Supplementary Table S1. Summary description of genome-wide association data used in this study

Exposure/Outcome	GWAS-ID	Population	N-cases (people)	Sample size (people)	Number of SNPs
$PM_{2.5}$	ukb-b-10817	European	–	423,796	9,851,867
Mets	ebi-a-GCST009602	European	59,677	291,107	9,463,307
WA	ukb-b-9405	European	–	462,166	9,851,867
HTN	ukb-b-12493	European	54,358	463,010	9,851,867
DM	ukb-b-10753	European	22,340	461,578	9,851,867
TG	ieu-b-111	European	–	441,016	12,321,875
HDL-C	ieu-b-109	European	–	403,943	12,321,875

Supplementary Table S2. Removed SNPs that may have other mechanistic pathways with MS

SNP	EA	OA	$PM_{2.5}$–BETA	$PM_{2.5}$–SE	$PM_{2.5}$–*P* value
rs12133063	A	C	0.01044	0.002265	4.00×10^{-6}
rs7573056	C	A	−0.01141	0.00217	1.50×10^{-7}
rs987204	A	G	0.010299	0.002167	2.00×10^{-6}
rs75738250	A	T	0.013337	0.00294	5.70×10^{-6}
rs1372504	A	G	0.012291	0.002219	3.10×10^{-8}
rs9260734	A	G	0.013983	0.003	3.10×10^{-6}
rs77205736	T	C	0.013522	0.002413	2.10×10^{-8}
rs1537371	A	C	0.012371	0.002149	8.50×10^{-9}
rs4933236	C	T	0.01001	0.002202	5.50×10^{-6}
rs10786736	C	G	0.015813	0.003571	9.50×10^{-6}
rs7093269	A	T	0.179809	0.04032	8.20×10^{-6}

Supplementary Table S3. Mendelian randomisation information for $PM_{2.5}$ and MS

Exposure	Outcome	No. snp	R^2	F-statistics
$PM_{2.5}$	MS	86	0.458%	22.585
$PM_{2.5}$	WA	92	0.490%	22.591
$PM_{2.5}$	HT	91	0.482%	22.453
$PM_{2.5}$	DM	81	0.431%	22.589
$PM_{2.5}$	TG	87	0.460%	22.418
$PM_{2.5}$	HDL-C	87	0.460%	22.418

Supplementary Table S4. GWAS reported $PM_{2.5}$ with MS summary statistics after MR analysis using SNPs

SNP	EA	OA	$PM_{2.5}$			MS			F
			BETA	SE	*P*	BETA	SE	*P*	
rs10203969	T	G	−0.01031	0.00227	5.50×10^{-6}	−0.0058	0.006897	0.40026	20.63
rs10961167	A	G	−0.01934	0.004066	2.00×10^{-6}	−0.01468	0.012346	0.234455	22.62
rs11042316	A	G	−0.01304	0.002498	1.80×10^{-7}	0.010394	0.007567	0.169538	27.25
rs11075636	G	A	−0.0131	0.002948	8.90×10^{-6}	−0.00935	0.008955	0.296563	19.75
rs11209977	G	A	0.013974	0.003145	8.90×10^{-6}	0.015261	0.009464	0.106844	19.74
rs114708313	T	A	0.024558	0.004478	4.20×10^{-6}	0.013396	0.014024	0.339479	30.08
rs11610713	T	A	0.03797	0.008066	2.50×10^{-6}	0.043792	0.024146	0.069735	22.16
rs11616726	G	T	−0.01765	0.003976	9.00×10^{-6}	0.002241	0.011965	0.851418	19.71
rs116259394	G	A	−0.03491	0.007841	8.50×10^{-6}	−0.00688	0.023712	0.771641	19.82
rs116925111	G	T	0.053321	0.010861	9.10×10^{-7}	−0.01222	0.032699	0.70865	24.10
rs1172955	A	T	0.010736	0.002368	5.80×10^{-6}	0.00328	0.007207	0.649014	20.56
rs117366154	T	C	−0.01933	0.00428	6.30×10^{-6}	−0.0184	0.013078	0.159458	20.40
rs117878224	G	A	−0.04804	0.010066	1.80×10^{-6}	−0.00571	0.031121	0.854417	22.78
rs1182891	T	G	0.012738	0.002773	4.40×10^{-6}	0.002311	0.008448	0.784398	21.10
rs11855821	A	G	−0.01262	0.002432	2.10×10^{-7}	−0.03074	0.007401	3.27×10^{-5}	26.93
rs1217106	G	A	0.012725	0.00262	1.20×10^{-6}	−0.01932	0.00792	0.014705	23.59
rs12203592	T	C	0.021666	0.002591	6.20×10^{-17}	−0.00314	0.008113	0.698962	69.92
rs12812511	G	A	0.011141	0.002391	3.20×10^{-6}	−0.00292	0.007275	0.688603	21.71
rs13035717	T	A	−0.01306	0.00285	4.60×10^{-6}	0.006577	0.008602	0.444484	21.00
rs1318845	C	T	−0.01397	0.002699	2.30×10^{-7}	−0.00563	0.008211	0.492554	26.79
rs1340247	A	G	−0.00994	0.002212	7.00×10^{-6}	0.000387	0.006712	0.95405	20.19
rs13429081	T	A	0.013647	0.002777	8.90×10^{-7}	0.013627	0.008416	0.10542	24.15
rs138685951	T	C	−0.03082	0.006786	5.60×10^{-6}	0.017101	0.020402	0.401925	20.63
rs140500108	G	C	−0.02217	0.004871	5.30×10^{-6}	−0.01518	0.014663	0.300606	20.72
rs147392452	T	C	−0.0282	0.006333	8.50×10^{-6}	0.027389	0.018821	0.145602	19.83
rs151323121	A	G	−0.0416	0.0092	6.10×10^{-6}	−0.00978	0.02845	0.731069	20.45
rs16957755	C	T	0.021686	0.004384	7.60×10^{-7}	0.015536	0.013297	0.242639	24.47
rs17070492	G	C	0.016888	0.003617	3.00×10^{-6}	0.010552	0.010986	0.336791	21.80
rs17103928	A	C	−0.01393	0.003009	3.70×10^{-6}	0.010238	0.009144	0.262898	21.43
rs17183854	G	T	−0.04343	0.00942	4.00×10^{-6}	−0.00357	0.02897	0.901804	21.26
rs17657881	C	T	−0.03711	0.008046	4.00×10^{-6}	0.061092	0.023926	0.01067	21.27
rs1933805	A	G	0.009601	0.002167	9.40×10^{-6}	−0.00478	0.00658	0.467634	19.63
rs2091322	C	T	−0.00978	0.002201	8.80×10^{-6}	−0.00767	0.00669	0.251746	19.74
rs2141531	G	T	−0.01142	0.002356	1.30×10^{-6}	−0.00268	0.007168	0.708458	23.50
rs2278801	G	A	0.010241	0.002268	6.30×10^{-6}	−0.00549	0.006893	0.425917	20.39
rs2292156	T	G	0.014681	0.002878	3.40×10^{-7}	−0.00683	0.008738	0.434595	26.02
rs2324898	T	C	0.010107	0.002256	7.50×10^{-6}	0.002215	0.00718	0.757716	20.07
rs27152	T	C	−0.01073	0.002305	3.20×10^{-6}	−0.00437	0.006997	0.532724	21.67
rs35703574	A	G	−0.02468	0.005345	3.90×10^{-6}	−0.01423	0.016071	0.375896	21.32

Continued

SNP	EA	OA	$PM_{2.5}$			MS			F
			BETA	SE	*P*	BETA	SE	*P*	
rs45485691	A	G	−0.01084	0.002414	7.20×10^{-6}	−0.00342	0.007339	0.641473	20.16
rs4854523	G	A	0.013445	0.002893	3.40×10^{-6}	0.003351	0.008788	0.702982	21.60
rs487230	G	A	−0.01164	0.002512	3.60×10^{-6}	−0.01132	0.00761	0.137044	21.47
rs4926311	T	C	−0.01037	0.002325	8.20×10^{-6}	−0.00512	0.007054	0.468343	19.89
rs56068671	T	G	−0.01819	0.003926	3.60×10^{-6}	−0.02945	0.011997	0.014095	21.47
rs56181709	T	C	−0.01165	0.002593	7.10×10^{-6}	−0.00701	0.007902	0.375032	20.19
rs58824859	C	A	0.012008	0.002305	1.90×10^{-7}	0.00714	0.006996	0.307473	27.14
rs6024877	C	T	0.024387	0.005511	9.70×10^{-6}	−0.03231	0.017077	0.058485	19.58
rs62119705	T	C	0.011135	0.002265	8.90×10^{-7}	−0.00317	0.006867	0.644091	24.17
rs62180462	A	G	−0.03511	0.007628	4.20×10^{-6}	0.008711	0.022738	0.701656	21.19
rs62368672	C	T	−0.01812	0.003929	4.00×10^{-6}	−0.00353	0.011893	0.766586	21.27
rs62484669	A	G	0.017816	0.003621	8.60×10^{-7}	0.013731	0.010965	0.210459	24.21
rs628913	T	C	−0.00993	0.002182	5.40×10^{-6}	0.001452	0.006629	0.826637	20.71
rs6432776	C	T	0.011436	0.002386	1.60×10^{-6}	0.016863	0.007288	0.020682	22.97
rs6547952	G	T	−0.01109	0.002283	1.20×10^{-6}	0.000258	0.006939	0.97036	23.60
rs656813	C	T	−0.01403	0.003158	8.90×10^{-6}	0.005149	0.009535	0.589181	19.74
rs66501886	G	C	−0.01025	0.002315	9.50×10^{-6}	−0.00595	0.007026	0.397199	19.60
rs6667345	T	C	0.011551	0.002562	6.50×10^{-6}	−0.00167	0.007782	0.829871	20.33
rs6749467	A	G	−0.01239	0.002183	1.40×10^{-8}	−0.00458	0.006634	0.49004	32.21
rs6937315	C	T	0.010179	0.002252	6.20×10^{-6}	0.003826	0.006842	0.576051	20.43
rs6960011	G	A	−0.01052	0.002275	3.70×10^{-6}	−0.00729	0.006899	0.290951	21.38
rs718059	A	G	−0.01351	0.002943	4.40×10^{-6}	0.006105	0.008937	0.49457	21.07
rs72655898	G	A	−0.01132	0.002398	2.40×10^{-6}	−0.00162	0.007269	0.824006	22.28
rs72700006	C	T	0.02003	0.004246	2.40×10^{-6}	−0.01282	0.012926	0.321366	22.25
rs72805044	C	T	−0.03735	0.008346	7.60×10^{-6}	−0.04117	0.025718	0.10946	20.03
rs72808024	C	A	−0.01609	0.00302	9.90×10^{-8}	−0.00987	0.009142	0.280233	28.39
rs7514956	C	A	−0.01298	0.00276	2.60×10^{-6}	0.005202	0.008358	0.533667	22.12
rs75730485	C	T	−0.02677	0.006053	9.80×10^{-6}	−0.0165	0.018266	0.366253	19.56
rs76230173	A	G	−0.02084	0.004655	7.60×10^{-6}	−0.01283	0.014067	0.361743	20.04
rs77147615	C	T	0.024822	0.005567	8.20×10^{-6}	−0.00499	0.016932	0.768271	19.88
rs77255816	T	C	0.031394	0.005728	4.20×10^{-8}	0.008359	0.017401	0.630984	30.04
rs7750418	G	T	0.010366	0.002304	6.80×10^{-6}	−0.00138	0.006995	0.843882	20.24
rs7776279	A	G	0.010947	0.002385	4.40×10^{-6}	−0.01132	0.007227	0.11737	21.07
rs77962859	C	T	−0.01575	0.003514	7.30×10^{-6}	0.004525	0.010717	0.672879	20.09
rs78230389	G	A	−0.04679	0.009485	8.10×10^{-7}	−0.0282	0.028893	0.329133	24.33
rs78467598	G	C	−0.038	0.007686	7.60×10^{-7}	−0.02073	0.023206	0.371763	24.44
rs78539764	C	T	−0.03352	0.00659	3.70×10^{-7}	−0.01471	0.019967	0.46133	25.87
rs78546077	C	T	−0.03172	0.006923	4.60×10^{-6}	−0.02824	0.020767	0.173861	20.99
rs79004040	G	C	−0.03223	0.007254	8.90×10^{-6}	0.021232	0.02176	0.329203	19.74

Continued

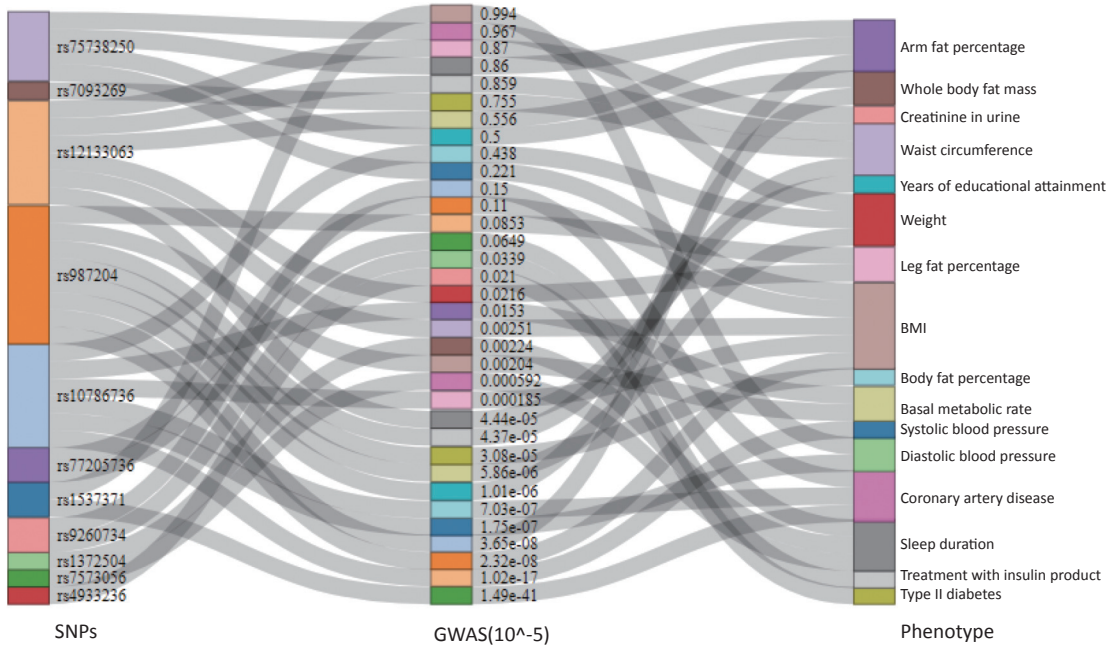
SNP	EA	OA	$PM_{2.5}$			MS			F
			BETA	SE	*P*	BETA	SE	*P*	
rs7910200	T	C	−0.00982	0.002175	6.30×10^{-6}	0.001309	0.006606	0.842972	20.38
rs79229868	A	G	0.044548	0.009946	7.50×10^{-6}	0.026595	0.030306	0.380191	20.06
rs800507	T	G	0.011213	0.002536	9.80×10^{-6}	0.021921	0.007697	0.004401	19.55
rs80123875	T	G	−0.01874	0.003867	1.30×10^{-6}	−0.00078	0.011685	0.947048	23.48
rs80347400	G	A	0.013727	0.003034	6.10×10^{-6}	0.020388	0.009151	0.025882	20.47
rs8614	A	C	0.01308	0.00279	2.80×10^{-6}	0.005701	0.008463	0.500554	21.98
rs875982	T	C	−0.01005	0.002215	5.70×10^{-6}	0.001891	0.00672	0.778447	20.59
rs9644485	C	T	0.009868	0.002159	4.90×10^{-6}	−0.00751	0.006549	0.251328	20.89

Supplementary Table S5. Results of the test for multiplicity and heterogeneity of SNPs for $PM_{2.5}$ in MS data

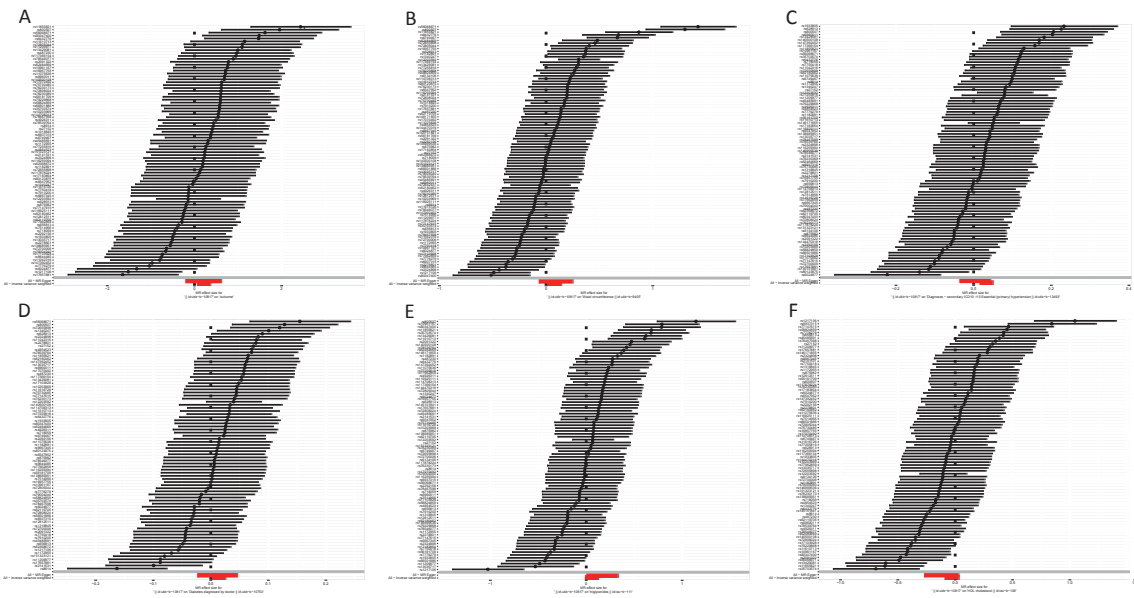
Index	Pleiotropy test			Heterogeneity test					
	MR−egger			MR−egger			Inverse variance weighted		
	Intercept	SE	*P*	Q	Q_df	*P*	Q	Q_df	*P*
MS	0.00012	0.0029	0.966	106.833	84	0.0470	106.835	85	0.054
WA	−0.00023	0.0011	0.842	305.630	90	2.869×10^{-25}	305.765	91	5.077×10^{-25}
HT	0.00047	0.0002	0.113	143.187	89	0.0002	147.287	90	0.0001
DM	3.72×10^{-5}	0.0002	0.879	121.651	79	0.0014	121.686	80	0.0018
TG	−0.00178	0.0012	0.147	225.044	85	1.319×10^{-14}	230.704	86	3.580×10^{-15}
HDL−C	0.00146	0.0011	0.196	205.380	85	5.836×10^{-12}	209.478	86	2.675×10^{-12}

Supplementary Table S6. Two-sample Mendelian randomization results for $PM_{2.5}$ and MS

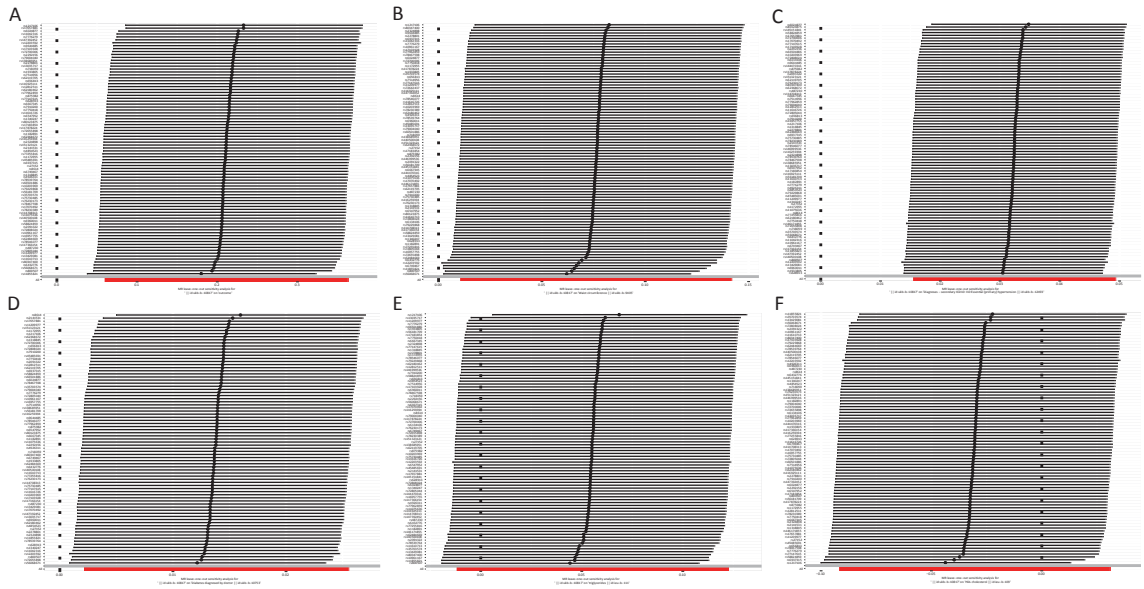
Exposure	Outcome	Method	Beta	SE	*OR*	*OR* 95% *CI*	*P*
$PM_{2.5}$	MS	MR−egger	0.203	0.208	1.225	(0.814, 1.844)	0.332
		Weighted median	0.234	0.098	1.264	(1.042, 1.534)	0.017
		Inverse variance weighted	0.211	0.077	1.235	(1.061, 1.437)	0.006
		Simple mode	0.486	0.276	1.625	(0.945, 2.797)	0.082
		Weighted mode	0.475	0.255	1.608	(0.974, 2.656)	0.066
$PM_{2.5}$	WA	MR−egger	0.090	0.080	1.094	(0.934, 1.283)	0.265
		Weighted median	0.025	0.029	1.026	(0.967, 1.088)	0.390
		Inverse variance weighted	0.076	0.033	1.079	(1.010, 1.152)	0.022
		Simple mode	0.004	0.084	1.004	(0.850, 1.186)	0.955
		Weighted mode	−0.0001	0.090	0.999	(0.836, 1.194)	0.998
$PM_{2.5}$	HT	MR−egger	0.0032	0.020	1.003	(0.964, 1.043)	0.872
		Weighted median	0.031	0.010	1.031	(1.010, 1.053)	0.002
		Inverse variance weighted	0.032	0.008	1.032	(1.015, 1.050)	0.0001
		Simple mode	0.037	0.028	1.037	(0.982, 1.096)	0.188
		Weighted mode	0.042	0.024	1.043	(0.995, 1.093)	0.082
$PM_{2.5}$	DM/FBG	MR−egger	0.011	0.017	1.011	(0.977, 1.046)	0.523
		Weighted median	0.014	0.007	1.014	(1.000, 1.029)	0.046
		Inverse variance weighted	0.013	0.005	1.013	(1.002, 1.025)	0.020
		Simple mode	0.021	0.019	1.021	(0.983, 1.060)	0.268
		Weighted mode	0.023	0.017	1.024	(0.988, 1.060)	0.186
$PM_{2.5}$	TG	MR−egger	0.166	0.083	1.180	(1.003, 1.390)	0.048
		Weighted median	0.058	0.033	1.060	(0.992, 1.132)	0.080
		Inverse variance weighted	0.055	0.034	1.056	(0.988, 1.130)	0.106
		Simple mode	0.067	0.075	1.069	(0.923, 1.239)	0.372
		Weighted mode	0.062	0.063	1.064	(0.939, 1.205)	0.331
$PM_{2.5}$	HDL−C	MR−egger	−0.121	0.076	0.885	(0.762, 1.028)	0.166
		Weighted median	−0.041	0.032	0.959	(0.899, 1.023)	0.209
		Inverse variance weighted	−0.030	0.031	0.970	(0.912, 1.031)	0.330
		Simple mode	−0.049	0.084	0.951	(0.805, 1.123)	0.558
		Weighted mode	−0.054	0.072	0.947	(0.821, 1.091)	0.454



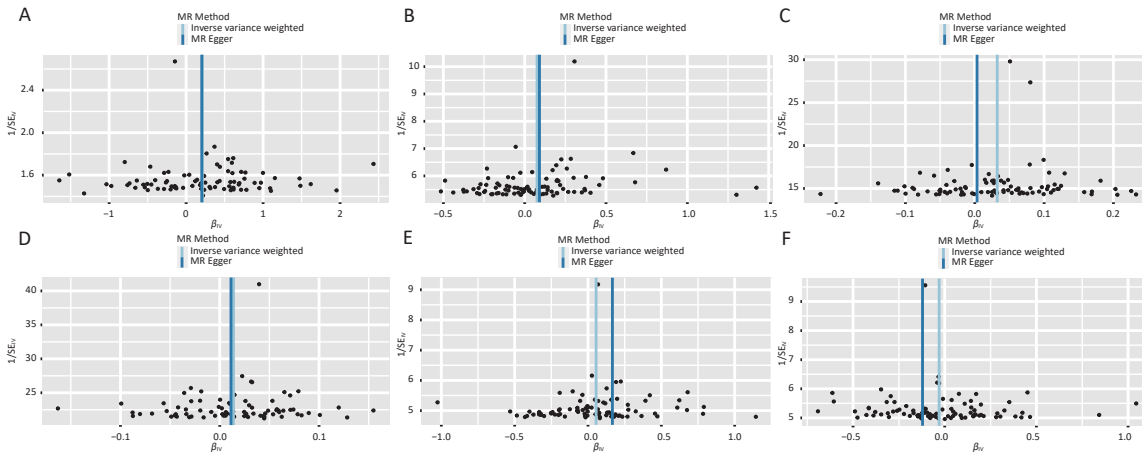
Supplementary Figure S1. Sankey diagram for confounding factor analysis. 11 SNPs were excluded.



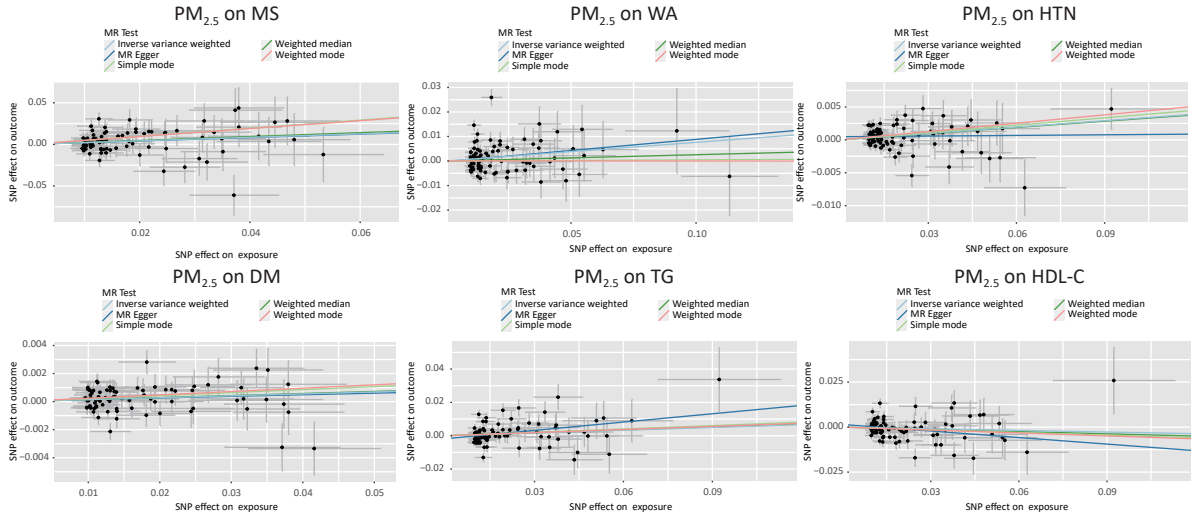
Supplementary Figure S2. Forest plot of the association between $PM_{2.5}$ and T2DM risk. (A) $PM_{2.5}$ on MS. (B) $PM_{2.5}$ on WA. (C) $PM_{2.5}$ on HTN. (D) $PM_{2.5}$ on DM. (E) $PM_{2.5}$ on TG. (F) PM2.5 on HDL-C. X-axis shows the magnitude of the MR effect of $PM_{2.5}$ on MS and its components, while the Y-axis shows the effect of each SNP.



Supplementary Figure S3. Results of sensitivity analysis using the leave-one-out method (A) $PM_{2.5}$ on MS. (B) $PM_{2.5}$ on WA. (C) $PM_{2.5}$ on HTN. (D) $PM_{2.5}$ on DM. (E) $PM_{2.5}$ on TG. (F) $PM_{2.5}$ on HDL-C.



Supplementary Figure S4. Funnel plot of $PM_{2.5}$ on MS Mendelian randomization analysis (A) $PM_{2.5}$ on MS. (B) $PM_{2.5}$ on WA. (C) $PM_{2.5}$ on HTN. (D) $PM_{2.5}$ on DM. (E) $PM_{2.5}$ on TG. (F) $PM_{2.5}$ on HDL-C.



Supplementary Figure S5. Individual SNP estimates of the causal effect of $PM_{2.5}$ on MS and its components. The X-axis is the $PM_{2.5}$ effect for each SNP, and the Y-axis is the effect of MS and components for each SNP. Regression lines for several methods are also given for MR-egger, weighted median, inverse variance weighted, simple mode and weighted mode.