Supplemental Materials for "Mendelian Randomization Analysis of a Time-varying Exposure for Binary Disease Outcomes using Functional Data Analysis Methods"

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Supplemental Methods

Mendelian Randomization (MR) Analysis by Individual Clinical Visits.

For cohort studies with a fixed number of clinical visits, an alternative way of conducting MR analysis for the longitudinal exposure data is to perform standard MR analysis by using the exposure data collected from each visit and then calculate the minimum p-value (minP). For example, the Offspring Cohort of the FHS study had seven clinical visits. We can conduct the standard MR analysis for each visit and then use the minP of the seven analyses as the final result. Following the notation in the main text, we let $J_1 = J_2 = \cdots = J_n = J$, meaning that all the subjects had the same number of measurements for the exposure variable. For $j = 1, \dots, J$, 2SRI is conducted. Specifically, a linear regression model is fitted for x_{ij} in the first stage: $x_{ij} = \beta_{0j} + \boldsymbol{\beta_{1j}} \boldsymbol{G_i} + \boldsymbol{\beta_{2j}} \boldsymbol{Z_i} + v_{ij}$ to obtain the fitted residual $\hat{v}_{ij}$. Then a logistic regression model is fitted in the second stage: $\log(\frac{E(y_i)}{1-E(y_i)}) = \alpha_{0j} + \alpha_{1j} x_{ij} + \boldsymbol{\alpha_{2j}} \boldsymbol{Z_i} + \alpha_{3j} \hat{v}_{ij}$, where $E(y_i)$ is the expected value of y_i. We can obtain the p-value p_j from testing the null hypothesis H_0: $\alpha_{1j} = 0$ using a Wald test with the robust standard error, for $j = 1, \dots, J$. Then $\text{minP} = \min(p_1, p_2, \dots, p_J)$ is compared with the Bonferroni corrected significance level, for example, $0.05/J$. The limitations of the minP method are: first, not all the subjects have data collected for each clinical visit, leading to varying sample size of each analysis, and second, the Bonferroni correction may lead to power loss.

Figure S1. The smoothed mean BMI function and mean HDL function by the PACE procedure.

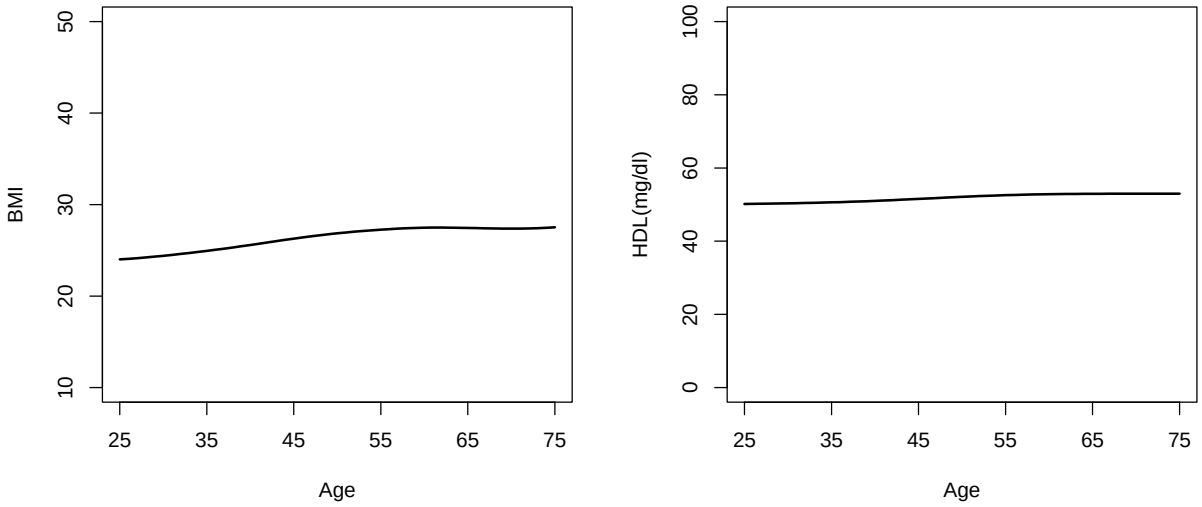

Figure S2. The corresponding eigen-functions of the top FPC scores estimated for FHS longitudinal BMI data and HDL data by the PACE procedure. The plot on the left shows the three estimated BMI eigen-functions corresponding to the top three FPC scores. The plot on the right shows the two estimated HDL eigen-functions corresponding to the top two FPC scores.

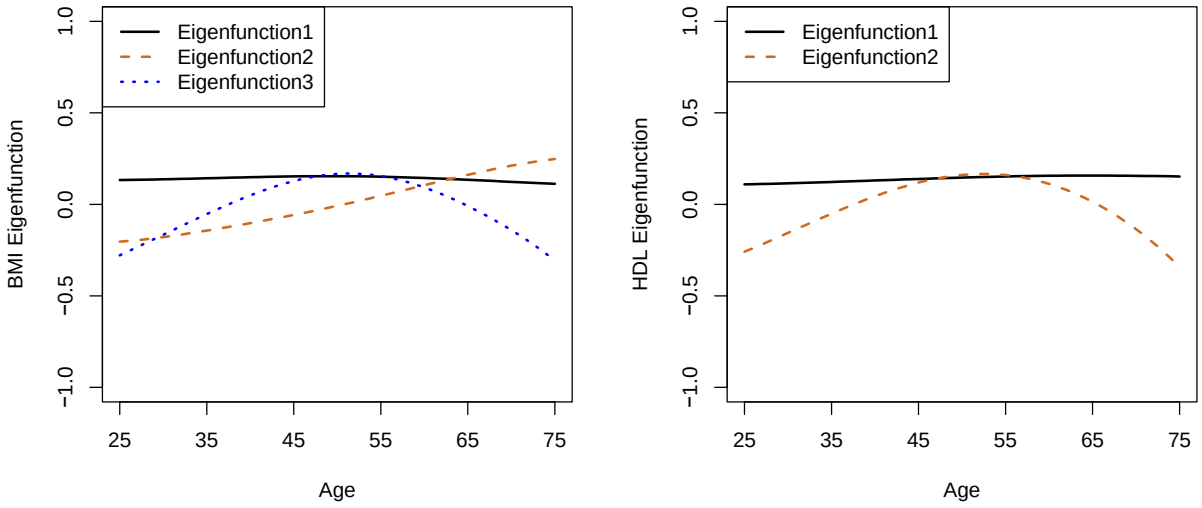

Figure S3. PACE-predicted vs. observed HDL data. Each plot shows the HDL data of a randomly selected subject.

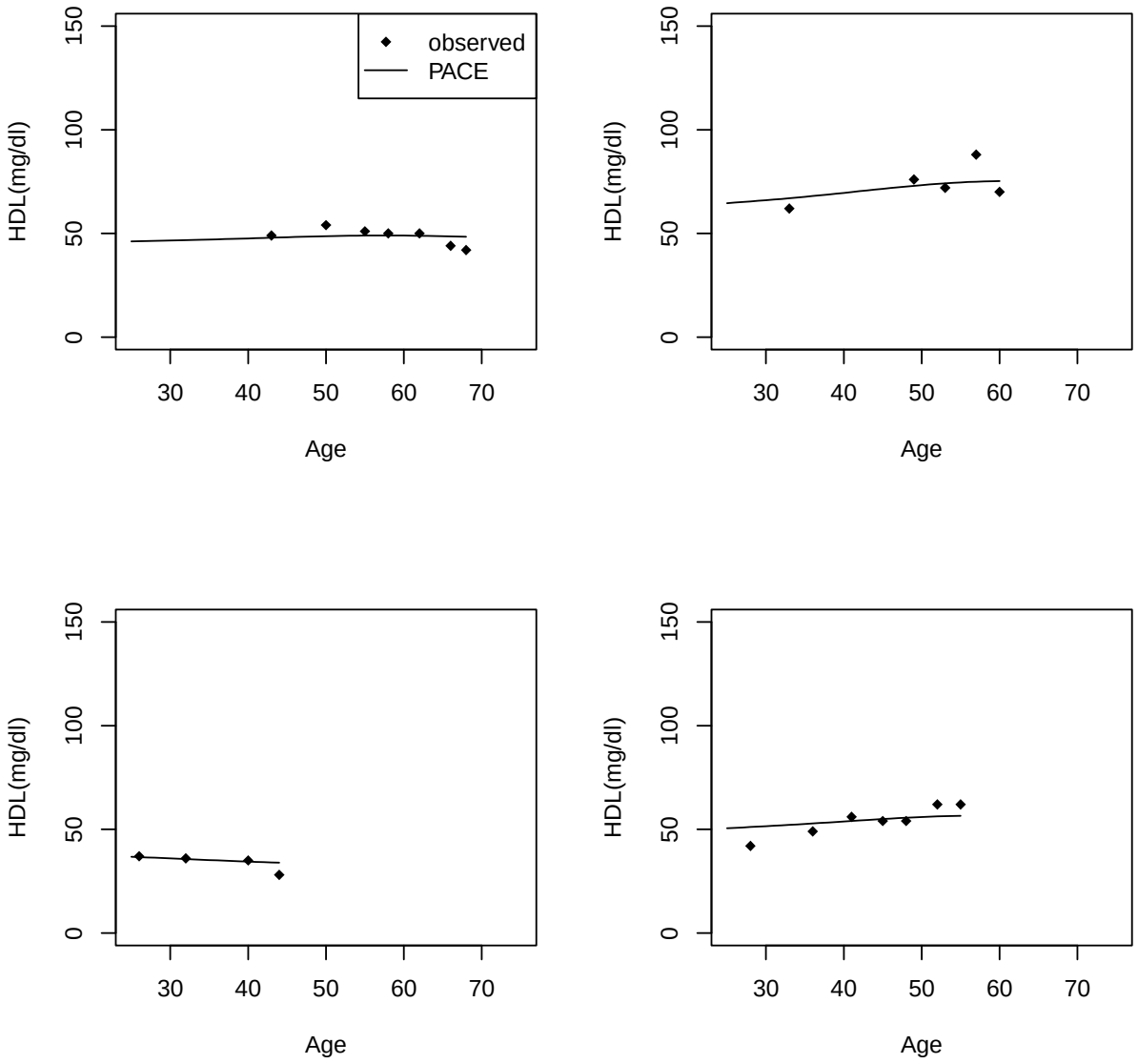

Figure S4. The mean of SNP-predicted BMI values by the effect allele count from the first stage of 2SFRI when 14 SNPs were used as separate IVs. The fitted BMI values only include the effects of 14 SNPs, not intercept or the effect of sex.

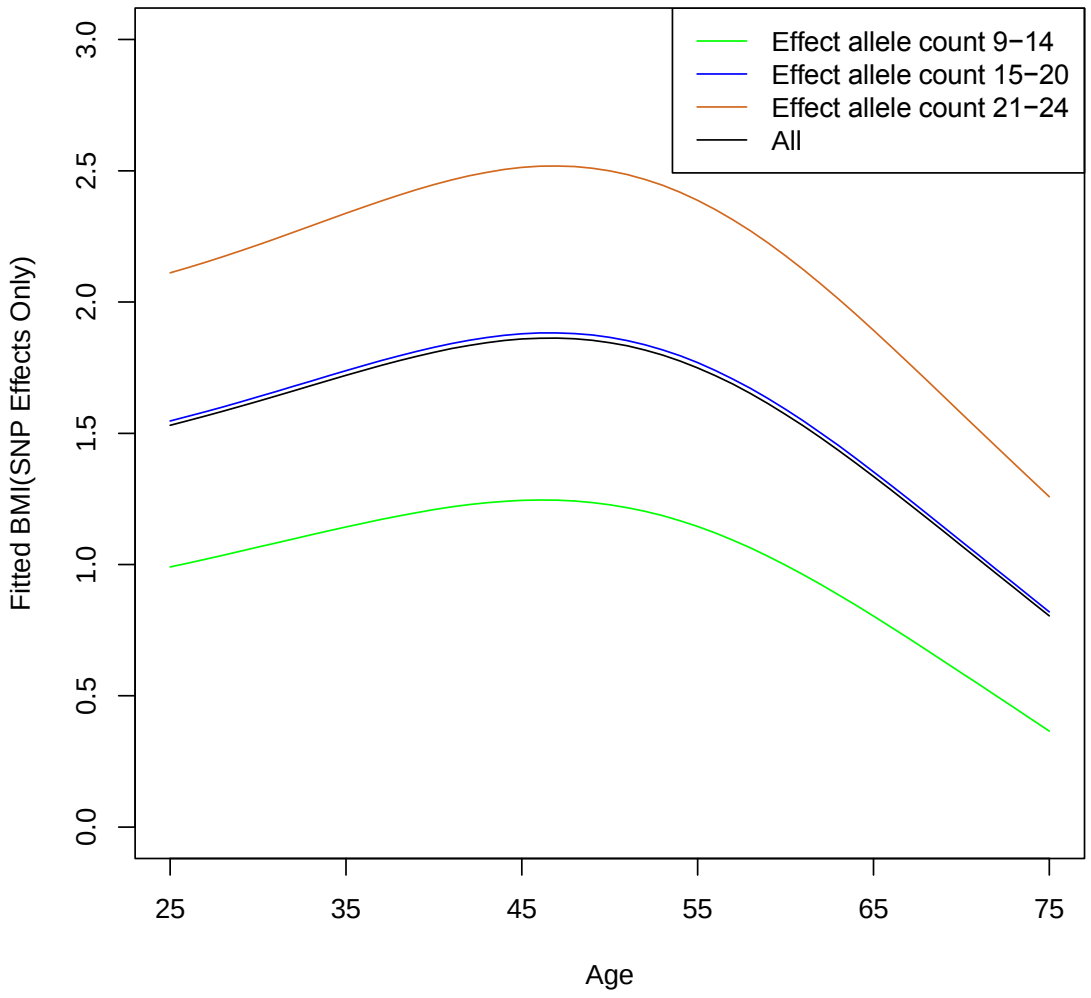

Table S1. Empirical Type I error rates of MR analysis by individual clinical visits in simulation set-up II.

IV	Visit1	Visit2	Visit3	Visit4	Visit5	Visit6	Visit7	Uncorrected minP	Bonferroni corrected minP
GRS	0.041	0.044	0.047	0.044	0.043	0.047	0.042	0.104	0.018
14 SNPs	0.058	0.050	0.049	0.052	0.058	0.059	0.060	0.161	0.036

Table S2. Empirical statistical power of MR analysis in simulation set-up II.

Simulation effect size			IV	By individual clinical visits							
FPC1	FPC2	FPC3		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Bonferroni corrected minP
0.027	-0.006	-0.064	GRS	0.155	0.146	0.139	0.164	0.188	0.173	0.151	0.083
			14 SNPs	0.329	0.266	0.323	0.359	0.369	0.329	0.338	0.283
0.054	-0.012	-0.128	GRS	0.338	0.254	0.298	0.347	0.437	0.366	0.413	0.238
			14 SNPs	0.709	0.556	0.668	0.724	0.701	0.689	0.728	0.690
0.027	0	0	GRS	0.142	0.138	0.149	0.135	0.171	0.161	0.152	0.077
			14 SNPs	0.273	0.251	0.328	0.345	0.327	0.319	0.351	0.266

Table S3. Analysis of the causal effect of BMI on the risk of T2D by individual clinical visits using the FHS data.

Clinical visit	Sample size	MR analysis p-value		Observation analysis p-value
		GRS	14SNPs	
1	1515	0.023	0.167	9.58E-22
2	1444	0.004	0.015	6.55E-24
3	1489	0.004	0.041	2.67E-20
4	1591	0.017	0.012	8.37E-22
5	1583	0.009	0.002	1.76E-20
6	1505	0.002	0.108	3.38E-14
7	1440	0.097	0.390	1.75E-08
Bonferroni corrected minP		0.014	0.014	4.59E-23

Table S4. Analysis of the causal effect of BMI on the risk of CHD by individual clinical visits using the FHS data.

Clinical visit	Sample size	MR analysis p-value		Observation analysis p-value
		GRS	14SNPs	
1	1503	0.399	0.448	0.007
2	1431	0.412	0.290	0.005
3	1471	0.390	0.365	0.030
4	1574	0.281	0.162	0.111
5	1563	0.298	0.145	0.264
6	1491	0.318	0.103	0.777
7	1454	0.132	0.241	0.734
Bonferroni corrected minP		0.924	0.721	0.035

Table S5. Analysis of the causal effect of HDL on the risk of CHD by individual clinical visits using the FHS data.

Clinical visit	Sample size	MR analysis p-value		Observation analysis p-value
		GRS	14SNPs	
1	1438	0.413	0.894	0.340
2	1366	0.493	0.753	0.015
3	1398	0.373	0.462	0.020
4	1506	0.656	0.870	0.028
5	1525	0.574	0.889	0.004
6	1450	0.682	0.782	0.192
7	1416	0.317	0.585	0.965
Bonferroni corrected minP		1	1	0.028