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Supplemental Data

A General Framework for Detecting Disease Associations with Rare Variants in Sequencing Studies

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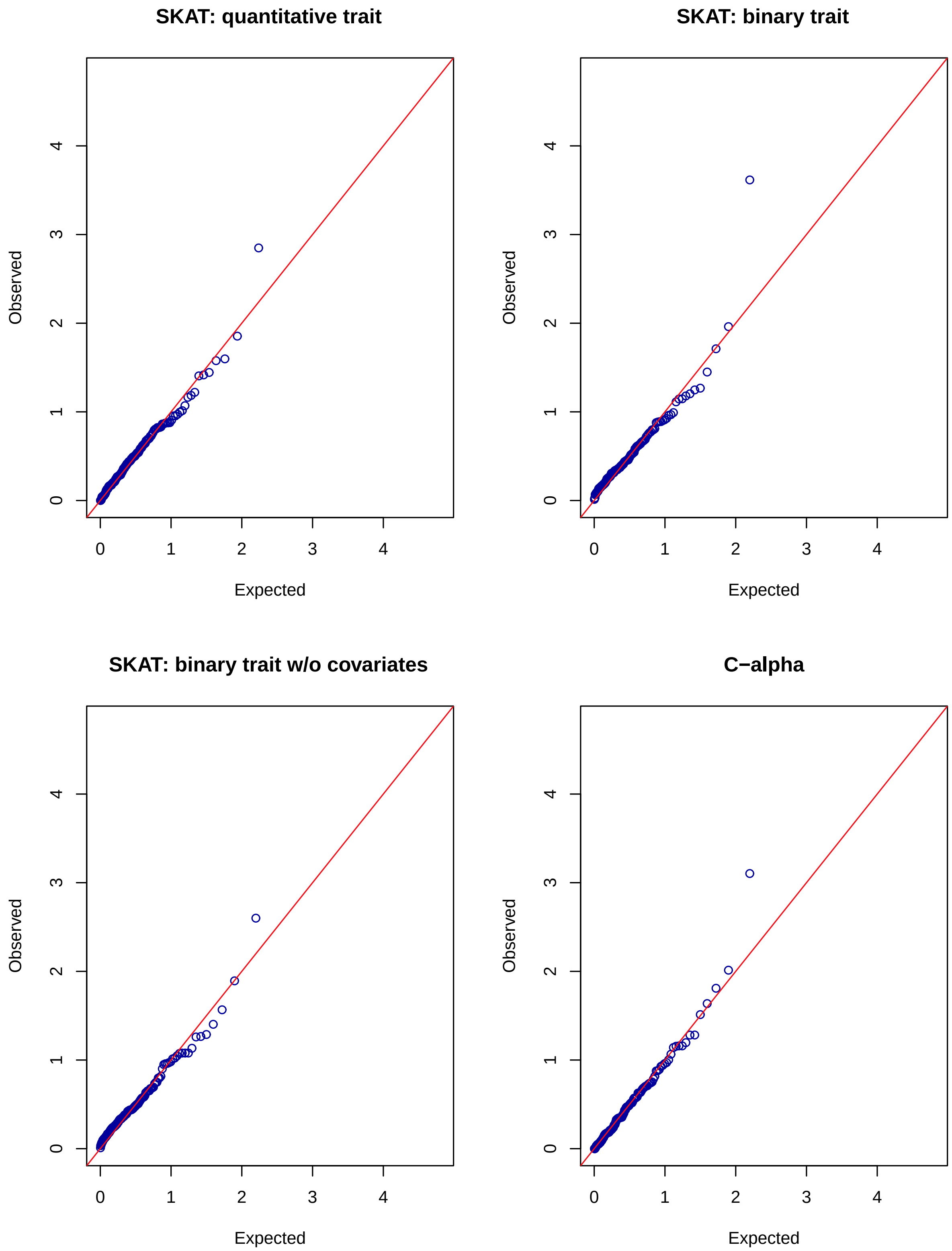

Figure S1. Quantile-quantile plots of $-\log_{10}(p\text{-values})$ for the SKAT in the quantitative and binary trait analyses of total cholesterol with covariates (top panel) and for the SKAT and C-alpha in the binary trait analysis of total cholesterol without covariates (bottom panel).

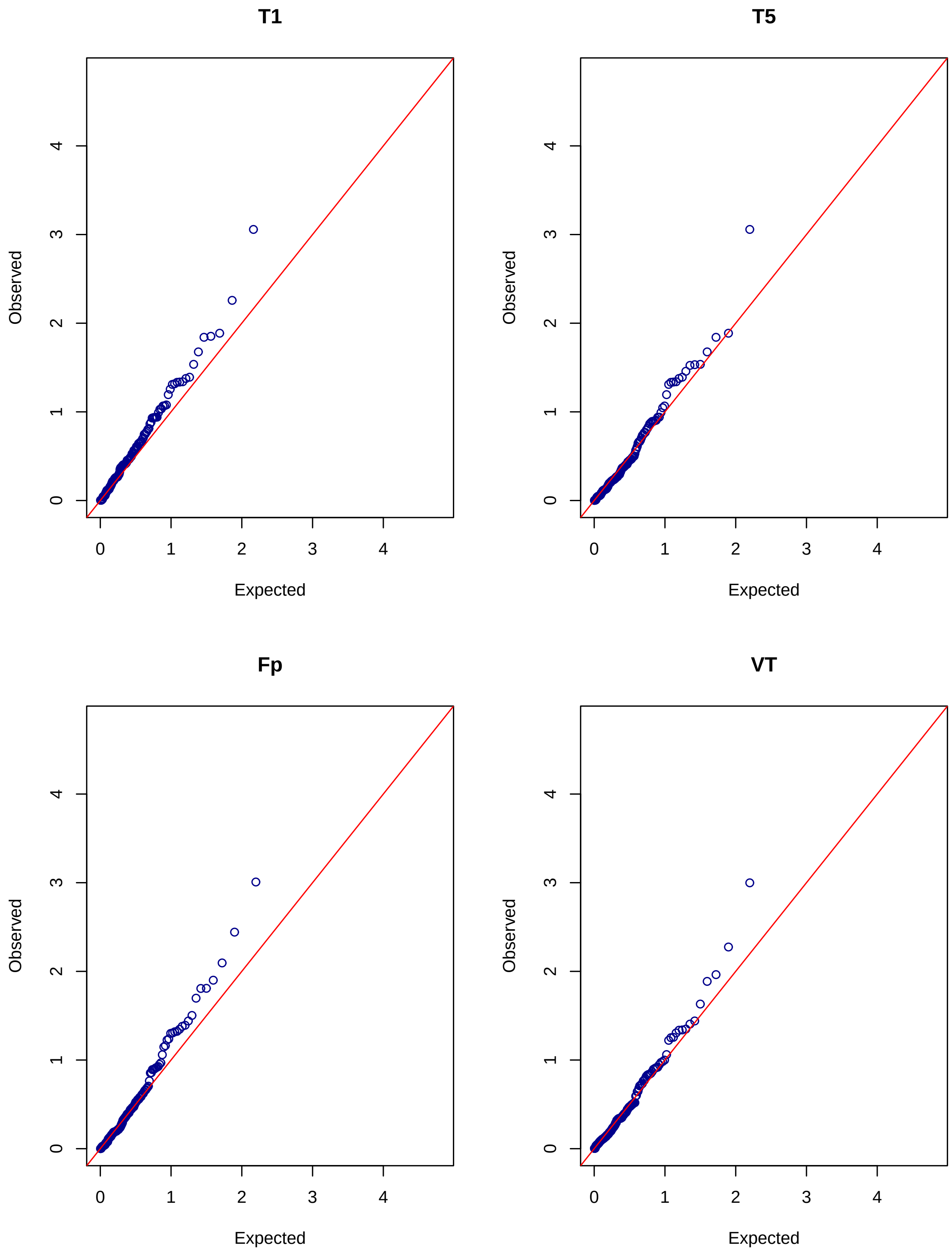

Figure S2. **Quantile-quantile plots of $-\log_{10}(p$-values) for the asymptotic T1, T5, F_p and VT tests in the binary trait analysis of total cholesterol without covariates.**

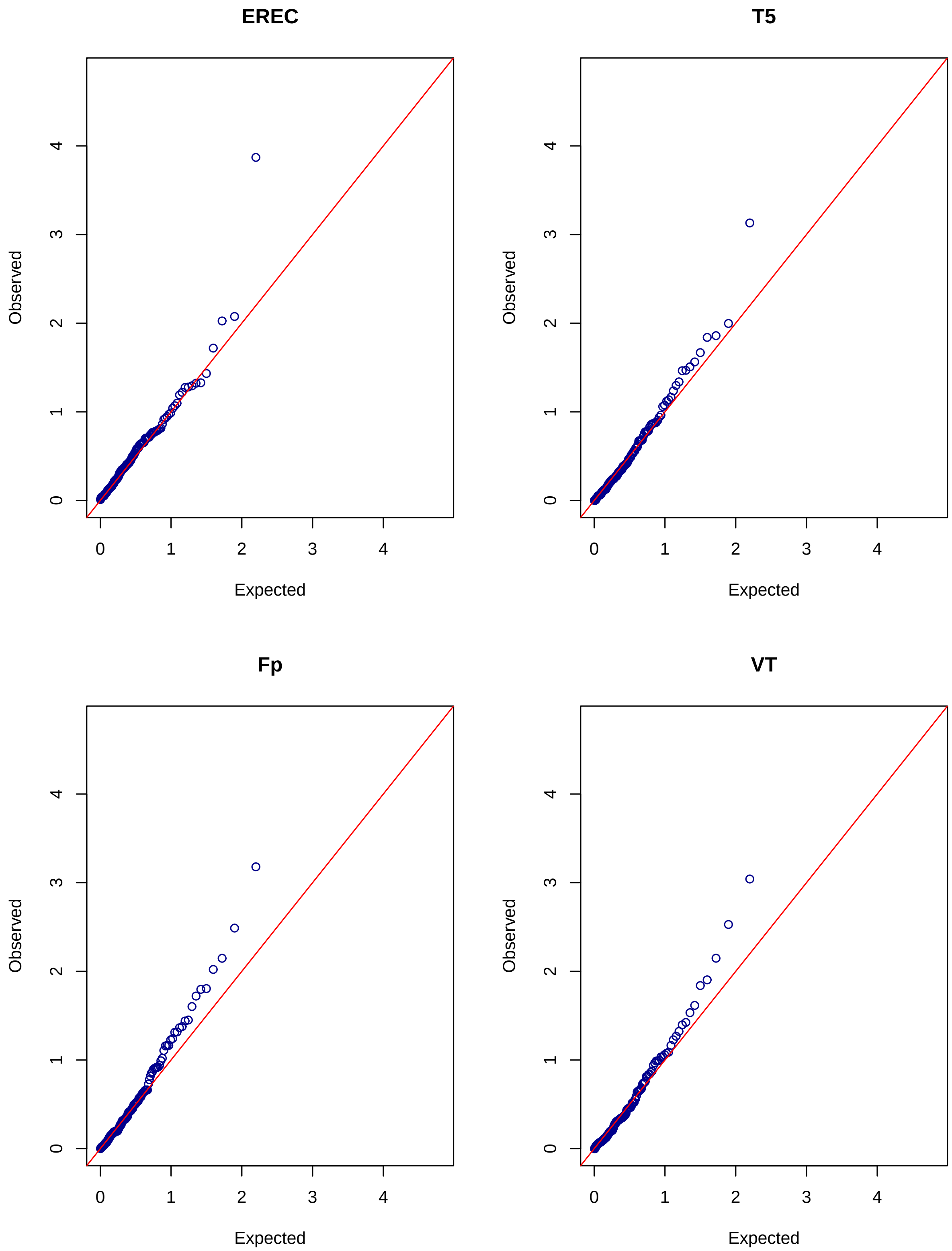

Figure S3. Quantile-quantile plots of $-\log_{10}(p$-values) for the permutation EREC, T5, F_p and VT tests in the binary trait analysis of total cholesterol without covariates.

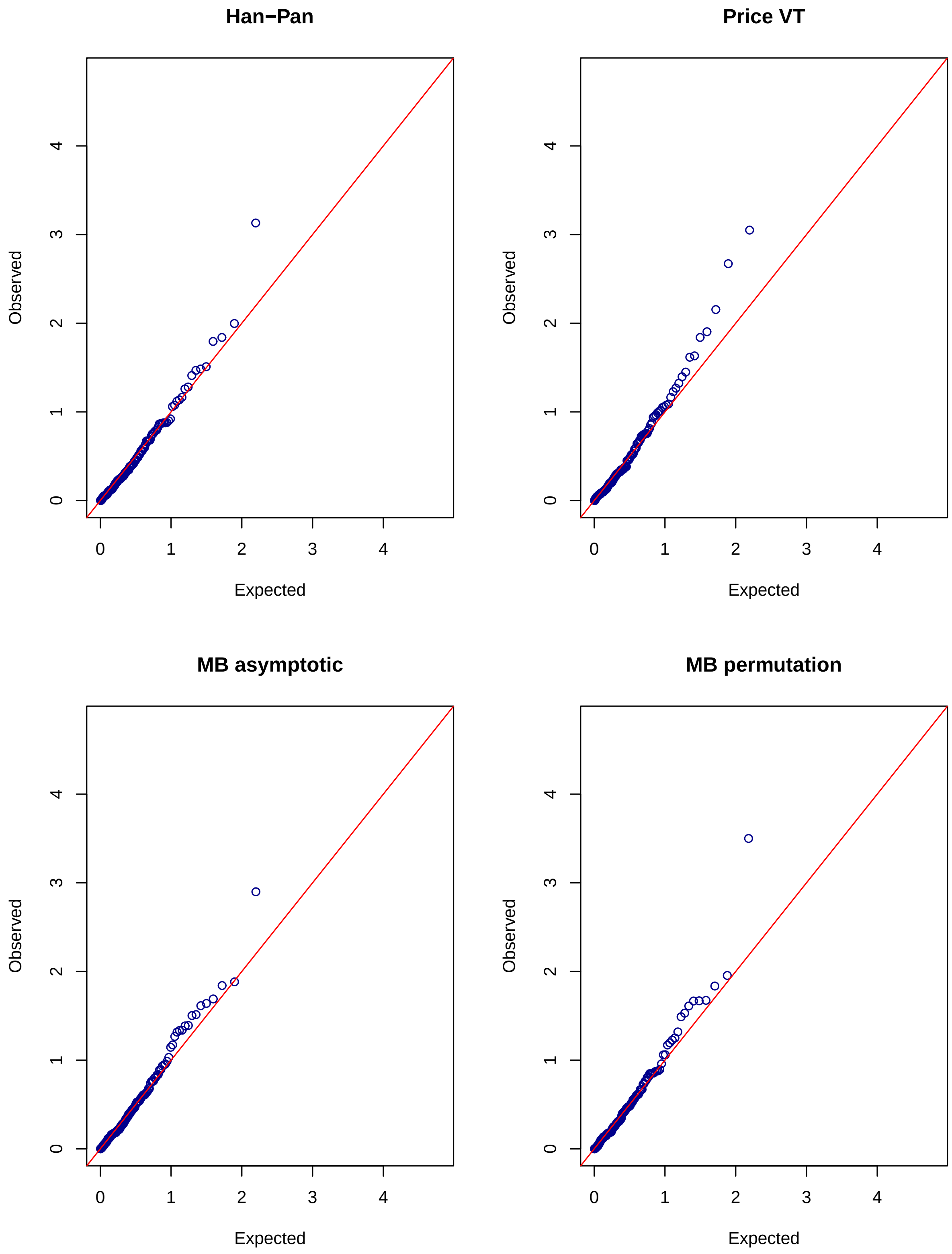

Figure S4. Quantile-quantile plots of $-\log_{10}(p\text{-values})$ for the Han-Pan test, Price et al.'s VT test, and the asymptotic and permutation versions of the MB test in the binary trait analysis of total cholesterol without covariates.

Table S1. Type I Error[a] and Power of Asymptotic Methods With Different Weight Functions Under $p_j = 0.0005j \ (j = 1, \cdots, 10)$

		$H_0 : \beta_j = 0$				$H_1 : \beta_j = x$				$\beta_j = x/\{p_j(1-p_j)\}^{1/2}$			
n	α	C	F_p	$T_{\max}$	F_u	C	F_p	$T_{\max}$	F_u	C	F_p	$T_{\max}$	F_u
500	10^{-2}	0.87	0.89	0.87	1.81	0.77	0.75	0.77	0.88	0.79	0.80	0.79	0.91
	10^{-3}	0.68	0.66	0.62	1.62	0.49	0.45	0.48	0.66	0.51	0.52	0.51	0.70
	10^{-4}	0.47	0.36	0.36	1.10	0.24	0.21	0.22	0.38	0.25	0.26	0.25	0.42
1000	10^{-2}	0.96	0.94	0.93	2.12	0.78	0.75	0.77	0.88	0.92	0.93	0.93	0.97
	10^{-3}	0.88	0.81	0.80	2.55	0.51	0.46	0.49	0.66	0.73	0.76	0.75	0.88
	10^{-4}	0.72	0.64	0.64	2.60	0.27	0.23	0.25	0.41	0.49	0.52	0.51	0.70
2000	10^{-2}	0.97	0.97	0.96	1.96	0.82	0.78	0.81	0.88	0.97	0.98	0.97	0.99
	10^{-3}	0.93	0.89	0.89	2.53	0.56	0.51	0.55	0.68	0.86	0.89	0.88	0.95
	10^{-4}	0.80	0.76	0.75	3.00	0.32	0.27	0.30	0.44	0.68	0.72	0.71	0.84
4000	10^{-2}	0.99	0.98	0.98	1.64	0.72	0.68	0.71	0.79	0.98	0.98	0.98	0.99
	10^{-3}	0.95	0.93	0.93	2.05	0.45	0.40	0.43	0.54	0.89	0.92	0.91	0.96
	10^{-4}	0.90	0.83	0.86	2.49	0.23	0.19	0.22	0.30	0.73	0.78	0.77	0.87

[a] divided by α

Table S2. Type I Error[a] and Power of Asymptotic Methods With Different Weight Functions Under $p_j = 0.00025j$ $(j = 1 \cdots, 20)$

		$H_0 : \beta_j = 0$				$H_1 : \beta_j = x$				$H_1 : \beta_j = x/\{p_j(1-p_j)\}^{1/2}$			
n	α	C	F_p	$T_{\max}$	F_u	C	F_p	$T_{\max}$	F_u	C	F_p	$T_{\max}$	F_u
500	10^{-2}	0.95	0.94	0.93	3.18	0.75	0.72	0.74	0.91	0.90	0.91	0.91	0.98
	10^{-3}	0.85	0.82	0.81	4.18	0.46	0.43	0.45	0.72	0.70	0.72	0.72	0.90
	10^{-4}	0.66	0.62	0.60	4.53	0.22	0.20	0.21	0.46	0.45	0.47	0.46	0.74
1000	10^{-2}	0.97	0.97	0.96	3.52	0.79	0.75	0.78	0.92	0.72	0.75	0.74	0.91
	10^{-3}	0.92	0.88	0.88	5.54	0.52	0.48	0.51	0.75	0.44	0.47	0.46	0.74
	10^{-4}	0.78	0.75	0.74	7.85	0.28	0.25	0.27	0.52	0.22	0.24	0.23	0.51
2000	10^{-2}	0.99	0.99	0.99	3.00	0.91	0.88	0.91	0.96	0.63	0.67	0.66	0.85
	10^{-3}	0.96	0.93	0.94	4.79	0.73	0.68	0.72	0.86	0.35	0.38	0.37	0.63
	10^{-4}	0.88	0.86	0.87	7.07	0.50	0.44	0.49	0.69	0.16	0.18	0.17	0.39
4000	10^{-2}	1.00	1.00	0.99	2.30	0.96	0.95	0.96	0.98	0.94	0.96	0.95	0.99
	10^{-3}	0.99	0.97	0.97	3.36	0.86	0.82	0.85	0.92	0.79	0.84	0.83	0.93
	10^{-4}	0.98	0.92	0.95	4.70	0.68	0.62	0.67	0.79	0.58	0.65	0.63	0.81

[a] divided by α

Table S3. Type I Error[a] and Power of Asymptotic Methods With Different Weight Functions Under $p_j = 0.005$ $(j = 1, \cdots, 10)$

		$H_0: \beta_j = 0$				$H_1: \beta_j = x$				$H_1: \beta_j = x/\{p_j(1-p_j)\}^{1/2}$			
n	α	C	F_p	$T_{\max}$	F_u	C	F_p	$T_{\max}$	F_u	C	F_p	$T_{\max}$	F_u
500	10^{-2}	0.94	0.94	0.93	2.34	0.72	0.70	0.71	0.85	0.79	0.78	0.79	0.90
	10^{-3}	0.82	0.81	0.80	2.83	0.43	0.41	0.42	0.62	0.51	0.50	0.51	0.70
	10^{-4}	0.62	0.60	0.58	2.86	0.20	0.19	0.19	0.36	0.27	0.25	0.26	0.44
1000	10^{-2}	0.98	0.98	0.97	2.13	0.76	0.75	0.76	0.86	0.91	0.91	0.91	0.96
	10^{-3}	0.92	0.91	0.91	2.94	0.49	0.48	0.49	0.64	0.74	0.72	0.73	0.84
	10^{-4}	0.81	0.74	0.76	3.76	0.26	0.25	0.25	0.40	0.50	0.48	0.49	0.65
2000	10^{-2}	0.98	0.98	0.98	1.61	0.89	0.89	0.89	0.94	0.97	0.96	0.97	0.98
	10^{-3}	0.96	0.96	0.96	2.06	0.70	0.70	0.70	0.79	0.86	0.86	0.86	0.91
	10^{-4}	0.90	0.91	0.91	2.56	0.47	0.46	0.46	0.58	0.68	0.67	0.68	0.78
4000	10^{-2}	0.99	0.99	0.99	1.29	0.96	0.96	0.96	0.97	0.98	0.98	0.98	0.99
	10^{-3}	0.97	0.97	0.97	1.48	0.84	0.83	0.84	0.88	0.90	0.90	0.90	0.93
	10^{-4}	0.94	0.92	0.92	1.67	0.65	0.64	0.64	0.72	0.74	0.74	0.74	0.81

[a] divided by α

Table S4. Type I Error[a] and Power of Asymptotic Methods With Different Weight Functions Under $p_j = 0.0025$ ($j = 1, \cdots, 10$)

		$H_0: \beta_j = 0$				$H_1: \beta_j = x$				$H_1: \beta_j = x/\{p_j(1-p_j)\}^{1/2}$			
n	α	C	F_p	$T_{\max}$	F_u	C	F_p	$T_{\max}$	F_u	C	F_p	$T_{\max}$	F_u
500	10^{-2}	0.85	0.88	0.86	1.85	0.82	0.81	0.82	0.92	0.82	0.81	0.82	0.92
	10^{-3}	0.67	0.64	0.62	1.58	0.56	0.54	0.55	0.73	0.56	0.54	0.55	0.74
	10^{-4}	0.41	0.36	0.32	0.92	0.29	0.27	0.28	0.46	0.29	0.27	0.28	0.46
1000	10^{-2}	0.97	0.94	0.94	2.36	0.93	0.93	0.93	0.97	0.94	0.93	0.93	0.97
	10^{-3}	0.86	0.82	0.81	2.91	0.78	0.76	0.77	0.89	0.78	0.76	0.77	0.89
	10^{-4}	0.66	0.64	0.62	3.00	0.55	0.53	0.54	0.72	0.55	0.53	0.54	0.72
2000	10^{-2}	0.97	0.97	0.96	2.13	0.91	0.91	0.91	0.96	0.98	0.97	0.97	0.99
	10^{-3}	0.91	0.89	0.89	2.94	0.73	0.72	0.72	0.84	0.89	0.89	0.89	0.94
	10^{-4}	0.84	0.82	0.82	3.64	0.49	0.48	0.49	0.65	0.73	0.72	0.72	0.84
4000	10^{-2}	0.99	0.99	0.99	1.61	0.90	0.90	0.90	0.94	0.98	0.98	0.98	0.99
	10^{-3}	0.95	0.95	0.94	2.06	0.71	0.70	0.70	0.80	0.92	0.91	0.92	0.95
	10^{-4}	0.91	0.93	0.91	2.62	0.47	0.47	0.47	0.59	0.78	0.78	0.78	0.86

[a] divided by α

Table S5. Type I Error[a] and Power of Asymptotic Methods With Different Weight Functions Under $p_j = 0.0025$ $(j = 1, \cdots, 20)$

		$H_0: \beta_j = 0$				$H_1: \beta_j = x$				$H_1: \beta_j = x/\{p_j(1-p_j)\}^{1/2}$			
n	α	C	F_p	$T_{\max}$	F_u	C	F_p	$T_{\max}$	F_u	C	F_p	$T_{\max}$	F_u
500	10^{-2}	0.94	0.94	0.93	3.52	0.72	0.70	0.71	0.91	0.93	0.92	0.92	0.99
	10^{-3}	0.82	0.81	0.80	4.68	0.43	0.41	0.42	0.72	0.76	0.73	0.75	0.92
	10^{-4}	0.65	0.65	0.62	5.11	0.20	0.19	0.20	0.46	0.51	0.49	0.50	0.78
1000	10^{-2}	0.97	0.97	0.97	4.13	0.76	0.75	0.76	0.92	0.76	0.75	0.76	0.92
	10^{-3}	0.93	0.92	0.90	6.92	0.49	0.47	0.48	0.76	0.49	0.47	0.48	0.76
	10^{-4}	0.79	0.80	0.77	10.09	0.25	0.24	0.25	0.53	0.26	0.24	0.25	0.53
2000	10^{-2}	0.99	0.99	0.99	3.30	0.90	0.89	0.89	0.97	0.68	0.67	0.67	0.85
	10^{-3}	0.96	0.95	0.95	5.60	0.70	0.69	0.70	0.87	0.39	0.38	0.39	0.63
	10^{-4}	0.86	0.88	0.85	8.94	0.46	0.45	0.46	0.70	0.19	0.18	0.18	0.40
4000	10^{-2}	0.99	0.99	0.99	2.17	0.96	0.95	0.96	0.98	0.96	0.95	0.95	0.98
	10^{-3}	0.98	0.98	0.98	3.17	0.84	0.83	0.83	0.92	0.84	0.83	0.83	0.92
	10^{-4}	0.98	1.00	1.00	4.54	0.64	0.64	0.64	0.79	0.65	0.64	0.64	0.79

[a] divided by α

Table S6. Type I Error[a] of Score, Wald and LR Tests With Covariates

		$p_j = 0.001j\ (j = 1, \cdots, 10)$						$p_j = 0.0005j\ (j = 1, \cdots, 10)$					
		Score		Wald		LR		Score		Wald		LR	
n	α	C	F_p	C	F_p	C	F_p	C	F_p	C	F_p	C	F_p
500	10^{-2}	0.98	0.97	0.84	0.79	1.05	1.06	0.94	0.92	0.65	0.59	1.09	1.10
	10^{-3}	0.90	0.85	0.59	0.49	1.08	1.09	0.81	0.76	0.26	0.20	1.15	1.17
	10^{-4}	0.78	0.70	0.31	0.23	1.08	1.09	0.67	0.58	0.08	0.04	1.27	1.27
1000	10^{-2}	0.99	0.98	0.92	0.88	1.03	1.03	0.97	0.96	0.84	0.79	1.04	1.05
	10^{-3}	0.95	0.92	0.78	0.69	1.03	1.04	0.90	0.86	0.59	0.49	1.07	1.07
	10^{-4}	0.90	0.84	0.61	0.50	1.04	1.06	0.80	0.78	0.36	0.26	1.11	1.13

[a] divided by α

Table S7. Power of Score, Wald and LR Tests With Covariates Under $H_1 : \beta_j = x$ $(j = 1, \ldots, 10)$

		$p_j = 0.001j\ (j = 1, \cdots, 10)$						$p_j = 0.0005j\ (j = 1, \cdots, 10)$					
		Score		Wald		LR		Score		Wald		LR	
n	α	C	F_p	C	F_p	C	F_p	C	F_p	C	F_p	C	F_p
500	10^{-2}	0.68	0.63	0.66	0.61	0.69	0.66	0.60	0.56	0.56	0.52	0.63	0.60
	10^{-3}	0.38	0.33	0.34	0.29	0.41	0.38	0.28	0.25	0.21	0.17	0.34	0.32
	10^{-4}	0.16	0.13	0.13	0.09	0.20	0.18	0.10	0.08	0.04	0.02	0.15	0.14
1000	10^{-2}	0.74	0.69	0.73	0.68	0.75	0.71	0.73	0.69	0.72	0.67	0.75	0.72
	10^{-3}	0.45	0.40	0.44	0.38	0.48	0.43	0.44	0.39	0.40	0.35	0.48	0.44
	10^{-4}	0.22	0.18	0.20	0.16	0.25	0.22	0.20	0.17	0.16	0.12	0.25	0.22

Table S8. Power of Score, Wald and LR Tests With Covariates Under $H_1 : \beta_j = x/\{p_j(1-p_j)\}^{1/2}$ $(j = 1, \ldots, 10)$

		$p_j = 0.001j$ $(j = 1, \cdots, 10)$						$p_j = 0.0005j$ $(j = 1, \cdots, 10)$					
		Score		Wald		LR		Score		Wald		LR	
n	α	C	F_p	C	F_p	C	F_p	C	F_p	C	F_p	C	F_p
500	10^{-2}	0.66	0.68	0.64	0.66	0.67	0.71	0.72	0.73	0.69	0.69	0.74	0.76
	10^{-3}	0.35	0.38	0.32	0.33	0.39	0.42	0.40	0.41	0.32	0.31	0.46	0.48
	10^{-4}	0.15	0.16	0.11	0.11	0.19	0.21	0.17	0.17	0.08	0.06	0.24	0.25
1000	10^{-2}	0.83	0.86	0.82	0.85	0.84	0.87	0.88	0.90	0.87	0.89	0.89	0.91
	10^{-3}	0.58	0.62	0.56	0.60	0.60	0.65	0.65	0.68	0.62	0.64	0.68	0.72
	10^{-4}	0.33	0.36	0.30	0.33	0.36	0.41	0.39	0.41	0.33	0.34	0.44	0.48