

Supporting information

Table S1. Impact of the lipidome on immune phenotypes(5-year survival rates for ER+BC)

Exposure	Outcome	Method	Se	Or	Or_lci95	Or_uci95	Pval
Ceramide (d40:2)	CD4-CD8- T cell %T cell	MR Egger	0.1320	1.2135	0.9369	1.5717	0.1598
Ceramide (d40:2)	CD4-CD8- T cell %T cells	Weighted median	0.0739	1.1672	1.0097	1.3492	0.0365
Ceramide (d40:2)	CD4-CD8- T cell %T cell	Inverse variance weighted	0.0525	1.1718	1.0572	1.2989	0.0025
Ceramide (d40:2)	CD4-CD8- T cell %T cell	Simple mode	0.1025	1.1481	0.9390	1.4037	0.1938
Ceramide (d40:2)	CD4-CD8- T cell %T cell	Weighted mode	0.0825	1.1441	0.9733	1.3448	0.1191
Phosphatidylcholine (O-16:0_20:4)	CD4 regulatory T cell %T cell	MR Egger	0.0832	1.1463	0.9738	1.3493	0.1124
Phosphatidylcholine (O-16:0_20:4)	CD4-CD8- T cell %T cell	Weighted median	0.0739	1.0998	0.9514	1.2713	0.1982
Phosphatidylcholine (O-16:0_20:4)	CD4-CD8- T cell %T cell	Inverse variance weighted	0.0472	1.1025	1.0050	1.2094	0.0388
Phosphatidylcholine (O-16:0_20:4)	CD4-CD8- T cell %T cell	Simple mode	0.1249	1.1579	0.9065	1.4791	0.2504
Phosphatidylcholine (O-16:0_20:4)	CD4-CD8- T cell %T cell	Weighted mode	0.0733	1.1072	0.9590	1.2782	0.1759

Table S2. Sensitivity analysis between lipidome and immune phenotypes(5-year survival rates for ER+BC)

Exposure	Outcome	Cochran's Q test (pval)	MR-Egger intercept (pval)
Ceramide (d40:2)	CD4-CD8- T cell %T cell	0.9429	0.7762
Phosphatidylcholine (O-16:0_20:4)	CD4-CD8- T cell %T cell	0.5197	0.5745

Table S3. Impact of the lipidome on immune phenotypes(15-year survival rates for ER+BC)

Exposure	Outcome	Method	Se	Or	Or_lci95	Or_uci95	Pval
Phosphatidylcholine (18:2_0:0)	CD4-CD8- T cell %T cell	MR Egger	0.2211	0.9154	0.5934	1.4120	0.6953
Phosphatidylcholine (18:2_0:0)	CD4-CD8- T cell %T cells	Weighted median	0.1061	0.8143	0.6615	1.0025	0.0528
Phosphatidylcholine (18:2_0:0)	CD4-CD8- T cell %T cell	Inverse variance weighted	0.0812	0.8227	0.7017	0.9647	0.0162
Phosphatidylcholine (18:2_0:0)	CD4-CD8- T cell %T cell	Simple mode	0.1410	0.8104	0.6148	1.0684	0.1568
Phosphatidylcholine (18:2_0:0)	CD4-CD8- T cell %T cell	Weighted mode	0.1153	0.8193	0.6535	1.0272	0.1046
Phosphatidylcholine (O-16:0_20:4)	CD28- CD4-CD8- T cell %CD4-CD8- T cell	MR Egger	0.2211	0.7483	0.4851	1.1543	0.2110
Phosphatidylcholine (O-16:0_20:4)	CD28- CD4-CD8- T cell %CD4-CD8- T cell	Weighted median	0.1120	0.8123	0.6522	1.0117	0.0634
Phosphatidylcholine (O-16:0_20:4)	CD28- CD4-CD8- T cell %CD4-CD8- T cell	Inverse variance weighted	0.0829	0.7896	0.6711	0.9290	0.0044
Phosphatidylcholine (O-16:0_20:4)	CD28- CD4-CD8- T cell %CD4-CD8- T cell	Simple mode	0.1558	0.8242	0.6073	1.1186	0.2338
Phosphatidylcholine (O-16:0_20:4)	CD28- CD4-CD8- T cell %CD4-CD8- T cell	Weighted mode	0.1352	0.8025	0.6157	1.0461	0.1246
Phosphatidylcholine (O-16:0_20:4)	CD28+CD4-CD8- T cell %CD4-CD8- T cell	MR Egger	0.2211	1.3363	0.8663	2.0614	0.2110
Phosphatidylcholine (O-16:0_20:4)	CD28+CD4-CD8- T cell %CD4-CD8- T cell	Weighted median	0.1122	1.2311	0.9881	1.5338	0.0638
Phosphatidylcholine (O-16:0_20:4)	CD28+CD4-CD8- T cell %CD4-CD8- T cell	Inverse variance weighted	0.0829	1.2665	1.0765	1.4901	0.0044
Phosphatidylcholine (O-16:0_20:4)	CD28+CD4-CD8- T cell %CD4-CD8- T cell	Simple mode	0.1636	1.2133	0.8804	1.6720	0.2558
Phosphatidylcholine (O-16:0_20:4)	CD28+CD4-CD8- T cell %CD4-CD8- T cell	Weighted mode	0.1540	1.2461	0.9215	1.6849	0.1735

Exposure	Outcome	Method	Se	Or	Or_lci95	Or_uci95	Pval
Phosphatidylcholine (O-16:0_20:4)	CD28- CD4-CD8- T cell %T cell	MR Egger	0.2286	0.7109	0.4542	1.1129	0.1578
Phosphatidylcholine (O-16:0_20:4)	CD28- CD4-CD8- T cell %T cell	Weighted median	0.1157	0.7644	0.6093	0.9591	0.0203
Phosphatidylcholine (O-16:0_20:4)	CD28- CD4-CD8- T cell %T cell	Inverse variance weighted	0.0849	0.7934	0.6718	0.9370	0.0064
Phosphatidylcholine (O-16:0_20:4)	CD28- CD4-CD8- T cell %T cell	Simple mode	0.1705	0.8126	0.5817	1.1351	0.2424
Phosphatidylcholine (O-16:0_20:4)	CD28- CD4-CD8- T cell %T cell	Weighted mode	0.1431	0.7935	0.5994	1.0504	0.1268
Phosphatidylcholine (16:0_16:0)	CD4 regulatory T cell %T cell	MR Egger	0.1902	1.6601	1.1435	2.4102	0.0138
Phosphatidylcholine (16:0_16:0)	CD4 regulatory T cell %T cell	Weighted median	0.0838	1.2156	1.0315	1.4327	0.0198
Phosphatidylcholine (16:0_16:0)	CD4 regulatory T cell %T cell	Inverse variance weighted	0.0621	1.1745	1.0400	1.3264	0.0096
Phosphatidylcholine (16:0_16:0)	CD4 regulatory T cell %T cell	Simple mode	0.1343	1.1967	0.9197	1.5570	0.1938
Phosphatidylcholine (16:0_16:0)	CD4 regulatory T cell %T cell	Weighted mode	0.1136	1.2023	0.9624	1.5020	0.1178
Phosphatidylcholine (18:1_20:2)	Terminally Differentiated CD4-CD8- T cell Absolute Count	MR Egger	0.0774	1.0268	0.8822	1.1951	0.7364
Phosphatidylcholine (18:1_20:2)	Terminally Differentiated CD4-CD8- T cell Absolute Count	Weighted median	0.0569	0.9356	0.8368	1.0460	0.2421
Phosphatidylcholine (18:1_20:2)	Terminally Differentiated CD4-CD8- T cell Absolute Count	Inverse variance weighted	0.0429	0.9156	0.8419	0.9959	0.0397
Phosphatidylcholine (18:1_20:2)	Terminally Differentiated CD4-CD8- T cell Absolute Count	Simple mode	0.0845	0.9741	0.8253	1.1496	0.7590
Phosphatidylcholine (18:1_20:2)	Terminally Differentiated CD4-CD8- T cell Absolute Count	Weighted mode	0.0500	0.9493	0.8608	1.0470	0.3095
Phosphatidylcholine (18:1_20:2)	CD4-CD8- T cell %T cell	MR Egger	0.0720	1.0054	0.8731	1.1577	0.9412
Phosphatidylcholine (18:1_20:2)	CD4-CD8- T cell %T cell	Weighted median	0.0547	0.9379	0.8426	1.0440	0.2411
Phosphatidylcholine (18:1_20:2)	CD4-CD8- T cell %T cell	Inverse variance weighted	0.0381	0.9257	0.8591	0.9974	0.0427
Phosphatidylcholine (18:1_20:2)	CD4-CD8- T cell %T cell	Simple mode	0.0753	0.9185	0.7925	1.0645	0.2708
Phosphatidylcholine (18:1_20:2)	CD4-CD8- T cell %T cell	Weighted mode	0.0503	0.9379	0.8497	1.0351	0.2158
Phosphatidylethanolamine (18:1_18:1)	CD28- CD4-CD8- T cell %CD4-CD8- T cell	MR Egger	0.1263	1.2756	0.9958	1.6340	0.0676
Phosphatidylethanolamine (18:1_18:1)	CD28- CD4-CD8- T cell %CD4-CD8- T cell	Weighted median	0.0746	1.0580	0.9140	1.2247	0.4499
Phosphatidylethanolamine (18:1_18:1)	CD28- CD4-CD8- T cell %CD4-CD8- T cell	Inverse variance weighted	0.0579	1.1287	1.0077	1.2643	0.0364
Phosphatidylethanolamine (18:1_18:1)	CD28- CD4-CD8- T cell %CD4-CD8- T cell	Simple mode	0.1225	1.0539	0.8290	1.3397	0.6726
Phosphatidylethanolamine (18:1_18:1)	CD28- CD4-CD8- T cell %CD4-CD8- T cell	Weighted mode	0.0795	1.0764	0.9210	1.2580	0.3648
Phosphatidylethanolamine (18:1_18:1)	CD28+CD4-CD8- T cell %CD4-CD8- T cell	MR Egger	0.1263	0.7839	0.6120	1.0042	0.0676
Phosphatidylethanolamine (18:1_18:1)	CD28+CD4-CD8- T cell %CD4-CD8- T cell	Weighted median	0.0739	0.9452	0.8177	1.0926	0.4457
Phosphatidylethanolamine (18:1_18:1)	CD28+CD4-CD8- T cell %CD4-CD8- T cell	Inverse variance weighted	0.0579	0.8859	0.7909	0.9924	0.0364
Phosphatidylethanolamine (18:1_18:1)	CD28+CD4-CD8- T cell %CD4-CD8- T cell	Simple mode	0.1281	0.9489	0.7382	1.2197	0.6861
Phosphatidylethanolamine (18:1_18:1)	CD28+CD4-CD8- T cell %CD4-CD8- T cell	Weighted mode	0.0795	0.9290	0.7950	1.0856	0.3644
triacylglycerol 54:4	CD19 on IgD+CD38- unswitched memory B cell	MR Egger	0.2491	1.5159	0.9304	2.4699	0.1090
triacylglycerol 54:4	CD19 on IgD+CD38- unswitched memory B cell	Weighted median	0.1232	1.0882	0.8547	1.3855	0.4930
triacylglycerol 54:4	CD19 on IgD+CD38- unswitched memory B cell	Inverse variance weighted	0.0884	1.2618	1.0611	1.5005	0.0085
triacylglycerol 54:4	CD19 on IgD+CD38- unswitched memory B cell	Simple mode	0.2352	1.2994	0.8195	2.0602	0.2770
triacylglycerol 54:4	CD19 on IgD+CD38- unswitched memory B cell	Weighted mode	0.1707	1.0131	0.7250	1.4157	0.9398

Table S4. Sensitivity analysis between lipidome and immune phenotypes(15-year survival rates for ER+BC)

Exposure	Outcome	Cochran's Q test (pval)	MR-Egger intercept (pval)
Phosphatidylcholine (18:2_0:0)	CD4-CD8- T cell %T cell	0.4055	0.6105
Phosphatidylcholine (O-16:0_20:4)	CD28- CD4-CD8- T cell %CD4-CD8- T cell	0.6591	0.7973
Phosphatidylcholine (O-16:0_20:4)	CD28+CD4-CD8- T cell %CD4-CD8- T cell	0.6591	0.7973
Phosphatidylcholine (O-16:0_20:4)	CD28- CD4-CD8- T cell %T cell	0.4794	0.6125
Phosphatidylcholine (16:0_16:0)	CD4 regulatory T cell %T cell	0.7561	0.0667
Phosphatidylcholine (18:1_20:2)	Terminally Differentiated CD4-CD8- T cell Absolute Count	0.2697	0.0958
Phosphatidylcholine (18:1_20:2)	CD4-CD8- T cell %T cell	0.5096	0.1907
Phosphatidylethanolamine (18:1_18:1)	CD28- CD4-CD8- T cell %CD4-CD8- T cell	0.1745	0.2888
Phosphatidylethanolamine (18:1_18:1)	CD28+CD4-CD8- T cell %CD4-CD8- T cell	0.1745	0.2888
Triacylglycerol 54:4	CD19 on IgD+CD38- unswitched memory B cell	0.1155	0.4387

Table S5. Impact of the immunophenotype as a mediator of 5- and 15-year survival in patients with ER+BC

Exposure	Outcome	SNP	Beta	Se	Pval	Cochran's Q test (pval)	MR-Egger intercept (pval)
IgD+CD38- B cell Absolute Count	ER+BC (5-year survival rate)	18	0.2301	0.1120	0.0400	0.3406	0.5284
CD20- CD38- B cell %B cell	ER+BC (5-year survival rate)	21	0.2278	0.0973	0.0193	0.5990	0.5852
Memory B cell %lymphocyte	ER+BC (5-year survival rate)	26	0.1239	0.0602	0.0397	0.4693	0.4800
CD4 regulatory T cell %T cell	ER+BC (5-year survival rate)	17	0.2197	0.0940	0.0195	0.2653	0.4206
Resting CD4 regulatory T cell Absolute Count	ER+BC (5-year survival rate)	22	-0.1786	0.0744	0.0164	0.6299	0.3370
T/B cell	ER+BC (5-year survival rate)	28	-0.1524	0.0775	0.0493	0.6678	0.2888
CD4-CD8- T cell %T cell	ER+BC (5-year survival rate)	14	-0.3342	0.1244	0.0072	0.8810	0.3669
CD4-CD8- Natural Killer T Absolute Count	ER+BC (5-year survival rate)	9	-0.3205	0.1563	0.0403	0.4526	0.3327
CD28- CD8+T cell Absolute Count	ER+BC (5-year survival rate)	14	0.3676	0.1449	0.0112	0.1176	0.6582
IgD+CD38- B cell Absolute Count	ER+BC (15-year survival rate)	18	0.1578	0.0635	0.0129	0.4351	0.8518
Unswitched memory B cell %B cell	ER+BC (15-year survival rate)	28	0.1253	0.0425	0.0032	0.4312	0.4223

Exposure	Outcome	SNP	Beta	Se	Pval	Cochran's Q test (pval)	MR-Egger intercept (pval)
CD20- CD38- B cell %B cell	ER+BC (15-year survival rate)	21	0.1887	0.0605	0.0018	0.3948	0.8242
IgD+CD38+B cell %lymphocyte	ER+BC (15-year survival rate)	26	-0.1532	0.0462	0.0009	0.4006	0.74377
IgD+CD24- B cell %lymphocyte	ER+BC (15-year survival rate)	22	-0.2161	0.0660	0.0011	0.3314	0.9978
CD62L- HLA DR++monocyte %monocyte	ER+BC (15-year survival rate)	13	0.1035	0.0486	0.0331	0.9374	0.6644
CD4 regulatory T cell %T cell	ER+BC (15-year survival rate)	17	0.1032	0.0508	0.0421	0.8982	0.6116
Resting CD4 regulatory T cell Absolute Count	ER+BC (15-year survival rate)	22	-0.0927	0.0468	0.0475	0.3730	0.4225
Naive CD8+T cell Absolute Count	ER+BC (15-year survival rate)	23	-0.1012	0.0508	0.0463	0.9647	0.5153
Terminally Differentiated CD4-CD8- T cell Absolute Count	ER+BC (15-year survival rate)	21	-0.1420	0.0511	0.0054	0.6394	0.2549
Transitional B cell Absolute Count	ER+BC (15-year survival rate)	30	-0.0974	0.0490	0.0465	0.3693	0.5044
CD4-CD8- T cell %T cell	ER+BC (15-year survival rate)	14	-0.1791	0.0798	0.0247	0.3313	0.7497
CD28- CD4-CD8- T cell %CD4-CD8- T cell	ER+BC (15-year survival rate)	25	-0.1131	0.0511	0.0269	0.2929	0.6137
CD28+CD4-CD8- T cell %T cell	ER+BC (15-year survival rate)	24	-0.0874	0.0440	0.0468	0.4862	0.6747
CD28+CD4-CD8- T cell %CD4-CD8- T cell	ER+BC (15-year survival rate)	25	0.1131	0.0511	0.0269	0.2929	0.6137
CD39+CD4+T cell %T cell	ER+BC (15-year survival rate)	29	-0.0685	0.0349	0.0500	0.5254	0.2839
CD28- CD8+T cell Absolute Count	ER+BC (15-year survival rate)	14	0.1903	0.0695	0.0062	0.9325	0.9427
CD28- CD4-CD8- T cell %T cell	ER+BC (15-year survival rate)	21	-0.1199	0.0499	0.0162	0.2647	0.4094
CD45RA+CD28- CD8+T cell %T cell	ER+BC (15-year survival rate)	140	0.0020	0.0007	0.0024	0.5015	0.7023

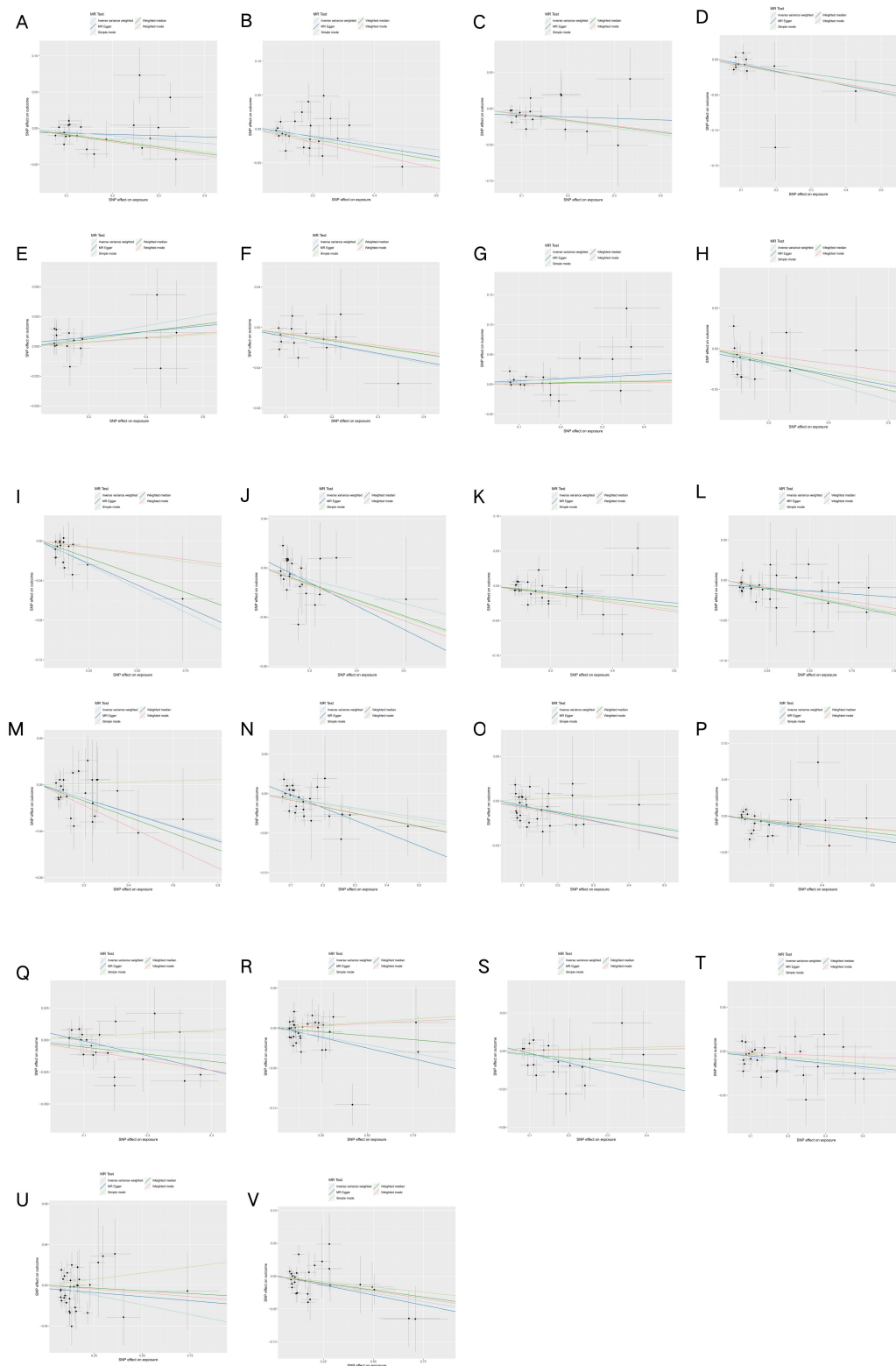


Figure S1. sensitivity analyses for the Mendelian randomization analyses of lipidome and risk of breast cancer.

A: Diacylglycerol (18:1_18:1) levels. B: Diacylglycerol (18:1_18:3) levels. C: Phosphatidylcholine (16:0_16:1) levels. D: Phosphatidylcholine (16:0_20:1) levels. E:

Phosphatidylcholine (O-16:1_18:0) levels. F: Phosphatidylcholine (O-18:0_16:1) levels. G: Phosphatidylcholine (O-18:2_18:2) levels. H: Phosphatidylethanolamine (O-18:2_18:2) levels. I: Phosphatidylinositol (16:0_18:1) levels. J: Phosphatidylinositol(16:0_18:2) levels. K: Phosphatidylinositol (18:1_20:4) levels. L: Triacylglycerol (50:5) levels. M: Triacylglycerol (52:2) levels. N: Triacylglycerol (52:4) levels. O: Triacylglycerol (52:5) levels. P: Triacylglycerol (52:6) levels. Q: Triacylglycerol (53:3) levels. R: Triacylglycerol (53:4) levels. S: Triacylglycerol (56:4) levels. T: Triacylglycerol (56:6) levels. U: Triacylglycerol (56:7) levels. V: Triacylglycerol (58:8) levels.

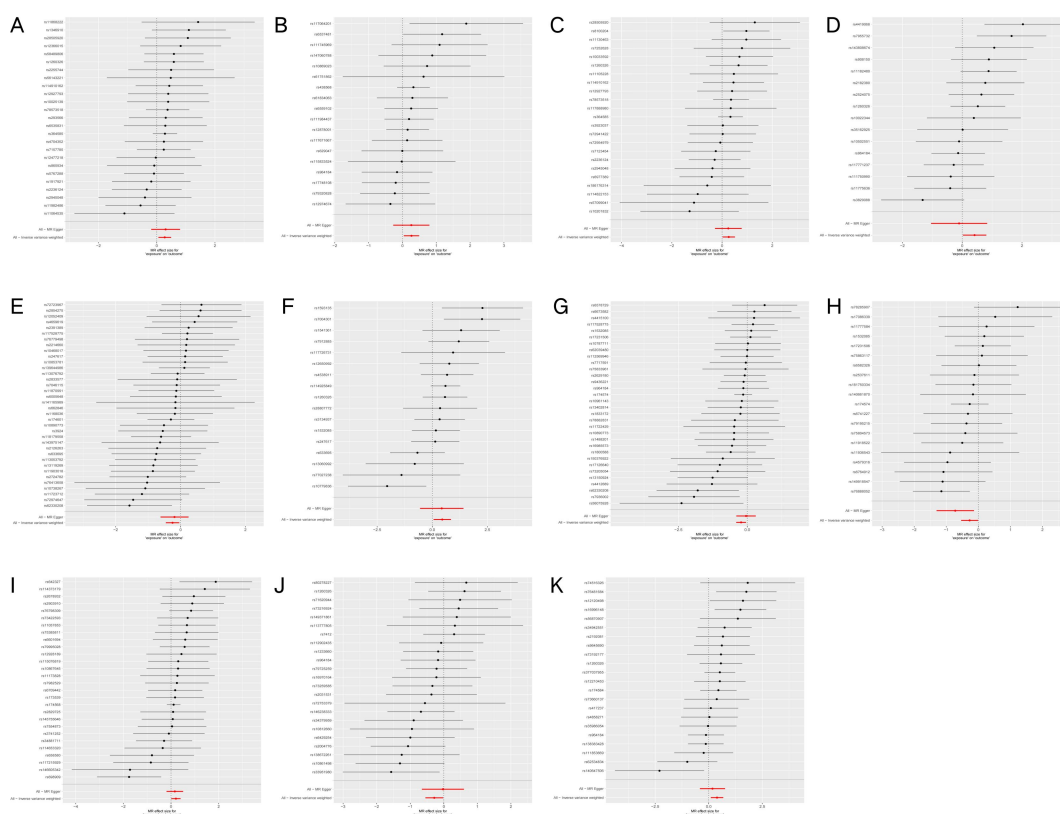


Figure S2. sensitivity analyses for the Mendelian randomization analyses of lipidome and breast cancer 5-year survival.

A: Ceramide (d40:1) levels. B: Ceramide (d40:2) levels. C: Ceramide (d42:1) levels. D: Diacylglycerol (16:1_18:1) levels. E: Phosphatidylcholine (16:0_18:0) levels. F: Phosphatidylcholine (16:0_18:1) levels. G: Phosphatidylcholine (16:0_18:2) levels. H: Phosphatidylcholine (O-16:0_18:2) levels. I: Phosphatidylcholine (O-16:0_20:4) levels. J: Triacylglycerol (49:1) levels. K: Triacylglycerol (54:7) levels.

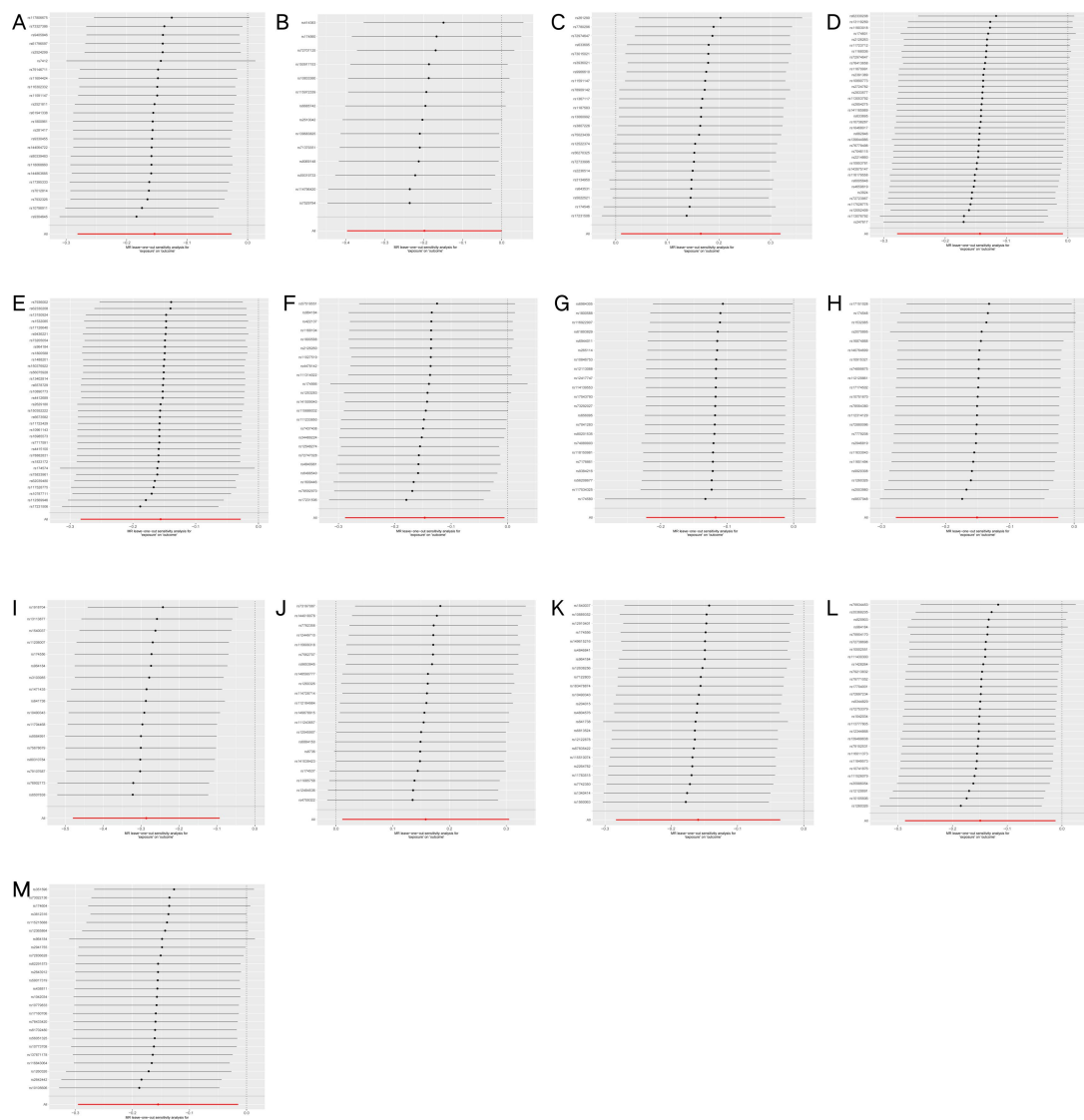


Figure S3. sensitivity analyses for the Mendelian randomization analyses of lipidome and breast cancer 15-year survival.

A: Sterol ester (27:1/18:2) levels. B: Phosphatidylcholine (18:2_0:0) levels. C: Phosphatidylcholine (16:0_16:0) levels. D: Phosphatidylcholine (16:0_18:0) levels. E: Phosphatidylcholine (16:0_18:2) levels. F: Phosphatidylcholine (17:0_18:2) levels. G: Phosphatidylcholine (18:1_20:2) levels. H: Phosphatidylethanolamine (18:1_18:1) levels. I: Phosphatidylinositol (16:0_18:1) levels. J: Phosphatidylinositol (16:0_20:4) levels. K: Phosphatidylinositol (18:0_18:1) levels. L: Triacylglycerol (50:3) levels. M: Triacylglycerol (54:4) levels.