

Twin analysis

Klaus Holst & Thomas Scheike

February 26, 2017

Contents

Mets package

This document provides a brief tutorial to analyzing twin data using the `mets` package:

```
1 library("mets")
2 options(warn=-1)
```

The development version may be installed from *github*, i.e., with the *devtools* package:

```
1 devtools::install_github("kkholst/lava")
2 devtools::install_github("kkholst/mets")
```

Twin analysis, continuous traits

In the following we examine the heritability of Body Mass Index^{1 2}, based on data on self-reported BMI-values from a random sample of 11,411 same-sex twins. First, we will load data

```
1 data("twinbmi")
2 head(twinbmi)
```

	tvparnr	bmi	age	gender	zyg
100001.1	100001	26.33289	57.57974	male	DZ
100002.1	100002	28.65014	57.04860	male	MZ
100003.1	100003	28.40909	57.67830	male	DZ
100004.1	100004	27.25089	53.51677	male	DZ
100005.1	100005	27.77778	52.57495	male	DZ
100006.1	100006	28.04282	52.57221	male	DZ

The data is on *long* format with one subject per row. we transpose the data allowing us to do pairwise analyses

```
1 twinwide <- fast.reshape(twinbmi, id="tvparnr",varying=c("bmi"))
2 head(twinwide)
```

	tvparnr	bmi1	age	gender	zyg	bmi2
100001.1	100001	26.33289	57.57974	male	DZ	25.46939
100002.1	100002	28.65014	57.04860	male	MZ	NA
100003.1	100003	28.40909	57.67830	male	DZ	NA
100004.1	100004	27.25089	53.51677	male	DZ	28.07504
100005.1	100005	27.77778	52.57495	male	DZ	NA
100006.1	100006	28.04282	52.57221	male	DZ	22.30936

Next we plot the association within each zygosity group

```
1 library("cowplot")
2
3 scatterdens <- function(x) {
4   sp <- ggplot(x,
5     aes_string(colnames(x)[1], colnames(x)[2])) +
6     theme_minimal() +
7     geom_point(alpha=0.3) + geom_density_2d()
8   xdens <- ggplot(x, aes_string(colnames(x)[1],fill=1)) +
9     theme_minimal() +
10    geom_density(alpha=.5)+
11    theme(axis.text.x = element_blank(),
```

¹ M. Korkeila, J. Kaprio, A. Rissanen, and M. Koskenvuo. Effects of gender and age on the heritability of body mass index. *Int J Obes*, 15(10):647–654, Oct 1991

² J. v. Hjelmborg, C. Fagnani, K. Silventoinen, M. McGue, M. Korkeila, K. Christensen, A. Rissanen, and J. Kaprio. Genetic influences on growth traits of BMI: a longitudinal study of adult twins. *Obesity (Silver Spring)*, 16(4):847–852, Apr 2008

tvparnr twin id

bmi Body Mass Index (kg/m²)

age Age (years)

gender Gender factor (male,female)

zyg zygosity (MZ,DZ)

```

12     legend.position = "none") + labs(x=NULL)
13   ydens <- ggplot(x, aes_string(colnames(x)[2], fill=1)) +
14     theme_minimal() +
15     geom_density(alpha=.5) +
16     theme(axis.text.y = element_blank(),
17           axis.text.x = element_text(angle=90, vjust=0),
18           legend.position = "none") +
19     labs(x=NULL) +
20     coord_flip()
21   g <- plot_grid(xdens, NULL, sp, ydens,
22                 ncol=2, nrow=2,
23                 rel_widths=c(4, 1.4), rel_heights=c(1.4, 4))
24   return(g)
25 }

```

We here show the log-transformed data which is slightly more symmetric and more appropriate for the twin analysis (see Figure 1 and 2)

```

1 mz <- log(subset(twinwide, zyg=="MZ"), c("bmi1", "bmi2"))
2 scatterdens(mz)

1 dz <- log(subset(twinwide, zyg=="DZ"), c("bmi1", "bmi2"))
2 scatterdens(dz)

```

The plots and raw association measures shows considerable stronger dependence in the MZ twins, thus indicating genetic influence of the trait

```

1 cor.test(mz[,1], mz[,2], method="spearman")

```

Spearman's rank correlation rho

```

data:  mz[, 1] and mz[, 2]
S = 165460000, p-value < 2.2e-16
alternative hypothesis: true rho is not equal to 0
sample estimates:
      rho
0.6956209

```

```

1 cor.test(dz[,1], dz[,2], method="spearman")

```

Spearman's rank correlation rho

```

data:  dz[, 1] and dz[, 2]
S = 2162500000, p-value < 2.2e-16
alternative hypothesis: true rho is not equal to 0
sample estimates:
      rho
0.4012686

```

Next we examine the marginal distribution (GEE model with working independence)

```

1 l0 <- lm(bmi ~ gender + I(age-40), data=twinbmi)
2 estimate(l0, id=twinbmi$tvparnr)

```

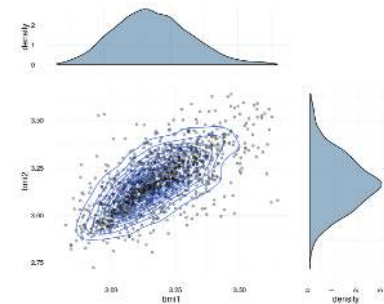


Figure 1: Scatter plot of logarithmic BMI measurements in MZ twins

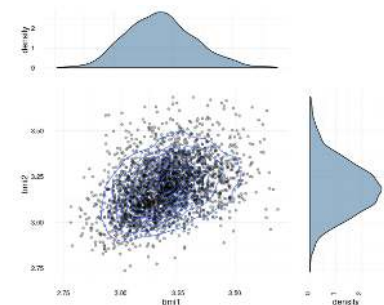


Figure 2: Scatter plot of logarithmic BMI measurements in DZ twins.

	Estimate	Std.Err	2.5%	97.5%	P-value
(Intercept)	23.369	0.05453	23.262	23.476	0.00e+00
gendermale	1.407	0.07322	1.264	1.551	2.35e-82
I(age - 40)	0.118	0.00479	0.108	0.127	2.00e-133

```

1 library("splines")
2 l1 <- lm(bmi ~ gender*ns(age,3), data=twinbmi)
3 marg1 <- estimate(l1, id=twinbmi$tvparnr)

4 dm <- Expand(twinbmi,
5               bmi=0,
6               gender=c("male"),
7               age=seq(33,61,length.out=50))
8 df <- Expand(twinbmi,
9               bmi=0,
10              gender=c("female"),
11              age=seq(33,61,length.out=50))

12 plot(marg1, function(p) model.matrix(l1,data=dm)%*%p,
13       data=dm["age"], ylab="BMI", xlab="Age",
14       ylim=c(22,26.5))
15 plot(marg1, function(p) model.matrix(l1,data=df)%*%p,
16       data=df["age"], col="red", add=TRUE)
17 legend("bottomright", c("Male","Female"),
18       col=c("black","red"), lty=1, bty="n")

```

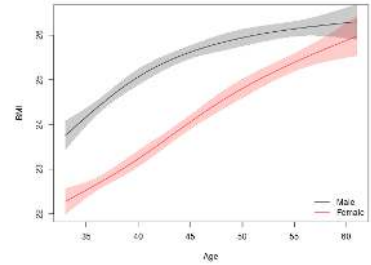


Figure 3: ...

Polygenic model

Decompose outcome into

$$Y_i = A_i + D_i + C + E_i, \quad i = 1, 2$$

A Additive genetic effects of alleles

D Dominant genetic effects of alleles

C Shared environmental effects

E Unique environmental genetic effects

Dissimilarity of MZ twins arises from unshared environmental effects only! $\text{Cor}(E_1, E_2) = 0$ and

$$\text{Cor}(A_1^{MZ}, A_2^{MZ}) = 1, \quad \text{Cor}(D_1^{MZ}, D_2^{MZ}) = 1,$$

$$\text{Cor}(A_1^{DZ}, A_2^{DZ}) = 0.5, \quad \text{Cor}(D_1^{DZ}, D_2^{DZ}) = 0.25,$$

$$Y_i = A_i + C_i + D_i + E_i$$

$$A_i \sim \mathcal{N}(0, \sigma_A^2), C_i \sim \mathcal{N}(0, \sigma_C^2), D_i \sim \mathcal{N}(0, \sigma_D^2), E_i \sim \mathcal{N}(0, \sigma_E^2)$$

$$\text{Cov}(Y_1, Y_2) = \begin{pmatrix} \sigma_A^2 & 2\Phi\sigma_A^2 \\ 2\Phi\sigma_A^2 & \sigma_A^2 \end{pmatrix} + \begin{pmatrix} \sigma_C^2 & \sigma_C^2 \\ \sigma_C^2 & \sigma_C^2 \end{pmatrix} + \begin{pmatrix} \sigma_D^2 & \Delta_7\sigma_D^2 \\ \Delta_7\sigma_D^2 & \sigma_D^2 \end{pmatrix} + \begin{pmatrix} \sigma_E^2 & 0 \\ 0 & \sigma_E^2 \end{pmatrix}$$

```

1 dd <- na.omit(twinbmi)
2 l0 <- twinlm(bmi ~ age+gender, data=dd,
3             DZ="DZ", zyg="zyg", id="tvparnr", type="sat")

```

```

1 l <- twinlm(bmi ~ ns(age,1)+gender, data=twinbmi,
2             DZ="DZ", zyg="zyg", id="tvparnr", type="cor", missing=TRUE)
3 summary(l)

```

```

-----
Group 1
              Estimate Std. Error   Z value Pr(>|z|)
Regressions:
  bmi.1~ns(age, 1).1    4.08914    0.16354  25.00328 <1e-12
  bmi.1~gendermale.1    1.41143    0.07285  19.37536 <1e-12
Intercepts:
  bmi.1                22.57414    0.07187 314.08431 <1e-12
Additional Parameters:
  log(var)              2.44584    0.01425 171.68385 <1e-12
  atanh(rhoMZ)          0.78216    0.02290  34.15832 <1e-12
-----

Group 2
              Estimate Std. Error   Z value Pr(>|z|)
Regressions:
  bmi.1~ns(age, 1).1    4.08914    0.16354  25.00328 <1e-12
  bmi.1~gendermale.1    1.41143    0.07285  19.37536 <1e-12
Intercepts:
  bmi.1                22.57414    0.07187 314.08431 <1e-12
Additional Parameters:
  log(var)              2.44584    0.01425 171.68385 <1e-12
  atanh(rhoDZ)          0.29927    0.01848  16.19766 <1e-12

              Estimate 2.5%   97.5%
Correlation within MZ: 0.65394 0.62750 0.67888
Correlation within DZ: 0.29064 0.25715 0.32344

'log Lik.' -29020.35 (df=6)
AIC: 58052.71
BIC: 58093.76

```

A formal test of genetic effects can be obtained by comparing the MZ and DZ correlation:

```

1 estimate(l,contr(5:6,6))

```

```

              Estimate Std.Err  2.5% 97.5% P-value
[1@atanh(rhoMZ)] - [4....    0.483 0.0418 0.401 0.565 6.4e-31

Null Hypothesis:
  [1@atanh(rhoMZ)] - [4@atanh(rhoDZ)] = 0

```

```

1 l <- twinlm(bmi ~ ns(age,1)+gender, data=twinbmi,
2             DZ="DZ", zyg="zyg", id="tvparnr", type="cor", missing=TRUE)
3 summary(l)

```

```

-----
Group 1
              Estimate Std. Error   Z value Pr(>|z|)
Regressions:
  bmi.1~ns(age, 1).1    4.08914    0.16354  25.00328 <1e-12
  bmi.1~gendermale.1    1.41143    0.07285  19.37536 <1e-12
Intercepts:
  bmi.1                22.57414    0.07187 314.08431 <1e-12

```

```

Additional Parameters:
  log(var)          2.44584    0.01425 171.68385 <1e-12
  atanh(rhoMZ)      0.78216    0.02290 34.15832 <1e-12
-----
Group 2
      Estimate Std. Error   Z value Pr(>|z|)
Regressions:
  bmi.1~ns(age, 1).1  4.08914    0.16354 25.00328 <1e-12
  bmi.1~gendermale.1  1.41143    0.07285 19.37536 <1e-12
Intercepts:
  bmi.1              22.57414    0.07187 314.08431 <1e-12
Additional Parameters:
  log(var)          2.44584    0.01425 171.68385 <1e-12
  atanh(rhoDZ)      0.29927    0.01848 16.19766 <1e-12

      Estimate 2.5%   97.5%
Correlation within MZ: 0.65394 0.62750 0.67888
Correlation within DZ: 0.29064 0.25715 0.32344

'log Lik.' -29020.35 (df=6)
AIC: 58052.71
BIC: 58093.76

```

Twin analysis, censored outcomes

Twin analysis, binary traits

Time to event

References

- [1] J. v. Hjelmborg, C. Fagnani, K. Silventoinen, M. McGue, M. Korkeila, K. Christensen, A. Rissanen, and J. Kaprio. Genetic influences on growth traits of BMI: a longitudinal study of adult twins. *Obesity (Silver Spring)*, 16(4):847–852, Apr 2008.
- [2] M. Korkeila, J. Kaprio, A. Rissanen, and M. Koskenvuo. Effects of gender and age on the heritability of body mass index. *Int J Obes*, 15(10):647–654, Oct 1991.