Analysis of Randomised Trials Including Multiple Births when Birth Size is Informative:

Additional Simulation Study Details (Yelland et al.)

Additional Simulation Results for Continuous Outcomes

In Table 1 of the main article, the average treatment effect estimates for CWGEE and GEE_{ind} are close to the true overall mother-level and infant-level treatment effects, respectively. For the linear model, these treatment effects can be determined using the equation

$$w_1\left(E\left[Y_{ij} \mid X_{1i}=1, X_{2i}=0\right]-E\left[Y_{ij} \mid X_{1i}=0, X_{2i}=0\right]\right)+w_2\left(E\left[Y_{ij} \mid X_{1i}=1, X_{2i}=1\right]-E\left[Y_{ij} \mid X_{1i}=0, X_{2i}=1\right]\right)$$

where w_1 and w_2 are weights that sum to one, $E\left[Y_{ij} \mid X_{1i}=1, X_{2i}=0\right]-E\left[Y_{ij} \mid X_{1i}=0, X_{2i}=0\right]$ is the true treatment effect for singletons (4 in this case), $E\left[Y_{ij} \mid X_{1i}=1, X_{2i}=1\right]-E\left[Y_{ij} \mid X_{1i}=0, X_{2i}=1\right]$ is the true treatment effect for twins (4, 2 or 6 in this case), and these treatment effects are expressed as differences in the mean outcome between the intervention and control groups. In other words, the true overall mother-level and infant-level treatment effects are weighted averages of the true treatment effects for singletons and twins. For mother-level treatment effects, w_1 and w_2 are the expected proportions of *mothers* with single and twin births (i.e. 0.8 and 0.2, respectively) and hence the true overall treatment effect is 4.00, 3.60 and 4.40 when the true treatment effect for twins is 4, 2 and 6, respectively. For infant-level treatment effects, w_1 and w_2 are the expected proportions of *infants* from single and twin births (i.e. 0.667 and 0.333, respectively) and hence the true overall treatment effect is 4.00, 3.33 and 4.67 when the true treatment effect for twins is 4, 2 and 6, respectively. In general, for a given multiple birth rate the difference between mother-level and infant-level treatment effects increases as the difference between treatment effects for singletons and twins increases.

To explore the relative magnitude of the differences in treatment effect estimates between methods seen in Table 1 of the main article, median percent differences in treatment effect estimates relative to GEE_{ind} (our recommended analysis approach) are presented in Table S1. When the treatment effect was the same for singletons and twins, median percent relative differences in treatment effect estimates between methods were close to zero. For scenarios where the effect of treatment differed between singletons and twins, median percent relative differences ranged from -6% to 8% for CWGEE and -5% to 7% for GEE_{exch}. The magnitude of the difference between GEE_{ind} and GEE_{exch} increased as the ICC increased.

The power to detect a treatment group by multiple birth interaction when present is shown in Table S2. The power was low (maximum 13.6%) and identical for all GEE methods.

Simulation Methods for Binary Outcomes

Binary outcomes were randomly generated with prevalence determined by the model

$$g\left(\pi_{ij}\right)=\beta_0+\beta_1 X_{1i}+\beta_2 X_{2i}+\beta_3 X_{1i} X_{2i}\,, \qquad (1)$$

where π_{ij} is the prevalence of the outcome for the jth infant from the ith mother, X_{1i} is the randomised treatment group (1=intervention, 0=control) and X_{2i} is the multiple birth status (1=multiple birth, 0=single birth). The link function g was chosen to be the logit or log link, i.e. $g\left(\pi_{ij}\right)=\log\left(\pi_{ij}/\left(1-\pi_{ij}\right)\right)$ or $g\left(\pi_{ij}\right)=\log\left(\pi_{ij}\right)$, such that model (1) was the logistic or log binomial model. This produced treatment effect estimates expressed as odds ratios or relative risks respectively, both of which are commonly reported in neonatal and perinatal trials.

For singletons, independent outcomes were generated from a binomial distribution. Both low and moderate prevalence settings were considered, where the probability of experiencing the outcome in the control group was set to 10% or 30% respectively. The former was chosen to reflect the prevalence of significant mental delay in the example dataset, as well as other outcomes of interest in many perinatal trials, such as small for gestational age. The latter was chosen to investigate potential differences between odds ratios and relative risks, since these are approximately equal for rare outcomes,[1] and the effect of varying the probability of a twin birth was studied in this setting only. The prevalence in the intervention group was chosen to produce an odds ratio (relative risk) of 0.5 when the logit (log) link function was used to generate the data.

For twins, correlated outcomes were generated from a beta-binomial distribution with parameters determined by the outcome prevalence and the ICC.[2] The prevalence in the control group was chosen to be 15% or 45% for the low and moderate prevalence settings respectively. A 50% increase in the prevalence for multiples compared with singletons is plausible based on the example dataset. The prevalence in the intervention group was chosen to produce an odds ratio (relative risk) among twins of 0.5 (to match the singletons), 0.75 or 0.25 when the logit (log) link function was used to generate the data, in order to explore the effect of ICS in the absence or presence of a treatment group by multiple birth interaction.

Parameter values for model (1) were thus set to $\beta_0=-2.197$ or -0.847, $\beta_1=-0.693$, $\beta_2=0.463$ or 0.647, and $\beta_3=0$, 0.405 or -0.693 for the logit link, and $\beta_0=-2.303$ or -1.204, $\beta_1=-0.693$, $\beta_2=0.405$ and $\beta_3=0$, 0.405 or -0.693 for the log link.

As with the continuous outcomes, the effect of treatment was estimated based on an unadjusted model $g\left(\pi_{ij}\right)=\beta_0+\beta_1X_{1i}$ and a model adjusting for the main effect of multiple birth status $g\left(\pi_{ij}\right)=\beta_0+\beta_1X_{1i}+\beta_2X_{2i}$, while model (1) was used to test for evidence of a treatment group by multiple birth interaction. Simulation results were summarised as for continuous outcomes. Additionally, odds ratios (relative risks) were estimated for data generated based on the logit (log) link function by taking the exponential of the treatment parameter (β_1) estimates. These were summarised using medians due to their skewed distribution. The median percent differences in odds ratio (relative risk) estimates relative to GEE_{ind} (our recommended analysis approach) were also calculated.

Simulation Results for Binary Outcomes

The simulation results are provided in Tables S3-S5 and Figure S1 for data generated based on the logit link, and Tables S6-S8 and Figure S2 for data generated based on the log link. The results are similar to

those for continuous outcomes, independently of both the outcome prevalence and choice of link function.

The power to detect an interaction effect when present ranged from 5-16% for the low prevalence settings and 16-54% for the moderate prevalence settings (Table S9), and all methods produced identical results for each simulated dataset when the correct interaction model (1) was fitted to the data (data not shown).

References

1. Zhang J, Yu KF. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *Journal of the American Medical Association* 1998; 280:1690-1691.
2. Austin PC. A comparison of the statistical power of different methods for the analysis of cluster randomization trials with binary outcomes. *Statistics in Medicine* 2007; 26:3550-3565.

Table S1: Median percent relative difference in treatment effect estimates for a continuous outcome with 20% twin births.

		CWGEE[b]		GEE_{exch}[b]	
Treatment Effect[a] (Singletons/Twins)	ICC	Unadjusted	Adjusted	Unadjusted	Adjusted
4/4	0.1	0.12	0.09	0.01	0.00
	0.5	0.11	0.06	0.07	0.03
	0.9	0.08	0.03	0.08	0.03
4/2	0.1	8.17	8.15	1.15	0.73
	0.5	7.98	7.94	5.12	4.93
	0.9	7.45	7.52	7.03	7.08
4/6	0.1	-5.72	-5.76	-0.59	-0.52
	0.5	-5.69	-5.65	-3.54	-3.50
	0.9	-5.73	-5.71	-5.36	-5.31

[a]True difference in mean outcome (intervention minus control) for singletons and twins.
[b]Median value of percent relative difference in treatment effect estimates compared with GEE_{ind} over 10,000 simulated datasets, calculated as $100\left(\hat{\beta}_1 - \hat{\beta}_{1ref}\right)\Big/\hat{\beta}_{1ref}$, where $\hat{\beta}_1$ is the treatment effect estimate based on CWGEE or GEE_{exch}, and $\hat{\beta}_{1ref}$ is the reference treatment effect estimate based on GEE_{ind}.

Table S2: Power to detect a treatment group by multiple birth interaction for a continuous outcome with 20% twin births.

Treatment Effect[a] (Singletons/Twins)	ICC	Power[b]
4/2	0.1	12.98
	0.5	12.33
	0.9	10.32
4/6	0.1	13.62
	0.5	11.77
	0.9	10.93

[a]True difference in mean outcome (intervention minus control) for singletons and twins.
[b]Power is the same for all methods of analysis.

Table S3: Simulation results for a binary outcome with low prevalence, 20% twin births and a logit link function.

			Unadjusted			Adjusted[e]		
Treatment Effect[a] (Singletons/Twins)	ICC	Method	Parameter Estimate[b]	Standard Error[c]	Odds Ratio[d]	Parameter Estimate[b]	Standard Error[c]	Odds Ratio[d]
0.5/0.5	0.1	CWGEE	-0.70	0.29	0.50	-0.71	0.29	0.50
		GEEind	-0.70	0.28	0.50	-0.70	0.28	0.50
		GEEexch	-0.70	0.28	0.50	-0.70	0.28	0.50
0.5/0.5	0.5	CWGEE	-0.71	0.30	0.50	-0.71	0.30	0.50
		GEEind	-0.70	0.30	0.50	-0.71	0.31	0.50
		GEEexch	-0.71	0.30	0.50	-0.71	0.30	0.49
0.5/0.5	0.9	CWGEE	-0.71	0.31	0.50	-0.71	0.31	0.50
		GEEind	-0.71	0.33	0.50	-0.71	0.33	0.50
		GEEexch	-0.71	0.31	0.50	-0.71	0.31	0.49
0.5/0.75	0.1	CWGEE	-0.57	0.28	0.57	-0.58	0.28	0.56
		GEEind	-0.51	0.27	0.61	-0.51	0.27	0.60
		GEEexch	-0.52	0.27	0.60	-0.52	0.27	0.60
0.5/0.75	0.5	CWGEE	-0.58	0.29	0.56	-0.58	0.29	0.56
		GEEind	-0.51	0.29	0.60	-0.51	0.29	0.60
		GEEexch	-0.56	0.29	0.57	-0.56	0.29	0.57
0.5/0.75	0.9	CWGEE	-0.58	0.30	0.57	-0.58	0.30	0.56
		GEEind	-0.51	0.31	0.61	-0.52	0.32	0.60
		GEEexch	-0.58	0.30	0.57	-0.58	0.30	0.56
0.5/0.25	0.1	CWGEE	-0.86	0.31	0.43	-0.86	0.31	0.43
		GEEind	-0.95	0.30	0.39	-0.96	0.31	0.39
		GEEexch	-0.94	0.30	0.40	-0.94	0.30	0.39
0.5/0.25	0.5	CWGEE	-0.86	0.32	0.43	-0.86	0.32	0.43
		GEEind	-0.96	0.32	0.39	-0.96	0.32	0.39
		GEEexch	-0.90	0.32	0.41	-0.91	0.32	0.41
0.5/0.25	0.9	CWGEE	-0.86	0.33	0.43	-0.86	0.33	0.43
		GEEind	-0.96	0.34	0.39	-0.96	0.34	0.39
		GEEexch	-0.87	0.33	0.43	-0.88	0.33	0.42

[a]True odds ratio (intervention versus control) for singletons and twins.
[b]Average treatment parameter estimate over 10,000 simulated datasets.
[c]Average estimated standard error of the treatment parameter estimate over 10,000 simulated datasets.
[d]Median odds ratio estimate over 10,000 simulated datasets.
[e]Results adjusted for multiple birth status.

Table S4: Simulation results for a binary outcome with moderate prevalence, 20% twin births and a logit link function.

			Unadjusted			Adjusted[e]		
Treatment Effect[a] (Singletons/Twins)	ICC	Method	Parameter Estimate[b]	Standard Error[c]	Odds Ratio[d]	Parameter Estimate[b]	Standard Error[c]	Odds Ratio[d]
0.5/0.5	0.1	CWGEE	-0.68	0.18	0.51	-0.69	0.18	0.50
		GEEind	-0.68	0.17	0.51	-0.69	0.18	0.50
		GEEexch	-0.68	0.17	0.51	-0.69	0.18	0.50
0.5/0.5	0.5	CWGEE	-0.69	0.18	0.50	-0.70	0.19	0.50
		GEEind	-0.68	0.19	0.51	-0.70	0.19	0.50
		GEEexch	-0.69	0.18	0.50	-0.70	0.18	0.50
0.5/0.5	0.9	CWGEE	-0.69	0.19	0.50	-0.70	0.19	0.50
		GEEind	-0.69	0.20	0.50	-0.70	0.20	0.50
		GEEexch	-0.69	0.19	0.50	-0.70	0.19	0.50
0.5/0.75	0.1	CWGEE	-0.57	0.18	0.57	-0.59	0.18	0.56
		GEEind	-0.51	0.17	0.60	-0.53	0.17	0.59
		GEEexch	-0.53	0.17	0.59	-0.54	0.17	0.59
0.5/0.75	0.5	CWGEE	-0.58	0.18	0.56	-0.59	0.18	0.55
		GEEind	-0.51	0.18	0.60	-0.53	0.19	0.59
		GEEexch	-0.56	0.18	0.57	-0.57	0.18	0.57
0.5/0.75	0.9	CWGEE	-0.58	0.19	0.56	-0.59	0.19	0.55
		GEEind	-0.51	0.19	0.60	-0.53	0.20	0.59
		GEEexch	-0.58	0.19	0.56	-0.59	0.19	0.55
0.5/0.25	0.1	CWGEE	-0.85	0.19	0.43	-0.85	0.19	0.43
		GEEind	-0.94	0.18	0.39	-0.95	0.18	0.39
		GEEexch	-0.92	0.18	0.40	-0.93	0.18	0.39
0.5/0.25	0.5	CWGEE	-0.85	0.19	0.43	-0.85	0.19	0.43
		GEEind	-0.94	0.19	0.39	-0.95	0.19	0.39
		GEEexch	-0.88	0.19	0.42	-0.89	0.19	0.41
0.5/0.25	0.9	CWGEE	-0.85	0.20	0.43	-0.85	0.20	0.43
		GEEind	-0.94	0.20	0.39	-0.95	0.21	0.39
		GEEexch	-0.85	0.20	0.43	-0.86	0.20	0.42

[a]True odds ratio (intervention versus control) for singletons and twins.
[b]Average treatment parameter estimate over 10,000 simulated datasets.
[c]Average estimated standard error of the treatment parameter estimate over 10,000 simulated datasets.
[d]Median odds ratio estimate over 10,000 simulated datasets.
[e]Results adjusted for multiple birth status.

Table S5: Median percent relative difference in odds ratio estimates for a binary outcome with 20% twin births and a logit link function.

			CWGEE[b]		GEE_{exch}[b]	
Prevalence	Treatment Effect[a] (Singletons/Twins)	ICC	Unadjusted	Adjusted	Unadjusted	Adjusted
Low	0.5/0.5	0.1	-0.04	0.05	0.00	0.00
		0.5	0.04	0.19	0.03	0.10
		0.9	-0.04	0.00	-0.04	0.00
Low	0.5/0.75	0.1	-6.40	-6.38	-0.71	-0.45
		0.5	-6.48	-6.45	-4.81	-3.86
		0.9	-6.43	-6.37	-6.39	-6.10
Low	0.5/0.25	0.1	10.21	10.29	0.82	0.70
		0.5	10.15	10.27	5.64	5.22
		0.9	10.40	10.48	9.30	9.27
Moderate	0.5/0.5	0.1	-0.39	-0.02	-0.03	0.00
		0.5	-0.40	-0.09	-0.28	-0.05
		0.9	-0.28	0.10	-0.28	0.10
Moderate	0.5/0.75	0.1	-6.08	-5.80	-1.36	-0.63
		0.5	-6.16	-5.87	-4.72	-3.68
		0.9	-6.20	-5.94	-6.20	-5.70
Moderate	0.5/0.25	0.1	9.87	10.18	1.46	1.18
		0.5	9.96	10.26	6.34	5.91
		0.9	10.13	10.40	9.74	9.41

[a]True odds ratio (intervention versus control) for singletons and twins.

[b]Median value of percent relative difference in odds ratio estimates compared with GEE_{ind} over 10,000 simulated datasets, calculated as $100\left(\hat{OR}_1 - \hat{OR}_{1ref}\right)\Big/\hat{OR}_{1ref}$, where $\hat{OR}_1$ is the odds ratio estimate based on CWGEE or GEE_{exch}, and $\hat{OR}_{1ref}$ is the reference odds ratio estimate based on GEE_{ind}.

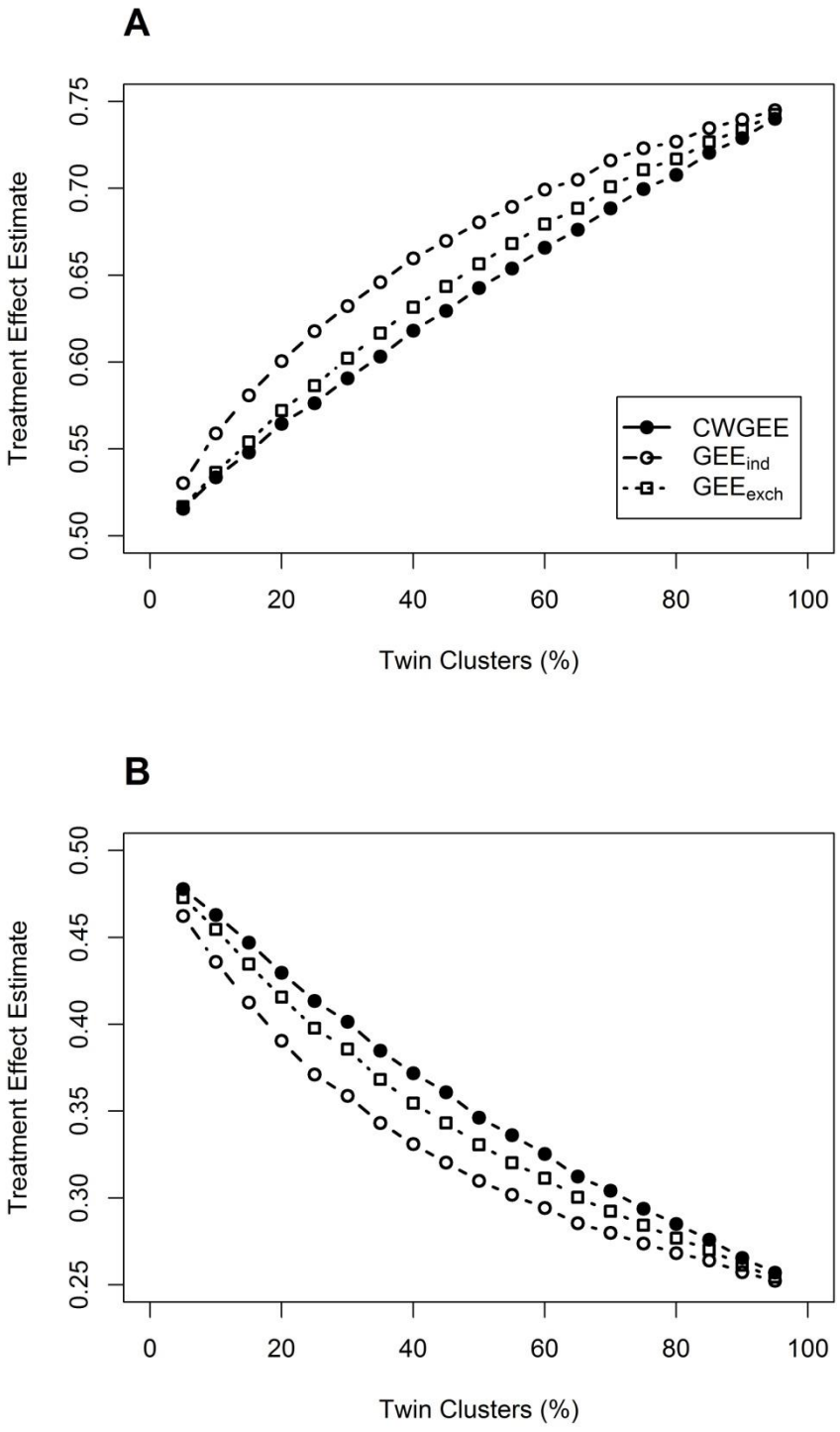

Figure S1: Median unadjusted odds ratio estimate for a binary outcome with moderate prevalence and an ICC of 0.5 by varying percentage of mothers with a twin birth when the odds ratio is 0.5 for singletons and (A) 0.75 or (B) 0.25 for twins.

Table S6: Simulation results for a binary outcome with low prevalence, 20% twin births and a log link function.

			Unadjusted			Adjusted[e]		
Treatment Effect[a] (Singletons/Twins)	ICC	Method	Parameter Estimate[b]	Standard Error[c]	Relative Risk[d]	Parameter Estimate[b]	Standard Error[c]	Relative Risk[d]
0.5/0.5	0.1	CWGEE	-0.71	0.28	0.50	-0.71	0.28	0.50
		GEEind	-0.71	0.27	0.50	-0.71	0.27	0.50
		GEEexch	-0.71	0.27	0.50	-0.71	0.27	0.50
0.5/0.5	0.5	CWGEE	-0.71	0.29	0.50	-0.71	0.28	0.50
		GEEind	-0.71	0.29	0.50	-0.71	0.29	0.50
		GEEexch	-0.71	0.28	0.50	-0.71	0.28	0.50
0.5/0.5	0.9	CWGEE	-0.71	0.30	0.50	-0.71	0.29	0.50
		GEEind	-0.71	0.31	0.50	-0.71	0.31	0.50
		GEEexch	-0.71	0.30	0.50	-0.72	0.29	0.49
0.5/0.75	0.1	CWGEE	-0.57	0.26	0.57	-0.57	0.26	0.57
		GEEind	-0.51	0.25	0.61	-0.50	0.25	0.61
		GEEexch	-0.52	0.25	0.60	-0.51	0.25	0.60
0.5/0.75	0.5	CWGEE	-0.57	0.27	0.57	-0.57	0.27	0.57
		GEEind	-0.51	0.27	0.61	-0.50	0.27	0.61
		GEEexch	-0.56	0.27	0.58	-0.55	0.27	0.58
0.5/0.75	0.9	CWGEE	-0.58	0.28	0.56	-0.58	0.28	0.57
		GEEind	-0.52	0.29	0.60	-0.51	0.29	0.61
		GEEexch	-0.58	0.28	0.57	-0.58	0.28	0.57
0.5/0.25	0.1	CWGEE	-0.86	0.30	0.43	-0.86	0.30	0.43
		GEEind	-0.95	0.29	0.39	-0.96	0.29	0.39
		GEEexch	-0.94	0.29	0.40	-0.95	0.29	0.39
0.5/0.25	0.5	CWGEE	-0.86	0.31	0.43	-0.86	0.31	0.43
		GEEind	-0.95	0.31	0.39	-0.96	0.31	0.39
		GEEexch	-0.90	0.30	0.41	-0.91	0.30	0.41
0.5/0.25	0.9	CWGEE	-0.87	0.31	0.42	-0.87	0.31	0.42
		GEEind	-0.96	0.32	0.39	-0.97	0.33	0.39
		GEEexch	-0.88	0.31	0.42	-0.89	0.31	0.42

[a]True relative risk (intervention versus control) for singletons and twins.
[b]Average treatment parameter estimate over 10,000 simulated datasets.
[c]Average estimated standard error of the treatment parameter estimate over 10,000 simulated datasets.
[d]Median relative risk estimate over 10,000 simulated datasets.
[e]Results adjusted for multiple birth status.

Table S7: Simulation results for a binary outcome with moderate prevalence, 20% twin births and a log link function.

			Unadjusted			Adjusted[e]		
Treatment Effect[a] (Singletons/Twins)	ICC	Method	Parameter Estimate[b]	Standard Error[c]	Relative Risk[d]	Parameter Estimate[b]	Standard Error[c]	Relative Risk[d]
0.5/0.5	0.1	CWGEE	-0.70	0.15	0.50	-0.70	0.14	0.50
		GEEind	-0.70	0.14	0.50	-0.70	0.14	0.50
		GEEexch	-0.70	0.14	0.50	-0.70	0.14	0.50
0.5/0.5	0.5	CWGEE	-0.70	0.15	0.50	-0.70	0.15	0.50
		GEEind	-0.70	0.15	0.50	-0.70	0.15	0.50
		GEEexch	-0.70	0.15	0.50	-0.70	0.15	0.50
0.5/0.5	0.9	CWGEE	-0.70	0.15	0.50	-0.70	0.15	0.50
		GEEind	-0.70	0.16	0.50	-0.70	0.16	0.50
		GEEexch	-0.70	0.15	0.50	-0.70	0.15	0.50
0.5/0.75	0.1	CWGEE	-0.57	0.14	0.57	-0.55	0.13	0.58
		GEEind	-0.50	0.13	0.61	-0.48	0.13	0.62
		GEEexch	-0.52	0.13	0.60	-0.49	0.13	0.61
0.5/0.75	0.5	CWGEE	-0.57	0.14	0.57	-0.55	0.14	0.58
		GEEind	-0.50	0.14	0.61	-0.48	0.14	0.62
		GEEexch	-0.56	0.14	0.57	-0.53	0.14	0.59
0.5/0.75	0.9	CWGEE	-0.57	0.15	0.57	-0.55	0.14	0.58
		GEEind	-0.50	0.15	0.61	-0.48	0.15	0.62
		GEEexch	-0.57	0.15	0.57	-0.55	0.14	0.58
0.5/0.25	0.1	CWGEE	-0.85	0.16	0.43	-0.85	0.16	0.43
		GEEind	-0.94	0.15	0.39	-0.95	0.15	0.39
		GEEexch	-0.92	0.15	0.40	-0.94	0.15	0.39
0.5/0.25	0.5	CWGEE	-0.85	0.16	0.43	-0.86	0.16	0.43
		GEEind	-0.94	0.16	0.39	-0.95	0.16	0.39
		GEEexch	-0.88	0.16	0.41	-0.90	0.16	0.41
0.5/0.25	0.9	CWGEE	-0.85	0.16	0.43	-0.85	0.16	0.43
		GEEind	-0.94	0.17	0.39	-0.95	0.17	0.39
		GEEexch	-0.85	0.16	0.43	-0.87	0.16	0.42

[a]True relative risk (intervention versus control) for singletons and twins.
[b]Average treatment parameter estimate over 10,000 simulated datasets.
[c]Average estimated standard error of the treatment parameter estimate over 10,000 simulated datasets.
[d]Median relative risk estimate over 10,000 simulated datasets.
[e]Results adjusted for multiple birth status.

Table S8: Median percent relative difference in relative risk estimates for a binary outcome with 20% twin births and a log link function.

			CWGEE[b]		GEE_{exch}[b]	
Prevalence	Treatment Effect[a] (Singletons/Twins)	ICC	Unadjusted	Adjusted	Unadjusted	Adjusted
Low	0.5/0.5	0.1	0.14	0.13	0.00	0.00
		0.5	0.39	0.38	0.24	0.21
		0.9	0.11	0.16	0.10	0.16
Low	0.5/0.75	0.1	-6.45	-6.51	-0.72	-0.46
		0.5	-6.16	-6.22	-4.54	-3.67
		0.9	-6.30	-6.33	-6.25	-6.13
Low	0.5/0.25	0.1	9.82	9.85	0.74	0.62
		0.5	10.16	10.17	5.59	5.09
		0.9	10.27	10.31	9.20	8.94
Moderate	0.5/0.5	0.1	0.03	0.02	0.00	0.00
		0.5	-0.01	0.02	-0.01	0.01
		0.9	-0.04	-0.03	-0.04	-0.02
Moderate	0.5/0.75	0.1	-6.38	-6.66	-1.46	-0.76
		0.5	-6.54	-6.78	-5.10	-4.27
		0.9	-6.36	-6.67	-6.36	-6.48
Moderate	0.5/0.25	0.1	10.07	10.26	1.48	1.17
		0.5	9.92	10.13	5.96	5.47
		0.9	10.09	10.33	9.41	8.97

[a]True relative risk (intervention versus control) for singletons and twins.

[b]Median value of percent relative difference in relative risk estimates compared with GEE_{ind} over 10,000 simulated datasets, calculated as $100\left(\hat{RR}_1 - \hat{RR}_{1ref}\right)\Big/\hat{RR}_{1ref}$, where $\hat{RR}_1$ is the relative risk estimate based on CWGEE or GEE_{exch}, and $\hat{RR}_{1ref}$ is the reference relative risk estimate based on GEE_{ind}.

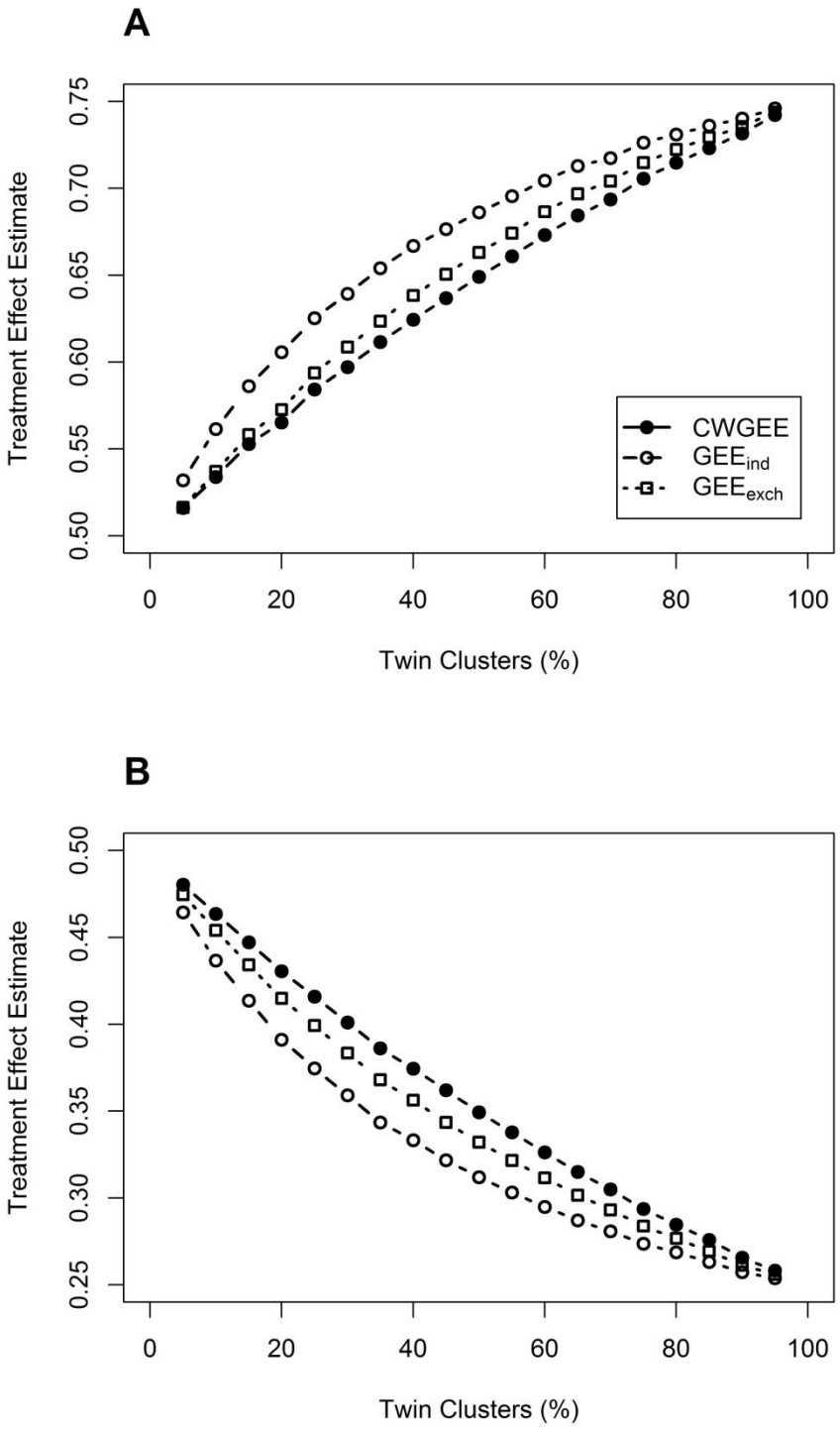

Figure S2: Median unadjusted relative risk estimate for a binary outcome with moderate prevalence and an ICC of 0.5 by varying percentage of mothers with a twin birth when the relative risk is 0.5 for singletons and (A) 0.75 or (B) 0.25 for twins.

Table S9: Power to detect a treatment group by multiple birth interaction for a binary outcome with 20% twin births.

		Power[b]			
Treatment Effect[a] (Singletons/Twins)	ICC	Low Prevalence, Logit Link	Moderate Prevalence, Logit Link	Low Prevalence, Log Link	Moderate Prevalence, Log Link
0.5/0.75	0.1	12.17	21.07	12.24	36.63
	0.5	11.23	18.03	11.57	33.02
	0.9	9.52	16.21	10.45	29.03
0.5/0.25	0.1	15.96	42.85	14.55	54.34
	0.5	12.67	36.41	12.11	43.15
	0.9	7.37	30.33	5.08	35.76

[a]True odds ratio (for logit link) or relative risk (for log link; intervention versus control) for singletons and twins.
[b]Power is the same for all methods of analysis.