Supplementary Materials

Titles

Table S1. Distribution of the urinary urinary volatile organic compounds (VOCs) levels in NHANES 2011-2016 (n = 29902).

Variable	LLOD	10th percentile	25th percentile	50th percentile	75th percentile	90th percentile
2MHA	5.000	2733.009	4552.665	6372.301	8191.947	10011.593
3MHA+4MHA	8.000	8254.811	13754.245	19253.679	24753.113	30252.547
AAMA	2.200	469.326	781.170	1093.014	1404.858	1716.702
AMCC	6.260	651.765	1083.322	1514.880	1946.436	2377.993
ATCA	15.00	372.010	612.950	853.890	1094.830	1335.770
BMA	0.500	199.801	332.765	465.730	598.695	731.659
BPMA	1.200	109.772	182.387	255.002	327.618	400.232
CEMA	6.960	734.682	1221.19	1707.698	2194.206	2680.714
CYMA	0.500	246.301	410.265	574.23	738.195	902.159
DHBMA	5.250	495.154	822.783	1150.412	1478.041	1805.670
DPMA	0.500	1.258	1.860	2.463	3.066	3.668
GAMA	9.400	73.903	118.737	163.573	208.408	253.242
HEMA	0.791	11.245	18.369	25.493	32.617	39.742
2GPMA	5.300	1477.688	2460.312	3442.938	4425.562	5408.188
3HPMA	13.000	4117.82	6856.900	9595.980	12335.06	15074.140
MA	12.000	4132.225	6881.375	9630.525	12379.675	15128.825
MHBMA1	0.700	0.754	0.926	1.099	1.271	1.444
MHBMA1	0.700	14.656	24.096	33.537	42.977	52.418
MHBMA3	0.700	61.41	102.068	142.726	183.383	224.041
PHEMA	0.700	82.921	137.871	192.822	247.772	302.723
PGA	0.700	4837.225	8056.375	11275.525	14494.675	17713.825
PMA	0.600	4.605	7.393	10.181	12.968	15.756
HPMMA	1.700	2131.020	3550.900	4970.780	6390.660	7810.540

VOCs, Volatile organic compounds. The variable names are detailed in the attached table.

Table S2. All detailed coefficients of WQS model.

Coefficients of WQS model with negative beta (elderly population)

	Estimate	Std.Error	t-value	Pr(>|t|)
(Intercept)	900.0715	179.5508	5.013	7.71e-07***
wqs	**4.5868**	**15.8905**	**0.289**	**0.773**
Gender	16.9741	27.5999	0.615	0.5389
Age	-0.414	2.2407	-0.185	0.8535
Race/Ethnicity	6.2908	12.7499	0.493	0.622
Education level	8.1399	14.922	0.545	0.5857
BMI	0.1213	2.0753	0.058	0.9534
Diabetes	-23.2139	28.9328	-0.802	0.4228
Hypertension	16.9359	26.2613	0.645	0.5193
Cigarette smoking	-35.6478	26.5239	-1.344	0.1796
Alcohol drinking	-45.9097	28.4529	-1.614	0.1073
Creatinine	-0.8771	0.4674	-1.877	0.0612

Coefficients of WQS model with positive beta (elderly population)

	Estimate	Std.Error	t-value	Pr(>|t|)
(Intercept)	890.0127	178.4074	4.989	8.69e-07***
wqs	**30.5502**	**15.6238**	**1.955**	**0.0512**
Gender	12.484	27.4338	0.455	0.6493
Age	-0.546	2.2325	-0.245	0.8069
Race/Ethnicity	4.9033	12.6927	0.386	0.6994
Education level	8.7694	14.8619	0.59	0.5554
BMI	-0.2823	2.0641	-0.137	0.8913
Diabetes	-24.0756	28.7898	-0.836	0.4035
Hypertension	20.2994	26.2045	0.775	0.439
Cigarette smoking	-43.0027	26.3328	-1.633	0.1032
Alcohol drinking	-49.7497	28.3698	-1.754	0.0802
Creatinine	-0.808	0.4666	-1.732	0.084

Coefficients of WQS model with negative beta (middle age population)

	Estimate	Std.Error	t-value	Pr(>|t|)
(Intercept)	1198.684	166.7394	7.189	2.22e-12***
wqs	-48.7976	17.7134	-2.755	0.00607**
Gender	62.595	30.3243	2.064	0.03948*
Age	-6.3411	2.5065	-2.53	0.01170*
Race/Ethnicity	18.9473	15.0063	1.263	0.20728
Education level	-4.3297	19.4676	-0.222	0.82408

Coefficients of WQS model with positive beta (middle age population)

	Estimate	Std.Error	t-value	Pr(>|t|)
(Intercept)	1143.7031	168.2139	6.799	2.84e-11***
wqs	-14.6113	17.0513	-0.857	0.3919
Gender	61.3949	30.7081	1.999	0.0461*
Age	-5.7584	2.5153	-2.289	0.0225*
Race/Ethnicity	16.2025	15.0821	1.074	0.2832
Education level	0.1895	19.5239	0.01	0.9923

BMI	-0.4238	2.0697	-0.205	0.83785	**BMI**	-0.9113	2.0748	-0.439	0.6607
Diabetes	-8.4067	42.0902	-0.2	0.84177	**Diabetes**	-8.4524	42.365	-0.2	0.8419
Hypertension	-29.4544	31.785	-0.927	0.35452	**Hypertension**	-28.8083	31.9897	-0.901	0.3682
Cigarette smoking	62.756	31.9414	1.965	0.04997 *	**Cigarette smoking**	38.9309	31.0951	1.252	0.2111

Coefficients of WQS model with negative beta (general population)

	Estimate	Std.Error	tvalue	Pr(>|t|)
(Intercept)	1016.2567	103.6113	9.808	< 2e-16***
wqs	-29.555	13.2675	-2.228	0.02613*
Gender	44.9184	22.3526	2.01	0.04475*
Age	-2.0725	1.0251	-2.022	0.04346*
Race/Ethnicity	28.6345	10.8211	2.646	0.00827**
Education level	-7.9556	13.1244	-0.606	0.54454
BMI	-0.8979	1.6152	-0.556	0.57842
Diabetes	-42.8391	26.6688	-1.606	0.10852
Hypertension	-5.2894	21.9303	-0.241	0.80945
Cigarette smoking	22.503	22.5852	0.996	0.31932

Coefficients of WQS model with positive beta(general population)

	Estimate	Std.Error	t-value	Pr(>|t|)
(Intercept)	979.3043	102.9162	9.516	<2e-16***
wqs	-16.0885	12.6015	-1.277	0.202
Gender	49.5841	23.2172	2.136	0.0330*
Age	-2.0597	1.0282	-2.003	0.0454*
Race/Ethnicity	26.4092	10.8539	2.433	0.0151*
Education level	-1.938	13.2711	-0.146	0.8839
BMI	-0.3392	1.5697	-0.216	0.829
Diabetes	-61.6946	26.4465	-2.333	0.0199*
Hypertension	13.1034	22.1501	0.592	0.5543
Cigarette smoking	18.5302	21.9175	0.845	0.3981

*, P < 0.05; **, P < 0.01; ***, P < 0.001.

Table S3. Posterior inclusion probabilities (PIPs) of all BKMR model.

	General	40-59 years	60-79 years
2MHA	0.0040	0.3478	0.0000
3MHA+4MHA	0.0000	0.4012	0.0000
AAMA	0.0012	0.3972	0.0000
AMCC	0.0642	0.4746	0.0202
ATCA	0.0044	0.3962	0.5652
BMA	0.0000	0.4190	0.0000
BPMA	0.0000	0.4204	0.0140
CEMA	0.0106	0.4910	0.0072
CYMA	0.0000	0.4454	0.0092
DHBMA	0.0000	0.5288	0.0000
2HPMA	0.0060	0.4796	0.0200
3HPMA	0.0224	0.4102	0.0218
MA	0.0000	0.4504	0.0154
MHBMA3	0.0436	0.4454	0.0762
PGA	0.0170	0.4408	0.0384
HPMMA	0.0166	0.4184	0.0030

2MHA, Urinary 2-Methylhippuric acid; 3MHA+4MHA, Urinary 3- and 4-Methylhippuric acid; AAMA, Urinary N-Acetyl-S-(2-carbamoylethyl)-L-cysteine; AMCC, Urinary N-Acetyl-S-(N-methylcarbamoyl)-L-cysteine; ATCA, Urinary 2-Aminothiazoline-4-carboxylic acid; BMA, Urinary N-Acetyl-S-(benzyl)-L-cysteine; BPMA, Urinary N-Acetyl-S-(n-propyl)-L-cysteine; CEMA, Urinary N-Acetyl-S-(2-carboxyethyl)-L-cysteine; CYMA, Urinary N-Acetyl-S-(2-cyanoethyl)-L-cysteine; DHBMA, Urinary N-Acetyl-S-(3,4-dihydroxybutyl)-L-cysteine; 2HPMA, Urinary N-Acetyl-S-(2-hydroxypropyl)-L-cysteine; 3HPMA, Urinary N-Acetyl-S-(3-hydroxypropyl)-L-cysteine; MA, Urinary Mandelic acid; MHBMA3, Urinary N-Acetyl-S-(4-hydroxy-2-butenyl)-L-cysteine; PGA, Urinary Phenylglyoxylic acid; HPMMA, Urinary N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine.

Table S4. The total and direct effects of urinary volatile organic compounds (VOCs) on Klotho in general population.

VOCs	Total effect (Mean±SE, *P* value)	Direct effect (95%CI)
2MHA	0.014±0.083, ns	0.026 (-0.183, 0.198)
3MHA+4MHA	-0.005±0.013, ns	-0.002(-0.029, 0.022)
AAMA	-0.138±0.095, ns	-0.089(-0.254, 0.094)
AMCC	**-0.063±0.024, ****	**-0.047(-0.093, -0.001)**
ATCA	-0.074±0.04, ns	-0.045 (-0.116, 0.026)
BMA	-0.039±0.281, ns	-0.154(-0.672, 0.286)
BPMA	-0.129±0.283, ns	-0.029(-0.433, 0.507)
CEMA	**-0.099±0.044, ***	-0.08(-0.170, 0.011)
CYMA	**-0.071±0.03, ****	**-0.067(-0.123, -0.011)**
DHBMA	-0.071±0.058, ns	-0.058(-0.158, 0.044)
2HPMA	**-0.027±0.011, *****	-0.021(-0.045, 0.003)
3HPMA	**-0.201±0.074, ***	**-0.174(-0.317, -0.033)**
MA	**-0.082±0.036, ****	**-0.07(-0.140, -0.004)**
MHBMA3	**-0.988±0.382, ***	-0.777(-1.541, 0.027)
PGA	**-0.086±0.032, ****	**-0.075(-0.144, -0.022)**
HPMMA	**-0.022±0.01, *****	-0.018(-0.038, 0.002)
Mixed VOCs	**-38.90±9.94, *****	**-30.50(-53.271, -8.034)**

*, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ns, not significant. 2MHA, Urinary 2-Methylhippuric acid; 3MHA+4MHA, Urinary 3- and 4-Methylhippuric acid; AAMA, Urinary N-Acetyl-S-(2-carbamoylethyl)-L-cysteine; AMCC, Urinary N-Acetyl-S-(N-methylcarbamoyl)-L-cysteine; ATCA, Urinary 2-Aminothiazoline-4-carboxylic acid; BMA, Urinary N-Acetyl-S-(benzyl)-L-cysteine; BPMA, Urinary N-Acetyl-S-(n-propyl)-L-cysteine; CEMA, Urinary N-Acetyl-S-(2-carboxyethyl)-L-cysteine; CYMA, Urinary N-Acetyl-S-(2-cyanoethyl)-L-cysteine; DHBMA, Urinary N-Acetyl-S-(3,4-dihydroxybutyl)-L-cysteine; 2HPMA, Urinary N-Acetyl-S-(2-hydroxypropyl)-L-cysteine; 3HPMA, Urinary N-Acetyl-S-(3-hydroxypropyl)-L-cysteine; MA, Urinary Mandelic acid; MHBMA3, Urinary N-Acetyl-S-(4-hydroxy-2-butenyl)-L-cysteine; PGA, Urinary Phenylglyoxylic acid; HPMMA, Urinary N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine.

Table S5. The mediation effect of urinary volatile organic compounds (VOCs) on Klotho with TB, ALT, AST and GGT in general population.

VOCs	Indirect effect (95%CI)			
	TB	ALT	AST	GGT
2MHA	-0.001(-0.015, 0.009)	0.001 (-0.017, 0.016)	-0.008(-0.039, 0.026)	-0.003(-0.015, 0.008)
3MHA+4MHA	0(-0.002, 0.002)	0.001 (-0.001, 0.004)	-0.004(-0.010, 0.000)	-0.001(-0.002, 0.001)
AAMA	**-0.018(-0.038, -0.003)**	0.036(-0.006, 0.068)	**-0.017(-0.135, -0.002)**	0.003(-0.008, 0.018)
AMCC	**-0.006(-0.011, -0.001)**	0.005 (-0.001, 0.011)	-0.015(-0.036, 0.000)	0(-0.003, 0.002)
ATCA	-0.009 (-0.019, -0.002)	0.01(-0.001, 0.021)	-0.033(-0.072, -0.000)	0.002 (-0.003, 0.007)
BMA	0.018(-0.019, 0.082)	-0.104(-0.227, 0.040)	0.207 (-0.085, 0.405)	-0.006 (-0.025, 0.023)
BPMA	-0.027(-0.073, 0.018)	0.023(-0.026, 0.071)	**-0.096(-0.190, -0.001)**	0 (-0.046, 0.039)
CEMA	**-0.009(-0.018, -0.002)**	0.011(-0.002, 0.023)	-0.021(-0.052, 0.001)	0(-0.003, 0.004)
CYMA	-0.004(-0.010, 0.001)	0.006(-0.001, 0.016)	-0.005(-0.022, 0.008)	0(-0.003, 0.003)
DHBMA	-0.006(-0.016, 0.003)	0.006 (-0.002, 0.016)	**-0.016(-0.033, -0.001)**	0.002(-0.003, 0.008)
2HPMA	**-0.004(-0.007, -0.001)**	**0.004 (0.001, 0.007)**	**-0.006(-0.014, -0.001)**	0 (-0.001, 0.001)
3HPMA	**-0.015 (-0.032, -0.003)**	0.022(-0.003, 0.043)	-0.032(-0.081, 0.004)	-0.002(-0.011, 0.006)
MA	-0.005(-0.016, 0.001)	0.007(-0.001, 0.016)	-0.012(-0.037, 0.003)	-0.001(-0.004, 0.003)
MHBMA3	**-0.099(-0.193, -0.024)**	0.13(-0.018, 0.253)	-0.242 (-0.541, 0.002)	-0.001(-0.031, 0.036)
PGA	-0.003(-0.010, 0.002)	0.009(-0.001, 0.018)	**-0.018(-0.041, -0.000)**	0.001(-0.002, 0.005)
HPMMA	**-0.002(-0.005, -0.001)**	**0.003(0.001, 0.005)**	-0.004(-0.011, 0.001)	0(-0.001, 0.001)
Mixed VOCs	**-2.231(-4.667, -0.425)**	1.332(-0.676, 4.370)	-7.453(-21.734, 0.502)	-0.041(-1.063, 1.118)

Estimate value (95% confidence interval). The confidence intervals were calculated using the bootstrap method and significance were denoted using bold font.

2MHA, Urinary 2-Methylhippuric acid; 3MHA+4MHA, Urinary 3- and 4-Methylhippuric acid; AAMA, Urinary N-Acetyl-S-(2-carbamoylethyl)-L-cysteine; AMCC, Urinary N-Acetyl-S-(N-methylcarbamoyl)-L-cysteine; ATCA, Urinary 2-Aminothiazoline-4-carboxylic acid; BMA, Urinary N-Acetyl-S-(benzyl)-L-cysteine; BPMA, Urinary N-Acetyl-S-(n-propyl)-L-cysteine; CEMA, Urinary N-Acetyl-S-(2-carboxyethyl)-L-cysteine; CYMA, Urinary N-Acetyl-S-(2-cyanoethyl)-L-cysteine; DHBMA, Urinary N-Acetyl-S-(3,4-dihydroxybutyl)-L-cysteine; 2HPMA, Urinary N-

Acetyl-S-(2-hydroxypropyl)-L-cysteine; 3HPMA, Urinary N-Acetyl-S-(3-hydroxypropyl)-L-cysteine; MA, Urinary Mandelic acid; MHBMA3, Urinary N-Acetyl-S-(4-hydroxy-2-butenyl)-L-cysteine; PGA, Urinary Phenylglyoxylic acid; HPMMA, Urinary N-Acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine.

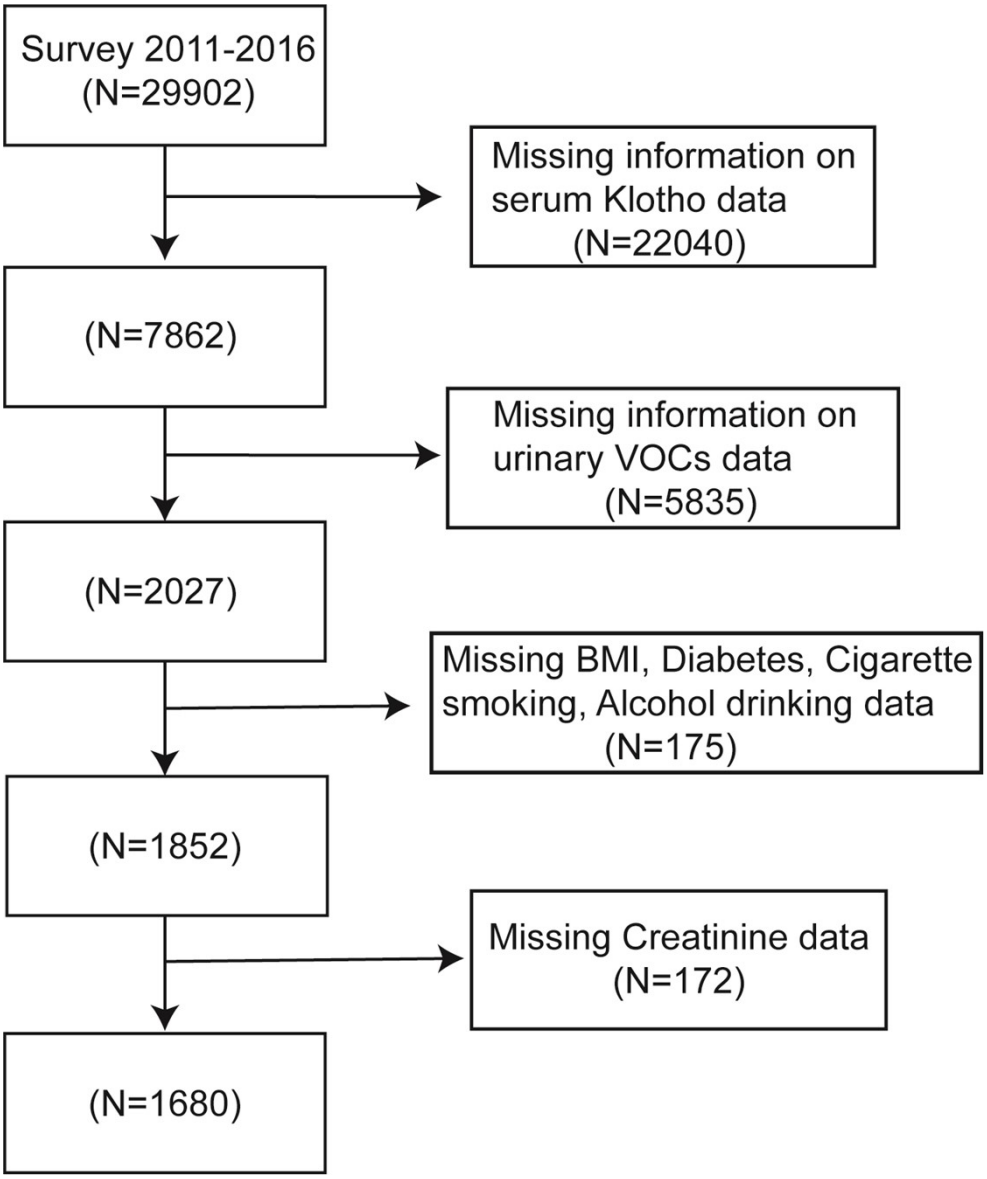

Figure S1. Flow chart of participants selection. NHANES, National Health and Nutrition Examination Survey.

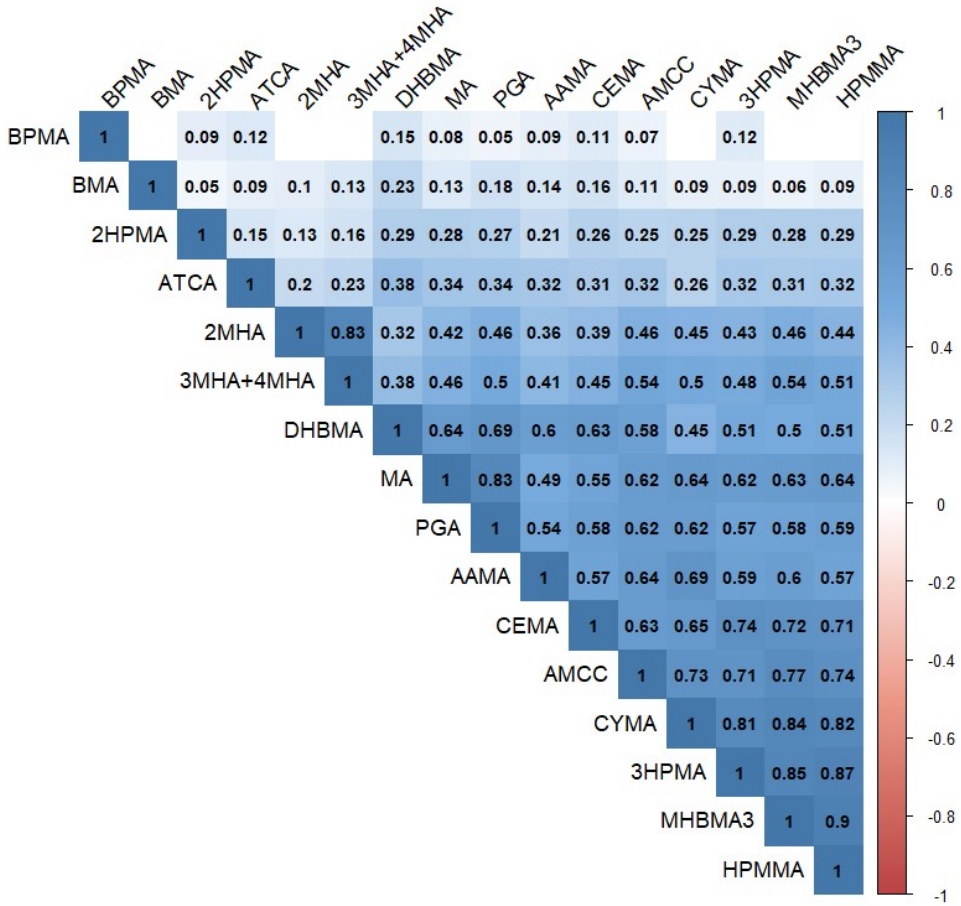

Figure S2. The Pearson correlation coefficients among all urinary volatile organic compounds (VOCs). The blank regions indicate a lack of significant correlation among the VOCs.

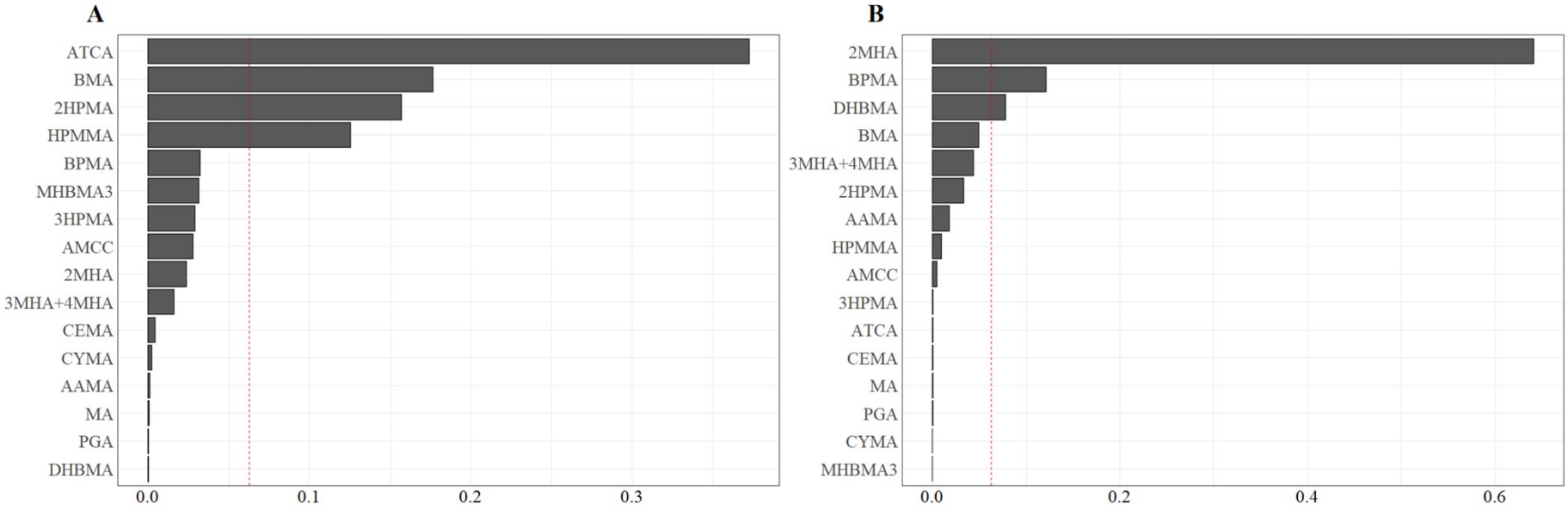

Figure S3. WQS model regression index weights with different population. (A) Positive WQS model regression index weights with middle age population (B) Positive WQS model regression index weights with elderly population. All P value of wqs > 0.05

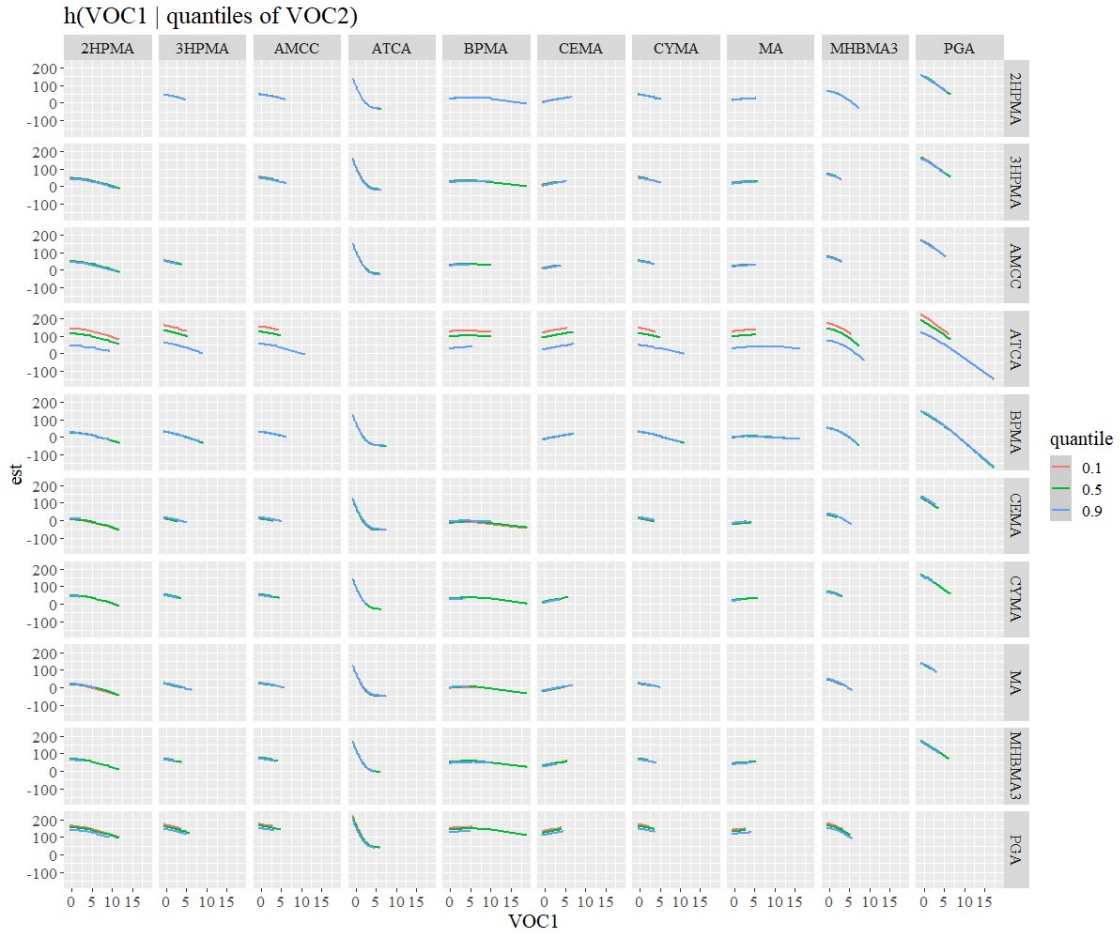

Figure S4. The bivariate exposure-response function for two urinary volatile organic compounds (VOCs). All of the other exposures are fixed at a particular quantile (0.1,0.5,0.9) in middle age population.

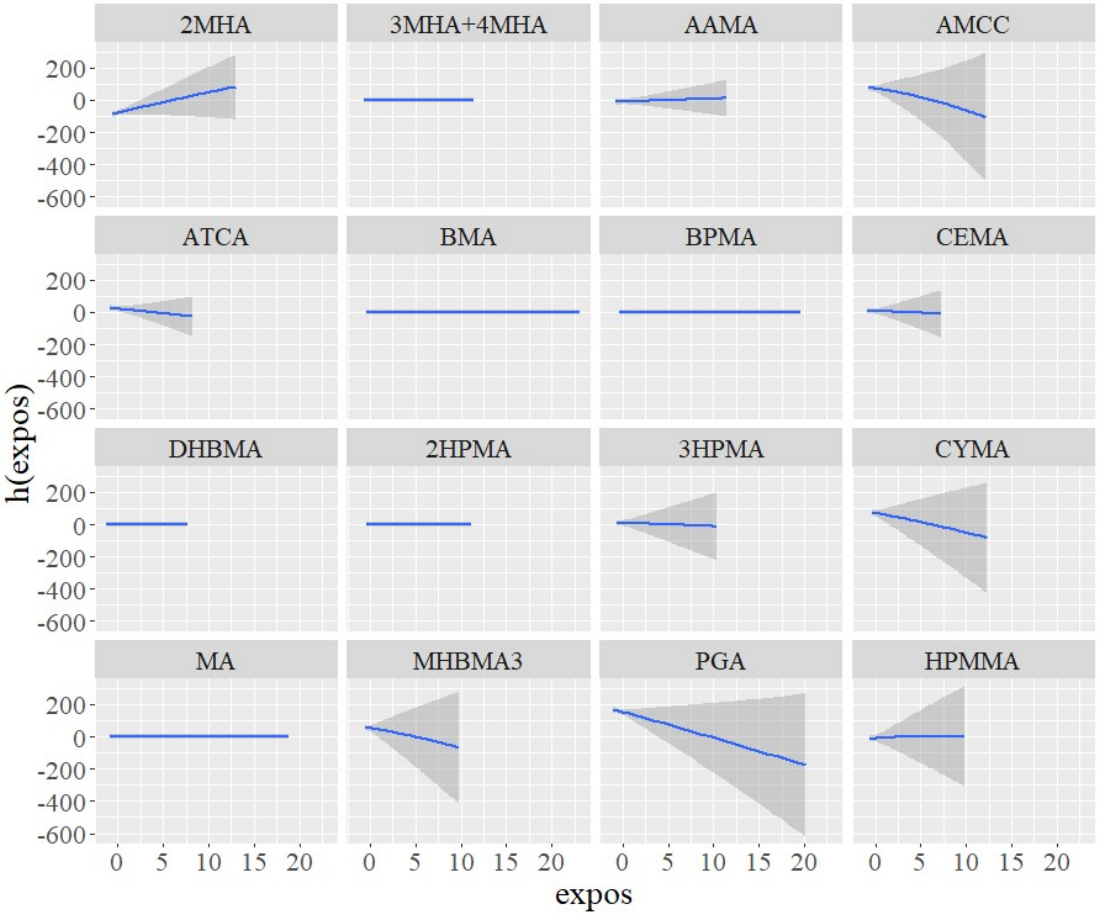

Figure S5. Single-variable effect (95% credible intervals) of the expos (normalized and centered urine VOCs concentration) on Klotho, where all of the other exposures are fixed to 50th quantile in general population (40-79 years) by BKMR models.

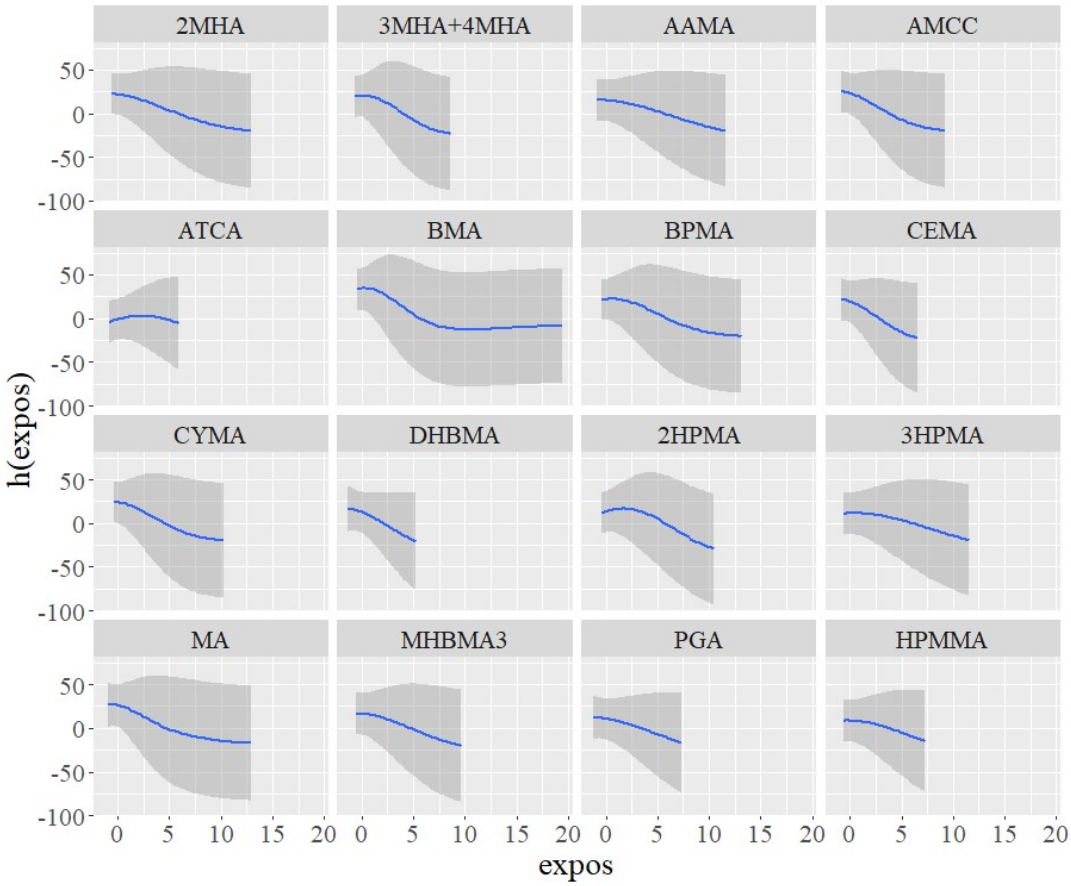

Figure S6. Single-variable effect (95% credible intervals) of the expos (normalized and centered urine VOCs concentration) on Klotho, where all of the other exposures are fixed to 50th quantile in elderly population (60-79 years) by BKMR models.

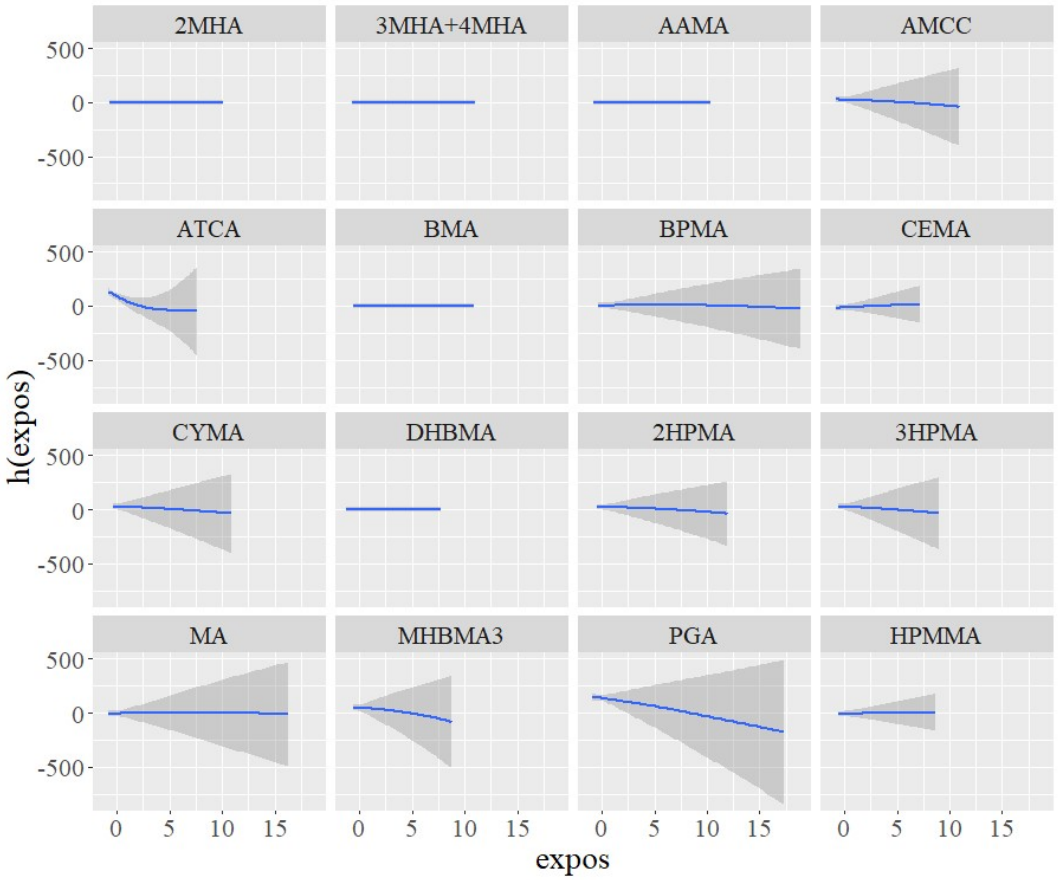

Figure S7. Single-variable effect (95% credible intervals) of the expos (normalized and centered urine VOCs concentration) on Klotho, where all of the other exposures are fixed to 50th quantile in middle age population (40-59 years) by BKMR models.