

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

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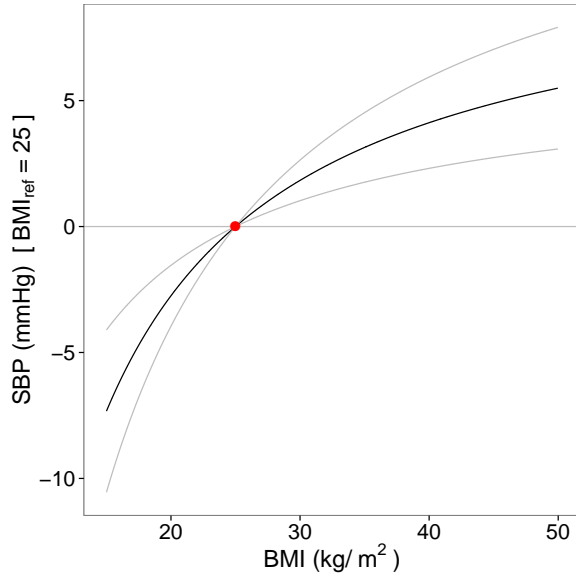
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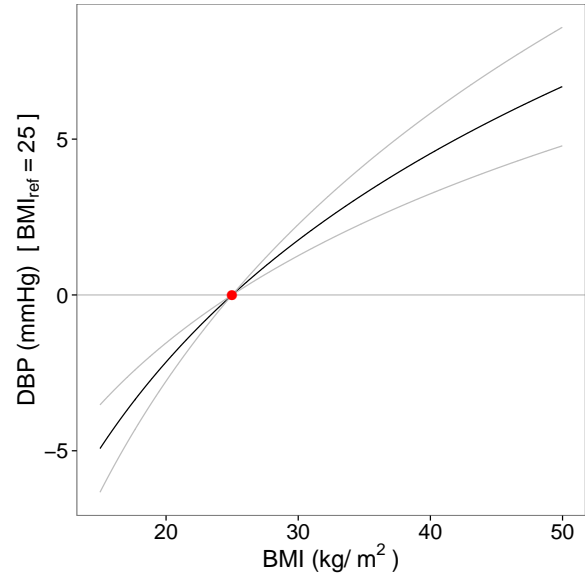
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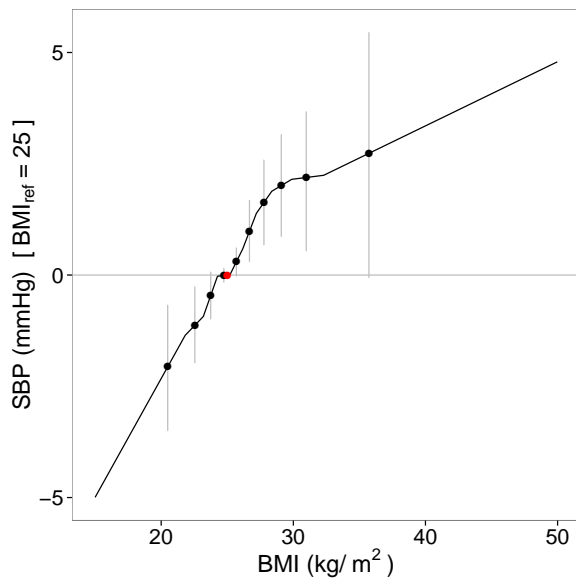
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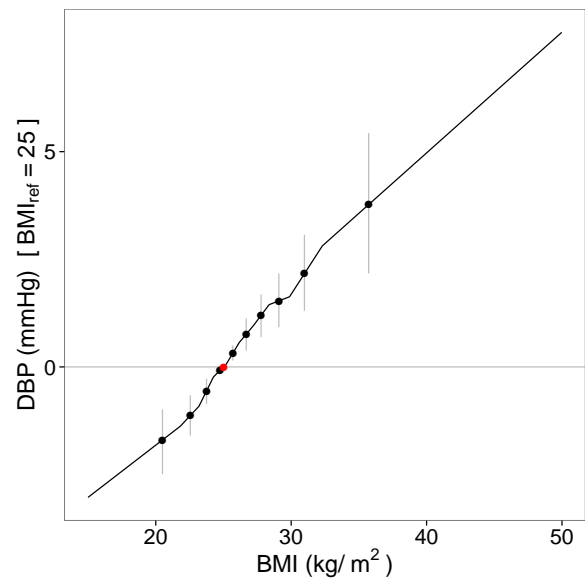
(a) SBP (Fractional polynomial model)



(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.

β	p	Fitting correct FP		Fitting all FPs				
		Mean (SD) [Mean SE]		Coverage	Powers		Heuristic	
		$\hat{\beta}_1$		$\hat{\beta}_1$	Correct	Set	Correct FP	Best FP
0	-2	0.030 (0.953) [0.933]	0.946	-	-	-	-	
1	-2	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)	
0	-1	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)	
2	-1	1.921 (0.654) [0.641]	0.946	0.142	0.956	1.06 (0.81)	1.21 (0.82)	
0	-0.5	-0.013 (0.774) [0.742]	0.922	-	-	-	-	
1	-0.5	0.981 (0.724) [0.743]	0.946	0.050	0.946	0.95 (0.75)	1.07 (0.79)	
2	-0.5	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	-	-	-	-	
1	0	0.979 (0.215) [0.210]	0.944	0.172	0.918	0.95 (0.74)	1.20 (0.79)	
2	0	1.976 (0.210) [0.212]	0.954	0.386	0.910	0.94 (0.72)	1.22 (0.76)	
0	0.5	0.000 (0.246) [0.233]	0.930	-	-	-	-	
1	0.5	1.003 (0.246) [0.234]	0.936	0.194	0.892	0.93 (0.70)	1.19 (0.75)	
2	0.5	1.987 (0.239) [0.235]	0.932	0.340	0.904	0.91 (0.68)	1.21 (0.79)	
0	1	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)	
2	1	1.997 (0.071) [0.068]	0.938	0.912	0.958	0.92 (0.70)	1.08 (0.91)	
0	2	0.000 (0.009) [0.008]	0.942	-	-	-	-	
1	2	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)	
0	3	0.000 (0.001) [0.001]	0.942	-	-	-	-	
1	3	1.034 (0.006) [0.005]	0.000	1.000	1.000	17.75 (3.10)	17.75 (3.10)	
2	3	2.068 (0.011) [0.009]	0.000	1.000	1.000	35.74 (5.64)	35.74 (5.64)	

β is the effect parameter, and p is the power. Coverage refers to the number of replications where the true β was contained within the corresponding 95% confidence interval. 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.

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

p		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% confidence interval. 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.

Table S3: Additional simulations to assess impact of violations of assumptions for fractional polynomials.

Varying	Model	β	Mean (SD) [Mean SE]	Coverage	Power of test		
					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% confidence interval. SD, standard deviation; SE, standard error; Quad, quadratic test for assessing non-linearity; Q, Cochran-Q test; FP; fractional polynomial test.

Table S4: Additional simulations to assess impact of violations of assumptions for the piecewise linear model 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

Varying	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% confidence interval. Quad, quadratic test for assessing non-linearity; Q, Cochran-Q test; FP; fractional polynomial test.