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Quantifying nonlinear effects in stochastic Markov simulation using UKPDS 68 and UKPDS 82 equations in type 2 diabetes modeling analysis with the IMS CORE Diabetes Model (CDM)

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Introduction

- Ensuring patient heterogeneity is adequately reflected in cost effectiveness models is essential if the model's output is to robustly inform on the expected changes in health benefit and costs associated with competing interventions.
- Modelling cohorts in health economic evaluations using a "mean" profile will typically fail to capture the timing of clinical events - as higher risk patients will inevitable progress sooner than lower risk patients.
- Previous studies using the CORE diabetes model (CDM) have demonstrated that incorporating parameter sampling (PS) within an analysis is crucial to capture nonlinear effects (NE) in cost effectiveness modeling [1]. This is routinely undertaken when conducting probabilistic analysis but is also required to ensure that the point estimates predicted by a model are unbiased.
- NE are, among other causes, driven by the degree through which the symmetric sampling of risk factors is translated into non-symmetrically distributed probabilities, for example, as generated by the model's risk equations.

Objectives

This study sought to assess degree by which the incorporation of NE through PS alters event rate predictions when utilizing either the UKPDS 68 (UK68) [2] or UKPDS 82 (UK82) [3] risk equations in a set of selected validation studies conducted with the CDM.

Methods

Model

- The CDM is a recently validated lifetime simulation model designed to assess the health outcomes and economic consequences of interventions in T1DM or T2DM. [4,5]
- The model structure comprises of 17 interdependent sub-modules that simulate the complications of diabetes (angina, myocardial infarction (MI), congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macula edema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy, end-stage renal disease, neuropathy, foot ulcer, amputation, pulmonary edema and depression) in addition to all-cause mortality.
- The model is a fixed-time increment (annual) stochastic simulation with each submodule using time, state, and diabetes-type dependent probabilities. Monte Carlo simulations are performed at the individual patient level using tracker variables to accommodate complex interactions between individual complication sub-modules.

Validation studies

- A total of 51 validation simulations were performed to data from: the Diabetes Control and Complications Trial (DCCT) [6]; United Kingdom Prospective Diabetes Study (UKPDS) 33 [7]; UKPDS 80 [8] the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN) [9]; the Veterans Affairs Diabetes Trial (VADT) [10]; the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)[11]; the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [12,13].
- Simulations mirroring cohort baseline characteristics of each of the trials were conducted with and without PS using UK68 and UK82 risk equations.
- Predicted versus observed macrovascular (MAC) and microvascular (MIC) complications and all cause mortality (ACM) were assessed using the coefficient of determination (R2) goodness of fit measure.

Results

- Figure 1 illustrates the impact that sampling cohort profiles have on predicted risk within the CDM (illustrated for 1st and 2nd myocardial infarction (MI) and mortality). Vertical lines demonstrating the event probability using a mean cohort profile: 1st MI = 0.049; 2nd MI = 0.041; death (with no history of prior complications) = 0.007; death (in year of diabetes related complication) = 0.189. The density plots were derived from cohorts of 1000 simulated patients.
- Figure 2 shows the percentage increase in predicted risk with and without PS for the UKPDS intensive (INT) and standard (STD) cohorts evaluated using UKPDS 82 and 68 risk equations. The use of PS consistently resulted in an increase in the predicted risk of complications compared to no PS, which varied from an increase in 4.3% (UK 68: myocardial infarction) to an increase of 66% (UK 82: stroke).
- When the CDM was run without PS, validation studies produced an R2 statistic of 0.898 using UK68 and 0.853 using UK82 RE. This compared to R2 statistics of 0.876 and 0.791 in analysis with PS for UK68 and UK82 REs, respectively. Overall, PS caused end point predictions for MAC, MIC and ACM to increase. Scatterplots of predicted versus observed events are shown in Figure 3.
- Internal validations against UKPDS 80 demonstrated that PS increased event rate predictions for myocardial infarction (MI), stroke, MIC and ACM by 4.4%, 21.5%, 19% and 16.4% when UK68 RE were applied and 26.3%, 64.7%, 14.9% and 34.8% with UK82 RE, respectively.

Figure 1) Density plots illustrating the impact that sampling cohort profiles has on predicted risk within the CDM (illustrated here for 1st and 2nd myocardial infarction (MI) and mortality). Vertical lines represent the probability of an event associated with using a mean cohort profile: 1st MI = 0.049; 2nd MI = 0.041; death (with no history of prior complications) = 0.007; death (in year of diabetes related complication) = 0.189. The density plots are derived from cohorts of 1000 simulated patients.

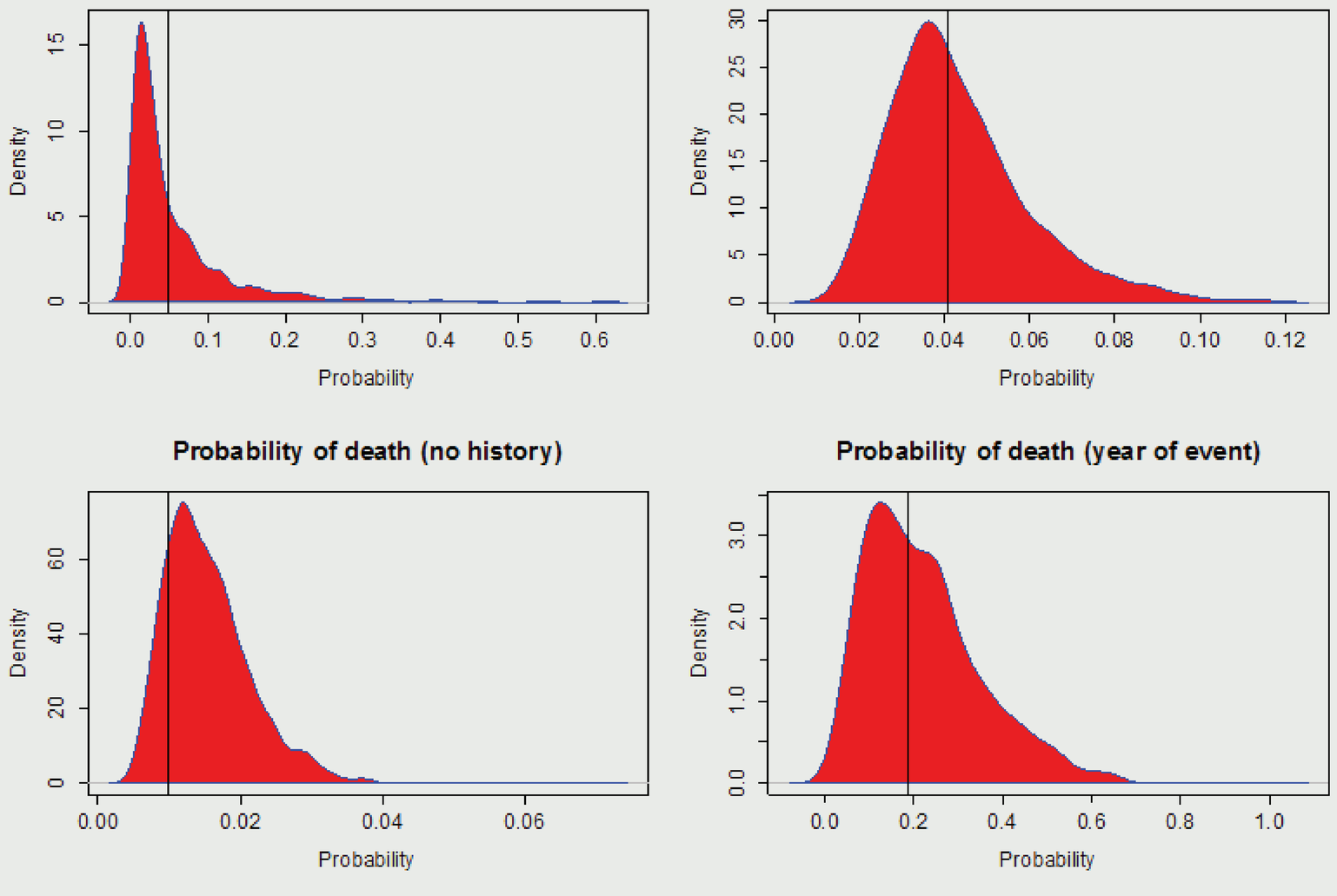
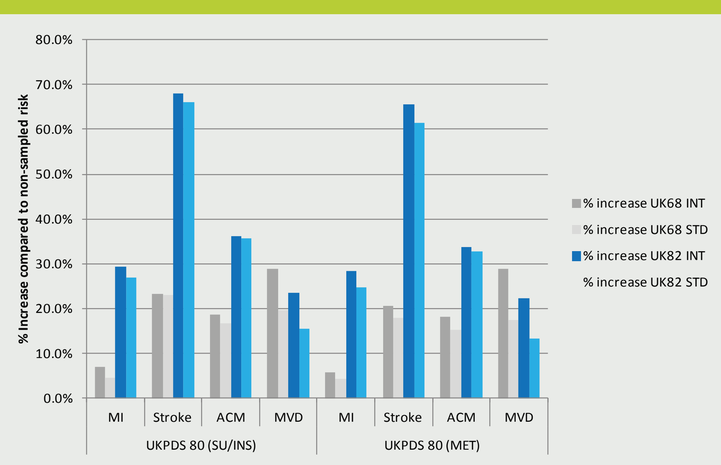


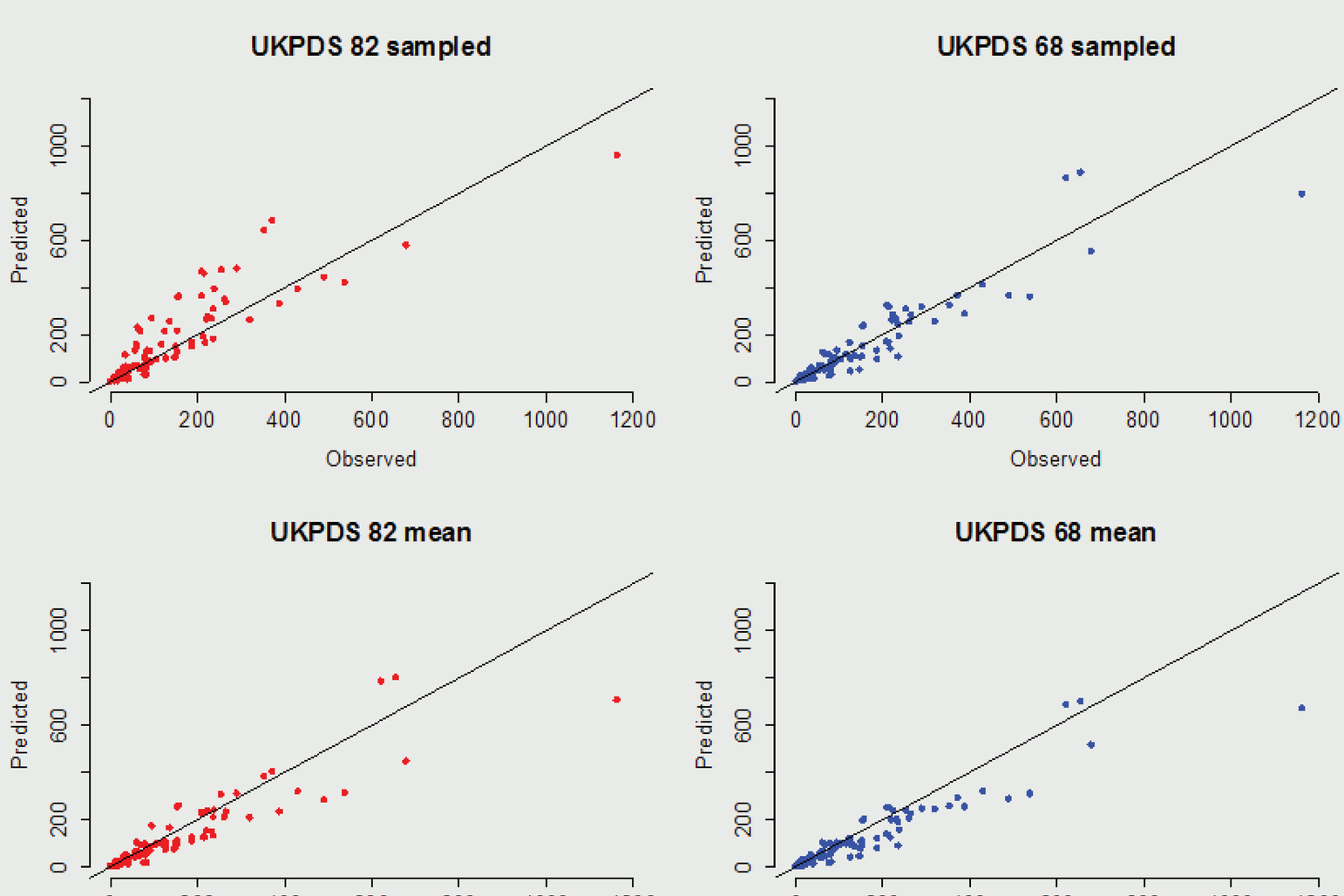
Figure 2) Comparing the percentage increase in predicted risk when using sampled versus non-sampled simulated cohort profiles. For the UKPDS intensive (INT) and standard (STD) cohorts evaluated using UKPDS 82 and 68 risk equations.



Conclusions

- The findings from this study illustrate that PS has a significant impact on predicted risk of complications. The goodness of fit, as measured by the coefficient of determination, indicates that the external validity of the model declined with PS in simulations using UK68 and UK82 risk equations.
- The degree by which PS increased end point predictions was considerable stronger in UK82 risk equation predictions for MAC and ACM but lower for MIC when compared to UK 68 risk equations.
- In this study the use of "mean" cohort values was associated with a modest improvement in validation fit. Importantly, the validation studies used in this analysis were typically less than five years in duration; consequently, longer-term event rates may be significantly underestimated when PS is not utilized.

Figure 3) Model predicted versus observed study endpoints using the UKPDS 82 and 68 risk equations within the CORE Diabetes Model with sampled versus non-sampled (mean) simulated cohort profiles. For mean cohort profiles, validation results for the CDM model produced an R2 statistic of 0.898 using UKPDS 68 and 0.853 using UKPDS 82 risk equations; this compared to R2 statistics of 0.876 and 0.791 in analysis with sampled cohort profiles for the UKPDS 68 and UKPDS 82 risk equations, respectively.



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