Analysis of bivariate binomial data: Twin analysis

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Overview

When looking at bivariate binomial data with the aim of learning about the dependence that is present, possibly after correcting for some covariates many models are available.

- Random-effects models logistic regression covered elsewhere (glmer in lme4).

  in the mets package you can fit the

- Pairwise odds ratio model
- Bivariate Probit model
  - With random effects
  - Special functionality for polygenic random effects modelling such as ACE, ADE ,AE and so forth.
- Additive gamma random effects model
  - Special functionality for polygenic random effects modelling such as ACE, ADE ,AE and so forth.

Typically it can be hard or impossible to specify random effects models with special structure among the parameters of the random effects. This is possible in our models.

To be concrete about the model structure assume that we have paired binomial data Y_1, Y_2, X_1, X_2 where the responses are Y_1, Y_2 and we have covariates X_1, X_2.

We start by giving a brief description of these different models. First we for bivariate data one can specify the marginal probability using logistic regression models

$$logit(P(Y_i = 1|X_i)) = \alpha_i + X_i^T \beta i = 1, 2.$$

These model can be estimated under working independence [1].

[1]

A typical twin analysis will typically consist of looking at both

- Pairwise odds ratio model
- Bivariate Probit model

The additive gamma can be used for the same as the bivariate probit model but is more restrictive in terms of dependence structure, but is nevertheless still valuable to have also as a check of results of the bivariate probit model.

Biprobit with random effects

For these model we assume that given random effects Z and a covariate vector V_{12} we have independent logistic regression models

$$probit(P(Y_i = 1|X_i, Z)) = \alpha_i + X_i^T\beta + V_{12}^T Zi = 1, 2.$$

where Z is a bivariate normal distribution with some covariance Σ. The general covariance structure Σ makes the model very flexible.

We note that

- Paramters β are subject specific
- The Σ will reflect dependence

The more standard link function *logit* rather than the *probit* link is often used and implemented in for example [2]. The advantage is that one now gets an odds-ratio interpretation of the subject specific effects, but one then needs numerical integration to fit the model.

#We note that

Pairwise odds ratio model

Now the pairwise odds ratio model the specifies that given X_1, X_2 the marginal models are

$$logit(P(Y_i = 1|X_i)) = \alpha_i + X_i^T\beta i = 1, 2$$

The primary object of interest are the odds ratio between Y_1 and Y_2

$$\gamma_{12} = \frac{P(Y_{ki} = 1, Y_{kj} = 1)P(Y_{ki} = 0, Y_{kj} = 0)}{P(Y_{ki} = 1, Y_{kj} = 0)P(Y_{ki} = 0, Y_{kj} = 1)}$$

given X_{ki}, X_{kj}, and Z_{kji}.

We model the odds ratio with the regression

$$\gamma_{12} = \exp(Z_{12}^T\lambda)$$

Where Z_{12} are some covarites that may influence the odds-ratio between between Y_1 and Y_2 and contains the marginal covariates, [3]. This odds-ratio is given covariates as well as marginal covariates. The odds-ratio and marginals specify the joint bivariate distribution via the so-called Placckett-distribution.

One way of fitting this model is the ALR algoritm, the alternating logistic regression ahd this has been described in several papers [4]. We here simply estimate the parameters in a two stage-procedure

- Estimating the marginal parameters via GEE
- Using marginal estimates, estimate dependence parameters

This gives efficient estimates of the dependence parameters because of orthogonality, but some efficiency may be gained for the marginal parameters by using the full likelihood or iterative fitting such as for the ALR.

The pairwise odds-ratio model is very useful, but one do not have a random effects model.

[2]

[3] ; ; ; and

[4] ; ; and

Additive gamma model

Again we operate under marginal logistic regression models are

$$logit(P(Y_i = 1|X_i)) = \alpha_i + X_i^T \beta i = 1, 2$$

First with just one random effect Z we assume that conditional on Z the responses are independent and follow the model

$$logit(P(Y_i = 1|X_i, Z)) = exp(-Z \cdot \Psi^{-1}(\lambda_\bullet, \lambda_\bullet, P(Y_i = 1|X_i)))$$

where Ψ is the laplace transform of Z where we assume that Z is gamma distributed with variance $\lambda_\bullet^{-1}$ and mean 1. In general $\Psi(\lambda_1, \lambda_2)$ is the laplace transform of a Gamma distributed random effect with Z with mean λ_1/λ_2 and variance λ_1/λ_2^2.

We fit this model by

- Estimating the marginal parameters via GEE
- Using marginal estimates, estimate dependence parameters

To deal with multiple random effects we consider random effects $Z_i i = 1, ..., d$ such that Z_i is gamma distributed with mean $\lambda_j/\lambda_\bullet$ and variance $\lambda_j/\lambda_\bullet^2$, where we define the scalar $\lambda_\bullet$ below.

Now given a cluster-specific design vector V_{12} we assume that

$$V_{12}^T Z$$

is gamma distributed with mean 1 and variance $\lambda_\bullet^{-1}$ such that critically the random effect variance is the same for all clusters. That is

$$\lambda_\bullet = V_{12}^T (\lambda_1, ..., \lambda_d)^T$$

We return to some specific models below, and show how to fit the ACE and AE model using this set-up.

One last option in the model-specification is to specify how the parameters $\lambda_1, ..., \lambda_d$ are related. We thus can specify a matrix M of dimension $p \times d$ such that

$$(\lambda_1, ..., \lambda_d)^T = M\theta$$

where θ is d-dimensional. If M is diagonal we have no restrictions on parameters.

This parametrization is obtained with the var.par=0 option that thus estimates θ.

The DEFAULT parametrization instead estimates the variances of the random effecs (var.par=1) via the parameters ν

$$M\nu = (\lambda_1/\lambda_\bullet^2, ..., \lambda_d/\lambda_\bullet^2)^T$$

The basic modelling assumption is now that given random effects $Z = (Z_1, ..., Z_d)$ we have independent probabilites

$$logit(P(Y_i = 1|X_i, Z)) = exp(-V_{12,i}^T Z \cdot \Psi^{-1}(\lambda_\bullet, \lambda_\bullet, P(Y_i = 1|X_i)))i = 1, 2$$

We fit this model by

- Estimating the marginal parameters via GEE
- Using marginal estimates, estimate dependence parameters

Even though the model not formaly in this formulation allows negative correlation in practice the paramters can be negative and this reflects negative correlation. An advanatage is that no numerical integration is needed.

The twin-stutter data

We consider the twin-stutter where for pairs of twins that are either dizygotic or monozygotic we have recorded whether the twins are stuttering [5]

[5]

We here consider MZ and same sex DZ twins.

Looking at the data

```
library(mets)
data(twinstut)
twinstut$binstut <- 1*(twinstut$stutter=="yes")
twinsall <- twinstut
twinstut <- subset(twinstut,zyg%in%c("mz","dz"))
head(twinstut)
```

```
Loading required package: timereg
Loading required package: survival
Loading required package: lava
lava version 1.5.1
mets version 1.2.1.2

Attaching package: 'mets'

The following object is masked _by_ '.GlobalEnv':

    object.defined

Warning message:
failed to assign RegisteredNativeSymbol for cor to cor since cor is already defined in the 'mets' namespace
   tvparnr zyg stutter    sex age nr binstut
1  2001005  mz      no female  71  1       0
2  2001005  mz      no female  71  2       0
3  2001006  dz      no female  71  1       0
8  2001012  mz      no female  71  1       0
9  2001012  mz      no female  71  2       0
11 2001015  dz      no   male  71  1       0
```

Pairwise odds ratio model

We start by fitting an overall dependence OR for both MZ and DZ even though the dependence is expected to be different across zygosity.

The first step is to fit the marginal model adjusting for marginal covariates. We here note that there is a rather strong gender effect in the risk of stuttering.

```
margbin <- glm(binstut~factor(sex)+age,data=twinstut,family=binomial())
summary(margbin)
```

```
Call:
glm(formula = binstut ~ factor(sex) + age, family = binomial(),
    data = twinstut)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-0.4419  -0.4078  -0.2842  -0.2672   2.6395

Coefficients:
                Estimate Std. Error z value Pr(>|z|)
(Intercept)     -3.027625   0.104012 -29.108  < 2e-16 ***
factor(sex)male  0.869826   0.062197  13.985  < 2e-16 ***
age             -0.005983   0.002172  -2.754  0.00588 **
---
Signif. codes:  0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 9328.6  on 21287  degrees of freedom
Residual deviance: 9117.0  on 21285  degrees of freedom
AIC: 9123

Number of Fisher Scoring iterations: 6
```

Now estimating the OR parameter. We see a strong dependence with an OR at around 8 that is clearly significant.

```
bina <- binomial.twostage(margbin,data=twinstut,var.link=1,
                      clusters=twinstut$tvparnr,detail=0)
summary(bina)
```

```
Dependence parameter for Odds-Ratio (Plackett) model
With log-link
$estimates
               theta        se
dependence1 2.085347 0.1274536

$or
            Estimate Std.Err 2.5% 97.5% P-value
dependence1     8.05    1.03 6.04  10.1 4.3e-15

$type
[1] "plackett"

attr(,"class")
[1] "summary.mets.twostage"
```

Now, and more interestingly, we consider an OR that depends on zygosity and note that MZ have a much larger OR than DZ twins. This type of trait is somewhat complicated to interpret, but clearly, one option is that that there is a genetic effect, alternatively there might be a stronger environmental effect for MZ twins.

```
### design for OR dependence
theta.des <- model.matrix( ~-1+factor(zyg),data=twinstut)
bin <- binomial.twostage(margbin,data=twinstut,var.link=1,
                         ↪  clusters=twinstut$tvparnr,theta.des=theta.des)
summary(bin)
```

```
Dependence parameter for Odds-Ratio (Plackett) model
With log-link
$estimates
```

```
                   theta        se
factor(zyg)dz 0.5221651 0.2401355
factor(zyg)mz 3.4853933 0.1866076

$or
              Estimate Std.Err   2.5% 97.5%  P-value
factor(zyg)dz     1.69   0.405  0.892  2.48 3.12e-05
factor(zyg)mz    32.64   6.090 20.699 44.57 8.38e-08

$type
[1] "plackett"

attr(,"class")
[1] "summary.mets.twostage"
```

We now consider further regression modelling of the OR structure by considering possible interactions between sex and zygozsity. We see that MZ has a much higher dependence and that males have a much lower dependence. We tested for interaction in this model and these were not significant.

```
twinstut$cage <- scale(twinstut$age)
theta.des <- model.matrix( ~-1+factor(zyg)+factor(sex),data=twinstut)
bina <- binomial.twostage(margbin,data=twinstut,var.link=1,
                          ↪  clusters=twinstut$tvparnr,theta.des=theta.des)
summary(bina)
```

```
Dependence parameter for Odds-Ratio (Plackett) model
With log-link
$estimates
                     theta        se
factor(zyg)dz    0.8098841 0.3138423
factor(zyg)mz    3.7318076 0.2632250
factor(sex)male -0.4075409 0.3055349

$or
                Estimate Std.Err   2.5% 97.5%  P-value
factor(zyg)dz      2.248   0.705  0.865  3.63 0.001441
factor(zyg)mz     41.755  10.991 20.213 63.30 0.000145
factor(sex)male    0.665   0.203  0.267  1.06 0.001064

$type
[1] "plackett"

attr(,"class")
[1] "summary.mets.twostage"
```

Alternative syntax

We now demonstrate how the models can fitted jointly and with anohter syntax, that ofcourse just fits the marginal model and subsequently fits the pairwise OR model.

First noticing as before that MZ twins have a much higher dependence.

```
## refers to zygosity of first subject in eash pair : zyg1
## could also use zyg2 (since zyg2=zyg1 within twinpair's)
out <- easy.binomial.twostage(stutter~factor(sex)+age,data=twinstut,
               response="binstut",id="tvparnr",var.link=1,
               theta.formula=~-1+factor(zyg1))
summary(out)
```

```
Dependence parameter for Odds-Ratio (Plackett) model
With log-link
$estimates
                    theta        se
factor(zyg1)dz 0.5221651 0.2401355
factor(zyg1)mz 3.4853933 0.1866076

$or
                Estimate Std.Err   2.5% 97.5%  P-value
factor(zyg1)dz     1.69   0.405  0.892  2.48 3.12e-05
factor(zyg1)mz    32.64   6.090 20.699 44.57 8.38e-08

$type
[1] "plackett"

attr(,"class")
[1] "summary.mets.twostage"
```

Now considering all data and estimating separate effects for the OR for opposite sex DZ twins and same sex twins. We here find that os twins are not markedly different from the same sex DZ twins.

```
## refers to zygosity of first subject in eash pair : zyg1
## could also use zyg2 (since zyg2=zyg1 within twinpair's))

desfs<-function(x,num1="zyg1",num2="zyg2")
        c(x[num1]=="dz",x[num1]=="mz",x[num1]=="os")*1

margbinall <-
  glm(binstut~factor(sex)+age,data=twinsall,family=binomial())
out3 <- easy.binomial.twostage(binstut~factor(sex)+age,
      data=twinsall,response="binstut",id="tvparnr",var.link=1,
      theta.formula=desfs,desnames=c("dz","mz","os"))
summary(out3)
```

```
Dependence parameter for Odds-Ratio (Plackett) model
With log-link
$estimates
       theta        se
dz 0.5278527 0.2396796
mz 3.4850037 0.1864190
os 0.7802940 0.2894394

$or
   Estimate Std.Err   2.5% 97.5%  P-value
dz     1.70   0.406  0.899  2.49 3.02e-05
mz    32.62   6.081 20.703 44.54 8.13e-08
os     2.18   0.632  0.944  3.42 5.50e-04

$type
[1] "plackett"

attr(,"class")
[1] "summary.mets.twostage"
```

Bivariate Probit model

```
library(mets)
data(twinstut)
twinstut <- subset(twinstut,zyg%in%c("mz","dz"))
twinstut$binstut <- 1*(twinstut$stutter=="yes")
head(twinstut)
```

```
   tvparnr zyg stutter    sex age nr binstut
1  2001005  mz      no female  71  1       0
2  2001005  mz      no female  71  2       0
3  2001006  dz      no female  71  1       0
8  2001012  mz      no female  71  1       0
9  2001012  mz      no female  71  2       0
11 2001015  dz      no   male  71  1       0
```

First testing for same dependence in MZ and DZ that we recommend doing by comparing the correlations of MZ and DZ twins. Apart from regression correction in the mean this is an un-structured model, and the useful concordance and casewise concordance estimates can be reported from this analysis.

```
b1 <-
 ↪  bptwin(binstut~sex,data=twinstut,id="tvparnr",zyg="zyg",DZ="dz",type="un")
summary(b1)
```

```
                Estimate    Std.Err          Z p-value
(Intercept)    -1.794823   0.023289 -77.066728  0.0000
sexmale         0.401432   0.030179  13.301813  0.0000
atanh(rho) MZ   1.096916   0.073574  14.909087  0.0000
atanh(rho) DZ   0.132458   0.062516   2.118800  0.0341

 Total MZ/DZ Complete pairs MZ/DZ
 8777/12511  3255/4058

                          Estimate 2.5%    97.5%
Tetrachoric correlation MZ 0.79939  0.74101 0.84577
Tetrachoric correlation DZ 0.13169  0.00993 0.24960

MZ:
                     Estimate 2.5%     97.5%
Concordance           0.01698  0.01411  0.02042
Casewise Concordance  0.46730  0.40383  0.53185
Marginal              0.03634  0.03287  0.04016
Rel.Recur.Risk       12.85882 10.87510 14.84253
log(OR)               3.75632  3.37975  4.13289
DZ:
                     Estimate 2.5%    97.5%
Concordance          0.00235  0.00140 0.00393
Casewise Concordance 0.06456  0.03937 0.10413
Marginal             0.03634  0.03287 0.04016
Rel.Recur.Risk       1.77662  0.92746 2.62577
log(OR)              0.63527  0.09013 1.18040

                         Estimate 2.5% 97.5%
Broad-sense heritability   1      NaN  NaN
```

Polygenic modelling

We now turn attention to specific polygenic modelling where special random effects are used to specify ACE, AE, ADE models and so forth. This is very easy with the bptwin function. The key parts of the output are the sizes of the genetic component A and the environmental component, and we can compare with the results of the unstructed model above. Also formally we can test if this submodel is acceptable by a likelihood ratio test.

```
b1 <-
 ↪  bptwin(binstut~sex,data=twinstut,id="tvparnr",zyg="zyg",DZ="dz",type="ace")
summary(b1)
```

```
              Estimate   Std.Err         Z p-value
(Intercept)  -3.70371   0.24449 -15.14855       0
sexmale       0.83310   0.08255  10.09201       0
log(var(A))   1.18278   0.17179   6.88512       0
log(var(C)) -29.99519        NA        NA      NA

 Total MZ/DZ Complete pairs MZ/DZ
 8777/12511  3255/4058

                   Estimate 2.5%    97.5%
A                  0.76545  0.70500 0.82590
C                  0.00000  0.00000 0.00000
E                  0.23455  0.17410 0.29500
MZ Tetrachoric Cor 0.76545  0.69793 0.81948
DZ Tetrachoric Cor 0.38272  0.35210 0.41253

MZ:
                     Estimate 2.5%     97.5%
Concordance           0.01560  0.01273  0.01912
Casewise Concordance  0.42830  0.36248  0.49677
Marginal              0.03643  0.03294  0.04027
Rel.Recur.Risk       11.75741  9.77237 13.74246
log(OR)               3.52382  3.13466  3.91298
DZ:
                     Estimate 2.5%    97.5%
Concordance          0.00558  0.00465 0.00670
Casewise Concordance 0.15327  0.13749 0.17050
Marginal             0.03643  0.03294 0.04027
Rel.Recur.Risk       4.20744  3.78588 4.62900
log(OR)              1.69996  1.57262 1.82730

                         Estimate 2.5%    97.5%
Broad-sense heritability 0.76545  0.70500 0.82590
```

```
b0 <-
 ↪  bptwin(binstut~sex,data=twinstut,id="tvparnr",zyg="zyg",DZ="dz",type="ae")
summary(b0)
```

```
              Estimate   Std.Err         Z p-value
(Intercept)  -3.70371   0.24449 -15.14855       0
sexmale       0.83310   0.08255  10.09201       0
log(var(A))   1.18278   0.17179   6.88512       0

 Total MZ/DZ Complete pairs MZ/DZ
 8777/12511  3255/4058

                   Estimate 2.5%    97.5%
A                  0.76545  0.70500 0.82590
E                  0.23455  0.17410 0.29500
MZ Tetrachoric Cor 0.76545  0.69793 0.81948
DZ Tetrachoric Cor 0.38272  0.35210 0.41253

MZ:
                     Estimate 2.5%     97.5%
Concordance           0.01560  0.01273  0.01912
Casewise Concordance  0.42830  0.36248  0.49677
Marginal              0.03643  0.03294  0.04027
Rel.Recur.Risk       11.75741  9.77237 13.74246
log(OR)               3.52382  3.13466  3.91298
DZ:
                     Estimate 2.5%    97.5%
Concordance          0.00558  0.00465 0.00670
```

```
Casewise Concordance 0.15327  0.13749 0.17050
Marginal             0.03643  0.03294 0.04027
Rel.Recur.Risk       4.20744  3.78588 4.62900
log(OR)              1.69996  1.57262 1.82730

                         Estimate 2.5%    97.5%
Broad-sense heritability 0.76545  0.70500 0.82590
```

Additive gamma random effects

Fitting first a model with different size random effects for MZ and DZ. We note that as before in the OR and biprobit model the dependence is much stronger for MZ twins. We also test if these are the same by parametrizing the OR model with an intercept. This clearly shows a significant difference.

```
theta.des <- model.matrix( ~-1+factor(zyg),data=twinstut)
margbin <- glm(binstut~sex,data=twinstut,family=binomial())
bintwin <- binomial.twostage(margbin,data=twinstut,model="gamma",
     clusters=twinstut$tvparnr,detail=0,theta=c(0.1)/1,var.link=1,
     theta.des=theta.des)
summary(bintwin)

### test for same dependence in MZ and DZ
theta.des <- model.matrix( ~factor(zyg),data=twinstut)
margbin <- glm(binstut~sex,data=twinstut,family=binomial())
bintwin <- binomial.twostage(margbin,data=twinstut,model="gamma",
     clusters=twinstut$tvparnr,detail=0,theta=c(0.1)/1,var.link=1,
     theta.des=theta.des)
summary(bintwin)
```

```
Dependence parameter for Clayton-Oakes model
Variance of Gamma distributed random effects
With log-link
$estimates
                    theta        se
factor(zyg)dz -2.61194495 0.4854454
factor(zyg)mz -0.01817181 0.1030735

$vargam
              Estimate Std.Err    2.5% 97.5%  P-value
factor(zyg)dz   0.0734  0.0356 0.00356 0.143 3.94e-02
factor(zyg)mz   0.9820  0.1012 0.78361 1.180 2.96e-22

$type
[1] "gamma"

attr(,"class")
[1] "summary.mets.twostage"
Dependence parameter for Clayton-Oakes model
Variance of Gamma distributed random effects
With log-link
$estimates
                  theta        se
(Intercept)   -2.611945 0.4854454
factor(zyg)mz  2.593773 0.4962675

$vargam
              Estimate Std.Err    2.5%  97.5% P-value
(Intercept)     0.0734  0.0356 0.00356  0.143  0.0394
factor(zyg)mz  13.3802  6.6401 0.36573 26.395  0.0439

$type
```

```
[1] "gamma"

attr(,"class")
[1] "summary.mets.twostage"
```

Polygenic modelling

First setting up the random effects design for the random effects and the the relationship between variance parameters. We see that the genetic random effect has size one for MZ and 0.5 for DZ subjects, that have shared and non-shared genetic components with variance 0.5 such that the total genetic variance is the same for all subjects. The shared environmental effect is the samme for all. Thus two parameters with these bands.

```
out <-
  ↪  twin.polygen.design(twinstut,id="tvparnr",zygname="zyg",zyg="dz",type="ace")
head(cbind(out$des.rv,twinstut$tvparnr),10)
out$pardes
```

```
   MZ DZ DZns1 DZns2 env
1   1  0     0     0   1 2001005
2   1  0     0     0   1 2001005
3   0  1     1     0   1 2001006
8   1  0     0     0   1 2001012
9   1  0     0     0   1 2001012
11  0  1     1     0   1 2001015
12  0  1     1     0   1 2001016
13  0  1     0     1   1 2001016
15  0  1     1     0   1 2001020
18  0  1     1     0   1 2001022
     [,1] [,2]
[1,]  1.0    0
[2,]  0.5    0
[3,]  0.5    0
[4,]  0.5    0
[5,]  0.0    1
```

Now, fitting the ACE model, we see that the variance of the genetic, component, is 1.5 and the environmental variance is -0.5. Thus suggesting that the ACE model does not fit the data. When the random design is given we automatically use the gamma fralty model.

```
margbin <- glm(binstut~sex,data=twinstut,family=binomial())
bintwin1 <- binomial.twostage(margbin,data=twinstut,
     clusters=twinstut$tvparnr,detail=0,theta=c(0.1)/1,var.link=0,
     random.design=out$des.rv,theta.des=out$pardes)
summary(bintwin1)
```

```
Dependence parameter for Clayton-Oakes model
Variance of Gamma distributed random effects
$estimates
                 theta        se
dependence1  1.5261839 0.2475041
dependence2 -0.5447955 0.1942159

$type
[1] "clayton.oakes"
```

```
$h
             Estimate Std.Err   2.5%  97.5%  P-value
dependence1     1.555   0.187  1.189  1.922 9.11e-17
dependence2    -0.555   0.187 -0.922 -0.189 2.99e-03

$vare
NULL

$vartot
   Estimate Std.Err  2.5% 97.5%  P-value
p1    0.981   0.102 0.781  1.18 8.29e-22

attr(,"class")
[1] "summary.mets.twostage"
```

For this model we estimate the concordance and casewise concordance as well as the marginal rates of stuttering for females.

```
concordance.twin.ace(bintwin1,type="ace")
```

```
$MZ
                     Estimate Std.Err   2.5%  97.5%  P-value
concordance            0.0182 0.00147 0.0153 0.0211 2.61e-35
casewise concordance   0.5033 0.03256 0.4395 0.5672 6.49e-54
marginal               0.0362 0.00188 0.0325 0.0399 7.15e-83

$DZ
                     Estimate  Std.Err   2.5%   97.5%  P-value
concordance           0.00235 0.000589 0.0012 0.00351 6.45e-05
casewise concordance  0.06501 0.015836 0.0340 0.09604 4.04e-05
marginal              0.03620 0.001877 0.0325 0.03988 7.15e-83
```

The E component was not consistent with the fit of the data and we now consider instead the AE model.

```
out <-
  ↪  twin.polygen.design(twinstut,id="tvparnr",zygname="zyg",zyg="dz",type="ae")

bintwin <- binomial.twostage(margbin,data=twinstut,
     clusters=twinstut$tvparnr,detail=0,theta=c(0.1)/1,var.link=0,
     random.design=out$des.rv,theta.des=out$pardes)
summary(bintwin)
```

```
Dependence parameter for Clayton-Oakes model
Variance of Gamma distributed random effects
$estimates
                theta         se
dependence1 0.9094847 0.09536268

$type
[1] "clayton.oakes"

$h
             Estimate Std.Err 2.5% 97.5% P-value
dependence1         1       0    1     1       0

$vare
NULL

$vartot
   Estimate Std.Err  2.5% 97.5%  P-value
p1    0.909  0.0954 0.723   1.1 1.47e-21

attr(,"class")
[1] "summary.mets.twostage"
```

Again, the concordance can be computed:

```
concordance.twin.ace(bintwin,type="ae")
```

```
$MZ
                     Estimate Std.Err   2.5%  97.5%  P-value
concordance            0.0174 0.00143 0.0146 0.0202 5.00e-34
casewise concordance   0.4795 0.03272 0.4154 0.5437 1.20e-48
marginal               0.0362 0.00188 0.0325 0.0399 7.15e-83

$DZ
                     Estimate  Std.Err   2.5%   97.5%   P-value
concordance           0.00477 0.000393 0.0040 0.00554  5.94e-34
casewise concordance  0.13175 0.005417 0.1211 0.14237 1.14e-130
marginal              0.03620 0.001877 0.0325 0.03988  7.15e-83
```