Supplementary file 3

Vitamin C and common cold-induced asthma: a systematic review and statistical analysis

Submitted to: Allergy, Asthma & Clinical Immunology

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http://www.mv.helsinki.fi/home/hemila/vitc_asthma.htm (papers on vitC-asthma)

Contents

Page

2 Anah 1980: imputed data set
Anah data for the negative binomial model, see supplementary file 2

3 Anah
Poisson distribution confidence intervals

4 Anah: all asthma attacks
Negative binomial model confidence intervals

5 Anah: severe and moderate asthma attacks
Negative binomial model confidence intervals

6 Bucca 1989: reconstructed data set
Bucca data set for the statistical analysis
See supplementary file 2 for the construction of the data set
The data is the log(PC20) levels

7-9 Bucca 1989: Bucca's AOV calculations and correct paired t-test
In the 1989 paper, Bucca et al. used the analysis of variance (AOV) to calculate the effect of vitamin C and to compare the “During Cold” and “After Recovery” days. However, the data are paired (4 measurements with the same person) and therefore paired t-test is correct. AOV corresponds to unpaired t-test

7 Comparison of baseline (pre) vs. post vitamin C on the “During Cold” day
8 Comparison of baseline (pre) vs. post vitamin C on the “After Recovery” day
9 Comparison of baseline (pre) values for the “During Cold” and “After Recovery” days

10 Interaction test: difference in vitamin C effect on the “During Cold” and “After Recovery” days

11 Correlations of pre and post vit C values between the two test days
12 Test of improvement of association when vitamin C effect is added to model
14 What can explain effect of vitamin C on the common cold day i.e. Cold_VC
> # Imputed Anah data set: Group 1 is vitamin C, Group 0 is Placebo
>
> Anah

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</table>
> # All Anah asthma attacks ** "Poisson.Test" program

> poisson.test(c(9, 35), c(22, 19))

Comparison of Poisson rates

data:  c(9, 35) time base: c(22, 19)

count1 = 9, expected count1 = 23.61, p-value = 1.122e-05
alternative hypothesis: true rate ratio is not equal to 1

95 percent confidence interval: 0.09387772 0.47128869

sample estimates:
rate ratio
0.2220779

> # Severe and moderate Anah asthma attacks ** "Poisson.Test" program

> poisson.test(c(3, 23), c(22, 19))

Comparison of Poisson rates

data:  c(3, 23) time base: c(22, 19)

count1 = 3, expected count1 = 13.951, p-value = 1.15e-05
alternative hypothesis: true rate ratio is not equal to 1

95 percent confidence interval: 0.02165246 0.37285085

sample estimates:
rate ratio
0.1126482
> # All Anah asthma attacks ** negative binomial model
> Anah_All <- glm.nb(All~Group, data=Anah)
> summary(Anah_All)

Call:
glm.nb(formula = All ~ Group, data = Anah, init.theta = 0.3630726678,
       link = log)

Deviance Residuals:
     Min       1Q   Median       3Q      Max
-1.1445  -0.7402  -0.7402   0.2958   1.7691

Coefficients:
            Estimate Std. Error z value Pr(>|z|)
(Intercept)   0.6109     0.4166   1.467   0.1425
Group        -1.5047     0.6402  -2.350  0.0188 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for Negative Binomial(0.3631) family taken to be 1)

    Null deviance: 36.522  on 40  degrees of freedom
Residual deviance: 30.907  on 39  degrees of freedom
AIC: 109.77

Number of Fisher Scoring iterations: 1

Theta:  0.363
Std. Err.:  0.179

2 x log-likelihood:  -103.767

> qt(0.975, 40)
[1] 2.021075

> logRRnbAll<-c(-1.5047, -1.5047-2.021*0.6402, -1.5047+2.021*0.6402)

> logRRnbAll
[1] -1.5047000 -2.7985442 -0.2108558

> exp(logRRnbAll)
[1] 0.22208391 0.06089865 0.80989084   # 95% CI is in bold
> # Severe and moderate Anah asthma attacks ** negative binominal model

> Anah_SevMod <- glm.nb(SevMod~Group, data=Anah)

> summary(Anah_SevMod)

Call:
glm.nb(formula = SevMod ~ Group, data = Anah, init.theta = 0.6089002017, link = log)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.1695  -1.1695  -0.4961   0.3262   1.2282

Coefficients:
              Estimate Std. Error z value Pr(>|z|)
(Intercept) 0.2336     0.3579   0.653  0.51394
Group        -2.2260     0.7322  -3.040 0.00236 **

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for Negative Binomial(0.6089) family taken to be 1)

Null deviance: 39.703  on 40  degrees of freedom
Residual deviance: 28.221  on 39  degrees of freedom

AIC: 82.886

Number of Fisher Scoring iterations: 1

Theta:  0.609
Std. Err.:  0.406

2 x log-likelihood:  -76.886

> logRRnbSevMod<-c(-2.2260, -2.2260-2.021*0.7322, -2.2260+2.021*0.7322)

> exp(logRRnbSevMod)
[1] 0.10795941 0.02458113 0.47415368   # 95%CI is in bold
Histamine Log(PC20) measurements:

These four variables are measured from Bucca (1992) fig.1 (suppl file 2)

Cold_pre: Participants had the common cold, level before vitamin C
Cold_post: Participants had the common cold, level after vitamin C
Reco_pre: Participants had recovered of the cold, level before vitamin C
Reco_post: Participants had recovered of the cold, level after vitamin C

These variables are calculated from the four above

Cold_VC = Cold_post - Cold_pre     (effect of vitamin C on common cold day)
Reco_VC = Reco_post - Reco_pre     (effect of vitamin C on after recovery day)
Diff_VC = Cold_VC - Reco_VC     (for analyzing the association on p.12)
Reco_pre_VC = Reco_pre - Diff_VC    (for analyzing the association on p.12)
Diff_VC_10 = 10exp(Diff_VC)        (vit C effect on the absolute scale)
Cold_pre_10 = 10exp(Cold_pre)       (baseline PC20 on the absolute scale)

# reconstructed Bucca data set

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<th>Cold_pre</th>
<th>Cold_pre_10</th>
<th>Cold_post</th>
<th>Cold_VC</th>
<th>Reco_pre</th>
<th>Reco_post</th>
<th>Reco_VC</th>
<th>Reco_pre_VC</th>
<th>Diff_VC</th>
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Data for Bucca AOV calculations

Cold: pre vitamin C and post vitamin C measurements on “Common Cold” day
Reco: pre vitamin C and post vitamin C measurements “After Recovery” day
Group: measurement pre or post vitamin C administration
Pre: pre vit C measurements on “During Cold” and “After Recovery” (6 week) days
GroupPre: day of the pre measurement (“During Cold” or “After Recovery”)

# Bucca data set for AOV calculations

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<tr>
<th>Person</th>
<th>Cold</th>
<th>Group</th>
<th>Reco</th>
<th>Pre</th>
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</table>
> # Bucca (1989) used Analysis of Variance [AOV] (corresponds to un-paired t-test)
> # The appropriate comparison is by the paired t-test
> # The Bucca statistics are re-calculated to show that the reconstructed data set gives the same F-statistics and to show that the Bucca calculations were un-paired (should have been paired)

> # 1: AOV Comparison of pre vs. post vitamin C on the "During Cold" day

> aov.1 = aov(Cold~Group, data=Bucca_aov)

> summary(aov.1)

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<th>Mean Sq</th>
<th>F value</th>
<th>Pr(&gt;F)</th>
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> # Bucca (1989) reported F = 17 which is consistent with the F value above

> # 1: UN-PAIRED t-test (corresponds to AOV)

> t.test(Bucca$Cold_post, Bucca$Cold_pre, alternative='two.sided', conf.level=.95, paired=FALSE)

   Welch Two Sample t-test

   data:  Bucca$Cold_post and Bucca$Cold_pre
   t = 4.1434, df = 15.934, p-value = 0.00077
   alternative hypothesis: true difference in means is not equal to 0
   95 percent confidence interval:
   0.2492174 0.7717604
   sample estimates:
   mean of x mean of y
   1.4062444 0.8957556

> # F = t*t > 17.1 = 4.14*4.14; AOV and un-paired t-test give the same result

> # 1: PAIRED t-test  (the correct test for paired data)

> t.test(Bucca$Cold_post, Bucca$Cold_pre, alternative='two.sided', conf.level=.95, paired=TRUE)

   Paired t-test

   data:  Bucca$Cold_post and Bucca$Cold_pre
   t = 6.0747, df = 8, p-value = 0.0002977
   alternative hypothesis: true difference in means is not equal to 0
   95 percent confidence interval:
   0.3167040 0.7042738
   sample estimates:
   mean of the differences
   0.5104889

> # 95% CI to absolute PC20 values for the "Common Cold day"
> log_PC20<-c(0.3167, 0.7042738, 0.5104889)
> log_PC20
[1] 0.3167000 0.7042738 0.5104889
> PC20<-10^(log_PC20)
> PC20
[1] 2.073481 5.061437 3.239581
> # 2: AOV of pre vs. post vit C on the "After Recovery" day (6 wk later)

> aov.2 = aov(Reco~Group, data=Bucca_aov)

> summary(aov.2)

Df Sum Sq Mean Sq F value Pr(>F)
Group 1 0.1819 0.1819 1.698 0.211
Residuals 16 1.7144 0.1071

> # Bucca (1989) reported F = 1.7 which is consistent with the F value above

> # 2: UN-PAIRED t-test (corresponds to AOV)

> t.test(Bucca$Reco_post, Bucca$Reco_pre, alternative='two.sided',
conf.level=.95, paired=FALSE)

Welch Two Sample t-test
data:  Bucca$Reco_post and Bucca$Reco_pre
t = 1.3029, df = 15.362, p-value = 0.2118
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
-0.1271803  0.5292692
sample estimates:
mean of x mean of y
1.395167  1.194122

> # F = t*t  >  1.7 = 1.3*1.3; AOV and un-paired t-test give the same result

> # 2: PAIRED t-test (the correct test for paired data)

> t.test(Bucca$Reco_post, Bucca$Reco_pre, alternative='two.sided',
conf.level=.95, paired=TRUE)

Paired t-test
data:  Bucca$Reco_post and Bucca$Reco_pre
t = 2.9077, df = 8, p-value = 0.01966
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
0.04160047 0.36048842
sample estimates:
mean of the differences
0.2010444

> # 95% CI to absolute PC20 values for the "After Recovery day"
> log_PC20_reco<-c(0.04163681, 0.36056319, 0.2011)
> log_PC20_reco

[1] 0.04163681 0.36056319 0.20110000

> PC20_reco<-10^(log_PC20_reco)
> PC20_reco

[1] 1.100619 2.293840 1.588913

> # Bucca (1989) reports that for the "being recovered" day, vitamin C effect
P>0.05
> # that is based on the AOV, whereas the paired t-test gives P=0.02 (above)
> # 3: AOV of pre vit C PC20 values on the "During Cold" and "After Recovery" days

> aov.3 = aov(Pre~GroupPre, data=Bucca_aov)

> summary(aov.3)

<table>
<thead>
<tr>
<th>DF</th>
<th>Sum Sq</th>
<th>Mean Sq</th>
<th>F value</th>
<th>Pr(&gt;F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GroupPre</td>
<td>1</td>
<td>0.4006</td>
<td>0.4006</td>
<td>5.369</td>
</tr>
<tr>
<td>Residuals</td>
<td>16</td>
<td>1.1938</td>
<td>0.0746</td>
<td></td>
</tr>
</tbody>
</table>

> # Bucca (1989) reported F = 5.23 which is consistent with the F value above

> # 3: UN-PAIRED t-test (corresponds to AOV)

> t.test(Bucca$Cold_pre, Bucca$Reco_pre, alternative='two.sided',
conf.level=.95, paired=FALSE)

Welch Two Sample t-test
data:  Bucca$Cold_pre and Bucca$Reco_pre
t = -2.3171, df = 15.678, p-value = 0.03438
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
-0.57179828 -0.02493506
sample estimates:
mean of x mean of y
0.8957556 1.1941222

> # F = t*t > 5.38 = 2.32*2.32; AOV and un-paired t-test give the same result

> # 3: PAIRED t-test (the correct test for paired data)

> t.test(Bucca$Cold_pre, Bucca$Reco_pre, alternative='two.sided',
conf.level=.95, paired=TRUE)

Paired t-test
data:  Bucca$Cold_pre and Bucca$Reco_pre
t = -3.9244, df = 8, p-value = 0.004391
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
-0.4736911 -0.1230422
sample estimates:
mean of the differences
-0.2983667

> log_PC20_pre_diff<-c(-0.4736911, -0.1230422, -0.2983667)
> log_PC20_pre_diff
[1] -0.4736911 -0.1230422 -0.2983667
> PC20_pre_diff<10^(log_PC20_pre_diff)
> PC20_pre_diff
[1] 0.3359765 0.7532824 0.5030757
> # Interaction test: difference in the vitamin C effect between the "During Cold" and "After Recovery" days

> # Small P-value means that the effect of vitamin C on the two study days is different

> t.test(Bucca$Cold_VC, Bucca$Reco_VC, alternative='two.sided', conf.level=.95, paired=TRUE)

Paired t-test
data:  Bucca$Cold_VC and Bucca$Reco_VC
t = 4.222, df = 8, p-value = 0.002908
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 0.1404389 0.4784944
sample estimates:
mean of the differences
 0.3094667

> # the t-test above is identical with the linear model:

> LinearModel.1 <- lm(Cold_VC ~ Reco_VC ~ 1, data=Bucca)

> summary(LinearModel.1)

Call:
  lm(formula = Cold_VC ~ Reco_VC ~ 1, data = Bucca)

Residuals:
   Min      1Q  Median      3Q     Max
-0.33367 -0.24417  0.05173  0.15383  0.28853

Coefficients:      Estimate Std. Error t value Pr(>|t|)
(Intercept)        0.3095     0.0733   4.222 0.00291 **

Residual standard error: 0.2199 on 8 degrees of freedom

> # and this is identical with (since Diff_VC = Cold_VC - Reco_VC, see p. 6)

> LinearModel.2 <- lm(Diff_VC ~ 1, data=Bucca)

> summary(LinearModel.2)

Call:
  lm(formula = Diff_VC ~ 1, data = Bucca)

Residuals:
   Min      1Q  Median      3Q     Max
-0.33368 -0.24428  0.05172  0.15382  0.28852

Coefficients:      Estimate Std. Error t value Pr(>|t|)
(Intercept)        0.3095     0.0733   4.222 0.00291 **

Residual standard error: 0.2199 on 8 degrees of freedom

Models 1 and 2 are the basis for a further model on pages 15 and 16
> # Correlation of PC20 values BEFORE vit C on the "During Cold" and "After Recovery" days

> cor.test(Bucca$Cold_pre, Bucca$Reco_pre, alternative="two.sided", method="pearson")

    Pearson's product-moment correlation

data:  Bucca$Cold_pre and Bucca$Reco_pre
t = 2.313, df = 7, p-value = 0.05395
alternative hypothesis: true correlation is not equal to 0
95 percent confidence interval:
 -0.01056197  0.92010969
sample estimates:
corr
0.6581765

> # Correlation of PC20 values AFTER vit C on the "During Cold" and "After Recovery" days

> cor.test(Bucca$Cold_post, Bucca$Reco_post, alternative="two.sided", method="pearson")

    Pearson's product-moment correlation

data:  Bucca$Cold_post and Bucca$Reco_post
t = 3.7229, df = 7, p-value = 0.007428
alternative hypothesis: true correlation is not equal to 0
95 percent confidence interval:
 0.3292318  0.9597136
sample estimates:
corr
0.8151262
Since (see p. 6)
Cold_post = [Cold_pre + Cold_VC]
Reco_post = [Reco_pre + Reco_VC]

This indicates that the correlation after vitamin C
\[\text{Cold_post} \leftrightarrow \text{Bucca}\$\text{Reco_post} \leftrightarrow [\text{Cold_pre} + \text{Cold_VC}] \leftrightarrow [\text{Reco_pre} + \text{Reco_VC}]\]

Since both sides have the vitamin C effect, they can be combined to the difference [Cold_VC - Reco_VC] = Diff_VC
Thus, the above correlation is related to the correlation
\[\text{Cold_pre} \leftrightarrow \text{Reco_pre} - \text{Diff_VC}\]

This correlation can be tested with linear regression

Let variable (p. 6)
Reco_pre_VC = [Reco_pre - (Cold_VC - Reco_VC)] = [Reco_pre - Diff_VC]

> # Correlation of log(PC20) values BEFORE vit C on the "During Cold" and Reco_pre_VC

> cor.test(Bucca$Cold_pre, Bucca$Reco_pre_VC, alternative="two.sided", method="pearson")

    Pearson's product-moment correlation

    data:  Bucca$Cold_pre and Bucca$Reco_pre_VC
    t = 4.9229, df = 7, p-value = 0.001708
    alternative hypothesis: true correlation is not equal to 0
    95 percent confidence interval:
    0.5222220 0.9747504
    sample estimates:
    cor
    0.8808487

Thus, PC20 level before vitamin C administration on the “During Cold” day can be explained by the PC20 level before vitamin C on the “After Recovery” day and the difference in the vitamin C effects on the two days.

This approach allows testing the influence of vitamin C on the association between the PC20 levels on the two days (“During Cold” and “After Recovery”).

On the next page, models 11 and 12 test whether the addition of Diff_VC to the linear model which has the Reco_pre variable improves the fit.
> # Below, the baseline log(PC20) level on the "During Cold" day is explained by the baseline log(PC20) level on the "After Recovery" day

> LinearModel.11 <- lm(Bucca$Cold_pre ~ 1 + Bucca$Reco_pre , data=Bucca)
> summary(LinearModel.11)

Call:
  lm(formula = Bucca$Cold_pre ~ 1 + Bucca$Reco_pre, data = Bucca)

Residuals:
   Min     1Q Median     3Q    Max
-0.2649 -0.1600  0.0187  0.1377  0.2976

Coefficients:                Estimate Std. Error t value Pr(>|t|)
(Intercept)      0.2154     0.3018   0.714   0.4985
Bucca$Reco_pre   0.5697     0.2463   2.313   0.0539 .

Residual standard error: 0.2035 on 7 degrees of freedom
Multiple R-squared: 0.4332, Adjusted R-squared: 0.3522
F-statistic:  5.35 on 1 and 7 DF,  p-value: 0.05395

> # Below, the difference in vitamin C effects is added to model 1 above

> LinearModel.12 <- lm(Bucca$Cold_pre ~ 1 + Bucca$Reco_pre + Bucca$Diff_VC , data=Bucca)
> summary(LinearModel.12)

Call:
  lm(formula = Bucca$Cold_pre ~ 1 + Bucca$Reco_pre + Bucca$Diff_VC, data = Bucca)

Residuals:
   Min     1Q Median     3Q    Max
-0.17733 -0.05837  0.05335  0.05571  0.15985

Coefficients:                Estimate Std. Error t value Pr(>|t|)
(Intercept)      0.5411     0.2195   2.465   0.0488 *
Bucca$Reco_pre   0.4792     0.1620   2.959   0.0253 *
Bucca$Diff_VC   -0.7030     0.2151  -3.268   0.0171 *

Residual standard error: 0.1318 on 6 degrees of freedom
Multiple R-squared: 0.7961, Adjusted R-squared: 0.7282
F-statistic: 11.71 on 2 and 6 DF,  p-value: 0.008476

> # likelihood ratio test of the models 11 and 12 above
> # see rationalization: http://en.wikipedia.org/wiki/Likelihood-ratio_test
> # small P-value means that the added variable improves the association

> lrtest(LinearModel.11,LinearModel.12)
Likelihood ratio test

Model 1: Bucca$Cold_pre ~ 1 + Bucca$Reco_pre
Model 2: Bucca$Cold_pre ~ 1 + Bucca$Reco_pre + Bucca$Diff_VC
    #Df LogLik Df Chisq Pr(>Chisq)
1     3  2.690
2     4  7.291  1 9.202  0.002418 **
What can explain the effect of vitamin C on the common cold day. i.e. the variable Cold_VC?

```r
LinearModel.21 <- lm( Bucca$Cold_VC ~ 1 + Bucca$Cold_pre + Bucca$Reco_pre + Bucca$Reco_VC, data=Bucca)
> summary(LinearModel.21)

Call:
lm(formula = Bucca$Cold_VC ~ 1 + Bucca$Cold_pre + Bucca$Reco_pre + Bucca$Reco_VC, data = Bucca)

Coefficients:  
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.6698     0.2533   2.645   0.0457 *
Bucca$Cold_pre -0.8842     0.3171  -2.788   0.0385 *
Bucca$Reco_pre  0.3754     0.2674   1.404   0.2193
Bucca$Reco_VC   0.9176     0.2909   3.154   0.0253 *

Residual standard error: 0.1631 on 5 degrees of freedom  
Multiple R-squared: 0.7385, Adjusted R-squared: 0.5816
F-statistic: 4.707 on 3 and 5 DF,  p-value: 0.0642
```

```r
LinearModel.22 <- lm( Bucca$Cold_VC ~ 1 + Bucca$Cold_pre + Bucca$Reco_VC, data=Bucca)
> summary(LinearModel.22)

Call:
lm(formula = Bucca$Cold_VC ~ 1 + Bucca$Cold_pre + Bucca$Reco_VC, data = Bucca)

Coefficients:  
            Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.8652     0.2281   3.793  0.00904 **
Bucca$Cold_pre -0.5840     0.2524  -2.314  0.05995 .
Bucca$Reco_VC  0.8377     0.3075   2.724  0.03446 *

Residual standard error: 0.1758 on 6 degrees of freedom  
Multiple R-squared: 0.6354, Adjusted R-squared: 0.5139
F-statistic: 5.229 on 2 and 6 DF,  p-value: 0.04846
```

```r
# thus, Reco_pre (baseline PC20 on the "after recovery" day) is unimportant
```
> LinearModel.23 <- lm( Bucca$Cold_VC ~ 1 , data=Bucca)

> summary(LinearModel.23)

Call:
  lm(formula = Bucca$Cold_VC ~ 1, data = Bucca)

Coefficients:
  Estimate Std. Error t value Pr(>|t|)
(Intercept)  0.51050    0.08404   6.074 0.000298 ***

Residual standard error: 0.2521 on 8 degrees of freedom

> lrtest(LinearModel.22,LinearModel.23)

Likelihood ratio test

Model 1: Bucca$Cold_VC ~ 1 + Bucca$Cold_pre + Bucca$Reco_VC
Model 2: Bucca$Cold_VC ~ 1

Df LogLik Df Chisq Pr(>Chisq)
1   4 4.7006
2   2 0.1601 -2 9.081 0.01067 *

> # thus, baseline PC20 on the "common cold day" and the vitamin C effect on the "after recovery day" explain the vitamin C effect on the "common cold day"
> # when the vitamin C effects are combined to the difference Diff_VC we get the
> following models 31 and 32:

> LinearModel.31 <- lm(Bucca$Diff_VC ~ 1 , data=Bucca)

> summary(LinearModel.31)

    Call:
    lm(formula = Bucca$Diff_VC ~ 1, data = Bucca)

    Coefficients:
    Estimate Std. Error t value Pr(>|t|)
    (Intercept)   0.3095     0.0733   4.222  0.00291 **

    Residual standard error: 0.2199 on 8 degrees of freedom

> # LinearModel.31 is identical with LinearModel.1 above,
> # because Diff_VC = Cold_VC - Reco_VC
> # thus 31 is the test of interaction between the two days

> # addition of the baseline histamine sensitivity on the common cold day

> LinearModel.32 <- lm(Bucca$Diff_VC ~ 1 + Bucca$Cold_pre , data=Bucca)

> summary(LinearModel.32)

    Call:
    lm(formula = Bucca$Diff_VC ~ 1 + Bucca$Cold_pre, data = Bucca)

    Coefficients:
    Estimate Std. Error t value Pr(>|t|)
    (Intercept)      0.8596     0.2158   3.984  0.0053 **
    Bucca$Cold_pre  -0.6142     0.2328  -2.638   0.0335 *

    Residual standard error: 0.1665 on 7 degrees of freedom
    Multiple R-squared: 0.4986,  Adjusted R-squared: 0.427
    F-statistic: 6.961 on 1 and 7 DF,  p-value: 0.0335

> lrtest(LinearModel.31,LinearModel.32)

Likelihood ratio test

    Df LogLik Df  Chisq Pr(>Chisq)
Model 1: Bucca$Diff_VC ~ 1
Model 2: Bucca$Diff_VC ~ 1 + Bucca$Cold_pre

    1  2 1.3905   
    2  3 4.4973 1 6.2135 0.01268 *

> # thus baseline histamine PC20 significantly improves the fit of the model