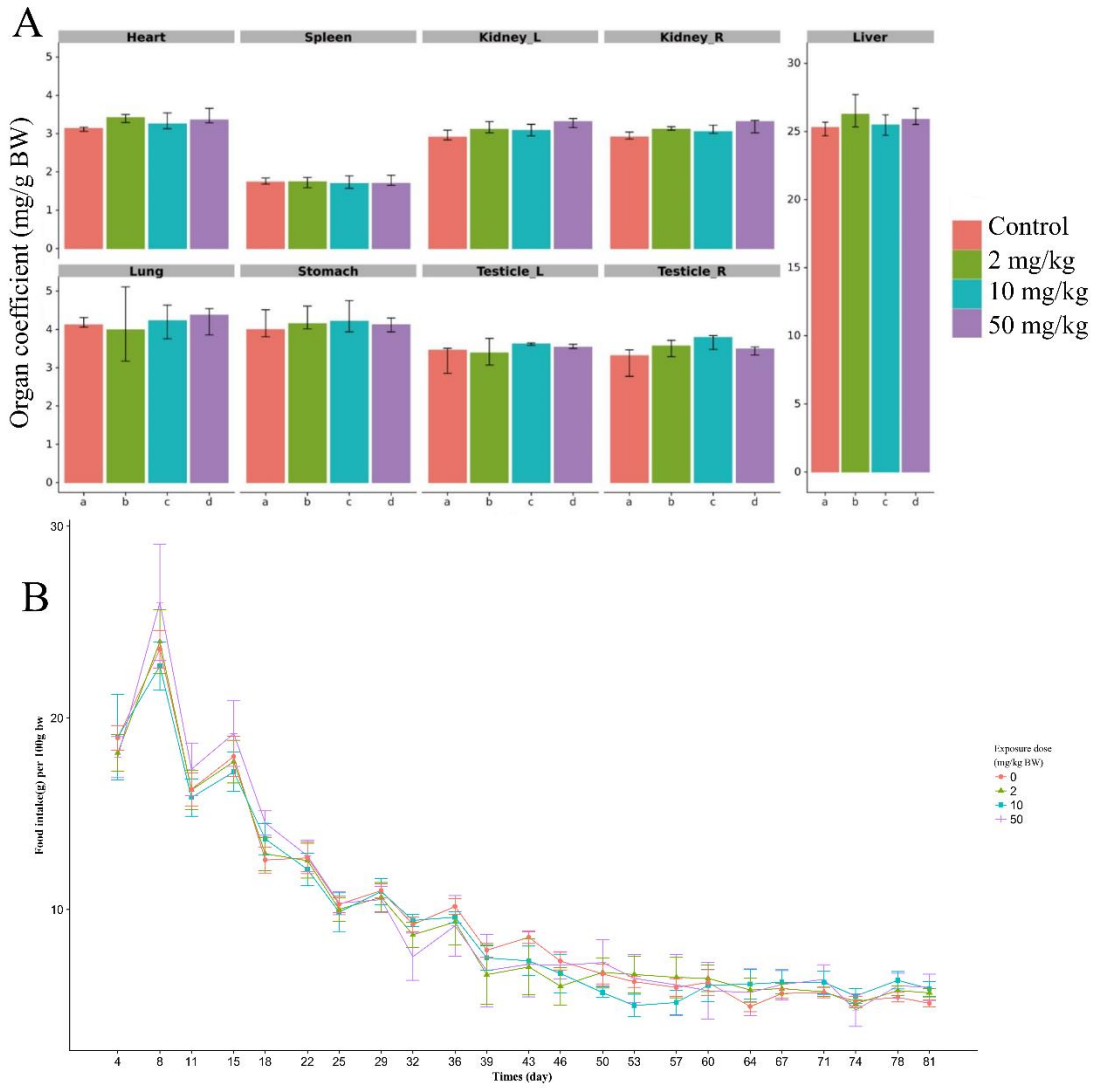

Figure S1. Organ coefficients and food intake of the rats after oral exposure to TiO_2 nanoparticles for 90 days (mean ± SD, n = 6). Kidney_L, left kidney; Kidney_R, right kidney; Testicle_L, left testicle; Testicle_R, right testicle.

Table S1. Key parameters for GC-MS/MS analysis.

	Parameters
Injection volume	2 μL
Front Inlet Mode	2:1
Carrier Gas	Helium
Column	DB-FFAP (30m x 0.25mm x 0.25um)
Column Flow	0.85 mL/min
Oven Temperature Ramp	90 ℃ hold on 1min, raised to 130 ℃ at a rate of 15 ℃/min ,raised to 230 ℃ at a rate of 20 ℃/min, hold on 4min, after running for 5 min
Front Injection Temperature	230 ℃
Transfer Line Temperature	230 ℃
Ion Source Temperature	230 ℃
Quad Temperature	150 ℃
Electron Energy	70 eV
Scan mode	MRM
Solvent Delay	3.3 min

Table S2. The differential lipophilic metabolites with good matches between the treated group (50 mg/kg) and the control group.

No.	MS2 name	MS2 score	Retention time, RT (min)	molecular mass	VIP	P value	FDR	Fold Change	log_2 Fold Change
1	Val Arg Ser	1.000	45.005	361.218	1.686	0.032	0.170	1.865	0.899
2	12-HETE	0.999	80.200	303.230	1.584	0.003	0.081	0.449	-1.154
3	DG(16:1(9Z)/22:5(7Z,10Z,13Z,16Z,19Z)/0:0)[iso2]	0.997	670.377	641.509	1.587	0.046	0.180	0.564	-0.825
4	PE(22:4(7Z,10Z,13Z,16Z)/21:0)	0.996	667.409	838.628	1.082	0.027	0.166	1.292	0.369
5	PC(22:4(7Z,10Z,13Z,16Z)/14:0)	0.995	609.008	782.567	1.794	0.001	0.055	1.550	0.632
6	PC(22:4(7Z,10Z,13Z,16Z)/16:0)	0.993	650.851	810.599	1.862	0.000	0.007	1.347	0.430
7	PE-NMe2(16:0/20:4(5Z,8Z,11Z,14Z))[S]	0.992	557.842	768.549	1.566	0.009	0.128	1.853	0.890
8	PC(O-18:2(9Z,12Z)/0:0)[U]	0.991	169.602	506.358	1.352	0.032	0.170	0.836	-0.258
9	PC(19:1(9Z)/17:2(9Z,12Z))	0.991	618.823	784.576	1.328	0.023	0.162	1.178	0.236
10	1-heptadecanoyl-sn-glycero-3-phosphocholine	0.989	135.903	510.354	1.503	0.007	0.117	0.738	-0.439
11	PC(22:1(11Z)/12:0)	0.989	648.742	760.577	1.308	0.042	0.176	1.153	0.206
12	TG(18:0/18:4(6Z,9Z,12Z,15Z)/18:4(6Z,9Z,12Z,15Z))[iso3]	0.988	786.576	875.706	1.721	0.021	0.159	0.575	-0.797
13	PC(20:1(11Z)/12:0)	0.988	610.953	732.550	1.077	0.028	0.167	1.383	0.468
14	PC(24:1(15Z)/18:4(6Z,9Z,12Z,15Z))	0.988	670.534	864.644	1.892	0.000	0.012	2.020	1.015
15	PI(22:0/21:0)	0.987	767.352	965.695	1.446	0.032	0.170	1.209	0.274
16	PC(O-16:0/2:0)	0.987	169.244	524.368	1.746	0.003	0.087	0.829	-0.270
17	PC(18:0/14:0)	0.985	652.853	734.566	1.709	0.009	0.132	1.360	0.443
18	PC(18:2(9Z,12Z)/22:1(11Z))	0.984	672.789	840.639	1.276	0.007	0.119	1.401	0.486
19	Ala Arg Pro	0.984	47.489	343.210	1.176	0.028	0.167	0.601	-0.734
20	TG(12:0/20:4(5Z,8Z,11Z,14Z)/22:3(10Z,13Z,16Z))[iso6]	0.984	802.383	877.723	1.561	0.022	0.161	0.718	-0.477
21	TG(12:0/20:3(8Z,11Z,14Z)/22:3(10Z,13Z,16Z))[iso6]	0.983	818.654	879.738	1.653	0.015	0.148	0.569	-0.814
22	PC(24:1(15Z)/18:3(6Z,9Z,12Z))	0.981	690.242	866.660	1.605	0.002	0.074	1.551	0.633
23	3alpha-Acetomethoxy-11alpha-oxo-12-ursen-24-oic acid	0.981	169.399	527.377	1.735	0.005	0.101	0.802	-0.318
24	TG(18:2(9Z,12Z)/18:0/18:3(9Z,12Z,15Z))[iso6]	0.981	837.016	881.751	1.559	0.027	0.166	0.619	-0.692
25	PC(22:1(11Z)/20:5(5Z,8Z,11Z,14Z,17Z))	0.980	660.084	862.626	1.321	0.031	0.169	1.219	0.285
26	N-stearoyl tyrosine	0.979	64.735	448.336	1.856	0.004	0.094	1.541	0.624
27	PC(22:2(13Z,16Z)/17:2(9Z,12Z))	0.977	662.109	824.613	1.664	0.001	0.068	1.562	0.643
28	PC(20:3(8Z,11Z,14Z)/17:1(9Z))	0.974	636.918	796.584	1.302	0.048	0.181	1.349	0.432
29	Oleamide	0.972	163.431	282.278	1.157	0.035	0.172	0.668	-0.582
30	PE(22:1(11Z)/20:2(11Z,14Z))	0.972	665.540	826.624	1.279	0.006	0.115	1.347	0.430
31	11-cis retro-gamma-retinal	0.970	79.854	285.220	1.578	0.003	0.084	0.453	-1.142
32	PC(O-16:0/3:1(2E))	0.967	139.567	536.369	1.846	0.000	0.038	0.644	-0.634
33	Estradiol-17-phenylpropionate	0.960	50.435	405.237	1.899	0.012	0.142	1.682	0.750
34	LysoPE(20:1(11Z)/0:0)	0.959	97.558	508.339	1.649	0.002	0.080	0.688	-0.540
35	C22 Sulfatide	0.956	59.585	864.623	1.784	0.029	0.168	2.097	1.068

Table S2. The differential lipophilic metabolites with good matches between the treated group (50 mg/kg) and the control group. (**Continued**)

No.	MS2 name	MS2 score	Retention time, RT (min)	molecular mass	VIP	P value	FDR	Fold Change	log_2 Fold Change
36	PE-NMe(16:0/16:0)	0.954	605.062	706.525	1.817	0.000	0.036	1.366	0.450
37	2-amino-octadecanoic acid	0.954	148.657	300.289	1.709	0.006	0.112	0.708	-0.499
38	PC(20:3(8Z,11Z,14Z)/0:0)	0.940	91.676	546.348	1.305	0.009	0.132	0.625	-0.679
39	LysoPC(P-16:0)	0.931	128.628	480.341	1.399	0.008	0.125	0.775	-0.368
40	lysoPC(26:1(5Z))	0.923	455.455	634.477	1.612	0.032	0.170	1.336	0.418
41	Tricosanamide	0.905	738.567	636.626	1.042	0.037	0.173	1.484	0.569
42	Lauryl diethanolamide	0.892	66.820	288.249	1.636	0.001	0.066	0.567	-0.818
43	PE(22:0/0:0)	0.889	199.073	538.386	1.345	0.014	0.147	0.753	-0.410
44	PC(22:6(4E,7E,10E,13E,16E,19E)/0:0)[U]	0.888	78.873	568.337	1.400	0.013	0.145	0.730	-0.454
45	Lyso-PAF C-18	0.860	205.212	510.391	1.813	0.000	0.036	0.610	-0.714
46	Oleoyl Ethyl Amide	0.858	240.921	310.309	1.375	0.039	0.174	0.460	-1.120
47	Asn Arg Arg Val	0.855	84.199	544.336	1.388	0.008	0.126	0.897	-0.156
48	PC(22:5(4Z,7Z,10Z,13Z,16Z)/20:2(11Z,14Z))	0.855	640.460	860.611	1.406	0.020	0.158	1.352	0.435
49	Enigmol	0.855	99.634	302.304	1.245	0.048	0.181	0.705	-0.504
50	PC(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/19:1(9Z))	0.853	665.925	846.605	1.561	0.009	0.130	1.398	0.483
51	PC(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/19:0)	0.836	656.395	848.622	1.266	0.039	0.174	1.244	0.315
52	C22-OH Sulfatide	0.823	53.259	880.618	1.915	0.031	0.169	2.113	1.079
53	PC(24:1(15Z)/22:4(7Z,10Z,13Z,16Z))	0.820	717.793	920.699	2.024	0.000	0.030	2.024	1.017
54	sn-Glycero-3-phosphocholine	0.811	42.073	258.110	1.290	0.045	0.179	0.577	-0.793
55	Lys Thr Arg Arg	0.792	196.008	560.367	1.529	0.015	0.149	0.622	-0.686
56	PC(24:0/20:5(5Z,8Z,11Z,14Z,17Z))	0.743	693.656	892.673	1.962	0.000	0.007	2.779	1.475
57	PC(P-15:0/0:0)	0.720	209.325	466.328	1.811	0.001	0.045	0.632	-0.661
58	PC(22:6(4Z,7Z,10Z,13Z,16Z,19Z)/15:1(9Z))	0.712	557.842	790.532	1.592	0.004	0.089	2.013	1.009
59	Oleoyl Ethanolamide-d2	0.690	224.540	328.319	1.522	0.042	0.177	0.760	-0.396
60	Scytophycin D	0.690	577.599	844.524	1.519	0.007	0.118	1.235	0.304
61	PC(O-16:0/15:0)	0.670	609.938	706.571	1.349	0.011	0.138	1.203	0.267
62	CerP(d18:1/12:0)	0.619	216.353	562.416	1.180	0.037	0.173	0.821	-0.285
63	PC(18:2(9Z,12Z)/0:0)	0.600	90.319	520.337	1.294	0.015	0.150	0.776	-0.366
64	Gentamicin C2b	0.572	142.638	464.313	1.373	0.013	0.144	0.746	-0.423
65	PC(19:3(10Z,13Z,16Z)/0:0)	0.569	139.919	532.334	1.505	0.012	0.141	0.645	-0.633
66	1-Oleoylglycerophosphocholine	0.547	117.136	522.352	1.646	0.001	0.061	0.762	-0.392
67	Leu Leu Lys Glu	0.534	132.836	502.328	1.474	0.017	0.154	0.624	-0.680
68	4S,5S-antillatoxin A	0.512	136.621	504.341	1.690	0.013	0.145	0.588	-0.766
69	Met Arg Arg Gln	0.464	80.042	590.318	1.330	0.018	0.154	0.758	-0.399

PC: Phosphatidylcholine; PE: Phosphatidylethanolamine. Red represents the concentration of metabolite in the treat group is higher than the control group, and blue represents the concentration of metabolite in the treat group is lower than the control group.

Table S3. Pathway analysis of differential metabolites in serum of rats orally exposed to TiO_2 NPs.

Pathway Name	Match Status	*P*[a]	-ln(*P*)	*Holm P*[b]	*FDR*[c]	Impact[d]
Glycerophospholipid metabolism	3/30	3.49×10^{-5}	10.262	0.0028	0.0028	0.20648
Linoleic acid metabolism	1/5	0.0142	4.2542	1	0.5753	0
alpha-Linolenic acid metabolism	1/9	0.0254	3.6707	1	0.6874	0
Arachidonic acid metabolism	1/36	0.0989	2.3134	1	1	0

[a] Primary P value of pathway enrichment analysis; [b] The P value was corrected by Holm method; [c] The P value was corrected by FDR; [d] The pathway impact was obtained by pathway topology analysis.

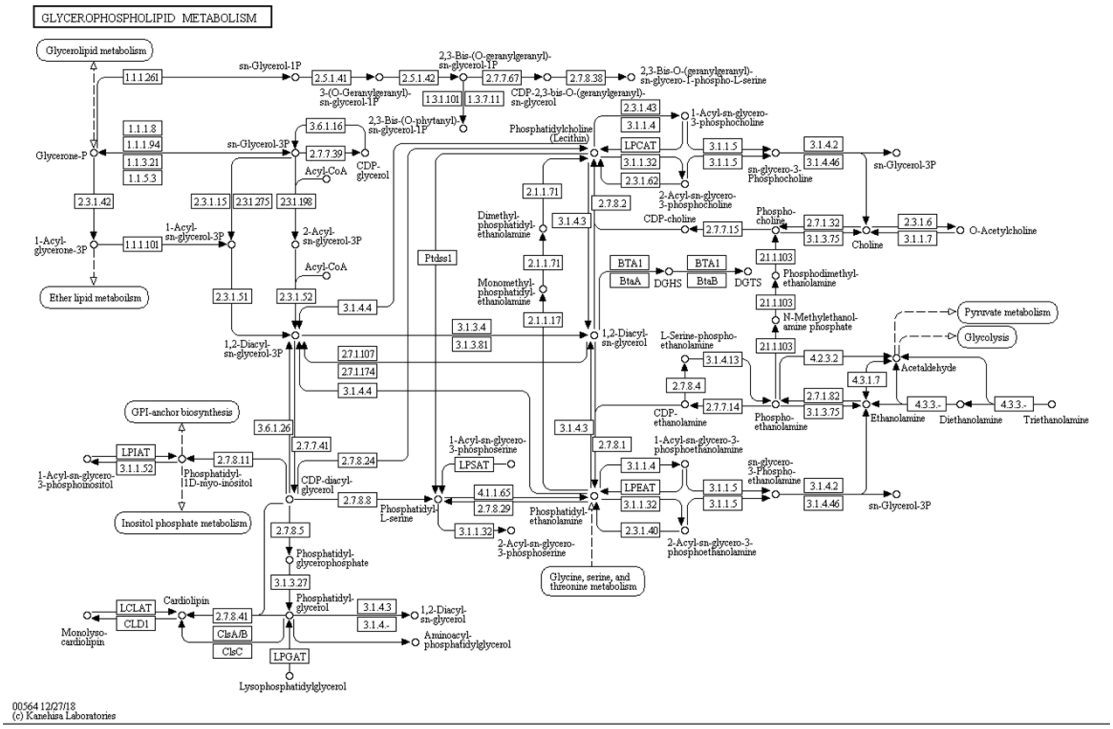

Figure S2 KEGG pathway map of glycerophospholipid metabolism.