MANCHESTER 1824

The University of Manchester

Multi-Outcome Risk Prediction Modelling: current state-of-play and future research

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Outline

1. Motivation for multivariate clinical prediction
2. Methods for multivariate risk prediction and how they compare with each other
3. Next steps: avenues for future research on this topic

What are Clinical Prediction Models (CPMs)?

About you

Age (25-84): 64

Sex: Male Female

Ethnicity: White or not stated

UK postcode: leave blank if unknown

Postcode:

Clinical information

Smoking status: non-smoker

Diabetes status: type 2

Angina or heart attack in a 1st degree relative < 60?

Chronic kidney disease (stage 3, 4 or 5)?

Atrial fibrillation?

On blood pressure treatment?

Do you have migraines?

Rheumatoid arthritis?

Systemic lupus erythematosus (SLE)?

Severe mental illness?
(this includes schizophrenia, bipolar disorder and moderate/severe depression)

On atypical antipsychotic medication?

Are you on regular steroid tablets?

A diagnosis of or treatment for erectile disfunction?

Leave blank if unknown

Cholesterol/HDL ratio:

Systolic blood pressure (mmHg):

Standard deviation of at least two most recent systolic blood pressure readings (mmHg):

Body mass index

Height (cm):

Weight (kg):

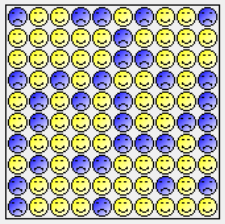
Calculate risk

Your results

Your risk of having a heart attack or stroke within the next 10 years is:

34.3%

In other words, in a crowd of 100 people with the same risk factors as you, 34 are likely to have a heart attack or stroke within the next 10 years.



Risk of a heart attack or stroke

Your score has been calculated using estimated data, as some information was left blank.

Your body mass index was estimated as 29.5 kg/m^2.

How does your 10-year score compare?

Your score

Your 10-year QRISK®3 score	34.3%
The score of a healthy person with the same age, sex, and ethnicity*	11.2%
Relative risk**	3.1
Your QRISK®3 Healthy Heart Age***	82

* This is the score of a healthy person of your age, sex and ethnic group, i.e. with no adverse clinical indicators and a cholesterol ratio of 4.0, a stable systolic blood pressure of 125, and BMI of 25.

** Your relative risk is your risk divided by the healthy person's risk.

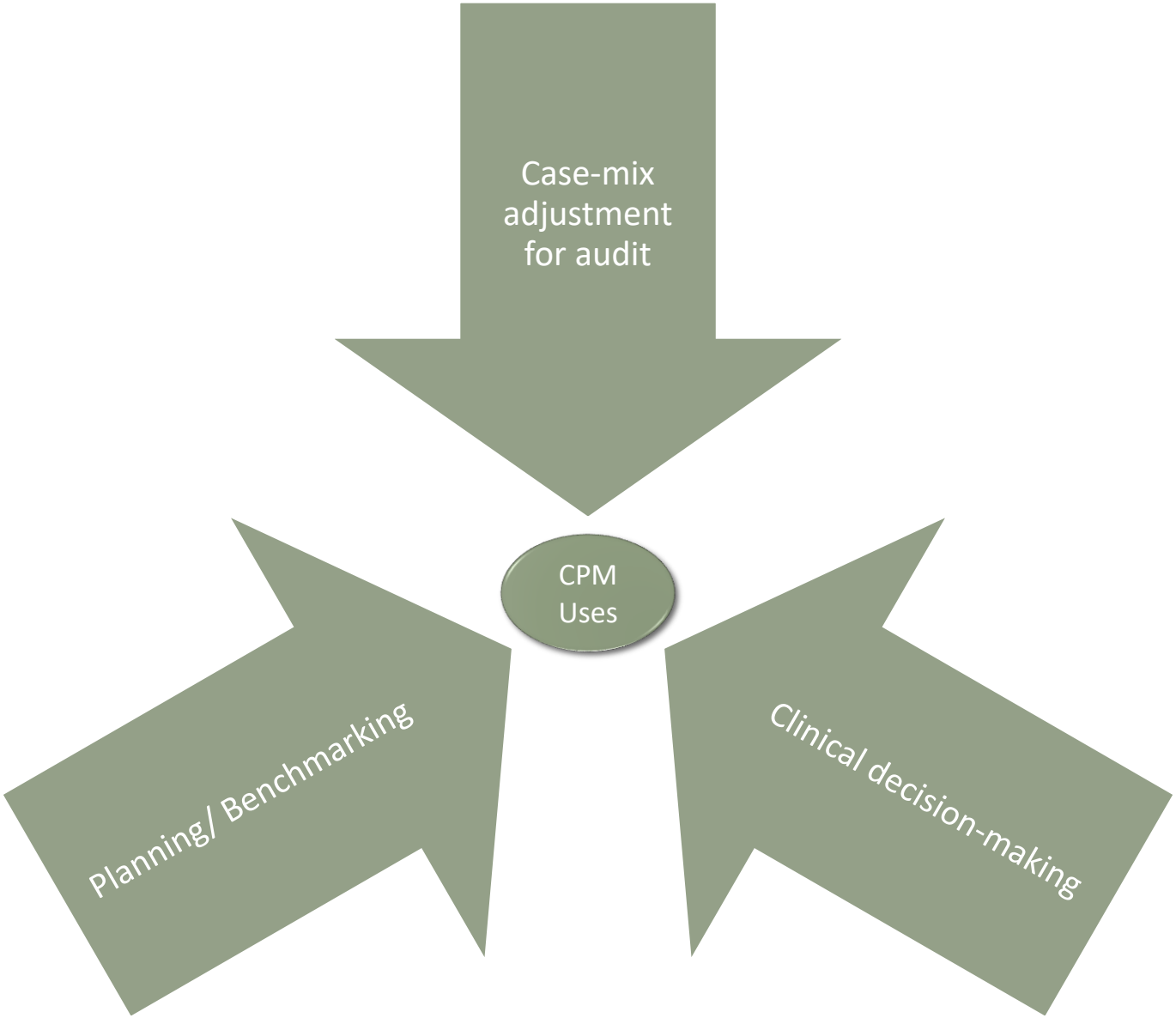
*** Your QRISK®3 Healthy Heart Age is the age at which a healthy person of your sex and ethnicity has your 10-year QRISK®3 score.

Screenshot from: https://qrisk.org/three/

Types of CPMs

- Diagnostic
  Predicts current presence of a disease or condition of interest, based on observed characteristics

- Prognostic
  Predicts the likelihood of a future clinical event, disease recurrence or progression, based on observed characteristics


Case-mix adjustment for audit
CPM Uses
Planning/ Benchmarking
Clinical decision-making

Vast numbers of CPM developed across medical domains

Very few make it into clinical practice

When Two (outcomes) are Better than One

Generally, different CPMs are developed in isolation, where each model considers only a single outcome

This is not (usually) how healthcare operates…

When Two (outcomes) are Better than One

Methodology | Open Access | Published: 21 January 2021

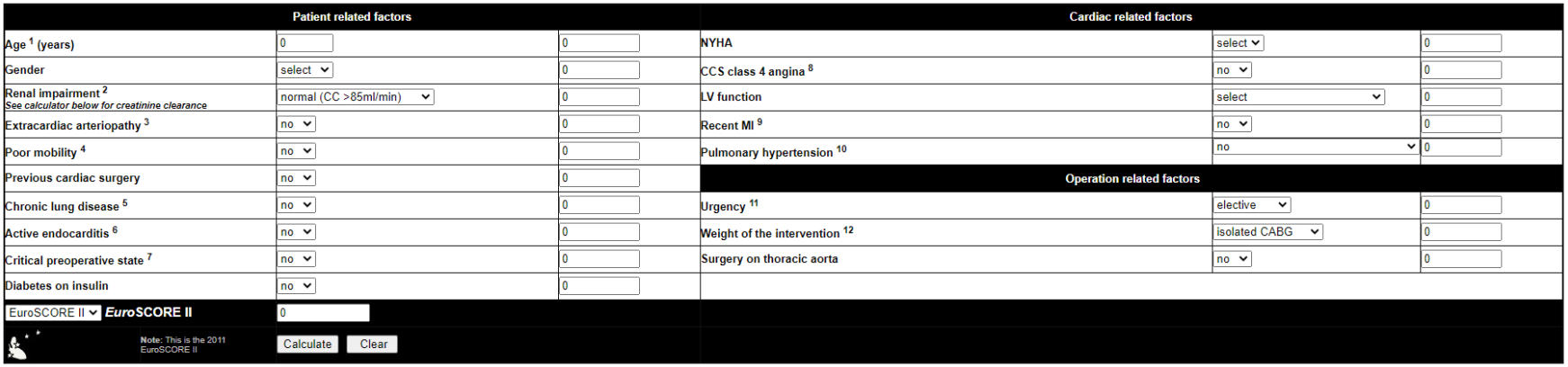
Multivariate prediction of mixed, multilevel, sequential outcomes arising from in vitro fertilisation

Jack Wilkinson, Andy Vail & Stephen A. Roberts

Diagnostic and Prognostic Research **5**, Article number: 2 (2021) | Cite this article

in vitro fertilisation (IVF): primary endpoint is birth, outcomes across each stage of treatment contain additional information and it would be useful to therefore predict stage-specific responses.

When Two (outcomes) are Better than One



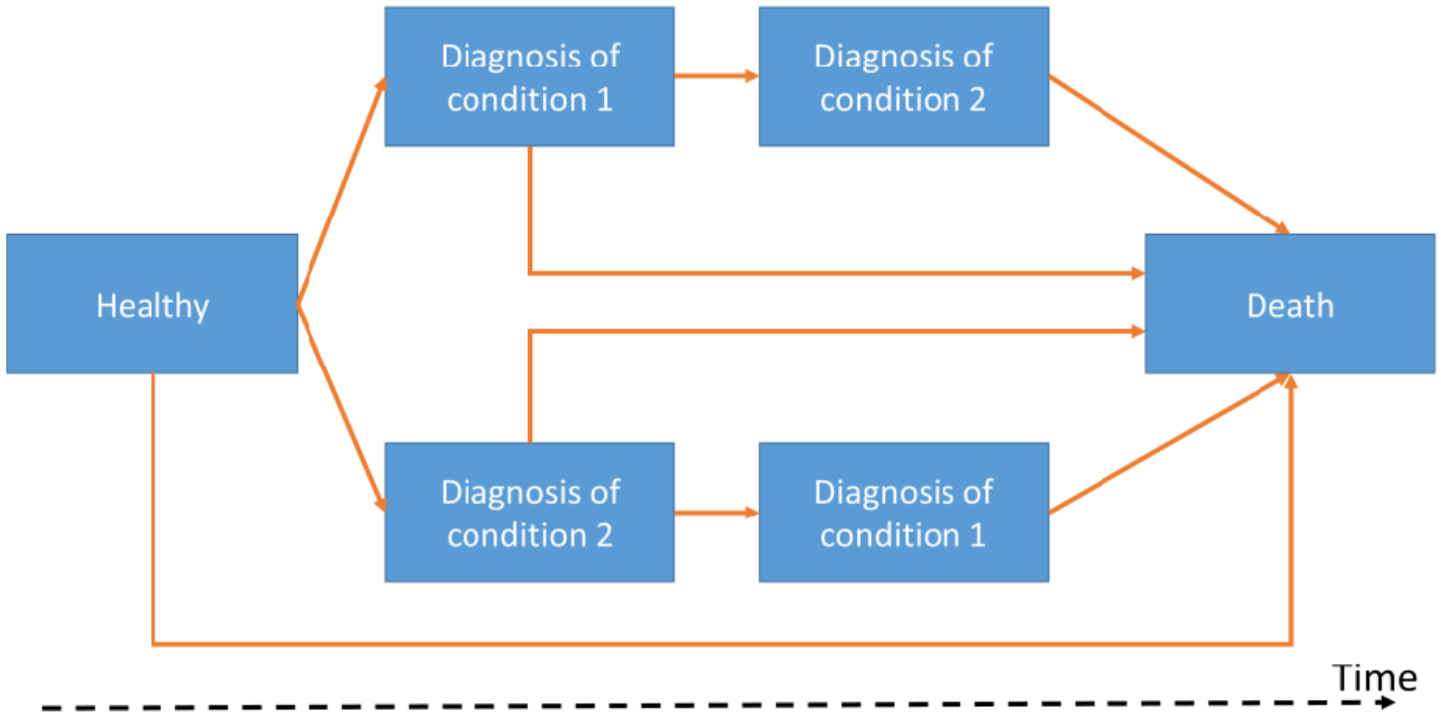
Patient related factors			Cardiac related factors		
Age [1] (years)	0	0	NYHA	select	0
Gender	select	0	CCS class 4 angina [8]	no	0
Renal impairment [2] *See calculator below for creatinine clearance*	normal (CC >85ml/min)	0	LV function	select	0
Extracardiac arteriopathy [3]	no	0	Recent MI [9]	no	0
Poor mobility [4]	no	0	Pulmonary hypertension [10]	no	0
Previous cardiac surgery	no	0	**Operation related factors**		
Chronic lung disease [5]	no	0	Urgency [11]	elective	0
Active endocarditis [6]	no	0	Weight of the intervention [12]	isolated CABG	0
Critical preoperative state [7]	no	0	Surgery on thoracic aorta	no	0
Diabetes on insulin	no	0			
EuroSCORE II — *EuroSCORE II*	0				
Note: This is the 2011 EuroSCORE II	Calculate	Clear			

EuroScore predicts 30-day mortality after cardiac surgery

Used to aid decision-making and risk stratification

But, clinical teams consider mortality, morbidity, and quality of life in their decision-making for performing cardiovascular surgery

When Two (outcomes) are Better than One ….Multi-Morbidity



Example

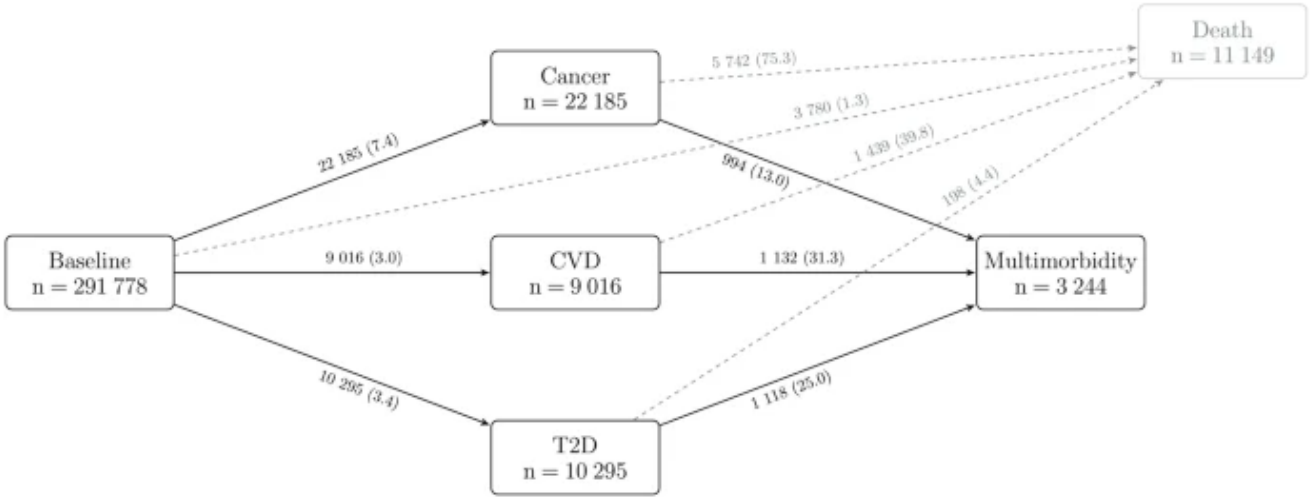
Research article | Open Access | Published: 10 January 2020

Lifestyle factors and risk of multimorbidity of cancer and cardiometabolic diseases: a multinational cohort study

Heinz Freisling ✉, Vivian Viallon, [...] Pietro Ferrari

BMC Medicine **18**, Article number: 5 (2020) | Cite this article

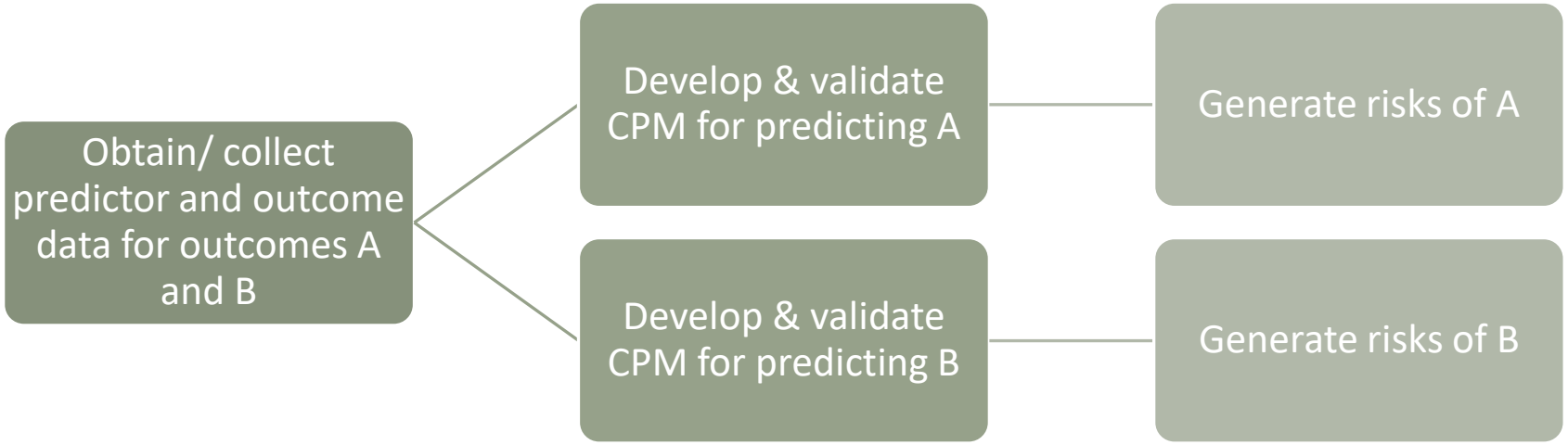
Fig. 1



Transitions from baseline to cancer, CVD, T2D, and subsequent cancer-cardiometabolic multimorbidity. Cancer refers to first malignant tumours at any site excl. non-melanoma skin cancer. Deaths were censored and not modelled as a separate outcome. State-specific number of events is reported in boxes, and transition-specific number of events and incidence rates per 1000 person-years (within brackets) are reported on arrows. *CVD* cardiovascular disease, *T2D* type 2 diabetes

Multi-outcome risk prediction: current approaches

CPM development is often outcome-specific



Can give accurate **marginal risk** estimates (i.e. risk of one outcome, irrespective of the other)

For **joint risk**, we know (statistically) that this is only valid if the outcomes are independent:

$$P(A \cap B) = P(A) \times P(B)$$

If A and B are independent events.

Statistically, multivariate (multi-outcome) modelling is not new…

STATISTICS IN MEDICINE
Statist. Med. 2009; **28**:1753–1773
Published online 8 April 2009 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/sim.3588

Correlated bivariate continuous and binary outcomes: Issues and applications

Armando Teixeira-Pinto[1,2,*,†] and Sharon-Lise T. Normand[2,3]

[1]*Faculty of Medicine, Department of Biostatistics and Medical Informatics, University of Porto, Porto, Portugal*
[2]*Harvard School of Public Health, Department of Biostatistics, Boston, U.S.A.*
[3]*Harvard Medical School, Department of Health Care Policy, Boston, U.S.A.*

Biometrika (1993), **80**, 3, *pp.* 517–26
Printed in Great Britain

Modelling multivariate binary data with alternating logistic regressions

BY VINCENT CAREY, SCOTT L. ZEGER
Department of Biostatistics, Johns Hopkins School of Hygiene and Public Health, 615 N. Wolfe Street, Baltimore, Maryland 21205, U.S.A.

AND PETER DIGGLE
School of Engineering, Computing, and Mathematical Sciences, Lancaster University, Lancaster, U.K.

Research article | Open Access | Published: 07 September 2016

Joint modelling of time-to-event and multivariate longitudinal outcomes: recent developments and issues

Graeme L. Hickey, Pete Philipson, Andrea Jorgensen & Ruwanthi Kolamunnage-Dona

BMC Medical Research Methodology **16**, Article number: 117 (2016) | Cite this article
9753 Accesses | **49** Citations | **7** Altmetric | Metrics

Analysis of multivariate probit models

SIDDHARTHA CHIB, EDWARD GREENBERG

Biometrika, Volume 85, Issue 2, June 1998, Pages 347–361,
https://doi.org/10.1093/biomet/85.2.347
Published: 01 June 1998 **Article history** ▾

Statistics
in Medicine

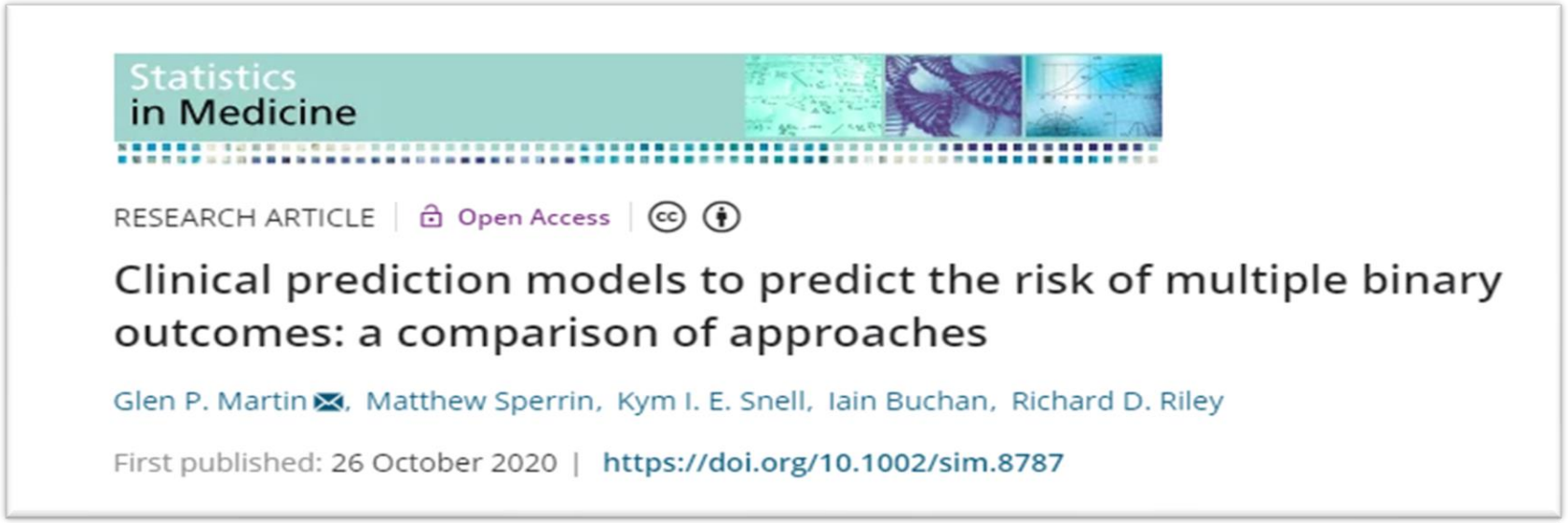
RESEARCH ARTICLE | Open Access

Clinical prediction models to predict the risk of multiple binary outcomes: a comparison of approaches

Glen P. Martin, Matthew Sperrin, Kym I. E. Snell, Iain Buchan, Richard D. Riley

First published: 26 October 2020 | https://doi.org/10.1002/sim.8787

Aim: to compare predictive performance of both marginal and joint probabilities of multiple binary outcomes under different modelling methods



Prediction Approaches under Conditional Independence

- Univariate CPMs

Prediction Approaches Accounting for Conditional Dependence

- Probabilistic Classifier Chains
- Multinomial Logistic Regression
- Multivariate Logistic Regression
- Multivariate Bayesian Probit CPM

Multinomial Logistic Regression

Suppose we have two binary outcomes, Y_{i1} and Y_{i2}

Can use multinomial logistic regression, where the combinations of these are each treated as a nominal outcome category

$$\log\left(\frac{P(Y_{i1}=1, Y_{i2}=1)}{P(Y_{i1}=0, Y_{i2}=0)}\right) = X\beta_1$$

$$\log\left(\frac{P(Y_{i1}=1, Y_{i2}=0)}{P(Y_{i1}=0, Y_{i2}=0)}\right) = X\beta_2$$

$$\log\left(\frac{P(Y_{i1}=0, Y_{i2}=1)}{P(Y_{i1}=0, Y_{i2}=0)}\right) = X\beta_3$$

From which we can get estimates of $P(Y_{i1}=1, Y_{i2}=1)$, etc. for new individuals

Methods

Simulation Study

- Generate two (potentially correlated) binary outcomes using a set of (simulated) covariates (normally distributed)
- Varied level of residual correlation between outcomes (ρ)
- Compare predictive performance (calibration and discrimination) of:
  - Marginal risks: $P(Y_1 = 1)$ and $P(Y_2 = 1)$
  - Join risks: $P(Y_1 = 1, Y_2 = 1)$, $P(Y_1 = 1, Y_2 = 0)$ and $P(Y_1 = 0, Y_2 = 1)$

Real-world data

- Data were obtained from the Medical Information Mart for Intensive Care III (MIMIC-III)
- N=24,459 for our study
- Considered the prediction of acute kidney injury (AKI) occurring within 48 hours after admission, and a binary indication of a total length of stay (LOS) over 5 days

Methods: Predictive Performance

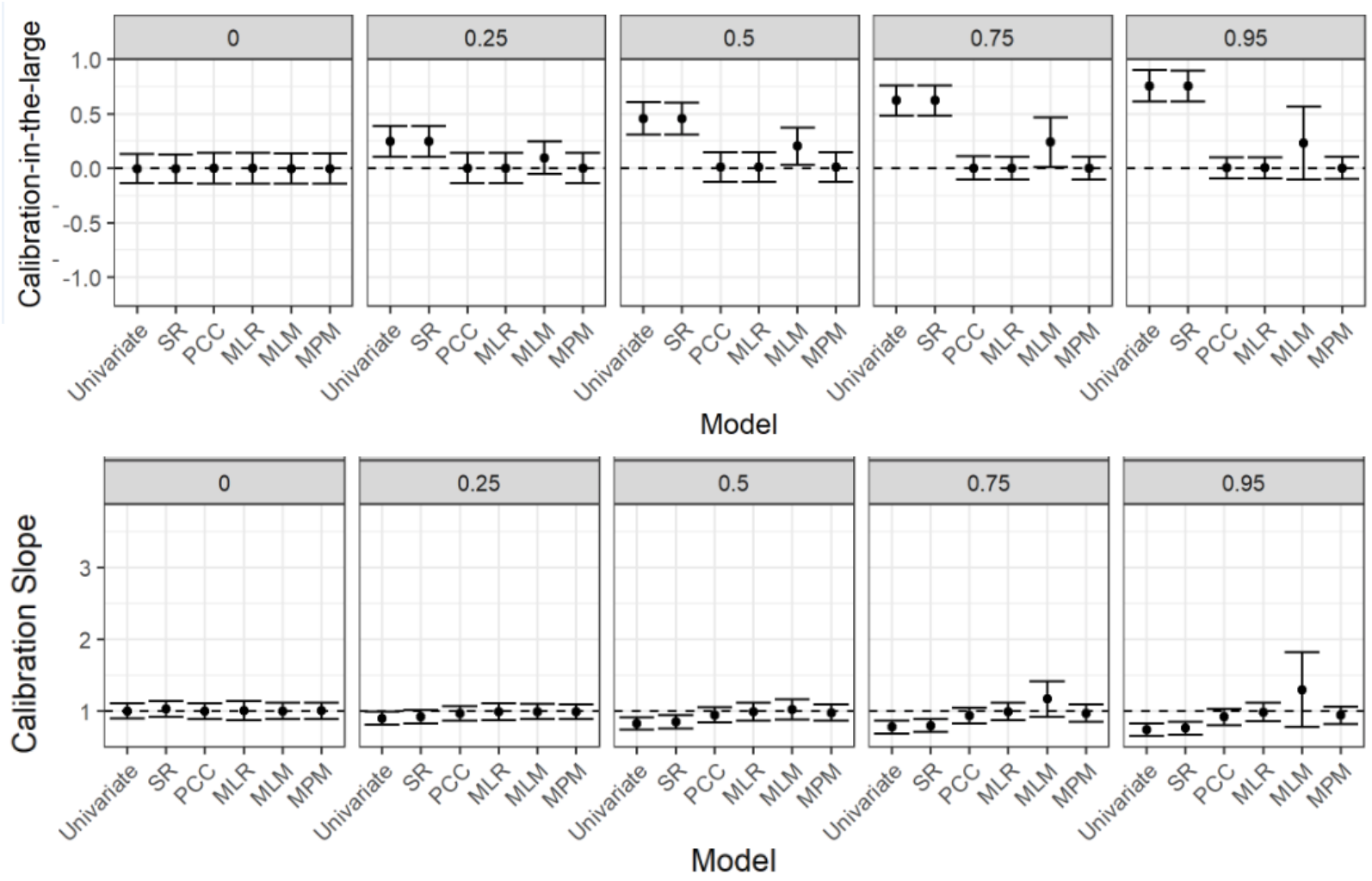
Calibration refers to agreement between the observed and expected outcome proportions

- Assessed using the multinomial calibration framework (Van Hoorde et al. 2014),
- Gives estimates of calibration-in-the-large and calibration slope

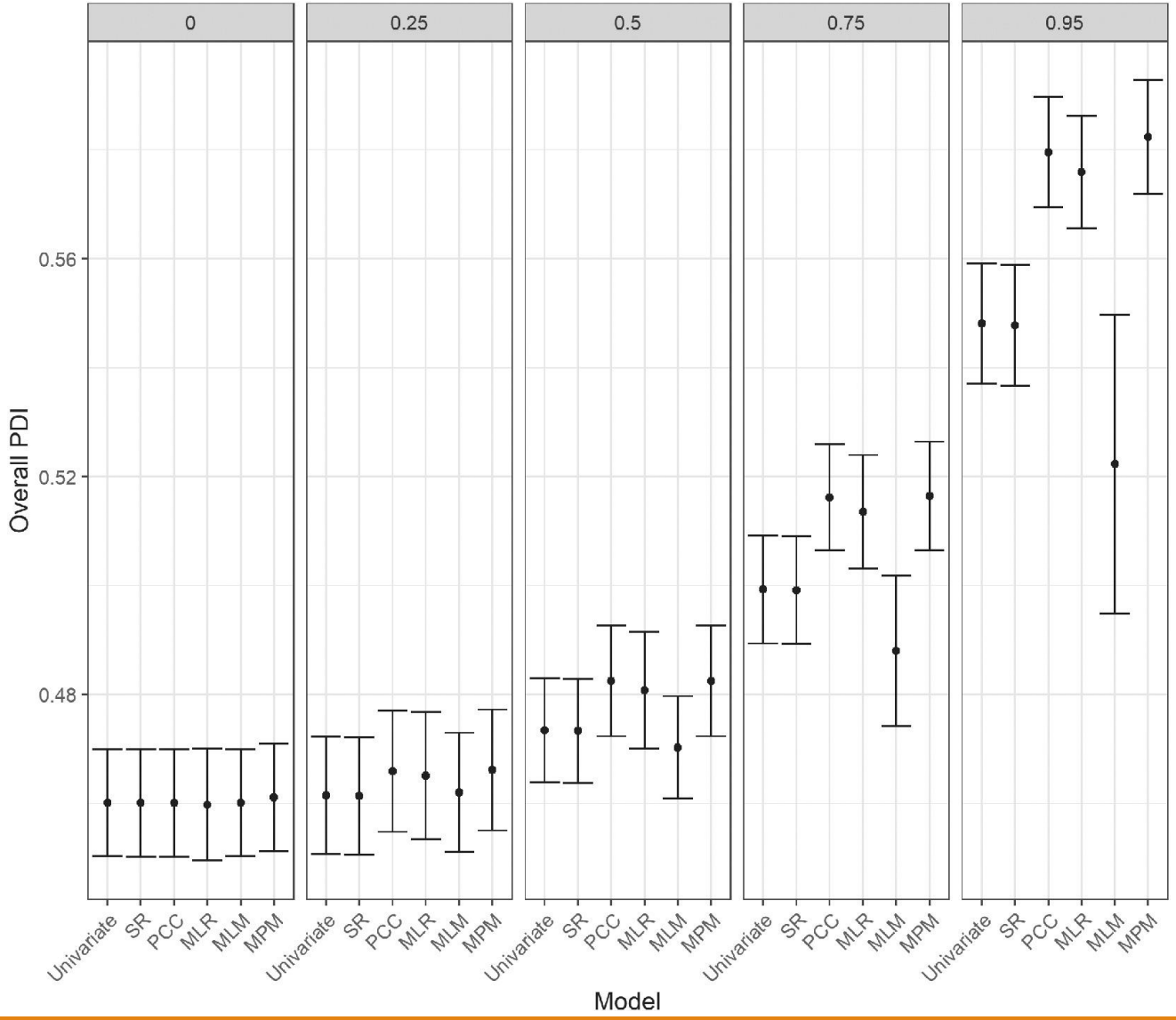
Discrimination refers to the ability of a CPM to separate patients who will develop an outcome from those who will not

- PDI (extension of area under a receiver operator characteristic, AUC for multiple-outcomes)

Simulation Results: calibration



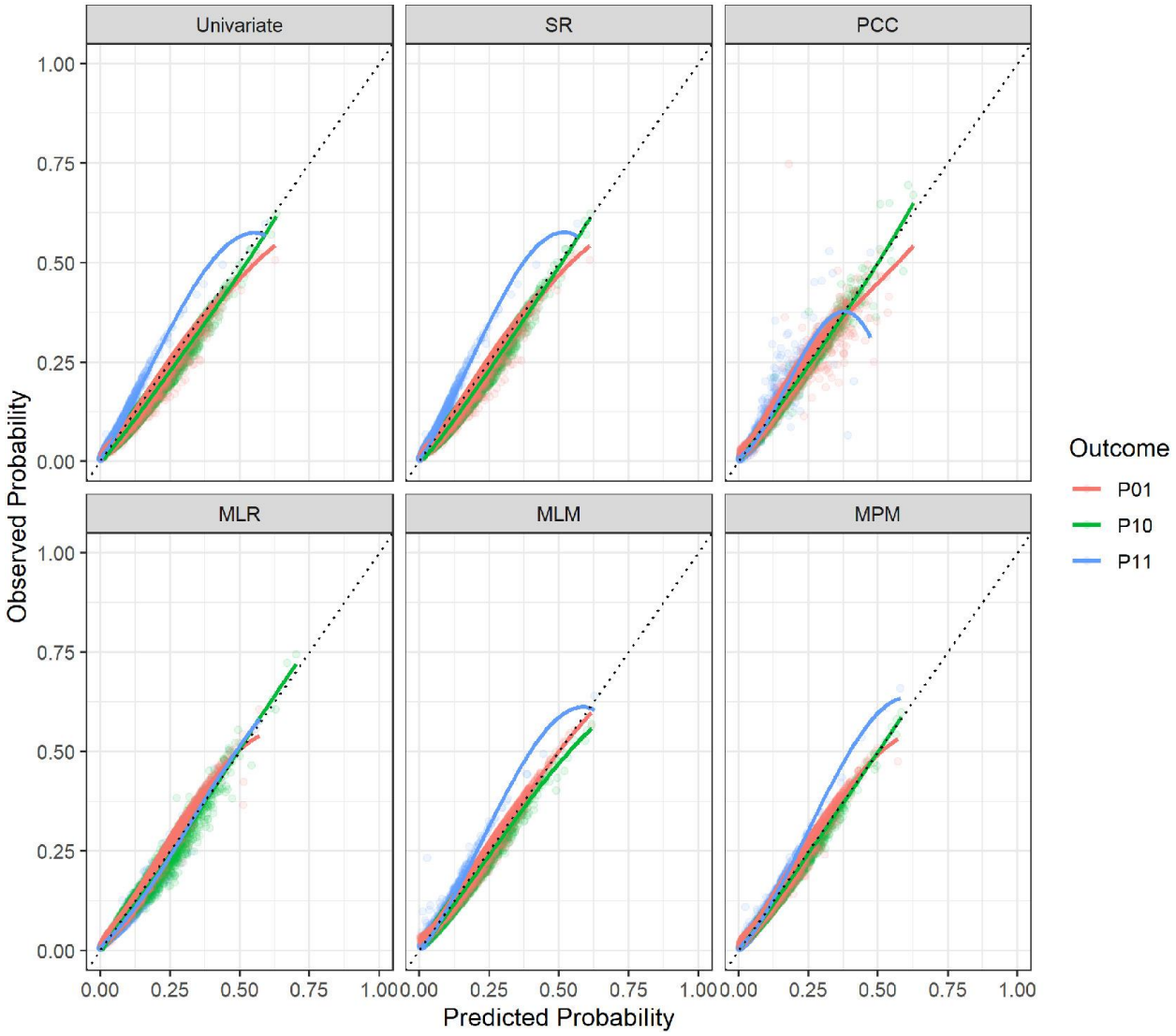
Simulation Results: discrimination



Empirical Study Results

Again, methods that account for dependence in the outcomes were well calibrated for all outcomes, particularly MLR and PCC

The models that do not account for outcome dependency significantly under-predicted the joint outcome risk.



Clinical Prediction Models to Predict the Risk of Multiple Binary Outcomes

To summarise the results from this paper:

- Four methods for developing CPMs that respect the dependence between multiple binary outcomes.
- Only the methods that condition on each outcome or model the correlation explicitly provide reliable estimates of joint risks

Unsurprising from a statistical perspective, but not commonly utilised in prediction field

So, what next?

Challenges to Multi-Outcome Risk Prediction

Combinatorial complexity of many outcomes

What about different outcome types?

Sample size and penalisation – minimise overfitting

Validation of multivariate risk models

Risk communication

Toward Holistic Approaches to Clinical Prediction of Multi-Morbidity

Recently funded 3-year MRC project will explore methodological issues in multi-outcome risk prediction

- Collaboration between Manchester, Keele and Liverpool universities

Feel free to get in touch if you are interested in collaborating.

Take-home Messages

1. Multiple outcomes should be considered more widely in prediction models, whenever **joint** risk is a required output (e.g. multi-morbidity)

2. Various methods to build prediction models for multiple outcomes

3. Further research is needed for a range of methodological considerations before wider use in a prediction context

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