Meta-analysis of dichotomous and ordinal tests without a gold standard

Enzo Cerullo\textsuperscript{1,2}, Hayley E. Jones\textsuperscript{3}, Terry J. Quinn\textsuperscript{4}, Nicola J. Cooper\textsuperscript{1,2}, and Alex J. Sutton\textsuperscript{1,2}

\textsuperscript{1}Biostatistics Research Group, Department of Health Sciences, University of Leicester, Leicester, UK
\textsuperscript{2}Complex Reviews Support Unit, University of Leicester & University of Glasgow, Glasgow, UK
\textsuperscript{3}Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
\textsuperscript{4}Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

Abstract

Standard methods for the meta-analysis of medical tests without a gold standard are limited to dichotomous data. Multivariate probit models are used to analyze correlated binary data, and can be extended to multivariate ordered probit models to model ordinal data. Within the context of an imperfect gold standard, they have previously been used for the analysis of dichotomous and ordinal tests in a single study, and for the meta-analysis of dichotomous tests. In this paper, we developed a hierarchical, latent class multivariate probit model for the simultaneous meta-analysis of ordinal and dichotomous tests without assuming a gold standard. The model can accommodate a hierarchical partial pooling model on the conditional within-study correlations, enabling one to obtain summary estimates of joint test accuracy. Dichotomous tests use probit regression likelihoods and ordinal tests use ordered probit regression likelihoods. We fitted the models using Stan, which uses a state-of-the-art Hamiltonian Monte Carlo algorithm. We applied the models to a dataset in which studies evaluated the accuracy of tests, and test combinations, for deep vein thrombosis. We first demonstrated the issues with dichotomising test accuracy data a priori without a gold standard by fitting models which dichotomised the ordinal test data, and then we applied models which do not dichotomise the data. Furthermore, we fitted and compared a variety of other models, including those which assumed conditional independence and dependence between tests, and those assuming perfect and an imperfect gold standard.

Keywords

Meta-Analysis, test accuracy, multivariate probit, latent class, imperfect gold, categorical tests

*Corresponding Author

Email address: enzo.cerullo@bath.edu
1 Introduction

Tests are used to screen, monitor and diagnose medical conditions. Test accuracy studies and meta-analyses typically evaluate the accuracy of tests by comparing the results obtained from a test under evaluation, referred to as the index test, to some existing test which is assumed to have a perfect sensitivity and specificity, known as the reference or gold standard test. Index tests may have a lower sensitivity or specificity than the gold standard, or both. However, they may be quicker, less invasive, or have a lower cost. When the accuracy of the gold standard is imperfect, ignoring this in the data analysis may produce biased estimates of test accuracy\(^1\). In other words, the accuracy of the index tests may be over or under-estimated when applying standard methods, such as those based on the ‘bivariate model’\(^2\) or the Rutter and Gatsonis hierarchical summary receiver operating characteristic (HSROC) model\(^3\) (models that are equivalent in practice unless covariates are included\(^4\)). Models which can accommodate an imperfect gold standard have been proposed\(^5,6,7,8,9\). These methods allow one to investigate whether assuming a perfect gold standard potentially changes the estimated accuracy of the index tests by a clinically important amount. Secondly, comparisons can also be made between the accuracy of the gold standard test and the index tests being evaluated, since the gold standard is no longer assumed to be perfect. In fact, it is not possible to show that the index test is superior to existing gold standards using standard models, unless we have access to a true gold standard and conduct comparative accuracy studies.

Test results tend to be correlated within disease categories. In general, correlated binary data can be modelled using multivariate probit models\(^10\), which can be extended to ordered probit models for ordinal data\(^11,12\). Unlike binary latent class models (BLCMs)\(^13\) which use aggregated data, these models use the underlying patient-level data, which is augmented with normally distributed latent variables, as proposed by Albert and Chib\(^10\). Multivariate probit models have previously been suggested for the analysis of a primary test accuracy study\(^13,14,15\). In 2009, Xu et al\(^13\) presented a latent class multivariate probit model to analyse binary test accuracy data evaluating multiple dichotomous tests without a gold standard. In 2013, the same authors\(^14\) extended their previous model\(^13\) to an ordered probit model. They used this to estimate the test accuracy when each test has intermediate (i.e., neither positive or negative) results - that is, when each test is a ordinal test with two thresholds. The model proposed by Qu et al\(^15\), which is often referred to as a ‘latent trait’ or ‘random-effects’ model in the biostatistical literature, is also a latent class multivariate probit model. However, unlike that of Xu et al\(^13\), the multivariate probit likelihood is defined implicitly by specifying a series of probit regression models, in which subject-specific latent variables are multiplied by a common term, often referred to as the ‘latent trait’ or ‘random effect’. In 2010, Sadatsafavi et al\(^8\) extended the model from Qu et al\(^15\) to the meta-analysis setting, analysing studies evaluating two or three dichotomous tests using direct comparisons. The model allows partial pooling (using the terminology from Gelman & Hill\(^16\), otherwise known as ‘random effects’) for the accuracy parameters and assumes complete pooling (i.e. ‘fixed effects’) for the within-study correlations.

For the meta-analysis of ordinal tests in the presence of a perfect gold standard, Hamza et al\(^17\) generalised the bivariate random-effects model of Reitsma et al\(^2\) to a multivariate random-effects model to estimate summary HSROC curves. This model uses multinomial within-study likelihoods, with the dimension of the multivariate between-study model equal to the number of categories for the index test. In 2013, Novielli et al\(^18\) proposed a model for meta-analysis in which the comparative accuracy studies evaluated up to one ordinal test with two thresholds and two dichotomous tests. This model was based on conditional probabilities, and could be used to estimate summary test accuracy at each threshold as well as joint test accuracy - that is, the accuracy of two or more tests used in combination, which is relevant for clinical practice as tests are often not used in isolation. This model accounted for the conditional dependence between the tests.

In this paper, we developed a model for the meta-analysis of studies evaluating ordinal and dichotomous tests without assuming a perfect gold standard. The model also enables the estimation of
joint test accuracy whilst allowing the conditional within-study correlations to vary between studies. The proposed model is an extension of previous models based on multivariate probit models which have been developed to analyse multiple tests in single study, as discussed above. Unlike the meta-analytic model proposed by Sadatsafavi et al, this model can account for ordinal tests by using ordinal regression, can use general within-study correlation structures, and allows partial pooling or no pooling (i.e. modelled independently) on the within-study correlations rather than complete pooling.

This paper is structured as follows. In section 2, we develop the models which enable the (simultaneous) meta-analysis of dichotomous and ordinal tests. The model can simultaneously accommodate a mixture of dichotomous and ordinal tests across a meta-analysis data set. In section 3, we describe the case study dataset. In section 4, we apply the proposed models to the case study dataset, and in section 5, we discuss the benefits and limitations of the model, as well as possible extensions.

2 Model Specification

Suppose that there are $S$ Studies each assessing $T \geq 2$ tests with $N_s$ individuals in each study, $s \in \{1, \ldots, S\}$. We assume that all studies report data on all categories of each test, and each test, $t \in \{1, \ldots, T\}$, has $K_t$ categories ($K_t - 1$ thresholds).

2.1 Within-study model

Within each study $s$, each individual $n \in \{1, \ldots, N_s\}$ has a vector of observed test responses, $y_{s,n}$, equal to

$$y_{s,n} = \{y_{s,n,1}, \ldots, y_{s,n,T}\}$$

Assume that each individual has latent disease status $d = d_{s,n} \in \{0 = \text{non-diseased}, 1 = \text{diseased}\}$. Conditional on the disease status of each individual, $d = d_{s,n} \in \{0, 1\}$, we augment the observed data with normally distributed latent variables $Z_{s,n}$,

$$Z_{s,n} \sim \text{MVN} \left( \nu_s^d, \Psi_s^d \right),$$

where,

$$Z_{s,n} = \begin{pmatrix} Z_{s,n,1} \\ \vdots \\ Z_{s,n,T} \end{pmatrix}, \nu_s^d = \begin{pmatrix} \nu_{s,1}^d \\ \vdots \\ \nu_{s,T}^d \end{pmatrix}, \Psi_s^d = \begin{pmatrix} (\tau_{s,1}^d)^2 & \cdots & \tau_{s,1}^d \cdot \tau_{s,T}^d \\ \vdots & \ddots & \vdots \\ \tau_{s,1}^d \cdot \tau_{s,T}^d & \cdots & (\tau_{s,T}^d)^2 \end{pmatrix}$$

We assume that the study-specific location parameters can be modelled by the unconstrained parameters $\nu_{s,t}^1 \in \mathbb{R}$ and $\nu_{s,t}^0 \in \mathbb{R}$ for the latent diseased and non-diseased populations, respectively.

For the variance-covariance matrices $\Psi_s^d$, for identifiability we need to set some restrictions. In this paper, we set $\tau_{s,t}^d = 1, \forall s \in \{1, \ldots, S\}, \forall t \in \{1, \ldots, T\}$, so that each $\Psi_s^d$ is a correlation matrix. This has the same form to the models proposed in Xu et al 2009 and Xu et al 2013. Note that the correlations, $\hat{\epsilon}_{s,t,t'}^d$, represent the pairwise correlation between the latent variables for tests $t$ and $t'$ in study $s$, conditional on the disease status $d$. $\hat{\epsilon}_{s,t,t'}^d$ is referred to as the polychoric correlation. If it is considered reasonable in a particular setting to assume that tests are conditionally independent given disease status, the correlations can be set to zero, so that $\Psi_s^d = \text{diag}(1, \ldots, 1)$. For dichotomous test $t$, the observed test results of each individual are given by,
\[ y_{s,n,t} = \begin{cases} 0 & \text{if } Z_{s,n,t} \leq 0 \\ 1 & \text{if } Z_{s,n,t} > 0 \end{cases} \] (2)

For ordinal tests, the observed test results of each individual for test \( t \) are given by,

\[ y_{s,n,t} = \begin{cases} 1 & \text{if } Z_{s,n,t} \leq C_{1,s,t}^{[d]} \\ 2 & \text{if } C_{1,s,t}^{[d]} < Z_{s,n,t} \leq C_{2,s,t}^{[d]} \\ \vdots & \text{if } C_{K_{t}-2,s,t}^{[d]} < Z_{s,n,t} \leq C_{K_{t}-1,s,t}^{[d]} \\ K_{t} & \text{if } Z_{s,n,t} > C_{K_{t}-1,s,t}^{[d]} \end{cases} \] (3)

Where \( C_{k,s,t}^{[d]} < C_{k+1,s,t}^{[d]} \) for \( k \in \{1, \ldots, K_{t}-2\} \) are the latent threshold parameters.

Conditional on the true disease status of each individual, \( d = d_{s,n} \in \{0, 1\} \), the probability of observing the test response vector \( y_{s,n} \) is given by,

\[
P \left( y_{s,n} | d_{s,n}, \nu^{[d]}_{s}, \Psi^{[d]}_{s}, C^{[d]}_{s} \right) = \int_{I_{s,n,1}}^{I_{s,n,T}} \Phi_{T} \left( k | \nu^{[d]}_{s}, \Psi^{[d]}_{s} \right) dk
\] (4)

where \( \Phi_{T} \left( \cdot | \nu^{[d]}_{s}, \Psi^{[d]}_{s} \right) \) denotes the cumulative distribution function of a multivariate normal distribution with dimension equal to the number of tests in each study, \( T \), with mean vector \( \nu^{[d]}_{s} \) and variance-covariance matrix \( \Psi^{[d]}_{s} \). For dichotomous tests, the intervals \( I_{s,n,t}^{[d]} \) are defined by,

\[
I_{s,n,t}^{[d]} = \begin{cases} (-\infty, 0] & \text{if } y_{s,n,t} = 0 \\ (0, \infty) & \text{if } y_{s,n,t} = 1 \end{cases}
\] (5)

This corresponds to a binary latent class multivariate probit model with probability density function, \( \pi(\cdot) \), is given by,

\[
\pi(k | \nu^{[d]}_{s,t}) = \begin{cases} 1 - \Phi \left( \nu^{[d]}_{s,t} \right) & \text{if } k = 0 \\ \Phi \left( \nu^{[d]}_{s,t} \right) & \text{if } k = 1 \end{cases}
\] (6)

Where \( \Phi(\cdot) \) denotes the cumulative density function of the standard normal distribution. The measures of test accuracy for each study are given by,

\[
Se_{s,t} = \Phi(\nu_{s,t}^{[1]}) \\
Sp_{s,t} = 1 - \Phi(\nu_{s,t}^{[0]})
\] (7)

For ordinal tests, the intervals, \( I_{s,n,t}^{[d]} \), are defined by,

\[
I_{s,n,t}^{[d]} = \begin{cases} (-\infty, C_{1,s,t}^{[d]}) & \text{if } y_{s,n,t} = 1 \\ (C_{1,s,t}^{[d]}, C_{2,s,t}^{[d]}) & \text{if } y_{s,n,t} = 2 \\ \vdots & \text{if } y_{s,n,t} = K_{t}-1 \\ (C_{K_{t}-2,s,t}^{[d]}, C_{K_{t}-1,s,t}^{[d]}) & \text{if } y_{s,n,t} = K_{t}-1 \\ (C_{K_{t}-1,s,t}^{[d]}, \infty) & \text{if } y_{s,n,t} = K_{t} \end{cases}
\] (8)
This corresponds to an ordered latent class multivariate probit model\textsuperscript{(12)} with probability density function for test \( t \) given by,

\[
\pi(k \mid \nu_{s,t}^{[d]}, C_{s,t}) = \begin{cases} 
\Phi(C_{1,s,t}^{[d]} - \nu_{s,t}^{[d]}) & \text{if } k = 1, \\
\Phi(C_{k,s,t}^{[d]} - \nu_{s,t}^{[d]}) - \Phi(C_{k-1,s,t}^{[d]} - \nu_{s,t}^{[d]}) & \text{if } 1 < k < K_t, \\
1 - \Phi(C_{K_t,s,t}^{[d]} - \nu_{s,t}^{[d]}) & \text{if } k = K_t.
\end{cases}
\]

(9)

Therefore, for a test which has decreasing sensitivity and increasing specificity with increasing threshold, the measures of test accuracy for test \( t \) at a threshold of \( k \) in study \( s \) are given by,

\[
Se_{s,t,k} = 1 - \Phi(\nu_{s,t}^{[1]} - C_{k,s,t}) \\
Sp_{s,t,k} = \Phi(\nu_{s,t}^{[0]} - C_{k,s,t})
\]

(10)

The likelihood contribution from each study \( s \in \{1, \ldots, S\} \) is given by a latent class model with two classes, where one component corresponds to the diseased group and the other to the non-diseased group. Using equation (11), we can write the likelihood function for each study as the sum of the log probability terms for each individual study,

\[
\log L(\theta \mid y_s) = \sum_{n=1}^{N_s} \log \left[ p_s \cdot P \left( y_{n,s} \mid d_n = 1, \nu_{s,t}^{[1]}, \Psi_{s,t}^{[1]}, C_{k,s,t}^{[1]} \right) + \left(1 - p_s\right) \cdot P \left( y_{n,s} \mid d_n = 0, \nu_{s,t}^{[0]}, \Psi_{s,t}^{[0]}, C_{k,s,t}^{[0]} \right) \right] + \sum_{n=1}^{N_s} d_n \cdot \log \left[ \Phi_T \left( \mathbf{z}_{s,n} \mid \nu_{s,t}^{[1]}, \Psi_{s,t}^{[1]} \right) \right] + \sum_{n=1}^{N_s} (1 - d_n) \cdot \log \left[ \Phi_T \left( \mathbf{z}_{s,n} \mid \nu_{s,t}^{[0]}, \Psi_{s,t}^{[0]} \right) \right] + \sum_{n=1}^{N_s} (1 - d_n) \cdot \log \left( \mathbf{I}_{s,n} \right) + \sum_{n=1}^{N_s} d_n \cdot \log \left( \mathbf{I}_{s,n} \right)
\]

(11)

Where \( p_s, s \in \{1, \ldots, S\} \) denotes the disease prevalence in each study and \( \theta \) denotes the vector of model parameters.

Using the augmented latent variables, \( Z_{s,n,t} \), we can write this as,

\[
\log L(\theta \mid y_s) = \sum_{n=1}^{N_s} \log \left[ P \left( y_{n,s} \mid d_n = 1, \nu_{s,t}^{[1]}, \Psi_{s,t}^{[1]} \right) + \left(1 - p_s\right) \cdot P \left( y_{n,s} \mid d_n = 0, \nu_{s,t}^{[0]}, \Psi_{s,t}^{[0]} \right) \right] + \sum_{n=1}^{N_s} d_n \cdot \log \left[ \Phi_T \left( \mathbf{z}_{s,n} \mid \nu_{s,t}^{[1]}, \Psi_{s,t}^{[1]} \right) \right] + \sum_{n=1}^{N_s} (1 - d_n) \cdot \log \left[ \Phi_T \left( \mathbf{z}_{s,n} \mid \nu_{s,t}^{[0]}, \Psi_{s,t}^{[0]} \right) \right] + \sum_{n=1}^{N_s} \left[ d_n \cdot \log \left( \mathbf{I}_{s,n} \right) + (1 - d_n) \cdot \log \left( \mathbf{I}_{s,n} \right) \right]
\]

(11)

2.2 Between-study model

Recall that \( \nu_{s,t}^{[d]} \) are the location parameters for study \( s \), test \( t \) in latent population \( d \). We define a vector \( \nu_{s,t} = (\nu_{s,t}^{[1]}, \nu_{s,t}^{[0]})' \) and assume a partial pooling, bivariate normal population model,

\[
\pi(\nu_{s,t} \mid \theta) = \text{MVN}(\mu_t, \Sigma_t),
\]

(12)

Where \( \mu_t = (\mu_t^{[1]}, \mu_t^{[0]})' \) is a vector containing the mean parameters, and

\[
\Sigma_t = \begin{pmatrix}
\sigma_t^{[1]} & \rho_t \cdot \sigma_t^{[1]} \\
\rho_t \cdot \sigma_t^{[1]} & \sigma_t^{[0]}
\end{pmatrix}
\]

is a variance-covariance matrix, where \( \sigma_t^{[1]} \) and \( \sigma_t^{[0]} \) represent the between-study standard deviations for the sensitivities and specificities, respectively, and \( \rho_t \) represents the between-study correlation between sensitivities and specificities.
We can incorporate meta-regression covariates into the model. Let \( \mathbf{X}_{1:t} \ldots \mathbf{X}_{M:t} \) be \( M \) vectors meta-regression covariates such that each \( \mathbf{X}_{m:t} = (X_{m,1:t}, \ldots, X_{m,S:t}) \in \mathbb{R}^S \). Let \( \gamma_{1:t} \ldots \gamma_{M:t} \) be \( M \) vectors of meta-regression coefficients, such that each \( \gamma_{m,t} = (\gamma_{m,t}^{[1]}, \gamma_{m,t}^{[0]})' \in \mathbb{R}^2 \), \( m \in \{1 \ldots M\} \). Then we write [12] as,

\[
\pi(\mathbf{v}_{s,t} \mid \theta) = \text{MVN}(\mu_t + X_{1,s:t} \cdot \gamma_{1,t} + \ldots + X_{M,s:t} \cdot \gamma_{M,t}, \Sigma_t),
\]

For the disease prevalence in each study, we implement a no pooling (i.e., independent effects) model, which does not assume any latent interactions between the individual disease prevalence parameters,

\[
\pi(p_1, \ldots, p_S) = \prod_{s=1}^{S} \pi(p_s)
\]

We can set a given test, \( t' \), to be a perfect gold standard (100% sensitive and specific) by setting \( \mu_{t'}^{[0]} = -5 \) and \( \mu_{t'}^{[1]} = 5 \), which correspond to 100% specificity and sensitivity, respectively, and by using a complete pooling model (in other words, assuming zero between study heterogeneity i.e. \( \sigma_{t'}^{[d]} = 0 \)).

### 2.2.1 Cutpoints for ordinal tests

We can order the threshold parameters for each study, \( C_{s,t}^{[d]} \), \( k \in \{1, \ldots, K_t - 1\} \) by reparameterizing the cutpoints. We define a map \( C_{s,t}^{[d]} \rightarrow \omega_{s,t}^{[d]} \) such that,

\[
\omega_{k,s,t} = \begin{cases} 
C_{1,s,t}^{[d]} & \text{if } k = 1, \\
\log \left( C_{k,s,t}^{[d]} - C_{k-1,s,t}^{[d]} \right) & \text{if } 1 < k \leq K.
\end{cases}
\]

Then, to ensure \( C_{k,s,t}^{[d]} < C_{k+1,s,t}^{[d]} \), each \( C_{k,s,t}^{[d]} \) can be expressed as,

\[
C_{k,s,t}^{[d]} = \omega_{1,s,t}^{[d]} + \sum_{i=2}^{k} \exp(\omega_{1,s,t}^{[d]})
\]

The threshold parameters can be modelled using an induced Dirichlet model, an approach which has been proposed by Betancourt[20] which we describe in more detail in Appendix [A]. This model applies a Dirichlet model directly to the ordinal probabilities, by mapping the latent cut point parameters in each study \( \{C_{1,s,t}^{[d]}, \ldots, C_{K_t-1,s,t}^{[d]}\} \) to the simplex of ordinal probabilities \( \{F_{1,s,t}^{[d]}, \ldots, F_{K_t-1,s,t}^{[d]}\} \) using an injective (i.e. one-to-one) function. The probability density function for the induced Dirichlet model is given by,

\[
\text{Induced-Dir} \left( C_{s,t}^{[d]} | \alpha_{s,t}^{[d]}, \phi \right) = \text{Dir} \left( \mathbf{P}(C_{s,t}^{[d]}), \phi \right) \cdot |J \left( C_{s,t}^{[d]} \right)|,
\]

Where \( C_{s,t}^{[d]} = (C_{1,s,t}^{[d]}, \ldots, C_{K_t-1,s,t}^{[d]})' \) is the vector of cutpoints for study \( s \) and test \( t \), \( \alpha_{s,t}^{[d]} = (\alpha_{1,s,t}^{[d]}, \ldots, \alpha_{K_t-1,s,t}^{[d]})' \) is the Dirichlet vector for study \( s \) and test \( t \), \( \mathbf{P}(C_{s,t}^{[d]}, \phi) \) represents the induced ordinal probabilities in terms of the thresholds \( C_{s,t}^{[d]} \) and an arbitrary anchor point \( \phi \), and \( |J \left( C_{s,t}^{[d]} \right)| \) is the determinant of the Jacobian matrix of partial derivatives (we need a Jacobian adjustment since we are directly modelling transformed parameters). We can use the induced Dirichlet model to directly specify a complete pooling model on the thresholds by setting \( C_{s,t}^{[d]} = C_{t}^{[d]} \) \( \forall s \), and specifying \( \alpha_{s,t}^{[d]} \forall s, \ t \) as constants. We can specify a partial pooling model on the thresholds by
setting $\mathbf{\alpha}^{[d]}_s = \mathbf{\alpha}^{[d]}_t \forall s$ as parameters, so that,

$$
\pi \left( C^{[d]}_{s,t} | \theta \right) = \text{Induced-Dir} \left( C^{[d]}_{s,t} | \mathbf{\alpha}^{[d]}_t \right) \cdot \pi \left( \mathbf{\alpha}^{[d]}_t \right)
$$

(16)

In this case, we can obtain an ’average’ vector of cutpoints, $\mathbf{C}^{[d]}_t$, by simulating repeatedly from (16) and averaging across draws.

### 2.2.2 Modelling conditional dependence between tests and joint test accuracy

We can model the within-study correlation matrices, $\Psi^{[d]}_s$, using a no pooling model so that $\pi \left( \Psi^{[d]}_1, \ldots, \Psi^{[d]}_S \right) = \prod_{s=1}^S \pi \left( \Psi^{[d]}_s \right)$. We can also use a partial pooling model; since a convex combination of correlation matrices is also a correlation matrix, as suggested by Goodrich,[23] the study level correlation matrices can be specified as a weighted linear combination of a summary correlation matrix across studies, $\Psi^{[d]}_G$, and a matrix of study-level deviations from this $\Psi^{[d]}_s$, with weight $\beta^{[d]}$,

$$
\Psi^{[d]}_s = \left( 1 - \beta^{[d]} \right) \cdot \Psi^{[d]}_G \cdot \Psi^{[d]}_s \cdot \beta^{[d]} \cdot \beta^{[d]} \in [0, 1]
$$

(17)

where $\Psi^{[d]}_G$ is the summary (i.e. global - hence the $G$ subscript) correlation matrix across studies, and $\Psi^{[d]}_s$ is the deviation from $\Psi^{[d]}_G$ in each study. $\eta_1, \eta_2 \in \mathbb{R}_+$ are constants and $\pi (\beta) = \text{Beta}(a, b)$ s.t. $a, b \in \mathbb{R}_+$. In this case, the population posterior predictive distribution is given by,

$$
\mathbf{Z}^{[d]}_G \sim \text{MVN} \left( \mu^{[d]}, \Psi^{[d]}_G \right),
$$

(18)

Now we discretize $\mathbf{Z}^{[d]}_G$ at a given threshold $k$. Let,

$$
y^{[d]}_{G,t,k} = \begin{cases} 
0 & \text{if } \mathbf{Z}^{[d]}_{G,t} \leq k \\
1 & \text{if } \mathbf{Z}^{[d]}_{G,t} > k 
\end{cases}
$$

We simulate from (18) repeatedly and hence obtain ordinal data vectors $y^{[d]}_{G,t,k}$. Then, we can obtain a summary estimate of Pearson’s correlation coefficient between tests $t$ and $t'$ at thresholds of $k$ and $k'$, within each disease class, $\rho^{[d]}_{G,t',kk'} = \text{Corr}(y^{[d]}_{G,t,k}, y^{[d]}_{G,t',k'})$, where Corr denotes the formula for Pearson’s correlation coefficient. The summary covariances between tests $t$ and $t'$ at thresholds of $k$ and $k'$ within each disease class $d$ are given by,

$$
cov^{[d]}_{G,t',kk'} = \rho^{[d]}_{G,t',kk'} \sqrt{\text{Se}_{G,t,k} \text{Se}_{G,t',k}(1 - \text{Se}_{G,t,k})(1 - \text{Se}_{G,t',k'})}
$$

$$
cov^{[d]}_{G,t',kk'} = \rho^{[d]}_{G,t',kk'} \sqrt{\text{Sp}_{G,t,k} \text{Sp}_{G,t',k}(1 - \text{Sp}_{G,t,k})(1 - \text{Sp}_{G,t',k'})}
$$

(19)

We can model the conditional dependence between only certain pairs of tests by setting the relevant correlations in $\Psi^{[d]}_s$ to zero. For the partial pooling model (see equation (17)), this can be achieved by setting the relevant terms in $\Psi^{[d]}_G$ and $\Psi^{[d]}_s$ to zero.

### 2.2.3 Prior model

For prior modelling, we can use normal priors for the location parameters (see section 2.2, equation 12) so that $\pi \left( \mu^{[d]}_t \right) = N(a, b)$ s.t. $a, b \in \mathbb{R}$. For the between-study heterogeneity parameters (see section 2.2, equation 12), we can decompose each $\Sigma_i$ into a vector $\mathbf{\sigma}_i = \left( \sigma^{[0]}_i, \sigma^{[1]}_i \right)^T$ and a correlation
matrix \( \Omega_t \),

\[
\Sigma_t = \text{diag}(\sigma_t) \times \Omega_t \times \text{diag}(\sigma_t),
\]

For the standard deviations, a natural choice is a half-normal prior \( \pi(a_i[d]) = N_{\geq 0}(0, a_i[d]) \), \( d \in \{0, 1\} \), \( a_i[d] \in \mathbb{R}_+ \)

For the between-study correlations, we use Lewandowski-Kurowicka-Joe (LKJ) \( \pi(\Omega_t) = \text{LKJcorr}(\Omega_t) \) priors,

\[
\pi(\Omega_t) = \text{LKJcorr}(\Omega_t) \propto \text{det}(\Omega_t)^{(\eta - 1)}, \eta \in \mathbb{R}_+
\]

For the disease prevalences (see section 2.2, equation 14), we can use beta priors, \( \pi(p_s) = \text{Beta}(a_s, b_s) \), \( a_s, b_s \in \mathbb{R}_+ \). If using a partial pooling model for the thresholds, for prior modelling on the Dirichlet population parameter vector, \( \alpha_i[d] \), as \( \alpha_i[d] = \kappa_i[d] \cdot \chi_i[d] \), where \( \kappa_i[d] \) is a scalar with prior \( \kappa_i[d] \sim N_{\geq 0}(0, a_i[d]) \) s.t. \( a_i[d] \in \mathbb{R}_+ \) and \( \chi_i[d] \) is a uniform simplex (i.e. a vector which sums to 1). For the within-study correlations (see section 2.2.2), if using a no pooling model we can use LKJ priors so that

\[
\pi(\Psi_s)[d,\Delta] = \text{LKJcorr}(\eta) \propto \text{det}(\Psi_s)[d,\Delta]^{(\eta - 1)} \text{ s.t. } \eta \in \mathbb{R}_+. \quad \text{If we use a partial pooling model, we can set beta priors on the weights so that } \pi(\beta[d]) = \text{Beta}(a, b) \text{ s.t. } a, b \in \mathbb{R}_+, \text{ and we can use LKJ priors on both the global correlation matrices, } \Psi_s[d,\Delta], \text{ and the deviance correlation matrices, } \Psi_s[d,\Delta], \text{ so that given } \eta_1, \eta_2 \in \mathbb{R}_+,
\]

\[
\pi(\Psi_s)[d,\Delta] = \text{LKJcorr}(\eta_1) \propto \text{det}(\Psi_s)[d,\Delta]^{(\eta_1 - 1)}
\]

\[
\pi(\Psi_s)[d,\Delta] = \text{LKJcorr}(\eta_2) \propto \text{det}(\Psi_s)[d,\Delta]^{(\eta_2 - 1)}
\]

### 2.2.4 Summary estimates of test accuracy

For dichotomous tests, the summary sensitivity and specificity estimates for test \( t \) are given by evaluating equation \( 17 \) at the means of the partial pooling model (see 12),

\[
\begin{align*}
S_{e,G,t} &= \Phi(\mu_t[1]) \\
S_{p,G,t} &= 1 - \Phi(\mu_t[0])
\end{align*}
\]

For ordinal tests, the summary measures of test accuracy for test \( t \) at a threshold of \( k \) are given by equation \( 10 \) evaluated at the means of the partial pooling model (see 12), and, if using a partial pooling model on the thresholds, at the 'average' cutpoints from the induced Dirichlet partial pooling model (see equation 16),

\[
\begin{align*}
S_{e,G,t,k} &= 1 - \Phi(C_{k,t}^{[1]} - \mu_t[1]) \\
S_{p,G,t,k} &= \Phi(C_{k,t}^{[0]} - \mu_t[0])
\end{align*}
\]

The summary joint test accuracy for tests \( t \) and \( t' \) at thresholds of \( k \) and \( k' \) are given by,

\[
\begin{align*}
S_{e,G,t,t',kk'} & = S_{e,G,t,k} \ast S_{e,G,t',k'} + \text{cov}_{G,t,t',kk'}^{[1]} \\
S_{p,G,t,t',kk'} & = 1 - ((1 - S_{p,G,t,k}) \ast (1 - S_{p,G,t',k'}) + \text{cov}_{G,t,t',kk'}^{[0]}) \\
S_{e,G,t,t',kk'} & = 1 - ((1 - S_{e,G,t,k}) \ast (1 - S_{e,G,t',k'}) + \text{cov}_{G,t,t',kk'}^{[1]}) \\
S_{p,G,t,t',kk'} & = S_{p,G,t,k} \ast S_{p,G,t',k'} + \text{cov}_{G,t,t',kk'}^{[0]}
\end{align*}
\]

7
Where BTN and BTP are ‘believe the negatives’ and ‘believe the positives’ testing strategies, respectively. We can generate predictions for a ‘new’ \((S+1)\)-th study by simulating a draw (at each iteration) from the posterior predictive distributions of the between-study normal hierarchical model, (see \[12\]), \(\nu_{S+1,t}\), and, if using a partial pooling model on the thresholds, a new vector of thresholds from the induced Dirichlet threshold model (see \[16\]), \(C_{S+1,t}^d\). The predicted sensitivities and specificities for an \((S+1)\)-th study are given by \(Se_{S+1,t} = \Phi(\nu_{S+1,t}^\dagger)\) and \(Sp_{S+1,t} = 1 - \Phi(\nu_{S+1,t}^\dagger)\) for dichotomous tests, and \(Se_{S+1,t,k} = 1 - \Phi(C_{S+1,k,t}^\dagger - \nu_{S+1,t}^\dagger)\) and \(Sp_{S+1,t,k} = \Phi(C_{S+1,k,t}^\dagger - \nu_{S+1,t}^\dagger)\) for ordinal tests.

### 2.3 Posterior predictive checking and model comparison

For posterior predictive checks, we can re-construct the study-specific 2x2 tables between tests and \(t'\) by dichotomising the tests at a given threshold. We calculate the probability of observing each test pattern by applying the BLCM formula\[21\[26\]

\[
Pr(+tk,+tk')_s = p_s* (Se_{s,t,k} * Se_{s,t',k'} + cov_{st',kk'}^{[1]} + (1-p_s) * ((1-Sp_{s,t,k}) * (1- Sp_{s,t',k'}) + cov_{st',kk'}^{[0]})
\]

\[
Pr(+tk,-tk')_s = p_s* ((1-Se_{s,t,k}) * Se_{s,t',k'} - cov_{st',kk'}^{[1]} + (1-p_s) * ((1- Sp_{s,t,k}) * (1- Sp_{s,t',k'}) - cov_{st',kk'}^{[0]})
\]

\[
Pr(-tk,+tk')_s = p_s* ((1-Se_{s,t,k}) * Se_{s,t',k'} - cov_{st',kk'}^{[1]} + (1-p_s) * (Sp_{s,t,k} * (1- Sp_{s,t',k'}) - cov_{st',kk'}^{[0]})
\]

\[
Pr(-tk,-tk')_s = p_s* ((1-Se_{s,t,k}) * (1- Se_{s,t',k'}) + cov_{st',kk'}^{[1]} + (1-p_s) * ((1- Sp_{s,t,k}) * (1- Sp_{s,t',k'}) + cov_{st',kk'}^{[0]})
\]

\[26\]

Where \(cov_{st',kk'}^{[d]}\) represent the study-specific covariances between tests \(t\) and \(t'\) at thresholds \(k\) and \(k'\). Then, we can calculate the model-predicted cell counts by multiplying each probability in \[26\] by the number of individuals in each study, \(N_s\). We can plot the model-predicted 2x2 tables against the observed 2x2 tables to inspect the fit. We can also plot the model-predicted correlations against the observed correlations to assess model fit, using the correlation residual plot proposed by Qu et al.\[25\]. The model-predicted correlations are given by,

\[
\rho_{tk,t'k'} = \frac{Pr(+tk,+tk')_s - Pr(+tk)Pr(+tk')}{\sqrt{Pr(+tk)Pr(+tk')(1-Pr(+tk))(1-Pr(+tk'))}},\text{ where}
\]

\[
Pr(+tk) = Pr(+tk,+tk')_s + Pr(+tk,-tk')_s
\]

\[
Pr(+tk') = Pr(+tk,+tk')_s + Pr(-tk,+tk')_s
\]

\[27\]

For model comparison, we can conduct estimated leave-one-out (LOO) cross-validation\[21\]. We used the 'loo' package\[25\] which computes the estimated LOO statistic using Pareto-smoothed importance sampling (PSIS-LOO). LOO is superior to both the deviance information criterion (DIC) and the widely applicable information criterion (WAIC). This is because the DIC is not fully Bayesian, as it is based on a point estimator,\[28\] and the LOO is invariant to parametrisation. Furthermore, both the DIC and the WAIC lack diagnostics, and the LOO is also more robust than both the DIC and the WAIC in the face of weak priors or influential observations\[24\].

### 2.4 Implementation

We implemented the models using the probabilistic programming language Stan\[22\], which uses a dynamic Hamiltonian Monte Carlo (HMC) sampler\[23\] using a PC with 32GB of RAM and an AMD Ryzen 3900X 12-core CPU with Linux Mint OS. We used Stan via the cmdstanr package\[24\] in R. Stan makes it easy to implement a model, since it only requires the user to derive the likelihood-prior function and the user does not need to derive the full conditional distributions, as one would do for a custom Gibbs sampler, or the joint kernels, as one would do for a custom HMC sampler. To implement the likelihood (equation \[11\]) for each study, we extended model code for a binary
multivariate probit model\textsuperscript{21} to the ordinal, latent class case. This uses the Geweke, Hajivassiliou and Keane (GHK) algorithm\textsuperscript{20} to generate truncated multivariate normals, which are required to partition the underlying latent variables. This is described in Goodrich 2017\textsuperscript{31} which we have summarised in appendix B. We implemented the partial pooling models on the within-study correlation matrices described in section 2.2.2 in Stan by using the function provided by Stephen Martin and Ben Goodrich\textsuperscript{32}. The ordered vectors described in section 2.2.1 can be implemented in Stan\textsuperscript{33} simply by declaring an ordered vector. Betancourt’s induced Dirichlet model\textsuperscript{20} described in section 2.2.1 and appendix A was implemented using code by Betancourt\textsuperscript{39}.

We ran all models using 4 chains until the split R-hat statistic was less than 1.05 for all parameters and the number of effective samples was satisfactory for all parameters\textsuperscript{33}. We only reported results when we obtained no warnings for divergent transitions or energy fraction of missing information (E-FMI), important diagnostics for geometric ergodicity\textsuperscript{28}; we used the CmDStanR diagnostic utility\textsuperscript{29} to check all of the aforementioned model diagnostics\textsuperscript{29}. We also inspected trace plots and plotted the posterior distributions to check they were not bimodal. Rather than using $\Phi(\cdot)$, which is prone to numerical instability, we can use the closely resembling logistic function, $\Phi'(x) = \frac{1}{1 + e^{-x}}$, which has an absolute maximum deviation from $\Phi(\cdot)$ of 0.0095. This is the same probit approximation used for the meta-analysis of dichotomous tuberculosis tests using latent trait models in Sadatsafavi et al\textsuperscript{8}.

The data, Stan model code specific to the case study, and R code to reproduce the results and figures for the case study application in section 4 is provided at https://github.com/CerulloE1996/dta-mvp-1.

### 3 Case study dataset

Deep vein thrombosis (DVT) is the formation of a blood clot in a deep vein, typically in the lower limbs, which can either be in the upper leg (proximal) or the lower leg (distal). DVT, particularly proximal DVT, can be dangerous and sometimes life-threatening. For example, a complication of DVT which can occur in up to a third of patients\textsuperscript{34} is pulmonary embolism (PE), which occurs when a blood vessel in the lung becomes blocked by the blood clot (due to DVT) travelling from the legs to the lungs.

A commonly used\textsuperscript{34} test in clinical practice to screen for DVT is the Wells score\textsuperscript{35}. This is a questionnaire with three categories ('low', 'intermediate', or 'high' risk). It is typically used to stratify patients and refer them for further assessment. Another test is the D-dimer assay, which measures the amount of D-dimer in the blood, higher concentrations of which suggest thrombosis\textsuperscript{36}. D-dimer is created by the body’s response to a thrombus - a blood clot which forms in a vessel and remains there - from any cause. Therefore, elevation of D-dimer is not specific to DVT, since a number of other conditions such as pregnancy and liver disease also elevate serum D-dimer concentrations\textsuperscript{34}. It is therefore more useful to rule out DVT in low-risk individuals, especially when used in combination with the Wells criteria\textsuperscript{34}.

Imaging, such as ultrasound, is often used to confirm the presence of DVT, since it is safe and cost-effective\textsuperscript{34,37,38,39}. Although the specificity for ultrasound is known to be very high (but nonetheless still imperfect enough to potentially bias estimates) for either distal or proximal DVT, the sensitivity is substantially lower for distal DVT compared to proximal DVT. For example, a systematic review and meta-analysis\textsuperscript{40} estimated the sensitivity of ultrasound to be 0.94 (95% confidence interval [ConfI] = [0.93, 0.95]) and 0.64 (95% ConfI = [0.60, 0.67]) for proximal and distal DVT, respectively. It estimated the specificity for either type of DVT to be 0.94 (95% ConfI = [0.93, 0.94]). Another systematic review investigating the accuracy of various tests specifically for proximal DVT\textsuperscript{41} found that sensitivity varied from 0.84 (95% ConfI = [0.72, 0.97]) to 0.97 (95% ConfI = [0.90, 1.00]) and the specificity varied from 0.93 (95% ConfI = [0.80, 1.00]) to 0.96 (95% ConfI = [0.87, 1.00]) for ultrasound. The best gold standard for the diagnosis of DVT is contrast venography, which is
considered to be almost 100% sensitive and specific for the diagnosis of DVT, i.e. approximately a true gold standard. However, it is invasive and rarely used in clinical practice\textsuperscript{42,43}.

We demonstrate the model using data from a previously published meta-analysis from Novielli et al\textsuperscript{18} of studies reporting numbers of individuals positive or negative on each combination of three tests for DVT: D-dimer, Wells score and ultrasound (the ‘gold standard’ test). A re-analysis of this data is relevant because the meta-analysis from Novielli et al\textsuperscript{18} assumed a perfect gold standard. However, studies used ultrasonography, which, as discussed above, is not a perfect test\textsuperscript{40}. This could have led to biased estimates of the other tests under evaluation. D-dimer and ultrasound data were supplied as dichotomous, while the Wells score data was supplied as a 3-category ordinal test. Novielli et al\textsuperscript{18} carried out several analyses based on different datasets – for instance, one based on the 11 studies which directly compared the D-dimer, Wells’ score and the gold standard, and another which also included studies which only analysed one test using indirect comparisons.

In this paper, we re-analysed the direct comparisons data (see Table 1) without assuming a perfect gold standard, using a variety of models described in section 2; namely, models which dichotomised the Wells score and those which modelled it as an ordinal test, those which assumed conditional independence and dependence, as well as models which assumed ultrasonography was perfect or imperfect. This dataset consisted of 11 studies, with a total of 4096 individuals and 12,288 observations. All of the 11 studies used the D-Dimer, ultrasound and the Wells score.

### Table 1: Sample of case study dataset

| Study | Ultrasound -'ve | Ultrasound +'ve |
|-------|-----------------|-----------------|
| D-Dimer -'ve | D-Dimer +'ve | D-Dimer -'ve | D-Dimer +'ve |
| Wells score\textsuperscript{1} | Wells score\textsuperscript{1} | Wells score\textsuperscript{1} | Wells score\textsuperscript{1} |
| L | M | H | L | M | H | L | M | H | L | M | H |
| 1 | 32 | 20 | 5 | 18 | 2 | 0 | 0 | 2 | 1 | 6 | 8 |
| ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... | ... |
| 11 | 243 | 16 | 3 | 233 | 104 | 29 | 1 | 0 | 0 | 28 | 117 | 109 |

Note: All test results are modelled at the individual level. We show the aggregate data in this table for ease of presentation.

\textsuperscript{1} The Wells score is classified as \( L = \text{Low}, M = \text{Moderate}, H = \text{High} \)

## 4 Application to case study

When faced with the task of analysing a dataset which contains test accuracy data from a non-dichotomous test, one might be tempted to dichotomise the data at each threshold and conduct a series of stratified analyses. In other words, one might dichotomise the Wells’ score as low+moderate vs high or as low vs moderate+high and then conduct stratified analyses. We applied this technique to this dataset using the models proposed in section 2 fitting both conditional independence (CI) and dependence (CD) models, and the results are shown in section 4.1. In section 4.2, we apply the models proposed in section 2 without dichotomising the Well’s score.

We fit all models using weak \( N_{\geq 0}(0, 0.5) \) priors for the between-study standard deviations, so that \( \sigma_t^{[d]} \sim N_{\geq 0}(0, 0.5) \) s.t. \( t \in \{1 = \text{Reference}, 2 = \text{D-Dimer}, 3 = \text{Wells}\}, \ d \in \{0, 1\}. \) These are weak priors since they weakly pull the study-specific sensitivities and specificities towards each other, whilst allowing a large between-study variation in accuracy estimates if the data demands. This is because a shift of 0.5 on the probit scale represents a large change on the sensitivity or specificity.
estimate. For example, if 0.8 is the value found for the summary sensitivity, and if $\sigma = 1$, then we would expect the study-specific estimates would be in the range of $(0.63, 0.91)$ with a 95% probability and if $\sigma = 2$ then they would be in the range of $(0.44, 0.97)$ with 95% probability. We also used weak priors on the between-study correlation parameters (see equation 12), so that $\Omega_t \sim \text{LKJcorr}(2)$ $\forall t$. We used $N(0, 1)$ priors for the means of the sensitivities and specificities of the D-Dimer and Well’s score on the probit scale i.e. $\mu_{i_t}^{[d]} \sim N(0, 1)$ s.t. $t \in \{2, 3\}$, which correspond to flat priors on the probability scale. For the gold standard, we used priors based on the literature discussed in section 3. More specifically, we used an informative $\mu_{1}^{[1]} \sim N(0.75, 0.40)$ prior, which corresponds to a 95% prior interval of $(0.49, 0.94)$ for the sensitivity, and $\mu_{1}^{[0]} \sim N(-1.70, 0.40)$ which corresponds to a 95% prior interval of $(0.82, 0.99)$ for the specificity. For conditional dependence models, we used the partial pooling model on the within-study correlations (see equation 17), with prior model $\beta \sim \text{Beta}(2, 2)$, $\Omega_{G}^{[d]} \sim \text{LKJcorr}(4)$ and $\Omega_{s}^{[d]} \sim \text{LKJcorr}(4)$. In sections 4.1 and 4.2 below, we will denote summary estimates with $X \ [Y, Z]$, where $X$ is the posterior median and $[Y, Z]$ is the 95% posterior interval.

### 4.1 The pitfalls of a priori dichotomisation in the presence of an imperfect gold standard

![Figure 1: Posterior medians and 95% posterior intervals for models dichotomising the Well’s score.](image)

Note: CD = Conditional Dependence; CI = Conditional Dependence
When assuming conditional independence between all three tests, we see that (figure 1) some of the estimates of the accuracy of the other two tests change substantially depending on whether we dichotomise the Wells score as low+moderate vs high, or as low vs moderate+high. For the former dichotomisation, the sensitivity of ultrasound was estimated as 0.80 [0.70, 0.88] whereas for the latter it was 0.69 [0.56, 0.82]. The specificity of ultrasound and the sensitivity of the D-Dimer were similar between both dichotomisations. However, there was a notable difference in the specificities of the D-Dimer test, where we obtained specificities of 0.69 [0.57, 0.78] and 0.76 [0.65, 0.85] for the low+moderate vs high and low vs moderate+high dichotomisations, respectively.

The differences in the results were similar when modelling conditional dependence between the three tests (see figure 1). For the low+moderate vs high dichotomisation, for the ultrasound sensitivity we obtained 0.83 [0.67, 0.92] and for the low vs moderate + high dichotomisation 0.74 [0.57, 0.89]. For the D-Dimer specificities, we obtained 0.67 [0.54, 0.78] and 0.71 [0.58, 0.83] for the low+moderate vs high and low vs moderate+high dichotomisations, respectively. As with conditional independence, the specificity of the ultrasound and the sensitivity of the D-Dimer were similar between the two dichotomisations. We can also see the estimates of disease prevalence increase for most studies for the low vs moderate + high dichotomisation relative to the low + moderate vs high dichotomisation, for both conditional independence (left panel of figure 2) and dependence models (right panel of figure 2).

Overall, regardless of whether we assume conditional independence or dependence, some of the accuracy estimates change notably depending on how we dichotomise the Wells score. This is not surprising, since imperfect gold standard models based on latent class analysis utilise the full
distribution of test responses from all tests to estimate accuracy and disease prevalence. This simple example demonstrates the importance of modelling all the available data for ordinal non-dichotomous tests, such as the Wells score, in the presence of an imperfect gold standard, as opposed to simply conducting multiple stratified analyses at each threshold of the ordinal test using simpler methods. This observation serves to motivate the implementation of ordinal regression into the models to appropriately model the ordinal nature of the Wells score.

4.2 Modelling the Wells score as an ordinal test

Now we fit the models without dichotomising the Wells score, by simultaneously modelling all three categories. For these models, for the Wells test we used weakly informative priors of $\mu_3 \sim N(0,1)$ for the location parameters. We used the partial pooling model on the Wells score threshold parameters (see equation 16). For the Dirichlet population parameters, we used a weakly informative prior $\kappa^d \sim N_{\geq 0}(0,50)$. This allows considerable asymmetry in the Dirichlet population vector $\alpha_k$, as can be seen from the prior predictive check (see figure 1 in appendix C). The rest of the priors were the same as those discussed in section 4.1. We fit the following models,

M1: Model assuming that ultrasound is a perfect gold standard and conditional independence between all three tests.
M2: Model assuming that ultrasound is a perfect gold standard, conditional dependence between the Well’s score and D-Dimer, and conditional independence between ultrasound and D-Dimer and between ultrasound and the Wells score.
M3: Model assuming ultrasound to be an imperfect gold standard and conditional independence between all three tests.
M4: Model assuming ultrasound to be an imperfect gold standard and conditional dependence between all three tests.
Figure 3: Posterior medians and 95% posterior intervals for summary sensitivities and specificities, for models 1 - 4. Note: The Wells score summary estimates are dichotomised as low vs moderate + high. CD = Conditional Dependence; CI = Conditional Dependence; GS= Gold Standard.

Figure 4: Posterior medians and 95% posterior intervals for the Well’s score stratum, for models 1 - 4. Note: CD = Conditional Dependence; CI = Conditional Dependence; GS= Gold Standard.
The results for the summary sensitivity and specificity estimates for the four models are shown in figure 3 and the results for each of the Wells score strata are shown in figure 4. The estimates for the two models assuming a perfect gold standard (M1 and M2) are within 2% of those obtained from Novielli et al. [18]. The similarity of the results is not surprising, since despite using different models and different link functions (logit vs approximate probit), the models make similar assumptions - assuming ultrasound is perfect and conditional dependence between the D-Dimer and the Wells score. Similarly to Novielli et al. [18], when assuming a perfect gold standard we found notable bias in the summary joint specificity estimates for the Wells & D-Dimer BTN testing strategy when assuming conditional independence (8% underestimate; 33 [25, 41] and 41 [32, 50] for M1 and M2, respectively) and for the BTN testing strategy specificity (9% overestimate; 74 [65, 82] and 83 [76, 88] for M1 and M2, respectively).

When modelling the imperfect gold standard, the results suggest that assuming conditional independence (M3) would result in some bias in the sensitivity of the Wells test (4% overestimate; 88 [81, 93] and 84 [74, 92] for M3 and M4, respectively), and the Wells & D-Dimer BTN testing strategy (5% overestimate; 89 [83, 94] and 84 [75, 92] for M3 and M4, respectively). The other differences between M3 and M4 were 3% or less (see figure 3). When comparing the two conditional dependence models (M2 and M4), we found 6% underestimation in the specificity of the Wells when assuming a perfect gold standard (52 [42, 63] and 58 [44, 72] for M2 and M4, respectively), 9% underestimation in the specificity of the D-Dimer (63 [51, 73] and 72 [59, 83] for M2 and M4, respectively). For the joint test accuracy summaries, we found 5% underestimation in the specificity of the Wells & D-Dimer BTP testing strategy (41 [32, 50] and 46 [34, 58] for M2 and M4, respectively) and a 10% difference in the specificity of the Wells & D-Dimer BTN testing strategy (74 [65, 82] and 84 [75, 92] for M2 and M4, respectively).

The summary receiver operating characteristic plot for M4 is shown in figure 5. The prediction intervals suggest that there is substantial between-study heterogeneity for the sensitivity and specificity for most estimates. However, we found relatively narrow prediction intervals for the specificity of ultrasound (the gold standard), which is not surprising since it reliably has near-perfect specificity, as well as the Wells and D-Dimer BTP sensitivity (since this combined approach has near-perfect
sensitivity), so we can be more confident in generalising our inferences for these very high estimates.

The LOO-CV results for all of the models are shown in table 2. For this case study, the conditional independence model assuming a perfect gold standard (M1) gave a notably poorer fit than the other models. Modelling the dependency between the D-Dimer and Wells tests (M2) improved the fit (LOO-IC = 16038.6 and 15819.0 in M1 and M2, respectively). Out of the two models not assuming a perfect gold standard, the model assuming conditional independence between tests (M3) gave a worse fit than the model which accounted for conditional dependence (M4) (difference in ELPD = -31.4, se = 6.4). The two conditional dependence models (M2 and M4) were the two best fitting models, with the model not assuming ultrasound to be a perfect test and accounting for the conditional dependence between tests giving the best fit out of all four models (difference in ELPD between M2 and M4 = -20.8, se = 6.2). The posterior predictive checks for the best fitting model, M4, are shown in figure 6 (correlation residual plot) and appendix C figure 2 (2x2 table count residual plot). Both plots suggest that the model fits the data well.

Table 2: Leave-One-Out Cross Validation (LOO-CV) for comparison of model fit for case study 1 dataset

| Model                  | LOO-IC   | $ELPD_{M4} - ELPD_{Mi}$ | $\text{se}(ELPD_{M4} - ELPD_{Mi})$ |
|------------------------|----------|--------------------------|-------------------------------------|
| 4 (Imperfect ultrasound + CD) | 15,777.4 | 0                        | 0                                   |
| 2 (Perfect ultrasound + CD)  | 15,819.0 | -20.8                    | 6.2                                 |
| 3 (Imperfect ultrasound + CI) | 15,840.1 | -31.4                    | 6.4                                 |
| 1 (Perfect ultrasound + CI)   | 16,038.6 | -130.6                   | 15.4                                |

1 Models are ordered from best to worst fitting
2 LOO-IC = Leave-One-Out Information Criterion; note that LOO-IC is on the deviance scale
3 ELPD = Estimated Log pointwise Predictive density for a new Dataset
4 $Mi$ denotes the $i$th model
CI = Conditional Independence; CD = Conditional Dependence

Figure 6: Posterior predictive check for model 4; correlation residual plot
5 Discussion

5.1 Summary

This paper addressed a novel problem - the ability to carry out meta-analysis of tests when there is no perfect gold standard and there are both ordinal and dichotomous test(s) under evaluation. We did this by developing a hierarchical, latent class multivariate probit model. The model can also account for conditional dependence between tests, and estimate summary joint test accuracy parameters whilst modelling conditional dependence.

In the case study (see section 4), we demonstrated why it is not ideal to treat ordinal tests as dichotomous when modelling an imperfect gold standard (see section 4.1). When assuming a perfect gold standard, we obtained approximately the same summary estimates as the model from Novielli et al. However, when modelling the imperfect gold standard and conditional dependence, we found notable imperfect standard bias for the specificity estimates for the D-Dimer and the Wells score, particularly for the joint specificity of the Wells and D-Dimer BTN testing strategy (see section 4.2). The analysis was limited due to between-study heterogeneity for most summary measures. In Novielli et al., studies had a mixture of distal and proximal DVT patients. However, there was insufficient data reported in primary studies to use a meta-regression covariate for proportion of patients who have proximal/distal DVT, nor was individual patient data supplied. If such data were available, a more principled analysis could be carried out to exploit the variation in the sensitivity of ultrasound between the two DVT groups.

The methods proposed have wide-ranging applicability, beyond the DVT case study shown in this paper. For example, a questionnaire for alcoholism, the CAGE (the name of which is an acronym of its 4 questions) is used as a screening tool to detect individuals who may be suffering from alcoholism. It is a 4-category ordinal test ("adequate", "good", "excellent", "too good"). Aetgeerts et al. performed a meta-analysis of this test, which was later re-analysed by Hamza et al. using a model which generalises the standard 'bivariate' model to multiple thresholds, as mentioned in the introduction. However, this model assumes that the gold standards used in each study - imperfect diagnostic interviews based on various iterations of the DSM criteria - are perfect, and hence also identical in each study. Furthermore, it precludes estimation of accuracy at each threshold, only yielding a summary ROC curve. Our proposed method could be used to model the imperfect gold standards for this data, as well as model the differences between gold standards (e.g., by using a meta-regression covariate for test type) to more appropriately estimate the accuracy of the CAGE. It could also be used to obtain accuracy estimates at each of the three thresholds of the CAGE, as opposed to only a summary ROC curve obtained from the model of Hamza et al.

5.2 Advantages over other models

The models proposed in this paper have several advantages compared to previously published models. Previous meta-analytic models based on probit regression (Sadatsafavi et al.) are based on extending the latent trait model proposed by Qu et al. This model can only model dichotomous data and assumes that the within-study correlations are fixed across studies. Furthermore, the model proposed in this paper can be used to specify more general correlation structures (e.g., setting certain correlations to zero) whereas latent trait models cannot. The most widely used approaches to model test accuracy data without a gold standard utilise BLCMs, which use aggregated data. BLCMs have been applied in primary studies evaluating at least two dichotomous tests, and more recently to meta-analysis and network-meta analysis. BLCMs are computationally inexpensive and are therefore fast using standard 'off the shelf', user-friendly probabilistic modelling software such as Stan. They can also be extended to model the conditional dependence (i.e. the conditional within-study correlations) between the gold standards and the index tests under evaluation.

A limitation of BLCMs is that they do not generalise to ordinal tests unless one assumes conditional
independence between tests, requiring the user to dichotomise the data a priori if they wish to model conditional dependence. One obvious benefit to modelling the ordinal tests without dichotomising is when studies analyse tests which have intermediate results, in which case being able to model the thresholds allows us to obtain less biased estimates since we can take these intermediate results into account\[14\]. In general, it is particularly important to not dichotomise the data when we do not have a gold standard, since models which do not assume a gold standard use the underlying test response patterns to estimate the parameters of interest, therefore modelling all the test categories without dichotomising allows us to model the data in its unaltered form. Hence, we may obtain different results for test accuracy estimates (besides the ordinal test we are dichotomising) as well as the disease prevalence’s when dichotomising the data a priori, depending on which threshold we dichotomise the data at, as shown in our first case study in section \[4.1\].

Meta-analytic methods utilising BLCM likelihoods\[5,6,7\] model the conditional dependence between tests by estimating study-specific covariance terms in each study. It is not straightforward to extend these models to estimate summary correlation parameters, since the study-specific covariance parameters have bounds which are determined by the sensitivity and specificity parameters in each study\[49,50\]. Attempting to extend these models to have a partial pooling model would mean that the summary correlation parameters would need to respect these multidimensional constraints, resulting in a questionable interpretation of any summary correlation parameters obtained, as these summary parameters would not necessarily respect these multidimensional constraints. This prohibits the calculation of summary joint test accuracy parameters. The multivariate probit model presented in this paper uses the polychoric correlations which do not have such multidimensional constraints. Hence, we can use this model to obtain summary within-study correlation parameters, as discussed in section \[2.2\].

5.3 Limitations and future work

As with all imperfect gold standard models based on latent class analysis, full cross-classification tables - that is, the full distribution of test results - are required for each study. This data is often not readily available and would hence need to be requested, although it is typically far easier to obtain than IPD, as it does not contain any patient-specific covariates. In our analysis in section \[4\] we did not perform sensitivity analyses to assess the influence of the prior distributions on the posterior estimates. However, it is important to note that we used the available subject-matter knowledge, as discussed in section \[3\] to construct appropriate priors for the accuracy of ultrasound (the gold standard), and weakly informative priors for the other parameters. Using more diffuse priors (i.e. improper priors - sometimes incorrectly referred to as ‘non-informative’) would be questionable. In fact, attempts to do so yielded diagnostic errors, as Stan is more sensitive at detecting non-identifiable in the posterior distributions and inappropriate specification of prior distributions compared to other ‘off-the-shelf’ software. Furthermore, the long run time of the models limited exploration of sensitivity analyses.

A limitation of this work is that the results in section \[4\] are based solely on empirical data, where the true values of the accuracy of each of the three tests is unknown. Ideally, a simulation study\[54\] would have been conducted to assess the performance of the method, as well as comparing it to other proposed models. However, it is important to note that, at the time of writing, no other models have been proposed to simultaneously meta-analyse both dichotomous and ordinal tests without assuming a perfect gold standard. Hence, a comparative simulation study may not be particularly useful, as there would be no other appropriate models to compare our proposed model to. Furthermore, a meaningful simulation study would be difficult to carry out due to the long run times. Once more models are proposed in the literature and more work is done for deriving faster algorithms, a simulation study to assess the general performance of the model in comparison to other approaches would be important future work.
For the case study used in this paper, all individuals in all studies had the same tests performed on them. However, it is straightforward to extend the model to the case where some studies analyse a subset of the total number of tests (i.e. there exists at least one study, \( s \in \{1, \ldots, S\} \) s.t. \( T_s < T \), where \( T_s \) is the number of tests in study \( s \)) to also be included in the analysis if these are available, using direct comparisons only. This could be further extended to allow indirect comparisons; for example, by assuming tests are missing at random (MAR)\(^55\), and extending the between-study model to an arm-based network-meta analysis model\(^{52,56}\). Another important extension would be to model patient-level covariates (IPD), for studies where this data is obtainable. This would be a somewhat straightforward extension, since the model described in this paper already involves modelling all test results at the individual rather than aggregate level. There has been some work with IPD in meta-analysis of test accuracy whilst assuming a perfect gold standard\(^57\), but not within the context of an imperfect gold standard. Incorporating patient-level covariates would lead to results which are more applicable to clinical practice, and can often more easily be generalised to patients when there is between-study heterogeneity, rather than providing summary estimates which relate only to some "average" patient.

Our proposed model could be extended to synthesize data from ordinal tests with missing thresholds between studies (i.e., when some or all studies only report accuracy at select thresholds), using either a partial pooling model or a complete pooling model on the thresholds, and viewing the thresholds as a missing data problem; either could be achieved by using the included Dirichlet model\(^{20}\) outlined in section \(2.2.1\).

Rather than estimating different sets of thresholds in each latent class and assuming the scales are equal to one, one could instead attempt to fit a model which estimates separate location and scale parameters in each disease class, whilst assuming the threshold parameters are fixed between studies and equal in both latent classes. Such a model would result in a smooth, non-symmetric ROC curve, which may be a reasonable assumption for most tests where the thresholds are known not to interact with the disease status, for example for biomarkers. Any of the aforementioned models would yield summary estimates at each reported threshold. One could also fit a model assuming the same vector of thresholds (which vary between studies) in both populations, and assume that the true positive rate is some location-scale change of the false positive rate, as in Dukic et al\(^58\) and Rutter & Gatsonis\(^3\). This would result in a more parsimonious model with a smooth ROC curve, whilst allowing for possible asymmetry. This modification would require extending the partial pooling induced Dirichlet model (see section \(2.2.1\)) to work with ordinal regression models with varying scales and thresholds between latent classes, which may not be possible. However, implementing such a model without the induced Dirichlet threshold model (see section \(2.2.2\)) would be more straightforward, but obtaining 'average' estimates at each threshold would be problematic due to the multidimensional constraints required, unless we assume the thresholds are fixed between studies. However, it would nonetheless be possible to compute a HSROC curve, in which case such a model would be an extension of previously proposed HSROC models for dichotomous tests without a gold standard\(^7\) and ordinal regression models for the analysis of a single index test whilst with a gold standard\(^58\).

Methods for the meta-analysis of continuous tests for the case when studies report test accuracy at explicit numerical thresholds have also been proposed, assuming a perfect gold standard. More specifically, these models allow one to synthesise data when each study reports accuracy at different (and different numbers of) numerical thresholds\(^{59,60}\) by assuming that the thresholds are constants rather than parameters (e.g., a log transform of the continuous test result), and estimating separate location and scale parameters in each disease class. Meta-analytic models which use latent class ordinal regression likelihoods (e.g. the models proposed in this paper) provide a useful framework for being able to achieve this without assuming a perfect gold standard. It is important to note that, even though such 'missing threshold' modelling extensions would be less biased than conducting stratified analyses, they are still less optimal than carrying out a full analysis where each study reports accuracy at each threshold, particularly in the presence of an imperfect gold standard (see
section 4.1), and should not be seen as a replacement for trying to get hold of more data from study authors. If full continuous data is available for each patient for any of the included studies in the meta-analysis, modelling continuous test data fully as a continuous outcome without any discretizing at all would be optimal. Another model extension would be to allow studies which partial count data for certain test response categories. Overall, the aforementioned modelling extensions would enable the network meta-analysis of dichotomous, ordinal and continuous test accuracy data without assuming a perfect gold standard, including both studies with and without IPD data, as well as tests in which the accuracy is reported at varying thresholds across studies.

An important area for future research would be to construct other models which can be used for the meta-analysis of ordinal tests without assuming a gold standard. In 2004, O’ Brien et al. formulated a Bayesian multivariate logistic distribution. This uses logistic link functions as opposed to probit (or approximate probit) links, which are more numerically stable than probit and may give better fit, depending on the dataset. It would also not require the use of approximate links as we used in this paper, giving greater precision in estimates and slightly better fit. Another type of model would be copula multivariate probit model. In these types of models, the marginal distributions are guassian, however, the joint distribution is not. This allows modelling of non-guassian dependence between outcomes (i.e. test responses). These can be extended to general copula-based multivariate model, where one can freely choose the univariate link function (e.g. logit) rather than using probit. An area for future research would be to formulate diagnostic test accuracy models using these likelihoods and comparing the models to one another. Another approach to modelling conditionally dependent ordinal diagnostic tests without assuming a perfect gold standard is log-linear models. These models have been used for the estimation of tests with intermediate results in a single study, as well as for meta-analysis of dichotomous tests. These models can also account for higher-order correlations, which may be important. However, this requires estimation of additional parameters, so it is likely to introduce identifiability issues. Like the multivariate probit models utilised in this paper, it may be possible to extend these models to meta-analyse multiple, imperfect diagnostic tests with multiple thresholds. Extending the aforementioned models to the meta-analysis of ordinal tests and joint test accuracy (i.e., the application used in this paper) is another area for future research.

The advantage of using ‘off-the-shelf’ probabilistic programming languages such as Stan is that the user only has to specify the likelihood-prior function. This is very convenient, particularly for relatively complex models, since it considerably reduces the effort and time needed to implement a model, as there is no need to derive the underlying algorithm, enabling the researcher to focus more on model development. The proposed models use multivariate probit likelihoods, which offer considerable flexibility over commonly used imperfect gold standard models, which use BLCM likelihoods. However, we found that the models proposed in this paper are considerably less efficient than BLCM models; they took several hours to run using Stan. Although this was not prohibitive for the case study used in this paper, the models will be intractable for larger N. Furthermore, such a long run time limits the exploration of likelihood extensions, fitting models with different prior distributions, sensitivity analyses, and comprehensive simulation studies. The slow sampling is not surprising; this is to be expected with models which augment the observed ordinal data with latent continuous variables and speeding up these models is an active area of research. Vectorisation can yield notable efficiency gains in Stan, however, Stan does not currently support vectorised mixtures. Even if it did, the specific parameterisation we used for the likelihood function which generates truncated multivariate latent normal distributions (see Appendix B) would not be possible to fully vectorise. Some possible solutions for acceptable efficiency, besides trying different parameterisations and different models (e.g. copula-based multivariate regression models), include custom-coded MCMC samplers such as calibrated data augmentation Gibbs sampling (CDA-Gibbs), HMC using Laplace approximations to marginalise out the latent normal variables, & approximate Bayesian methods, such as newer versions of automatic differentiation variational inference (ADVI), nor-
malizing flow,\textsuperscript{68,69,70} and the recently proposed Transport Monte Carlo\textsuperscript{71}. An important area for future research would be to apply the models developed in this paper using one of the more efficient algorithms described above and implement them in an R package. This would make multivariate probit models more suitable for general use for the meta-analysis of diagnostic test accuracy with multiple thresholds and ordinal tests without a gold standard. Furthermore, all of the standard uniform nuisance parameters (see Appendix B) needed for the likelihood need to be saved and stored on disk, since (at the time of writing) Stan does not yet allow local variable declarations with bounds, nor does it yet allow the user to only save a subset of the global parameters. For large meta-analyses (> 100,000 individuals), this will create very large files (> 10 gigabytes). This means that another issue, besides the slow sampling, is the fact that the user will then need to wait several more hours for the files to be written after the model has finished running. This issue may be resolved with future updates to Stan.

Acknowledgements

The authors would like to thank Elpida Vounzoulaki for proofreading the manuscript. The authors would also like to thank various members of the Stan community forums (see https://discourse.mc-stan.org/) including Ben Goodrich, Michael Betancourt, Stephen Martin, Staffan Betnér, Martin Modrák, Niko Huurre, Bob Carpenter and Aki Vehtari and for providing functions which were utilised in the models and for useful discussions.

Funding: The work was carried out whilst EC was funded by a National Institute for Health Research (NIHR) Complex Reviews Support Unit (project number 14/178/29) and by a National Institute for Health Research Systematic Review Fellowship (project number RM-SR-2017-09-023). The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health. The NIHR had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript. This project is funded by the NIHR Applied Research Collaboration East Midlands (ARC EM). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

Data availability statement

Data, R and Stan code to reproduce the results and figures from section 4 is available on Github at https://github.com/CerulloE1996/dta-ma-mvp-1.

References

[1] S. L. Hui and S. D. Walter. “Estimating the Error Rates of Diagnostic Tests”. In: Biometrics (1980). ISSN: 0006341X. DOI: 10.2307/2530508.

[2] Johannes B. Reitsma et al. “Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews”. In: Journal of Clinical Epidemiology (2005). ISSN: 08954356. DOI: 10.1016/j.jclinepi.2005.02.022.

[3] Carolyn M. Rutter and Constantine A. Gatsonis. “A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations”. In: Statistics in Medicine (2001). ISSN: 02776715. DOI: 10.1002/sim.942.

[4] Roger M. Harbord et al. “A unification of models for meta-analysis of diagnostic accuracy studies”. In: Biostatistics (2007). ISSN: 14654644. DOI: 10.1093/biostatistics/kx1004.

[5] Haitao Chu, Sining Chen, and Thomas A. Louis. “Random effects models in a meta-analysis of the accuracy of two diagnostic tests without a gold standard”. In: Journal of the American Statistical Association (2009). ISSN: 01621459. DOI: 10.1198/jasa.2009.0017.
[6] J. Menten, M. Boelaert, and E. Lesaffre. “Bayesian meta-analysis of diagnostic tests allowing for imperfect reference standards”. In: *Statistics in Medicine* (2013). ISSN: 10970258. DOI: 10.1002/sim.5959.

[7] Nandini Dendukuri et al. “Bayesian Meta-Analysis of the Accuracy of a Test for Tuberculous Pleuritis in the Absence of a Gold Standard Reference”. In: *Biometrics* (2012). ISSN: 0006341X. DOI: 10.1111/j.1541-0420.2012.01773.x.

[8] Mohsen Sadatsafavi et al. “A statistical method was used for the meta-analysis of tests for latent TB in the absence of a gold standard, combining random-effect and latent-class methods to estimate test accuracy”. In: *Journal of Clinical Epidemiology* (2010). ISSN: 08954356. DOI: 10.1016/j.jclinepi.2009.04.008.

[9] Jian Kang, Rollin Brant, and William A. Ghali. “Statistical methods for the meta-analysis of diagnostic tests must take into account the use of surrogate standards”. In: *Journal of Clinical Epidemiology* (2013). ISSN: 18785921. DOI: 10.1016/j.jclinepi.2012.12.008.

[10] WH William H. Greene. *Econometric analysis 7th Ed*. 2012. ISBN: 978-0-273-75356-8.

[11] John S. Uebersax. “Probit Latent Class Analysis with Dichotomous or Ordered Category Measures: Conditional Independence/Dependence Models”. In: *Applied Psychological Measurement* 23.4 (1999), pp. 283–297. DOI: 10.1177/01466219922031400.

[12] Andrew Gelman and Jennifer Hill. *Data Analysis Using Regression and Multilevel/Hierarchical Models*. 2006. DOI: 10.1017/cbo9780511790942.

[13] Huiping Xu, Michael A. Black, and Bruce A. Craig. “Evaluating accuracy of diagnostic tests with intermediate results in the absence of a gold standard”. In: *Statistics in Medicine* (2013). ISSN: 02776715. DOI: 10.2307/2290350.

[14] Huiping Xu, Michael A. Black, and Bruce A. Craig. “A probit latent class model with general correlation structures for evaluating accuracy of diagnostic tests”. In: *Biometrics* (2009). ISSN: 0006341X. DOI: 10.1111/j.1541-0420.2008.01194.x.

[15] Ben Goodrich. *A better parameterization of the multivariate probit model*. https://github.com/stan-dev/example-models/commit/d6f0282d64382b627d9d6c5f67f9a851bda3f537. 2016.

[16] Michael Betancourt. *Hierarchical Modeling*. https://github.com/betanalpha/knitr_case_studies/tree/master/hierarchical_modeling. commit 27c1d260e9ceca710465dc3b02f959f59b729ca43. 2020.
[23] Daniel Lewandowski, Dorota Kurowicka, and Harry Joe. “Generating random correlation matrices based on vines and extended onion method”. In: Journal of Multivariate Analysis (2009). issn: 0047-259X. doi: 10.1016/j.jmva.2009.04.008

[24] Aki Vehtari, Andrew Gelman, and Jonah Gabry. “Practical Bayesian model evaluation using leave-one-out cross-validation and WAIC”. In: Statistics and Computing (2017). issn: 1573-1375. doi: 10.1007/s11222-016-9696-4, arXiv: 1507.04544

[25] Aki Vehtari et al. loo: Efficient leave-one-out cross-validation and WAIC for Bayesian models. R package version 2.4.1. 2020. url: https://mc-stan.org/loo/.

[26] Martyn Plummer. “Penalized loss functions for Bayesian model comparison”. In: Biostatistics (2008). issn: 1465-4644. doi: 10.1093/biostatistics/kxm049

[27] Bob Carpenter et al. Stan: A probabilistic programming language. In: Journal of Statistical Software (2017). issn: 1548-7660. doi: 10.18637/jss.v076.i01

[28] Martyn Plummer. “Penalized loss functions for Bayesian model comparison”. In: Biostatistics (2008). issn: 1465-4644. doi: 10.1093/biostatistics/kxm049

[29] Bob Carpenter et al. “Stan: A probabilistic programming language”. In: Journal of Statistical Software (2017). issn: 1548-7660. doi: 10.18637/jss.v076.i01

[30] Vassilis A. Hajivassiliou and Paul A. Ruud. Chapter 40 Classical estimation methods for LDV models using simulation. 1994. doi: 10.1016/S1573-4412(05)80009-1

[33] Stan Modeling Language Users Guide and Reference Manual. https://mc-stan.org/docs/2_25/reference-manual/ 2020.

[36] C. Kearon et al. “Noninvasive diagnosis of deep venous thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative”. In: Annals of Internal Medicine 128.8 (Apr. 15, 1998), pp. 663–677. issn: 0003-4819. doi: 10.7326/0003-4819-128-8-199804150-00011

[37] Seung-Kee Min et al. “Diagnosis and Treatment of Lower Extremity Deep Vein Thrombosis: Korean Practice Guidelines”. In: Vascular Specialist International 32.3 (Sept. 2016), pp. 77–104. issn: 2288-7970. doi: 10.5758/vsi.2016.32.3.77

[38] Vincent B. Ho et al. “ACR Appropriateness Criteria® on suspected lower extremity deep vein thrombosis”. In: Journal of the American College of Radiology: JACR 8.6 (June 2011), pp. 383–387. issn: 1558-349X. doi: 10.1016/j.jacr.2011.02.016

[39] M. Di Nisio et al. “Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: A systematic review”. In: Journal of Thrombosis and Haemostasis (2010). issn: 15387933. doi: 10.1111/j.1538-7836.2010.03771.x
[61] Sean M. O’Brien and David B. Dunson. “Bayesian Multivariate Logistic Regression”. In: Biometrics 60.3 (2004), pp. 739–746. DOI: https://doi.org/10.1111/j.0006-341X.2004.00224.x

[62] Rainer Winkelmann. “COPULA BIVARIATE PROBIT MODELS: WITH AN APPLICATION TO MEDICAL EXPENDITURES”. In: Health Economics 21.12 (2012), pp. 1444–1455. DOI: https://doi.org/10.1002/hec.1801

[63] Michael Eichler, Hans Manner, and Dennis Turk. Dynamic copula based multivariate discrete choice models with applications. https://wisostat.uni-koeln.de/sites/statistik/user_upload/DCMDC.pdf, 2017.

[64] Leo L. Duan, James E. Johndrow, and David B. Dunson. “Scaling up Data Augmentation MCMC via Calibration”. In: J. Mach. Learn. Res. 19.1 (Jan. 2018), 2575–2608. ISSN: 1532-4435.

[65] Charles C. Margossian et al. Hamiltonian Monte Carlo using an adjoint-differentiated Laplace approximation: Bayesian inference for latent Gaussian models and beyond. 2020. arXiv: 2004.12550 [stat.CO]

[66] Akash Kumar Dhaka et al. Robust, Accurate Stochastic Optimization for Variational Inference. 2020. arXiv: 2009.00666 [cs.LG]

[67] David M. Blei, Alp Kucukelbir, and Jon D. McAuliffe. “Variational Inference: A Review for Statisticians”. In: Journal of the American Statistical Association 112.518 (2017), pp. 859–877. DOI: 10.1080/01621459.2017.1285773

[68] Laurent Dinh, Jascha Sohl-Dickstein, and Samy Bengio. Density estimation using Real NVP. 2017. arXiv: 1605.08803 [cs.LG]

[69] George Papamakarios, Theo Pavlakou, and Iain Murray. Masked Autoregressive Flow for Density Estimation. 2018. arXiv: 1705.07057 [stat.ML]

[70] Danilo Jimenez Rezende and Shakir Mohamed. Variational Inference with Normalizing Flows. 2016. arXiv: 1505.05770 [stat.ML]

[71] Leo L. Duan. Transport Monte Carlo. 2020. arXiv: 1907.10448 [stat.CO]
Appendix A  Induced Dirichlet threshold model (Betancourt, 2019)

The induced Dirichlet model allows us to move away from the abstract latent space in which the thresholds are defined, and applies a Dirichlet model directly to the ordinal probabilities. We need to find an injective (i.e., one-to-one) function which maps the latent cut point parameters in each study \( \{C_1^{[d]}, \ldots, C_{K-1}^{[d]}\} \) to the ordinal probabilities \( \{P_1^{[d]}, \ldots, P_{K-1}^{[d]}\} \). Let \( S^{[d]} = \sum_{k=1}^{K} P_k^{[d]} = 1 \) and let \( g : \mathbb{R} \rightarrow (0,1) \) be a differentiable, monotonically increasing latent probability density function, with inverse \( g^{-1} \). We condition on an arbitrary anchor point, \( \phi \), and then define a map \( \varphi^{[d]}_{\phi} : \{C_1^{[d]}, \ldots, C_{K-1}^{[d]}\} \rightarrow \{P_1^{[d]}, \ldots, P_{K-1}^{[d]}\} \). The induced ordinal probabilities for each of the latent classes are given by,

\[
\varphi^{[d]}_{\phi}(C_{k,s,t}^{[d]}, C_{k-1,s,t}^{[d]}) = g(C_{k,s,t}^{[d]} - \phi) - g(C_{k-1,s,t}^{[d]} - \phi) = P_{k,s,t}^{[d]}, \quad S^{[d]} = 1
\]  

(28)

with \( \varphi^{[d]}_{\phi}^{-1} \) given by,

\[
\varphi^{[d]}_{\phi}^{-1}(P_{k,s,t}^{[d]}) = g^{-1}(P_{k,s,t}^{[d]} + \phi) = C_{k,s,t}^{[d]}
\]

\[
\varphi^{[d]}_{\phi}^{-1}(P_{k,s,t}^{[d]} | C_{k-1,s,t}^{[d]}) = \phi + g^{-1}\left(P_{k,s,t}^{[d]} + g[C_{k-1,s,t}^{[d]} - \phi]\right) = C_{k,s,t}^{[d]}
\]

(29)

The probability density function for the induced Dirichlet model is given by,

\[
\text{Induced-Dir} \left( C_{s,t}^{[d]}, \alpha_t^{[d]} | \phi \right) = \text{Dir} \left( P(C_{s,t}^{[d]}, \phi) | C_{s,t}^{[d]} \right) \cdot |J\left(C_{s,t}^{[d]}\right)|, \quad \text{(30)}
\]

Where \( C_{s,t}^{[d]} = \left( C_{1,s,t}^{[d]}, \ldots, C_{K-1,s,t}^{[d]} \right) \), \( \alpha_t^{[d]} = \left( \alpha_{1,t}^{[d]}, \ldots, \alpha_{K,t}^{[d]} \right) \) and \( J\left(C_{s,t}^{[d]}\right) \) is the Jacobian matrix of partial derivatives,

\[
J_{k,1}^{[d]} = \frac{\partial P_{k,s,t}^{[d]}}{\partial S^{[d]}} = 1, \quad J_{k,k}^{[d]} = \frac{\partial P_{k,s,t}^{[d]}}{\partial C_{k-1}^{[d]}} = -g'\left(C_{k-1}^{[d]}\right), \quad J_{k-1,k}^{[d]} = \frac{\partial P_{k-1,s,t}^{[d]}}{\partial C_{k-1}^{[d]}} = g'(C_{k-1}^{[d]}),
\]

and zeros everywhere else. We can use the induced Dirichlet model to directly specify a partial pooling model for the Dirichlet parameters \( \alpha_t^{[d]} \), so that,

\[
\pi \left( C_{s,t}^{[d]}, \alpha_t^{[d]} \right) = \text{induced-Dir} \left( C_{s,t}^{[d]} | \alpha_t^{[d]} \right) \cdot \pi \left( \alpha_t^{[d]} \right)
\]

(31)

Where \( C_{s,t}^{[d]} = \left( C_{1,s,t}, \ldots, C_{K-1,s,t} \right) \), and \( \alpha_t^{[d]} = \left( \alpha_{1,t}, \ldots, \alpha_{K,t} \right) \).

In this paper, we use a normal probability density function so that \( g(\cdot) = \Phi(\cdot) \) and define the arbitrary anchor point at zero, \( \phi = 0 \). For prior modelling on the Dirichlet population parameters, we can use a half normal prior \( \pi(\alpha_t^{[d]} = N_{\geq 0}(a^{[d]}, b^{[d]}) \) s.t. \( a^{[d]}, b^{[d]} \in \mathbb{R}_{K_i}^{+} \) or exponential prior, \( \pi(\alpha_t^{[d]} = \text{exponential}(a^{[d]} \) s.t. \( a^{[d]} \in \mathbb{R}_{K_i}^{+} \).

Appendix B  Generating the truncated multivariate normal densities (Geweke, Hajivassiliou and Keane [1994] algorithm and Goodrich [2017])

Implementing the likelihood for each study requires integrating over truncated multivariate normal densities. We used the GHK algorithm to generate the truncated multivariate normal distributions in Stan. This is described in Goodrich 2017, which we summarise below.
We can parametrise the multivariate normal densities to be truncated for each study in terms of its Cholesky factor. We notional simplicity denote \( z = Z_{s,n}, \nu = \nu_s[d] \), and let \( \Psi = \Psi_s[d] \). We can write each multivariate normal distribution, \( z \), as

\[
\begin{align*}
  z = \nu + L \cdot x
\end{align*}
\]

Where \( x \sim N(0,1) \) and \( L \) is the Cholesky factor matrix of \( \Psi = L \cdot L^T \).

We can write this as,

\[
\begin{bmatrix}
  x_1 \\
  x_k \\
  x_3
\end{bmatrix} = \begin{bmatrix}
  \nu_1 \\
  \nu_k \\
  \nu_3
\end{bmatrix} + \begin{bmatrix}
  L_{11} & 0 & 0 \\
  L_{k1} & L_{kk} & 0 \\
  L_{31} & L_{3k} & L_{33}
\end{bmatrix} \begin{bmatrix}
  z_1 \\
  z_k \\
  z_3
\end{bmatrix}
\]

Where \( L_{11} \) and \( L_{33} \) are lower triangular submatrices, \( L_{31} \) is a submatrix, \( L_{kk} \in \mathbb{R}_+ \) is a scalar, \( L_{k1} \in \mathbb{R}^{1 \times (k-1)} \) contains the elements of \( L \) to the left of \( L_{kk} \), and \( L_{3k} \in \mathbb{R}^{k-1} \) contains the elements below \( L_{kk} \).

Let \( x(u) = \Phi^{-1}(u) \) where \( u \sim \text{Uniform}(0,1) \), i.e. \( x(u) \) can be generated by the inverse CDF method, so that we can write \( z \) as

\[
\begin{align*}
  z = \nu + L \cdot x(u)
\end{align*}
\]

Suppose that we have a bound, \( B_1 \), on the first element of \( z_1 = \nu_1 + L_{11} \cdot x(u_1) \). Then, the constraint binds at \( x'(u_1) = \frac{B_1 - \nu_1}{L_{11}} \), and \( u^*_1 = \Phi \left( \frac{B_1 - \nu_1}{L_{11}} \right) \). If \( B_1 = \overline{B}_1 \) is an upper bound on \( z_1 \) then \( v_1 = u_1 \cdot u^*_1 \sim \text{Uniform}(0,u^*_1) \) since \( u_1 \sim \text{Uniform}(0,1) \) with \( \pi(v_1) = \frac{1}{v_1} \). If \( B_1 = \underline{B}_1 \) is a lower bound on \( z_1 \) then \( v_1 = u_1^* + (1 - u_1) \cdot x(u_1) \sim \text{Uniform}(u_1^*, u_1) \) with \( \pi(v_1) = \frac{1}{u_1 - u_1^*} \) if we have both an upper and lower bound, then \( v_1 = u_1^* + (\overline{u}_1 - \underline{u}_1) \cdot x(u_1) \sim \text{Uniform}(u_1^*, \overline{u}_1) \) with \( \pi(v_1) = \frac{1}{\overline{u}_1 - u_1^*} \). Then, given \( u_1 \) we can consider a known bound, \( B_2 \), on the second element \( z_2 = v_2 + L_{21} \cdot x_1 + L_{22} \cdot x(u_2) \) of \( z \). Following the same steps as before, we solve for \( u^*_2 = \Phi \left( \frac{B_2 - (v_2 + L_{21} \cdot x_1)}{L_{22}} \right) \), with \( \pi(v_2) = \frac{1}{u_2} \) if \( B_2 = \overline{B}_2 \), \( \pi(v_2) = \frac{1}{1-u_2} \) if \( B_2 = \underline{B}_2 \), \( \pi(v_2) = \frac{1}{u_2 - \overline{u}_2} \) if we have both an upper and lower bound.

In general, given \( x_1 = \Phi^{-1}(\{u_1, \ldots, u_{k-1}\}) \) we can consider a known bound \( B_k \) on \( z_k = \nu_k + L_{k1} \cdot x_1 + L_{kk} \cdot x_k \) and solve for \( u^*_k = \Phi \left( \frac{B_k - (\nu_k + L_{k1} \cdot x_1)}{L_{kk}} \right) \). Then,

\[
\begin{align*}
  \pi(v_k|u^*_k) = \begin{cases}
    \frac{1}{v_k} & \text{if we have an upper bound} \\
    \frac{1}{1-u_k} & \text{if we have a lower bound} \\
    \frac{1}{u_k - u^*_k} & \text{if we have both an upper and lower bound}
  \end{cases}
\end{align*}
\]

Stan only allows bounds on vectors declared in the parameters block, so we need to declare the \( u_k \) as nuisance parameters, and construct each \( v_k \). Since \( v_k \) is a transformed parameter, we need a Jacobian adjustment, i.e. we need to adjust the log-kernel by the log of the absolute value of the derivative of the transformation function \( v_k \rightarrow u_k \).

\[
\log \left( \frac{dv_k}{du_k} \right) = \begin{cases}
    \log(u_k^*) & \text{if we have an upper bound} \\
    \log(1-u_k^*) & \text{if we have a lower bound} \\
    \log(u_k^* - u_k^*) & \text{if we have both an upper and lower bound}
  \end{cases}
\]

\[27\]
Appendix C  Prior and posterior predictive checks

Figure 1: Prior predictive check for $\kappa^{[d]} \sim N_{\geq 0}(0, 50)$ prior. Note that the count is out of a total of 10,000 simulations
Figure 2: Posterior predictive check for model 4; 2x2 table count residual plot