PSA density versus PSA as a selection biomarker before MRI for prostate cancer screening

A secondary analysis of the paired, screen-positive STHLM3-MRI trial

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This document contains additional information on the secondary analysis in the manuscript entitled "*PSA density as a selection tool before MRI in prostate cancer screening: an analysis from the STHLM3-MRI randomized clinical trial*" (Björnebo et al., 2025).

1 Notation and aim

Define the following events:

1. A: PSA$\geq$ 3 ng/ml;
2. $B(x)$: PSAd $> x$ ng/ml^2. This event depends on the PSAd cut-off $x > 0$. The set $B(0)$ contains all study participants;
3. C_i $(i = 1, \dots, 7)$: positive *outcome*, where *outcome* refers to any of the 7 outcomes considered: {elevated PSA or PSAd, performed MRI scan, performed biopsy, benign biopsy, ISUP1, ISUP2+, ISUP3+}.

A bar above an event denotes its complement (e.g. $\bar{A}$).

The aim is to use **parametric models** to model the following target quantities:

1. The detection probability $P(A, B(x), C_i)$;
2. The Relative Positive Fraction $\text{RPF}_i(x) = \frac{P(B(x)|A,C_i)}{P(B(0)|A,C_i)}$ (Karlsson et al., 2021).

2 Identifiability

We expand $P(A, B(x), C_i)$ as the product of two probabilities:

$$P(A, B(x), C_i) = P(B(x)|A, C_i)P(A, C_i). \tag{1}$$

The probabilities $P(A, B(x), C_i)$ and $P(A, C_i)$ are identifiable in a study with a screen-positive design, such as the STHLM3-MRI trial (cfr. *detection proabilities*, §7.2.2, in

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Pepe, 2003). $P(B(x)|A, C_i)$ is also identifiable, because of the conditioning on A. Table 1 will provide more intuition, if needed. Throughout, we assume that $P(A, C_i) > 0$.

Table 1: Contingency table for a paired screen-positive study. Frequencies between brackets are not observed due to the screen-positive study design; $a + b + ... + h = N$.

	C_i			$\bar{C}_i$	
	A	$\bar{A}$		A	$\bar{A}$
$B(x)$	a	b	$B(x)$	e	f
$\bar{B}(x)$	c	$[d]$	$\bar{B}(x)$	g	$[h]$

3 Modelling

$P(A, C_i)$ is the probability of having PSA$\geq$ 3 ng/ml and positive outcome i. It is estimated as the ratio between the number of men satisfying the joint condition (A, C_i) and N. No modelling is required.

$P(B(x)|A, C_i)$ are probabilities from the survival function for PSAd, given PSA$\geq$ 3 ng/ml and positive outcome i: $P(B(x)|A, C_i) = P(\text{PSAd} > x|A, C_i) = S(x|A, C_i)$. This survival function can be modelled using parametric models. In particular, we propose to use flexible parametric models:

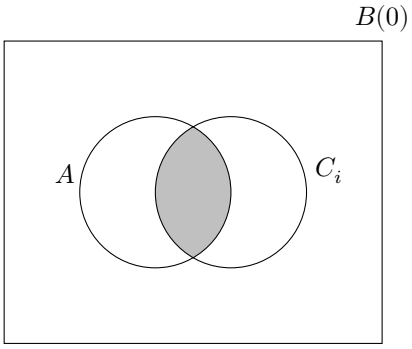
$$g(S(x|A, C_i)) = s(\ln x; \alpha),$$

where $g(S)$ is a suitable link function and $s(\ln x; \alpha)$ a flexible function having adjustable parameter vector α (e.g. natural splines) (Royston and Parmar, 2002; Liu et al., 2018; Bottai et al., 2021).

We now contrast the joint probabilities $P(B(x)|A, C_i)$ versus $P(B(0)|A, C_i)$, which is the referent strategy based on PSA$\geq$ 3 ng/ml alone, by taking their ratio. We refer to this ratio as the RPF (Karlsson et al., 2021), which simplifies as follows:

$$\begin{aligned} \text{RPF}_i(x) &= \frac{P(B(x)|A, C_i)}{P(B(0)|A, C_i)} \\ &= \frac{P(B(x)|A, C_i)}{1} \\ &= S(x|A, C_i), \end{aligned} \tag{2}$$

where the first equality follows from $A \cap C_i \subseteq B(0)$.



Of note, Equations (1) and (2) imply that modelling $P(B(x)|A, C_i)$ is sufficient to model both target quantities. Also, from Equation (1) it follows that $\text{RPF}_i(x) = P(A, B(x), C_i)/P(A, C_i)$.

4 Standard errors

The asymptotic standard error (ASE) for $P(A, B(x), C_i)$ is derived with the delta method:

$$ASE[P(A, B(x), C_i)] = \sqrt{P(B(x)|A, C_i)^2 ASE[P(A, C_i)]^2 + P(A, C_i)^2 ASE[P(B(x)|A, C_i)]^2}.$$

The formula for $ASE[P(B(x)|A, C_i)]$, which is also the ASE for the RPF, depends on the specific model for the survival function. The $ASE[P(A, C_i)]$ is equal to $\sqrt{P(A, C_i)(1 - P(A, C_i))/N)}$.

5 Heterogeneity of the Relative Positive Fractions

Outcome-specific heterogeneity of the RPF for all PSAd cut-offs with respect to a variable Z (e.g. age, previous benign biopsy,...) can be tested by including the variable in the model for the survival function:

$$g(S(x|A, C_i, Z = z)) = s(\ln x; \alpha) + \beta z.$$

Any statistical test for the regression coefficient $\beta \neq 0$ is a test for (overall) heterogeneity of the RPF. The interpretation of the regression coefficient β depends on the specific link function used in the analysis.

More complex models including interaction (product) terms between $s(\ln x; \alpha)$ and Z can be used to test for the heterogeneity of the RPF at specific PSAd cut-offs.

6 Application to the STHLM3-MRI trial data

In the analysis of the STHLM3-MRI trial (Nordström et al., 2021), we fitted separate models with link $g(S) = -\text{logit}(S)$ for each event C_i. These models are known as

proportional-odds models and provided a good fit to the the data while spending fewer degrees of freedom than proportional-hazards models. The number of degrees of freedom was selected based on the AIC. Models were fit using the `stpm2` function from the `rstpm2` R package. The ASEs for $S(x|A, C_i)$ were obtained using the delta method implemented in the `predict` function.

7 References

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