

Semiparametric methods for estimation of a non-linear
exposure–outcome relationship using instrumental variables with
application to Mendelian randomization: Supplementary Data

James R Staley¹ & Stephen Burgess¹

¹Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care,
University of Cambridge, United Kingdom.

Correspondence:

Dr Stephen Burgess

Department of Public Health & Primary Care

Strangeways Research Laboratory

Wort's Causeway

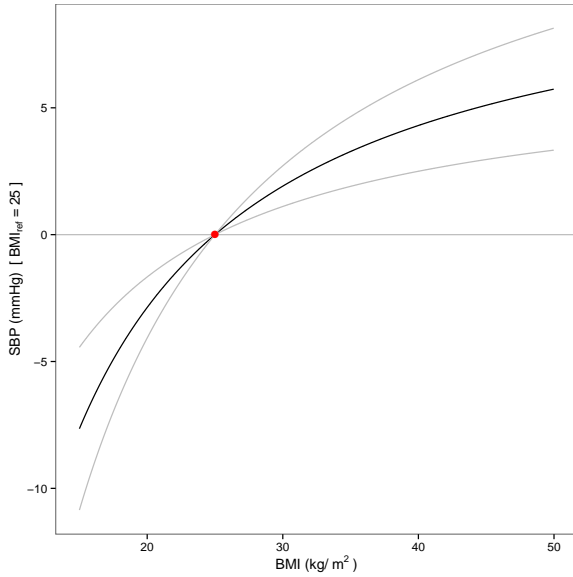
Cambridge

CB1 8RN

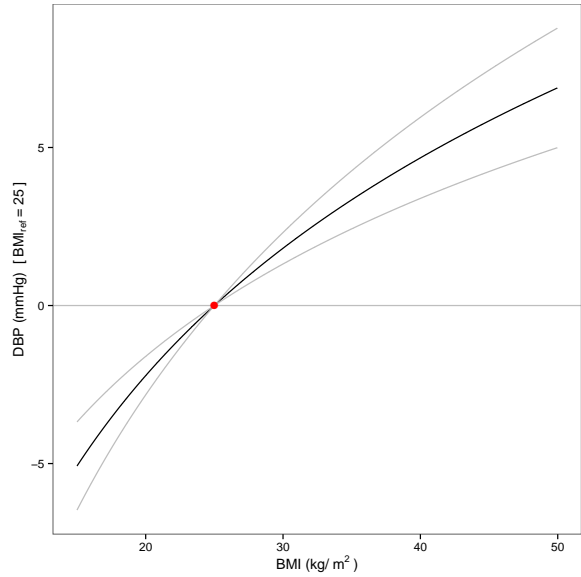
UK

Email: sb452@medschl.cam.ac.uk

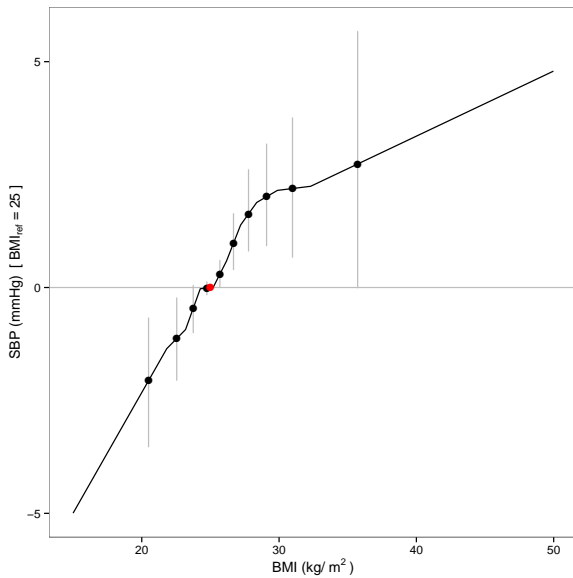
Telephone: +44 (0) 1223 748651



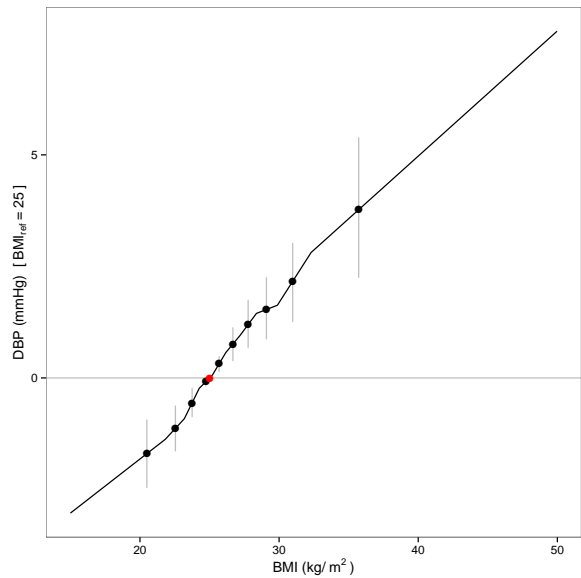
(a) SBP (Fractional polynomial model)



(b) DBP (Fractional polynomial model)



(c) SBP (Piecewise linear model)



(d) DBP (Piecewise linear model)

Figure S1 Causal effects of body mass index (BMI) on blood pressure (systolic blood pressure, SBP; diastolic blood pressure, DBP) in individuals with no history of hypertension using the fractional polynomial and piecewise linear methods on data from UK Biobank. The red point represents the reference point of BMI of 25 kg/m². Grey lines represent 95% CIs. The fractional polynomial method used 100 strata, whereas the piecewise linear method used 10 strata.

Table S1: Simulation results for fractional polynomials of degree 1.

p	β	Fitting correct FP		Fitting all FPs				
		Mean (SD) [Mean SE]		Coverage	Powers		Heuristic	
		$\hat{\beta}$		$\hat{\beta}$	Correct	Set	Correct FP	Best FP
-2	0	0.030 (0.953)	[0.933]	0.946	-	-	-	-
-2	1	1.006 (0.924)	[0.929]	0.960	0.434	0.952	1.14 (0.87)	1.21 (0.85)
-2	2	2.012 (0.956)	[0.933]	0.928	0.496	0.942	1.17 (0.92)	1.29 (0.92)
-1	0	0.046 (0.700)	[0.646]	0.932	-	-	-	-
-1	1	0.936 (0.635)	[0.643]	0.956	0.070	0.950	1.03 (0.80)	1.13 (0.84)
-1	2	1.921 (0.654)	[0.641]	0.946	0.142	0.956	1.06 (0.81)	1.21 (0.82)
-0.5	0	-0.013 (0.774)	[0.742]	0.922	-	-	-	-
-0.5	1	0.981 (0.724)	[0.743]	0.946	0.050	0.946	0.95 (0.75)	1.07 (0.79)
-0.5	2	1.959 (0.752)	[0.740]	0.938	0.088	0.912	0.99 (0.78)	1.17 (0.83)
0	0	-0.009 (0.221)	[0.211]	0.934	-	-	-	-
0	1	0.979 (0.215)	[0.210]	0.944	0.172	0.918	0.95 (0.74)	1.20 (0.79)
0	2	1.976 (0.210)	[0.212]	0.954	0.386	0.910	0.94 (0.72)	1.22 (0.76)
0.5	0	0.000 (0.246)	[0.233]	0.930	-	-	-	-
0.5	1	1.003 (0.246)	[0.234]	0.936	0.194	0.892	0.93 (0.70)	1.19 (0.75)
0.5	2	1.987 (0.239)	[0.235]	0.932	0.340	0.904	0.91 (0.68)	1.21 (0.79)
1	0	0.003 (0.064)	[0.064]	0.938	-	-	-	-
1	1	0.997 (0.066)	[0.065]	0.944	0.748	0.938	0.88 (0.64)	1.12 (0.79)
1	2	1.997 (0.071)	[0.068]	0.938	0.912	0.958	0.92 (0.70)	1.08 (0.91)
2	0	0.000 (0.009)	[0.008]	0.942	-	-	-	-
2	1	1.015 (0.012)	[0.012]	0.756	1.000	1.000	1.66 (1.07)	1.66 (1.07)
2	2	2.031 (0.015)	[0.015]	0.436	1.000	1.000	3.16 (1.49)	3.16 (1.49)
3	0	0.000 (0.001)	[0.001]	0.942	-	-	-	-
3	1	1.034 (0.006)	[0.005]	0.000	1.000	1.000	17.75 (3.10)	17.75 (3.10)
3	2	2.068 (0.011)	[0.009]	0.000	1.000	1.000	35.74 (5.64)	35.74 (5.64)

p is the power, and β is the effect parameter. Coverage refers to the number of replications where the true β was contained within the corresponding 95%CI. The power was correctly chosen (Correct) if the best-fitting fractional polynomial was also the correct fractional polynomial, whilst the correct model was within the set of powers that fit the data equally as well as the best-fitting fractional polynomial (Set) if the difference between twice the log-likelihood for the correct model and the best-fitting model was less than the 90th percentile of the relevant χ^2 distribution. The heuristic statistic (mean (SD) across simulations) is the sum of the absolute values of the predicted value of the outcome minus the correct value of the outcome at the mean value of the exposure in deciles of the IV-free distribution. The heuristic statistic is calculated both for the correct fractional polynomial (Correct FP), and for the best-fitted fractional polynomial (Best FP). SD, standard deviation; SE, standard error; FP, fractional polynomial; IV, instrumental variable; CI, confidence interval.

Table S2: Simulation results for fractional polynomials of degree 2 with $\beta_1 = 1$ and $\beta_2 = 2$.

		Fitting correct FP						Fitting all FPs					
		Mean (SD) [Mean SE]				Coverage		Powers		Heuristic			
p_1	p_2	$\hat{\beta}_1$		$\hat{\beta}_2$		$\hat{\beta}_1$	$\hat{\beta}_2$	Correct	Set	Correct FP	Best FP		
-2	-2	0.856 (3.756)	[3.606]	2.178 (6.653)	[6.502]	0.926	0.942	0.272	0.988	1.55 (1.08)	1.48 (1.02)		
-2	-1	0.433 (5.995)	[5.994]	2.281 (4.170)	[4.160]	0.950	0.950	0.012	0.974	1.41 (0.91)	1.43 (0.89)		
-2	-0.5	1.305 (4.041)	[3.833]	1.784 (3.173)	[3.070]	0.934	0.944	0.010	0.986	1.45 (0.93)	1.44 (0.94)		
-2	0	0.812 (2.786)	[2.805]	1.955 (0.624)	[0.636]	0.946	0.950	0.026	0.958	1.34 (0.83)	1.48 (0.91)		
-2	0.5	0.954 (2.142)	[2.187]	1.999 (0.552)	[0.552]	0.958	0.954	0.036	0.964	1.28 (0.79)	1.44 (0.93)		
-2	1	1.102 (1.887)	[1.974]	2.003 (0.135)	[0.140]	0.948	0.948	0.072	0.964	1.40 (0.88)	1.67 (1.07)		
-2	2	0.310 (2.830)	[2.514]	2.025 (0.034)	[0.030]	0.908	0.828	0.314	0.964	3.91 (1.73)	5.01 (2.70)		
-2	3	-6.114 (8.221)	[6.580]	2.051 (0.023)	[0.018]	0.812	0.280	0.440	0.980	37.67 (5.59)	34.6 (6.79)		
-1	-1	1.004 (0.713)	[0.718]	2.067 (3.855)	[3.776]	0.946	0.946	0.008	0.980	1.31 (0.87)	1.37 (0.95)		
-1	-0.5	0.525 (7.081)	[7.247]	2.551 (8.175)	[8.363]	0.952	0.948	0.002	0.962	1.31 (0.87)	1.38 (0.91)		
-1	0	1.399 (3.551)	[3.505]	2.109 (1.184)	[1.146]	0.944	0.938	0.006	0.968	1.30 (0.78)	1.47 (0.91)		
-1	0.5	0.815 (2.166)	[2.265]	1.929 (0.784)	[0.824]	0.954	0.958	0.006	0.964	1.29 (0.83)	1.49 (0.99)		
-1	1	0.871 (1.915)	[1.887]	1.985 (0.193)	[0.192]	0.942	0.938	0.004	0.962	1.33 (0.79)	1.70 (1.05)		
-1	2	0.293 (2.488)	[2.204]	2.020 (0.043)	[0.037]	0.900	0.902	0.026	0.956	3.74 (1.54)	4.73 (2.61)		
-1	3	-3.729 (6.988)	[5.521]	2.051 (0.029)	[0.022]	0.820	0.432	0.026	0.966	36.58 (5.29)	34.62 (6.74)		
-0.5	-0.5	1.021 (3.551)	[3.588]	1.959 (3.903)	[3.974]	0.938	0.946	0.018	0.990	1.28 (0.81)	1.37 (0.86)		
-0.5	0	1.113 (7.621)	[7.615]	2.008 (2.159)	[2.158]	0.956	0.952	0.002	0.982	1.25 (0.84)	1.44 (0.99)		
-0.5	0.5	1.296 (3.715)	[3.688]	2.093 (1.162)	[1.162]	0.944	0.946	0.002	0.968	1.20 (0.79)	1.5 (1.05)		
-0.5	1	0.752 (2.843)	[2.787]	1.979 (0.246)	[0.246]	0.944	0.946	0.002	0.938	1.30 (0.79)	1.76 (1.08)		
-0.5	2	0.314 (3.249)	[3.012]	2.022 (0.049)	[0.044]	0.922	0.896	0.012	0.974	3.66 (1.52)	4.51 (2.33)		
-0.5	3	-5.579 (8.982)	[7.322]	2.049 (0.031)	[0.025]	0.836	0.500	0.022	0.954	36.60 (5.48)	35.21 (7.03)		
0	0	0.891 (1.287)	[1.336]	2.036 (0.553)	[0.576]	0.952	0.956	0.008	0.966	1.23 (0.78)	1.64 (1.07)		
0	0.5	0.996 (2.106)	[2.033]	1.977 (2.346)	[2.262]	0.938	0.934	0.004	0.964	1.21 (0.72)	1.53 (0.95)		
0	1	1.004 (1.149)	[1.172]	1.996 (0.353)	[0.362]	0.940	0.940	0.012	0.948	1.22 (0.77)	1.69 (1.10)		
0	2	1.303 (1.248)	[1.087]	2.017 (0.064)	[0.055]	0.898	0.902	0.026	0.954	3.72 (1.46)	4.88 (2.60)		
0	3	3.223 (2.986)	[2.469]	2.044 (0.036)	[0.029]	0.840	0.610	0.026	0.968	35.52 (5.56)	34.02 (7.52)		
0.5	0.5	1.031 (4.390)	[3.986]	1.979 (1.377)	[1.252]	0.912	0.918	0.006	0.952	1.3 (0.79)	1.72 (1.09)		
0.5	1	1.025 (2.603)	[2.557]	1.996 (0.716)	[0.705]	0.938	0.940	0.010	0.954	1.27 (0.74)	1.76 (1.11)		
0.5	2	1.477 (1.784)	[1.633]	2.011 (0.079)	[0.072]	0.936	0.934	0.024	0.970	3.64 (1.53)	4.9 (2.66)		
0.5	3	3.956 (3.832)	[3.399]	2.040 (0.039)	[0.034]	0.864	0.774	0.016	0.964	34.85 (5.68)	34.91 (7.20)		
1	1	1.071 (0.990)	[0.959]	1.979 (0.452)	[0.438]	0.942	0.936	0.086	0.966	1.47 (0.83)	2.14 (1.33)		
1	2	1.231 (0.776)	[0.703]	1.995 (0.121)	[0.110]	0.912	0.908	0.030	0.960	3.64 (1.42)	4.88 (2.58)		
1	3	2.180 (1.425)	[1.224]	2.028 (0.051)	[0.042]	0.826	0.846	0.038	0.968	34.2 (5.94)	34.48 (7.81)		
2	2	1.233 (0.362)	[0.306]	1.920 (0.219)	[0.184]	0.858	0.900	0.246	0.944	10.44 (2.47)	12.35 (6.31)		
2	3	1.389 (0.504)	[0.419]	1.990 (0.108)	[0.089]	0.846	0.918	0.136	0.948	34.82 (7.11)	39.65 (11.21)		
3	3	1.377 (0.295)	[0.233]	1.864 (0.202)	[0.157]	0.660	0.842	0.704	0.966	84.13 (17.71)	74.39 (18.89)		

β_1 and β_2 are the effect parameters, and p_1 and p_2 are the powers. Coverage refers to the number of replications where the true β was contained within the corresponding 95%CI. The powers were correctly chosen (Correct) if the best-fitting fractional polynomial was also the correct fractional polynomial, whilst the correct model was within the set of powers that fit the data equally as well as the best-fitting fractional polynomial (Set) if the difference between twice the log-likelihood for the correct model and the best-fitting model was less than the 90th percentile of the relevant χ^2 distribution. The heuristic statistic (mean (SD) across simulations) is the sum of the absolute values of the predicted value of the outcome minus the correct value of the outcome at the mean value of the exposure in deciles of the IV-free distribution. The heuristic statistic is calculated both for the correct fractional polynomial (Correct FP), and for the best-fitted fractional polynomial (Best FP). SD, standard deviation; SE, standard error; FP, fractional polynomial; IV, instrumental variable; CI, confidence interval.

Table S3: Simulations to assess the impact of violations of the assumptions for the fractional polynomial method.

Simulation	Model	β	Fitting correct FP			Power of test		
			Mean (SD) [Mean SE]	Coverage	Quad	Q	FP	
IV–exposure	Linear	0	0.003 (0.064) [0.064]	0.940	0.048	0.078	0.020	
	Linear	1	1.001 (0.063) [0.065]	0.952	0.036	0.046	0.022	
	Logarithm	2	1.967 (0.226) [0.211]	0.926	0.550	0.274	0.582	
	Square root	2	1.974 (0.242) [0.235]	0.934	0.174	0.094	0.176	
	Quadratic	0.1	0.101 (0.009) [0.009]	0.954	0.612	0.318	0.586	
Exposure–outcome	Linear	0	-0.001 (0.079) [0.078]	0.938	0.050	0.058	0.006	
	Linear	1	1.003 (0.080) [0.078]	0.944	0.044	0.068	0.030	
	Logarithm	2	1.977 (0.220) [0.216]	0.938	0.456	0.230	0.496	
	Square root	2	1.980 (0.248) [0.250]	0.946	0.144	0.080	0.140	
	Quadratic	0.1	0.101 (0.026) [0.024]	0.940	0.114	0.098	0.092	
Both	Linear	0	0.009 (0.081) [0.077]	0.936	0.062	0.060	0.012	
	Linear	1	0.991 (0.080) [0.078]	0.930	0.056	0.070	0.042	
	Logarithm	2	1.972 (0.218) [0.216]	0.942	0.490	0.250	0.516	
	Square root	2	2.005 (0.250) [0.250]	0.960	0.134	0.092	0.138	
	Quadratic	0.1	0.103 (0.024) [0.024]	0.956	0.128	0.100	0.116	
Both ($\rho = 0.2$)	Linear	0	0.015 (0.082) [0.077]	0.938	0.114	0.086	0.022	
	Linear	1	1.004 (0.076) [0.078]	0.956	0.114	0.064	0.084	
	Logarithm	2	1.957 (0.208) [0.218]	0.950	0.352	0.162	0.382	
	Square root	2	1.997 (0.258) [0.248]	0.938	0.078	0.064	0.088	
	Quadratic	0.1	0.100 (0.026) [0.024]	0.924	0.668	0.408	0.576	

IV–exposure refers to the simulation setting where the IV–exposure association was allowed to vary across individuals. Exposure–outcome refers to the simulation setting where the exposure–outcome association was allowed to vary across individuals. Both refers to the simulation setting where both the IV–exposure and exposure–outcome associations were allowed to vary across individuals. Both ($\rho = 0.2$) refers to the simulation setting where both the IV–exposure and exposure–outcome associations were allowed to vary across individuals with correlation of 0.2. β is the effect parameter. Coverage refers to the number of replications where the true β was contained within the corresponding 95%CI. SD, standard deviation; SE, standard error; Quad, quadratic test for assessing non-linearity; Q, Cochran-Q test; FP; fractional polynomial test; IV, instrumental variable; CI, confidence interval.

Table S4: Simulations to assess the impact of violations of the assumptions for the piecewise linear method assuming a threshold effect with $\beta = 0.5$

(a) Overall results

Varying	Power of test		
	Quad	Q	FP
IV-exposure	0.848	0.706	0.772
Exposure-outcome	0.826	0.638	0.716
Both	0.774	0.644	0.708
Both ($\rho = 0.2$)	0.858	0.712	0.792

(b) Quantile results

Simulation	Parameter	Decile of the IV-free exposure distribution									
		1	2	3	4	5	6	7	8	9	10
IV-exposure	Correct	0.000	0.000	0.000	0.000	0.000	0.000	0.057	0.227	0.488	1.182
	Mean	0.023	0.039	0.044	0.039	0.033	0.045	0.115	0.275	0.543	1.244
	Coverage	0.934	0.928	0.934	0.938	0.934	0.918	0.908	0.932	0.934	0.926
Exposure-outcome	Correct	0.000	0.000	0.000	0.000	0.000	0.000	0.054	0.224	0.486	1.179
	Mean	0.005	0.007	0.005	0.004	0.004	0.015	0.080	0.235	0.498	1.182
	Coverage	0.936	0.924	0.924	0.932	0.930	0.926	0.932	0.948	0.952	0.950
Both	Correct	0.000	0.000	0.000	0.000	0.000	0.000	0.057	0.227	0.488	1.182
	Mean	0.025	0.041	0.045	0.042	0.038	0.048	0.116	0.270	0.530	1.222
	Coverage	0.936	0.926	0.938	0.936	0.928	0.932	0.922	0.924	0.924	0.942
Both ($\rho = 0.2$)	Correct	0.000	0.000	0.000	0.000	0.000	0.000	0.057	0.227	0.488	1.182
	Mean	0.028	0.045	0.049	0.043	0.036	0.046	0.115	0.275	0.542	1.286
	Coverage	0.934	0.936	0.926	0.932	0.950	0.942	0.940	0.940	0.942	0.936

IV-exposure refers to the simulation setting where the IV-exposure association was allowed to vary across individuals. Exposure-outcome refers to the simulation setting where the exposure-outcome association was allowed to vary across individuals. Both refers to the simulation setting where both the IV-exposure and exposure-outcome associations were allowed to vary across individuals. Both ($\rho = 0.2$) refers to the simulation setting where both the IV-exposure and exposure-outcome associations were allowed to vary across individuals with correlation of 0.2. Coverage refers to the number of replications where the true mean value of the outcome for that decile was contained within the corresponding 95% prediction interval. Quad, quadratic test for assessing non-linearity; Q, Cochran-Q test; FP; fractional polynomial test; IV, instrumental variable.

Table S5: Additional simulations to assess the impact of varying the effect of the IV on the exposure for the fractional polynomial method.

Simulation	Model	β	Fitting correct FP			Power of test		
			Mean (SD) [Mean SE]	Coverage	Quad	Q	FP	
Low frequency	Linear	0	-0.001 (0.056) [0.057]	0.958	0.014	0.046	0.042	
	Linear	1	0.999 (0.059) [0.058]	0.940	0.036	0.054	0.054	
	Logarithm	2	1.811 (0.197) [0.183]	0.800	0.524	0.504	0.266	
	Square root	2	1.894 (0.208) [0.207]	0.904	0.180	0.182	0.094	
	Quadratic	0.1	0.110 (0.008) [0.008]	0.770	0.686	0.748	0.432	
Super-additive	Linear	0	0.011 (0.077) [0.072]	0.922	0.014	0.056	0.072	
	Linear	1	1.000 (0.074) [0.075]	0.952	0.040	0.058	0.064	
	Logarithm	2	1.994 (0.238) [0.242]	0.946	0.472	0.446	0.224	
	Square root	2	1.983 (0.279) [0.268]	0.950	0.144	0.144	0.076	
	Quadratic	0.1	0.101 (0.010) [0.010]	0.938	0.524	0.532	0.270	
Sub-additive	Linear	0	0.012 (0.095) [0.088]	0.924	0.014	0.052	0.062	
	Linear	1	0.995 (0.089) [0.091]	0.958	0.044	0.056	0.068	
	Logarithm	2	1.986 (0.279) [0.286]	0.952	0.360	0.318	0.170	
	Square root	2	1.972 (0.336) [0.322]	0.948	0.112	0.108	0.070	
	Quadratic	0.1	0.100 (0.012) [0.013]	0.946	0.372	0.380	0.186	

Low frequency refers to the simulation setting where the IV is a low frequency variant (minor allele frequency = 0.03) with a large effect on the exposure (0.75). Super-additive refers to the simulation setting where the first allele of the genetic variant increases the exposure by 0.1 units and the second allele by 0.3 units. Sub-additive refers to the simulation setting where the first allele of the genetic variant increases the exposure by 0.3 units and the second allele by 0.1 units. β is the effect parameter. Coverage refers to the number of replications where the true β was contained within the corresponding 95%CI. SD, standard deviation; SE, standard error; Quad, quadratic test for assessing non-linearity; Q, Cochran-Q test; FP; fractional polynomial test; IV, instrumental variable; CI, confidence interval.

Table S6: Additional simulations to assess the impact of varying the effect of the IV on the exposure for the piecewise linear method assuming a threshold effect with $\beta = 0.5$.

(a) Overall results

Varying	Power of test		
	Quad	Q	FP
Low Frequency	0.844	0.892	0.754
Super-additive	0.636	0.698	0.552
Sub-additive	0.406	0.536	0.372

(b) Quantile results

Simulation	Parameter	Decile of the IV-free exposure distribution									
		1	2	3	4	5	6	7	8	9	10
Low frequency	Correct	0.000	0.000	0.000	0.000	0.000	0.000	0.005	0.174	0.436	1.130
	Mean	0.005	0.010	0.012	0.017	0.036	0.085	0.184	0.348	0.615	1.313
	Coverage	0.948	0.946	0.942	0.938	0.928	0.852	0.678	0.742	0.786	0.886
Super-additive	Correct	0.000	0.000	0.000	0.000	0.000	0.000	0.028	0.198	0.459	1.153
	Mean	0.031	0.053	0.064	0.064	0.057	0.061	0.119	0.272	0.542	1.242
	Coverage	0.940	0.938	0.944	0.936	0.942	0.952	0.914	0.940	0.942	0.946
Sub-additive	Correct	0.000	0.000	0.000	0.000	0.000	0.000	0.049	0.219	0.480	1.174
	Mean	0.030	0.049	0.053	0.047	0.040	0.046	0.110	0.274	0.546	1.241
	Coverage	0.962	0.962	0.970	0.952	0.952	0.952	0.942	0.952	0.968	0.950

Low frequency refers to the simulation setting where the IV is a low frequency variant (minor allele frequency = 0.03) with a large effect on the exposure (0.75). Super-additive refers to the simulation setting where the first allele of the genetic variant increases the exposure by 0.1 units and the second allele by 0.3 units. Sub-additive refers to the simulation setting where where the first allele of the genetic variant increases the exposure by 0.3 units and the second allele by 0.1 units. Coverage refers to the number of replications where the true mean value of the outcome for that decile was contained within the corresponding 95% prediction interval. Quad, quadratic test for assessing non-linearity; Q, Cochran-Q test; FP; fractional polynomial test; IV, instrumental variable.