Assessing the Dependence of Sensitivity and Specificity on Prevalence in Meta-analysis

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Appendix

In the following proofs we consider four different cases:

Case I:	p_i and $\mathtt{S}_i$ are known;
Case II:	p_i are known, $\mathtt{S}_i$ are unknown and estimated by $\hat{\mathtt{se}}_i$;
Case III:	$\mathtt{S}_i$ are known, p_i are unknown and estimated by $\hat{p}_i$;
Case IV:	p_i and $\mathtt{S}_i$ are unknown and estimated by $\hat{p}_i$ and $\hat{\mathtt{se}}_i$, respectively.

Case I is the most ideal state where complete knowledge about p_i and $\mathtt{S}_i$ are acquired in all studies. The examination of the relationship between these two quantities could be done in a standard analysis. Cases II and III allow one of the two quantities to be known exactly while the other has to be estimated. In a real meta analysis, Case IV may be the

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most relevant to practice where both are estimated. We note that in the main manuscript we only present the theoretical results for Case IV. We introduce Case I - III to describe via comparison how the estimation of correlation between $\texttt{se}_i$ and p_i is gradually influenced by the fact that these population-specific parameters themselves are estimated from the data.

0.1 Consistency of $\hat{\rho}$

Proof of Theorem 3.1. It is easy to see that $\hat{\rho}$ is consistent for Case I (Fisher (1925)). We only show the results for Case IV since other cases can be proved by following similar arguments. We note that

$$\begin{aligned}\sum_{i=1}^{n} w_i(\hat{\texttt{se}}_i - \bar{\texttt{se}})(\hat{p}_i - \bar{p}) &= \sum_{i=1}^{n} w_i(\hat{\texttt{se}}_i - \texttt{se})(\hat{p}_i - \mu_p) + (\texttt{se} - \bar{\texttt{se}})(n^{-1}\sum_{i=1}^{n} w_i\hat{p}_i - \bar{p}) \\ &\quad + (n^{-1}\sum_{i=1}^{n} w_i\hat{\texttt{se}}_i - \bar{\texttt{se}})(\mu_p - \bar{p}).\end{aligned}$$

Applying the strong law of large number (Theorem 1.14 in Shao (1999)) for independent random variables with finite expectations, we can argue that as $n \to \infty$ the second and third terms in the above equation vanish to zero almost surely whereas the first term converges to

$$\begin{aligned}&n^{-1}\sum_{i=1}^{n} E[w_i(\hat{\texttt{se}}_i - \texttt{se})(\hat{p}_i - \mu_p)] \\ =\ &n^{-1}\sum_{i=1}^{n} E[w_i(\texttt{S}_i - \texttt{se})(\hat{p}_i - p_i)] + n^{-1}\sum_{i=1}^{n} E[w_i(\texttt{S}_i - \texttt{se})(p_i - \mu_p)].\end{aligned}$$

with probability one. Followed by the consistency of $\hat{p}_i$ and the use of a version of dominated convergence theorem (ex 6.3 in Durrett (2005)), it can be shown that

$$n^{-1}\sum_{i=1}^{n} E[w_i(\hat{\texttt{se}}_i - \texttt{se})(\hat{p}_i - \mu_p)] \to \mu_w E(\texttt{S} - \texttt{se})(p - \mu_p).$$

Similarly, we can show

$$n^{-1}\sum_{i=1}^{n} w_i(\hat{\mathtt{se}}_i - \bar{\mathtt{se}})^2 \rightarrow_{a.s.} \mu_w E(\mathtt{S} - \mathtt{se})^2,$$
$$n^{-1}\sum_{i=1}^{n} w_i(\hat{p}_i - \bar{p})^2 \rightarrow_{a.s.} \mu_w E(p - \mu_p)^2.$$

Finally we use the continuous mapping theorem (Theorem 1.10 in Shao (1999)) to conclude

$$\hat{\rho} \rightarrow_{a.s.} \rho.$$

□

0.2 Consistency and normality of $\hat{\boldsymbol{\alpha}}$

Proof of Theorem 4.1. By using strong law of large number for independent variables, we have

$$n^{-1}\sum_{i=1}^{n} w_i \frac{(\hat{\mathtt{se}}_i - f(\hat{p}_i, \boldsymbol{\alpha}))\dot{f}_{\boldsymbol{\alpha}}}{f(\hat{p}_i, \boldsymbol{\alpha})(1 - f(\hat{p}_i, \boldsymbol{\alpha}))} \rightarrow_{a.s.} \mu_w n^{-1}\sum_{i=1}^{n} E\frac{(\hat{\mathtt{se}}_i - f(\hat{p}_i, \boldsymbol{\alpha}))\dot{f}_{\boldsymbol{\alpha}}}{f(\hat{p}_i, \boldsymbol{\alpha})(1 - f(\hat{p}_i, \boldsymbol{\alpha}))}. \tag{1}$$

By using dominated convergence theorem, the fact that $\hat{se}_i$ is uncorrelated to $\hat{p}_i$ and the consistency of $\hat{p}_i$ to p_i, we have

$$E\frac{(\hat{\mathtt{se}}_i - f(\hat{p}_i, \boldsymbol{\alpha}))\dot{f}_{\boldsymbol{\alpha}}}{f(\hat{p}_i, \boldsymbol{\alpha})(1 - f(\hat{p}_i, \boldsymbol{\alpha}))} \rightarrow E\frac{(\mathtt{S}_i - f(p_i, \boldsymbol{\alpha}))\dot{f}_{\boldsymbol{\alpha}}}{f(p_i, \boldsymbol{\alpha})(1 - f(p_i, \boldsymbol{\alpha}))}.$$

The limit on the right-hand-side is zero when evaluated at the true parameter. This verifies that the estimating equation defined in (4.2) is asymptotically unbiased and the consistency of $\hat{\boldsymbol{\alpha}}$ follows (eg. Lemma 5.10 in van der Vaart (1998)).

□

Proof of Theorem 4.2. The asymptotic normality of $\sqrt{n}(\hat{\boldsymbol{\alpha}}-\boldsymbol{\alpha})$ is now a consequence of Theorem 5.21 in van der Vaart (1998). We consider Case I first. Denote $V_i(\boldsymbol{\alpha}) = w_i \frac{(\mathtt{S}_i - f(p_i,\boldsymbol{\alpha}))\dot{f}_{\boldsymbol{\alpha}}}{f(\hat{p}_i,\boldsymbol{\alpha})(1-f(\hat{p}_i,\boldsymbol{\alpha}))}$. We then have

$$n^{-1/2}\sum_{i=1}^{n} V_i(\boldsymbol{\alpha}) \rightarrow_d N(0, \tilde{W}_2),$$

where

$$\tilde{W}_2 \quad = \quad \lim_{n\to\infty} n^{-1} E[\sum_{i=1}^{n} w_i^2 \frac{\mathrm{var}(\mathtt{S}_i|p_i)\dot{f}_{\boldsymbol{\alpha}}\dot{f}_{\boldsymbol{\alpha}}^T}{f(p_i,\boldsymbol{\alpha})^2(1-f(p_i,\boldsymbol{\alpha}))^2}]$$

The derivative of the estimating equation (4.2) with respect to $\boldsymbol{\alpha}$ is given by

$$\begin{aligned} H_n(\boldsymbol{\alpha}) \quad &= \quad n^{-1}\sum_{i=1}^{n} w_i[\frac{\mathtt{S}_i - f(p_i,\boldsymbol{\alpha})}{f(p_i,\boldsymbol{\alpha})(1-f(p_i,\boldsymbol{\alpha}))}\ddot{f}_{\boldsymbol{\alpha}} + \frac{(\mathtt{S}_i - f(p_i,\boldsymbol{\alpha}))(2f(p_i,\boldsymbol{\alpha})-1)\dot{f}_{\boldsymbol{\alpha}}(p_i)\dot{f}_{\boldsymbol{\alpha}}(p_i)^T}{f(p_i,\boldsymbol{\alpha})^2(1-f(p_i,\boldsymbol{\alpha}))^2} \\ &\quad + \frac{\dot{f}_{\boldsymbol{\alpha}}(p_i)\dot{f}_{\boldsymbol{\alpha}}(p_i)^T}{f(p_i,\boldsymbol{\alpha})(1-f(p_i,\boldsymbol{\alpha}))}]. \end{aligned}$$

It follows that the summations of the first two terms converge to zero and the third term converges to

$$H = \lim_{n\to\infty} n^{-1}\sum_{i=1}^{n} w_i E\frac{\dot{f}_{\boldsymbol{\alpha}}(p_i)\dot{f}_{\boldsymbol{\alpha}}(p_i)^T}{f(p_i,\boldsymbol{\alpha})(1-f(p_i,\boldsymbol{\alpha}))} = \mu_w E\frac{\dot{f}_{\boldsymbol{\alpha}}(p)\dot{f}_{\boldsymbol{\alpha}}(p)^T}{f(p,\boldsymbol{\alpha})(1-f(p,\boldsymbol{\alpha}))}.$$

Therefore, under Case I, the sequence of $\sqrt{n}(\hat{\boldsymbol{\alpha}}-\boldsymbol{\alpha})$ is asymptotically normal with mean zero and covariance matrix $H^{-1}\tilde{W}_2H^{-1}$.

We then consider Case II. The estimating equations (4.2) can now be decomposed into

$$n^{-1}\sum_{n=1}^{n} U_i(\boldsymbol{\alpha}) + n^{-1}\sum_{i=1}^{n} V_i(\boldsymbol{\alpha}),$$

where $U_i(\boldsymbol{\alpha}) = w_i \frac{(\hat{\mathtt{se}}_i - \mathtt{S}_i)\dot{f}_{\boldsymbol{\alpha}}}{f(p_i,\boldsymbol{\alpha})(1-f(p_i,\boldsymbol{\alpha}))}$.

For the first term, we have

$$n^{-1/2}\sum_{i=1}^{n} U_i(\boldsymbol{\alpha}) \to_d N(0,\tilde{W}_1),$$

where

$$\begin{aligned}\tilde{W}_1 &= \lim_{n\to\infty} n^{-1}E[\sum_{i=1}^{n} w_i^2 \frac{\mathrm{var}(\hat{\mathtt{se}}_i|\mathtt{S}_i)\dot{f}_{\boldsymbol{\alpha}}\dot{f}_{\boldsymbol{\alpha}}^T}{f(p_i,\boldsymbol{\alpha})^2(1-f(p_i,\boldsymbol{\alpha}))^2}] \\ &= \lim_{n\to\infty} n^{-1}\sum_{i=1}^{n} E[w_i^2 \frac{\mathtt{S}_i(1-\mathtt{S}_i)\dot{f}_{\boldsymbol{\alpha}}(p_i)\dot{f}_{\boldsymbol{\alpha}}(p_i)^T}{N_i f(p_i,\boldsymbol{\alpha})^2(1-f(p_i,\boldsymbol{\alpha}))^2}],\end{aligned}$$

where the second equality follows from $\mathrm{var}(\hat{\mathtt{se}}_i|\mathtt{S}_i) = \mathtt{S}_i(1-\mathtt{S}_i)/N_i$.

The second term converges to the same normal distribution as argued previously. Furthermore, the two terms are orthogonal if we observe

$$\begin{aligned}E(U_iV_i^T) &= E\{E(U_iV_i^T|\mathtt{S}_i,p_i)\} \\ &= E\{\frac{w_i^2\dot{f}_{\boldsymbol{\alpha}}\dot{f}_{\boldsymbol{\alpha}}^T}{f(p_i,\boldsymbol{\alpha})^2(1-f(p_i,\boldsymbol{\alpha}))^2}E((\hat{\mathtt{se}}_i-\mathtt{S}_i)(\mathtt{S}_i-f(p_i,\boldsymbol{\alpha}))|\mathtt{S}_i,p_i)\} \\ &= E\{\frac{w_i^2\dot{f}_{\boldsymbol{\alpha}}\dot{f}_{\boldsymbol{\alpha}}^T}{f(p_i,\boldsymbol{\alpha})^2(1-f(p_i,\boldsymbol{\alpha}))^2}(E(\hat{\mathtt{se}}_i|\mathtt{S}_i)-\mathtt{S}_i)(\mathtt{S}_i-f(p_i,\boldsymbol{\alpha}))\} = 0.\end{aligned}$$

The derivative of the estimating equation (4.2) with respect to $\boldsymbol{\alpha}$ in this case is given by

$$\begin{aligned}H_n^*(\boldsymbol{\alpha}) &= n^{-1}\sum_{i=1}^{n} w_i[\frac{\hat{\mathtt{se}}_i-f(p_i,\boldsymbol{\alpha})}{f(p_i,\boldsymbol{\alpha})(1-f(p_i,\boldsymbol{\alpha}))}\ddot{f}_{\boldsymbol{\alpha}}(p_i) + \frac{(\hat{\mathtt{se}}_i-f(p_i,\boldsymbol{\alpha}))(2f(p_i,\boldsymbol{\alpha})-1)\dot{f}_{\boldsymbol{\alpha}}(p_i)\dot{f}_{\boldsymbol{\alpha}}(p_i)^T}{f(p_i,\boldsymbol{\alpha})^2(1-f(p_i,\boldsymbol{\alpha}))^2} \\ &\quad + \frac{\dot{f}_{\boldsymbol{\alpha}}(p_i)\dot{f}_{\boldsymbol{\alpha}}(p_i)^T}{f(p_i,\boldsymbol{\alpha})(1-f(p_i,\boldsymbol{\alpha}))}],\end{aligned}$$

which converges to H in probability again. Therefore $\sqrt{n}(\hat{\boldsymbol{\alpha}}-\boldsymbol{\alpha})$ is asymptotically normal with mean zero and covariance matrix $H^{-1}(\tilde{W}_1+\tilde{W}_2)H^{-1}$.

We skip Case III since its proof can be mimicked partially from what we show in the following case. In Case IV where p_i is also replaced by $\hat{p}_i$ in estimating equations (4.2), the equations can be written as

$$n^{-1}\sum_{i=1}^{n} U_i^*(\boldsymbol{\alpha}) + n^{-1}\sum_{i=1}^{n} V_i^*(\boldsymbol{\alpha}) + n^{-1}\sum_{i=1}^{n} W_i^*(\boldsymbol{\alpha}),$$

where we denote $U_i^*(\boldsymbol{\alpha}) = w_i \frac{(\hat{\mathtt{se}}_i - \mathtt{S}_i)\dot{f}_{\boldsymbol{\alpha}}(\hat{p}_i)}{f(\hat{p}_i,\boldsymbol{\alpha})(1-f(\hat{p}_i,\boldsymbol{\alpha}))}$, $V_i^*(\boldsymbol{\alpha}) = w_i \frac{(\mathtt{S}_i - f(p_i,\boldsymbol{\alpha}))\dot{f}_{\boldsymbol{\alpha}}(\hat{p}_i)}{f(\hat{p}_i,\boldsymbol{\alpha})(1-f(\hat{p}_i,\boldsymbol{\alpha}))}$, and $W_i^*(\boldsymbol{\alpha}) = w_i \frac{(f(p_i,\boldsymbol{\alpha}) - f(\hat{p}_i,\boldsymbol{\alpha}))\dot{f}_{\boldsymbol{\alpha}}(\hat{p}_i)}{f(\hat{p}_i,\boldsymbol{\alpha})(1-f(\hat{p}_i,\boldsymbol{\alpha}))}$. The three pieces are asymptotically equivalent to $U_i(\boldsymbol{\alpha})$, $V_i(\boldsymbol{\alpha})$, and $W_i(\boldsymbol{\alpha}) = w_i \frac{(f(p_i,\boldsymbol{\alpha}) - f(\hat{p}_i,\boldsymbol{\alpha}))\dot{f}_{\boldsymbol{\alpha}}(p_i)}{f(p_i,\boldsymbol{\alpha})(1-f(p_i,\boldsymbol{\alpha}))}$, respectively.

The first two terms thus converges to two normal distributions as argued before. For the last term, we have

$$\begin{aligned}
\mathrm{var}(n^{-1/2}\sum_{i=1}^{n} W_i(\boldsymbol{\alpha})) &= n^{-1}E[\sum_{i=1}^{n} w_i^2 \frac{\mathrm{var}(f(\hat{p}_i,\boldsymbol{\alpha})|p_i)\dot{f}_{\boldsymbol{\alpha}}\dot{f}_{\boldsymbol{\alpha}}^T}{f(p_i,\boldsymbol{\alpha})^2(1-f(p_i,\boldsymbol{\alpha}))^2}] \\
&= n^{-1}\sum_{i=1}^{n} w_i^2 E\frac{f'(p_i,\boldsymbol{\alpha})^2\lambda_i \dot{f}_{\boldsymbol{\alpha}}(p_i)\dot{f}_{\boldsymbol{\alpha}}(p_i)^T}{M_i f(p_i,\boldsymbol{\alpha})^2(1-f(p_i,\boldsymbol{\alpha}))^2} \\
&\to n^{-1}\sum_{i=1}^{n} \lambda_i \frac{w_i^2}{M_i} E\frac{f'(p,\boldsymbol{\alpha})^2\dot{f}_{\boldsymbol{\alpha}}(p)\dot{f}_{\boldsymbol{\alpha}}(p)^T}{f(p,\boldsymbol{\alpha})^2(1-f(p,\boldsymbol{\alpha}))^2} \qquad \text{as } n\to\infty, \\
&\to 0 \qquad \text{as } M_i \to \infty,
\end{aligned}$$

where the second equality follows a Taylor expansion and $f'(x_0,\boldsymbol{\alpha})$ is the derivative of $f(x,\boldsymbol{\alpha})$ with respect to x evaluated at x_0. Hence the last term converges to zero in probability.

The derivative of the estimating equation (4.2) with respect to $\boldsymbol{\alpha}$ in this case is given by

$$\begin{aligned}
H_n^{**}(\boldsymbol{\alpha}) &= n^{-1}\sum_{i=1}^{n} w_i[\frac{\hat{\mathtt{se}}_i - f(\hat{p}_i,\boldsymbol{\alpha})}{f(\hat{p}_i,\boldsymbol{\alpha})(1-f(\hat{p}_i,\boldsymbol{\alpha}))}\ddot{f}_{\boldsymbol{\alpha}}(\hat{p}_i) + \frac{(\hat{\mathtt{se}}_i - f(\hat{p}_i,\boldsymbol{\alpha}))(2f(\hat{p}_i,\boldsymbol{\alpha})-1)\dot{f}_{\boldsymbol{\alpha}}(\hat{p}_i)\dot{f}_{\boldsymbol{\alpha}}(\hat{p}_i)^T}{f(\hat{p}_i,\boldsymbol{\alpha})^2(1-f(\hat{p}_i,\boldsymbol{\alpha}))^2} \\
&\quad + \frac{\dot{f}_{\boldsymbol{\alpha}}(\hat{p}_i)\dot{f}_{\boldsymbol{\alpha}}(\hat{p}_i)^T}{f(\hat{p}_i,\boldsymbol{\alpha})(1-f(\hat{p}_i,\boldsymbol{\alpha}))}].
\end{aligned}$$

It follows that the first two terms converge to zero and the third term converges to

$$n^{-1}\sum_{i=1}^{n} E\Big[w_i \frac{\dot{f}_{\boldsymbol{\alpha}}(\hat{p}_i)\dot{f}_{\boldsymbol{\alpha}}(\hat{p}_i)^T}{f(\hat{p}_i,\boldsymbol{\alpha})(1-f(\hat{p}_i,\boldsymbol{\alpha}))}\Big].$$

By using similar arguments as the proof of Theorem 4.1, we can show that $H_n^{**}(\boldsymbol{\alpha})$ converges in probability to H.

Combining all of the above results and using Slutsky's theorem, we conclude that under Case III the sequence of $\sqrt{n}(\hat{\boldsymbol{\alpha}}-\boldsymbol{\alpha})$ is asymptotically normal with mean zero and covariance matrix $H^{-1}(\tilde{W}_1+\tilde{W}_2)H^{-1}$.

□

References

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Table 1: Data for Example 1

Study	Prevalence (%)	Sensitivity (%)	Specificity (%)
1	45.0	78.2	73.3
2	60.0	62.5	83.3
3	58.0	48.9	76.9
4	52.2	72.7	77.1
5	47.8	68.6	34.4
6	53.6	80.0	84.6
7	70.3	45.5	51.9
8	55.0	72.2	72.7
9	51.8	66.7	44.8
10	57.1	63.2	61.6
11	47.0	65.5	59.7
12	58.2	64.1	46.4
13	79.5	64.2	45.1
14	41.5	89.6	78.5
15	59.7	69.4	33.7

Table 2: Data for Example 2

Study	Prevalence (%)	Sensitivity (%)	Specificity (%)
1	22	55	75
2	28	100	85
3	73	94	100
4	38	93	77
5	34	93	73
6	53	100	95
7	32	70	75
8	35	83	87
9	57	100	89
10	57	86	100
11	33	88	89