumference (cm), mean (SD)	86.8 (12.3)	85.4 (12.4)
Hip circumference (cm), mean (SD)	104.6 (10)	103.6 (10.3)
Physical activity, n (%)		
Low	907 (18.9)	23,386 (18.2)
Moderate	2,169 (45.2)	55,589 (43.1)
High	1,724 (35.9)	49,910 (38.7)
Alcohol drinking, n (%)		
Daily or almost daily	1,206 (18.9)	28,747 (16.9)
3 to 4 times a week	1,325 (20.7)	33,820 (19.9)
1 to 2 times a week	1,544 (24.2)	42,343 (24.9)
1 to 3 times a month	775 (12.1)	21,254 (12.5)
Special occasions only	941 (14.7)	26,598 (15.7)
Never	596 (9.3)	17,233 (10.1)
Smoking status, n (%)		
Never	3,601 (56.5)	99,292 (58.6)
Previous	2,207 (34.7)	56,246 (33.2)
Current	560 (8.8)	13,918 (8.2)
Qualification, n (%)		
None of the above	1,333 (21.3)	35,931 (21.5)
College or University degree	1,803 (28.8)	46,864 (28.1)
A levels/AS levels or equivalent	709 (11.3)	18,075 (10.8)
O levels/GCSEs or equivalent	1,506 (24.0)	39,299 (23.5)
CSEs or equivalent	248 (3.9)	7,385 (4.4)
NVQ or HND or HNC or equivalent	275 (4.4)	8,073 (4.8)
Other professional	389 (6.2)	11,389 (6.8)
Ever use of oral contraceptive, n (%)		
No	1,406 (22.1)	36,877 (21.7)
Yes	4,966 (77.9)	132,772 (78.3)
Ever use of menopausal hormone therapy, n (%)		
No	2,969 (46.6)	83,903 (49.5)
Yes	3,397 (53.4)	85,694 (50.5)
Healthy diet score, n (%)		
0 (unhealthy)	4 (0.1)	134 (0.1)
1	54 (0.8)	1,328 (0.8)
2	301 (4.7)	7,611 (4.5)
3	1,387 (21.7)	36,621 (21.5)
4	2,992 (46.8)	79,577 (46.7)
5	1,472 (23.0)	39,495 (23.2)

6 (healthy)	187 (2.9)	5,524 (3.2)
Screening mammogram, n (%)		
No	209 (3.3)	9,255 (5.4)
Yes	6,177 (96.7)	160,737 (94.6)
Ethnicity, n (%)		
White	6,158 (96.6)	162,088 (95.5)
Mixed	24 (0.4)	821 (0.5)
Asian	89 (1.4)	2,538 (1.5)
Black	56 (0.9)	2,331 (1.4)
Chinese	10 (0.1)	499 (0.3)
Other ethnic group	37 (0.6)	1,385 (0.8)

Mean (Standard deviation) and Counts (Percentages) are presented for continuous and categorical variables respectively

BMI: body mass index, WHR: waist-to-hip ratio, healthy diet score (from unhealthy to healthy) was calculated based on consumption of these commonly food groups (fruits, vegetables, fish, processed meats, unprocessed red meats, whole grains, and refined grains) [28], Sedentary behaviour = sum of time spent watching television, time spent using computer and time spent driving, Qualification : A: advanced, AS: advanced subsidiary, O: ordinary, GCSE: general certificate of secondary education, CSE: certificate of secondary education, NVQ: national vocational qualification, HND: higher national diploma, HNC: higher national certificate

Supplementary Table 2: Distribution of the main biomarkers of postmenopausal women from the UK Biobank cohort study

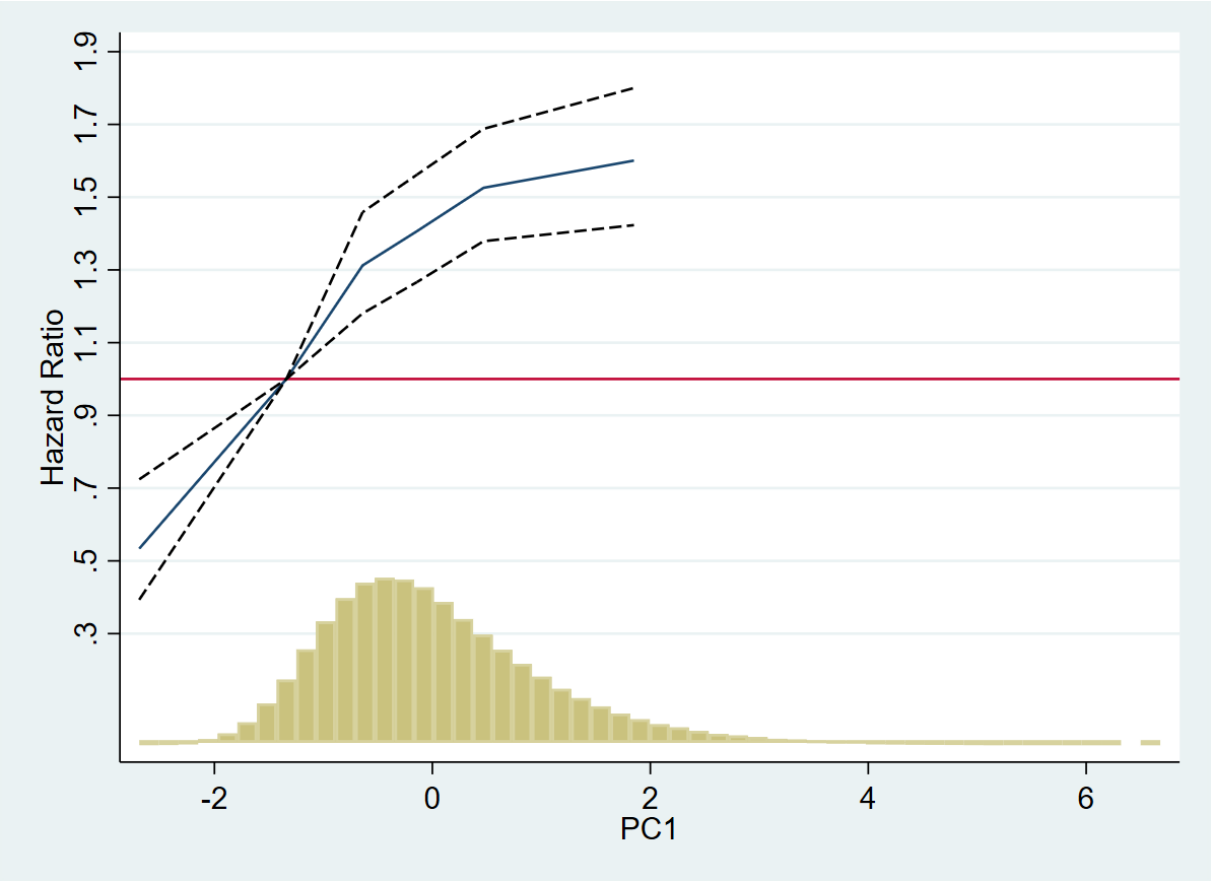
	Cases		Non cases	
Biomarkers	**Median**	**P25-P75**	**Median**	**P25-P75**
Cholesterol (mmol/L)	6.00	5.26 - 6.76	6.01	5.27 -6.76
C-reactive protein (mg/L)	1.68	0.83 - 3.44	1.48	0.72 -3.11
Glycated haemoglobin (HbA1c) (mmol/mol)	35.8	33.5 - 38.3	35.9	33.6 -38.3
HDL-cholesterol (mmol/L)	1.56	1.32 - 1.84	1.57	1.34 -1.84
IGF-1 (nmol/L)	20.2	16.4 - 23.8	19.9	16.3 -23.5
SHBG (nmol/L)	52.2	37.0 - 70.9	54.8	39.0 -74.7
Testosterone (nmol/L)	1.02	0.74 - 1.40	0.97	0.69 -1.32
Total protein (g/L)	72.1	69.6 - 74.8	72.3	69.7 -75.0
Triglycerides (mmol/L)	1.46	1.06 - 2.02	1.42	1.04 -2.0
Albumin (g/L)	45.0	43.2 - 46.6	45.0	43.3 - 46.7
Glucose (mmol/L)	4.99	4.66 - 5.35	4.96	4.64 - 5.33
Alanine aminotransferase (U/L)	18.6	14.9 - 24.6	18.3	14.6 -23.9
Apolipoprotein A (g/L)	1.63	1.45 - 1.81	1.63	1.47 - 1.81
Apolipoprotein B (g/L)	1.05	0.90 - 1.21	1.05	0.90 - 1.21
Cystatin C (mg/L)	0.89	0.81 - 0.98	0.88	0.80 - 0.98
Gamma-glutamyltransferase (U/L)	23.6	17.6 - 35.9	22.6	17 - 33.8
Total bilirubin (umol/L)	7.27	5.93 - 9.16	7.23	5.92 -9.1
Urate (umol/L)	275.5	235.4 - 321.4	270.9	231.3 - 316.4

HDL cholesterol: high-density lipoprotein cholesterol, IGF1: insulin-like growth factor, SHBG: sex hormone-binding globulin.

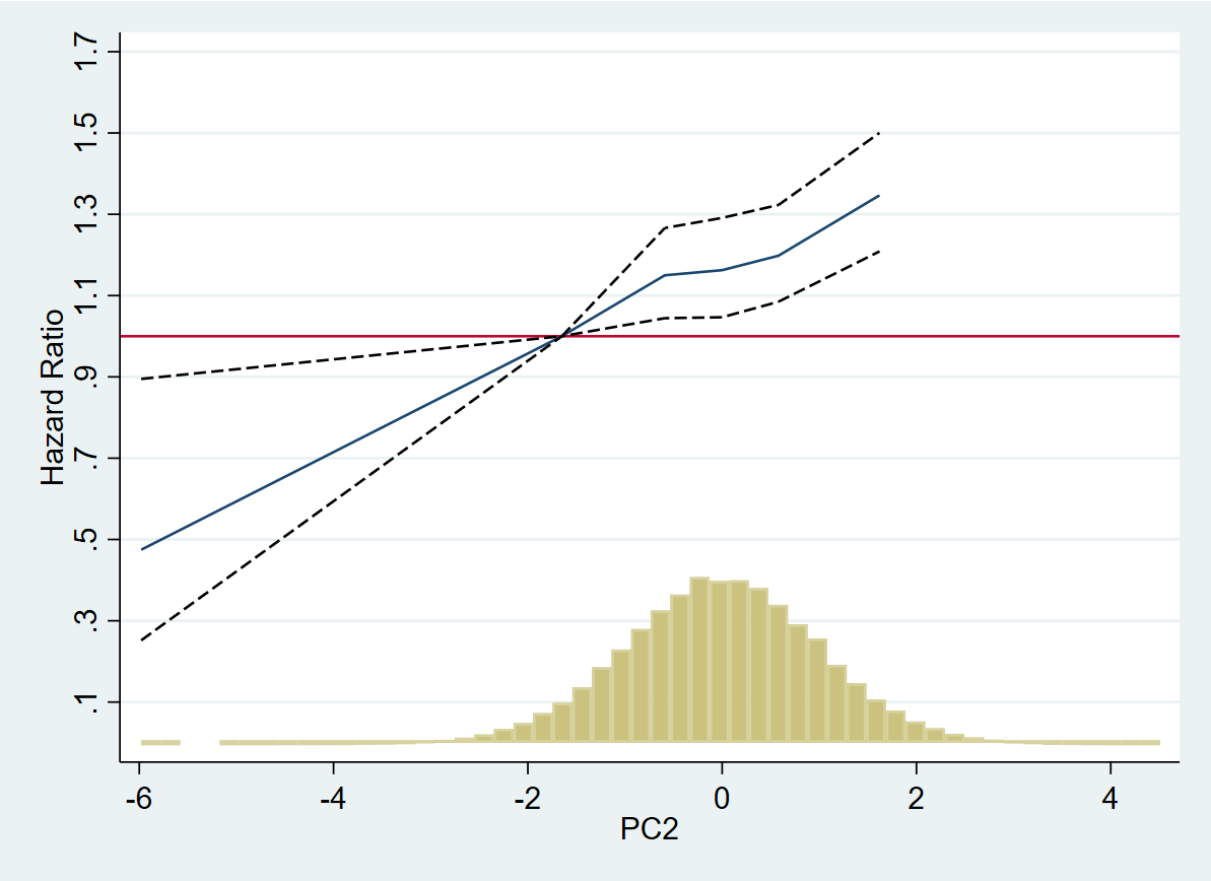
Supplementary Table 3: Loadings and explained variance of the principal components for women

	PC1	PC2	PC3	PC4	PC5	PC6
Height	0.043	0.851	0.449	0.022	0.269	-0.012
Weight	0.481	0.226	-0.086	0.489	-0.686	0.033
BMI	0.479	-0.106	-0.272	0.479	0.675	-0.027
Hip	0.457	0.182	-0.353	-0.609	0.015	0.511
Waist	0.489	-0.111	0.184	-0.399	-0.037	-0.745
WHR	0.300	-0.411	0.747	0.028	0.021	0.427
Explained variance (%)	65.71	19.10	13.50	1.61	0.04	0.04

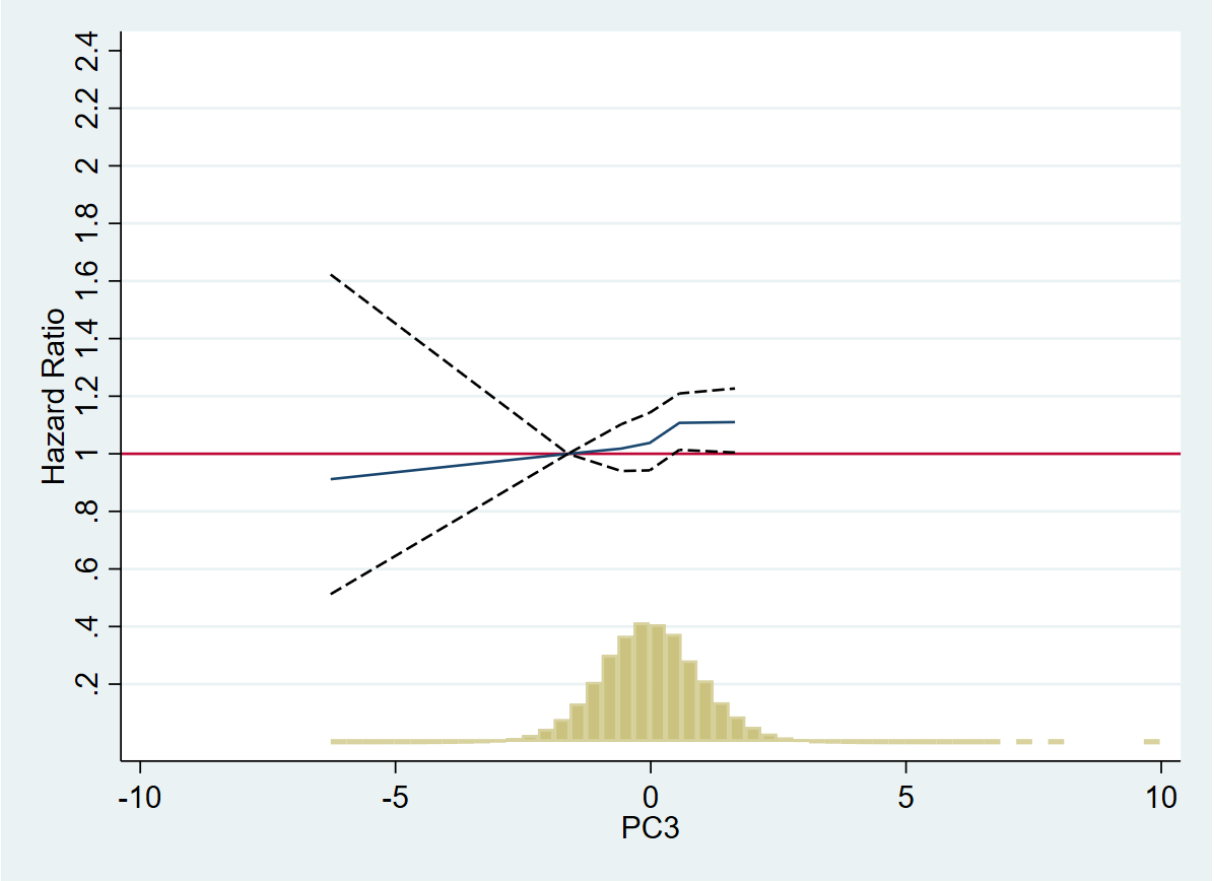
PC: principal component, BMI: body mass index, WHR: waist-to-hip ratio.



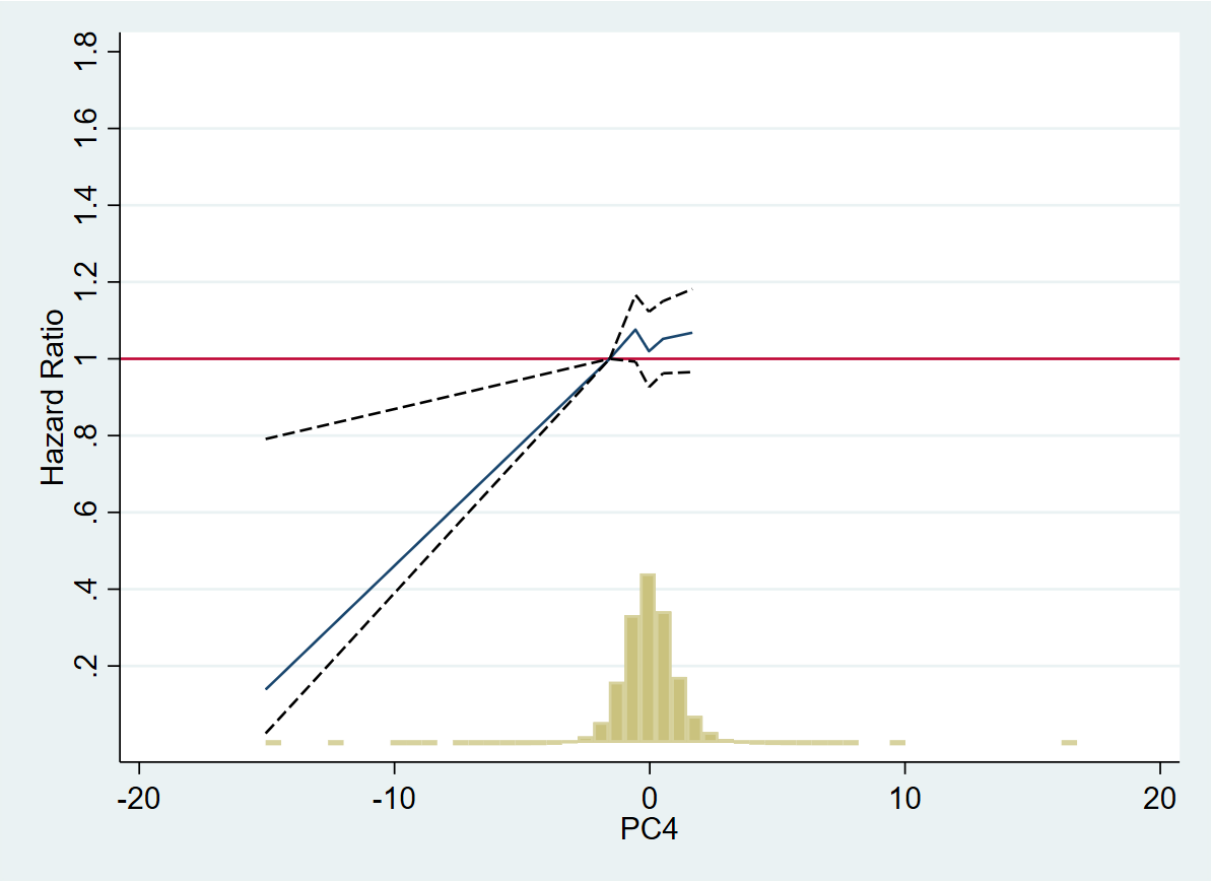
Supplementary Figure 3: Cubic spline modelling of the relationship between PC1 and postmenopausal breast cancer risk. Multivariable adjusted hazard ratios (continuous line) and 95% confidence intervals (dotted line) obtained using five-knot restricted cubic splines with the P5th value used as reference. Models were stratified by age at recruitment in 5-year categories, study center, and adjusted for alcohol intake, smoking status, oral contraceptive, menopausal hormone treatment, physical activity, qualifications, Townsend deprivation index and sedentary behavior.



Supplementary Figure 4: Cubic spline modelling of the relationship between PC2 and postmenopausal breast cancer risk. Multivariable adjusted hazard ratios (continuous line) and 95% confidence intervals (dotted line) obtained using five-knot restricted cubic splines with the P5th value used as reference. Models were stratified by age at recruitment in 5-year categories, study center, and adjusted for alcohol intake, smoking status, oral contraceptive, menopausal hormone treatment, physical activity, qualifications, Townsend deprivation index and sedentary behavior.



Supplementary Figure 5: Cubic spline modelling of the relationship between PC3 and postmenopausal breast cancer risk. Multivariable adjusted hazard ratios (continuous line) and 95% confidence intervals (dotted line) obtained using five-knot restricted cubic splines with the P5th value used as reference. Models were stratified by age at recruitment in 5-year categories, study center, and adjusted for alcohol intake, smoking status, oral contraceptive, menopausal hormone treatment, physical activity, qualifications, Townsend deprivation index and sedentary behavior.



Supplementary Figure 6: Cubic spline modelling of the relationship between PC4 and postmenopausal breast cancer risk. Multivariable adjusted hazard ratios (continuous line) and 95% confidence intervals (dotted line) obtained using five-knot restricted cubic splines with the P5th value used as reference. Models were stratified by age at recruitment in 5-year categories, study center, and adjusted for alcohol intake, smoking status, oral contraceptive, menopausal hormone treatment, physical activity, qualifications, Townsend deprivation index and sedentary behavior.

Supplementary Table 4: Associations between principal components and postmenopausal breast cancer risk (per 1 SD increment)

	PC1		PC2		PC3		PC4	
	Cases/non cases	HR (95% CI)	Cases/non cases	HR (95% CI)	Cases/non cases	HR (95% CI)	Cases/non cases	HR (95% CI)
Sensitivity analyses								
1	3,850 /123,406	1.13 (1.09-1.17)	3,850 /123,406	1.08 (1.05-1.12)	3,850 /123,406	1.03 (1.00-1.07)	3,850 /123,406	1.02 (0.98-1.05)
2	6,396/170,290	1.13 (1.11-1.16)	6,396/170,290	1.10 (1.07-1.12)	6,396/170,290	1.05 (1.02-1.08)	6,396/170,290	1.03 (1.00-1.06)
3	3,912/108,842	1.14 (1.10-1.18)	3,912/108,842	1.08 (1.04-1.11)	3,912/108,842	1.04 (1.00-1.07)	3,912/108,842	1.00 (0.97-1.03)

Hazard ratios per 1 standard deviation (SD) increment in each PC from Cox proportional hazards regression using age as the underlying time metric. Stratified by age in 5-year categories, center and diet, and adjusted for age alcohol frequency, smoking status, oral contraceptive, menopausal hormone treatment, physical activity, qualifications, townsend deprivation index and sedentary behavior. All four principal components were mutually adjusted.

1: Excluding participants with the first 2 years of follow-up, n = 127,256

2: Multiple imputation, n =176,686

3: Exclusively on postmenopausal women, who answered having their periods stopped at least 1 year, n = 108,754

Supplementary Table 5: Hazard ratios and 95% CI for the association of baseline levels of metabolic and biological markers with risk of incident post-menopausal breast cancer

Biomarkers	**Cases**	**Non cases**	**HR (95% CI)**
Cholesterol (mmol/L)	4,400	121,899	0.98 (0.95-1.01)
C-reactive protein (mg/L)	4,394	121,701	1.04 (1.01-1.07)
Glycated haemoglobin (HbA1c) (mmol/mol)	4,352	121,108	0.99 (0.96-1.02)
HDL-cholesterol (mmol/L)	4,038	110,815	0.95 (0.92-0.98)
IGF-1 (nmol/L)	4,365	121,223	1.05 (1.02-1.08)
SHBG (nmol/L)	3,987	109,672	0.93 (0.90-0.96)
Testosterone (nmol/L)	3,718	98,656	1.07 (1.05-1.09)
Total protein (g/L)	4,038	110,757	0.97 (0.94-1.01)
Triglycerides (mmol/L)	4,397	121,835	1.02 (0.99-1.05)
Albumin (g/L)	4,041	110,861	0.95 (0.92-0.98)
Glucose (mmol/L)	4,032	110,738	1.02 (0.99-1.05)
Alanine aminotransferase (U/L)	4,400	121,904	1.03 (1.00-1.05)
Apolipoprotein A (g/L)	3,994	109,646	0.96 (0.93-0.99)
Apolipoprotein B (g/L)	4,386	121,539	1.00 (0.97-1.03)
Cystatin C (mg/L)	4,396	121,887	1.03 (1.00-1.06)
Gamma-glutamyltransferase (U/L)	4,396	121,858	1.03 (1.01-1.06)
Total bilirubin (umol/L)	4,381	121,425	1.03 (1.00-1.06)
Urate (umol/L)	4,393	121,761	1.06 (1.03-1.09)

Hazard ratios per 1 standard deviation (SD) increment in each PC from Cox proportional hazards regression using age as the underlying time metric. Stratified by age in 5-year categories, center and diet, and adjusted for age alcohol frequency, smoking status, oral contraceptive, menopausal hormone treatment, physical activity, qualifications, townsend deprivation index and sedentary behavior.
HDL cholesterol: high-density lipoprotein cholesterol, IGF-1: insulin-like growth factor, SHBG: sex hormone-binding globulin.

Supplementary Table 6: Beta coefficient and P value of the association between principal components and biomarkers

Biomarkers		PC1		PC2		PC3		PC4	
	n	Beta	P value	Beta	P value	Beta	P value	Beta	P value
Cholesterol (mmol/L)	121,899	-0.039	<0.001	-0.042	<0.001	0.022	<0.001	-0.020	<0.001
C-reactive protein (mg/L)	121,701	1.223	<0.001	-0.262	<0.001	-0.159	<0.001	0.074	<0.001
Glycated haemoglobin (HbA1c) (mmol/mol)	121,108	1.319	<0.001	-0.441	<0.001	0.410	<0.001	0.206	<0.001
HDL-cholesterol (mmol/L)	110,815	-0.131	<0.001	0.348	<0.001	-0.045	<0.001	-0.022	<0.001
IGF-1 (nmol/L)	121,223	-0.678	<0.001	0.199	<0.001	0.214	<0.001	0.004	0.780
SHBG (nmol/L)	109,672	-12.899	<0.001	3.748	0.034	-2.280	<0.001	-1.446	<0.001
Testosterone (nmol/L)	98,656	0.050	<0.001	-0.004	0.038	-0.018	<0.001	0.008	<0.001
Total protein (g/L)	110,757	0.018	0.164	-0.201	0.032	0.110	<0.001	0.042	0.001
Triglycerides (mmol/L)	121,835	0.261	<0.001	-0.132	<0.001	0.136	<0.001	0.029	<0.001
Albumin (g/L)	110,861	-0.428	<0.001	-0.065	<0.001	0.177	<0.001	0.045	<0.001
Glucose (mmol/L)	110,738	0.167	<0.001	-0.054	<0.001	0.053	<0.001	0.032	<0.001
Alanine aminotransferase (U/L)	121,904	2.629	<0.001	-1.162	<0.001	0.816	<0.001	0.386	<0.001
Apolipoprotein A (g/L)	109,646	-0.067	<0.001	0.012	<0.001	-0.021	<0.001	-0.013	<0.001
Apolipoprotein B (g/L)	121,539	0.021	<0.001	-0.019	<0.001	0.014	<0.001	0.001	0.087
Cystatin C (mg/L)	121,887	0.047	0.383	0.000	0.461	-0.004	<0.001	0.004	<0.001
Gamma-glutamyltransferase (U/L)	121,858	5.413	<0.001	-2.822	0.094	1.448	<0.001	0.246	0.014
Total bilirubin (umol/L)	121,425	-0.280	<0.001	0.243	<0.001	0.053	<0.001	0.052	<0.001
Urate (umol/L)	121,761	29.526	<0.001	-5.707	<0.001	0.777	<0.001	4.069	<0.001

HDL cholesterol: high-density lipoprotein cholesterol, IGF-1: insulin-like growth factor, SHBG: sex hormone-binding globulin

Supplementary Table 7: Beta coefficient (standard error) and P value for the four-way decomposition of each mediator of the associations between principal component 1 of body shape and postmenopausal breast cancer risk

Biomarkers	TE		CDE		Intref		Intmed		PIE	
	Beta coef (SE)	P value	Beta coef (SE)	P value	Beta coef (SE)	P value	Beta coef (SE)	P value	Beta coef (SE)	P value
C-reactive protein (mg/L)	0.168 (0.030)	<0.001	0.172 (0.031)	<0.001	-0.007 (0.003)	0.028	-0.009 (0.004)	0.045	0.011 (0.006)	0.008
HDL-cholesterol (mmol/L)	0.154 (0.030)	<0.001	0.150 (0.029)	<0.001	0.003 (0.004)	0.425	-0.017 (0.002)	0.418	0.003 (0.004)	0.532
IGF-1 (nmol/L)	0.143 (0.029)	<0.001	0.146 (0.029)	<0.001	0.015 (0.005)	0.003	-0.012 (0.004)	0.003	-0.006 (0.005)	0.205
SHBG (nmol/L)	0.170 (0.029)	<0.001	0.150 (0.029)	<0.001	0.009 (0.012)	0.458	-0.009 (0.012)	0.449	0.017 (0.009)	0.069
Testosterone (nmol/L)	0.151 (0.029)	<0.001	0.134 (0.029)	<0.001	-0.0006 (0.005)	0.233	0.002 (0.003)	0.413	0.015 (0.003)	<0.001
Triglycerides (mmol/L)	0.145 (0.029)	<0.001	0.148 (0.030)	<0.001	-0.002 (0.004)	0.616	-0.0004 (0.001)	0.613	-0.0005 (0.001)	0.658
Albumin (g/L)	0.162 (0.030)	<0.001	0.151 (0.030)	<0.001	0.001 (0.003)	0.591	-0.003 (0.004)	0.548	0.012 (0.005)	0.022
Glucose (mmol/L)	0.147 (0.030)	<0.001	0.148 (0.030)	<0.001	-0.001 (0.001)	0.422	-0.002 (0.002)	0.398	0.001 (0.003)	0.629
Alanine Aminotransferase (U/L)	0.146 (0.029)	<0.001	0.146 (0.030)	<0.001	0.0000 (0.0003)	0.933	-0.0003 (0.004)	0.947	0.0002 (0.004)	0.950
Apolipoprotein A (g/L)	0.149 (0.029)	<0.001	0.146 (0.029)	<0.001	0.012 (0.002)	0.475	0.0008 (0.001)	0.463	0.0007 (0.003)	0.815
Gamma-Glutamyltransferase (U/L)	0.146 (0.029)	<0.001	0.148 (0.030)	<0.001	-0.003 (0.005)	0.566	-0.00001 (0.0002)	0.749	0.0001 (0.0002)	0.512
Total bilirubin (umol/L)	0.143 (0.029)	<0.001	0.142 (0.030)	<0.001	0.003 (0.007)	0.687	-0.0005 (0.001)	0.682	-0.002 (0.001)	0.103
Urate (umol/L)	0.144 (0.032)	<0.001	0.149 (0.032)	<0.001	0.001 (0.003)	0.629	-0.004 (0.009)	0.637	-0.001 (0.009)	0.873

TE=total effect (total excess relative risk); CDE=excess relative risk due to controlled direct effect; INTref=excess relative risk due to reference interaction; INTmed=excess relative risk due to mediated interaction; PIE=excess relative risk due to pure indirect effect. Output of mediation analysis with causal effects estimated for a change in PC from the 25th to the 75th percentile. Controlled direct effects are computed fixing the mediators at their median levels.
HDL cholesterol: High-density lipoprotein cholesterol, IGF-1: insulin-like growth factor, SHBG: Sex hormone-binding globulin.
Models adjusted for age, center and diet, and adjusted for age alcohol frequency, smoking status, oral contraceptive, menopausal hormone treatment, physical activity, qualifications, townsend deprivation index and sedentary behavior, and mutually adjusted for biomarkers.

Supplementary Table 8: Beta coefficient (standard error) and P value for the four-way decomposition of each mediator of the associations between principal component 2 of body shape and postmenopausal breast cancer risk

Biomarkers	TE		CDE		Intref		Intmed		PIE	
	Beta coef (SE)	P value	Beta coef (SE)	P value	Beta coef (SE)	P value	Beta coef (SE)	P value	Beta coef (SE)	P value
C-reactive protein (mg/L)	0.127 (0.029)	<0.001	0.125 (0.029)	<0.001	0.0031 (0.008)	0.682	-0.0002 (0.001)	0.682	-0.0006 (0.001)	0.221
HDL-cholesterol (mmol/L)	0.128 (0.029)	<0.001	0.126 (0.029)	<0.001	0.0026 (0.002)	0.253	0.0007 (0.001)	0.251	-0.0022 (0.001)	0.109
IGF-1 (nmol/L)	0.130 (0.029)	<0.001	0.132 (0.029)	<0.001	-0.0039 0.003)	0.158	-0.0017 (0.001)	0.173	0.0036 (0.001)	0.002
SHBG (nmol/L)	0.123 (0.029)	<0.001	0.123 (0.029)	<0.001	0.0044 (0.002)	0.051	0.0037 (0.002)	0.024	-0.0075 (0.002)	0.000
Testosterone (nmol/L)	0.127 (0.029)	<0.001	0.128 (0.029)	<0.001	-0.0002 (0.003)	0.936	-0.0001 (0.0002)	0.841	-0.0009 (0.001)	0.114
Triglycerides (mmol/L)	0.130 (0.029)	<0.001	0.134 (0.030)	<0.001	-0.0066 (0.005)	0.190	0.0019 (0.002)	0.211	0.0002 (0.001)	0.882
Albumin (g/L)	0.131 (0.029)	<0.001	0.128 (0.029)	<0.001	-0.0004 (0.001)	0.656	0.0004 (0.0003)	0.731	0.0029 (0.001)	0.041
Glucose (mmol/L)	0.128 (0.029)	<0.001	0.130 (0.029)	<0.001	-0.0018 (0.002)	0.458	0.0002 (0.003)	0.521	-0.0001 (0.0002)	0.638
Alanine Aminotransferase (U/L)	0.127 (0.029)	<0.001	0.129 (0.029)	<0.001	-0.0004 (0.003)	0.886	0.0001 (0.001)	0.892	-0.0008 (0.001)	0.455
Apolipoprotein A (g/L)	0.129 (0.029)	<0.001	0.124 (0.029)	<0.001	0.0062 (0.003)	0.058	-0.0012 (0.001)	0.058	-0.0005 (0.001)	0.644
Gamma-Glutamyltransferase (U/L)	0.127 (0.029)	<0.001	0.129 (0.029)	<0.001	-0.0011 (0.005)	0.817	0.0001 (0.001)	0.818	-0.0007 (0.001)	0.303
Total bilirubin (umol/L)	0.130 (0.029)	<0.001	0.127 (0.030)	<0.001	0.0008 (0.005)	0.880	0.0003 (0.002)	0.874	0.0019 (0.001)	0.250
Urate (umol/L)	0.128 (0.029)	<0.001	0.129 (0.029)	<0.001	-0.0006 (0.003)	0.827	0.00002 (0.0001)	0.874	-0.0001 (0.0001)	0.545

TE=total effect (total excess relative risk); CDE=excess relative risk due to controlled direct effect; INTref=excess relative risk due to reference interaction; INTmed=excess relative risk due to mediated interaction; PIE=excess relative risk due to pure indirect effect. Output of mediation analysis with causal effects estimated for a change in PC from the 25th to the 75th percentile. Controlled direct effects are computed fixing the mediators at their median levels.
HDL cholesterol: High-density lipoprotein cholesterol, IGF-1: insulin-like growth factor, SHBG: Sex hormone-binding globulin.
Models adjusted for age, center and diet, and adjusted for age alcohol frequency, smoking status, oral contraceptive, menopausal hormone treatment, physical activity, qualifications, townsend deprivation index and sedentary behavior, and mutually adjusted for biomarkers

IGF-1

	Observed coefficient	Bootstrap std. err.	z	P>|z|	Normal-based [95% conf.	interval]
tereri	.1432835	.0288904	4.96	0.000	.0866594	.1999075
ereri_cde	.1460793	.0287295	5.08	0.000	.0897706	.2023881
ereri_intref	.0147622	.0049431	2.99	0.003	.005074	.0244505
ereri_intmed	-.0117102	.0039147	-2.99	0.003	-.0193828	-.0040376
ereri_pie	-.0058479	.0046108	-1.27	0.205	-.0148849	.003189
terira	1.143283	.0288904	39.57	0.000	1.086659	1.199908
p_cde	1.019513	.0405858	25.12	0.000	.9399662	1.099059
p_intref	.1030282	.0418417	2.46	0.014	.0210199	.1850365
p_intmed	-.0817274	.0333519	-2.45	0.014	-.1470959	-.016359
p_pie	-.0408136	.040317	-1.01	0.311	-.1198335	.0382063
op_m	-.122541	.0419845	-2.92	0.004	-.2048292	-.0402529
op_ati	.0213008	.0102017	2.09	0.037	.0013057	.0412958
op_e	-.0195128	.0405858	-0.48	0.631	-.0990595	.0600338

Testosterone

	Observed coefficient	Bootstrap std. err.	z	P>|z|	Normal-based [95% conf.	interval]
tereri	.1505901	.0287699	5.23	0.000	.094202	.2069781
ereri_cde	.1339706	.0285755	4.69	0.000	.0779636	.1899777
ereri_intref	-.0006152	.0005156	-1.19	0.233	-.0016258	.0003954
ereri_intmed	.0023999	.0029327	0.82	0.413	-.0033481	.0081478
ereri_pie	.0148348	.002701	5.49	0.000	.0095409	.0201286
terira	1.15059	.0287699	39.99	0.000	1.094202	1.206978
p_cde	.8896379	.0343197	25.92	0.000	.8223725	.9569032
p_intref	-.0040852	.0035525	-1.15	0.250	-.011048	.0028776
p_intmed	.0159363	.0207071	0.77	0.442	-.0246487	.0565214
p_pie	.098511	.0316922	3.11	0.002	.0363955	.1606265
op_m	.1144473	.0325882	3.51	0.000	.0505757	.1783189
op_ati	.0118511	.0230466	0.51	0.607	-.0333193	.0570216
op_e	.1103621	.0343197	3.22	0.001	.0430968	.1776275

tereri=total excess relative risk; ereri_cde=excess relative risk due to controlled direct effect; ereri_intref=excess relative risk due to reference interaction; ereri_intmed=excess relative risk due to mediated interaction; ereri_pie=excess relative risk due to pure indirect effect; terira=total effect risk ratio; p_cde=proportion controlled direct effect; p_intref=proportion reference interaction; p_intmed=proportion mediated interaction; p_pie=proportion pure indirect effect; op_m=overall proportion mediated; op_ati=overall proportion attributable to interaction; op_e=overall proportion eliminated.

Supplementary Figure 7: Full output of the 4-way decomposition mediation analysis with IGF-1 and testosterone and as mediators, PC1 as exposure and breast cancer as outcome. Causal effects were estimated for a change in PC1 from the 25th to the 75th percentile. Controlled direct effects are computed fixing the mediators at their median levels.

Models adjusted for age, center and diet, and adjusted for age alcohol frequency, smoking status, oral contraceptive, menopausal hormone treatment, physical activity, qualifications, townsend deprivation index and sedentary behavior, and mutually adjusted for biomarkers.
IGF-1: insulin-like growth factor.

IGF-1

	Observed coefficient	Bootstrap std. err.	z	P>|z|	Normal-based [95% conf.	interval]
tereri	.1295395	.029398	4.41	0.000	.0719204	.1871585
ereri_cde	.1316067	.0289244	4.55	0.000	.0749159	.1882975
ereri_intref	-.0038917	.0027555	-1.41	0.158	-.0092923	.0015089
ereri_intmed	-.0017456	.0012821	-1.36	0.173	-.0042584	.0007672
ereri_pie	.00357	.0011356	3.14	0.002	.0013444	.0057957
terira	1.129539	.029398	38.42	0.000	1.07192	1.187159
p_cde	1.015958	.0288839	35.17	0.000	.959347	1.07257
p_intref	-.0300424	.024259	-1.24	0.216	-.0775891	.0175043
p_intmed	-.0134753	.0115133	-1.17	0.242	-.0360411	.0090904
p_pie	.0275594	.0109097	2.53	0.012	.0061767	.048942
op_m	.014084	.0096744	1.46	0.145	-.0048773	.0330454
op_ati	-.0435178	.0354482	-1.23	0.220	-.112995	.0259595
op_e	-.0159584	.0288839	-0.55	0.581	-.0725698	.040653

SHBG

	Observed coefficient	Bootstrap std. err.	z	P>|z|	Normal-based [95% conf.	interval]
tereri	.1231685	.0288803	4.26	0.000	.0665641	.179773
ereri_cde	.1225965	.0292238	4.20	0.000	.0653189	.1798741
ereri_intref	.0043523	.0022311	1.95	0.051	-.0000206	.0087252
ereri_intmed	.0037417	.0016522	2.26	0.024	.0005034	.00698
ereri_pie	-.007522	.0020868	-3.60	0.000	-.011612	-.003432
terira	1.123169	.0288803	38.89	0.000	1.066564	1.179773
p_cde	.9953558	.0336199	29.61	0.000	.929462	1.06125
p_intref	.035336	.0199921	1.77	0.077	-.0038478	.0745199
p_intmed	.0303787	.0151206	2.01	0.045	.0007429	.0600144
p_pie	-.0610705	.0243592	-2.51	0.012	-.1088138	-.0133273
op_m	-.0306919	.0194641	-1.58	0.115	-.0688407	.007457
op_ati	.0657147	.0337184	1.95	0.051	-.0003721	.1318015
op_e	.0046442	.0336199	0.14	0.890	-.0612497	.070538

tereri=total excess relative risk; ereri_cde=excess relative risk due to controlled direct effect; ereri_intref=excess relative risk due to reference interaction; ereri_intmed=excess relative risk due to mediated interaction; ereri_pie=excess relative risk due to pure indirect effect; terira=total effect risk ratio; p_cde=proportion controlled direct effect; p_intref=proportion reference interaction; p_intmed=proportion mediated interaction; p_pie=proportion pure indirect effect; op_m=overall proportion mediated; op_ati=overall proportion attributable to interaction; op_e=overall proportion eliminated.

Supplementary Figure 8: Full output of the 4-way decomposition mediation analysis with IGF-1 and SHBG and as mediators, PC2 as exposure and breast cancer as outcome. Causal effects were estimated for a change in PC1 from the 25th to the 75th percentile. Controlled direct effects are computed fixing the mediators at their median levels.

Models adjusted for age, center and diet, and adjusted for age alcohol frequency, smoking status, oral contraceptive, menopausal hormone treatment, physical activity, qualifications, townsend deprivation index and sedentary behavior, and mutually adjusted for biomarkers.
IGF-1: insulin-like growth factor, SHBG: Sex hormone-binding globulin.

Supplementary Table 9 Beta coefficient (standard error) and P value for the four-way decomposition of each mediator of the associations between principal component 1 of body shape and postmenopausal breast cancer risk

	TE		CDE		Intref		Intmed		PIE	
Biomarkers	Beta coef (SE)	P value	Beta coef (SE)	P value	Beta coef (SE)	P value	Beta coef (SE)	P value	Beta coef (SE)	P value
C-reactive protein (mg/L)	0.185 (0.021)	<0.001	0.191 (0.024)	<0.001	-0.005 (0.002)	0.006	-0.016 (0.006)	0.009	0.015 (0.006)	0.013
HDL-cholesterol (mmol/L)	0.182 (0.026)	<0.001	0.173 (0.027)	<0.001	0.018 (0.009)	0.040	-0.022 (0.010)	0.034	0.012 (0.009)	0.170
IGF-1 (nmol/L)	0.173 (0.026)	<0.001	0.178 (0.025)	<0.001	0.010 (0.004)	0.014	-0.007 (0.003)	0.011	-0.007 (0.003)	0.019
SHBG (nmol/L)	0.178 (0.024)	<0.001	0.155 (0.025)	<0.001	0.023 (0.011)	0.045	-0.026 (0.013)	0.037	0.027 (0.012)	0.023
Testosterone (nmol/L)	0.162 (0.026)	<0.001	0.147 (0.027)	<0.001	-0.001 (0.001)	0.339	0.001 (0.002)	0.519	0.014 (0.002)	<0.001
Triglycerides (mmol/L)	0.170 (0.021)	<0.001	0.178 (0.022)	<0.001	0.0004 (0.001)	0.447	-0.010 (0.007)	0.162	0.002 (0.009)	0.822
Albumin (g/L)	0.176 (0.025)	<0.001	0.169 (0.025)	<0.001	0.003 (0.002)	0.116	-0.007 (0.004)	0.075	0.011 (0.004)	0.008
Glucose (mmol/L)	0.172 (0.024)	<0.001	0.173 (0.025	<0.001	-0.001 (0.001)	0.293	-0.004 (0.003)	0.134	0.005 (0.005)	0.303
Alanine Aminotransferase (U/L)	0.166 (0.023)	<0.001	0.165 (0.024)	<0.001	0.0005 (0.001)	0.725	-0.002 (0.005)	0.738	0.003 (0.006)	0.609
Apolipoprotein A (g/L)	0.177 (0.025)	<0.001	0.169 (0.025)	<0.001	0.010 (0.006)	0.121	-0.012 (0.007)	0.114	0.010 (0.006)	0.113
Gamma-Glutamyltransferase (U/L)	0.167 (0.023)	<0.001	0.165 (0.023)	<0.001	-0.002 (0.003)	0.394	-0.002 (0.003)	0.414	0.006 (0.004)	0.074
Total bilirubin (umol/L)	0.166 (0.023)	<0.001	0.166 (0.024)	<0.001	0.005 (0.008)	0.484	-0.002 (0.002)	0.474	-0.003 (0.001)	0.043
Urate (umol/L)	0.176 (0.024)	<0.001	0.167 (0.026)	<0.001	0.007 (0.006)	0.212	-0.013 (0.011)	0.208	0.016 (0.011)	0.160

TE=total effect (total excess relative risk); CDE=excess relative risk due to controlled direct effect; INTref=excess relative risk due to reference interaction; INTmed=excess relative risk due to mediated interaction; PIE=excess relative risk due to pure indirect effect. Output of mediation analysis with causal effects estimated for a change in PC from the 25th to the 75th percentile. Controlled direct effects are computed fixing the mediators at their median levels
HDL cholesterol: high-density lipoprotein cholesterol, IGF-1: insulin-like growth factor, SHBG: sex hormone-binding globulin.
Models adjusted for age, center and diet, and adjusted for age alcohol frequency, smoking status, oral contraceptive, menopausal hormone treatment, physical activity, qualifications, townsend deprivation index and sedentary behavior

Supplementary Table 10: Proportion attributable for the four-way decomposition of each mediator of the associations between principal component 1 of body shape and postmenopausal breast cancer risk

Biomarkers	P_ CDE		P_ INTref		P_INTmed		P_PIE		OP_M	
	Proportion	P value	Proportion	P value	Proportion	P value	Proportion	P value	Proportion	P value
C-reactive protein (mg/L)	103.4%	<0.001	-2.7%	0.003	-8.6%	0.006	8.0%	0.009	-0.6%	0.876
HDL-cholesterol (mmol/L)	94.9%	<0.001	10.1%	0.036	-11.9%	0.030	6.8%	0.201	-5.0%	0.447
IGF1 (nmol/L)	102.8%	<0.001	5.6%	0.014	-4.3%	0.010	-4.1%	0.054	-8.4%	<0.001
SHBG (nmol/L)	87.2%	<0.001	12.7%	0.050	-14.8%	0.042	15.0%	0.033	0.2%	0.983
Testosterone (nmol/L)	90.7%	<0.001	-0.4%	0.342	0.8%	0.538	8.9%	<0.001	9.7%	<0.001
Triglycerides (mmol/L)	104.9%	<0.001	-0.3%	0.443	-5.9%	0.183	1.2%	0.828	-4.7%	0.336
Albumin (g/L)	95.7%	<0.001	1.8%	0.127	-3.9%	0.089	6.5%	0.011	2.6%	0.312
Glucose (mmol/L)	100.3%	<0.001	-0.7%	0.298	-2.5%	0.143	2.9%	0.323	0.3%	0.885
Alanine aminotransferase (U/L)	99.5%	<0.001	-0.3%	0.734	-0.9%	0.746	1.7%	0.634	0.8%	0.828
Apolipoprotein A (g/L)	95.2%	<0.001	5.6%	0.113	-6.6%	0.107	5.8%	0.109	-0.8%	0.853
Gamma-glutamyltransferase (U/L)	99.0%	<0.001	-1.4%	0.414	-1.5%	0.428	3.9%	0.094	2.4%	0.228
Total bilirubin (umol/L)	99.6%	<0.001	3.2%	0.507	-0.9%	0.499	-1.8%	0.049	-2.7%	0.053
Urate (umol/L)	94.7%	<0.001	3.9%	0.216	-7.5%	0.212	8.9%	0.185	1.4%	0.844

P_CDE=proportion of controlled direct effect. P_INTref=proportion of reference interaction. P_INTmed=proportion of mediated interaction. P_PIE=proportion of pure indirect effect. OP_M=overall proportion mediated. Output of mediation analysis with causal effects estimated for a change in PC from the 25th to the 75th percentile. Controlled direct effects are computed fixing the mediators at their median levels.

HDL cholesterol: high-density lipoprotein cholesterol, IGF-1: insulin-like growth factor, SHBG: sex hormone-binding globulin.

Models adjusted for age, center and diet, and adjusted for age alcohol frequency, smoking status, oral contraceptive, menopausal hormone treatment, physical activity, qualifications, townsend deprivation index and sedentary behavior

Supplementary Table 11: Beta coefficient (standard error) and P value for the four-way decomposition of each mediator of the associations between principal component 2 of body shape and postmenopausal breast cancer risk

	TE		CDE		Intref		Intmed		PIE	
Biomarkers	Beta coef (SE)	P value	Beta coef (SE)	P value	Beta coef (SE)	P value	Beta coef (SE)	P value	Beta coef (SE)	P value
C-reactive protein (mg/L)	0.11 (0.022)	<0.001	0.11 (0.022)	<0.001	0.004 (0.005)	0.487	-0.001 (0.001)	0.482	-0.002 (0.001)	0.038
HDL-cholesterol (mmol/L)	0.11 (0.025)	<0.001	0.12 (0.025)	<0.001	0.001 (0.001)	0.397	0.003 (0.002)	0.172	-0.009 (0.002)	0.001
IGF-1 (nmol/L)	0.11 (0.026)	<0.001	0.11 (0.026)	<0.001	-0.002 (0.002)	0.382	-0.001 (0.001)	0.428	0.003 (0.001)	0.001
SHBG (nmol/L)	0.11 (0.026)	<0.001	0.12 (0.602)	<0.001	0.001 (0.001)	0.429	0.009 (0.003)	0.009	-0.018 (0.003)	<0.001
Testosterone (nmol/L)	0.11 (0.027)	<0.001	0.11 (0.027)	<0.001	-0.001 (0.002)	0.823	0.00002 (0.0001)	0.889	-0.001 (0.001)	0.174
Triglycerides (mmol/L)	0.11 (0.026)	<0.001	0.12 (0.026)	<0.001	-0.013 (0.006)	0.032	0.007 (0.003)	0.035	-0.009 (0.003)	0.007
Albumin (g/L)	0.12 (0.025)	<0.001	0.11 (0.025)	<0.001	0.0001 (0.0003)	0.781	0.0005 (0.001)	0.572	0.002 (0.001)	0.017
Glucose (mmol/L)	0.12 (0.023)	<0.001	0.12 (0.023)	<0.001	-0.001 (0.003)	0.615	0.0004 (0.001)	0.620	-0.001 (0.001)	0.128
Alanine aminotransferase (U/L)	0.11 (0.024)	<0.001	0.12 (0.024)	<0.001	-0.002 (0.005)	0.700	0.001 (0.002)	0.715	-0.004 (0.002)	0.042
Apolipoprotein A (g/L)	0.11 (0.023)	<0.001	0.11 (0.023)	<0.001	0.001 (0.001)	0.344	0.001 (0.001)	0.207	-0.003 (0.001)	0.002
Gamma-glutamyltransferase (U/L)	0.11 (0.024)	<0.001	0.11 (0.024)	<0.001	0.003 (0.005)	0.592	-0.001 (0.002)	0.584	-0.004 (0.001)	0.002
Total bilirubin (umol/L)	0.11 (0.022)	<0.001	0.10 (0.023)	<0.001	0.004 (0.004)	0.420	0.001 (0.002)	0.414	0.001 (0.002)	0.461
Urate (umol/L)	0.11 (0.021)	<0.001	0.12 (0.021)	<0.001	-0.001 (0.003)	0.871	0.000 (0.002)	0.916	-0.006 (0.002)	<0.001

TE=total effect (total excess relative risk); CDE=excess relative risk due to controlled direct effect; INTref=excess relative risk due to reference interaction; INTmed=excess relative risk due to mediated interaction; PIE=excess relative risk due to pure indirect effect. Output of mediation analysis with causal effects estimated for a change in PC from the 25th to the 75th percentile. Controlled direct effects are computed fixing the mediators at their median levels
HDL cholesterol: high-density lipoprotein cholesterol, IGF-1: insulin-like growth factor, SHBG: sex hormone-binding globulin.
Models adjusted for age, center and diet, and adjusted for age alcohol frequency, smoking status, oral contraceptive, menopausal hormone treatment, physical activity, qualifications, townsend deprivation index and sedentary behavior

Supplementary Table 12: Proportion attributable for the four-way decomposition of each mediator of the associations between principal component 2 of body shape and postmenopausal breast cancer risk

Biomarkers	P_ CDE		P_ INTref		P_INTmed		P_PIE		OP_M	
	Proportion	P value	Proportion	P value	Proportion	P value	Proportion	P value	Proportion	P value
C-reactive protein (mg/L)	99.7%	<0.001	3.2%	0.475	-0.7%	0.469	-2.3%	0.061	-3.0%	0.011
HDL-cholesterol (mmol/L)	104.1%	<0.001	0.6%	0.429	2.9%	0.234	-7.6%	0.010	-4.7%	0.024
IGF1 (nmol/L)	99.6%	<0.001	-1.6%	0.487	-0.7%	0.492	2.7%	0.039	2.0%	0.067
SHBG (nmol/L)	107.6%	<0.001	1.1%	0.447	7.5%	0.026	-16.2%	<0.001	-8.7%	0.018
Testosterone (nmol/L)	101.3%	<0.001	-0.5%	0.837	0.0%	0.896	-0.8%	0.240	-0.8%	0.217
Triglycerides (mmol/L)	113.7%	<0.001	-12.2%	0.067	6.8%	0.068	-8.3%	0.054	-1.5%	0.712
Albumin (g/L)	98.0%	<0.001	-0.1%	0.805	0.4%	0.611	1.7%	0.051	2.1%	0.040
Glucose (mmol/L)	102.1%	<0.001	-1.3%	0.650	0.4%	0.657	-1.3%	0.184	-0.9%	0.510
Alanine aminotransferase (U/L)	104.6%	<0.001	-1.6%	0.726	0.6%	0.739	-3.5%	0.099	-2.9%	0.191
Apolipoprotein A (g/L)	100.7%	<0.001	0.9%	0.366	1.3%	0.247	-3.0%	0.019	-1.7%	0.145
Gamma-glutamyltransferase (U/L)	101.8%	<0.001	2.6%	0.651	-0.8%	0.641	-3.6%	0.034	-4.4%	0.063
Total bilirubin (umol/L)	94.1%	<0.001	3.2%	0.470	1.4%	0.464	1.3%	0.516	2.7%	0.096
Urate (umol/L)	106.1%	<0.001	-0.5%	0.880	0.2%	0.921	-5.8%	0.012	-5.6%	0.011

P_CDE=proportion of controlled direct effect. P_INTref=proportion of reference interaction. P_INTmed=proportion of mediated interaction. P_PIE=proportion of pure indirect effect. OP_M=overall proportion mediated. Output of mediation analysis with causal effects estimated for a change in PC from the 25th to the 75th percentile. Controlled direct effects are computed fixing the mediators at their median levels.

HDL cholesterol: high-density lipoprotein cholesterol, IGF-1: insulin-like growth factor, SHBG: sex hormone-binding globulin.

Models adjusted for age, center and diet, and adjusted for age alcohol frequency, smoking status, oral contraceptive, menopausal hormone treatment, physical activity, qualifications, townsend deprivation index and sedentary behavior