Health e-Research Centre

Farr

MANCHESTER 1824
The University of Manchester

Wearable Clinic WS2
Dynamic, Multi-Dimensional Risk Prediction

Wednesday 5 July 2017

Matthew Sperrin, Paolo Fraccaro, Glen Martin, Iain Buchan, Niels Peek

Health e-Research Centre

WS2: Aim

"To develop dynamic multidimensional methods for predicting health risks in patients with one or more LTCs from electronic health record (EHR) data and published models."

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WS2: Aim

WS 2.1: Dynamic risk prediction from longitudinal EHR data

WS 2.2: Integration of different models for multi-dimensional risk prediction

Clinical Prediction Model

- Tool for predicting (future) outcomes in patients, given what is known now.
- E.g. What is P[CKD onset within 10 years] for ‘healthy’ patient at GP?
- May want to know for:
  1) Clinical decision making (individual).
  2) Case-mix adjustment for audit.
  3) Commissioning and planning.
- Usual models: logistic regression or survival models.

WS2.1: Dynamic risk prediction from longitudinal EHR data

- Existing risk prediction models do not exploit longitudinal data AND are not dynamic

ClinRisk

Welcome to the QKidney®-2016 risk calculator: http://qkidney.org

This calculator is only valid if you do not already have a diagnosis of chronic kidney disease, stage 3b or worse. Ask your doctor if you are unsure.

About you

Age (35-74): 64

Sex: (•) Male ( ) Female

Ethnicity: White or not stated

UK postcode: leave blank if unknown

Postcode:

Clinical information

Smoking status: non-smoker

Do you currently have...

diabetes? No

heart failure? ☐

peripheral vascular disease? ☐

high blood pressure requiring treatment? ☐

rheumatoid arthritis? (not osteoarthritis/"wear and tear") ☐

systemic lupus erythematosis (SLE)? ☐

Have you had ...

a heart attack, angina, stroke or TIA ☐

kidney stones? ☐

Family history

Do immediate family* have kidney disease? *mother, father, brothers or sisters? ☐

Leave blank if unknown

Body mass index

Height (cm):

Weight (kg):

Systolic blood pressure (mmHg):

Calculate risk over 5 years. Calculate risk

Welcome to the QKidney®-2016 risk calculator

Welcome to the QKidney®-2016 Web Calculator. You can use this calculator to work out your risk of developing moderate to se questions.

The QKidney®-2016 algorithms have been developed by Julia Hippisley-Cox and Carol Coupland and are based on routinely co freely contributed data to the QResearch database for medical research.

QKidney®-2016 has been developed for the UK population, and is intended for use in the UK. All medical decisions need to be sponsors accept no responsibility for clinical use or misuse of this score.

The science underpinning the original QKidney® equations is published in BMC Family Practice. See the "Publications" page fo page.

WS2.1: Dynamic risk prediction from longitudinal EHR data

- Existing risk prediction models do not exploit longitudinal data AND are not dynamic

- **Qkidney**
  - Crude information about patient history and events.
  - No information about repeated measures of risk factors.
  - Manually updated annually.

Research Article

Statistics in Medicine

Received 15 January 2016, Accepted 18 September 2016 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.7144

The use of repeated blood pressure measures for cardiovascular risk prediction: a comparison of statistical models in the ARIC study

Michael J. Sweeting*†‡, Jessica K. Barrett‡, Simon G. Thompson and Angela M. Wood

Many prediction models have been developed for the risk assessment and the prevention of cardiovascular disease in primary care. Recent efforts have focused on improving the accuracy of these prediction models by adding novel biomarkers to a common set of baseline risk predictors. Few have considered incorporating repeated measures of the common risk predictors. Through application to the Atherosclerosis Risk in Communities study and simulations, we compare models that use simple summary measures of the repeat information on systolic blood pressure, such as (i) baseline only; (ii) last observation carried forward; and (iii) cumulative mean, against more complex methods that model the repeat information using (iv) ordinary regression calibration; (v) risk-set regression calibration; and (vi) joint longitudinal and survival models. In comparison with the baseline-only model, we observed modest improvements in discrimination and calibration using the cumulative mean of systolic blood pressure, but little further improvement from any of the complex methods. © 2016 The Authors. *Statistics in Medicine* Published by John Wiley & Sons Ltd.

Keywords: repeat measures; cardiovascular risk prediction; joint models; C-index; regression calibration

1. Introduction

Primary prevention of cardiovascular disease (CVD) in individuals is centred on the use of risk prediction equations to target preventive interventions, such as lifestyle and pharmacological treatments, to people who should benefit most from them. These algorithms estimate risk of CVD events from prediction models that incorporate information on several risk factors, such as age, sex, smoking habits, history of diabetes mellitus, and levels of systolic blood pressure (SBP) and serum lipids. Recently, most research has focused on improving the accuracy of these prediction models by including novel biomarkers [1] or a broader set of predictors using available information in electronic health records (e.g. QRISK [2]).

However, most CVD risk algorithms have been derived using risk predictors measured at a single time point. If the risk factor is volatile (i.e. within-person variability is high) or measured with error (e.g. SBP), then using a single measurement will lead to imprecise risk predictions. Furthermore, incorporating knowledge regarding the rate of change in a biomarker over time may also improve CVD risk prediction. Much of the previous research into the benefit of including repeat measurements in CVD risk prediction has focused on a single repeat measurement [3,4].

Developing a CVD risk prediction algorithm generally involves fitting a time-to-event survival model to a prospectively collected cohort of, initially, disease-free individuals. To incorporate a risk factor, or biomarker, that varies over time requires a more complex statistical model or simplifying assumptions

Statistics in Medicine

Research Article

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A comparison of risk prediction methods using repeated observations: an application to electronic health records for hemodialysis

Benjamin A. Goldstein,[a,c*†] Gina Maria Pomann,[a] Wolfgang C. Winkelmayer[b] and Michael J. Pencina[a,c]

An increasingly important data source for the development of clinical risk prediction models is electronic health records (EHRs). One of their key advantages is that they contain data on many individuals collected over time. This allows one to incorporate more clinical information into a risk model. However, traditional methods for developing risk models are not well suited to these irregularly collected clinical covariates. In this paper, we compare a range of approaches for using longitudinal predictors in a clinical risk model. Using data from an EHR for patients undergoing hemodialysis, we incorporate five different clinical predictors into a risk model for patient mortality. We consider different approaches for treating the repeated measurements including use of summary statistics, machine learning methods, functional data analysis, and joint models. We follow up our empirical findings with a simulation study. Overall, our results suggest that simple approaches perform just as well, if not better, than more complex analytic approaches. These results have important implication for development of risk prediction models with EHRs. Copyright © 2017 John Wiley & Sons, Ltd.

Keywords: electronic health records; clinical risk prediction; longitudinal data; functional data analysis; joint models; hemodialysis; end-stage renal disease

1. Introduction

Electronic health records (EHRs) data constitute a new and exciting resource for clinical research. They present the opportunity to observe dense and diverse information on many patients. However, because EHR data are not collected for research purposes, there are also many challenges in their analysis. One of the key opportunities as well as challenges with EHR data is the longitudinal nature of the data. Unlike well-designed clinical studies, the longitudinal data in EHRs are collected irregularly. Some measurements may be very dense over time (e.g., blood pressure measurements from the intensive care unit) while others may be more sparsely collected (e.g., glucose measurements for diabetic patients).

One of the key ways that EHRs have been used is for the development of risk prediction models. Using EHRs to develop risk models is appealing for a multitude of reasons: large sample sizes allow one to model rarer events; many predictors are available; and the risk score is directly applicable to the clinical population used to derive the model. However, a key analytic question is how best to handle repeated predictor measurements.

A recent review of EHR-based prediction studies by our group found that out of 107 studies, only 36 (33%) used longitudinal predictors [1]. Among these studies, most aggregated the repeated measures into summary statistics such as mean/median or extreme values, and only 9 (25%) incorporated disaggregated time-varying data. It is possible that such summarization is a missed analytic

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1. Introducti

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MEDINFO 2015: eHealth-enabled Health
I.N. Sarkar et al. (Eds.)

doi:10.3233/978-1-61499-564-7-696

A Two-stage Dynamic Model to Enable Updating of Clinical Risk Prediction from Longitudinal Health Record Data: Illustrated with Kidney Function

Artur Akbarov[a], Richard Williams[a,c], Benjamin Brown[a,c], Mamas Mamas[a,b], Niels Peek[a,c], Iain Buchan[a,c], Matthew Sperrin[a]

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[b] *Institute of Cardiov ascular Sciences, University of Manchester, UK*
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Abstract

We demonstrate the use of electronic records and repeated measures of risk factors therein, to enable deeper understanding of the relationship between the full longitudinal trajectory of risk factors and outcomes. To illustrate, dynamic mixed effect modelling is used to summarise the level, trend and monitoring intensity of kidney function. The output from this model then forms covariates for a recurrent event Cox proportional hazards model for predicting adverse events (AE). Using data from Salford, UK, our multivariate model finds that steeper declines in kidney function raise the hazard of AE (HR: 1.13, 95% CI (1.05, 1.22)). There is a non-proportional relationship between the hazard of AE and the monitoring intensity of kidney function. Neither of these variables would be present in a classical risk prediction model.. This work

(CKD) [1]; CKD is strongly associated with increased mortality and accelerated cardiovascular disease [2]. Patients with T2DM are also more likely to experience acute renal failure than patients without diabetes (adjusted hazard ratio: 2.5, 95% CI 2.2 – 2.7) [3]. Like CKD, acute renal failure is also associated with high mortality rate, around 50% [4].

Data from the EuroHeart Failure survey suggest that patients with T2DM and impaired kidney function have amongst the worst short and long-term outcomes [5]. A recent study [6], showed that the combination of poor heart and kidney function is a particularly strong and discrete risk factor for death. Another study [7] found that T2DM was a statistically significant predictor of all-cause mortality in patients with CHF, but only those who had eGFR between 30 and 90 ml/min*1.73m^2. Heart and kidney dysfunction are closely linked [8] and diabetes

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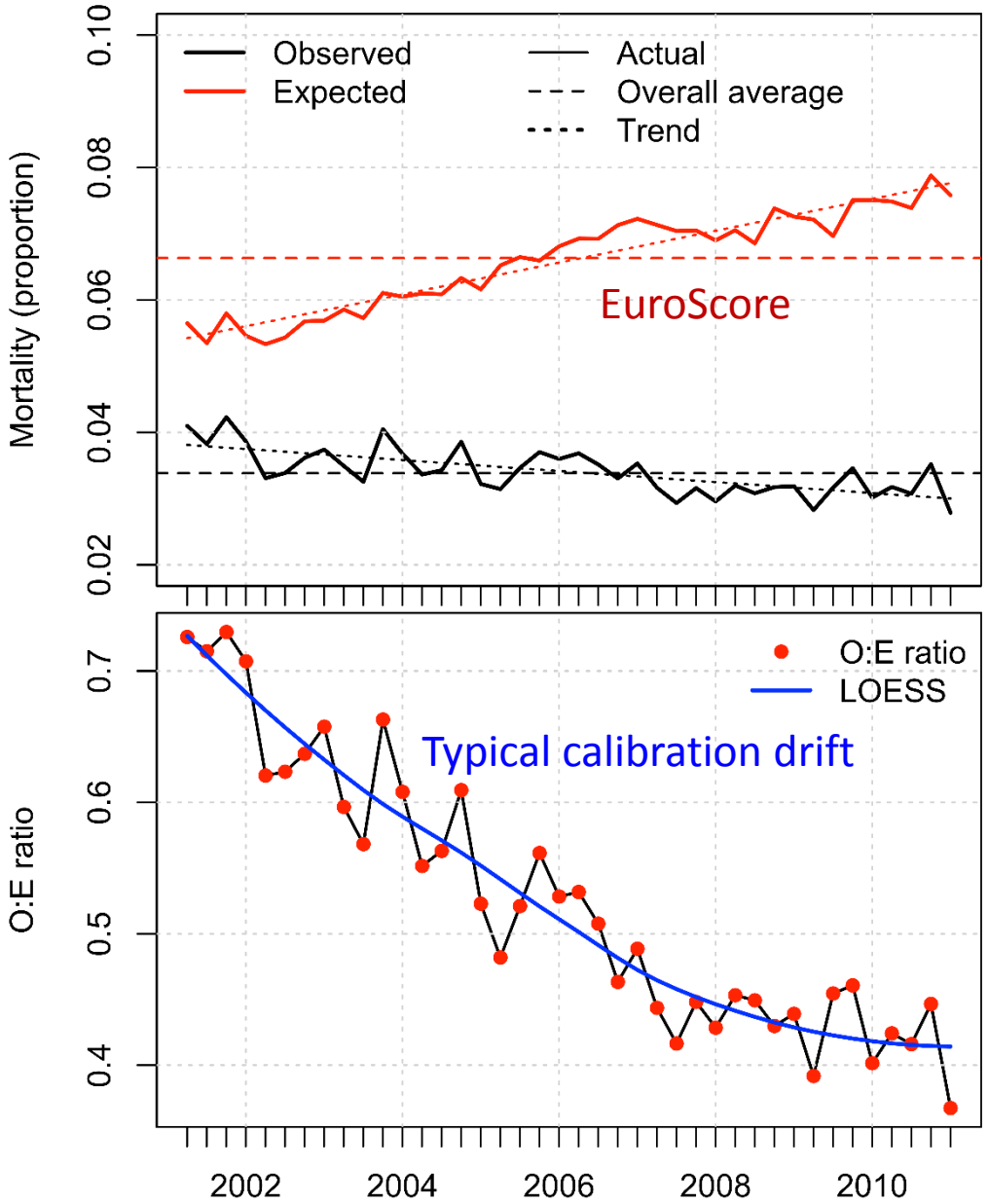
Prediction models need to be dynamic



Production line of clinical prediction models is broken

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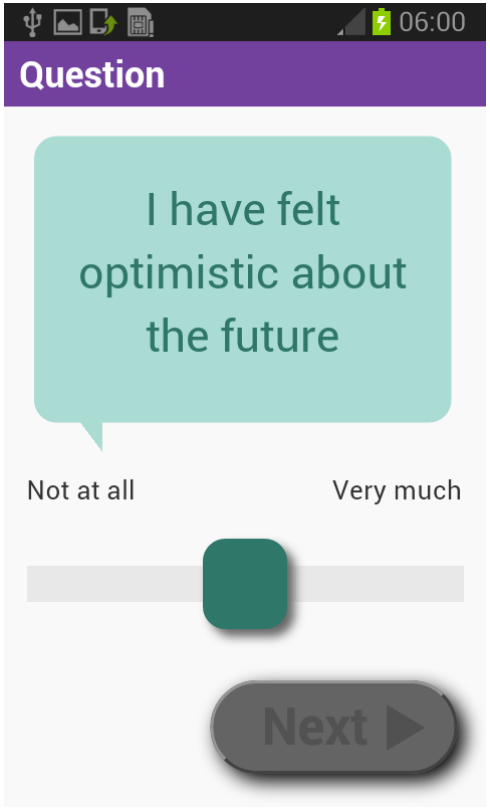
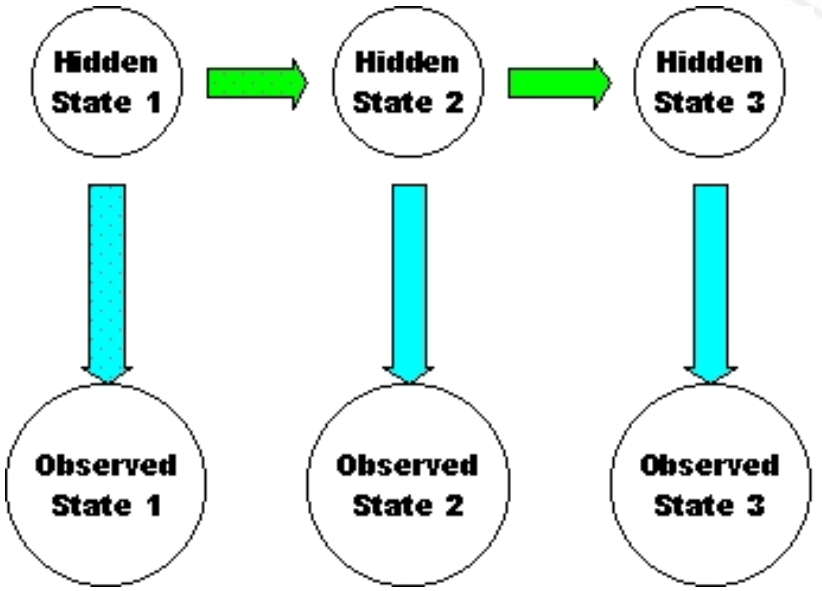
From G. Hickey & B. Bridgewater

Exploiting data from wearables

ClinTouch





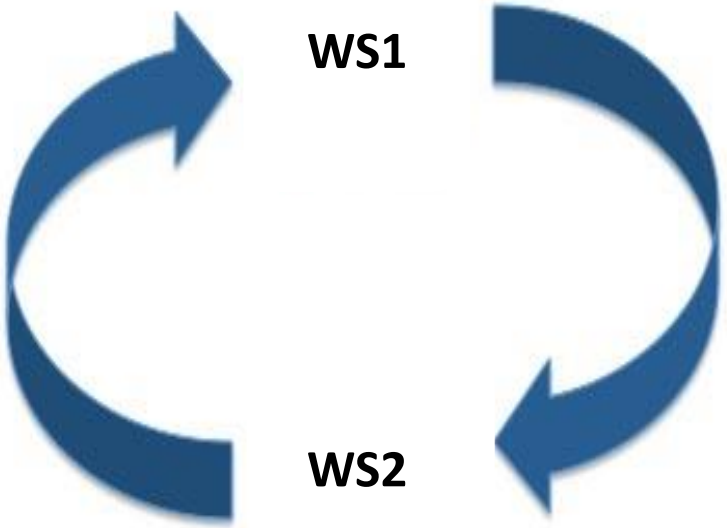
Hidden Markov Model

The Farr Institute of Health Informatics Research

From J. Ainsworth & S. Lewis

Exploiting data from wearables

biobank uk



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From J. Ainsworth & S. Lewis

WS 2.2: Integration of different models for multi-dimensional risk prediction

- First, multiple models for the same outcome.
- Then, combine multiple models for many different outcomes…

Fraccaro et al. BMC Medicine (2016) 14:104
DOI 10.1186/s12916-016-0650-2

BMC Medicine

RESEARCH ARTICLE Open Access

An external validation of models to predict the onset of chronic kidney disease using population-based electronic health records from Salford, UK

Paolo Fraccaro[1,2,3], Sabine van der Veer[2,3], Benjamin Brown[1,2,3], Mattia Prosperi[2,3,4], Donal O'Donoghue[5], Gary S. Collins[6], Iain Buchan[1,2,3] and Niels Peek[1,2,3*]

Abstract

Background: Chronic kidney disease (CKD) is a major and increasing constituent of disease burdens worldwide. Early identification of patients at increased risk of developing CKD can guide interventions to slow disease progression, initiate timely referral to appropriate kidney care services, and support targeting of care resources. Risk prediction models can extend laboratory-based CKD screening to earlier stages of disease; however, to date, only a few of them have been externally validated or directly compared outside development populations. Our objective was to validate published CKD prediction models applicable in primary care.

Methods: We synthesised two recent systematic reviews of CKD risk prediction models and externally validated selected models for a 5-year horizon of disease onset. We used linked, anonymised, structured (coded) primary and secondary care data from patients resident in Salford (population ~234 k), UK. All adult patients with at least one record in 2009 were followed-up until the end of 2014, death, or CKD onset ($n = 178{,}399$). CKD onset was defined as repeated impaired eGFR measures over a period of at least 3 months, or physician diagnosis of CKD Stage 3–5. For each model, we assessed discrimination, calibration, and decision curve analysis.

Results: Seven relevant CKD risk prediction models were identified. Five models also had an associated simplified scoring system. All models discriminated well between patients developing CKD or not, with c-statistics around 0.90. Most of the models were poorly calibrated to our population, substantially over-predicting risk. The two models that did not require recalibration were also the ones that had the best performance in the decision curve analysis.

Conclusions: Included CKD prediction models showed good discriminative ability but over-predicted the actual 5-year CKD risk in English primary care patients. QKidney, the only UK-developed model, outperformed the others. Clinical prediction models should be (re)calibrated for their intended uses.

Keywords: Chronic kidney disease, Clinical prediction models, eGFR, Decision support, Electronic health records, Model validation, Model calibration

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Martin et al. BMC Medical Research Methodology (2017) 17:1
DOI 10.1186/s12874-016-0277-1

BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

Clinical prediction in defined populations: a simulation study investigating when and how to aggregate existing models

Glen P. Martin[1*], Mamas A. Mamas[1,2], Niels Peek[1,3], Iain Buchan[1,3] and Matthew Sperrin[1]

Abstract

Background: Clinical prediction models (CPMs) are increasingly deployed to support healthcare decisions but they are derived inconsistently, in part due to limited data. An emerging alternative is to aggregate existing CPMs developed for similar settings and outcomes. This simulation study aimed to investigate the impact of between-population-heterogeneity and sample size on aggregating existing CPMs in a defined population, compared with developing a model de novo.

Methods: Simulations were designed to mimic a scenario in which multiple CPMs for a binary outcome had been derived in distinct, heterogeneous populations, with potentially different predictors available in each. We then generated a new 'local' population and compared the performance of CPMs developed for this population by aggregation, using stacked regression, principal component analysis or partial least squares, with redevelopment from scratch using backwards selection and penalised regression.

Results: While redevelopment approaches resulted in models that were miscalibrated for local datasets of less than 500 observations, model aggregation methods were well calibrated across all simulation scenarios. When the size of local data was less than 1000 observations and between-population-heterogeneity was small, aggregating existing CPMs gave better discrimination and had the lowest mean square error in the predicted risks compared with deriving a new model. Conversely, given greater than 1000 observations and significant between-population-heterogeneity, then redevelopment outperformed the aggregation approaches. In all other scenarios, both aggregation and de novo derivation resulted in similar predictive performance.

Conclusion: This study demonstrates a pragmatic approach to contextualising CPMs to defined populations. When aiming to develop models in defined populations, modellers should consider existing CPMs, with aggregation approaches being a suitable modelling strategy particularly with sparse data on the local population.

Keywords: Clinical prediction models, Model aggregation, Validation, Computer simulation, Contextual heterogeneity

Background

Clinical prediction models (CPMs), which compute the risk of an outcome for a given set of patient characteristics, are fundamental to clinical decision support systems. For instance, practical uses of CPMs include facilitating discussions about the risks associated with a proposed treatment strategy, assisting audit analyses and benchmarking post-procedural outcomes. Consequently, there is growing interest in developing CPMs to support local healthcare decisions [1, 2]. Although there might be existing models derived for similar outcomes and populations, it is vital they are appropriately updated, validated and transferred between different contexts of use. Baseline risk and predictor effects may differ across populations, which can cause model performance to decrease when transferring an existing CPM to the local population [3–6]. This between-population-heterogeneity frequently leads to researchers rejecting existing models

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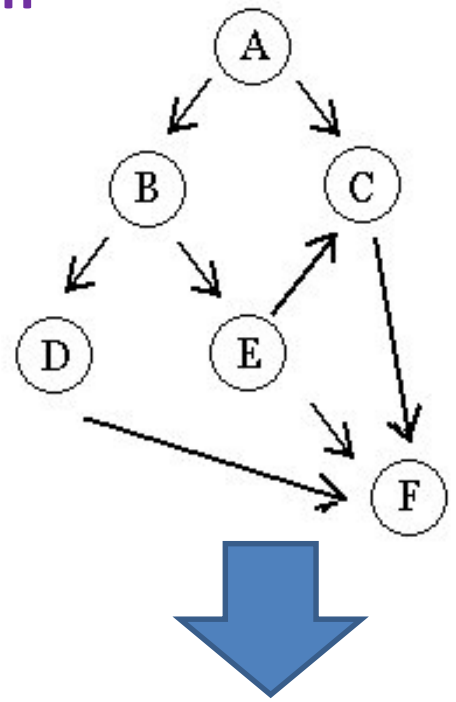
Multi-dimensional risk prediction

- Aggregating models for predicting chronic kidney disease onset in the UK primary care.
  - Builds on our existing work
- Integrating different models for multi-dimensional risk prediction.
  - Bayesian networks.
  - Synthesis over risks of different diseases.



WS3

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WS2 – planned work

- **2.1: Dynamic risk prediction from longitudinal EHR data**
  - Use of geolocation data in serious mental illness: a systematic review.
  - Geolocation data collected through smartphones to assess out-of-home behaviour in healthy volunteers
  - Predicting relapse in schizophrenia patients
  - Adaptive/dynamic modelling to predict deterioration in patients with moderate to severe renal function.
  - Dynamic prediction modelling to monitor renal function in patients with Chronic Heart Failure.

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WS2 – planned work

- **2.2: Integration of different models for multi-dimensional risk prediction**
  - Aggregating models for predicting chronic kidney disease onset in the UK primary care
  - Integrating different models for multi-dimensional risk prediction
- **WP2 -> 1:**
  - Informing Discovery of computable behaviour phenotypes for signal compression
  - Incorporation of signal into risk prediction models
- **WP2 -> 3:**
  - Use of multidimensional risk prediction models to inform adaptive, personalised care planning.
- **WP 2 -> 4:**
  - Informed by stakeholder preferences
  - Deployment

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