Supplementary Materials: A Versatile and Efficient Novel Approach for Mendelian Randomization Analysis with Application to Assess the Causal Effect of Fetal Hemoglobin on Anemia in Sickle Cell Anemia

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S1. Method

S1.1. Derivation of Relation in (6)

To simplify the derivation of the joint density (3) in evaluating likelihood (2), it is necessary to evaluate $\Pr(S_i = 1|\mathbf{Z}_i, G_i)$ using the relation (5). We start the derivation using (5) as below.

$$\begin{aligned}
&\Pr(S_i = 1|\mathbf{Z}_i, G_i)\\
&= \frac{1}{2\pi\sqrt{\sigma_{xx}\sigma_{yy}(1-\rho^2)}}\int_y\int_{-\infty}^{\infty}\exp\left\{\frac{-1}{2(1-\rho^2)}\left[\left(\frac{y-\boldsymbol{\beta}_1^T\mathbf{Z}_i-\beta_2 x}{\sqrt{\sigma_{yy}}}\right)^2\right.\right.\\
&\left.\left.+\left(\frac{x-\gamma_1^T\mathbf{Z}_i-\gamma_2 G_i}{\sqrt{\sigma_{xx}}}\right)^2-2\rho\left(\frac{y-\boldsymbol{\beta}_1^T\mathbf{Z}_i-\beta_2 x}{\sqrt{\sigma_{yy}}}\right)\left(\frac{x-\gamma_1^T\mathbf{Z}_i-\gamma_2 G_i}{\sqrt{\sigma_{xx}}}\right)\right]\right\}dxdy.
\end{aligned} \tag{S1}$$

Let $\theta_1 = \gamma_1\mathbf{Z}_i + \gamma_2 G_i$ and $\theta_2 = \boldsymbol{\beta}_1^T\mathbf{Z}_i$. Then,

$$\begin{aligned}
&\Pr(S_i = 1|\mathbf{Z}_i, G_i)\\
&= \frac{1}{2\pi\sqrt{\sigma_{xx}\sigma_{yy}(1-\rho^2)}}\int_y\int_{-\infty}^{\infty}\exp\left\{\frac{-1}{2(1-\rho^2)}\left[\left(\frac{y-\theta_2-\beta_2 x}{\sqrt{\sigma_{yy}}}\right)^2+\left(\frac{x-\theta_1}{\sqrt{\sigma_{xx}}}\right)^2\right.\right.\\
&\left.\left.-2\rho\left(\frac{y-\theta_2-\beta_2 x}{\sqrt{\sigma_{yy}}}\right)\left(\frac{x-\theta_1}{\sqrt{\sigma_{xx}}}\right)\right]\right\}dxdy\\
&= \frac{1}{2\pi\sqrt{\sigma_{xx}\sigma_{yy}(1-\rho^2)}}\int_y\int_{-\infty}^{\infty}\exp\left\{\frac{-1}{2(1-\rho^2)}\left[\left(\frac{\sigma_{xx}\beta_2^2+\sigma_{yy}+2\rho\beta_2\sqrt{\sigma_{xx}\sigma_{yy}}}{\sigma_{xx}\sigma_{yy}}\right)x^2\right.\right.\\
&-2\left(\frac{\sigma_{xx}\beta_2[y-\theta_2]+\sigma_{yy}\theta_1+\rho\sqrt{\sigma_{xx}\sigma_{yy}}[y-\theta_2+\theta_1\beta_2]}{\sigma_{xx}\sigma_{yy}}\right)x+\frac{[y-\theta_2]^2}{\sigma_{yy}}+\frac{2\rho\theta_1}{\sqrt{\sigma_{xx}\sigma_{yy}}}[y-\theta_2]\\
&\left.\left.+\frac{\theta_1^2}{\sigma_{xx}}\right]\right\}dxdy.
\end{aligned} \tag{S2}$$

Let $\mu = [(y-\theta_2)(\sigma_{xx}\beta_2+\rho\sqrt{\sigma_{xx}\sigma_{yy}})+\theta_1\sigma_{yy}+\rho\sqrt{\sigma_{xx}\sigma_{yy}}\theta_1\beta_2]/[\sigma_{xx}\beta_2^2+\sigma_{yy}+2\rho\beta_2\sqrt{\sigma_{xx}\sigma_{yy}}]$. Then (S2) can be further simplified as

$$
\begin{aligned}
&\Pr(S_i = 1|\mathbf{Z}_i, G_i) \\
&= \frac{1}{2\pi\sqrt{\sigma_{xx}\sigma_{yy}(1-\rho^2)}} \int_y \int_{-\infty}^{\infty} \exp\left\{ \frac{-1}{2(1-\rho^2)} \left[\left(\frac{\sigma_{xx}\beta_2^2 + \sigma_{yy} + 2\rho\beta_2\sqrt{\sigma_{xx}\sigma_{yy}}}{\sigma_{xx}\sigma_{yy}} \right) [x^2 - 2\mu x] \right.\right. \\
&\left.\left. + \frac{[y-\theta_2]^2}{\sigma_{yy}} + \frac{2\rho\theta_1}{\sqrt{\sigma_{xx}\sigma_{yy}}}[y-\theta_2] + \frac{\theta_1^2}{\sigma_{xx}} \right] \right\} dxdy \\
&= \frac{1}{2\pi\sqrt{\sigma_{xx}\sigma_{yy}(1-\rho^2)}} \int_y \int_{-\infty}^{\infty} \exp\left\{ \frac{-1}{2(1-\rho^2)} \left[\left(\frac{\sigma_{xx}\beta_2^2 + \sigma_{yy} + 2\rho\beta_2\sqrt{\sigma_{xx}\sigma_{yy}}}{\sigma_{xx}\sigma_{yy}} \right) [x - \mu]^2 \right.\right. \\
&\left.\left. - \left(\frac{\sigma_{xx}\beta_2^2 + \sigma_{yy} + 2\rho\beta_2\sqrt{\sigma_{xx}\sigma_{yy}}}{\sigma_{xx}\sigma_{yy}} \right)\mu^2 + \frac{[y-\theta_2]^2}{\sigma_{xx}} + \frac{2\rho\theta_1}{\sqrt{\sigma_{xx}\sigma_{yy}}}[y-\theta_2] + \frac{\theta_1^2}{\sigma_{xx}} \right] \right\} dxdy
\end{aligned}
$$

$$
\begin{aligned}
&= \frac{1}{2\pi\sqrt{\sigma_{xx}\sigma_{yy}(1-\rho^2)}} \int_y \int_{-\infty}^{\infty} \exp\left\{ \frac{-1}{2(1-\rho^2)} \left[\left(\frac{\sigma_{xx}\beta_2^2 + \sigma_{yy} + 2\rho\beta_2\sqrt{\sigma_{xx}\sigma_{yy}}}{\sigma_{xx}\sigma_{yy}} \right) [x - \mu]^2 \right.\right. \\
&+ [y-\theta_2]^2 \left(\frac{1}{\sigma_{yy}} - \frac{[\sigma_{xx}\beta_2 + \rho\sqrt{\sigma_{xx}\sigma_{yy}}]^2}{\sigma_{xx}\sigma_{yy}[\sigma_{xx}\beta_2^2 + \sigma_{yy} + 2\rho\beta_2\sqrt{\sigma_{xx}\sigma_{yy}}]} \right) \\
&- 2(y-\theta_2)\left(\frac{[\sigma_{yy}\theta_1 + \rho\theta_1\beta_2\sqrt{\sigma_{xx}\sigma_{yy}}][\sigma_{xx}\beta_2 + \rho\sqrt{\sigma_{xx}\sigma_{yy}}]}{\sigma_{xx}\sigma_{yy}[\sigma_{xx}\beta_2^2 + \sigma_{yy} + 2\rho\beta_2\sqrt{\sigma_{xx}\sigma_{yy}}]} - \frac{\rho\theta_1}{\sqrt{\sigma_{xx}\sigma_{yy}}} \right) + \frac{\theta_1^2}{\sigma_{xx}} \\
&\left.\left. - \frac{[\sigma_{yy}\theta_1 + \rho\sqrt{\sigma_{xx}\sigma_{yy}}\theta_1\beta_2]^2}{\sigma_{xx}\sigma_{yy}[\sigma_{xx}\beta_2^2 + \sigma_{yy} + 2\rho\beta_2\sqrt{\sigma_{xx}\sigma_{yy}}]} \right] \right\} dxdy \\
&= \frac{1}{2\pi\sqrt{\sigma_{xx}\sigma_{yy}(1-\rho^2)}} \int_y \int_{-\infty}^{\infty} \exp\left\{ \frac{-1}{2(1-\rho^2)} \left[\left(\frac{\sigma_{xx}\beta_2^2 + \sigma_{yy} + 2\rho\beta_2\sqrt{\sigma_{xx}\sigma_{yy}}}{\sigma_{xx}\sigma_{yy}} \right) [x - \mu]^2 \right.\right. \\
&\left.\left. + \frac{1-\rho^2}{\sigma_{xx}\beta_2^2 + \sigma_{yy} + 2\rho\beta_2\sqrt{\sigma_{xx}\sigma_{yy}}}[y - \theta_2 - \theta_1\beta_2]^2 \right] \right\} dxdy. \qquad \text{(S3)}
\end{aligned}
$$

Let $\sigma_1^2 = (1-\rho^2)\sigma_{xx}\sigma_{yy}/\sigma_2^2$ and $\sigma_2^2 = \sigma_{xx}\beta_2^2 + \sigma_{yy} + 2\rho\beta_2\sqrt{\sigma_{xx}\sigma_{yy}}$. Then, the above relation can be written as

$$
\begin{aligned}
&\Pr(S_i = 1|\mathbf{Z}_i, G_i) \\
&= \int_{-\infty}^{\infty} \frac{1}{\sqrt{2\pi\sigma_1^2}} \exp\left\{ -\frac{1}{2}\left(\frac{x-\mu}{\sigma_1} \right)^2 \right\} dx \int_y \frac{1}{\sqrt{2\pi\sigma_2^2}} \exp\left\{ -\frac{1}{2}\left(\frac{y-\theta_2-\theta_1\beta_2}{\sigma_2} \right)^2 \right\} dy,
\end{aligned}
$$

which is equivalent to

$$
\begin{aligned}
&Pr(S_i = 1|\mathbf{Z}_i, G_i) \\
&\qquad = \mathrm{F}_{(\theta_2+\theta_1\beta_2,\sigma_2)}(y_1) - \mathrm{F}_{(\theta_2+\theta_1\beta_2,\sigma_2)}(y_0) + \mathrm{F}_{(\theta_2+\theta_1\beta_2,\sigma_2)}(y_3) - \mathrm{F}_{(\theta_2+\theta_1\beta_2,\sigma_2)}(y_2),
\end{aligned}
$$

where $\mathrm{F}_{(\theta_2+\theta_1\beta_2,\sigma_2)}(\cdot)$ is the normal cumulative distribution with mean $\theta_2 + \theta_1\beta_2$ and standard deviation σ_2.

S1.2. Figures and Tables

Table S1. Average estimators, average standard errors, bias percentages, rejection proportions, and coverage percentages obtained through MREPS and 2SLS under EPS^X and random designs.

Design	Number of SNPs	β_2	Mean $\hat{\beta}_2$		Mean SE		Bias %		Rejection proportion		CP	
			MREPS	2SLS	MREPS	2SLS	MREPS	2SLS	MREPS	2SLS	MREPS	2SLS
(a) Equal- sized IV - risk factor associations												
EPS^X	9	0	0.003	0.16	0.12	0.02	-	-	0.05	1	95.1	0
		0.2	0.2	0.36	0.12	0.02	-1.31	-79.43	0.41	1	95	0
		0.4	0.4	0.56	0.12	0.02	-0.65	-39.71	0.89	1	95	0
	25	0	0.001	0.16	0.19	0.04	-	-	0.04	0.99	95.8	1.2
		0.2	0.2	0.36	0.19	0.04	-0.34	-80.43	0.21	1	95.8	1.2
		0.4	0.4	0.56	0.19	0.04	-0.17	-40.21	0.58	1	95.7	1.2
(b) Different- sized IV - risk factor associations												
	9	0	6×10^{-5}	0.16	0.12	0.02	-	-	0.06	1	94.5	0
		0.2	0.2	0.36	0.12	0.02	-0.03	-79.12	0.4	1	94.5	0
		0.4	0.4	0.56	0.12	0.02	-0.02	-39.56	0.9	1	94.5	0
	25	0	-0.007	0.16	0.19	0.04	-	-	0.07	0.98	93.5	2.2
		0.2	0,.19	0.36	0.19	0.04	3.4	-79.84	0.22	1	93.5	2.2
		0.4	0.39	0.56	0.19	0.04	1.7	-39.92	0.57	1	93.6	2.2
(c) A combination of few large and many small IV - risk factor associations												
	9	0	0.006	0.16	0.09	0.02	-	-	0.05	1	95.2	0
		0.2	0.21	0.36	0.09	0.02	-2.84	-78.63	0.59	1	95.2	0
		0.4	0.41	0.56	0.09	0.02	-1.42	-39.32	0.98	1	95.2	0
	25	0	0.002	0.15	0.08	0.02	-	-	0.05	1	94.9	0
		0.3	0.2	0.35	0.08	0.02	-0.82	-77.15	0.69	1	94.9	0
		0.4	0.4	0.55	0.08	0.02	-0.41	-38.57	0.99	1	94.9	0
(d) A combination of valid and invalid IV - risk factor associations												
	9	0	-0.001	0.15	0.09	0.02	-	-	0.05	1	95.3	0
		0.2	0.2	0.35	0.09	0.02	0.52	-77.43	0.63	1	95.4	0
		0.4	0.4	0.55	0.09	0.02	0.26	-38.72	0.99	1	95.4	0
	25	0	0.004	0.16	0.13	0.03	-	-	0.05	1	95	0.1
		0.2	0.2	0.36	0.13	0.03	-2.01	-79.89	0.36	1	95.1	0.1
		0.4	0.4	0.56	0.13	0.03	-1	-39.94	0.86	1	95.1	0.1
(a) Equal- sized IV - risk factor associations												
Random	9	0	-0.01	-0.01	0.14	0.15	-	-	0.06	0.03	94	96.9
		0.2	0.19	0.19	0.14	0.15	4.14	5.59	0.36	0.31	94.9	96.9
		0.4	0.39	0.39	0.14	0.15	1.53	2.8	0.79	0.75	94.6	96.9
	25	0	-0.02	-0.02	0.22	0.26	-	-	0.04	0.03	95.6	97
		0.2	0.18	0.18	0.22	0.26	12.48	10.52	0.26	0.21	95.2	97
		0.4	0.38	0.38	0.21	0.26	4.78	5.26	0.59	0.52	94.7	97
(b) Different- sized IV - risk factor associations												
	9	0	-0.008	-0.008	0.13	0.14	-	-	0.05	0.03	94.7	96.7
		0.2	0.2	0.19	0.13	0.14	2.43	3.99	0.41	0.36	95.2	96.7
		0.4	0.4	0.39	0.13	0.14	0.71	2	0.84	0.81	94.7	96.7
	25	0	-0.02	-0.02	0.23	0.26	-	-	0.05	0.03	95.5	97.3
		0.2	0.18	0.2	0.23	0.26	8.67	10.59	0.27	0.23	95.7	97.3
		0.4	0.38	0.4	0.22	0.26	3.82	5.29	0.59	0.53	95.4	97.3
(c) A combination of few large and many small IV - risk factor associations												
	9	0	-0.009	-0.009	0.1	0.1	-	-	0.06	0.05	93.7	95.3
		0.2	0.19	0.19	0.1	0.1	2.91	4.44	0.54	0.51	93.3	95.3
		0.4	0.4	0.39	0.1	0.1	0.91	2.22	0.94	0.92	93.5	95.3
	25	0	-0.003	-0.002	0.09	0.09	-	-	0.06	0.04	94.6	96
		0.3	0.2	0.2	0.09	0.09	-0.4	1.2	0.63	0.6	94.9	96
		0.4	0.4	0.4	0.09	0.09	-0.66	0.6	0.98	0.98	94.4	96
(d) A combination of valid and invalid IV - risk factor associations												
	9	0	-0.007	-0.007	0.09	0.1	-	-	0.06	0.04	94.5	95.8
		0.2	0.2	0.19	0.09	0.1	1.73	3.29	0.58	0.55	94.3	95.8
		0.4	0.4	0.39	0.09	0.1	0.32	1.64	0.96	0.95	94.7	95.8
	25	0	-0.006	-0.005	0.15	0.16	-	-	0.05	0.04	94.6	95.9
		0.2	0.2	0.19	0.15	0.16	1.15	2.65	0.38	0.35	93.3	95.9
		0.4	0.4	0.39	0.15	0.16	0.1	1.32	0.76	0.74	93.7	95.9

SE = Standard Error; CP = Coverage Percentage.

S2. Real Data Application

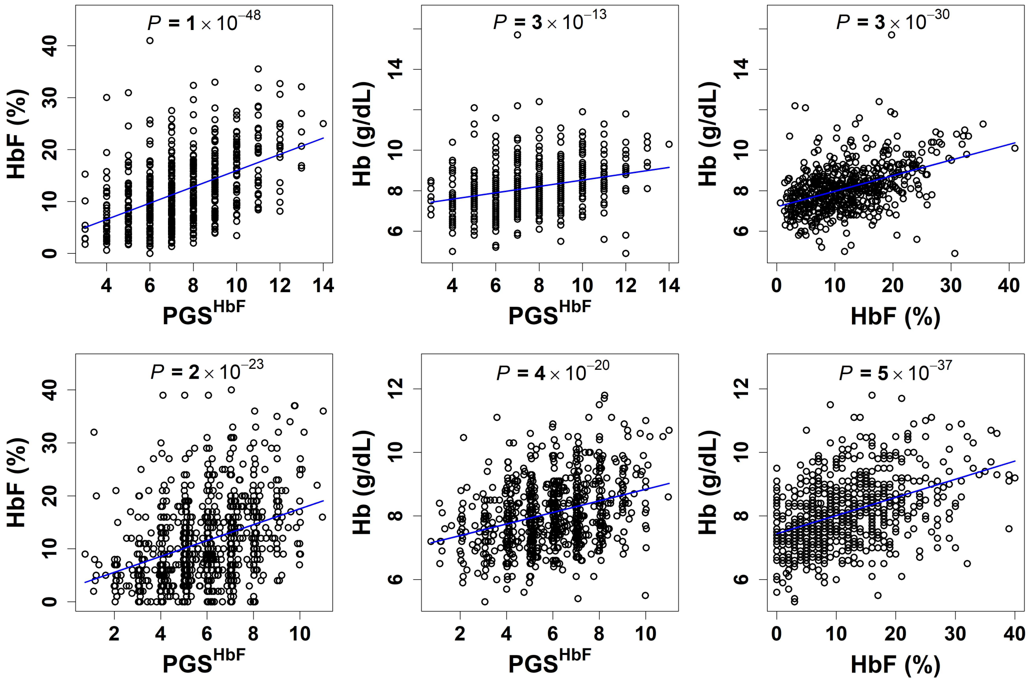

Figure S1. Top panel: Comparison between the effects of PGS^{HbF} on HbF and Hb and correlation between HbF and Hb in SCCRIP/BCM cohort. The p values were calculated using linear regression model, adjusting for covariates of cubic-spline–defined age, sex, site location, transfusion history (Yes/No), SS or SB0, and top 5 PCs. Bottom panel: Comparison between the effects of PGS^{HbF} on HbF and Hb and correlation between HbF and Hb in SIT cohort. The p values were calculated using linear regression model, adjusting for covariates of cubic-spline–defined age, sex, sickle diagnosis (Yes/No), SS or SB0, and top 5 PCs. SCCRIP/BMC = Sickle Cell Clinical Research Intervention Program study and Baylor College of Medicine; SIT = Silent Cerebral Infarct Transfusion trial.

Table S2. MR analyses to assess the causal effect of HbF on Hb of patients from two cohorts of SCCRIP/BCM and SIT. Instrumental variables are 10 different SNPs.

		$\hat{\beta}_2$		SE ($\hat{\beta}_2$)		*p*-Value (β_2)		$\hat{\gamma}_2$		SE ($\hat{\gamma}_2$)		*p*-Value (γ_2)	
Cohort/Design	**IV**	**MREPS**	**2SLS**	**MREPS**	**2SLS**	**MREPS**	**2SLS**	**MREPS**	**2SLS**	**MREPS**	**2SLS**	**MREPS**	**2SLS**
SCCRIP/BCM	*rs*7606173	0.046	0.045	0.019	0.02	0.012	0.023	−3.3	-	0.33	-	0	-
	*rs*6738440	0.087	0.084	0.026	0.029	8×10^{-4}	0.0038	−2.4	-	0.33	-	3×10^{-13}	-
	*rs*9494142	0.15	0.14	0.025	0.027	3×10^{-9}	2×10^{-7}	3.5	-	0.44	-	2×10^{-15}	-
	*rs*9389268	0.21	0.2	0.077	0.08	0.0074	0.011	1.3	-	0.47	-	0.0061	-
	*rs*61028892	0.09	0.089	0.02	0.023	9×10^{-6}	1×10^{-4}	8.5	-	0.98	-	0	-
	*rs*66650371	0.16	0.16	0.037	0.042	1×10^{-5}	1×10^{-4}	3.3	-	0.6	-	2×10^{-8}	-
	*rs*968857	0.15	0.15	0.056	0.073	0.0064	0.042	−1.1	-	0.37	-	0.0023	-
	*rs*10128556	0.097	0.095	0.027	0.036	4×10^{-4}	0.009	3.1	-	0.58	-	1×10^{-7}	-
	*rs*28440105	0.12	0.12	0.054	0.081	0.029	0.15	−1.9	-	0.73	-	0.011	-
	*rs*3834466	0.46	1.6	0.11	9.3	3×10^{-5}	0.86	0.75	-	0.57	-	0.19	-
SIT	*rs*7606173	0.13	0.12	0.019	0.023	8×10^{-12}	6×10^{-8}	−3.1	-	0.47	-	4×10^{-11}	-
	*rs*6738440	0.18	0.18	0.05	0.056	3×10^{-4}	0.0014	−1.9	-	0.57	-	9×10^{-4}	-
	*rs*9494142	0.14	0.14	0.048	0.053	0.0028	0.0081	2.1	-	0.75	-	0.0061	-
	*rs*9389268	0.42	4.6	0.087	130	2×10^{-6}	0.97	−0.23	-	0.2	-	0.25	-
	*rs*61028892	0.11	0.11	0.037	0.039	0.0028	0.0056	6.5	-	1.7	-	2×10^{-4}	-
	*rs*968857	0.025	0.024	0.047	0.057	0.59	0.67	−1.3	-	0.66	-	0.051	-
	*rs*10128556	0.17	0.17	0.029	0.093	2×10^{-9}	0.068	1.5	-	0.68	-	0.024	-
	*rs*28440105	0.052	0.05	0.034	0.039	0.13	0.2	−3.5	-	1.1	-	0.0014	-
	*rs*3834466	0.28	0.28	0.16	0.26	0.077	0.29	2.5	-	1.8	-	0.16	-
Combined	*rs*7606173	0.08	0.079	0.01	0.012	1×10^{-14}	8×10^{-11}	−3.4	-	0.21	-	0	-
	*rs*6738440	0.1	0.1	0.018	0.018	3×10^{-9}	1×10^{-8}	−2.6	-	0.25	-	0	-
	*rs*9494142	0.14	0.14	0.02	0.022	7×10^{-12}	6×10^{-10}	2.9	-	0.35	-	1×10^{-16}	-
	*rs*9389268	0.078	0.077	0.041	0.042	0.054	0.067	0.96	-	0.24	-	7×10^{-5}	-
	*rs*61028892	0.089	0.088	0.018	0.018	5×10^{-7}	2×10^{-6}	7.6	-	0.83	-	0	-
	*rs*968857	0.082	0.081	0.039	0.042	0.034	0.056	−1.2	-	0.28	-	1×10^{-5}	-
	*rs*10128556	0.1	0.099	0.026	0.028	1×10^{-4}	5×10^{-4}	2.4	-	0.33	-	2×10^{-12}	-
	*rs*28440105	0.095	0.093	0.046	0.055	0.039	0.088	−1.8	-	0.52	-	5^{-4}	-
	*rs*3834466	0.3	0.29	0.13	0.2	0.018	0.14	1.4	-	0.91	-	0.13	-
EPS^{Y}	*rs*7606173	0.1	0.099	0.016	0.018	8×10^{-10}	4×10^{-8}	−3.6	-	0.39	-	0	-
	*rs*6738440	0.12	0.12	0.025	0.027	6×10^{-7}	1×10^{-5}	−2.7	-	0.46	-	2×10^{-9}	-
	*rs*9494142	0.12	0.12	0.026	0.028	2×10^{-6}	1×10^{-5}	3.4	-	0.58	-	6×10^{-9}	-
	*rs*9389268	0.22	−0.069	0.014	0.32	0	0.83	−0.043	-	0.28	-	0.88	-
	*rs*61028892	0.1	0.1	0.024	0.031	3×10^{-5}	0.0011	7.3	-	1.6	-	7×10^{-6}	-
	*rs*968857	0.15	0.15	0.073	0.11	0.039	0.17	−0.84	-	0.48	-	0.08	-
	*rs*10128556	0.089	0.089	0.041	0.046	0.03	0.055	2.2	-	0.54	-	7×10^{-5}	-
	*rs*28440105	0.093	0.09	0.12	0.15	0.43	0.55	−0.99	-	0.9	-	0.27	-
	*rs*3834466	0.029	0.029	0.14	0.15	0.84	0.85	−1.7	-	1.7	-	0.34	-
EPS^{X}	*rs*7606173	0.074	0.08	0.013	0.019	2×10^{-8}	3×10^{-5}	−4.9	-	0.61	-	2×10^{-15}	-
	*rs*6738440	−0.37	0.11	0.047	0.034	8×10^{-15}	8×10^{-4}	0.11	-	0.17	-	0.53	-
	*rs*9494142	−1	0.13	0.082	0.033	0	1×10^{-4}	−0.14	-	0.087	-	0.1	-
	*rs*9389268	−0.36	−0.15	0.023	0.27	0	0.57	0.24	-	0.14	-	0.076	-
	*rs*61028892	−0.91	0.12	0.11	0.038	0	0.0019	−0.27	-	0.25	-	0.29	-
	*rs*968857	-0.37	0.067	0.011	0.095	0	0.48	−0.048	-	0.18	-	0.79	-
	*rs*10128556	−0.41	0.12	0.0082	0.057	0	0.042	−0.096	-	0.21	-	0.65	-
	*rs*28440105	−0.38	0.081	0.0077	0.13	0	0.53	−0.027	-	0.33	-	0.93	-
	*rs*3834466	-0.32	−0.15	0.033	0.21	0	0.48	−1.2	-	0.55	-	0.024	-

SE = Standard Error; SCCRIP/BCM: Sickle Cell Clinical Research Intervention Program study and Baylor College of Medicine; SIT = Silent Cerebral Infarct Transfusion trial; HbF = total fetal hemoglobin; PGS^{HbF} = Polygenic Score of HbF.

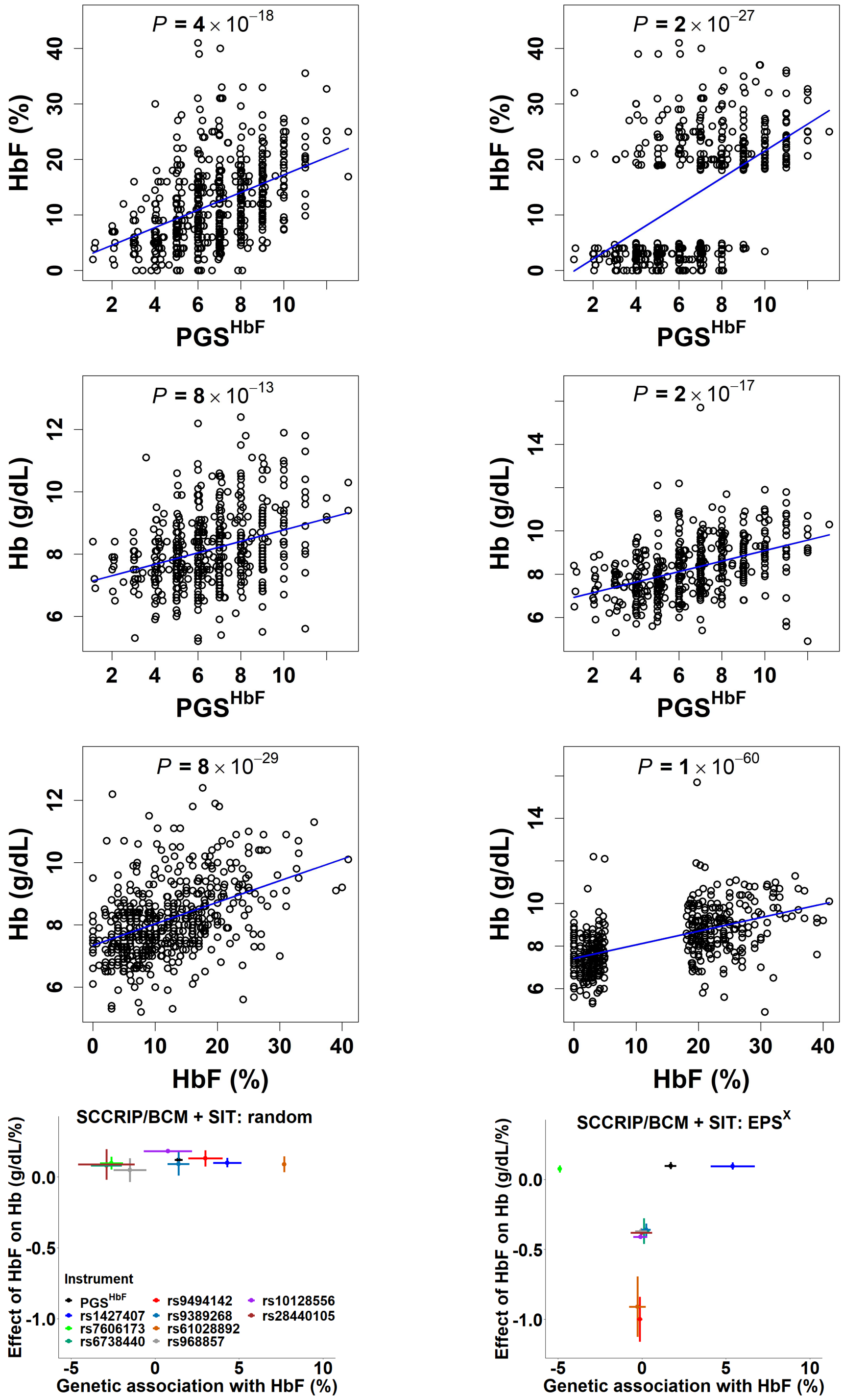

Figure S2. Top left and right panels: comparison between the effects of PGS^{HbF} on HbF and Hb and correlation between HbF and Hb in random sample and EPS^{Y} derived from SCCRIP/BCM and SIT combined cohort, respectively. The p values were calculated using linear regression model, adjusting for covariates of cubic-spline–defined age, sex, sickle diagnosis (Yes/No), and top 5 PCs. Bottom panel: HbF induced by *BCL11A* and $HBS1L - MYB$ causally influences Hb in random sample (left) and EPS^{Y} (right) patients. X-axis: Genetic association with HbF (%). Y-axis: (Causal) Effect of HbF on Hb (g/dL/%). SCCRIP/BMC = Sickle Cell Clinical Research Intervention Program study and Baylor College of Medicine; SIT = Silent Cerebral Infarct Transfusion trial.

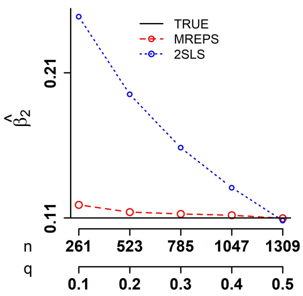

Figure S3. The behavior of the estimators, due to the change of sample size or the proportion of the extreme tails, obtained through MREPS and 2SLS under the $\mathrm{EPS}^{\mathrm{Y}}$.

Table S3. Average estimators, average standard errors, bias percentages, rejection proportions, and coverage percentages obtained through MREPS and 2SLS under $\mathrm{EPS}^{\mathrm{Y}}$ design.

n	q	β_2	Mean $\hat{\beta}_2$		Mean SE		Bias %		Rejection proportion		CP	
			MREPS	2SLS	MREPS	2SLS	MREPS	2SLS	MREPS	2SLS	MREPS	2SLS
261	0.1	0.11	0.117	0.212	0.051	0.090	−6.28	−93.02	0.6	0.7	94.3	74.8
523	0.2	0.11	0.113	0.178	0.039	0.060	−3.15	−61.69	0.8	0.8	93.7	75.4
785	0.3	0.11	0.112	0.150	0.035	0.046	−1.99	−36.26	0.9	0.9	93.5	83.6
1047	0.4	0.11	0.111	0.127	0.033	0.038	−1.22	−15.89	0.9	0.9	93.7	90.7
1309	0.5	0.11	0.110	0.109	0.032	0.032	−0.10	1.18	0.9	0.9	94.9	95.4

SE = Standard Error, CP = Coverage Percentage.