

Chapter 11

Analysis of Correlated Data

Aim: Upon completing the chapter, the learner should be able to fit a linear regression with correlated data.

11.1 Regression Models with Correlated Data

When the measurements are part of a group of individuals, then it is possible that these measurements will be correlated. For example, patients receiving medical care in a hospital (private or public) and who are assigned to a doctor (generalist or specialist), it is possible that the treatments that these patients receive will be very similar. The patients are observed nested within certain type of doctors and hospitals.

Another example of correlated data is in cross-sectional studies, when a complex sampling design of households is used ([Figure 11.1](#)); the possibility exists that the responses of the people who reside on the same census block about lifestyle habits will be similar.

Another situation in which there might be correlated data is when repeated measurements are made; for example, the different weights of a single child at different visits to his or her pediatrician. There are various alternatives for analyzing these data, and which alternatives to use will depend on the objectives of the investigator. One alternative is to analyze the independent measurements separately, which results in a loss of information and statistical power. For example, assume the following data with regard to 20 different children, each one visiting his or her pediatrician three different times, being weighed at each visit, and information on whether they practice a sport on a regular basis (1 = yes vs. 0 = no):

	id	weight1	weight2	weight3	sport
1.	1	66	67	68	0
2.	2	71	71	65	0
3.	3	70	66	62	0
4.	4	64	62	66	1
5.	5	67	66	68	1
6.	6	65	64	65	1
7.	7	67	67	63	0
8.	8	65	66	66	1
9.	9	69	70	68	0
10.	10	63	62	63	1
11.	11	61	60	60	1
12.	12	66	68	68	1
13.	13	68	68	70	0
14.	14	67	69	65	0
15.	15	65	67	63	1
16.	16	64	62	64	1
17.	17	65	64	55	0
18.	18	65	65	66	0
19.	19	64	63	62	1
20.	20	67	66	63	0

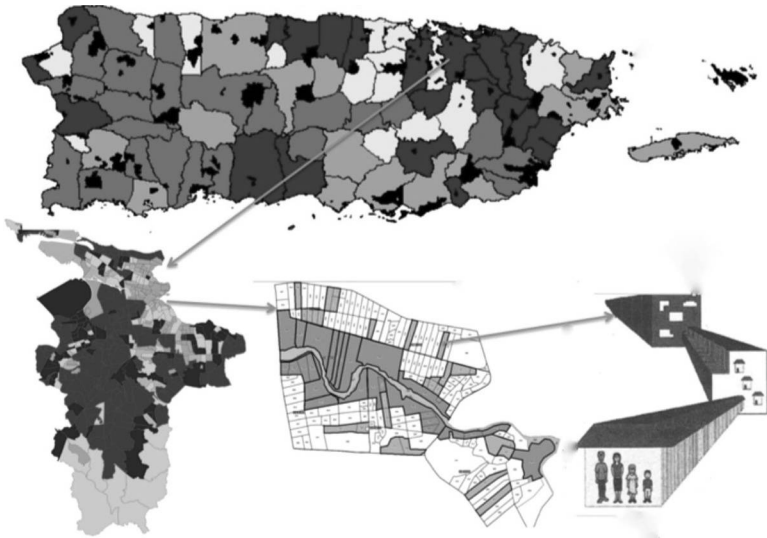


Figure 11.1 Sampling design in Puerto Rico.

To perform the analysis with independent measurements, assuming that the objective is to compare the average weight by type of sport, we could carry out a simple linear regression analysis of the weight of each child, using the following command lines at each visit:

For the first visit:

```
reg weight1 sport
```

Output

Source	SS	df	MS	Number of obs	=	20
Model	48.05	1	48.05	F(1, 18)	=	14.20
Residual	60.9	18	3.3833333	Prob > F	=	0.0014
				R-squared	=	0.4410
				Adj R-squared	=	0.4100
Total	108.95	19	5.7342105	Root MSE	=	1.8394

weight1	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
sport	-3.1	.8225975	-3.77	0.001	-4.828213 -1.371787
_cons	67.5	.5816643	116.05	0.000	66.27797 68.72203

The results show a significant effect of the predictor *sport* on mean weight at visit 1 (P -value = .001). The estimated regression coefficient for the predictor *sport* is the difference between the mean weights by sport in visit 1. The following command line can be used to compute the observed mean weight by sport:

```
table sport, c(mean weight1)
```

Output

sport	mean(weight1)
0	67.5
1	64.4

The difference in the mean weights at visit 1 is -3.1 , so the children who practice regularly a sport weigh less, on average, than those who do not practice regularly a sport. To explore the differences in mean weight in each visit, a line can be drawn between the estimated weights from a linear regression model by sport. For example, in the first visit the following Stata commands for visualizing this line can be used to create [Figure 11.2](#):

```
predict weightlexp
twoway (line weightlexp sport, sort), ytitle(Mean weight)
xtitle(Sport) xlabel(0(1)1) legend(off)
```

We repeat the previous steps for the second visit:

```
reg weight2 sport
```

Output

Source	SS	df	MS	Number of obs	=	20
Model	54.45	1	54.45	F(1, 18)	=	9.24
Residual	106.1	18	5.89444444	Prob > F	=	0.0071
				R-squared	=	0.3391
				Adj R-squared	=	0.3024
Total	160.55	19	8.45	Root MSE	=	2.4278

weight2	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]	
sport	-3.3	1.085766	-3.04	0.007	-5.581111	-1.018889
_cons	67.3	.7677529	87.66	0.000	65.68701	68.91299

```
table sport, c(mean weight2)
```

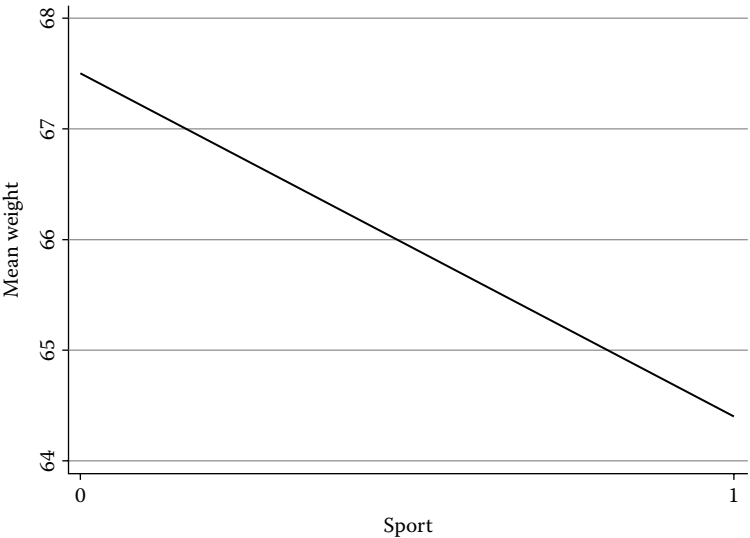


Figure 11.2 Mean weight in the first visit.

Output

sport	mean(weight2)
0	67.3
1	64

The results also show a significant effect of the predictor sport on mean weight at visit 2 (P -value = .007). The difference in the mean weights at the second visit is -3.3 ; children who practice regularly a sport weight less, on average, than those who do not practice regularly a sport. To draw the estimated weight by sport at visit 2, the following Stata commands are used to create [Figure 11.3](#):

```
predict weight2exp
twoway (line weight2exp sport, sort), ytitle(Mean weight)
xtitle(Sport) xlabel(0(1)1) legend(off)
```

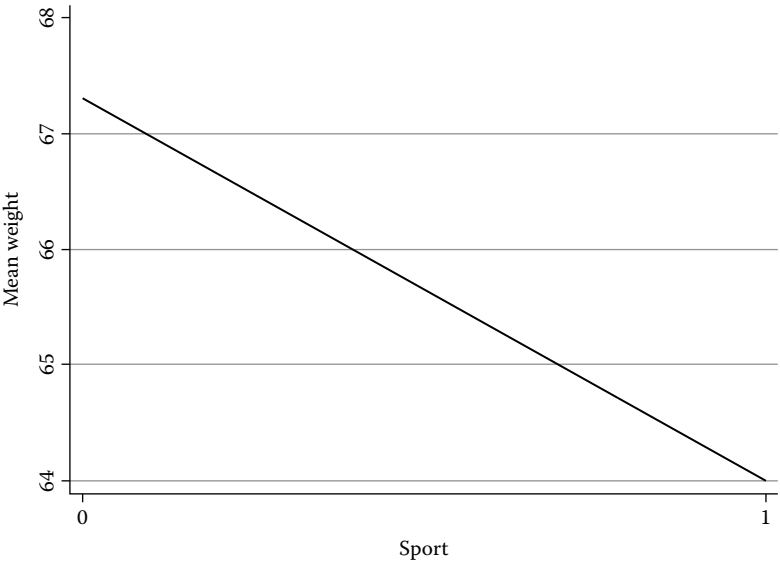


Figure 11.3 Mean weight in the second visit.

The Stata commands on the third visit are:

```
reg weight3 sport
```

Output

Source	SS	df	MS	Number of obs	=	20
Model	0	1	0	F(1, 18)	=	0.00
Residual	219	18	12.1666667	Prob > F	=	1.0000
				R-squared	=	0.0000
				Adj R-squared	=	-0.0556
Total	219	19	11.5263158	Root MSE	=	3.4881

weight3	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
sport	0	1.559915	0.00	1.000	-3.277259 3.277259
_cons	64.5	1.103026	58.48	0.000	62.18263 66.81737

```
table sport, c(mean weight3)
```

Output

sport	mean(weight3)
0	64.5
1	64.5

The results do not show a significant effect of the predictor sport on mean weight at visit 3 (P -value $> .1$). There is no difference in the mean weights at the third visit. To draw the estimated weight by sport on the third visit, the following Stata commands are used to create [Figure 11.4](#):

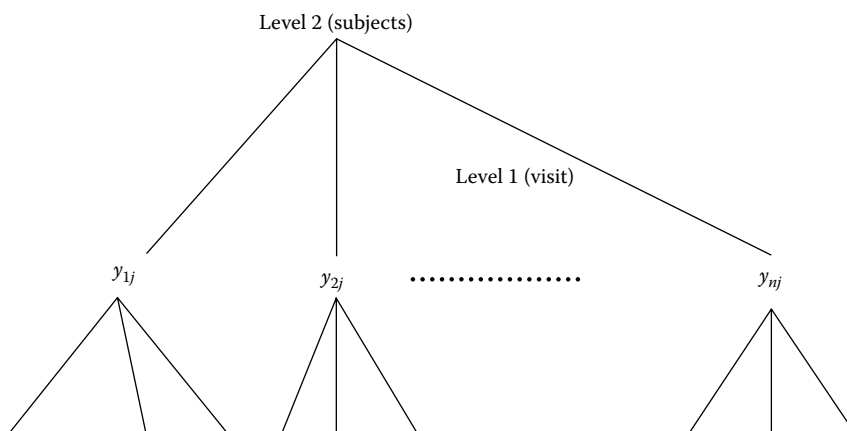
```
predict weight3exp  
twoway (line weight3exp sex, sort), ytitle(Mean weight)  
xtitle(Sport) xlabel(0(1)1) legend(off)
```

11.2 Mixed Models

The other alternative for analyzing correlated data is to use mixed models or multi-level models that allow us to correct the statistical relationship due to the potential correlation between measurements. For example, the simplest scheme of correlation is the repeated measures study; the same subject is measured several times, as illustrated in [Figure 11.5](#).



Figure 11.4 Mean weight in the third visit.



y_{ij} indicates the value of Y in the j th visit for the i th subject.

Level 1 refers to the set of weights of each subject on different visits.

Level 2 refers to the set of subjects.

Figure 11.5 Repeated measures of weight in the same subject.

Mixed models can be expressed in various forms to explain the expected value of the *main outcome* (Y) of the study. The construction of these models depends on the following variations:

1. $\bar{Y}_i$ may be different between subjects at baseline (variability between measurements).
2. $\bar{Y}_i$ may change according to the conditions in each subject (variability within measurements).

When an association is established between a continuous random variable, Y , and a quantitative variable, X , through a simple linear regression model, $\mu_{Y|X} = \beta_0 + \beta_1 * X$, in a mixed model approach, the intercept (β_0) and the slope (β_1) could be fixed or random. The following table indicates the possible combinations of these alternatives:

<i>Intercept</i> (β_0)	<i>Slope</i> (β_1)
Fixed	Fixed
Fixed	Random
Random	Fixed
Random	Random

Based on the previous example of the estimated weights by sport, we need to identify the possible patterns of the linear relationships. According to the previous graphs, the respective patterns in the lines suggest a model with a random intercept considering the first two visits, similar slopes but different intercept; it means that the difference in the mean weight, between those who practice regularly a sport and those who do not, is independent of the visit. However, if the three visits are considered, a model with random intercept and slope is suggested; the difference in the mean weight, between those who practice sport and those who do not, is not independent of the visit.

11.3 Random Intercept

The definition of a linear mixed model with a random intercept is as follows (Rabe-Hesketh and Skrondal, 2005):

$$Y_{ij} = \beta_{0i} + \beta_1 * X_{ij} + e_{ij}$$

where:

$\beta_{0i} = \gamma_{00} + U_{0i}$ (random coefficient)

β_1 indicates the coefficients (fixed) associated to the predictor X

$U_{0i} \sim N(0, \sigma_{U_0}^2)$

γ_{00} indicates the average intercept in a design with two levels

σ_{u0}^2 indicates the variance of the intercept between subjects

The variance of Y_{ij} conditional on the value of X_{ij} is given by the following expression:

$$\text{var}(Y_{ij}|X_{ij}) = \text{var}(U_{0j}) + \text{var}(\varepsilon_{ij}) = \sigma_{u0}^2 + \sigma_{\varepsilon}^2$$

where σ_{ε}^2 indicates the variance of Y within the subjects (variance of the residuals).

Using the data of the previous example, the correlation between two different visits ($j \neq j'$) of the i th subject is calculated through the covariance expression, as follows:

$$\text{cov}(Y_{ij}, Y_{ij'} | X_{ij}, X_{ij'}) = \text{var}(U_{0j}) = \sigma_{u0}^2$$

Therefore, the correlation between the measurements of Y in a subject, when Y is fitted by X , is defined with the following equation:

$$\rho(Y_{ij} | X_{ij}) = \frac{\text{cov}(Y_{ij}, Y_{ij'} | X_{ij}, X_{ij'})}{\text{var}(Y_{ij} | X_{ij})} = \frac{\sigma_{u0}^2}{\sigma_{u0}^2 + \sigma_{\varepsilon}^2}$$

This measurement is known as an intraclass correlation coefficient, which does not change according to the value of X .

11.4 Using the *mixed* and *gllamm* Commands with a Random Intercept

To run the mixed model with the assumption of a random intercept, we need the database to be in the long format. The following command needed to get a long database from a wide database is:

```
reshape long weight, i(id) j(visit)
```

After submitting this command, the database is changed as follows:

	id	visit	weight	sport
1.	1	1	66	0
2.	1	2	67	0
3.	1	3	68	0
4.	2	1	71	0
5.	2	2	71	0
6.	2	3	65	0
7.	3	1	70	0
8.	3	2	66	0
9.	3	3	62	0
10.	4	1	64	1
11.	4	2	62	1
12.	4	3	66	1
13.	5	1	67	1
14.	5	2	66	1
15.	5	3	68	1
16.	6	1	65	1
17.	6	2	64	1
18.	6	3	65	1
19.	7	1	67	0
20.	7	2	67	0
21.	7	3	63	0
22.	8	1	65	1
23.	8	2	66	1
24.	8	3	66	1
25.	9	1	69	0
26.	9	2	70	0
27.	9	3	68	0
28.	10	1	63	1
29.	10	2	62	1
30.	10	3	63	1
31.	11	1	61	1
32.	11	2	60	1
33.	11	3	60	1
34.	12	1	66	1
35.	12	2	68	1

36.	12	3	68	1
37.	13	1	68	0
38.	13	2	68	0
39.	13	3	70	0
40.	14	1	67	0

41.	14	2	69	0
42.	14	3	65	0
43.	15	1	65	1
44.	15	2	67	1
45.	15	3	63	1

46.	16	1	64	1
47.	16	2	62	1
48.	16	3	64	1
49.	17	1	65	0
50.	17	2	64	0

51.	17	3	55	0
52.	18	1	65	0
53.	18	2	65	0
54.	18	3	66	0
55.	19	1	64	1

56.	19	2	63	1
57.	19	3	62	1
58.	20	1	67	0
59.	20	2	66	0
60.	20	3	63	0
+-----+				

Subsequently, the *mixed* command is used for the first two visits as can be seen below:

```
mixed weight sport if visit < 3, || id:, stddev
```

Output

Mixed-effects ML regression	Number of obs	=	40
Group variable: id	Number of groups	=	20
Obs per group:			
	min	=	2
	avg	=	2.0
	max	=	2
	Wald chi2(1)	=	14.12
Log likelihood = -77.965175	Prob > chi2	=	0.0002

weight	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	
sport	-3.2	.8514694	-3.76	0.000	-4.868849	-1.531151
_cons	67.4	.6020798	111.95	0.000	66.21995	68.58005

Random-effects Parameters		Estimate	Std. Err.	[95% Conf. Interval]	
id: Identity					
	sd(_cons)	1.746425	.3322952	1.202792	2.535768
	sd(Residual)	1.07238	.1695582	.7866148	1.46196
LR test vs. linear model: chibar2(01) = 14.99 Prob >= chibar2 = 0.0001					

The results indicate that there is a significant change in the expected weight by sport (P -value <.001), even after controlling for the effect between subjects ($\hat{\beta}_1 = -3.2$ 95% CI: $-4.87, -1.53$). The intraclass correlation coefficient is determined with the following estimates:

$$\hat{\sigma}_{u_0} = 1.74$$

$$\hat{\sigma}_e = 1.07$$

$$\hat{\rho} = \frac{1.74^2}{1.74^2 + 1.07^2} = .73$$

We can see that the average intercept is $\hat{\gamma}_{00} = 67.4$ and varies per visit ± 1.74 . Another option when running the mixed model with a random intercept is to use the *gllamm* command, which may be downloaded from www.gllamm.org. The result is the following, assuming that the data are in the long format:

```
gllamm weight sport if visit < 3, i(id) nlp(20)
```

Output

```
gllamm model
log likelihood = -77.94849
```

weight	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]
sport	-3.194099	.8346379	-3.83	0.000	-4.829959 -1.558239
_cons	67.38501	.570114	118.20	0.000	66.26761 68.50241

Variance at level 1

1.1368944 (.37024967)

Variances and covariances of random effects

***level 2 (id)

var(1): 3.1128248 (1.2621798)

The results of both *mixed* and *gllamm* are similar, with a slight difference in the log-likelihood estimate and in the variance of random effects.

11.5 Using the *mixed* Command with Random Intercept and Slope

Another way to express a mixed model that explains the expected values of $Y(\mu_{ij})$ is to assume that the intercept and the slope are random variables, as follows:

$$\mu_{ij} = \beta_{0i} + \beta_{1i} * X_{ij}$$

where:

$\beta_{0i} = \gamma_{00} + U_{0i}$ (random coefficient)

β_{1i} indicates a random coefficient associated with the predictor X , which is defined as follows: $\gamma_{01} + U_{1i}$

$U_{0i} \sim N(0, \sigma_{U_0}^2)$

$U_{1i} \sim N(0, \sigma_{U_1}^2)$

γ_{00} indicates the average intercept in a design with two levels

γ_{01} indicates the average slope in a design with two levels

σ_{u0}^2 indicates the variance of the intercept between subjects

σ_{u1}^2 indicates the variance of the slope between subjects

In this mixed model, the variance of Y_{ij} , given X_{ij} , is enumerated by the following expression:

$$\text{var}(Y_{ij} | X_{ij}) = \sigma_{u0}^2 + 2\sigma_{01}X_{ij} + \sigma_{u1}^2X_{ij}^2 + \sigma_e^2,$$

where σ_{01} is the covariance between the intercept and the slope.

In addition, there is a possibility that there is a correlation between each of two different visits ($j \neq j'$) by the same subject, which is calculated from the covariance, as follows:

$$\text{Cov}(Y_{ij}, Y_{ij'} | X_{ij}, X_{ij'}) = \sigma_{u0}^2 + \sigma_{01}(X_{ij} + X_{ij'}) + \sigma_{u1}^2 * X_{ij} * X_{ij'}$$

As a consequence, the intraclass correlation coefficients with random intercept and random slope will be defined as follows:

$$\rho(Y_{ij}|X_{ij}) = \frac{\text{Cov}(Y_{ij}, Y_{ij'} | X_{ij}, X_{ij'})}{\text{Var}(Y_{ij}|X_{ij})} = \frac{\sigma_{u0}^2 + \sigma_{01}(X_{ij} + X_{ij'}) + \sigma_{u1}^2 X_{ij} * X_{ij'}}{\sigma_{u0}^2 + 2\sigma_{01}X_{ij} + \sigma_{u1}^2X_{ij}^2 + \sigma_e^2}$$

Therefore, this intraclass correlation coefficient will depend on the value of X .

When the intercept and slope are random in a mixed model, we can use the Stata command *mixed* with the previous database considering the three visits as follows:

```
mixed weight sport, || id: || sport:, stddev
```

Output

Mixed-effects ML regression				Number of obs	=	60

Group Variable	No. of Groups	Observations per Group				
		Minimum	Average	Maximum		

id	20	3	3.0	3		
sport	20	3	3.0	3		

Log likelihood = -140.95844				Wald chi2(1)	=	5.16
				Prob > chi2	=	0.0231

weight	Coef.	Std. Err.	z	P> z	[95% Conf. Interval]	

sport	-2.133333	.9387534	-2.27	0.023	-3.973256	-.2934105
_cons	66.43333	.6637989	100.08	0.000	65.13231	67.73436

Random-effects Parameters		Estimate	Std. Err.	[95% Conf. Interval]	
id: Identity					
	sd(_cons)	1.206639	18.1424	1.92e-13	7.58e+12
sport: Identity					
	sd(_cons)	1.206645	18.14232	1.92e-13	7.58e+12
	sd(Residual)	2.1173	.2367064	1.700675	2.635989
LR test vs. linear model: chi2(2) = 8.40 Prob > chi2 = 0.0150					

The results indicate that there is a significant change in the average expected weight by sport (P -value = .023), even after controlling for the effect between subjects ($\hat{\gamma}_{01} = -2.13$, 95% CI: $-3.97, -0.29$). However, the average of the slopes associated with the sport predictor will vary ± 1.21 , so the pattern of change in the average weight will depend on each visit.

11.6 Mixed Models in a Sampling Design

Let us assume that we have the following information from a random sample of 88 subjects, which will be used to assess the association between hepatitis C virus infection (hcv: 1 = present; 0 = absent) and cocaine metabolite assay result (co: 1 = positive; 0 = negative), controlling for the variables age (age2: 1 = <45 years; 2 = ≥ 45 years) and residential block (block), selected randomly:

	block	co	hcv	age2
1.	3	0	0	2
2.	4	1	1	1
3.	4	1	0	2
4.	1	0	0	2
5.	1	0	0	1
6.	1	1	1	1
7.	4	1	0	1
8.	4	0	0	1
9.	2	0	0	1
10.	2	0	0	1
11.	3	0	1	2
12.	2	0	0	1
13.	2	1	0	2
14.	4	0	0	1
15.	3	0	0	1

16.	1	1	0	2
17.	1	0	0	1
18.	4	1	0	1
19.	2	1	1	1
20.	2	1	0	1

21.	2	0	0	1
22.	2	1	0	1
23.	3	0	0	1
24.	3	1	0	1
25.	3	0	0	1

26.	3	0	0	2
27.	1	1	0	1
28.	1	1	0	1
29.	4	0	0	2
30.	4	0	0	1

31.	4	1	1	2
32.	4	1	1	1
33.	1	0	0	1
34.	2	0	1	1
35.	2	0	0	1

36.	3	0	0	2
37.	3	0	1	1
38.	2	1	0	2
39.	4	0	0	1
40.	4	0	1	1

41.	1	0	0	1
42.	4	0	0	2
43.	4	0	0	1
44.	1	0	0	1
45.	2	1	0	2

46.	2	0	0	1
47.	1	1	1	1
48.	1	1	0	1
49.	3	0	0	1
50.	3	0	0	2

51.	2	0	1	1
52.	2	1	0	1
53.	2	0	0	1
54.	4	0	0	1
55.	4	0	0	1

56.	4	1	1	1
57.	4	0	0	1
58.	4	0	0	1
59.	3	1	0	1
60.	3	1	0	2

61.	3	1	0	1
62.	4	1	1	2
63.	2	0	0	1
64.	2	0	0	1
65.	2	0	0	2

66.	1	0	0	2
67.	2	0	0	1
68.	2	0	0	2
69.	4	0	0	1
70.	2	0	0	2

71.	2	1	0	1
72.	2	1	0	2
73.	2	0	0	2
74.	2	0	0	1
75.	2	0	0	1

76.	3	1	0	2
77.	3	0	0	2
78.	3	0	0	1
79.	1	0	0	1
80.	1	0	0	2

81.	1	0	0	2
82.	3	1	0	2
83.	1	1	0	2
84.	1	0	0	2
85.	2	1	0	1

86.	2	0	0	1
87.	2	1	0	2
88.	1	1	0	1
+-----+				

If the data are analyzed under the assumption that there is a possible correlation between the subjects that reside in the same block (random intercept), the syntax of the *gllamm* command line to estimate the prevalence ratio using a logistic regression model with the option *link(log)*, which is called log-binomial regression model, is as follows:

```
xi:gllamm hcv i.co i.age2,fam(bin) i(block) eform link(log)
```

Output

gllamm model

log likelihood = -34.37179

<i>hcv</i>	<i>exp(b)</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>[95% Conf. Interval]</i>	
<i>_Ico_1</i>	2.834653	1.482238	1.99	0.046	1.017202	7.899373
<i>_Iage2_2</i>	.5385232	.3316394	-1.01	0.315	.1610675	1.800532
<i>_cons</i>	.1036169	.0489457	-4.80	0.000	.0410533	.2615254

Variances and covariances of random effects

****level 2 (block)*

var(1): .0386266 (.20576199)

The results show that the prevalence of HCV infection among cocaine users is 2.83 (95% CI: 1.02, 7.90) times the prevalence of HCV infection among cocaine nonusers, adjusting for age and block of residence. This excess was statistically significant (P -value = .046).

There are other applications of multilevel modeling in health sciences that can be explored in Stata, including ordinal outcomes, count outcomes, and censored outcomes. These topics are beyond the scope of this book, but an extensive review of multilevel modeling can be found in Snijders and Bosker (2003), Leyland and Goldstein (2001), Twisk (2003), and Rabe-Hesketh and Skrondal (2005).