Joint meta-analysis of two diagnostic tests using bivariate copulas to model within-study dependencies in Health Technology Assessment (HTA) of novel biomarkers in Alzheimer's disease dementia

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Athena L. Sheppard[1,2], Tasos Papanikos[3], Terence J. Quinn[4], Keith R. Abrams[5], Sylwia Bujkiewicz[2], Rhiannon K. Owen[1]

1. Population Data Science, Swansea University Medical School, Swansea University, UK
2. Biostatistics Research Group, Department of Population Health Sciences, University of Leicester, UK
3. GlaxoSmithKline R&D Centre, GlaxoSmithKline, Stevenage, UK
4. School of Cardiovascular & Metabolic Health, University of Glasgow, UK
5. Department of Statistics & Warwick Medical School (WMS), University of Warwick, Coventry, UK

UKRI Medical Research Council

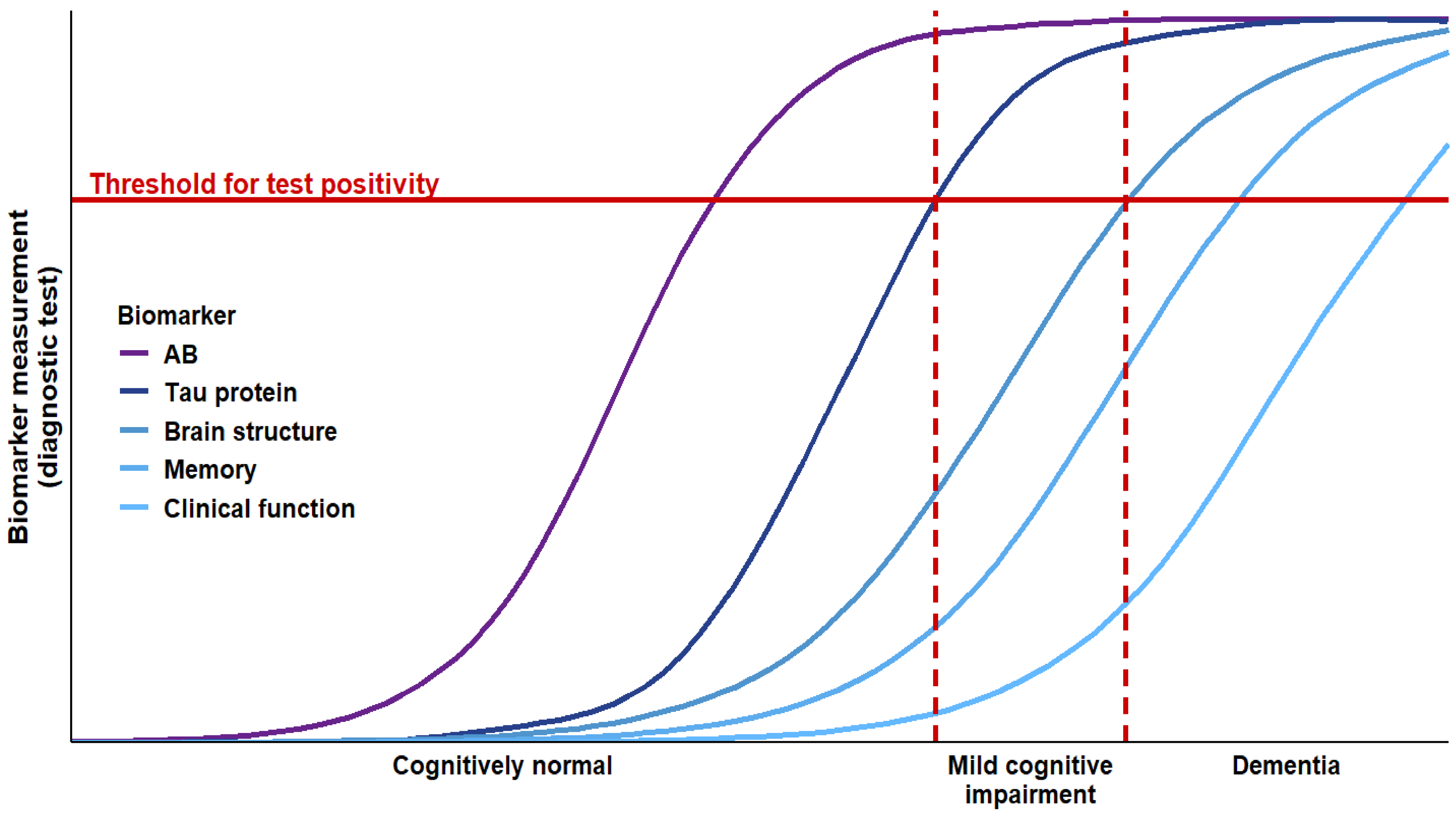
Ymchwil Iechyd a Gofal Cymru / Health and Care Research Wales

HDRUK Health Data Research UK

Background

- Health Technology Assessments (HTAs) considered by the National Institute for Health and Care Excellence (NICE) Diagnostics Assessment Programme often concern the **comparative or combined accuracy of two or more diagnostic tests**.[1] Their estimation requires modelling techniques that account for **within-study correlations** between the tests.
- We describe a novel application of a **meta-analytic model with copulas** [2] to capture within-study dependencies between two tests assessed in the same patients, using **study- or individual-level data** where available.
- The methodology is applied to a motivating example assessing the accuracy of emerging biomarkers in **Alzheimer's disease dementia** (Figure 1).

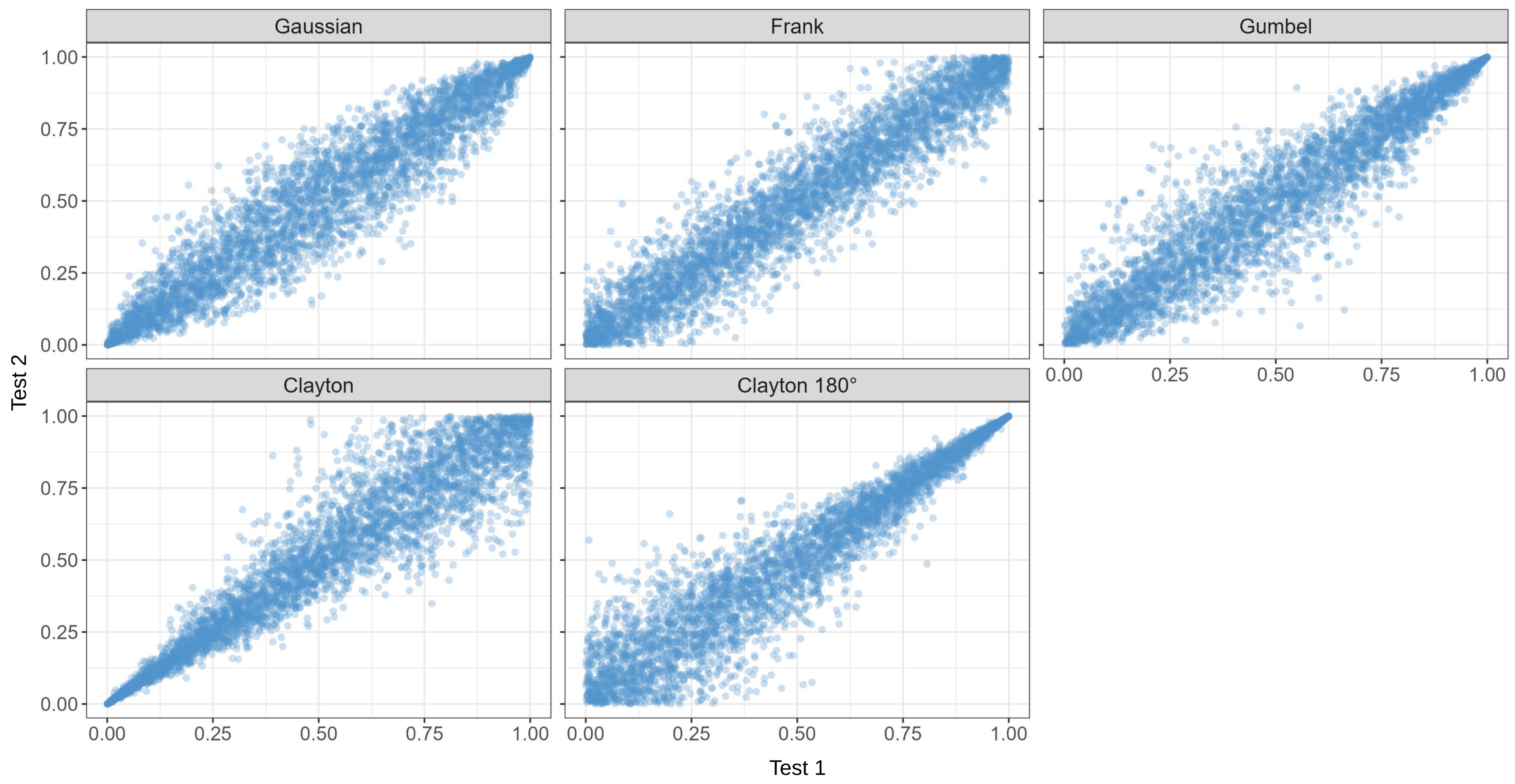
Figure 1: Theoretical progression of different biomarkers over time, adapted from a schematic diagram by Jack et al (2010).[3]



Aim: Develop novel meta-analysis models for jointly synthesising diagnostic accuracy data on two tests for Alzheimer's disease dementia

Methods

Figure 2: Simulated samples from the different types of copulas.

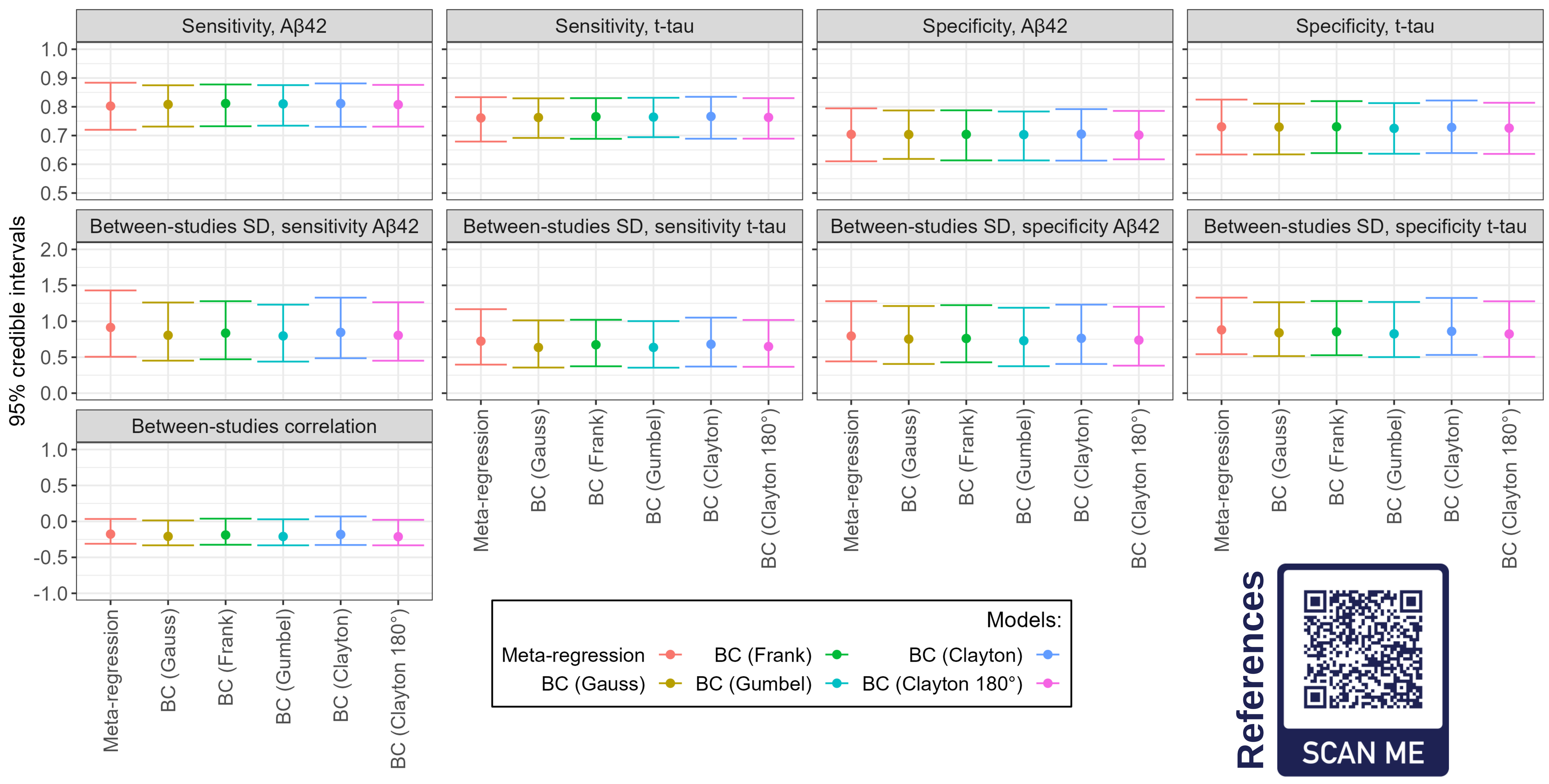


- Novel **Bayesian meta-analysis models** for evaluating the accuracy of two diagnostic tests in the same patients were developed using a motivating example in Alzheimer's disease dementia.
- **Bivariate copulas** were used to **flexibly capture within-study dependencies** between the two tests, relaxing the need for individual participant data from all studies.
- **Five bivariate copula models** capturing different dependence structures were fit to the data: Gaussian, Frank, Gumbel, Clayton and Clayton rotated 180° (Figure 2).
- The models were compared to the **currently recommended meta-regression approach** [4] for modelling two cerebrospinal fluid biomarker (CSF) tests for diagnosing Alzheimer's disease dementia: amyloid-β 42 ($A\beta_{42}$) and total tau (t-tau).
- Model fit was assessed using the widely applicable information criterion (WAIC).[5]

Results

- **CSF $A\beta_{42}$ and t-tau** demonstrated **sensitivities** of 80.9% (95% credible interval: 73.4%, 87.5%) and 76.4% (69.4%, 83.1%), respectively.
- Summary **specificity** was 70.3% (61.3%, 78.4%) and 72.5% (63.7%, 81.3%), respectively.
- The bivariate copula models resulted in a **better fit** compared to the meta-regression model, and **increased precision** in estimates of sensitivity and specificity by as much as a **15% reduction in the width of the 95% credible intervals** (Figure 3).

Figure 3: Posterior medians (solid dots) and 95% CrIs (solid bars) of test accuracy parameters.



Conclusions

- The bivariate copula framework **supports HTA**, enabling test comparisons while accounting for **complex dependence structures** arising between tests.
- Increased precision in sensitivity and specificity estimates aids the evaluation of **clinical and cost-effectiveness of diagnostic tests**, enabling more appropriate decisions regarding the most **efficient use of health resources**.
- This novel methodological development is applicable to a **broad range of disease areas**.

References

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Contact:
@athenalsheppard
athena.sheppard@swansea.ac.uk

Swansea University Prifysgol Abertawe | Medical School Ysgol Feddygaeth