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 2026): 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")
```

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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 τ. H_0 is rejected at 5% when the 95% confidence interval for τ 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 2026) 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 `x`) into account. With nonparanormal 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 $\mathbf{\Lambda}$ (see Sec. 2.2 in Dandl and Hothorn 2026), 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 = "Lambda")))
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 2026) obtained by

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

```
[1] 0.3844
```

suggests an improvement of the conditional over the marginal model.

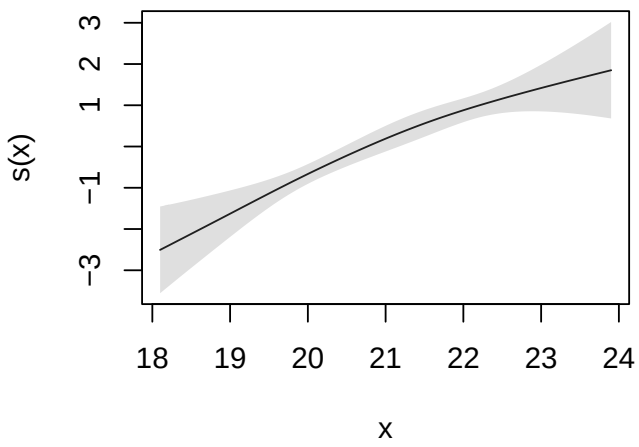
2.3. Model diagnosis

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:

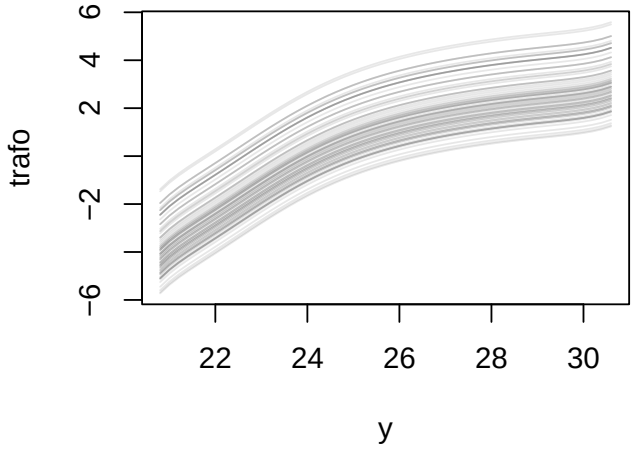
```
R> plot(smooth_terms(mad))
```



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 = "Omega"))[,,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> CAOsurv$ypT0ypN0 <- factor(CAOsurv$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 = CAOsurv, 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 = CAOsurv)
R> msex <- Polr(geschlecht ~ 1, data = CAOsurv, method = "probit")
R> CAOsurv$ecog_o <- as.ordered(CAOsurv$ecog_b)
R> mecog <- Polr(ecog_o ~ 1, data = CAOsurv, na.action = na.pass,
+                method = "probit")
R> mentf <- Polr(bentf ~ 1, data = CAOsurv, na.action = na.pass,
+                method = "probit")
R> mT <- Polr(strat_t ~ 1, data = CAOsurv, method = "probit")
R> mN <- Polr(strat_n ~ 1, data = CAOsurv, 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 = CAOsurv, 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 χ^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 = "Omega"))[,,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 = "Omega"))[,,1]
R> 1 - Omega[nrow(Omega), ncol(Omega)]^(-2)
```

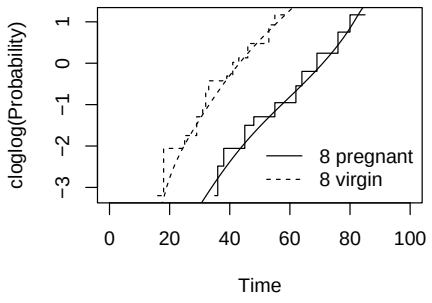
```
[1] 0.678
```

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:

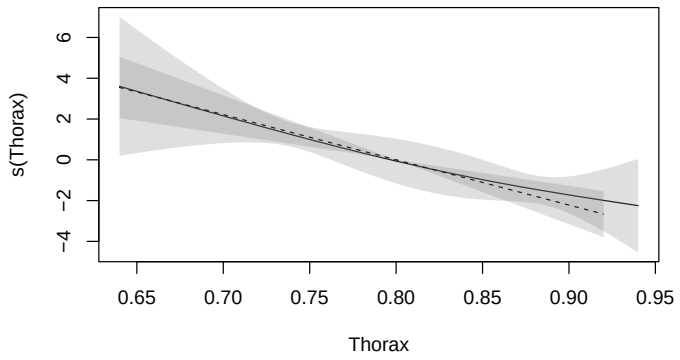
```
R> q <- 0:100
R> cols <- c("grey20", "grey70")
R>
R> plot(q, log(-log(1 - ecdf(subset(flies,  ### nonparametric
+       Treatment == "8 pregnant")$survival[,1])(q))),
+       main = "", xlab = "Time", type = "S", lwd = 1,
+       ylab = "cloglog(Probability)")
R> lines(q, log(-log(1 - ecdf(subset(flies,
+       Treatment == "8 virgin")$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 χ^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 (2026) 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.

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Affiliation:

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