Stillbirths in Multiple Births: Test of Independence

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The stillbirth rate (SBR) in twins is a more sensitive indicator of environmental hazards than the stillbirth rate in singletons. Medical care or other socioeconomic factors may be more influential for perinatal survival in twin than in single deliveries. Studies have indicated that stillbirths among children in a set of multiple maternities are not independent. Models were considered assuming independent outcomes within a set of multiple maternities. Analyses of the stillbirth rates confirm that the risk of stillbirth among males is almost constantly higher than among females. Any model introduced should assume different stillbirth rates for males and females. The models were tested with both maximum likelihood and minimum \( \chi^2 \) methods.

Material


Our Swedish series starts with birth data for the period 1869 to 1878, published by Berg (1880), where exactly observed numbers were given for the composition of twin pairs and triplet sets with respect to live-births or stillbirths and to sex combinations. Similar information published by Statistics Sweden was available for Sweden for the period 1901 to 1967. Swedish data have also been considered by Fellman and Eriksson (2006b) and Eriksson and Fellman (2006). In Fellman and Eriksson (2006c), the variation in the secondary sex ratio was considered among singletons and twins, and the frequencies of MZ and DZ twin maternities and the reliability of Weinberg’s differential rule estimated. In Fellman and Eriksson (2006b), the temporal variations in the SBR were considered among singletons, twins and triplets. In that study

The stillbirth rate (SBR) in twins is a more sensitive indicator of environmental hazards than the stillbirth rate in singletons (Boklage, 1987; Källén, 1991; Lommatzsch, 1902; Wedervang, 1924). Consequently, variations in medical care or other socioeconomic factors may be more influential to perinatal survival in twin than in singleton deliveries. Studies of offspring in multiple maternities have indicated that stillbirths among the children in a set of multiple maternities are not independent (Salihu et al., 2004). The aim of this study was to identify the effects of such dependence using stochastic models based on the assumption of independence. Preliminary studies of the effect of different SBRs for monozygotic (MZ) and dizygotic (DZ) twins were also performed, but the effect of zygosity will be discussed in more detail in a forthcoming paper (Fellman & Eriksson, 2006a). Analyses of the SBRs for different types of twin pairs confirm that the liability to stillbirth is almost constantly higher among males than among females (Fellman & Eriksson, 2006b; Eriksson & Fellman, 2006). Consequently, in the models introduced, we assumed different SBRs for males and females. The models were tested with both the maximum likelihood (ML) and the minimum \( \chi^2 \) methods.
the temporal trends only were of interest, and not
the influence of additional factors such as marital
status, urbanisation or the sex combination of mul-
tiple births. Therefore, the whole period 1869 to
2001 could be considered. Eriksson and Fellman
(2006) also included influential factors and the
analyses were based on Swedish data for the period
1869 to 1967.
Lommatzsch (1902) analyzed data from Saxony,
1876 to 1900, in detail. Especially, he presented mul-
tiple birth data for the period 1881 to 1900 containing
information about the sex combination and the condi-
tion at birth (live or still).
Eriksson (1973) presented twin data from Åland,
1653 to 1949. We included this data for the period
1750 to 1949 in the present study. The condition at
birth and the sex combination of the twin sets are
crucial and consequently, in our opinion, the data
before 1750 contain too many cases with unknown
sex and condition at birth. Furthermore, the registered
number of twin sets indicates that before 1750 there
may be missing data.
Lowe and Record (1951) presented the distribu-
tion of twin sets for England and Wales (1936–1948)
according to the number of stillborn children. These
data, especially Table 5, are also analyzed by the
authors. However, Lowe and Record published data
are not as informative as the authors’ data from
Sweden, the Åland Islands and England and Wales, or
Lommatzsch’s data from Saxony. Using the percent-
ages presented by Lowe and Record (1951), the
numbers of twin sets were recalculated by the authors
in the different classes. A more restrictive limitation in
Lowe and Record data was that they did not distin-
guish between males and females. Consequently, our
analyses of Lowe and Record data are based on
the assumptions that the SBRs are the same for
males and females.

**Methods**

**Dependence Among the Stillbirths in a Twin Set**

It is obvious that the events of live-birth and stillbirth
among the individuals in a multiple birth set are
dependent (Boklage, 1987; Källén, 1991; Salihu et al.,
2004; Wedervang, 1924). In this study, we investi-
gated the dependence by applying stochastic models.
We assumed the null hypothesis that the outcomes of
two twins in a twin set are independent and that the
probability of a stillborn male is p and of a stillborn
female q. When these probabilities are multiplied by
1000, one obtains estimates of the SBRs. We first con-
sidered the data of same-sexed (SS) twin pairs. We
analyzed the male–male case in detail, and the analysis
of the female–female case was similar.

Assume that the number of twin sets with two live-
born is \( n_{11} \), with one live-born and one stillborn is \( n_{12} \),
with two stillborn is \( n_{22} \) and that \( n = n_{11} + n_{12} + n_{22} \).
Starting from the independence model in Table 1, we
obtain the likelihood function

\[
L(p) = \left[(1-p)^n\right]^{n_{11}} \left[2p(1-p)^{n_{12}}\right]^{n_{12}} C p^{n_{22}} (1-p)^n_{22}
\]

and the log-likelihood function

\[
l(p) = (2n_{12} + n_{11}) \ln( p ) + (2n_{11} + n_{22}) \ln(1 - p)
\]

We obtain

\[
\frac{dl}{dp} = \frac{2n_{12} + n_{11}}{p} - \frac{2n_{11} + n_{22}}{1-p}
\]

and

\[
\frac{d^2l}{dp^2} = \frac{2n_{12} + n_{11}}{p^2} - \frac{2n_{11} + n_{22}}{(1-p)^2}
\]

The equation \( \frac{dl}{dp} = 0 \) gives the maximum likelihood esti-
mator (MLE)

\[
\hat{p} = \frac{n_{12} + 2n_{22}}{2n}
\]

that is, the relative frequency of a stillborn among all
twins. Still assuming independence, we estimate

\[
\hat{q} = \frac{n_{12} + 2n_{22}}{2n} \quad \text{and} \quad \text{Var}( \hat{q} ) = \frac{q(1-q)}{2n}
\]

Consider the model in Table 3 for opposite-sexed (OS)
pairs. We obtain the likelihood function

\[
L(p) = \left[(1-p)^n\right]^{n_{12}} \left[2p(1-p)^{n_{11}}\right]^{n_{11}} p^{n_{22}} q^{n_{22}}
\]

and the log-likelihood function

\[
l(p) = (n_{22} + n_{12}) \ln(p) + (n_{11} + n_{22}) \ln(1 - p) + (n_{22} + n_{12}) \ln(q) + (n_{11} + n_{22}) \ln(1 - q)
\]

The derivatives are

\[
\frac{dl}{dp} = \frac{n_{22} + n_{11}}{p} - \frac{n_{11} + n_{22}}{1-p} \quad \text{and} \quad \frac{dl}{dq} = \frac{n_{22} + n_{11}}{q} - \frac{n_{11} + n_{22}}{1-q}
\]

The second derivatives are

\[
\frac{d^2l}{dp^2} = -\frac{n_{22} + n_{11}}{p^2} - \frac{n_{11} + n_{22}}{(1-p)^2} \quad \text{and} \quad \frac{d^2l}{dpdq} = 0
\]

and

\[
\frac{d^2l}{dq^2} = -\frac{n_{22} + n_{11}}{q^2} - \frac{n_{11} + n_{22}}{(1-q)^2}
\]

The equations

\[
\frac{dl}{dp} = \frac{dl}{dq} = 0
\]
give the MLEs
\[
\hat{p} = \frac{n_1 + n_2}{n} \quad \text{and} \quad \hat{q} = \frac{n_1 + n_3}{n},
\]
that is, the relative frequencies of stillborn male and female twins, respectively. In order to obtain the
variances we estimate
\[
\left( \frac{\partial^2 \chi^2}{\partial p^2} \right) = \frac{n}{p(1-p)} \quad \text{and obtain} \quad \text{Var}(\hat{p}) = \frac{p(1-p)}{n},
\]
and analogously from
\[
- E \left( \frac{\partial^2 \chi^2}{\partial q^2} \right) = \frac{n}{q(1-q)} \quad \text{the variance} \quad \text{Var}(\hat{q}) = \frac{q(1-q)}{n}.
\]
Note that
\[
- E \left( \frac{\partial^2 \chi^2}{\partial p \partial q} \right) = 0
\]
and consequently, the estimators are uncorrelated and \( \text{Cov}(\hat{p}, \hat{q}) = 0 \).

**Minimum \( \chi^2 \) Estimation**

In the Results section we observe that the proposed model does not fit the data. Especially, we note that,
measured with the contribution to the \( \chi^2 \) value, the frequency of sets with two stillborn children diverges most strongly from the proposed model. An alternative method of fitting the data to the model is to use the minimum \( \chi^2 \) estimation. This method minimizes the function
\[
\chi^2 = \sum (n_i - n_i(p))^2/n_i(p)
\]
where \( n_i \) is the observed number, \( n_i(p) \) is the expected number according to the proposed model and \( p \) is the unknown parameter(s). This procedure yields the absolute minimum for the \( \chi^2 \), which indicates that a better fit, measured with the \( \chi^2 \) value, cannot be obtained with any other method. When the models hold, the MLEs and the minimum \( \chi^2 \) estimates are asymptotically equally efficient. However, we prefer the MLEs, because they equal the relative frequency of stillborn, that is, if they are given in per 1000, they are identical to the traditional SBRs.

**The Effect of Zygosity**

One possible factor causing the failure to fit the independence model is that the SS twin series consists of both MZ and DZ twins. If the SBRs among the MZ and DZ twins are different, then the formula \( np^2 \) for the expected number of sets with two stillborn does not hold.

We analyze the effect of zygosity, using the following notations:
\[
n_1 \quad \text{is the number of MZ (male–male) twin sets}
\]
\[
p_1 \quad \text{is the SBR among the MZ twins}
\]
\[
n_2 \quad \text{is the number of DZ (male–male) twin sets}
\]
\[
p_2 \quad \text{is the SBR among the DZ twins and} \quad p_1 + p_2 = 1.
\]

For the total series, we introduce the notations \( n = n_1 + n_2 \) and
\[
p = \frac{n_1 p_1 + n_2 p_2}{n}.
\]

If we do not know or if we ignore the division into MZ and DZ sets, the expected number of twin sets with two stillborn is still \( np^2 \). However, if we consider the division into MZ and DZ twin sets, the expected number of twin sets with two stillborn is \( n_1 p_1^2 + n_2 p_2^2 \).

In order to estimate the effect of the information about MZ and DZ twin sets, we consider the difference
\[
n_1 p_1^2 + n_2 p_2^2 - \left( \frac{n_1 p_1 + n_2 p_2}{n} \right)^2 = n_1 p_1^2 + n_2 (p_1 + \delta)^2 - \left( \frac{n_1 p_1 + n_2 (p_1 + \delta)}{n} \right)^2,
\]
\[
= n_1 p_1^2 + n_2 (\delta^2 + 2p_1 \delta) - \left( \frac{n_1 p_1 + n_2 \delta}{n} \right)^2
\]
\[
= \frac{np_1^2 + n_2 \delta^2 + 2np_1 \delta}{n} - \frac{(np_1 + n_2 \delta)^2}{n} = \frac{nm_1 \delta^2 - n_2 \delta^2}{n} = \frac{n_1(n_1 - n_2)\delta^2}{n} \geq 0.
\]

Note that, independently of the sign of \( \delta \), this difference is always positive. Consequently, if one includes in the model the division of the series into MZ and DZ sets, then the expected number of sets with two stillborn is slightly increased. Hence, the ratio between the observed and the expected is somewhat decreased.

However, in the Results section we observe that this improvement can reduce the high ratio values only to a small degree. Furthermore, the improvement of the model for SS twins reduces the \( \chi^2 \) values only to a small extent. Consequently, the discrepancies with respect to the model are still statistically significant. In addition, this attempt cannot reduce the high ratio values for OS twins. In a forthcoming paper (Fellman & Eriksson, 2006a) we analyze the SBR among MZ and DZ twins in more detail.

**Sets of Triplets and Higher Multiple Maternities**

The statistical ideas discussed above can be generalized to higher multiple maternities. Assume still independence and that the probability of a stillborn male is \( p \) and of a stillborn female is \( q \). Consider a \( k \)-tuple matenity containing \( u \) live-born males, \( v \) live-born females, \( r \) stillborn males and \( s \) stillborn females, that is \( u + v + r + s = k \). The probability for such a \( k \)-tuple is
\[
P_{u,v,r,s} = \frac{k!}{u!v!r!s!} (1-p)^u (1-q)^v p^r q^s.
\]
Within this framework we can consider all types of multiple maternities. However, the data sets for twins are often large enough for more detailed and more informative methods. On the other hand, for higher
multiple maternities the data are usually so rare that reliable results based on this model seem to be unobtainable. Consequently, in our opinion, this method is mainly applicable to triplet data.

Starting from the probability distribution introduced above, we can build a likelihood function and obtain MLEs for $p$ and $q$. Skipping detailed mathematical steps, which are analogous with the derivations presented above, we note that for higher multiple maternities the estimates are

$$
\hat{p} = \frac{\text{number of stillborn males}}{\text{total number of males}}
$$

and

$$
\hat{q} = \frac{\text{number of stillborn females}}{\text{total number of females}}.
$$

The corresponding variances are

$$
\text{Var}(\hat{p}) = \frac{p(1-p)}{kn} \quad \text{and} \quad \text{Var}(\hat{q}) = \frac{q(1-q)}{kn}
$$

respectively.

Although this model is, in practice, applicable to triplet data, a simpler control of the independence can also be suggested. Consider the probability that all the children in the $k$-tuplet are stillborn. If we note that $u = 0$ and $v = 0$, the probability of this case is

$$
\sum_{k,r,s,t} P_{u,v,r,s,t} = \sum_{k,r,s,t} \frac{k!}{s!t!r!} p^r q^s (1-p)^{k-r} (1-q)^{k-s} = (p + q)^k.
$$

The probabilities $p$ and $q$ can be estimated using the whole triplet data set. After that, the estimated probability $(\hat{p} + \hat{q})^k$ can be compared with the observed relative frequency of sets with only stillborn children.

**Results**

The independence models and the observed data from Sweden are given in Tables 1, 2 and 3. In the tables are also given the MLEs, $\hat{p}$ and $\hat{q}$ and the $\chi^2$ values, which have one degree of freedom. According to the $\chi^2$ tests, the models do not fit the empirical data, and the null hypothesis (independence) has to be rejected. Tests of the models based on parameters estimated by the minimum $\chi^2$ method yield somewhat lower $\chi^2$ values, but still statistically significant results.

The strongest discrepancy, measured with the contribution to the $\chi^2$ value, is the number of sets with two stillborn children. Consequently, we pay this discrepancy special attention. If we assume that the models hold, then the expected number of male–male twin sets with two stillborn males is $np^2$, female–female twin sets with two stillborn females is $nq^2$, and male–female twin sets with a stillborn male and a stillborn female is $npq$. We combine the two parameters in the male–female case to one argument by introducing the geometric mean $\bar{p} = \sqrt{pq}$. Consequently, the expected number of twin sets with two stillborn is $npq = n\bar{p}^2$. The number $n$ is the total number of the corresponding type of twin set. In Figure 1a and 1b we present the ratio between the observed number of sets with two stillborn and the number expected under the independence hypothesis. In Figure 1a we present the data compiled by the authors, that is, the Swedish data and the data from England and Wales for the period 1996–2003.

We include in Figure 1b data for the Åland Islands, 1750 to 1949, Saxony, 1881 to 1900 (Lommatzsch, 1902), and for England and Wales, 1938 to 1948 (Lowe & Record, 1951). As pointed out above, our analyses of the data of Lowe and Record must be based on the additional assumption that the SBRs are the same for males and females. In both figures we use the SBR per 1000 as the argument.

We observe that the ratios between the observed and the expected numbers are markedly above the expected value of one, being almost always over three. When the SBR is low, the ratio is extremely high, especially for female–female sets. This indicates that when the SBR decreases, the number of sets with two stillborn decreases more slowly than expected according

<table>
<thead>
<tr>
<th>Period</th>
<th>Live–Live</th>
<th>Live–Still</th>
<th>Still–Still</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>$n(1-p)^2$</td>
<td>$2np(1-p)$</td>
<td>$np^2$</td>
<td>$n$</td>
</tr>
<tr>
<td>1899–78</td>
<td>5103</td>
<td>888</td>
<td>264</td>
<td>6255</td>
</tr>
<tr>
<td>1901–10</td>
<td>5606</td>
<td>759</td>
<td>301</td>
<td>6666</td>
</tr>
<tr>
<td>1911–20</td>
<td>5156</td>
<td>686</td>
<td>258</td>
<td>6100</td>
</tr>
<tr>
<td>1921–30</td>
<td>4309</td>
<td>551</td>
<td>170</td>
<td>5030</td>
</tr>
<tr>
<td>1931–40</td>
<td>3380</td>
<td>454</td>
<td>138</td>
<td>3972</td>
</tr>
<tr>
<td>1941–50</td>
<td>4542</td>
<td>459</td>
<td>122</td>
<td>5123</td>
</tr>
<tr>
<td>1951–60</td>
<td>3641</td>
<td>288</td>
<td>64</td>
<td>3993</td>
</tr>
<tr>
<td>1961–67</td>
<td>2577</td>
<td>133</td>
<td>38</td>
<td>2748</td>
</tr>
<tr>
<td>Total</td>
<td>34,314</td>
<td>4218</td>
<td>1355</td>
<td>39,887</td>
</tr>
</tbody>
</table>

Note: The probability $\hat{p}$ was estimated according to the independence model for stillbirths. The estimate is the relative frequency of stillbirths. Consequently, if it is multiplied by 1000 one obtains the SBR per 1000. The $\chi^2$ values were obtained when the observed data were tested against the numbers estimated according to the model.
to the independence model. The points representing different countries in Figure 1a and 1b fit in well with the general pattern. Consequently, the dependence of the outcomes in the twin pairs causing an excess of twin sets containing two stillborns seems to be universal, following a certain trend.

In the Methods section we stressed that if it is possible to differentiate the SS twins into MZ and DZ twins, then the expected number of twin sets with two stillborn children is slightly increased. Preliminary studies of our different data sets indicate that the ratios are reduced by, at most, 20%. Such a reduction cannot solve the central problem concerning the high ratio values. Furthermore, if we assume that the independence holds within the MZ and DZ twin series, then the improvement of the goodness-of-fit is only minute and the deviations from the models are still statistically strongly significant. Furthermore, no similar reduction among OS twins is possible.

We also present an alternative attempt to consider the proportion of twin sets with two stillborn. Let this proportion be \( p_{22} \). According to the independence model, \( p_{22} = p^2 \) among male–male twin sets, \( p_{22} = q^2 \) among female–female twin sets and \( p_{22} = pq = p^2 \) among OS twin sets. Consequently, the general formula should be \( p_{22} = p^2 \). In Figure 1a and 1b we observed an excess of twin sets with two stillborn. We tried to fit two alternative regression models, the first one, \( p_{22} = \alpha + \beta p^2 + \epsilon \), with an intercept and the second, \( p_{22} = \beta p^2 + \epsilon \), without the intercept. An excess of twin sets with two stillborn should result in an estimate \( \hat{\beta} > 1 \). We estimated the parameters in the models by weighted least squares. As weights the total number of twin sets was used. The argument for this is that the regressand \( p_{22} \) is a relative frequency and its variance is proportional to \( n^{-1} \) (Fellman & Eriksson, 1987). Figures 1a and 1b indicate that one can expect the same model to hold for different populations. Consequently, we considered all the data sets, but we

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analyzed SS, OS and all twin sets separately. The estimates are given in Table 4. We observe that, for both models, the differences between the $\beta$ estimates for SS and OS data are not statistically significant. Consequently we used the whole material and estimated common parameters. Irrespective of the model chosen, estimate $\hat{\beta}$ is statistically significantly greater than one. This result supports our earlier finding that the proportion of twin sets with two stillborns differs from the expected. The intercept differs significantly from zero and, consequently, we have two alternative models, but both support our earlier conclusions. The model without an intercept seems to be more logical, because $p_{22}$ has to be zero if $p = 0$. However, the positive intercept supports the observed increasing trend discussed in Figure 1a and 1b. In addition, the interval under study is $(10 \leq \text{SBR} \leq 113)$ and, within this interval, the model with the intercept can also be considered relevant.

In Figure 2 we present the data and the curves based on both models and also include the curve $p_{22} = p^2$ corresponding to the independence model. All the data points observed are above that curve.

**Triplet Sets**

Above we have noted that if the probability of a stillborn male in a triplet set is $p$ and of a stillborn female
is \( q \), then the expected number of triplet sets with three stillborn children is \( n(p + q)^3 \). Among the 3594 triplets from Sweden, 1869 to 1967, 414 were stillborn. The estimated SBR for triplet males is \( p = 0.1135 \) and for females \( q = 0.1163 \). The observed number of triplet sets with three stillborn children is 34 and the estimated number is \( n(p + q)^3 = 14.54 \). Consequently, the ratio between the observed and the estimated number is 2.3.

Among the 5670 triplets for England and Wales, 1996 to 2003, 157 were stillborn. The estimated SBR for triplet males is \( p = 0.0301 \) and for females \( q = 0.0252 \). The observed number of triplet sets with three stillborn children is six and the estimated number is \( n(p + q)^3 = 0.319 \). Consequently, the ratio between the observed and the estimated number is 18.8 (cf. Figure 1a, 1b). Lommatzsch (1902) presented triplets in Saxony, 1881 to 1900. He noted 345 triplet sets with known sex combination and known health condition and among these there were seven triplet sets with three stillborn. According to his data, we obtained an SBR among males of 0.1058 and among females 0.1284. Consequently, the expected number of sets with all stillborn is 4.43, and the ratio is 1.6.

Our studies of the twin and triplet data sets indicate that if the information concerning stillbirths among multiple births is only the relative frequency of

### Table 4

<table>
<thead>
<tr>
<th>Model</th>
<th>( n )</th>
<th>( \alpha )</th>
<th>( \beta )</th>
<th>( \hat{\beta} )</th>
<th>( \hat{\alpha} )</th>
<th>( \hat{\beta} )</th>
</tr>
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<tr>
<td>Same-sexed twin sets</td>
<td>27</td>
<td>Estimate</td>
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<td>0.009165</td>
<td>3.349</td>
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</tr>
<tr>
<td>SE</td>
<td>0.209</td>
<td></td>
<td>0.001415</td>
<td>0.244</td>
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<td></td>
</tr>
<tr>
<td>( t )</td>
<td>17.62</td>
<td></td>
<td>6.477</td>
<td>9.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opposite-sexed twin sets</td>
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<td>Estimate</td>
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<td>0.002689</td>
<td>3.342</td>
<td></td>
</tr>
<tr>
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<td></td>
<td>0.001287</td>
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</tr>
<tr>
<td>( t )</td>
<td>13.38</td>
<td></td>
<td>2.090</td>
<td>5.81</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Estimate</td>
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<td>0.005181</td>
<td>3.745</td>
<td></td>
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<td></td>
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<td>21.91</td>
<td></td>
<td>4.253</td>
<td>11.30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The \( t \) values were obtained when the intercept estimates were tested against zero and the regression parameter estimates against one.
sets with two stillborns, then estimates of the SBRs based on this frequency have positive biases.

**Discussion**

Wedervang (1924, p. 259) noted that the proportion of twin maternities with two stillborn children is much higher among SS than among OS twin sets. Salihu et al. (2004) stated that siblings within a plurality set are generally subjected to similar prevailing conditions in the womb and are equally affected by the same attributes that characterize the mother. It is logical to expect conditions leading to the stillbirth of the member of a plurality set to have affected the other siblings as well, although unexplained factors determining vulnerability may vary. In short, one has to distinguish between the intracluster variation, that is the variation between individual twins or triplets, and the intercluster variation, that is the variation between mothers.

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**References**


