Chapter 5

Example of Multicenter Studies

5.1 Smoking Cessation

The first example is a multicenter study of 59 trials that evaluate the effect of nicotine-replacement therapy (NRT) on smoking cessation. These data are taken from DuMouchel and Normand [27].

It is of interest to find out whether NRT helps a person to stop smoking. However, there are two different forms of NRT (patch and gum) and two different types of support (high support and low support). Low-support is defined as part of the provision of routine care. If duration of time spent with the smokers is greater than 30 minutes, or the number of further assessment and reinforcement visits is greater than 2, the level of support is defined as high. These are two possible sources of heterogeneity in this multicenter study.

It might be of interest to see if the success relative risk of quitting smoking is dependent on the form of NRT (gum/patch), and/or on the type of support (low/high).

The data from 59 trials, where the effect of NRT on smoking cessation was evaluated, are displayed in Table 5.1. We have determined that *NRT* is the binary covariate to describe the form of NRT; patch (NRT=1) or gum (NRT=0); and *Support* is the binary covariate to describe the type of support; high (Support=1) or low (Support=0).

Table 5.1: Count Data and Characteristics of 59 Trials on the Efficacy of Nicotine Replacement Therapy on Smoking Cessation

Study	Name	Year	x^T	n^T	x^C	n^C	NRT	Support
1	Puska	1979	29	116	21	113	0	1
2	Malcom	1980	6	73	3	121	0	1
3	Fagerstrom	1982	30	50	23	50	0	1
4	Fee	1982	23	180	15	172	0	1
5	Jarvis	1982	22	58	9	58	0	1
6	Hjalmarson	1984	31	106	16	100	0	1
7	Killen	1984	16	44	6	20	0	1
8	Schneider	1985	9	30	6	30	0	1
9	Hall	1987	30	71	14	68	0	1
10	Tonnesen	1988	23	60	12	53	0	1
11	Blondal	1989	37	92	24	90	0	1
12	Garcia	1989	21	68	5	38	0	1
13	Killen	1990	129	600	112	617	0	1
14	Nakamura	1990	13	30	5	30	0	1
15	Campbell	1991	21	107	21	105	0	1
16	Jensen	1991	90	211	28	82	0	1
17	McGovern	1992	51	146	40	127	0	1
18	Pirie	1992	75	206	50	211	0	1
19	Zelman	1992	23	58	18	58	0	1
20	Herrera-1	1995	37	76	17	78	0	1
21	Buchkremer	1981	11	42	16	89	1	1
22	Hurt	1990	8	31	6	31	1	1
23	Ehrsam	1991	7	56	2	56	1	1
24	Tnsg	1991	111	537	31	271	1	1
25	Sachs	1993	28	113	10	107	1	1
26	Westman	1993	16	78	2	80	1	1
27	Fiore-1	1994	15	44	9	43	1	1
28	Fiore-2	1994	10	57	4	55	1	1
29	Hurt	1994	33	120	17	120	1	1

Note. x^T=number of smokers who quit smoking in treatment group,
n^T=number of smokers in treatment group,
x^C=number of smokers who quit smoking in control group,
n^C=number of smokers in control group.

Table 5.1: Count Data and Characteristics of 59 Trials on the Efficacy of Nicotine Replacement Therapy on Smoking Cessation

Study	Name	Year	x^T	n^T	x^C	n^C	NRT	Support
30	ICRF	1994	76	842	53	844	1	1
31	Richmond	1994	40	160	19	157	1	1
32	Kornitzer	1995	19	150	10	75	1	1
33	Stapleton	1995	77	800	19	400	1	1
34	Campbell	1996	24	115	17	119	1	1
35	BR SOCIETY	1983	39	410	111	1208	0	0
36	Russell	1983	81	729	78	1377	0	0
37	Fagerstrom	1984	28	106	5	49	0	0
38	Jamrozik	1984	10	101	8	99	0	0
39	Jarvik	1984	7	25	4	23	0	0
40	Clavel-Chapel	1985	24	205	6	222	0	0
41	Schneidera	1985	2	13	2	23	0	0
42	Page	1986	9	93	13	182	0	0
43	Campbell	1987	13	424	9	412	0	0
44	Sutton	1987	21	270	1	64	0	0
45	Areechon	1988	56	99	37	101	0	0
46	Harackiewicz	1988	12	99	7	52	0	0
47	Llivina	1988	61	113	28	103	0	0
48	Sutton	1988	5	79	2	82	0	0
49	Gilbert	1989	11	112	9	111	0	0
50	Hughes	1989	23	210	6	105	0	0
51	Hughes	1990	15	59	5	19	0	0
52	Mori	1992	30	178	22	186	0	0
53	Nebot	1992	5	106	13	319	0	0
54	Fortmann	1995	44	262	42	261	0	0
55	Abelin	1989	17	100	11	99	1	0
56	Daughton	1991	28	106	4	52	1	0
57	Tonneson	1991	17	145	2	144	1	0
58	Burton	1992	29	115	22	119	1	0
59	Paoletti	1996	15	60	4	60	1	0

Note. x^T=number of smokers who quit smoking in treatment group,
n^T=number of smokers in treatment group,
x^C=number of smokers who quit smoking in control group,
n^C=number of smokers in control group.

The results of fitting various models to the multicenter trial of smoking cessation are presented in Table 5.2. When we fitted the profile log-likelihood model (4.5) with no covariates, the estimate of the intercept coefficient is equal to 0.4483 with standard error 0.0392 leading to a 95% confidence interval of the intercept coefficient from 0.3715 to 0.5251. This corresponds to an estimate of 1.5656 with a 95% confidence interval from 1.4500 to 1.6905 for the relative risk itself. Thus we can conclude that the treatment increases success of quitting smoking by an average of 57% .

The results in Table 5.2 show that the form of NRT (patch versus gum) yields the only significant change of effect for quitting smoking. There is no interaction between form of NRT and type of support.

The results of the estimation of relative risk with 95% confidence interval according to the selected model in Table 5.2 are shown in Table 5.3. The estimated relative risk for patch equals 1.8499 with 95% confidence interval from 1.5942 to 2.1466 and the estimated relative risk for gum equals 1.4697 with 95% confidence interval from 1.3431 to 1.6081. This suggests that there is an increase of quitting smoking of 85 per cent in patch groups and an increase of quitting smoking of 47 per cent in gum groups. Figure 5.1 shows the estimated relative risks and 95% CI according to the model with no covariates and for the selected model.

Table 5.2: Results of Fitting Various Models to the Multicenter Trial of Smoking Cessation

$L^*(\hat{\beta})$	Covariates	$\hat{\beta}_j$	S.E.	P-value
−17218.81	Intercept	0.4483	0.0392	0.0000
−17215.40[§]	Intercept	0.3850	0.0459	0.0000
	NRT	0.2301	0.0887	0.0047
−17218.73	Intercept	0.4700	0.0647	0.0000
	Support	-0.0343	0.0813	0.3367
−17214.84	Intercept	0.4356	0.0661	0.0000
	NRT	0.2526	0.0912	0.0028
	Support	-0.0893	0.0838	0.1434
−17214.65	Intercept	0.4222	0.0697	0.0000
	NRT	0.3558	0.1950	0.0340
	Support	-0.0657	0.0926	0.2391
	NRT*Support	-0.1328	0.2207	0.2738

[§] Selected model for multicenter trial of smoking cessation.

Table 5.3: The Results of Estimation of RR with 95% CI according to the Selected Model of the Multicenter Trial of Smoking Cessation

Form of NRT	S.E.	RR (95% CI)
Patch	0.0759	1.8499 (1.5942, 2.1466)
Gum	0.0459	1.4697 (1.3431, 1.6081)

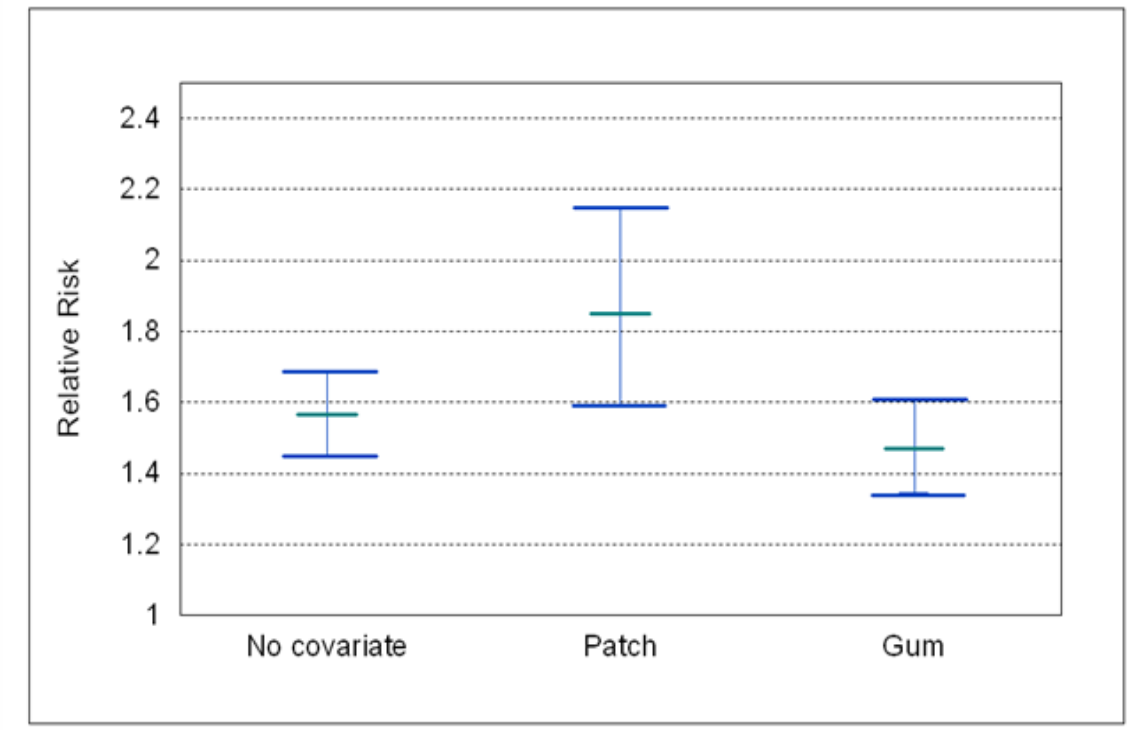

Figure 5.1: Estimated Relative Risks with 95% CI according to Model without Covariates and Selected Model of the Multicenter Trial of Smoking Cessation

5.2 Central Venous Catheters

The second example is a meta-analysis of 12 studies to assess the efficacy of antiseptic-impregnated catheters in reducing nosocomial catheter colonization (NCC) in a hospital setting, which was originally reported by Veenstra et al. [39], with further details of the methodology discussed in Dietz and Weist [12].

The investigators compared two arms, here denoted as treatment and control arm. The treatment arm consists of impregnated central venous catheters with the combination antiseptic chlorhexidine-silver sulfadiazine, and the control arm consists of nonimpregnated central venous catheters. The focus of interest is catheter colonization which is defined as isolation of an organism from a subcutaneous or intravenous catheter segment on catheter removal.

This multicenter study shows a potential of heterogeneity of treatment effects. Figure 5.2 shows the relative risk for the efficacy of antiseptic-impregnated catheters in reducing NCC of 12 studies. Based on a review of this literature, there are several sources of heterogeneity between trials, which could be used as covariates in our analysis. Six covariates are potentially associated with the efficacy of antiseptic-impregnated catheters in reducing NCC: 1) the mean catheter duration in the treatment group (MCDT), 2) Cultural methods (CM) which defines catheter colonization as growth from a catheter segment using semiquantitative or quantitative culture techniques, 3) Number of catheters per patient (NCP) which indicates whether studies have allowed subjects to receive more than one catheter during the study period, 4) Randomization procedures (RP) which indicate studies randomized catheters or patients, 5) Number of catheter lumen (NCL) which indicates whether studies have used only triple-lumen, and 6) Patient population (PP) which defines 3-categorical characteristic of the patient population of the study: patients in a general hospital setting (emergency department, transplant ward etc.), patients receiving total parenteral nutrition, and patients in an intensive care unit.

In order to describe situations where the efficacy of antiseptic-impregnated catheters is particularly high, the profile log-likelihood with covariate information model (4.5) was applied to the central venous catheter trials data. Studies that did not provide sufficient information were excluded from the analysis. A total of 11 studies were included in an analysis to assess the efficacy of antiseptic-impregnated catheters for the reduction of NCC. The count data and characteristics of the 11 studies are given in Table 5.4. Details of covariate information are presented in Table 5.5.

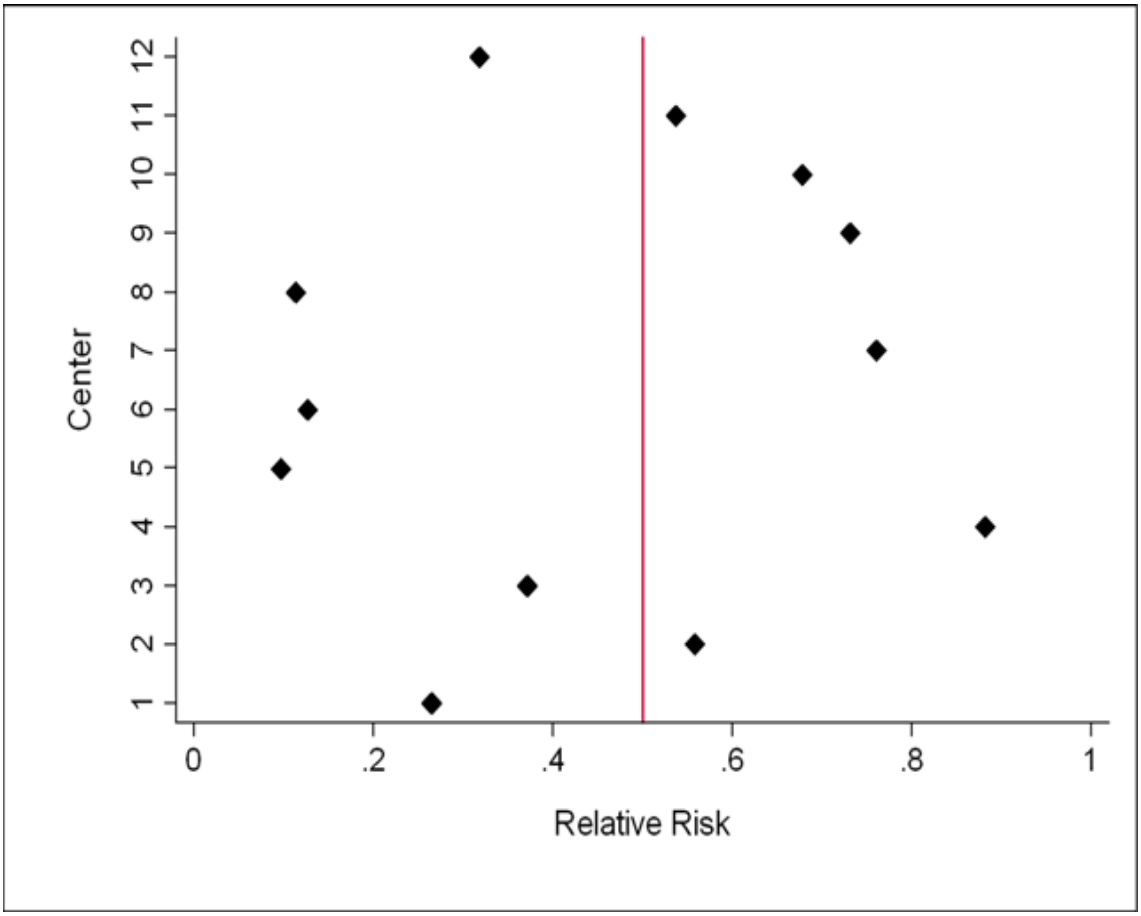

Figure 5.2: Estimated Relative Risks for the effect of Antiseptic-Impregnated Catheter in Reducing NCC of 12 Studies

Table 5.4: Count Data and Characteristics of 11 Studies on the Efficacy of Impregnated Central Venous Catheters for the Prevention of NCC

Study i	x^T	n^T	x^C	n^C	MCDT	CM	NCP	RP	NCL	PP
1	8	137	32	145	5.1	1	0	0	0	1
2	28	208	47	195	6.0	1	1	1	1	3
3	4	28	10	26	6.6	1	0	0	1	3
4	22	68	22	60	7.0	1	0	1	1	3
5	0	14	4	12	7.0	0	0	0	1	3
6	2	116	16	117	7.7	0	0	1	0	1
7	60	151	82	157	8.5	1	1	0	1	3
8	2	98	25	139	9.0	1	1	0	0	1
9	15	124	21	127	9.6	1	1	0	1	2
10	45	199	63	189	10.9	1	0	0	1	1
11	16	123	24	99	11.2	1	1	0	1	1

Note. x^T=number of colonized impregnated catheters, n^T=number of impregnated catheters, x^C=number of colonized non-impregnated catheters, n^C=number of non-impregnated catheters.

Table 5.5: The Covariate Information of NCC Data

No.	Covariates	Type	Value label
1	MCDT	continuous	
2	CM	binary	1=semiquantitative
			0=quantitative
3	NCP	binary	1=more than 1 catheter per patient
			0=one catheter per patient
4	RP	binary	1=randomized by catheter
			0=randomized by patient
5	NCL	binary	1=only used triple lumen catheter
			0=used any type of catheter lumens
6	PP	categorical	1=in general hospital setting
			2=receiving total parenteral nutrition
			3=in intensive care unit

The results of fitting the profile log-likelihood model with six singly included covariates are presented in Table 5.6, showing that only four covariates provide some significant explanation of the possible sources of heterogeneity. These are: mean catheter duration in treatment groups, cultural methods, number of catheter lumens, and patient population. Note that no difference was observed in the risk of NCC between patients who received total parenteral nutrition and patients in a general hospital setting. The patient population was then divided into two groups, which are patients who were in ICU and patients who were not in ICU. In order to select the set of covariates that should be used to explain the heterogenous effect of the antiseptic catheter impregnation in reducing the risk of NCC, a forward selection procedure and likelihood ratio test were applied. Details on forward selection and likelihood ratio test are given in Table 5.7 to Table 5.10.

Consequently, only three covariates: mean catheter duration in treatment groups, cultural methods, and patient population are significantly associated with the efficacy of antiseptic catheter impregnation in reducing the risk of NCC. Details of the selected model are given in Table 5.11, and the results of estimation of RR with 95% CI according to the selected model in Table 5.11 are presented in Table 5.12.

From Table 5.12, we conclude that the reduction in mean catheter duration is related to the reduction of the risk of NCC in the treatment group. For example, at mean catheter duration of 11.2, the estimated relative risk of NCC for antiseptic catheter impregnation is 0.6406, whereas the estimated relative risk is 0.2615 at mean catheter duration of 5.1. Moreover, the efficacy of antiseptic catheter impregnation for the reduction of NCC is greater in patients who were not in ICU. For example, in patients who were not in ICU and at a mean catheter duration of 9.0, the estimated relative risk is 0.4637, whereas the estimated relative risk is 0.7971 in patients who were in ICU and at a mean catheter duration of 8.5. However, the efficacy of antiseptic catheter impregnation is higher in the studies where the quantitative culture method was used to define catheter colonization.

Table 5.6: Results of Fitting Various Single-Covariate Models to the Multicenter Trial of Central Venous Catheters

$L^*(\hat{\beta})$	Covariates	$\hat{\beta}_j$	S.E.	P-value
-3055.93	Intercept	-0.5545	0.0887	0.0000
-3054.91[§]	Intercept	-1.1096	0.4007	0.0028
	MCDT	0.0652	0.0458	0.0770
-3051.25[§]	Intercept	-2.3252	0.7418	0.0009
	CM	1.8207	0.7472	0.0074
-3055.59	Intercept	-0.6417	0.1384	0.0000
	NCP	0.1491	0.1803	0.2041
-3055.93	Intercept	-0.5506	0.1026	0.0000
	RP	-0.0154	0.2038	0.4698
-3046.45[§]	Intercept	-1.6734	0.3119	0.0000
	NCL	1.2675	0.3259	0.0001
-3053.27[§]	Intercept	-0.7996	0.1416	0.0000
	PP-2	0.4870	0.3665	0.0920
	PP-3	0.4063	0.1868	0.0148

[§]Note that these covariates are potential sources of heterogeneity.

Table 5.7: Model Comparison of the Multicenter Trial of Central Venous Catheters: Start with MCDT

$L^*(\hat{\beta})$	Covariates	$\hat{\beta}_j$	S.E.	P-value	LR-Test†
MCDT					
-3054.91	Intercept	-1.1096	0.4007	0.0028	
	MCDT	0.0652	0.0458	0.0770	
MCDT+CM					
-3050.57	Intercept	-2.7258	0.8181	0.0004	8.666*
	MCDT	0.0530	0.0457	0.1230	
	CM	1.7689	0.7485	0.0091	
MCDT+NCL					
-3046.45	Intercept	-1.6584	0.4571	0.0001	16.914*
	MCDT	-0.0022	0.0495	0.4821	
	NCL	1.2720	0.3407	0.0001	
MCDT+PP					
-3049.59	Intercept	-2.4327	0.6123	0.0000	10.636*
	MCDT	0.1755	0.0607	0.0019	
	PP	0.7259	0.2297	0.0008	
MCDT+PP+CM					
-3046.87	Intercept	-3.5775	0.8943	0.0000	5.430‡
	MCDT	0.1469	0.0604	0.0075	
	PP	0.6151	0.2320	0.0040	
	CM	1.4873	0.7590	0.0250	
MCDT+PP+NCL					
-3046.42	Intercept	-1.7729	0.6834	0.0047	6.328‡
	MCDT	0.0147	0.0896	0.4348	
	PP	0.0792	0.3494	0.4104	
	NCL	1.1907	0.4934	0.0079	

† Critical value (5% level) for the chi-square distribution (df=1) is 3.841.

* Comparison of the current model with MCDT model.

‡ Comparison of the current model with MCDT+PP model.

Table 5.7: Model Comparison of the Multicenter Trial of Central Venous Catheters: Start with MCDT

$L^*(\hat{\beta})$	Covariates	$\hat{\beta}_j$	S.E.	P-value	LR-Test[†]
MCDT+PP+CM+NCL					
−3045.03	Intercept	-2.8234	0.9915	0.0022	3.680[§]
	MCDT	0.0264	0.0886	0.3826	
	PP	0.1318	0.3469	0.3520	
	CM	1.1681	0.7843	0.0682	
	NCL	0.9472	0.5100	0.0316	

[†] Critical value (5% level) for the chi-square distribution (df=1) is 3.841.

[§] Comparison of the current model with MCDT+PP+CM model.

Table 5.8: Model Comparison of the Multicenter Trial of Central Venous Catheters: Start with CM

$L^*(\hat{\beta})$	Covariates	$\hat{\beta}_j$	S.E.	P-value	LR-Test†
CM					
-3051.25	Intercept	-2.3252	0.7418	0.0009	
	CM	1.8207	0.7472	0.0074	
CM+MCDT					
-3050.57	Intercept	-2.7258	0.8181	0.0004	1.354*
	CM	1.7689	0.7485	0.0091	
	MCDT	0.0530	0.0457	0.1230	
CM+NCL					
-3045.11	Intercept	-2.6285	0.7636	0.0003	12.288*
	CM	1.1467	0.7825	0.0714	
	NCL	1.0846	0.3379	0.0007	
CM+PP					
-3050.05	Intercept	-2.3868	0.7440	0.0007	2.410*
	CM	1.7336	0.7501	0.0104	
	PP	0.2789	0.1800	0.0606	
CM+NCL+MCDT					
-3045.11	Intercept	-2.6184	0.8314	0.0008	0.000‡
	CM	1.1466	0.7826	0.0714	
	NCL	1.0878	0.3542	0.0011	
	MCDT	-0.0015	0.0493	0.4877	
CM+NCL+PP					
-3045.08	Intercept	-2.6349	0.7646	0.0003	0.056‡
	CM	1.1538	0.7833	0.0704	
	NCL	1.0563	0.3583	0.0016	
	PP	0.0458	0.1934	0.4064	

† Critical value (5% level) for the chi-square distribution (df=1) is 3.841.

* Comparison of the current model with CM model.

‡ Comparison of the current model with CM+NCL model.

Table 5.9: Model Comparison of the Multicenter Trial of Central Venous Catheters: Start with NCL

$L^*(\hat{\beta})$	Covariates	$\hat{\beta}_j$	S.E.	P-value	LR-Test†
NCL					
−3046.45	Intercept	-1.6734	0.3119	0.0000	
	NCL	1.2675	0.3259	0.0001	
NCL+MCDT					
−3046.45	Intercept	-1.6584	0.4571	0.0001	0.002*
	NCL	1.2720	0.3407	0.0001	
	MCDT	-0.0022	0.0495	0.4821	
NCL+CM					
−3045.11	Intercept	-2.6285	0.7636	0.0003	2.688*
	NCL	1.0846	0.3379	0.0007	
	CM	1.1467	0.7825	0.0714	
NCL+PP					
−3046.44	Intercept	-1.6734	0.3119	0.0000	0.026*
	NCL	1.2487	0.3460	0.0002	
	PP	0.0314	0.1931	0.4355	
NCL+CM+MCDT					
−3045.11	Intercept	-2.6184	0.8314	0.0008	0.000‡
	NCL	1.0878	0.3542	0.0011	
	CM	1.1466	0.7826	0.0714	
	MCDT	-0.0015	0.0493	0.4877	
NCL+CM+PP					
−3045.08	Intercept	-2.6349	0.7646	0.0003	0.056‡
	NCL	1.0563	0.3583	0.0016	
	CM	1.1538	0.7833	0.0704	
	PP	0.0458	0.1934	0.4064	

† Critical value (5% level) for the chi-square distribution (df=1) is 3.841.

* Comparison of the current model with NCL model.

‡ Comparison of the current model with NCL+CM model.

Table 5.10: Model Comparison of the Multicenter Trial of Central Venous Catheters: Start with PP

$L^*(\hat{\beta})$	Covariates	$\hat{\beta}_j$	S.E.	P-value	LR-Test†
PP					
-3054.13	Intercept	-0.7306	0.1302	0.0000	
	PP	0.3373	0.1784	0.0293	
PP+MCDT					
-3049.59	Intercept	-2.4327	0.6123	0.0000	9.088*
	PP	0.7259	0.2297	0.0008	
	MCDT	0.1755	0.0607	0.0019	
PP+CM					
-3050.05	Intercept	-2.3868	0.7440	0.0007	8.174*
	PP	0.2789	0.1800	0.0606	
	CM	1.7336	0.7501	0.0104	
PP+NCL					
-3046.44	Intercept	-1.6734	0.3119	0.0000	15.390*
	PP	0.0314	0.1931	0.4355	
	NCL	1.2487	0.3460	0.0002	
PP+MCDT+CM					
-3046.87	Intercept	-3.5775	0.8943	0.0000	5.430‡
	PP	0.6151	0.2320	0.0040	
	MCDT	0.1469	0.0604	0.0075	
	CM	1.4873	0.7590	0.0250	
PP+MCDT+NCL					
-3046.42	Intercept	-1.7729	0.6834	0.0047	6.328‡
	PP	0.0792	0.3494	0.4104	
	MCDT	0.0147	0.0896	0.4348	
	NCL	1.1907	0.4934	0.0079	

† Critical value (5% level) for the chi-square distribution (df=1) is 3.841.

* Comparison of the current model with PP model.

‡ Comparison of the current model with PP+MCDT model.

Table 5.10: Model Comparison of the Multicenter Trial of Central Venous Catheters: Start with PP

$L^*(\hat{\beta})$	Covariates	$\hat{\beta}_j$	S.E.	P-value	LR-Test[†]
PP+MCDT+CM+NCL					
−3045.03	Intercept	-2.8234	0.9915	0.0022	3.680[§]
	PP	0.1318	0.3469	0.3520	
	MCDT	0.0264	0.0886	0.3826	
	CM	1.1681	0.7843	0.0682	
	NCL	0.9472	0.5100	0.0316	

[†] Critical value (5% level) for the chi-square distribution (df=1) is 3.841.

[§] Comparison of the current model with PP+MCDT+CM model.

Table 5.11: The Results of Selected Models of the Multicenter Trials of Central Venous Catheters

$L^*(\hat{\beta})$	Covariates	$\hat{\beta}_j$	S.E.	P-value
-3046.87	Intercept	-3.5775	0.8943	0.0000
	MCDT	0.1469	0.0604	0.0075
	PP	0.6151	0.2320	0.0040
	CM	1.4873	0.7590	0.0250

Table 5.12: The Results of Estimation of RR with 95% CI according to the selected model of the Multicenter Trials of Central Venous Catheters

MCDT	CM	PP	S.E.	RR (95% CI)
11.2	1	0	0.1554	0.6406 (0.4724, 0.8686)
10.9	1	0	0.1471	0.6130 (0.4594, 0.8179)
9.6	1	0	0.1358	0.5064 (0.3881, 0.6608)
9.0	1	0	0.1453	0.4637 (0.3488, 0.6164)
5.1	1	0	0.3201	0.2615 (0.1397, 0.4897)
8.5	1	1	0.1361	0.7971 (0.6105, 1.0408)
7.0	1	1	0.1262	0.6395 (0.4994, 0.8190)
6.6	1	1	0.1342	0.6030 (0.4635, 0.7845)
6.0	1	1	0.1527	0.5522 (0.4093, 0.7448)
7.7	0	0	0.7467	0.0866 (0.0200, 0.3741)
7.0	0	1	0.7597	0.1445 (0.0326, 0.6406)

5.3 Ischaemic Heart Disease Events

The third example is a multicenter study of 28 trials that study the effect of the average reduction in serum cholesterol on the reduction of the risk of ischaemic heart disease (IHD) events. These data are taken from Thompson and Sharp [36].

An ischaemic heart disease event is defined as a fatal and non-fatal myocardial infarction. The cholesterol reduction is determined as the reduction in the treated group minus that in the control group, averaged over the follow-up period of the trial. This average extent of cholesterol reduction varied widely across the trials, from 0.3 to 1.5 mmol/l. All subjects of the 28 trials were randomly allocated to interventions.

In these trials, cholesterol was reduced by a variety of interventions. They consist of diets, drugs, and, in one case, surgery. Moreover, the duration of trials varied widely across the trials, from 0.3 to 12 years. In our analysis, we divided the duration of the trials into three groups: less than 2 years, between 2.1 and 5 years, and between 5.1 and 12 years. Therefore, it might be interesting to investigate one continuous covariate effect (cholesterol reduction) and two categorical covariate effects (type of intervention and the duration of the trials) on the reduction in the risk of IHD.

Trial-specific count data and study characteristics of 28 trials are given in Table 5.13. We determine that *Chol* is the continuous covariate to describe the reduction in serum cholesterol; *Treat* is the categorical covariate to describe the type of intervention: dietary (Treat=1), drugs (Treat=2), and surgery (Treat=3); and *Time* is the categorical covariate to describe the duration of the trials: less than 2 years (Time=1), between 2.1 and 5 years (Time=2), and between 5.1 and 12 years (Time=3). The results of fitting various models of the multicenter trial of IHD are presented in Table 5.14.

The results from Table 5.14 indicate that only cholesterol reduction has a significant effect on the risk of IHD. In addition, the estimate of $\hat{\beta}$ for cholesterol reduction covariate was negative, meaning that the reduction in the risk of IHD actually increases according to the extent of cholesterol reduction. This relation is illustrated in Figure 5.3. The estimation of RR with 95% CI according to the selected model in Table 5.14 are presented in Table 5.15.

Table 5.13: Count Data and Study Characteristics of 28 Clinical Trials on the Serum Cholesterol Reduction to Reduce the Risk of IHD

Trial	x^T	n^T	x^C	n^C	Chol	Treat	Time
1	173	5331	210	5296	0.55	2	3
2	54	244	85	253	0.68	2	2
3	54	350	75	367	0.85	2	2
4	676	2222	936	2789	0.55	2	2
5	42	145	69	284	0.59	2	2
6	73	279	101	276	0.84	2	2
7	157	1906	193	1900	0.65	2	3
8	6	71	11	72	0.85	2	3
9	36	1149	42	1129	0.49	2	2
10	2	88	2	30	0.68	2	1
11	56	2051	84	2030	0.69	2	3
12	1	94	5	94	1.35	2	1
13	131	4541	121	4516	0.70	1	2
14	52	424	65	422	0.87	1	3
15	45	199	52	194	0.95	1	3
16	61	229	81	229	1.13	1	2
17	37	221	24	237	0.31	1	2
18	8	28	11	52	0.61	1	1
19	47	130	50	134	0.57	1	2
20	82	421	125	417	1.43	3	3
21	62	6582	20	1663	1.08	2	1
22	2	94	0	52	1.48	2	1
23	1	23	0	29	0.56	2	1
24	3	60	5	30	1.06	1	2
25	132	1018	144	1015	0.26	1	1
26	35	311	24	317	0.76	2	2
27	3	79	4	78	0.54	2	1
28	7	76	19	79	0.68	2	2

Note. x^T=number of patients with IHD in treatment group,
n^T=number of patients in treatment group,
x^C=number of patients with IHD in control group,
n^C=number of patients in control group.

Table 5.14: Results of Fitting Various Models to the Multicenter Trial of IHD

$L^*(\hat{\beta})$	Covariates	$\hat{\beta}_j$	S.E.	P-value
-35905.32	Intercept	-0.1541	0.0299	0.0000
-35900.66[§]	Intercept	0.0921	0.0861	0.1424
	Cholesterol	-0.3717	0.1222	0.0012
-35902.19	Intercept	-0.0619	0.0613	0.1563
	Treat-2	-0.1053	0.0707	0.0683
	Treat-3	-0.3693	0.1548	0.0085
-35902.42	Intercept	-0.1152	0.1044	0.1348
	Time-2	0.0079	0.1109	0.4716
	Time-3	-0.1515	0.1183	0.1001
-35899.26	Intercept	0.1995	0.1241	0.0540
	Cholesterol	-0.4014	0.1658	0.0077
	Treat-2	-0.1186	0.0710	0.0474
	Treat-3	-0.0566	0.2016	0.3894

[§]Selected model for multicenter trial of IHD.

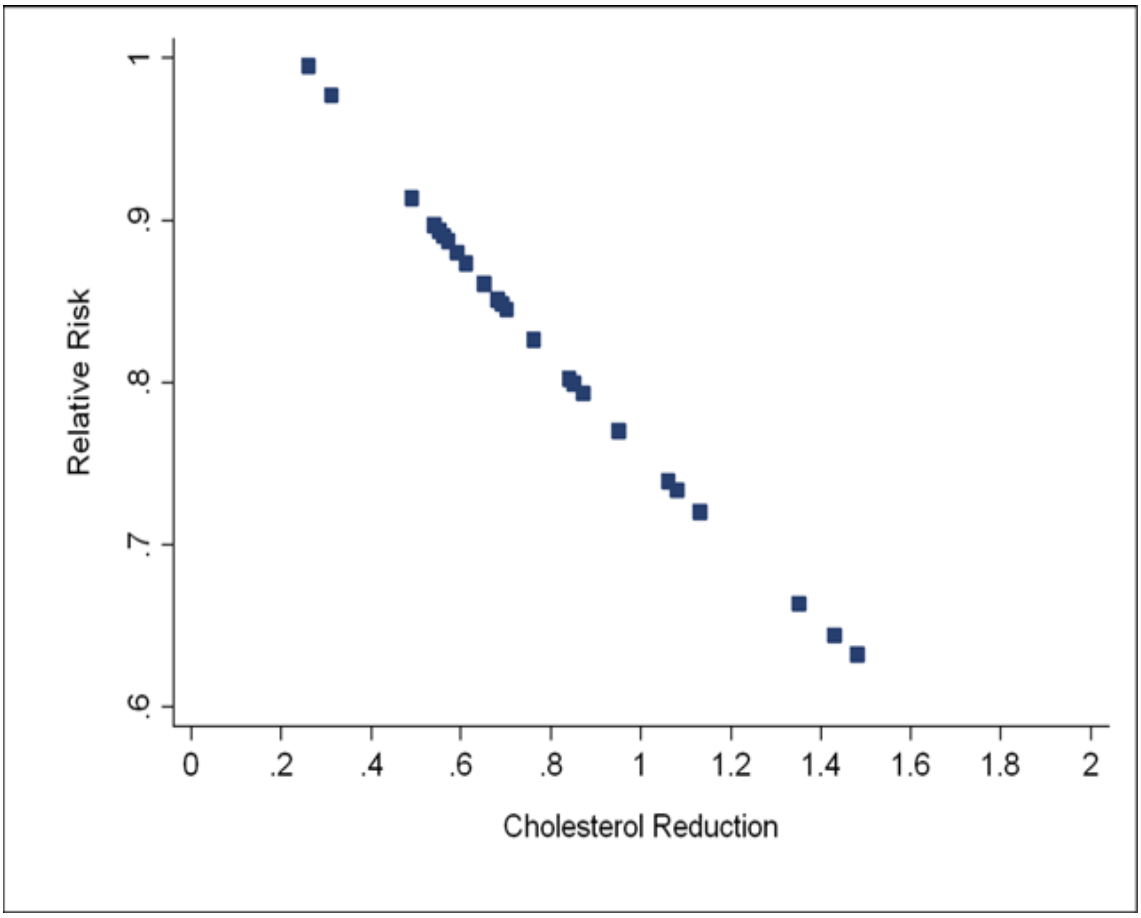

Figure 5.3: Estimated Relative Risks and Average of Cholesterol Reduction of the Multicenter Trial of IHD

Table 5.15: The Results of Estimation of RR with 95% CI according to the Selected Model of the Multicenter Trials of IHD

Cholesterol	S.E.	RR (95% CI)
0.26	0.0574	0.9955 (0.8895, 1.1140)
0.31	0.0523	0.9771 (0.8820, 1.0826)
0.49	0.0365	0.9139 (0.8508, 0.9816)
0.54	0.0333	0.8971 (0.8403, 0.9577)
0.55	0.0328	0.8937 (0.8381, 0.9531)
0.56	0.0323	0.8904 (0.8357, 0.9487)
0.57	0.0319	0.8871 (0.8334, 0.9443)
0.59	0.0311	0.8805 (0.8284, 0.9359)
0.61	0.0305	0.8740 (0.8233, 0.9279)
0.65	0.0299	0.8611 (0.8121, 0.9131)
0.68	0.0300	0.8516 (0.8030, 0.9031)
0.69	0.0301	0.8484 (0.7998, 0.8999)
0.70	0.0302	0.8453 (0.7966, 0.8969)
0.76	0.0322	0.8266 (0.7760, 0.8805)
0.84	0.0370	0.8024 (0.7463, 0.8628)
0.85	0.0377	0.7994 (0.7424, 0.8608)
0.87	0.0393	0.7935 (0.7347, 0.8570)
0.95	0.0462	0.7703 (0.7035, 0.8433)
1.06	0.0571	0.7394 (0.6611, 0.8270)
1.08	0.0592	0.7339 (0.6535, 0.8243)
1.13	0.0646	0.7204 (0.6347, 0.8176)
1.35	0.0893	0.6638 (0.5573, 0.7908)
1.43	0.0985	0.6444 (0.5312, 0.7817)
1.48	0.1044	0.6325 (0.5155, 0.7761)

5.4 BCG Vaccine for Prevention of Tuberculosis

The fourth example is a meta-analysis of 13 clinical trials to assess the efficacy of Bacillus Calmette-Guérin (BCG) vaccine for the prevention of tuberculosis (TB), which was originally reported by Colditz *et al.* [11] and with further details of methodology discussed in Berkey *et al.* [4], Sutton *et al* [33] and van Houwelingen *et al* [38]. We have extracted data on covariates that might explain the heterogeneity among study results from those articles.

The investigators compared two arms. The treatment arm is defined as receiving BCG-vaccine, and the control arm as not receiving BCG-vaccine. All trials have equivalent surveillance procedures and similar lengths of follow-up among the vaccinated and non-vaccinated group. The focus of interest is the occurrence of TB.

Latitude is one of several factors which is historically suspected of being associated with the efficacy of BCG vaccine. Latitude represents the variation in rainfall, humidity, environmental mycobacteria that may produce the level of natural immunity against TB, and other factors that may have an influence on the efficacy of BCG vaccine. In the literature, there are a variety of methods of treatment allocation which could be used as covariates that might explain the heterogeneity of study results. The method of treatment allocation consists of random, alternate, and systematic. However, reviewed studies have been conducted over a period of more than 60 years, so the year of publication could also be used as one covariate in our analysis.

Therefore, we have used the profile-log likelihood with the incorporating covariate information model to find out whether distance of each trial from the equator (absolute latitude), direction of latitude from equation, method of treatment allocation, and year of publication are associated with the efficacy of BCG vaccine.

The count data and characteristics of the 13 studies on the efficacy of BCG vaccine for prevention of TB are presented in Table 5.16. We determine that *Latitude* is a continuous covariate to describe distance of each trial from the equator; *Direct* is the binary covariate to describe direction of latitude from the equator; North (Direct=0) or South (Direct=1); *Alloc* is the categorical covariate to describe method of allocation of subjects to BCG vaccine and control groups; random allocation (Alloc=1) or alternate allocation (Alloc=2) or systematic allocation (Alloc=3); and *Year* is continuous covariate to describe the year of publication. The results of fitting various models of the multicenter trials to the efficacy of BCG vaccine are presented in Table 5.17. Note that no difference was observed in the efficacy of BCG vaccine for prevention of TB

between random and systematic allocation. The method of treatment allocation was then divided into two groups, random or systematic allocation and alternate allocation.

The results in Table 5.17 indicate that latitude and method of treatment allocation are significantly associated with the efficacy of BCG vaccine for prevention of TB. The estimation of RR with 95% CI according to the selected model in Table 5.17 are presented in Table 5.18. It is clear that the efficacy of BCG vaccination increases with increasing distance from the equator. For example, at latitude 19 the estimated relative risk is 0.7812 for a mean protective effect of 22 percent, whereas at latitude 55, with the same method of treatment allocation, the estimated relative risk is 0.2369 for a mean protective effect of 76 percent. However, the efficacy of BCG vaccination is greater in studies where the random method for allocation of subjects to vaccination was used.

Table 5.16: Count Data and Characteristics of 13 Studies on the Efficacy of BCG Vaccine for Prevention of TB

Trial	x^T	n^T	x^C	n^C	Latitude	Direct	Alloc	Year
1	4	123	11	139	44	0	1	48
2	6	306	29	303	55	0	1	49
3	3	231	11	220	42	0	1	60
4	62	13598	248	12867	52	0	1	77
5	33	5069	47	5808	13	0	2	73
6	180	1541	372	1451	44	0	2	53
7	8	2545	10	629	19	0	1	73
8	505	88391	499	88391	13	0	1	80
9	29	7499	45	7277	27	1	1	68
10	17	1716	65	1665	42	0	3	61
11	186	50634	141	27338	18	0	3	74
12	5	2498	3	2341	33	0	3	69
13	27	16913	29	17854	33	0	3	76

Note. x^T=number of TB cases in vaccinated group,
n^T=number of persons in vaccinated group,
x^C=number of TB cases in unvaccinated group,
n^C=number of persons in unvaccinated group.

Table 5.17: Results of Fitting Various Single-Covariate Models to the Multicenter Trial of BCG Vaccine

$L^*(\hat{\beta})$	Covariates	$\hat{\beta}_j$	S.E.	P-value
-26636.72	Intercept	-0.4551	0.0403	0.0000
-26570.82	Intercept	0.3571	0.0814	0.0000
	Latitude	-0.0301	0.0027	0.0000
-26636.72	Intercept	-0.4547	0.0409	0.0000
	Direction	-0.0147	0.2416	0.4757
-26630.06	Intercept	-0.3530	0.0530	0.0000
	Allocate-2	-0.3596	0.0995	0.0002
	Allocate-3	-0.0876	0.1069	0.2064
-26612.95	Intercept	-2.3085	0.2787	0.0000
	Year	0.0260	0.0038	0.0000
-26568.81[§]	Intercept	0.3828	0.0827	0.0000
	Latitude	-0.0331	0.0031	0.0000
	Allocate	0.2245	0.1122	0.0227
-26569.79	Intercept	1.0288	0.4802	0.0161
	Latitude	-0.0341	0.0039	0.0000
	Year	-0.0079	0.0056	0.0775

[§] Selected model of multicenter trial of BCG vaccine.

Table 5.18: The Results of Estimation of RR with 95% CI according to the Selected Model of the Multicenter Trial of BCG Vaccine

Latitude	Allocate	S.E.	RR (95% CI)
13	random	0.0547	0.9530 (0.8562, 1.0608)
19	random	0.0482	0.7812 (0.7107, 0.8586)
27	random	0.0503	0.5992 (0.5430, 0.6613)
42	random	0.0793	0.3644 (0.3120, 0.4257)
44	random	0.0844	0.3411 (0.2891, 0.4024)
52	random	0.1060	0.2616 (0.2125, 0.3220)
55	random	0.1145	0.2369 (0.1893, 0.2964)
18	systematic	0.0488	0.8075 (0.7338, 0.8886)
33	systematic	0.0592	0.4911 (0.4373, 0.5516)
42	systematic	0.0793	0.3644 (0.3120, 0.4257)
13	alternate	0.1187	1.1929 (0.9452, 1.5054)
44	alternate	0.0861	0.4269 (0.3606, 0.5054)