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 article *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). For more information on the STHLM3-MRI trial, see Nordström et al. (2021).

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 $x > 0$;
3. C_i $(i = 1, \ldots, 7)$: 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 $\text{RPF}_i(x) = \frac{P(A,B(x)|C_i)}{P(A|C_i)}$.

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 probabilities*, Section 7.2.2,

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in 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.

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

	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.

$P(B(x)|A, C_i)$ 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:

$$g(S(x|A, C_i)) = s(\ln x; \alpha), \tag{2}$$

where $g(x)$ 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 probabilities $P(A, B(x)|C_i)$ and $P(A|C_i)$ by taking their ratio. We refer to this ratio as the RPF, which generalises the relative true and false positive fractions for > 2 health or disease states (Karlsson et al., 2021)[1]. The RPF can be simplified as follows:

$$\begin{aligned} \text{RPF}_i(x) &= \frac{P(A, B(x)|C_i)}{P(A|C_i)} \\ &= \frac{P(B(x)|A, C_i)}{1} \\ &= S(x|A, C_i), \end{aligned} \tag{3}$$

where the first equality follows from multiplying and dividing by $P(A|C_i)$.

Of note, Equations (1) and (3) imply that modelling $P(B(x)|A, C_i)$ is sufficient to model both target quantities. Also, from Equation (1) it follows that $\text{RPF}_i(x) = P(A, B(x), C_i)/P(A, C_i)$.

[1]For example, if $\text{RPF}_6(0.10) = 0.8$, the probability of testing PSA$\geq$ 3 ng/ml and PSAd$>$ 0.10 ng/ml^2 is 20% lower than testing PSA$\geq$ 3 ng/ml, given an ISUP2+ cancer diagnosis.

4 Standard errors

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

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

where

$$ASE[P(B(x)|A, C_i)] = \sqrt{\left(\frac{d}{d\alpha} g^{-1}(s(\ln x; \alpha))\right)^T \mathbf{\Sigma} \left(\frac{d}{d\alpha} g^{-1}(s(\ln x; \alpha))\right)},$$
$$ASE[P(A, C_i)] = \sqrt{P(A, C_i)(1 - P(A, C_i))/N)},$$

$g^{-1}(x)$ is the inverse link function, and $\mathbf{\Sigma}$ is the variance-covariance matrix for the model in Equation (2).

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 this secondary analysis of the STHLM3-MRI trial (Nordström et al., 2021), we fitted separate models with link $g(x) = -\text{logit}(x)$ 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 ($g(x) = \log(-\log(x))$). The number of degrees of freedom was selected based on the AIC. Models were fitted using the `stpm2` function from the `rstpm2` R package (Liu et al., 2018).

7 References

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