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# Partially identified prevalence estimation under misclassification using the kappa coefficient 

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## ARTICLEINFO

## Article history:

Available online 27 June 2012

## Keywords:

Partial identification
Sensitivity analysis
Prevalence estimation
Kappa coefficient
Misclassification
Identification region


#### Abstract

We discuss prevalence estimation under misclassification. That is we are concerned with the estimation of a proportion of units having a certain property (being diseased, showing deviant behavior, etc.) from a random sample when the true variable of interest cannot be observed, but a related proxy variable (e.g. the outcome of a diagnostic test) is available. If the misclassification probabilities were known then unbiased prevalence estimation would be possible. We focus on the frequent case where the misclassification probabilities are unknown but two independent replicate measurements have been taken. While in the traditional precise probabilistic framework a correction from this information is not possible due to non-identifiability, the imprecise probability methodology of partial identification and systematic sensitivity analysis allows to obtain valuable insights into possible bias due to misclassification. We derive tight identification intervals and corresponding confidence regions for the true prevalence, based on the often reported kappa coefficient, which condenses the information of the replicates by measuring agreement between the two measurements. Our method is illustrated in several theoretical scenarios and in an example from oral health on prevalence of caries in children.


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## 1. Introduction

Many data in social sciences, econometrics, biometrics and epidemiology are complex in the sense that the available data at hand do not exactly convey the information one is looking for. Frequently, the variables of material interest cannot be observed directly or measured correctly, and one has to be satisfied with so-called surrogates or proxies, i.e., with somehow related, but different variables. This problem of non-ascertainability of certain ideal variables is referred to as measurement error (ME in the following) if the variables are continuous and as misclassification (MC) if they are discrete variables. If one ignores the fundamental difference between the ideal variables and their observable counterparts and just plugs in the surrogates instead of the ideal variables ('naive estimation'), then all the parameter estimators must be suspected to be severely biased. For the distorting effects of MC in different applications, see, e.g., $[9,24,25,32,41,54,56]$.

In the last years there has been a considerable progress in developing methods how to adjust for measurement error and misclassification in statistical models. Many correction procedures are available for consistent estimation in the presence of ME or MC, see in particular the monographs [7,18], or, e.g., [17,45]. Most of those procedures are based on precise information about the process of measurement (and in complex models typically on Bayesian methods with precise priors, e.g., [44]). In the case of an additive measurement error, usually the variance of measurement error has to be known or to be estimated, e.g. by replicate measurements, to enable consistent estimation. In the presence of MC, knowledge of

[^0]the conditional probabilities of correct classification, in the binary case called sensitivity and specificity, allows for general estimation procedures even in complex models; see $[21,40]$ for fundamental work concerned with response misclassification and, e.g., $[28,30,31,60]$ for methods handling misclassified covariates. When no such information about ME or MC is available, identification problems arise and no consistent parameter estimation is possible. Important examples include the estimation in simple linear regression with covariate ME as well as the problem of estimating probability distributions of outcomes in the presence of MC. In this paper, we examine the latter problem in the spirit of the methodology of partial identification (e.g., [33]) and systematic sensitivity analysis (e.g., [53]).

One important example for estimating probability distributions in medical and clinical research is prevalence estimation, i.e. estimating the probability that a randomly sampled person of the population has a certain property, e.g. is diseased. ${ }^{1}$ In the presence of MC , induced, e.g., by a medical examiner or a diagnostic tool, prevalence estimation using the relative frequency ignoring MC (naive estimation) is inconsistent. In this situation, a consistent estimator is available when the conditional probabilities of correct diagnosis (sensitivity and specificity) are known or can be estimated consistently. However, estimating sensitivity and specificity using a validation study usually relies on the availability of a correct diagnostic method (gold standard) in the validation sample. If such a gold standard method is not available, then it is usual practice to replicate measurements on the same unit to get some information on the quality of the measurement procedure. In the case of the availability of three independent measurements with identical sensitivity and specificity, it is still possible to obtain consistent estimators of prevalence; for a recent discussion, see [42]. Another scenario, where the parameters are identified, is the availability of two independent measurements with identical sensitivity and specificity in two different populations, see [47].

When only two replicate measurements in one population are available, the quality of measurement can be characterized by Cohen's kappa coefficient [10], which is based on the agreement of the replicates ('inter rater reliability'). Although there is a long discussion about the problems of using the kappa coefficient (e.g., [6,15,51]), it is usually reported in those studies. However, no further correction is performed, since the resulting estimation model is not well-identified, making the derivation of a precise-valued estimator impossible. In contrast, the concept of partial identification and systematic sensitivity analysis provides valuable insights into the magnitude of the misclassification bias. We derive identification regions of the misclassification probabilities and the true prevalence, and confidence regions for the latter, additionally taking sample variation into account. In our example, we use data from a validation study, which consists of a subsample of our data to estimate kappa coefficient.

We understand our contribution as a typical example where imprecise probabilistic methodology provides powerful quantitative insights into the underlying structure, while the traditional precise approach, forced to choose between the extremes 'precise solution' or 'no solution', necessarily has to surrender. The general methodology underlying our investigation adapts recent progress in the area of partial identification and systematic sensitivity analysis for possibly deficient data, also strongly related to the conservative handling of deficient data in imprecise probability settings (e.g., [13,50,59]). Up to now, such methods have been mostly applied to the case of missing or coarse data with an unknown deficiency mechanism (e.g., [34,37], for surveys), notably with regard to missingness due to counterfactuality when analysing treatment effects (see e.g., $[8,16,26,35,36,49]$ ). Corresponding ideas have, for instance, been proposed in general settings in [14,19], or more specifically to handle publication bias in meta analysis [12,22], in the reanalysis of a public opinion survey [3] or to derive tight bounds on demand responses [5], and may provide an alternative to some neighborhood models in robust statistics [1, Section 5]. Recently partial identification has also been applied in the context of misclassification [2,20,38].

The paper is organized as follows. In Section 2, we deduce basic formulas for the relationship between the fundamental quantities characterizing our situation, i.e. observed prevalence, sensitivity, specificity and the kappa coefficient. From that, identification regions for the true prevalence are derived. In Section 3, sampling variability is incorporated into our estimates resulting in confidence intervals. In Section 4, we apply our findings to a data set of caries research before we conclude with a brief further discussion of our approach in Section 5 .

## 2. Prevalence estimation under misclassification

At the beginning of this section the basic situation is described and notation and terminology are fixed (cf. also Table 1). We address the problem of estimating the prevalence of a certain disease, i.e. a probability

$$
p:=P(Y=1)
$$

where

$$
Y=\left\{\begin{array}{l}
1 \text { diseased } \\
0 \text { not diseased }
\end{array}\right.
$$

[^1]Table 1
Basic notions.

denotes the indicator for the (true) disease status. Due to the possible presence of MC we cannot observe $Y$ directly, but instead the diagnosis of an examiner, which is denoted by

$$
Y^{*}=\left\{\begin{array}{l}
1 \text { diagnosis positive } \\
0 \text { diagnosis negative }
\end{array}\right.
$$

The naive estimator $\frac{1}{n} \sum_{i=1}^{n} Y_{i}^{*}$ based on a simple random sample $Y_{1}^{*}, \ldots, Y_{n}^{*}$ of $Y^{*}$ of size $n$ is biased and converges to $P\left(Y^{*}=1\right)$. We call $p^{*}:=P\left(Y^{*}=1\right)$ the naive prevalence and denote the naive estimator based on the observed relative frequency by $\widehat{p^{*}}$.

The relationship between the true and the naive prevalence using sensitivity sens $:=P\left(Y^{*}=1 \mid Y=1\right)$ and specificity spec $:=P\left(Y^{*}=0 \mid Y=0\right)$ of the diagnosis is directly obtained from the law of total probability.

$$
\begin{align*}
p^{*} & =P\left(Y^{*}=1\right)=P\left(Y^{*}=1 \mid Y=1\right) \cdot P(Y=1)+P\left(Y^{*}=1 \mid Y=0\right) \cdot P(Y=0) \\
& =p \cdot \operatorname{sens}+(1-p) \cdot(1-\text { spec }) . \tag{1}
\end{align*}
$$

For technical reasons only we have to fix additionally the assumption that throughout the paper

$$
\begin{equation*}
\text { sens }+ \text { spec }>1 \tag{2}
\end{equation*}
$$



Fig. 1. Illustration of misclassification bias (deviation from the angle bisector): naive (observed) prevalence $p^{*}$ in dependence of the true prevalence $p$ for different values of specificity and sensitivity $=1$.


Fig. 2. Illustration of misclassification bias (deviation from the angle bisector): naive (observed) prevalence $p^{*}$ in dependence of the true prevalence $p$ for different values of sensitivity and specificity.

This commonly used constraint is not a substantial restriction, since otherwise the diagnosis does not contain any useful information.

If sensitivity and specificity are known, Eq. (1) yields an unbiased estimator of $p$ by

$$
\begin{equation*}
\hat{p}=\frac{\widehat{p^{*}}+\text { spec }-1}{\text { sens }+ \text { spec }-1} . \tag{3}
\end{equation*}
$$

Moreover, Eq. (1) allows to illustrate the potentially rather high distorting effects of misclassification. In Figs. 1 and 2 the naive prevalence $p^{*}$ is plotted in dependence of the true prevalence $p$ for different misclassification probabilities. Fig. 1 shows the bias in the situation of a test with optimal sensitivity, which would detect every diseased unit, but may produce a certain amount of false positive results.

Fig. 2 illustrates the more realistic situation of possibly false positive and false negative units. Note that in all situations the bias depends on the true, but unknown(!) value of $p$. Moreover, as in Fig. 2, the bias usually is complex in the sense that, in contrast e.g. to single-variable classical measurement error in linear regression models, even its sign cannot be determined without additional knowledge. In dependence on the concrete constellation of sense, spec, and $p$, over- and underestimation of the true prevalence is possible.

### 2.1. Establishing a relationship between the kappa coefficient, misclassification probabilities and prevalence

We now assume that we have two replicate measurements $Y_{1}^{*}, Y_{2}^{*}$ on the same units. These replicates relate to two examiners and the data can be displayed in a $2 \times 2$ table. We define the corresponding probabilities by

$$
\begin{equation*}
p_{j k}:=P\left(Y_{1}^{*}=j, Y_{2}^{*}=k\right), j, k=0,1 \tag{4}
\end{equation*}
$$

The kappa coefficient $\kappa$ as proposed by [10], see also, e.g., [43,46] for recent developments, assesses the chance corrected agreement among the replicate measurements (inter rater agreement). The (theoretical) kappa coefficient is defined by

$$
\begin{align*}
\kappa & :=\frac{p_{0}-p_{e}}{1-p_{e}}  \tag{5}\\
p_{0} & :=p_{00}+p_{11} \\
p_{e} & :=\left(p_{00}+p_{01}\right) \cdot\left(p_{00}+p_{10}\right)+\left(p_{10}+p_{11}\right) \cdot\left(p_{01}+p_{11}\right) \tag{6}
\end{align*}
$$

Here, $p_{0}$ is the probability of the observed agreement and $p_{e}$ is the probability of agreement if both ratings are unconditionally independent. The closer $\kappa$ is to 1 , the better the agreement of the examiners. Landis and Koch [29, p. 165] suggested a classification of the strength of agreement that is widely adopted. They introduced the following categories: $\kappa<0.00$ : poor; $\kappa \in$ [0.00, 0.20]: slight; $\kappa \in$ [0.21, 0.40]: fair; $\kappa \in$ [0.41, 0.60]: moderate; $\kappa \in$ [0.61 - 0.80]: substantial; $\kappa \in[0.81-1.00]:$ almost perfect.

Remark 2.1. There is an explicit relation between the kappa coefficient, the prevalence and the probabilities of misclassification, which will be useful to identify regions for the prevalence. Under the assumptions
(AS1) independent conditional distributions $Y_{1}^{*} \mid Y$ and $Y_{2}^{*} \mid Y$ for both replicates,
(AS2) equal sensitivity and specificity for both replicates
the following equation holds $(p \in(0 ; 1)$ and sens and spec satisfying (2)):

$$
\begin{equation*}
\kappa=\frac{p(1-p)(\text { sens }+ \text { spec }-1)^{2}}{(\text { spec }-p(\text { sens }+ \text { spec }-1))} \cdot \frac{1}{(1-\text { spec }+p(\text { sens }+ \text { spec }-1))} . \tag{7}
\end{equation*}
$$

Eq. (7) is deduced by using the assumptions (AS1) and (AS2) that imply

$$
\begin{align*}
& p_{00}=(1-p) \cdot \text { spec }^{2}+p \cdot\left(1-\text { sens }^{2}{ }^{2}\right. \\
& p_{01}=(1-p) \cdot \text { spec } \cdot(1-\text { spec })+p \cdot(1-\text { sens }) \cdot \text { sens } \\
& p_{10}=p_{01}  \tag{8}\\
& p_{11}=(1-p) \cdot(1-\text { spec })^{2}+p \cdot \text { sens }^{2} . \tag{9}
\end{align*}
$$

This leads, together with (5), to formula (7). Note that the kappa coefficient can be seen as a parameter of one scoring process. It is a measurement of agreement when it is independently applied on the same subject twice. It can be estimated by a validation study, where two independent scorings are available for a (sub)sample of individuals.

Note that the assumptions (AS1) of conditional independence and (AS2) of identical sensitivity and specificity may be violated if the two replicates correspond to two different examiners, for a further discussion we refer to Section 5. Strong violations of assumption (AS2) can be detected by the McNemar test, which is designed for the comparison of two probabilities for dependent data. It basically checks the identity (8), see also our example in Section 4.

### 2.2. Bias correction using the kappa coefficient

We want to estimate the true prevalence $p$ using the naive estimator $\widehat{p^{*}}$ and a given or consistently estimated kappa coefficient. The basic approach is to use Eqs. (7) and (1) and solve them for $p$. Since there are unknowns ( $p$, sens, spec) and only two equations, there is a lack of identifiability and no direct estimator can be deduced. However, nontrivial intervals $I\left(\vartheta \| p^{*}, \kappa\right)$ for the possible solutions for the three parameters $\vartheta \in\{p$, sens, spec $\}$ can be derived, by additionally relying on the constraint that all probabilities are in [0; 1]. Following [33], these solutions are called identification regions. In [53], they are called ignorance regions since they relate to ignorance in contrast to sampling error.

Theorem 2.2 (Identification regions for $p$, sens and spec using $p^{*}$ and $\kappa$ ). Let the assumptions (AS1) and (AS2) hold. Additionally, let $\kappa \in(0,1]$ and sens + spec $>1$ (see (2)). Then the identification regions for the prevalence $p$, the sensitivity sens and the specificity spec based on the naive prevalence $p^{*} \in[0,1]$, are

$$
\begin{equation*}
I\left(p \| p^{*}, \kappa\right)=\left[\frac{p^{*}}{p^{*}+\kappa^{-1}\left(1-p^{*}\right)} ; \quad \frac{p^{*}}{p^{*}+\kappa\left(1-p^{*}\right)}\right] \tag{10}
\end{equation*}
$$

$$
\begin{align*}
& I\left(\text { sens } \| p^{*}, \kappa\right)=\left[p^{*}+\kappa\left(1-p^{*}\right) ; 1\right]  \tag{11}\\
& I\left(\text { spec } \| p^{*}, \kappa\right)=\left[1-p^{*}+p^{*} \kappa ; 1\right] \tag{12}
\end{align*}
$$

The regions in the theorem follow directly by solving Eqs. (7) and (1), and therefore are the best that we can learn from the given values of $p^{*}$ and $\kappa$, without adding further assumptions. Details of the derivation are given in Appendix A.

Naturally, the width of the intervals decreases when the kappa coefficient $\kappa$ increases. Indeed, considering the extreme case where the examiners' assignments are almost random, $(\kappa \rightarrow 0)$ leads to the vacuous statement $I_{p}=[0 ; 1]$. On the other hand, complete agreement, and therefore $\kappa=1$, results in point identification, where the region for $p$ degenerates to $p^{*}$ and sens $=$ spec $=1$. In Fig. 3, the identification regions are displayed as a function of the kappa coefficient for fixed values of $p^{*}$. For reasonable agreement of the measurements, in particular, the intervals are small enough to provide valuable insight into the true prevalence.

Note that, by construction, the method is based on the data in a conservative manner. Consequently, the identification region necessarily contains $p^{*}$ : by $\kappa \leq 1$, one obtains for the interval limits in (10)


Fig. 3. Identification regions (dashed lines) for the true prevalence $p$ (solid line) in dependence of $\kappa$ for different values of the naive preference $p^{*}=0.01$ (upper left, with different scale!), $p^{*}=0.1$ (upper right), $p^{*}=0.3$ (lower left) and $p^{*}=0.5$ (lower right).

$$
\begin{aligned}
\frac{p^{*}}{p^{*}+\kappa^{-1}\left(1-p^{*}\right)} & \leq \frac{p^{*}}{p^{*}+\left(1-p^{*}\right)}=p^{*} \\
\frac{p^{*}}{p^{*}+\kappa\left(1-p^{*}\right)} & \geq \frac{p^{*}}{p^{*}+\left(1-p^{*}\right)}=p^{*}
\end{aligned}
$$

The regions given in Theorem 2.2 are the best we can conclude from the data alone. If we interpret them as probability assignments they describe coherent interval-valued probabilities and F-probabilities in the sense of [55] and [57,58], for details see Appendix B. Note that $\kappa$ and $p^{*}$ bear sufficient information for determining the probabilities $\left(p_{00}, p_{01}, p_{10}, p_{11}\right)$, i.e. using those probabilities would not lead to an improvement of the bounds. Since the assumptions (AS1) and (AS2) imply $p_{01}=p_{10}$ and the probabilities add to 1 , there are only two free parameters. An explicit formula is presented in Appendix C.

Theorem 2.2 enables us to calculate identification regions for the prevalence, sensitivity and specificity from the naive estimator $\widehat{p^{*}}$ and an estimated kappa value $\hat{\kappa}$, by substituting $p^{*}$ and $\kappa$ with their estimators in Eqs. (10)-(12). Note that these intervals correspond to point estimators and, in particular, are not confidence intervals. Strategies for finding confidence intervals, i.e. additionally taking the sampling variation into account, are given in the following section.

## 3. Taking additionally sampling variation into account: confidence intervals

We follow here the strategy from [53] and define a parameter $\gamma$, which is not identified by our data, but the other parameters of our models are identified conditional on this parameter. As a suitable choice for this identifying parameter we propose in our context $\gamma:=\frac{\operatorname{sens}}{\text { spec }}$, which indeed would result in a point identified estimator, see (16) below. The parameter $\gamma$ has an obvious interpretation relating the probabilities of the two types of misclassification. In the framework of [53] it is called a sensitivity parameter. We do not use this technical term here to avoid confusion with the sensitivity of the diagnosis sens. The parameter $\gamma$ is restricted by (11) and (12). Therefore, the range of $\gamma$ is given by

$$
\begin{equation*}
\left[\gamma_{\min }, \gamma_{\max }\right]=\left[p^{*}+\kappa\left(1-p^{*}\right), \quad \frac{1}{1-p^{*}+p^{*} \kappa}\right] \tag{13}
\end{equation*}
$$

We now assume that a consistent asymptotic normal estimator $\left(\widehat{p^{*}}, \hat{\kappa}\right)$ with asymptotic covariance matrix $\Sigma$ is available. If the estimator of $\kappa$ is estimated by an independent validation study, $\Sigma$ is diagonal. If we assume that $\kappa$ to be known, then the corresponding entries in $\Sigma$ are 0 .

To construct a confidence interval $\left[L\left(\widehat{p^{*}}, \hat{\kappa}\right) ; U\left(\widehat{p^{*}}, \hat{\kappa}\right)\right]$ for the parameter $p$ we have to ensure that the coverage probability exceeds the confidence level $1-\alpha$ for every $\gamma \in\left[\gamma_{\min }, \gamma_{\max }\right]$, i.e.

$$
\begin{equation*}
\inf _{\gamma \in\left[\hat{\gamma_{\text {min }}}, \hat{\gamma}_{\text {max }}\right]} P_{\gamma}\left(p \in\left[L\left(\widehat{p^{*}}, \hat{\kappa}\right) ; U\left(\widehat{p^{*}}, \hat{\kappa}\right)\right]\right) \geq 1-\alpha \tag{14}
\end{equation*}
$$

This can be achieved by defining the confidence interval as the union of confidence intervals over the identification parameter $\gamma$

$$
\begin{equation*}
\left[L\left(\widehat{p^{*}}, \hat{\kappa}\right) ; U\left(\widehat{p^{*}}, \hat{\kappa}\right)\right]:=\bigcup_{\gamma \in\left[\hat{\gamma}_{\text {min }}, \hat{\gamma}_{\text {max }}\right]}\left[L\left(\widehat{p^{*}}, \hat{\kappa}, \gamma\right) ; U\left(\widehat{p^{*}}, \hat{\kappa}, \gamma\right)\right] \tag{15}
\end{equation*}
$$

with $\left[L\left(\widehat{p^{*}}, \hat{\kappa}, \gamma\right) ; U\left(\widehat{p^{*}}, \hat{\kappa}, \gamma\right)\right]$ as suitable confidence intervals for fixed parameter $\gamma$. To calculate the latter, we apply the delta method (e.g., [4, Sec. 5.3.2]) and use for fixed $\gamma$ the point estimator for $p$ given by

$$
\begin{equation*}
\hat{p}\left(\widehat{p^{*}}, \hat{\kappa}, \gamma\right)=\frac{\left(1-\widehat{p^{*}}\right) \cdot \gamma-\widehat{p^{*}}-\sqrt{\hat{w}}}{\left(\widehat{p^{*}}-1\right) \cdot \gamma^{2}+(1-\sqrt{\hat{w}}) \cdot \gamma-\widehat{p^{*}}-\sqrt{\hat{\hat{w}}}} \tag{16}
\end{equation*}
$$

with

$$
\hat{w}=\left(\widehat{p^{*}}-1\right)^{2} \cdot \gamma^{2}-2 \cdot \widehat{p^{*}} \cdot\left(\widehat{p^{*}}-1\right) \cdot(2 \cdot \hat{\kappa}-1) \cdot \gamma+\left(\widehat{p^{*}}\right)^{2}
$$

derived from (7) and (1), see Appendix D. The asymptotic variance is given by the delta method

$$
\begin{equation*}
\operatorname{Var}\left(\hat{p}\left(\widehat{p^{*}}, \hat{\kappa}, \gamma\right)\right)=D_{p}^{T} \Sigma D_{p} \tag{17}
\end{equation*}
$$

Here, $D_{p}$ is the vector of derivatives of $\hat{p}\left(\widehat{p^{*}}, \hat{\kappa}, \gamma\right)$ with respect to $\widehat{p^{*}}$ and $\hat{\kappa}$, and $\Sigma$ is the corresponding covariance matrix. Details are again postponed to Appendix D. Since the relationship (16) between $\gamma$ and $p$ is monotone (for a proof see Appendix D.1), the choice of the confidence intervals in (15) can be optimized, see [53] or [23,48]. If the local confidence intervals are small compared to the identification region, then it is actually justified to rely on the ( $1-\alpha$ ) $100 \%$-quantile $z_{1-\alpha}$, instead of the $(1-\alpha / 2) \cdot 100 \%$-quantile of the standard normal distribution. Thus, the confidence interval is given by

$$
\begin{align*}
& {\left[L\left(\hat{p}^{*} ; \hat{\kappa}\right), U(\hat{p}, \hat{\kappa})\right]} \\
& \quad=\left[\hat{p}\left(\widehat{p^{*}}, \hat{\kappa}, \hat{\gamma}_{\max }\right)-z_{1-\alpha} \cdot \sqrt{\widehat{\operatorname{Var}}\left(\hat{p}\left(\widehat{p^{*}}, \hat{\kappa}, \hat{\gamma}_{\max }\right)\right)}, \hat{p}\left(\widehat{p^{*}}, \hat{\kappa}, \hat{\gamma}_{\min }\right)+z_{1-\alpha} \cdot \sqrt{\widehat{\operatorname{Var}}\left(\hat{p}\left(\widehat{p^{*}}, \hat{\kappa}, \hat{\gamma}_{\min }\right)\right)}\right] . \tag{18}
\end{align*}
$$

The range for $\gamma$ is estimated using (13). Since the estimator of $\left(\widehat{p^{*}}, \hat{\kappa}\right)$ is consistent, the probability that the interval [ $\hat{\gamma}_{\text {min }}, \hat{\gamma}_{\text {max }}$ ] covers the true parameter $\gamma$ tends to 1 as sample size $n$ goes to infinity. Therefore, (15) is an asymptotic confidence interval. Note that we define our confidence intervals for the parameter and not for the entire identified set, see, in particular, [23] for a discussion of that distinction.

## 4. Example

### 4.1. The Signal-Tandmobiel® study

The Signal-Tandmobiel ${ }^{\circledR}$ study is a 6-year longitudinal oral health study, conducted in Flanders (Belgium) involving 4468 children. Data were collected on oral hygiene, gingival condition, dental trauma, prevalence and extent of enamel

Table 2
Signal-Tandmobiel® study: estimation of $\widehat{p^{*}}$ per year.

| Year | $n$ | $\widehat{p^{*}}$ | se $\left(\widehat{p^{*}}\right)$ |
| :---: | :--- | :--- | :--- |
| 1996 (age 6) | 3378 | 0.118 |  |
| 1998 (age 8) | 3657 | 0.280 | 0.006 |
| 2000 (age 10) | 3415 | 0.380 | 0.007 |
|  |  |  |  |

Table 3
Results of the validation study with two raters. $\hat{\kappa}$ indicates the kappa statistics with standard error in brackets.

| 1996 |  |  |
| :---: | :---: | :---: |
| Rater 1 |  |  |
| Rater 278 | 7 | 85 |
| 13 | 22 | 35 |
| 91 | 29 | 120 |
| $\begin{aligned} & p \text {-value }=0.1797(\text { McNemar }) \\ & \hat{\kappa}=0.5752(0.084) \end{aligned}$ |  |  |
| 1998 |  |  |
| Rater 1 |  |  |
| Rater 285 | 13 | 98 |
| 16 | 43 | 59 |
| 101 | 56 | 157 |
| $\begin{aligned} & p \text {-value }=0.5775(\text { McNemar }) \\ & \hat{\kappa}=0.6023(0.066) \end{aligned}$ |  |  |
| 2000 |  |  |
| Rater 1 |  |  |
| Rater 289 | 14 | 103 |
| 3 | 42 | 45 |
| 92 | 56 | 148 |
| $\begin{aligned} & p \text {-value }=0.0076(\text { McNemar }) \\ & \hat{\kappa}=0.7461(0.057) \end{aligned}$ |  |  |

developmental defects, fluorosis, tooth decay, presence of restoration, missing teeth, stage of tooth eruption and orthodontic treatment need, all by using established criteria, see [52]. The children were examined annually during 1996-2001. Measurement of interest is the dmft index, which is the sum of the number of decayed, missing due to caries or filled teeth.

We use the dmft index as an indicator for the presence or absence of caries for each child to examine the prevalence of caries. The observed disease status $Y_{i}^{*}$ for child $i$ is

$$
Y_{i}^{*}=\left\{\begin{array}{lll}
1 & i \text { diagnosed with caries } & (d m f t>0) \\
0 & i \text { not diagnosed with caries } & (d m f t=0)
\end{array}\right.
$$

For illustration of our methods, we estimate the naive prevalence and its variance for the years 1996 (age 6), 1998 (age 8) and 2000 (age 10), see Table 2. These are the years in which a calibration study was conducted. The longitudinal structure is ignored and the naive prevalence naturally increases over the years, i.e. with the age of the children, and its standard error is very low due to the high sample size $n$.

In the calibration study in [39], the observations of the 16 regular examiners were compared to a gold standard examiner resulting in estimation of sensitivity and specificity. However, letting one single person be the gold standard examiner can still not guarantee correctness. For illustration of our methods and to incorporate this possibility of an error, the gold standard examiner is now considered a 'common' examiner. In the validation study we now have two observations per child. The results are presented in Table 3. However, since assumption (AS2) is questionable in our setting, we performed a McNemar test, which is based on the difference of the off diagonal cells of the two by two table. In case of the two by two table for 2000, the test indicates a significant deviation from the assumption. Therefore, we present results of our method only for the years 1996 and 1998.

The kappa coefficient is estimated using the relationships (5) and (6). The corresponding estimates of the standard errors of $\hat{\kappa}$ are rather high due to the small sample size.

### 4.2. Correction for misclassification

We use the methods developed in this paper to correct the estimated prevalence for misclassification. In Table 4, the corresponding identification regions based on the point estimation of $p^{*}$ and $\kappa$ using Theorem 2.2 are presented. The regions for the prevalence are wide. This is a consequence of the low kappa coefficient, reflecting the low agreement among the examiners. As discussed, the estimated regions necessarily include the naive estimator, but it becomes evident that the naive estimator could be seriously biased. Moreover, the regions for specificity, and especially for sensitivity are wide, too.

If the kappa coefficient was considered known, the confidence intervals are only slightly smaller, indicating that the main problem is in the partial identification of our setting.

In a second step, the confidence intervals for the prevalence following the strategy from Section 3 are presented in Table 5, once while incorporating the sample variability of the estimators $\widehat{p^{*}}$ and $\hat{\kappa}$ and, for illustration, assuming $\kappa$ to be

Table 4
Signal-Tandmobiel® study: Estimated identification regions for $p$, sens and spec.

| Year | $\widehat{p^{*}}$ | $\hat{\kappa}$ | $I\left(p \\| \widehat{\left.p^{*}, \hat{\kappa}\right)}\right.$ |
| :--- | :--- | :--- | :--- |
| 1996 | 0.118 | 0.577 | $[0.072 ; 0.188]$ |
| 1998 | 0.280 | 0.602 | $[0.190 ; 0.393]$ |
|  |  |  |  |
|  | $I\left(\right.$ sens $\\| \widehat{\left.p^{*}, \hat{\kappa}\right)}$ | $I\left(\right.$ spec $\\| \widehat{\left.p^{*}, \hat{\kappa}\right)}$ |  |
|  |  |  |  |
| 1996 | $[0.627 ; 1.000]$ | $[0.950 ; 1.000]$ |  |
|  | $[0.714 ; 1.000]$ | $[0.889 ; 1.000]$ |  |

Table 5
Signal-Tandmobiel® study: confidence intervals for the prevalence with and without taking the variability of $\hat{\kappa}$ into account.

| Year | With sampling variation of $\hat{\kappa}$ | Fixed $\kappa$ |
| :---: | :---: | :---: |
| 1996 | $[0.057 ; 0.219]$ | $[0.065 ; 0.205]$ |
| 1998 | $[0.170 ; 0.416]$ | $[0.179 ; 0.409]$ |
|  |  |  |

known at its estimated value. The asymptotic confidence intervals for the naive prevalence are pretty small compared to the identification regions and to the corresponding confidence intervals, which are both based on the additional information from the kappa coefficient. Consequently, the confidence regions based on naive prevalence estimation still suffer from a severe overprecision. Although being somewhat large, the identification region and the corresponding confidence regions still provide valuable insight into the prevalence. For example, the hypothesis $H_{0}: p \geq 0.25$ could be rejected at the 5 percent-level for the 6 year old children.

If further nontrivial bounds on sensitivity and specificity are available by some external information, then this can be incorporated in an analogous way resulting in smaller identification regions and smaller confidence intervals based on them.

## 5. Discussion

The concept of using identification regions or intervals of ignorance in the case of misclassification with partial information on sensitivity and specificity provided by the kappa coefficient has been shown as a powerful tool for data analysis. It avoids the potentially substantial bias arising from simply ignoring misclassification if no direct correction method is available. The resulting identification regions are tight in the sense that they cannot be improved without adding further assumptions. Thus they are the best that we can conclude from the data alone in this context. Our example shows that the possible effect of misclassification is rather high, even when the inter rater reliability is 'substantial' in terms of [29]'s classification. Furthermore, the strategy of distinguishing between sampling error and ignorance due to non-identifiability is useful, since it highlights possible shortcomings in the sampling of the data structure, which cannot be compensated by a large sample size.

Since we use the value of the kappa coefficient from validation data or from other sources of information, one crucial assumption for our analysis is that this value is also correct for the main data set. This will be the case if our replication data are a random sample from our main study (internal validation). Otherwise this assumption could be disputable. It is well-known that the kappa coefficient depends on the prevalence when sensitivity and specificity are fixed [11]. So our procedure cannot be used when the prevalence in the validation data differs from the prevalence in the main study, even if we assume that the scoring procedure has fixed sensitivity and specificity. However, the latter assumption could also be problem, see the discussion in [51]. In our example, the validation study was part of a training program for the examiners. On the one hand the prevalence was higher for the validation but on the other hand there were possibly more children in that sample that were difficult to score. This could lead to values of sensitivity and specificity which are different in the main study. Nevertheless, the kappa coefficient could be nearly identical in both parts of the study. Vach [51] performs some calculations and presents plausible scenarios supporting this assumption. Thus, our procedure can also be applied to studies where the value of the kappa coefficient can be transferred from the validation data to the main study even if this is not true for sensitivity and specificity. Obviously, this issue has to be treated with great care.

Our results are a vivid illustration of the power of imprecise probability methods in statistical analysis based on misclassified data. As a topic of further research the conditional independence assumption (AS1) in Remark 2.1 should be investigated further. As mentioned above, it may be violated if the assessments of two raters are used as substitutes for replication data,
because then certain characteristics of the units may impose some dependence on the raters' judgments. We are currently studying the use of Frechet bounds and related methods in this setting. If no reliable information is available about the misclassification probabilities, our approach could be adopted to the case where sensitivity and specificity vary in certain ranges, closely relating our procedure to the 'direct method' of [38]. Then our identification parameter is two dimensional, which will result in larger identification regions.

The methodology underlying our work promises, mutatis mutandis, to be also powerful for other types of error-prone data, like misclassification of more than two categories and for (additive or multiplicative) measurement error with unknown variance. In the latter case, the availability of replicates would yield identification in many instances, but often no information about the measurement error is available, and then partially identified corrected estimators are again the best option available.

## Acknowledgments

The paper benefited substantially from the very stimulating and constructive comments of its reviewers. We are very grateful to the two anonymous referees of the ISIPTA'11 contribution [27] underlying this work and the additional reviewer of this submission to IJAR for their generous sharing of interesting ideas and their important support. We also thank Serafin Moral for further very helpful suggestions and G. Walter, M. Cattaneo and many participants of ISIPTA'11 as well as ISIPTA'09's poster session for stimulating discussions influencing the paper.
The data collection of Signal-Tandmobiel® study was supported by Unilever, Belgium. The Signal-Tandmobiel® project comprises following partners: D. Declerck (Dental School, Catholic Univ. Leuven), L. Martens (Dental School, Univ. Ghent), J. Vanobbergen (Working Group Oral Health Promotion and Prevention, Flemish Dental Association; Dental School, Univ. Ghent), P. Pottenberg (Dental School, Univ. Brussels), E. Lesaffre (L-Biostat, Univ. Leuven, Dep. of Biostatistics, Erasmus MC, Rotterdam), K. Hoppenbrouwers (Youth Health Dep., Catholic Univ. Leuven; Flemish Assoc. for Youth Health Care).

## Appendix A. Proof of Theorem 2.2

Assume $p^{*} \in(0 ; 1)$ and $\kappa \in(0 ; 1)$ to be fixed and let the assumptions (2), (AS1) and (AS2) hold. To prove the theorem the set of equations (see Eqs. (1) and (7))

$$
\begin{align*}
p^{*} & =p \cdot \text { sens }+(1-p) \cdot(1-\text { spec }) \\
\kappa & =\frac{p(1-p)(\text { sens }+ \text { spec }-1)^{2}}{(\text { spec }-p(\text { sens }+ \text { spec }-1))} \cdot \frac{1}{(1-\text { spec }+p(\text { sens }+ \text { spec }-1))} \tag{A.1}
\end{align*}
$$

is considered. It consists of the relation of $p$, sens and spec to $p^{*}$ and to $\kappa$, respectively.
Throughout Section 2, the quantities that can be estimated from the data, i.e. $p^{*}$ and $\kappa$, are treated as fixed, known values. If we use them to get information about the unknown parameters $p$, spec and sens we have 2 equations and 3 unknowns, and thus $p$, spec, sens cannot be uniquely be derived from (A.1). However, implicit functions between these unknowns are still defined, which we use to construct our identification regions.

For the proof, two Lemmata are useful.
We first consider the maximal upper range of sens and spec.
Lemma Appendix A.1. The maximal values sens $\max$ and spec $_{\max }$ for sensitivity and specificity based on the set of equations (A.1) are

$$
\operatorname{sens}_{\max }=1 \quad \text { and } \quad \operatorname{spec}_{\max }=1
$$

This is easily proven by showing that substituting sens $=1$, and spec $=1$, respectively, into (A.1) gives admissible solutions in $(0 ; 1)$. Indeed, sens $=1$ leads to the unique solution

$$
p=p^{*}\left[p^{*}+\kappa^{-1}\left(1-p^{*}\right)\right]^{-1} \in(0 ; 1)
$$

and

$$
\text { spec }=1-p^{*}+p^{*} \kappa \in(0 ; 1)
$$

while substituting spec $=1$ results in

$$
p=p^{*}\left[p^{*}+\kappa\left(1-p^{*}\right)\right]^{-1} \in(0 ; 1)
$$

and

$$
\text { sens }=p^{*}+\kappa\left(1-p^{*}\right) \in(0 ; 1)
$$

Secondly, we prove monotonicity of the underlying implicit functions.
Lemma Appendix A.2. Assume again that $p^{*}$ and $\kappa$ are fixed.
(a) Then $p$ is increasing with increasing spec.
(b) Then $p$ is decreasing with increasing sens and vice versa.
(c) Then sens is decreasing with increasing spec and vice versa.

As a first step to prove this lemma note that, with assumption (2) sens + spec $>1 \Longleftrightarrow 1-$ spec $<$ sens and the first line in (A.1) (i.e.. Eq. (1)), we get

$$
\begin{equation*}
p^{*}<p \cdot \text { sens }+(1-p) \cdot \text { sens }=\text { sens } \tag{A.1}
\end{equation*}
$$

and analogously

$$
\begin{equation*}
p^{*}>1-s p e c \tag{A.2}
\end{equation*}
$$

Then the relation of $p$, sens and spec based on the set of equations (A.1) is analyzed, which leads to the statements 2.(a)-(c). In detail the following relationships arise from elementary calculations:
(a) For $p$ in dependence of spec one obtains

$$
\begin{aligned}
& p(\text { spec })=\frac{\left(1-p^{*}-\text { spec }\right)^{2}}{\left(1-p^{*}-\text { spec }\right)^{2}+\kappa p^{*}\left(1-p^{*}\right)} \\
& \frac{\partial p(\text { spec })}{\partial \text { spec }}=\frac{2 \kappa p^{*}\left(1-p^{*}\right)\left(p^{*}+\text { spec }-1\right)}{\left(\left(1-p^{*}-\text { spec }\right)^{2}+\kappa p^{*}\left(1-p^{*}\right)\right)^{2}}>0
\end{aligned}
$$

since, according to (A.2), spec $>1-p^{*}$.
(b) For $p$ in dependence of sens one obtains

$$
\begin{aligned}
& p(\text { sens })=\frac{\kappa p^{*}\left(1-p^{*}\right)}{\kappa p^{*}\left(1-p^{*}\right)+\left(p^{*}-\text { sens }\right)^{2}} \\
& \frac{\partial p(\text { sens })}{\partial \text { sens }}=\frac{2 \kappa p^{*}\left(1-p^{*}\right)\left(p^{*}-\text { sens }\right)}{\left(\kappa p^{*}\left(1-p^{*}\right)+\left(p^{*}-\text { sens }\right)^{2}\right)^{2}}<0
\end{aligned}
$$

since, in the light of (A.1), sens $>p^{*}$.
(c) Finally, considering sens in dependence of spec yields

$$
\begin{aligned}
& \operatorname{sens}(\text { spec })=\frac{\left(1-p^{*}-\text { spec }\right) p^{*}-\kappa p^{*}\left(1-p^{*}\right)}{1-p^{*}-\operatorname{spec}} \\
& \frac{\partial \text { sens }(\text { spec })}{\partial \text { spec }}=\frac{\kappa p^{*}\left(p^{*}-1\right)}{\left(1-p^{*}-\text { spec }\right)^{2}}<0
\end{aligned}
$$

since, by (A.2), in particular, spec $\neq 1-p^{*}$.
Finally, using Lemmas Appendix A. 1 and Appendix A.2, the limits $\underline{I}\left(p \| p^{*}, \kappa\right)$ and $\bar{I}\left(p \| p^{*}, \kappa\right)$ of $I\left(p \| p^{*}, \kappa\right)$ are solutions of the set of equations (A.1), calculated as follows: Inserting the maximal value $\bar{I}\left(\right.$ sens $\left.\| p^{*}, \kappa\right)=1$ and solving (A.1) leads to $\underline{I}\left(p \| p^{*}, \kappa\right)$ and inserting $\bar{I}\left(\operatorname{spec} \| p^{*}, \kappa\right)=1$ to $\bar{I}\left(p \| p^{*}, \kappa\right)$, see formula (10).

For $p^{*}=0, p^{*}=1$ and $\kappa=1$ the identification regions are not defined, but continuously extendable.
The calculation of $\underline{I}\left(\right.$ sens $\left.\| p^{*}, \kappa\right)$ and $\underline{I}\left(\right.$ spec $\left.\| p^{*}, \kappa\right)$ is analogous.

## Appendix B. Recoding and identification regions

Here we briefly discuss the fact that the identification regions are logically coherent in the sense that recoding does not change the conclusions to be drawn.

Remark Appendix B.1. Denote after transition from $Y$ to $\widetilde{Y}:=1-Y$ and $Y^{*}$ to $\widetilde{Y}^{*}:=1-Y^{*}$ the corresponding prevalence by $\widetilde{p}$, the corresponding naive prevalence by $\widetilde{p}^{*}$, and the corresponding sensitivity and specificity by $\widetilde{\operatorname{sens}}$ and $\widetilde{\text { spec }}$, respectively. Then one obtains:
(i) $\widetilde{p}=P(\widetilde{Y}=1)=1-p$ and $\tilde{p}^{*}=P\left(\widetilde{Y}^{*}=1\right)=1-p^{*}$.
(ii) Sensitivity and specificity simply exchange their role, $\dot{\operatorname{sens}}=P\left(\widetilde{Y}^{*}=1 \mid \widetilde{Y}=1\right)=P\left(Y^{*}=0 \mid Y=0\right)=$ spec and $\widehat{\text { spec }}=P\left(\widetilde{Y}^{*}=0 \mid \widetilde{Y}=0\right)=P\left(Y^{*}=1 \mid Y=1\right)=$ sens, while $\kappa$ is not changed by this recoding procedure. i.e. $\kappa=\tilde{\kappa}$ :
(iii) The corresponding identification regions are conjugated., i.e. the lower bound of $I\left(p \| p^{*}, \kappa\right)$ and the upper bound of $I\left(\tilde{p} \| \tilde{p}^{*}, \tilde{\kappa}\right)$ as well as the upper bound of $I\left(p \| p^{*}, \kappa\right)$ and the lower bound of $I\left(\tilde{p} \| \tilde{p}^{*}, \tilde{\kappa}\right)$ sum up to one, and thus, since $Y$ is dichotomous, $I\left(p \| p^{*}, \kappa\right)$ and $I\left(\tilde{p} \| \tilde{p}^{*}, \tilde{\kappa}\right)$ are, interpreted as probability assignments, coherent interval-valued probabilities and F-probabilities in the sense of [55,58]. Moreover, the identification regions of sens and $\widetilde{\text { spec, }}$, as well as of spec and $\widetilde{\text { sens, coincide. }}$

Proof. All these statements directly follow from elementary algebraic transformations. For instance,

$$
\begin{aligned}
\widetilde{\kappa} & =\frac{\widetilde{p}(1-\widetilde{p})(\widetilde{\text { sens }}+\widetilde{\text { spec }}-1)^{2}}{(\text { spec }-\widetilde{p}(\sqrt{\text { sens }}+\widetilde{\text { spec }}-1))} \cdot \frac{1}{(1-\widetilde{\text { spec }}+\widetilde{p} \text { sens }+\widetilde{\text { spec }}-1))} \\
& =\frac{(1-p) p(\text { spec }+ \text { sens }-1)^{2}}{(\text { sens }-(1-p) \cdot(\text { spec }+ \text { sens }-1))} \cdot \frac{1}{(1-\text { sens }+(1-p) \cdot(\text { spec }+ \text { sens }-1))}=\kappa .
\end{aligned}
$$

## Appendix C. No information loss when using the kappa coefficient

We use the kappa coefficient and the probability $p^{*}$ as an input to estimate the true probability $p$. The information of the validation data includes the outcome of two replicate measurements $Y_{1}^{*}$ and $Y_{2}^{*}$. The corresponding probabilities are $p_{00}, p_{10}, p_{01}, p_{11}$. A natural question, also posed by one of the referees of the ISIPTA'11 contribution [27] underlying this work, is whether the bounds derived in Sections 2 and 3 could be improved by using those probabilities immediately, instead of $\kappa$ and $p^{*}$. Indeed, this is not the case. As the following lemma shows no further improvement of the bounds for $p$ is possible by using $p_{i j}, i, j=0,1$, directly, and thus the identification regions given are the best that can be learned from the data without additional assumptions.

Lemma Appendix C.1. There is a one-to-one correspondence between the parameters $\kappa$ and $p^{*}$ and the four probabilities $p_{i j}$, $i, j=0,1$.

For the proof note that $p_{00}+p_{10}+p_{01}+p_{11}=1$ and our assumptions (AS1) and (AS2) imply in addition $p_{10}=p_{01}$. Furthermore, we can derive with some algebra from the definition of $\kappa$ and $p^{*}=p_{11}+p_{01}$ the relationships

$$
\begin{aligned}
& p_{11}=(1-\kappa) p^{* 2}+\kappa p^{*} \\
& p_{10}=(1-\kappa)\left(p^{*}-p^{* 2}\right) \\
& p_{01}=p_{10} \\
& p_{00}=1-p_{11}-p_{01}-p_{10}
\end{aligned}
$$

indeed expressing the four probabilities directly in terms $\kappa$ and $p^{*}$.

## Appendix D. Details of Section 3

Appendix D.1. Monotonicity of $p(\gamma)$
Lemma Appendix D.1. In the situation of Section 3 the following monotonicity relationships hold:
(i) $\operatorname{spec}(\gamma)$ is decreasing in $\gamma$.
(ii) $p(\gamma)$ is decreasing in $\gamma$.

For the proof use that with $\gamma=\frac{\text { sens }}{\text { spec }}>0$ the set of equations (A.1) now has the form

$$
\begin{aligned}
p^{*} & =p \cdot \gamma \cdot \text { spec }+(1-p) \cdot(1-\text { spec }) \\
\kappa & =\frac{p(1-p)(\gamma \cdot \text { spec }+ \text { spec }-1)^{2}}{(\text { spec }-p(\gamma \cdot \text { spec }+ \text { spec }-1))} \cdot \frac{1}{(1-\text { spec }+p(\gamma \cdot \text { spec }+ \text { spec }-1))}
\end{aligned}
$$

which leads to the following formulas for $p$ and spec in dependence of $\gamma$ :

$$
\begin{aligned}
& p(\gamma)=-\frac{\left(p^{*}-1\right) \gamma+p^{*}+\sqrt{w}}{\left(p^{*}-1\right) \gamma^{2}+(1-\sqrt{w}) \gamma-p^{*}-\sqrt{w}} \\
& \operatorname{spec}(\gamma)=0.5\left(1-p^{*}+\gamma^{-1}\left(p^{*}+\sqrt{w}\right)\right)
\end{aligned}
$$

with

$$
\begin{equation*}
w=\left(p^{*}-1\right)^{2} \cdot \gamma^{2}-2 \cdot p^{*} \cdot\left(p^{*}-1\right) \cdot(2 \cdot \kappa-1) \cdot \gamma+p^{* 2} \tag{D.1}
\end{equation*}
$$

For relation (i) we then obtain

$$
\frac{\partial \text { spec }}{\partial \gamma}=-\frac{0.5 p^{*}}{\sqrt{w} \gamma^{2}}\left(p^{*} \gamma-\gamma-2 \kappa \gamma\left(1-p^{*}\right)+p^{*}+\sqrt{w}\right)
$$

Since $\kappa>0, \gamma>0$,

$$
w \geq\left(p^{*}-1\right)^{2} \gamma^{2}+2 p^{*}\left(p^{*}-1\right) \gamma+\left(p^{*}\right)^{2}=\left(\left(p^{*}-1\right) \gamma+p^{*}\right)^{2} .
$$

Using in the second factor again $\kappa>0, \gamma>0$ and replacing $w$ there, yields

$$
\left.\frac{\partial \text { spec }}{\partial \gamma} \leq-\frac{0.5 p^{*}}{\sqrt{w} \gamma^{2}}\left(\left(p^{*}-1\right) \gamma+p^{*}\right)+\sqrt{\left(\left(p^{*}-1\right) \gamma+p^{*}\right)^{2}}\right) \leq 0
$$

Since, according to Lemma Appendix A.2, the function $p$ (spec) is increasing in spec, relationship (i) also directly implies relationship (ii).

## Appendix D.2. Asymptotic variance of $\widehat{p}(\gamma)$ and $\widehat{\operatorname{spec}}(\gamma)$

Lemma Appendix D.2. The asymptotic variances of the corresponding estimators $\widehat{p}(\gamma)$ and $\widehat{\operatorname{spec}(\gamma)}$ in dependence of $\gamma$ are given by

$$
\begin{aligned}
\operatorname{var}(\widehat{p}(\gamma))= & \frac{16 \gamma^{4}}{\left(\gamma-p^{*}-\sqrt{w}+\gamma^{2}\left(p^{*}-1\right)-\sqrt{w} \gamma\right)^{4} w} \\
& \cdot\left[\left(1+2 \gamma+\gamma^{2}\right) \operatorname{var}(\hat{\kappa}) p^{* 6}-\left(2+6 \gamma+4 \gamma^{2}\right) \operatorname{var}(\hat{\kappa}) p^{* 5}\right. \\
& +\left(1+6 \gamma+6 \gamma^{2}\right) \operatorname{var}(\hat{\kappa}) p^{* 4}-\left(4 \gamma^{2}+2 \gamma\right) \operatorname{var}(\hat{\kappa}) p^{* 3} \\
& +\left(\kappa^{2} \operatorname{var}\left(\widehat{p^{*}}\right) \gamma^{2}+\kappa^{2} \operatorname{var}\left(\widehat{p^{*}}\right)-2 \kappa^{2} \operatorname{var}\left(\widehat{p^{*}}\right) \gamma+\operatorname{var}(\hat{\kappa}) \gamma^{2}\right) p^{* 2} \\
& \left.+\left(-2 \kappa^{2} \operatorname{var}\left(\widehat{p^{*}}\right) \gamma^{2}+2 \kappa^{2} \operatorname{var}\left(\widehat{p^{*}}\right) \gamma\right) p^{*}+\kappa^{2} \operatorname{var}\left(\widehat{p^{*}}\right) \gamma^{2}\right],
\end{aligned}
$$

with $w$ from (D.1), and by

$$
\operatorname{var}(\widehat{\operatorname{spec}(\gamma)})=\frac{A \cdot \operatorname{var}\left(\widehat{p^{*}}\right)}{4 w \gamma^{2}}+\frac{p^{* 2}\left(p^{*}-1\right)^{2} \operatorname{var}(\hat{\kappa})}{w}
$$

with

$$
A:=\left(\left(1-p^{*}\right) \gamma^{2}+\left(\sqrt{w}+4 \kappa p^{*}-2 \kappa-2 p^{*}+1\right) \gamma-\sqrt{w}-p^{*}\right)^{2}
$$

respectively.
Proof. These expressions follow from applying the delta method (e.g., [4, Sec. 5.3.2]) to the situation under consideration.

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[^1]:    ${ }^{1}$ For ease of argumentation and influenced by the example from oral health discussed in Section 4, we use biometric terminology throughout the paper, without limiting the application of our results to that area.

