

**Example 9.4. Analysis of odds ratios from various studies.** Suppose the odds ratios measuring the effect of smoking on lung cancer presented in Table 9.6. In the seven studies listed in Table 9.6, only the 95% confidence intervals are available. For three additional studies, the full  $2 \times 2$  contingency tables were also available given in Table 9.7. The aim in this illustrative example is to obtain an overall estimate of the odds ratio using information available from all 10 studies of Tables 9.6 and 9.7.

**Table 9.6** Odds ratios of lung cancer for smokers versus nonsmokers for studies 1–7

Study	Odds ratio	95% CI
1	3.89	0.92 – 16.30
2	3.97	2.20 – 7.16
3	3.88	2.47 – 6.08
4	17.47	14.24 – 21.43
5	5.35	2.44 – 11.74
6	9.10	5.57 – 14.86
7	3.41	2.94 – 3.96

**Table 9.7**  $2 \times 2$  contingency tables of lung cancer and smoking for studies 8–10

Study	Odds Ratio		Cases	Controls
8	3.48	Smokers	49	29958
		Nonsmokers	33	70186
9	33.10	Smokers	12	0
		Nonsmokers	89	118
10	3.43	Smokers	29	4
		Nonsmokers	171	81

Bear in mind that the sample estimates of the log-odds ratios are asymptotically normal, we may use the normal distribution to model the available information of Table 9.6. Hence we may use the following simple hierarchical model

$$\begin{aligned} \log \widehat{\text{OR}}_k &\sim N(\theta_k, \hat{\sigma}_k^2) \\ \theta_k &\sim N(\theta, \sigma_\theta^2) \text{ for } k = 1, 2, \dots, 7, \quad i = 1, 2, \end{aligned}$$

where  $\widehat{\text{OR}}_k$  are the estimated odds ratio for the  $k$ th study as provided in Table 9.7, while  $\hat{\sigma}_k$  is the standard error of the corresponding  $\log \widehat{\text{OR}}_k$  calculated by  $\hat{\sigma}_k = \log(U/L)/(2 \times 1.96)$ , with  $U$  and  $L$ , respectively, denoting the upper and the lower limits of the 95% confidence interval of the odds ratio of Table 9.6. The first equation approximates the likelihood of each study since the original data of the corresponding  $2 \times 2$  contingency tables are not

available. For the last three studies the full data are available, and therefore the following model can be used

$$\begin{aligned}
 Y_{i1k} &\sim \text{binomial}(\pi_{i1k}, Y_{i1k} + Y_{i2k}), \\
 \log\left(\frac{\pi_{i1k}}{1 - \pi_{i1k}}\right) &= a_k + \theta_k I(i = 1) \\
 \theta_k &\sim N(\theta, \sigma_\theta^2) \text{ for } k = 8, 9, 10, \quad i = 1, 2,
 \end{aligned}$$

where  $Y_{ijk}$  refers to the number of observations in the  $k$ th study with smoking and cancer status  $i$  (1=smokers, 2=nonsmokers) and  $j$  (1=case, 2=control), respectively. Parameter  $\theta_k$  is the corresponding odds ratio, while  $a$  is the odds of the disease for the nonsmoking group. Usual noninformative prior distributions can be used for  $a_k$ ,  $\theta$ , and  $\sigma_\theta^2$ .

The code for the first part (seven studies) of the hierarchical model can be specified in WinBUGS using the following syntax

```

for (k in 1:K1){
  logor[k] <- log(or[k])
  selogor[k] <- log(U[k]/L[k])/(2*1.96)
  precision.logor[k] <- 1/pow( selogor[k], 2)
  logor[k] ~ dnorm( theta[k], precision.logor[k] )
  theta[k] ~ dnorm( mu.theta, tau.theta )
  OR[k] <- exp(theta[k])
}

```

while for the second part (studies 8–10) the model is specified using the following syntax:

```

for (k in 1:K2){
  for (i in 1:2){
    N[i,k] <- Y[i,1,k]+Y[i,2,k]
    Y[i,1,k] ~ dbin( p[i,k], N[i,k] )
    logit(p[i,k]) <- a[k] + theta[K1+k] * equals(i,1)
  }
  theta[K1+k] ~ dnorm( mu.theta, tau.theta )
  OR[K1+k] <- exp(theta[K1+k])
}

```

Finally, the prior distributions are defined as usual by

```

for( k in 1:3) { a[k] ~ dnorm( 0.0, 0.001) }
mu.theta ~ dnorm( 0.0, 0.001)
tau.theta ~ dgamma( 0.001, 0.001)

```

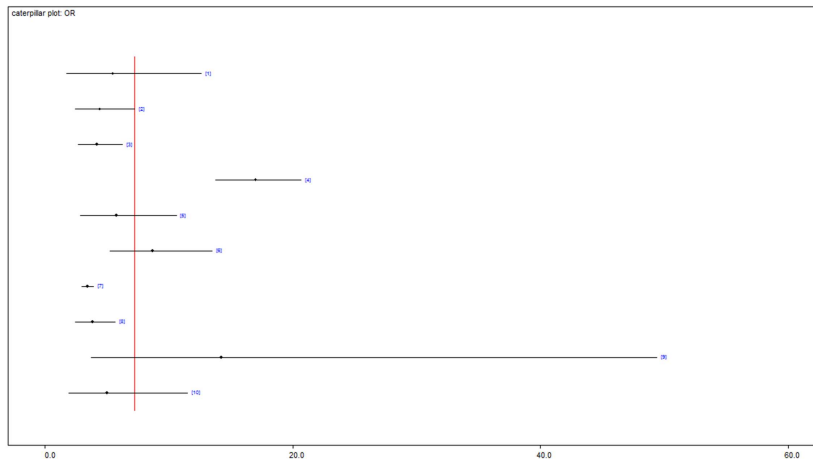
while estimated odds ratios for each study using the preceding model are given by  $e^{\theta_k}$ . The overall estimate of the odds ratio is given by  $e^\theta$ .

The posterior mean of the overall odds ratio is found equal to 5.92, with 95% of the posterior values ranging from 3.55 to 9.44. Error bars of the estimated odds ratios of each study using the hierarchical model presented above are depicted in Figure 9.6.

Additional details concerning hierarchical models and meta-analysis can be found in Woodworth (2004, chap. 11).

### 9.3 THE GENERALIZED LINEAR MIXED MODEL FORMULATION

A popular hierarchical model formulation is that for the so called *generalized linear mixed models*, which is based on the GLM formulation also having a hierarchical structure by including random coefficients/effects in the usual linear predictor.



**Figure 9.6** 95% posterior intervals of adjusted odds ratios of lung cancer for smokers versus nonsmokers for each study in Example 9.4.

Hence the model can be formulated as

$$\mathbf{Y} \sim \mathcal{D}(\boldsymbol{\theta}) \tag{9.2}$$

$$E(\mathbf{Y}) = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{b} \tag{9.3}$$

$$\mathbf{b} \sim N(\mathbf{0}, \mathbf{G}), \tag{9.4}$$

where  $\mathbf{Y}$  is a random response vector that may include repeated measures of the same variable or measurements of correlated variables and  $\mathbf{X}, \mathbf{Z}$  are the data or design matrices for fixed and random effects  $\boldsymbol{\beta}$  and  $\mathbf{b}$ , respectively.

The assumption of normal random effects [Eq. (9.4) in the formulation above] can be easily substituted by another distribution without any difficulty within Bayesian inference, resulting in a different marginal sampling distribution for  $\mathbf{Y}$  assumed by the adopted model.

The normal model is a special case of the preceding formulation for  $\mathcal{D} = \text{normal}$  and  $\boldsymbol{\theta} = (\boldsymbol{\mu}, \boldsymbol{\Sigma})$ . Note that some structure must be imposed on  $\boldsymbol{\Sigma}$  in order to avoid an over-parametrized model. The simplest case is to set  $\boldsymbol{\Sigma} = \sigma^2 \mathbf{I}$ . Variance components in normal models are calculated using logic similar to that followed in Section 9.2.1.1. The total variability is calculated via  $\text{Var}(Y_{ij})$ , while partial variances are provided by the corresponding random effects variances. Correlations within each level of hierarchy also provide useful decomposition and interpretation concerning the source of variability and the necessity of the corresponding random effects and levels of hierarchy.

### 9.3.1 A hierarchical normal model: A simple crossover trial

A frequent implementation of hierarchical models is within the context of crossover trials, in which different treatments are given with different sequences in groups of patients. Here we illustrate a simple two treatment two-period crossover trial in which patients are divided into two groups. The first group receives treatment A for the first period and treatment B for the second period of the study, while the other group receives the same treatments in the reverse order. Random effects are used to capture the correlation that results from the