

# Some Applications of Nonparanormal Adjusted Marginal Inference

Susanne Dandl  
Universität Zürich

Torsten Hothorn  
Universität Zürich

---

## Abstract

Covariate adjustment is recommended to improve precision of estimated treatment effects, even in randomized trials. For noncollapsible effect measures (such as Cohen's  $d$ , odds and hazard ratios), conditioning on covariates can alter the effect interpretation such that effects are not comparable given different adjustment sets. A novel nonparanormal adjusted marginal inference approach (NAMI) can be formulated for randomized controlled trials to derive marginal effects from the estimated joint distribution of covariates and outcomes. NAMI preserves the interpretation of treatment effects regardless of covariates used, while enhancing precision. We demonstrate applications of NAMI to continuous, binary, and right-censored survival outcomes, as well as to a fixed-effect meta-analysis. Data are analyzed by a proof-of-concept implementation of NAMI available in the **tram** add-on package to the R system for statistical computing.

*Keywords:* marginal effect, noncollapsibility, covariate adjustment, randomized trial, transformation model.

---

## 1. Introduction

We present four applications from different domains illustrating the potential to estimate treatment effects more precisely with nonparanormal adjusted marginal inference (NAMI, [Dandl and Hothorn 2025](#)): A toxicity study demonstrates equivalence of a continuous outcome by Cohen's  $d$ , an efficiency trial compares a binary outcome between two arms by means of an odds ratio, and a survival study measures differences in terms of a hazard ratio. In Section 5, we show that NAMI enables comparable estimates across studies with an application to fixed-effect meta-analysis.

We apply the proof-of-concept implementation of nonparanormal adjusted marginal inference available in package **tram**. All results of this document can be reproduced from the NAMI demo available in the package:

```
R> install.packages("tram")  
R> demo("NAMI", package = "tram")
```

---

Please cite this document as: Susanne Dandl and Torsten Hothorn (2025) Some Applications of Nonparanormal Adjusted Marginal Inference. R package vignette version 1.3-2, URL <https://doi.org/10.32614/CRAN.package.tram>.

## 2. Continuous outcome: Immunotoxicity study on Chloramine

We aim to assess toxicity of Chloramine using a study on mice that was conducted as part of the [National Toxicology Program \(2000\)](#). Female mice were randomly assigned to two groups, of which one group received Chloramine-dosed water and the other not. Repeated measurements of weights were conducted on days 1, 8, 15, 22, and 29 in five dose groups (0, 2, 10, 20, 100 mg/kg).

The following data set is a subset of the data obtained from the [National Toxicology Program \(2000\)](#). It focuses on the comparison of the highest dose group ( $W = 1, N_1 = 40$ ) with the control group ( $W = 0, N_0 = 40$ ) with respect to the weight at day 29 (denoted as outcome  $Y$ ). Information on the weight on day 1 is also available and is used for adjustment, in the following.

We translated the research question of “no effect of Chloramine on weight” into the hypotheses  $H_0 : |\tau| \geq \delta$  and  $H_1 : |\tau| < \delta$  where Cohen’s  $d$  is the marginal treatment effect  $\tau$ .  $H_0$  is rejected at 5% when the 95% confidence interval for  $\tau$  is completely contained in the equivalence interval  $(-\delta, \delta)$ . We set  $\delta = 0.36$  as recommended by [Wellek \(2010\)](#) (Table 1.1.), acknowledging this as a potential oversimplification.

### 2.1. Unadjusted marginal inference

Because the study is a randomized trial, an unadjusted marginal outcome model fitted with `Lm()` gives an unbiased estimate in terms of Cohen’s  $d$ :

```
R> m0 <- Lm(y ~ w, data = immun)

R> coef(m0) ### marginal Cohen's d

      w100
0.04817

R> sqrt(vcov(m0)) ### SE from observed info

      w100
w100 0.2236

R> sqrt(2/nrow(immun) * (coef(m0)^2/4 + 2)) ### SE from expected info (Lemma 1)

      w100
0.2236

R> confint(m0) ### Wald

      2.5 % 97.5 %
w100 -0.3902 0.4865
```

The unadjusted estimate of Cohen's  $d$  is  $\hat{\tau} = 0.048$ . The standard error based on the observed Fisher information is  $\text{SE}(\hat{\tau}) = 0.224$ . It is identical to the expected Fisher information (see Lemma 1 in [Dandl and Hothorn 2025](#)) evaluated at  $\hat{\tau}$ . The resulting 95% Wald interval obtained is  $(-0.390, 0.486)$ . Because the confidence interval is not fully contained in  $(-0.36, 0.36)$ , the unadjusted analysis cannot reject  $H_0$ .

## 2.2. Nonparanormal adjusted marginal inference

The marginal model did not take the weight at baseline (variable  $\mathbf{x}$ ) into account. With non-paranormal adjusted marginal inference, we adjust for weight while still obtaining a marginal effect parameter. As input to this approach, we use a marginal model `m1` for baseline weight (with transformation function in Bernstein form of order six) in addition to the marginal model for the outcome `m0` and estimate all marginal and copula parameters simultaneously with `Mmlt()`:

```
R> m1 <- BoxCox(x ~ 1, data = immun)
R> m <- Mmlt(m0, m1, formula = ~ 1, data = immun)

R> (cf1 <- coef(m)["y.w100"]) ### marginal adjusted Cohen's d

      y.w100
-0.005104

R> sqrt(diag(vcov(m))["y.w100"]) ### SE from observed info

      y.w100
0.1757
```

We obtain  $\hat{\tau} = -0.005$  as marginal adjusted Cohen's  $d$ . The standard error based on the observed Fisher information is 0.176.

Given an estimate of the copula parameters in  $\Lambda$  (see Sec. 2.2 in [Dandl and Hothorn 2025](#)), we can confirm that the observed Fisher information is equal to the expected Fisher information evaluated at the maximum-likelihood estimates  $\hat{\tau}$  and  $\hat{\lambda}$ :

```
R> lambda <- c(unclass(coef(m, type = "Lambdapar")))
R> sqrt(2/nrow(immun) * ((1 + lambda^2)*cf1^2 + 8)/(4*(1 + lambda^2)))

      y.w100
0.1754

R> ### SE from expected info (Lemma 2)
```

Compared to the Wald interval of the marginal model, the Wald interval of NAMI  $(-0.349, 0.339)$  is completely contained in the equivalence interval  $(-0.36, 0.36)$  and thus the absence of an effect of Chloramine on weight can be inferred:

```
R> confint(m)["y.w100",]
```

```

      2.5 %   97.5 %
-0.3494  0.3392

```

This finding is in accordance with previous research by [Guo \*et al.\* \(2011\)](#). The reduction in standard error comes from the high correlation between the outcome  $Y$  and the covariate which can be estimated via

```
R> coef(m, type = "Corr")
```

```
, , 1
```

```

      y      x
y 1.00 0.62
x 0.62 1.00

```

The coefficient of determination  $R^2$  (see Section 2.2 in [Dandl and Hothorn 2025](#)) obtained by

```
R> Omega <- as.array(coef(m, type = "Lambda"))[, , 1]
R> 1 - Omega[nrow(Omega), ncol(Omega)]^(-2)
```

```
[1] 0.3844
```

suggests an improvement of the conditional over the marginal model.

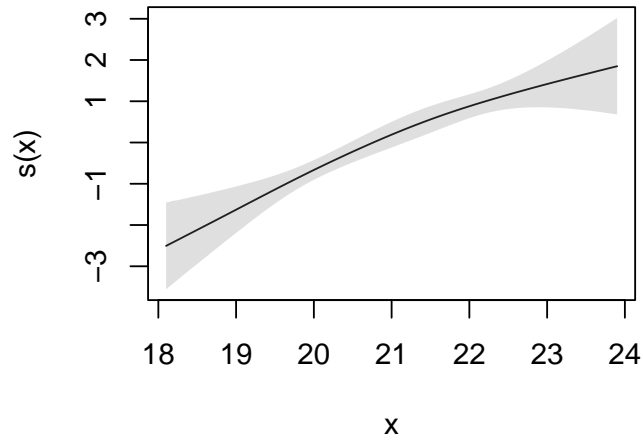
### 2.3. Model diagnosis

Model diagnosis can be conducted by fitting an additive transformation model for  $Y$  using the **tramME** package:

```
R> mad <- BoxCoxME(y ~ w + s(x), data = immun)
```

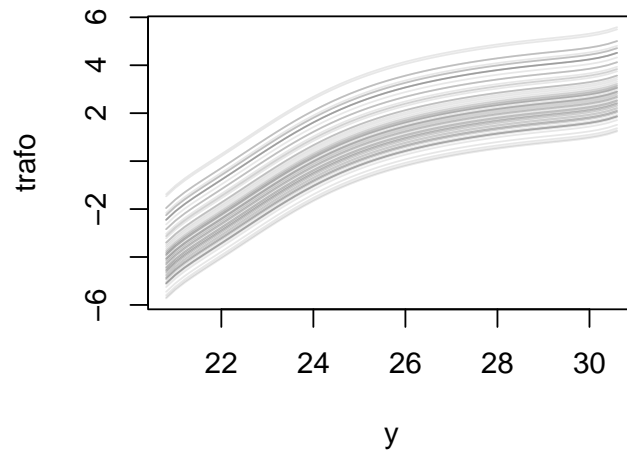
Inspecting the monotonicity of the estimated smooth functions of the baseline covariate allows assessing the copula fit. The following plot shows the smooth function for baseline weight estimated from the additive transformation model:

```
R> plot(smooth_terms(mad))
```



Because the functions are monotonically increasing, the copula fit seems to be appropriate. The marginal model `m0` for  $Y$  relies on the normality assumption and assumes that a linear transformation is sufficient. Via `plot()`, linearity of the transformation function of  $Y$  can be assessed using the additive transformation model:

```
R> plot(mad)
```



The plot suggests that a more flexible model allowing a nonlinear transformation  $h$  for  $Y$  might be better suited. This can be done in the **tram** package using `BoxCox()` for fitting a marginal model. The function estimates a nonlinear transformation function for  $Y$  in the form of polynomials in Bernstein form of order  $M$  ( $M = 6$  is the default):

```
R> m0 <- BoxCox(y ~ w, data = immun)
R> m <- Mmlt(m0, m1, formula = ~ 1, data = immun)
```

The coefficient of determination  $R^2$  can be obtained via

```
R> Omega <- as.array(coef(m, type = "Lambda"))[, , 1]
R> 1 - Omega[nrow(Omega), ncol(Omega)]^(-2)
```

```
[1] 0.5141
```

suggesting an improved model fit over nonparanormal adjusted marginal inference with a linear transformation. This generalised version of Cohen's  $d$  is then

```
R> (cf1 <- coef(m)["y.w100"])
```

```
      y.w100
-0.0001576
```

```
R> confint(m)["y.w100",]
```

```
      2.5 %   97.5 %
-0.3086  0.3083
```

The obtained treatment effect  $\hat{\tau} = -0.000$  with Wald interval  $(-0.309, 0.308)$  is interpreted as the mean difference on the latent normal scale in this model. Transforming this estimate to the probabilistic index via  $\Phi(\hat{\tau}/\sqrt{2})$ , provides a more intuitive interpretation in terms of the probability of obtaining a lower outcome in the control than in the treatment group:

```
R> pnorm(cf1 / sqrt(2))
```

```
y.w100
0.5
```

### 3. Binary outcome: Efficacy study of new chemotherapy

We want to assess whether combining standard care with a new form of therapy – Oxaliplatin – is beneficial for patients with rectal cancer. Data from the completed trial ([Rödel \*et al.\* 2015](#)) are available in the **TH.data** package.

623 patients received the Fluorouracil-based standard of care ( $W = 0$ ), and 613 patients received a combination therapy adding Oxaliplatin ( $W = 1$ ). Early effects were assessed based on a binary outcome `ypT0ypN0` – the absence of viable tumor cells in the primary tumor and lymph nodes after surgery:

```
R> CA0surv$ypT0ypN0 <- factor(CA0surv$path_stad == "ypT0ypN0")
```

### 3.1. Unadjusted marginal inference

Under proper randomization, we can obtain an unbiased estimate of our treatment effect in the form of an unadjusted odds ratio using a binary logistic regression model. The outcome variable `ypT0ypN0` contains 48 missings. Using the `Polr()` function of the **tram** package, the missing values in the outcome are retained in the data set, but are ignored in the log-likelihood by choosing `na.action = na.pass`:

```
R> mpCR <- Polr(ypT0ypN0 ~ randarm, data = CA0surv, na.action = na.pass,
+             method = "logistic")
R> exp(coef(mpCR)["randarm5-FU + Oxaliplatin"])

randarm5-FU + Oxaliplatin
                1.422

R> exp(confint(glht(mpCR, coef. = function(...) coef(..., fixed = FALSE)),
+             calpha = univariate_calpha())$confint)

                Estimate      lwr      upr
randarm5-FU + Oxaliplatin    1.422 1.037 1.949
attr(,"conf.level")
[1] 0.95
attr(,"calpha")
[1] 1.96
```

### 3.2. Nonparanormal adjusted marginal inference

We want to assess whether we can obtain a more precise estimate of the odds ratio by exploiting the information on six potentially prognostic covariates: `age`, sex (`geschlecht`), ECOG performance status (`ecog_o`), distance to the anal verge of the tumor (`bentf`), and the two stratum variables lymph node involvement (`strat_n`) and clinical T category (`strat_t`). We use nonparanormal adjusted marginal inference to receive an estimate that is still comparable to the estimate of the unadjusted model. We define one marginal model for each covariate: a Box-Cox-type model for the continuous variable `age`, and binary or ordinal probit models for the remaining binary or ordinal covariates. The ECOG performance status and the distance to the anal verge have 14 missing values, respectively. As for the outcome model, all missing values are retained in the data set but ignored in the marginal log-likelihoods (by setting `na.action = na.pass`):

```
R> mage <- BoxCox(age ~ 1, data = CA0surv)
R> msex <- Polr(geschlecht ~ 1, data = CA0surv, method = "probit")
R> CA0surv$ecog_o <- as.ordered(CA0surv$ecog_b)
R> mecog <- Polr(ecog_o ~ 1, data = CA0surv, na.action = na.pass,
+             method = "probit")
R> mentf <- Polr(bentf ~ 1, data = CA0surv, na.action = na.pass,
+             method = "probit")
R> mT <- Polr(strat_t ~ 1, data = CA0surv, method = "probit")
R> mN <- Polr(strat_n ~ 1, data = CA0surv, method = "probit")
```

The joint model is fitted with `Mmlt()`. It is important to note that, unlike the marginal models, this is not a complete case analysis. If, for example, the outcome is missing for one observation, the corresponding data point is still taken into account. The log-likelihood contribution is obtained by integrating out the missing dimension from the model. Details on the estimation of the mixed continuous-discrete likelihood are given in [Hothorn \(2024\)](#).

Here, we fit the model

```
R> ### results in the paper were produced using M = 250; to reduce CRAN
R> ### checking times, we use M = 50 here we also speed up things by
R> ### allowing the optimiser to stop early
R> fastoptH <- mltoptim(abstol = 1e-3, reltol = 1e-3, hessian = TRUE)
R> m <- Mmlt(mage, msex, mecog, mentf, mT, mN, mpCR,
+           data = CA0surv, args = list(type = "ghalton", M = 50),
+           optim = fastoptH)
R> prm <- "ypT0ypN0.randarm5-FU + Oxaliplatin"
R> exp(coef(m)[prm])
```

```
ypT0ypN0.randarm5-FU + Oxaliplatin
                        1.402
```

and compute an adjusted confidence interval for the marginal log-odds ratio

```
R> ci <- confint(glht(m, coef. = function(...) coef(..., fixed = FALSE)),
+             calpha = univariate_calpha())$confint
R> exp(ci[prm, -1])

      lwr      upr
1.023 1.922
```

The corresponding odds ratio 1.402 with Wald interval (1.023, 1.922) is very close to the initial results obtained by [Rödel \*et al.\* \(2012\)](#). [Rödel \*et al.\* \(2012\)](#) reported an adjusted odds ratio of 1.4 with 95% confidence interval (1.02, 1.92) based on a Cochran-Mantel-Haenszel  $\chi^2$  test (without continuity correction) stratified by lymph node involvement and clinical T category. The reason for equality of the marginal and conditional estimates is that none of the six variables (including the stratum variables) carries strong prognostic information. The covariate with the largest association with the binary outcome can be identified by ranking the covariates according to their linear correlation after transformation to normality:

```
R> mr <- as.array(coef(m, type = "Cor"))["ypT0ypN0", , 1]
R> i <- which.max(abs(mr[-length(mr)]))
R> (ni <- names(mr)[i])

[1] "ecog_o"

R> (mr <- mr[i])

      ecog_o
-0.1521
```



`ecog_o` is the variable with the largest association with the outcome, but its linear correlation under transformation to normality only has a value of  $\hat{\rho}_{J, \text{ECOG}} = -0.152$ . Consequently, adjusting for covariates did not improve fit nor precision, reflected in a low  $R^2$ :

```
R> Omega <- as.array(coef(m, type = "Lambda"))[, , 1]
R> 1 - Omega[nrow(Omega), ncol(Omega)]^(-2)
```

```
[1] 0.03043
```

However, the standard error does not increase despite the adjustment for multiple covariates, as the following comparison to the standard error of the marginal model shows:

```
R> sqrt(vcov(mpCR))
```

```

                                randarm5-FU + Oxaliplatin
randarm5-FU + Oxaliplatin                                0.1611
```

```
R> sqrt(vcov(m)[prm, prm])
```

```
[1] 0.1609
```

## 4. Survival outcome: Longevity study of male fruit flies

Partridge and Farquhar (1981) conducted a study on the sexual behavior of fruit flies. The aim was to investigate whether increased sexual activity leads to shorter life spans for male fruit flies. They randomly assigned a total of 125 male fruit flies into five groups of 25 flies: males that live alone, males that live with one or eight receptive females, and males that live with one or eight nonreceptive females. The data set `FruitFlies` is available in the **Stat2Data** package:

```
R> data("FruitFlies", package = "Stat2Data")
```

We follow Negassa and Hanley (2007) and are interested in assessing the effect in the two groups with eight female flies added that were either all nonreceptive ( $W = 0$ ) or receptive ( $W = 1$ ):

```
R> flies <- FruitFlies
R> flies <- flies[flies$Treatment %in% c("8 virgin", "8 pregnant"),]
R> flies$Treatment <- flies$Treatment[, drop = TRUE]
R> flies$Longevity <- as.double(flies$Longevity)
R> flies$survival <- Surv(flies$Longevity)
```

Of interest is the survival time  $Y$  of male flies in days. Because thorax length of the male flies is strongly associated with longevity (Partridge and Farquhar 1981), we use it as a covariate in this analysis.

#### 4.1. Unadjusted marginal inference

We first conduct an unadjusted effect analysis by fitting a marginal Cox proportional hazards model for time to death. We use the `Coxph()` function of the **tram** package, which does not leave the baseline log-cumulative hazard function unspecified but parameterizes it as a polynomial in Bernstein form of order six:

```
R> coxph_w <- Coxph(survival ~ Treatment, data = flies)
R> coef(coxph_w)          ### log-hazard ratio
```

```
Treatment8 virgin
          2.087
```

```
R> confint(coxph_w)      ### Wald
```

```
          2.5 % 97.5 %
Treatment8 virgin 1.297  2.877
```

The marginal treatment effect is defined as a log-hazard ratio  $\hat{\tau} = 2.087$  with 95% Wald interval (1.297, 2.877). Consequently, the hazard of dying in the sexually active group is around  $\exp(\hat{\tau}) = 8.060$  times higher than for the non-active group.

#### 4.2. Nonparanormal adjusted marginal inference

We want to investigate whether we receive more precise estimates if we exploit the information on the thorax using nonparanormal adjusted marginal inference. We parameterize the transformation function  $h_1$  in the marginal model of thorax length in Bernstein form with order six. The joint distribution of both variables is expressed by a Gaussian copula model:

```
R> xmod <- BoxCox(Thorax ~ 1, data = flies)
R> m <- Mmlt(xmod, coxph_w, data = flies, formula = ~ 1)
R> (cf1 <- coef(m)["survival.Treatment8 virgin"])
```

```
survival.Treatment8 virgin
          1.964
```

```
R> (ci1 <- confint(m)["survival.Treatment8 virgin",])
```

```
          2.5 % 97.5 %
          1.384  2.544
```

The log-hazard ratio of nonparanormal adjusted marginal inference is 1.964, with a shorter 95% Wald interval of (1.384, 2.544). The coefficient of determination indicates that thorax length is highly prognostic:

```
R> Omega <- as.array(coef(m, type = "Lambda"))[, , 1]
R> 1 - Omega[nrow(Omega), ncol(Omega)]^(-2)
```

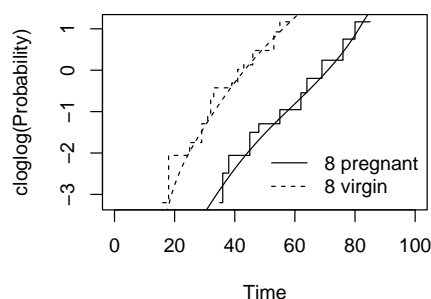
[1] 0.678

### 4.3. Model diagnosis

Model diagnosis is conducted on the level of the marginal model for the outcome and on the level of the Gaussian copula parameterizing the joint model.

On the level of the marginal model, we compare model-based and nonparametric estimators of the distribution functions of time-to-death on the complementary log-log scale. Plots of these functions are parallel under proportional hazards:

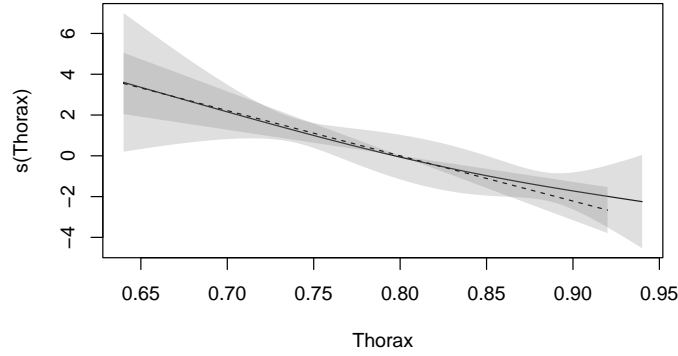
```
R> q <- 0:100
R> cols <- c("grey20", "grey70")
R>
R> plot(q, log(-log(1 - ecdf(subset(flies, ### nonparametric
+   Treatment == "8 pregnant")$survival[,1])(q))),
+   main = "", xlab = "Time", type = "S", lwd = 1,
+   ylab = "cloglog(Probability)")
R> lines(q, log(-log(1 - ecdf(subset(flies,
+   Treatment == "8 virgin")$survival[,1])(q))),
+   type = "S", lty = 2, lwd = 1)
R> legend("bottomright", lty = c(1, 2),
+   legend = levels(flies$Treatment), bty = "n")
R>
R> nd <- expand.grid(survival = q, ### model-based
+   Treatment = sort(unique(flies$Treatment)))
R> nd$h <- predict(as.mlt(coxph_w), newdata = nd, type = "trafo")
R> fm <- nd$Treatment == "8 virgin"
R> lines(nd$survival[fm], nd$h[fm], lty = 2)
R> fm <- nd$Treatment == "8 pregnant"
R> lines(nd$survival[fm], nd$h[fm], lty = 1)
```



From the obtained plot, we see that the smooth model-based transformation functions closely follow the transformed ECDFs (step function). This reflects that the transformation function fits well. The ECDF-based step functions are parallel, revealing that the proportional hazards function of the Cox model is appropriate.

To assess the fit of the Gaussian copula, we fit a more flexible additive transformation model for the outcome given the covariate thorax length as splines for each treatment group:

```
R> m <- CoxphME(survival ~ s(Thorax, k = 5), data = flies,
+               subset = Treatment == levels(Treatment)[1])
R> plot(smooth_terms(m))
R> m <- CoxphME(survival ~ s(Thorax, k = 5), data = flies,
+               subset = Treatment == levels(Treatment)[2])
R> plot(smooth_terms(m), add = TRUE, lty = 2)
```



Because the smooth functions reflecting the effect of thorax length in both treatment groups were monotone, the Gaussian copula seems to be appropriate.

## 5. Meta-analysis: Efficacy study of Enoxaparin

[Barco et al. \(2023\)](#) was interested in whether Enoxaparin can reduce the rate of hospitalizations and all-cause death in ambulatory COVID-19 patients as compared to standard of care. A study with this aim was conducted between 2020 and 2022 – the so-called OVID trial which is described in [Barco et al. \(2022\)](#). The primary outcome is a composite score of 30-day all-cause hospitalizations and all-cause death. An overview of the event rates per age and treatment group is given in Table 1 based on the Supplementary Table in [Barco et al. \(2023\)](#).

Trial	Treatment	Age 30 – 70	Age > 70	Overall
OVID	Control	2.66% (6/226)	16.67% (2/12)	3.36% 8/238
OVID	Enoxaparin	3.60% (8/222)	0% (0/12)	3.42% 8/234

Table 1: Success rates of two treatment arms for the OVID trial, overall rates as well as rates per age group (30 – 70 and > 70 years).

Based on this, we generate a table of frequencies for further analysis:

```
R> trt <- gl(2, 1, labels = c("Control", "Enoxaparin"))
R> age <- gl(2, 1, labels = c("30-70", "> 70"))
```

```
R> outcome <- gl(2, 1, labels = c("No event", "Event"))
R> ovid <- expand.grid(trt = trt, age = age, outcome = outcome)
R> ovid$weights <- c(220, 214, 10, 12, 6, 8, 2, 0)
R> (ovid)
```

	trt	age	outcome	weights
1	Control	30-70	No event	220
2	Enoxaparin	30-70	No event	214
3	Control	> 70	No event	10
4	Enoxaparin	> 70	No event	12
5	Control	30-70	Event	6
6	Enoxaparin	30-70	Event	8
7	Control	> 70	Event	2
8	Enoxaparin	> 70	Event	0

Of the 472 patients in the data set, 238 patients received standard of care (control) and 234 Enoxaparin. 16 had a composite event, 8 of control and 8 in the Enoxaparin group. In the original analysis, a binary age group variable was used as a stratum variable; 448 patients are 30 – 70 years old, while only 24 are over 70. The event rates stratified per **age** and treatment group (**trt**) are also given in Table 1. A Cochran-Mantel-Haenszel  $\chi^2$  test (without continuity correction) stratified by age group (30 – 70 vs. > 70 years)

```
R> mt <- mantelhaen.test(xtabs(weights ~ trt + outcome + age, data = ovid))
R> (lORx_mt <- log(mt$estimate))
```

```
common odds ratio
      0.01604
```

gives an estimate of the log-odds ratio of 0.016. This indicates that Enoxaparin had no significant effect on the composite score. The results are equivalent to the results of a conditional binary logistic regression model with treatment and age group as independent variables:

```
R> mtrtx_ovid <- glm(outcome ~ trt + age, data = ovid, weights = weights,
+                    family = binomial())
R> (lORx_ovid <- coef(mtrtx_ovid)["trtEnoxaparin"])
```

```
trtEnoxaparin
      0.01624
```

We want to compare the estimate of the OVID trial with the estimate of another trial – the ETHIC trial (Cools *et al.* 2022) in terms of a log-odds ratio. However, unlike the OVID trial, the ETHIC trial did not use age as an adjustment variable (Cools *et al.* 2022). To be able to compare the effect estimate of the OVID trial adjusting for age with the ETHIC trial not adjusting, we apply nonparanormal adjusted marginal inference on the OVID trial data. First, we define the marginal models for the outcome given the treatment indicator and for the age group. Since both are binary, we set up binary logistic regression models:

```
R> mtrt_ovid<- Polr(outcome ~ trt, data = ovid, weights = weights,
+                  method = "logistic")
R> mage_ovid <- Polr(age ~ 1, data = ovid, weights = weights)
```

The marginal models are inputs to the `Mmlt()` function which estimates all model parameters jointly:

```
R> m_ovid <- Mmlt(mtrt_ovid, mage_ovid, data = ovid)
R> prm <- "outcome.trtEnoxaparin"
R> (lORm_ovid <- coef(m_ovid)[prm])
```

```
outcome.trtEnoxaparin
0.04836
```

```
R> (SE_ovid <- sqrt(vcov(m_ovid)[prm, prm]))
```

```
[1] 0.5076
```

The obtained marginal log-odds ratio of NAMI is 0.048. This marginal estimate of the OVID trial is comparable to the log-odds ratio obtained from a marginal model based on the ETHIC trial which we fit next.

Of the 208 patients in the ETHIC trial, 108 received the standard-of-care treatment and 100 Enoxaparin. 24 had an event, 12 in the control and 12 in the Enoxaparin group. These frequencies were obtained from [Barco et al. \(2023\)](#). With the following code, we make the data available in the form of a frequency table:

```
R> trt <- gl(2, 1, labels = c("Control", "Enoxaparin"))
R> outcome <- gl(2, 1, labels = c("No event", "Event"))
R> ethic <- expand.grid(trt = trt, outcome = outcome)
R> ethic$weights <- c(96, 88, 12, 12)
R> (ethic)
```

	trt	outcome	weights
1	Control	No event	96
2	Enoxaparin	No event	88
3	Control	Event	12
4	Enoxaparin	Event	12

We use this frequency table as an input to `Polr()` which fits a logistic regression model that estimates a marginal log-odds ratio:

```
R> mtrt_ethic <- Polr(outcome ~ trt, data = ethic,
+                  weights = weights, method = "logistic")
R> prmeth <- "trtEnoxaparin"
R> (lOR_ethic <- coef(mtrt_ethic)[prmeth])
```

```
trtEnoxaparin
      0.08701
```

```
R> (SE_ethic <- sqrt(vcov(mtrt_ethic)[prmeth, prmeth]))
```

```
[1] 0.4341
```

The estimated marginal log-odds ratio of the ETHIC trial without adjustment for the age group is 0.087. This estimate can be compared to the NAMI estimate obtained from the OVID trial data, an overview is given in Table 2.

Trial	Log-odds ratio	Standard error
OVID	0.048	0.508
ETHIC	0.087	0.434

Table 2: Estimated marginal log-odds ratios of the OVID and ETHIC trial. For the OVID trial, the estimates were obtained by nonparanormal adjusted marginal inference, while for ETHIC, it is based on an unadjusted marginal logistic regression model.

We can conclude that, in both studies, we found no significant effect of Enoxaparin on hospitalization rates or all-cause mortality and that the marginal effect of the ETHIC trial is slightly higher than the marginal effect of the OVID trial obtained from NAMI. Table 2 can be used as a basis for fixed-effects meta-analyses. Compared to the unadjusted model based on the ETHIC trial, we can assess whether the age group was prognostic in the NAMI approach fitted to the OVID trial data. We can look at the polychoric correlations (Jöreskog 1994), i.e., the correlation of age group and outcome on the latent standard normal scale:

```
R> (polycor <- as.array(coef(m_ovid, type = "Cor"))["outcome", "age", 1])
```

```
[1] 0.2321
```

This indicates that the age group did not have a strong prognostic effect (0.232). Using NAMI allows us to balance transparency – by directly assessing whether age is prognostic – and interpretability, as the method provides a marginal and not a conditional effect. The former (transparent assessment of prognostic effects) is not possible in a marginal model, whereas the latter (obtaining marginal effects) is not feasible in a conditional model – if the treatment effect is nonzero, which cannot be known a priori.

## 6. Conclusion

The present vignette complements the theoretical work in Dandl and Hothorn (2025) by discussing four application cases of nonparanormal adjusted marginal inference with diverse outcomes. Nonparanormal adjusted marginal inference should be seen as a general framework that allows applicability to a wide range of use cases – even more complex ones that are beyond the scope of this vignette. It was shown that nonparanormal adjusted marginal inference can identify the marginal effect of the treatment of interest with higher precision (narrower

confidence intervals) as compared to unadjusted analysis if at least one relevant prognostic covariate exists. Nonparanormal adjusted marginal inference also has the advantage that the prognostic level can be directly assessed (e.g., in the form of polychoric correlations as seen in Section 5). In addition, model diagnosis tools were discussed that equip users with helpful tools to assess model fit which puts model assumptions under test.

## References

- Barco S, Virdone S, Götschi A, Ageno W, Arcelus JI, Bingisser R, Colucci G, Cools F, Duerschmied D, Gibbs H, Fumagalli RM, Gerber B, Haas S, Himmelreich JC, Hobbs R, Hobohm L, Jacobson B, Kayani G, Lopes RD, MacCallum P, Micieli E, Righini M, Robert-Ebadi H, Rocha AT, Rosemann T, Sawhney J, Schellong S, Sebastian T, Spirk D, Stortecky S, Turpie AG, Voci D, Kucher N, Pieper K, Held U, Kakkar AK (2023). “Enoxaparin for Symptomatic COVID-19 Managed in the Ambulatory Setting: An Individual Patient Level Analysis of the OVID and ETHIC Trials.” *Thrombosis Research*, **230**, 27–32. doi: [10.1016/j.thromres.2023.08.009](https://doi.org/10.1016/j.thromres.2023.08.009).
- Barco S, Voci D, Held U, Sebastian T, Bingisser R, Colucci G, Duerschmied D, Frenk A, Gerber B, Götschi A, Konstantinides SV, Mach F, Robert-Ebadi H, Rosemann T, Simon NR, Spechbach H, Spirk D, Stortecky S, Vaisnora L, Righini M, Kucher N, Barco S, Voci D, Held U, Sebastian T, Bingisser R, Colucci G, Duerschmied D, Frenk A, Gerber B, Götschi A, Konstantinides SV, Mach F, Robert-Ebadi H, Rosemann T, Simon NR, Spechbach H, Spirk D, Stortecky S, Vaisnora L, Righini M, Kucher N, Roth Zetzsche S, Spescha R, Leeger C, Butscheid Y, Probst E, Micieli E, Forgo G, Johnner F, Grigorean A, Vatsakis G, Keller Lang D, Rampini Speck S, Hasse B, Rueegg M, Arnold I, Nickel C, Busch J, Blondon M, Glauser F, Cittone MG, Kessler C, Gjermani D, Olivier CB, Gauchel N, Biever P, Hobohm L, Becker D, Schindewolf M, Kuenzi A, Ulrich S (2022). “Enoxaparin for Primary Thromboprophylaxis in Symptomatic Outpatients With COVID-19 (OVID): A Randomised, Open-Label, Parallel-Group, Multicentre, Phase 3 Trial.” *The Lancet Haematology*, **9**(8), e585–e593. doi: [10.1016/S2352-3026\(22\)00175-2](https://doi.org/10.1016/S2352-3026(22)00175-2).
- Cools F, Virdone S, Sawhney J, Lopes RD, Jacobson B, Arcelus JI, Hobbs FDR, Gibbs H, Himmelreich JCL, MacCallum P, Schellong S, Haas S, Turpie AGG, Ageno W, Rocha AT, Kayani G, Pieper K, Kakkar AK, Avhad A, Antunes M, Thereza Rocha A, Gonzales Lama J, Abyankar A, Kormann APM, Van Zyl L, Kaul U, Adams F, Aloysius I, Capehorn M, Kumar P, Mahajan R (2022). “Thromboprophylactic Low-Molecular-Weight Heparin Versus Standard of Care in Unvaccinated, At-Risk Outpatients With COVID-19 (ETHIC): An Open-Label, Multicentre, Randomised, Controlled, Phase 3b Trial.” *The Lancet Haematology*, **9**(8), e594–e604. doi: [10.1016/S2352-3026\(22\)00173-9](https://doi.org/10.1016/S2352-3026(22)00173-9).
- Dandl S, Hothorn T (2025). “Nonparanormal Adjusted Marginal Inference.” *Technical report*, arXiv 2503.01657. doi: [10.48550/arXiv.2503.01657](https://doi.org/10.48550/arXiv.2503.01657).
- Guo TL, Germolec DR, Collins BJ, Luebke RW, Auttachoat W, Smith MJ, White KL (2011). “Immunotoxicological Profile of Chloramine in Female B6C3F1 Mice When Administered in the Drinking Water for 28 Days.” *Journal of Immunotoxicology*, **8**(4), 381–388. doi: [10.3109/1547691x.2011.622317](https://doi.org/10.3109/1547691x.2011.622317).



- Hothorn T (2024). “On Nonparanormal Likelihoods.” *Technical report*, arXiv 2408.17346. doi:10.48550/arXiv.2408.17346.
- Jöreskog KG (1994). “On the Estimation of Polychoric Correlations and their Asymptotic Covariance Matrix.” *Psychometrika*, **59**(3), 381–389. doi:10.1007/bf02296131.
- National Toxicology Program (2000). “28-Day Study of Chloramine (10599-90-3) in MICE:B6C3F1.” Last visited 2024-12-22, URL <https://cebs.niehs.nih.gov/cebs/study/002-01851-0001-0000-8>.
- Negassa A, Hanley JA (2007). “The Effect of Omitted Covariates on Confidence Interval and Study Power in Binary Outcome Analysis: A Simulation Study.” *Contemporary Clinical Trials*, **28**(3), 242–248. doi:10.1016/j.cct.2006.08.007.
- Partridge L, Farquhar M (1981). “Sexual Activity Reduces Lifespan of Male Fruitflies.” *Nature*, **294**(5841), 580–582. doi:10.1038/294580a0.
- Rödel C, Graeven U, Fietkau R, Hohenberger W, Hothorn T, Arnold D, Hofheinz RD, Ghadimi M, Wolff HA, Lang-Welzenbach M, Raab HR, Wittekind C, Ströbel P, Staib L, Wilhelm M, Grabenbauer GG, Hoffmanns H, Lindemann F, Schlenska-Lange A, Folprecht G, Sauer R, Torsten Liersch on behalf of the German Rectal Cancer Study Group (2015). “Oxaliplatin Added to Fluorouracil-based Preoperative Chemoradiotherapy and Postoperative Chemotherapy of Locally Advanced Rectal Cancer (the German CAO/ARO/AIO-04 study): Final Results of the Multicentre, Open-label, Randomised, Phase 3 Trial.” *The Lancet Oncology*, **16**(8), 979–989. doi:10.1016/S1470-2045(15)00159-X.
- Rödel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T, Graeven U, Arnold D, Lang-Welzenbach M, Raab HR, Sülberg H, Wittekind C, Potapov S, Staib L, Hess C, Weigang-Köhler K, Grabenbauer GG, Hoffmanns H, Lindemann F, Schlenska-Lange A, Folprecht G, Sauer R (2012). “Preoperative Chemoradiotherapy and Postoperative Chemotherapy With Fluorouracil and Oxaliplatin Versus Fluorouracil Alone in Locally Advanced Rectal Cancer: Initial Results of the German CAO/ARO/AIO-04 Randomised Phase 3 Trial.” *The Lancet Oncology*, **13**(7), 679–687. doi:10.1016/s1470-2045(12)70187-0.
- Wellek S (2010). *Testing Statistical Hypotheses of Equivalence and Noninferiority*. 2nd edition. Chapman and Hall/CRC, Boca Raton, Florida, U.S.A. doi:10.1201/ebk1439808184.

**Affiliation:**

Susanne Dandl & Torsten Hothorn  
Institut für Epidemiologie, Biostatistik und Prävention  
Universität Zürich  
Hirschengraben 84, CH-8001 Zürich, Switzerland  
Torsten.Hothorn@R-project.org