Comments on "Making the Most of Case-Mother/Control-Mother Studies"

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Case-parent Triad Designs

Genotypes of a case and both of his or her parents are available, which enables the investigator to differentiate fetal genetic effects from maternally mediated genetic effects and detect genomic imprinting.

Pros:

- Offer robustness against a potential source of bias called "genetic population stratification".
- No need to recruit population contorls

Cons:

- Fathers may be hard to recruit.
- The case-parent triad design does not permit estimation of main effects of exposures.

Case-Mother/Control-Mother Desgins

Comparing randomly sampled mother-offspring pairs in which the offspring is healthy (control-mother pairs) with mother-offspring pairs in which the offspring has the condition under study (case-mother pairs).

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Idea: Control-mother pairs would help to estimate the mating frequencies, while case-mother pairs would provide information about the risk due to fetal genetic effect and maternal effect.

Familial Genotype Combinations

Mother's genotype×Father's genotype	M,F,C	M,F,C Frequencies	Penatrance$\|M,F,C$
$NN \times NN$	000	μ_{00}	p
$NN \times SN$	010	$(1/2)\mu_{01}$	p
	011	$(1/2)\mu_{01}$	pR_1
$NN \times SS$	021	μ_{02}	pR_1
$SN \times NN$	100	$(1/2)\mu_{10}$	pS_1
	101	$(1/2)\mu_{10}$	pR_1S_1
$SN \times SN$	110	$(1/4)\mu_{11}$	pS_1
	111	$(1/2)\mu_{11}$	pR_1S_1
	112	$(1/4)\mu_{11}$	pR_2S_1
$SN \times SS$	121	$(1/2)\mu_{12}$	pR_1S_1
	122	$(1/2)\mu_{12}$	pR_2S_1
$SS \times NN$	201	μ_{20}	pR_1S_2
$SS \times SN$	211	$(1/2)\mu_{21}$	pR_1S_2
	212	$(1/2)\mu_{21}$	pR_2S_2
$SS \times SS$	222	μ_{22}	pR_2S_2

- Mother and father's genotype: S stands for the disease susceptibility allele, N stands for the normal allele.
- M,F,C: M, F and C denote the number of disease susceptibility alleles carried by mother, father and child, each of which can take a value among 0, 1 or 2.
- μ_{mf} is the mating frequency of the parents with genotypes $M = m$ and $F = f$.
- R_c is the relative risk due to the child carrying c copies of the disease susceptibility alleles; S_m is the relative risk due to the mother carrying m copies of the disease susceptibility alleles.

Case-Parent Triads $\longrightarrow$ Case-Mother/Control-Mother Pairs

Mother's genotype×Father's genotype	M,F,C	M,F,C Frequencies	Penatrance$\mid M,F,C$
$NN \times NN$	000	μ_{00}	p
$NN \times SN$	010	$(1/2)\mu_{01}$	p
	011	$(1/2)\mu_{01}$	pR_1
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$SS \times SS$	222	μ_{22}	pR_2S_2

Table: Expected frequencies of case-mother pairs

	$C = 0$	$C = 1$	$C = 2$
$M = 0$	$B[\mu_{00} + (1/2)\mu_{01}]$	$BR_1[(1/2)\mu_{01} + \mu_{02}]$	0
$M = 1$	$BS_1[(1/2)\mu_{10} + (1/4)\mu_{11}]$	$BR_1S_1(1/2)[\mu_{10} + \mu_{11} + \mu_{12}]$	$BR_2S_1[(1/4)\mu_{11} + (1/2)\mu_{12}]$
$M = 2$	0	$BR_1S_2[\mu_{20} + (1/2)\mu_{21}]$	$BR_2S_2[\mu_{22} + (1/2)\mu_{21}]$

Case-Parent Triads → Case-Mother/Control-Mother Pairs

Mother's genotype×Father's genotype	M,F,C	M,F,C Frequencies	Penatrance$\|M,F,C$
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$SS \times SS$	222	μ_{22}	pR_2S_2

Table: Expected frequencies of control-mother pairs

	$C=0$	$C=1$	$C=2$
$M=0$	$B'(1-p)[\mu_{00}+(1/2)\mu_{01}]$	$B'(1-pR_1)[(1/2)\mu_{01}+\mu_{02}]$	0
$M=1$	$B'(1-pS_1)[(1/2)\mu_{10}+(1/4)\mu_{11}]$	$B'(1-pR_1S_1)(1/2)[\mu_{10}+\mu_{11}+\mu_{12}]$	$B'(1-pR_2S_1)[(1/4)\mu_{11}+(1/2)\mu_{12}]$
$M=2$	0	$B'(1-pR_1S_2)[\mu_{20}+(1/2)\mu_{21}]$	$B'(1-pR_2S_2)[\mu_{22}+(1/2)\mu_{21}]$

Case-Parent Triads → Case-Mother/Control-Mother Pairs

Mother's genotype×Father's genotype	M,F,C	M,F,C Frequencies	Penatrance$\|M,F,C$
$NN \times NN$	000	μ_{00}	p
$NN \times SN$	010	$(1/2)\mu_{01}$	p
	011	$(1/2)\mu_{01}$	pR_1
$NN \times SS$	021	μ_{02}	pR_1
$SN \times NN$	100	$(1/2)\mu_{10}$	pS_1
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$SS \times SS$	222	μ_{22}	pR_2S_2

Table: Approximate expected frequencies of control-mother pairs when prevalence is small (Table 1 in the paper)

	$C = 0$	$C = 1$	$C = 2$
$M = 0$	$\mu_{00} + (1/2)\mu_{01}$	$(1/2)\mu_{01} + \mu_{02}$	0
$M = 1$	$(1/2)\mu_{10} + (1/4)\mu_{11}$	$(1/2)[\mu_{10} + \mu_{11} + \mu_{12}]$	$(1/4)\mu_{11} + (1/2)\mu_{12}$
$M = 2$	0	$\mu_{20} + (1/2)\mu_{21}$	$\mu_{22} + (1/2)\mu_{21}$

Logistic and Log-linear Regression

	$C=0$	$C=1$	$C=2$
$M=0$	$B[\mu_{00}+(1/2)\mu_{01}]$	$BR_1[(1/2)\mu_{01}+\mu_{02}]$	0
$M=1$	$BS_1[(1/2)\mu_{10}+(1/4)\mu_{11}]$	$BR_1S_1(1/2)[\mu_{10}+\mu_{11}+\mu_{12}]$	$BR_2S_1[(1/4)\mu_{11}+(1/2)\mu_{12}]$
$M=2$	0	$BR_1S_2[\mu_{20}+(1/2)\mu_{21}]$	$BR_2S_2[\mu_{22}+(1/2)\mu_{21}]$

	$C=0$	$C=1$	$C=2$
$M=0$	$\mu_{00}+(1/2)\mu_{01}$	$(1/2)\mu_{01}+\mu_{02}$	0
$M=1$	$(1/2)\mu_{10}+(1/4)\mu_{11}$	$(1/2)[\mu_{10}+\mu_{11}+\mu_{12}]$	$(1/4)\mu_{11}+(1/2)\mu_{12}$
$M=2$	0	$\mu_{20}+(1/2)\mu_{21}$	$\mu_{22}+(1/2)\mu_{21}$

Logistic Regression: Model 7 counts N_{mc1} out of the $N_{mc}=N_{mc0}+N_{mc1}$

$$\log\frac{E(N_{mc1})}{E(N_{mc0})}=\log\frac{Pr(M,C|D=1)\times N}{Pr(M,C|D=0)\times N}=\log\frac{Pr(D=1|M,C)P(M,C)/P(D=1)}{Pr(D=0|M,C)P(M,C)/P(D=0)}$$

$$=\log[\frac{Pr(D=1|M,C)}{1-Pr(D=1|M,C)}\cdot\frac{P(D=0)}{P(D=1)}]$$

$$=\mu+\beta_1 I_{(c=1)}+\beta_2 I_{(c=2)}+\gamma_1 I_{(m=1)}+\gamma_2 I_{(m=2)}$$

Log-linear Regression: Model 14 counts N_{mc0} and N_{mc1}.

$$\log[E(N_{mcd})]=\theta_{mc}+d\times[\delta+\beta_1 I_{(c=1)}+\beta_2 I_{(c=2)}+\gamma_1 I_{(m=1)}+\gamma_2 I_{(m=2)}]$$

$$\beta_1=\log(R_1),\beta_2=\log(R_2),\gamma_1=\log(S_1),\gamma_2=\log(S_2)$$

Three Constraints

Table: Approximate expected frequencies of control-mother pairs when prevalence is small (Table 1 in the paper)

	$C = 0$	$C = 1$	$C = 2$
$M = 0$	$\mu_{00} + (1/2)\mu_{01}$	$(1/2)\mu_{01} + \mu_{02}$	0
$M = 1$	$(1/2)\mu_{10} + (1/4)\mu_{11}$	$(1/2)[\mu_{10} + \mu_{11} + \mu_{12}]$	$(1/4)\mu_{11} + (1/2)\mu_{12}$
$M = 2$	0	$\mu_{20} + (1/2)\mu_{21}$	$\mu_{22} + (1/2)\mu_{21}$

- **Mendelian inheritance:**

$$N_{(M=1,C=1,d=0)} = N_{(M=1,C=0,d=0)} + N_{(M=1,C=2,d=0)}$$

- **Mating symmetry:** $\mu_{mf} = \mu_{fm}$

$$N_{(M=1,C=0,d=0)} - N_{(M=0,C=1,d=0)} = N_{(M=1,C=2,d=0)} - N_{(M=2,C=1,d=0)}$$

- **Allaelic exchangeability:** $\mu_{11} = 4\mu_{02} = 4\mu_{20}$

$$N_{(M=1,C=0,d=0)} - N_{(M=0,C=1,d=0)} = N_{(M=1,C=2,d=0)} - N_{(M=2,C=1,d=0)} = 0$$

Simulation

- Fix prevalence at 5% 15%
- 4 risk settings, same as in the paper

R_1	R_2	S_1	S_2	
1	1	1	1	(Null)
2	3	1	1	(There is fetal genetic effect (smaller), but no maternal effect)
1	3	1	1	(There is fetal genetic effect (larger), but no maternal effect)
1	3	2	2	(There are both fetal genetic and maternal effects)

- 9 disease allele frequencies 0.1 to 0.9 by 0.1
- Constraints satisfied (generate a population in HWE) and constraints not satisfied (disturb the HWE by introducing inbreeding factor)

Power

Constraints are not satisfied, prevalence=0.05

Logistic Regression

p	setting_1	setting_2	setting_3	setting_4
0.1	0.061	0.665	0.174	0.798
0.2	0.053	0.803	0.488	0.983
0.3	0.050	0.822	0.814	0.999
0.4	0.063	0.819	0.939	1.000
0.5	0.047	0.771	0.981	1.000
0.6	0.063	0.688	0.984	1.000
0.7	0.053	0.521	0.984	0.997
0.8	0.056	0.383	0.937	0.991
0.9	0.061	0.196	0.700	0.838

Log-linear Regression

p	setting_1	setting_2	setting_3	setting_4
0.1	0.351	0.117	0.000	0.000
0.2	0.449	0.978	0.415	0.956
0.3	0.489	0.980	0.722	0.993
0.4	0.507	0.981	0.902	0.997
0.5	0.520	0.977	0.962	1.000
0.6	0.507	0.942	0.986	0.999
0.7	0.510	0.846	0.980	0.991
0.8	0.440	0.701	0.940	0.979
0.9	0.363	0.379	0.741	0.792

Power

Constraints are not satisfied, prevalence=0.05

Log-linear Regression without Constraint

p	setting_1	setting_2	setting_3	setting_4
0.1	0.060	0.660	0.174	0.794
0.2	0.053	0.803	0.488	0.983
0.3	0.050	0.822	0.814	0.999
0.4	0.063	0.819	0.939	1.000
0.5	0.047	0.771	0.981	1.000
0.6	0.063	0.688	0.984	1.000
0.7	0.053	0.521	0.984	0.997
0.8	0.056	0.383	0.936	0.979
0.9	0.056	0.187	0.642	0.767

Bias: Logistic Regression(Prevalence=0.05)

p	setting	bias_R1	bias_R2	bias_S1	bias_S2
0.1	1	0.51%	−4.68%	−0.95%	0.59%
0.1	2	4.73%	17.91%	1.57%	3.76%
0.1	3	1.33%	34.68%	−0.91%	0.45%
0.1	4	−1.64%	42.62%	6.30%	8.04%
0.2	1	−2.01%	−4.42%	1.71%	−0.56%
0.2	2	4.01%	12.15%	2.33%	2.48%
0.2	3	1.38%	17.25%	−1.86%	−0.42%
0.2	4	−2.62%	21.35%	4.46%	6.79%
0.3	1	−0.07%	−3.08%	1.66%	2.08%
0.3	2	2.21%	7.50%	2.23%	2.63%
0.3	3	2.11%	10.44%	−2.30%	−1.45%
0.3	4	−1.29%	15.08%	2.36%	2.40%
0.4	1	−0.20%	−1.81%	1.22%	1.99%
0.4	2	1.51%	5.14%	−0.42%	2.53%
0.4	3	−0.97%	5.50%	−0.16%	2.10%
0.4	4	0.32%	15.60%	2.67%	4.68%
0.5	1	0.77%	2.48%	−0.73%	−1.16%
0.5	2	3.94%	6.94%	−0.25%	2.09%
0.5	3	−0.28%	7.35%	−3.31%	−1.20%
0.5	4	1.75%	11.89%	5.91%	4.64%
0.6	1	2.52%	1.85%	0.53%	−1.95%
0.6	2	5.49%	11.28%	−1.29%	−3.27%
0.6	3	2.34%	7.17%	0.22%	0.05%
0.6	4	−2.30%	8.15%	6.04%	5.17%
0.7	1	−0.15%	−0.86%	−3.34%	−2.07%
0.7	2	1.57%	2.65%	0.53%	1.68%
0.7	3	2.23%	7.49%	1.24%	2.81%
0.7	4	1.07%	10.20%	5.18%	2.90%
0.8	1	−2.81%	−3.33%	−0.81%	−1.59%
0.8	2	8.68%	7.92%	−2.81%	0.39%
0.8	3	5.65%	5.61%	6.63%	5.40%
0.8	4	0.46%	7.25%	8.13%	7.70%
0.9	1	13.76%	15.13%	−0.48%	−1.50%
0.9	2	−10.31%	4.78%	7.83%	4.05%
0.9	3	7.00%	16.40%	1.76%	2.88%
0.9	4	8.00%	11.33%	26.74%	25.29%

Bias: Log-linear Regression(Prevalence=0.05)

p	setting	bias_R1	bias_R2	bias_S1	bias_S2
0.1	1	19.89%	−63.53%	−18.40%	51.12%
0.1	2	23.54%	−55.31%	−16.45%	58.63%
0.1	3	20.02%	−55.07%	−19.15%	63.35%
0.1	4	20.39%	−52.90%	−18.19%	75.52%
0.2	1	21.03%	−37.10%	−20.70%	30.40%
0.2	2	24.74%	−31.95%	−19.64%	39.11%
0.2	3	23.25%	−30.97%	−21.57%	36.40%
0.2	4	19.72%	−29.45%	−19.24%	47.50%
0.3	1	23.50%	−20.63%	−21.37%	18.53%
0.3	2	26.21%	−18.35%	−21.23%	24.04%
0.3	3	23.00%	−18.12%	−24.02%	20.74%
0.3	4	27.03%	−15.25%	−23.51%	27.81%
0.4	1	28.23%	−9.27%	−24.28%	9.41%
0.4	2	31.34%	−7.38%	−24.32%	13.07%
0.4	3	25.56%	−8.92%	−24.92%	11.56%
0.4	4	32.60%	−2.94%	−24.98%	18.06%
0.5	1	34.16%	0.71%	−27.57%	−0.59%
0.5	2	38.84%	5.05%	−26.83%	3.49%
0.5	3	34.59%	5.92%	−28.22%	1.59%
0.5	4	38.13%	8.39%	−26.17%	6.12%
0.6	1	43.42%	10.23%	−30.02%	−8.59%
0.6	2	47.51%	18.06%	−30.07%	−6.02%
0.6	3	45.27%	16.54%	−31.40%	−5.73%
0.6	4	45.03%	19.46%	−29.38%	0.38%
0.7	1	58.06%	28.44%	−36.95%	−18.28%
0.7	2	54.67%	26.84%	−33.73%	−13.11%
0.7	3	62.09%	31.24%	−34.84%	−13.55%
0.7	4	64.70%	38.96%	−32.56%	−9.51%
0.8	1	80.66%	48.38%	−40.74%	−24.36%
0.8	2	96.14%	64.31%	−38.37%	−21.84%
0.8	3	97.06%	64.01%	−36.51%	−19.88%
0.8	4	104.41%	72.37%	−35.54%	−15.80%
0.9	1	227.58%	169.92%	−47.39%	−34.08%
0.9	2	39660.3%	34062.1%	−39.65%	−28.37%
0.9	3	38918.5%	33625.5%	−44.00%	−30.73%
0.9	4	47980.2%	44125.8%	−34.55%	−19.45%

Bias: LL without Constraint(Prevalence=0.05)

p	setting	bias_R1	bias_R2	bias_S1	bias_S2
0.1	1	0.51%	−17.83%	−0.96%	0.65%
0.1	2	4.72%	17.91%	1.56%	3.73%
0.1	3	1.32%	34.68%	−0.88%	0.47%
0.1	4	−1.65%	42.57%	6.30%	8.13%
0.2	1	−2.02%	−4.40%	1.71%	−0.55%
0.2	2	4.01%	12.19%	2.33%	2.46%
0.2	3	1.38%	17.27%	−1.85%	−0.44%
0.2	4	−2.62%	21.35%	4.45%	6.76%
0.3	1	−0.07%	−3.09%	1.66%	2.09%
0.3	2	2.22%	7.49%	2.23%	2.63%
0.3	3	2.11%	10.44%	−2.31%	−1.46%
0.3	4	−1.29%	15.06%	2.37%	2.41%
0.4	1	−0.21%	−1.82%	1.22%	1.99%
0.4	2	1.52%	5.13%	−0.42%	2.54%
0.4	3	−0.97%	5.52%	−0.14%	2.10%
0.4	4	0.32%	15.58%	2.67%	4.69%
0.5	1	0.76%	2.48%	−0.72%	−1.16%
0.5	2	3.95%	6.94%	−0.26%	2.09%
0.5	3	−0.28%	7.34%	−3.32%	−1.18%
0.5	4	1.74%	11.90%	5.92%	4.65%
0.6	1	2.52%	1.85%	0.52%	−1.96%
0.6	2	5.50%	11.30%	−1.28%	−3.28%
0.6	3	2.36%	7.19%	0.21%	0.04%
0.6	4	−2.30%	8.14%	6.00%	5.15%
0.7	1	−0.16%	−0.82%	−3.30%	−2.09%
0.7	2	1.60%	2.65%	0.52%	1.68%
0.7	3	2.23%	7.44%	1.22%	2.84%
0.7	4	1.07%	10.18%	5.18%	2.87%
0.8	1	−2.81%	−3.32%	−0.77%	−1.62%
0.8	2	8.53%	7.88%	−2.79%	0.42%
0.8	3	6.38%	5.78%	6.61%	5.39%
0.8	4	0.92%	7.17%	7.99%	7.42%
0.9	1	17.21%	20.52%	−0.49%	−1.54%
0.9	2	185.50%	168.99%	7.72%	3.77%
0.9	3	221.32%	237.52%	1.78%	2.92%
0.9	4	142.67%	164.84%	26.78%	25.64%

Power

Constraints are not satisfied, prevalence=0.15

Logistic Regression

p	setting_1	setting_2	setting_3	setting_4
0.1	0.061	0.759	0.217	0.935
0.2	0.053	0.884	0.597	0.998
0.3	0.050	0.894	0.883	1.000
0.4	0.063	0.888	0.967	1.000
0.5	0.047	0.824	0.988	1.000
0.6	0.063	0.746	0.991	1.000
0.7	0.053	0.584	0.992	1.000
0.8	0.056	0.428	0.964	0.997
0.9	0.061	0.228	0.763	0.916

Log-linear Regression

p	setting_1	setting_2	setting_3	setting_4
0.1	0.351	0.944	0.208	0.859
0.2	0.449	0.987	0.470	0.986
0.3	0.489	0.986	0.785	0.999
0.4	0.507	0.987	0.936	1.000
0.5	0.520	0.986	0.983	1.000
0.6	0.507	0.948	0.988	1.000
0.7	0.510	0.873	0.985	0.999
0.8	0.440	0.722	0.959	0.992
0.9	0.363	0.418	0.782	0.843

Power

Constraints are not satisfied, prevalence=0.15

Log-linear Regression without Constraint

p	setting_1	setting_2	setting_3	setting_4
0.1	0.060	0.758	0.216	0.935
0.2	0.053	0.884	0.597	0.998
0.3	0.050	0.894	0.883	1.000
0.4	0.063	0.888	0.967	1.000
0.5	0.047	0.824	0.988	1.000
0.6	0.063	0.746	0.991	1.000
0.7	0.053	0.584	0.992	1.000
0.8	0.056	0.428	0.964	0.991
0.9	0.056	0.215	0.698	0.841

Bias: Logistic Regression(Prevalence=0.15)

p	setting	bias_R1	bias_R2	bias_S1	bias_S2
0.1	1	0.51%	−4.68%	−0.95%	0.59%
0.1	2	18.98%	51.13%	1.17%	0.23%
0.1	3	0.50%	77.22%	−2.25%	2.35%
0.1	4	−0.87%	2.221E9%	19.38%	23.67%
0.2	1	−2.01%	−4.42%	1.71%	−0.56%
0.2	2	13.30%	34.59%	2.17%	4.02%
0.2	3	1.50%	43.06%	−0.57%	−2.42%
0.2	4	−3.41%	117.11%	13.87%	15.69%
0.3	1	−0.07%	−3.08%	1.66%	2.08%
0.3	2	8.52%	25.47%	1.82%	2.71%
0.3	3	1.82%	29.12%	−1.95%	−1.45%
0.3	4	−1.14%	69.94%	9.06%	11.36%
0.4	1	−0.20%	−1.81%	1.22%	1.99%
0.4	2	7.12%	18.78%	−0.16%	1.90%
0.4	3	−0.59%	17.44%	−0.23%	0.70%
0.4	4	−0.38%	54.51%	9.02%	10.05%
0.5	1	0.77%	2.48%	−0.73%	−1.16%
0.5	2	9.22%	17.57%	−0.30%	2.06%
0.5	3	0.19%	18.16%	−3.40%	−0.76%
0.5	4	1.15%	38.40%	10.67%	8.82%
0.6	1	2.52%	1.85%	0.53%	−1.95%
0.6	2	8.64%	16.89%	−1.39%	−2.64%
0.6	3	−1.05%	13.11%	−2.63%	0.16%
0.6	4	−2.36%	29.44%	8.71%	8.07%
0.7	1	−0.15%	−0.86%	−3.34%	−2.07%
0.7	2	3.98%	9.82%	0.06%	1.44%
0.7	3	2.11%	14.56%	1.25%	3.80%
0.7	4	0.04%	26.17%	7.96%	6.63%
0.8	1	−2.81%	−3.33%	−0.81%	−1.59%
0.8	2	12.86%	16.92%	−3.29%	1.29%
0.8	3	6.44%	10.76%	6.20%	4.21%
0.8	4	−1.56%	22.20%	10.58%	11.24%
0.9	1	13.76%	15.13%	−0.48%	−1.50%
0.9	2	14.11%	20.88%	4.37%	5.26%
0.9	3	41.44%	66.56%	8.62%	4.61%
0.9	4	19.76%	39.11%	29.41%	25.57%

Bias: Log-linear Regression(Prevalence=0.15)

p	setting	bias_R1	bias_R2	bias_S1	bias_S2
0.1	1	19.89%	−63.53%	−18.40%	51.12%
0.1	2	32.40%	−53.45%	−11.37%	68.63%
0.1	3	18.42%	−53.87%	−20.78%	75.38%
0.1	4	26.26%	−40.56%	−13.94%	113.91%
0.2	1	21.03%	−37.10%	−20.70%	30.40%
0.2	2	30.68%	−26.45%	−16.38%	49.58%
0.2	3	23.21%	−26.44%	−21.80%	45.81%
0.2	4	23.68%	−12.39%	−16.75%	83.74%
0.3	1	23.50%	−20.63%	−21.37%	18.53%
0.3	2	31.43%	−12.33%	−18.91%	31.38%
0.3	3	22.36%	−13.65%	−24.50%	28.63%
0.3	4	29.38%	1.40%	−21.55%	52.24%
0.4	1	28.23%	−9.27%	−24.28%	9.41%
0.4	2	34.76%	−2.06%	−22.23%	18.28%
0.4	3	24.92%	−4.18%	−25.52%	17.36%
0.4	4	34.80%	12.39%	−23.64%	37.34%
0.5	1	34.16%	0.71%	−27.57%	−0.59%
0.5	2	41.56%	9.77%	−25.00%	7.62%
0.5	3	34.00%	10.40%	−28.74%	6.53%
0.5	4	39.93%	21.51%	−25.30%	19.47%
0.6	1	43.42%	10.23%	−30.02%	−8.59%
0.6	2	50.61%	21.55%	−29.14%	−3.67%
0.6	3	41.10%	19.72%	−32.06%	−4.16%
0.6	4	45.77%	29.84%	−28.80%	10.63%
0.7	1	58.06%	28.44%	−36.95%	−18.28%
0.7	2	58.80%	30.60%	−33.47%	−11.49%
0.7	3	61.30%	35.21%	−34.69%	−11.18%
0.7	4	64.42%	48.87%	−32.34%	−4.43%
0.8	1	80.66%	48.38%	−40.74%	−24.36%
0.8	2	97.90%	67.49%	−38.11%	−21.12%
0.8	3	96.52%	68.21%	−37.22%	−17.10%
0.8	4	102.97%	83.75%	−35.18%	−10.45%
0.9	1	227.58%	169.92%	−47.39%	−34.08%
0.9	2	39176.9%	32108.0%	−42.27%	−26.62%
0.9	3	39202.1%	36477.0%	−41.54%	−27.79%
0.9	4	42801.4%	43650.8%	−33.49%	−13.71%

Bias: LL without Constraint(Prevalence=0.15)

p	setting	bias_R1	bias_R2	bias_S1	bias_S2
0.1	1	0.51%	−17.83%	−0.96%	0.65%
0.1	2	18.97%	50.07%	1.18%	0.22%
0.1	3	0.50%	77.20%	−2.24%	2.42%
0.1	4	−0.86%	141567%	19.38%	23.63%
0.2	1	−2.02%	−4.40%	1.71%	−0.55%
0.2	2	13.30%	34.54%	2.17%	4.03%
0.2	3	1.51%	43.07%	−0.57%	−2.41%
0.2	4	−3.42%	116.97%	13.87%	15.69%
0.3	1	−0.07%	−3.09%	1.66%	2.09%
0.3	2	8.52%	25.48%	1.80%	2.72%
0.3	3	1.82%	29.11%	−1.97%	−1.45%
0.3	4	−1.16%	69.96%	9.07%	11.34%
0.4	1	−0.21%	−1.82%	1.22%	1.99%
0.4	2	7.12%	18.76%	−0.16%	1.89%
0.4	3	−0.61%	17.43%	−0.23%	0.69%
0.4	4	−0.39%	54.52%	9.02%	10.03%
0.5	1	0.76%	2.48%	−0.72%	−1.16%
0.5	2	9.24%	17.57%	−0.28%	2.04%
0.5	3	0.20%	18.16%	−3.41%	−0.75%
0.5	4	1.15%	38.39%	10.67%	8.81%
0.6	1	2.52%	1.85%	0.52%	−1.96%
0.6	2	8.66%	16.89%	−1.40%	−2.63%
0.6	3	−1.03%	13.06%	−2.63%	0.15%
0.6	4	−2.36%	29.42%	8.67%	8.08%
0.7	1	−0.16%	−0.82%	−3.30%	−2.09%
0.7	2	3.96%	9.83%	0.09%	1.45%
0.7	3	2.13%	14.58%	1.26%	3.79%
0.7	4	0.01%	26.16%	7.93%	6.60%
0.8	1	−2.81%	−3.32%	−0.77%	−1.62%
0.8	2	12.90%	16.85%	−3.31%	1.25%
0.8	3	7.02%	10.82%	6.19%	4.22%
0.8	4	−1.49%	22.44%	10.60%	11.06%
0.9	1	17.21%	20.52%	−0.49%	−1.54%
0.9	2	201.19%	192.46%	4.46%	5.00%
0.9	3	256.76%	357.00%	8.70%	4.81%
0.9	4	145.86%	206.29%	29.54%	25.43%

Conclusion

- In the paper "Making the Most of Case-Mother/Control-Mother Studies", the authors compared the approximated power of the likelihood ratio test of $H_0 : R_1 = R_2 = S_1 = S_2 = 1$ vs. H_a : At least one of the 4 parameters is not 1, when the 3 constraints are satisfied.
- They conclude that the log-linear model outperforms the logistic model in terms of the power and the flexibility to accomodate the 3 constraints.
- We'd rather advocate to use the logistic model for case-mother/control-mother studies, since the logistic model has the robustness to the invalidation of the mating symmetry assumption.
- Though we get different conclusion toward the analysis plan, case-mother/control mother designs have obvious advantage over case-parent traid designs.