Drug exposure as a predictor in diabetic retinopathy risk prediction models; a systematic review and meta-analysis

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Background

Various diabetic retinopathy (DR) prediction models include drugs as predictors. Drug exposure however is not consistently assessed for model inclusion, with substantial variation identified in how drug exposure is coded.

Aims

We aimed to assess drug exposure handling, identify the drugs associated with DR by performing a network meta-analysis and determine which drugs enhance model performance by undertaking a meta-analysis.

Methods

We searched EMBASE, MEDLINE and SCOPUS from inception to July 2022. We evaluated the quality of studies using the Prediction model Risk of Bias Assessment Tool (PROBAST). We conducted network meta-analysis (NMA) and a meta-analysis to estimate the odds ratio (OR) and pooled C-statistic, respectively (PROSPERO: CRD42022349764).

Results

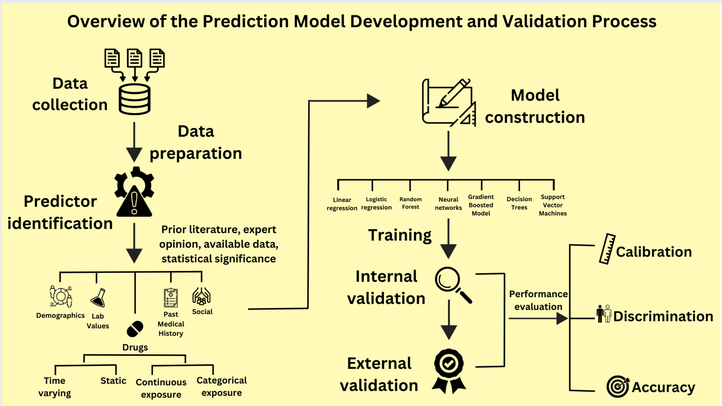


Figure 1: Simplified overview of the prediction model development and validation process, including drug handling considerations.

We included 19 records of 396,844 participants with type 1 or 2 diabetes, of which 27,374 (6.7%) had DR.

12 studies recruited type 2 diabetes participants, four type 1 and 2, one type 1, and two were unspecified.

Seven studies of type 2 diabetes participants contributed to the NMA (n=40,630 participants; 12,303 DR events).

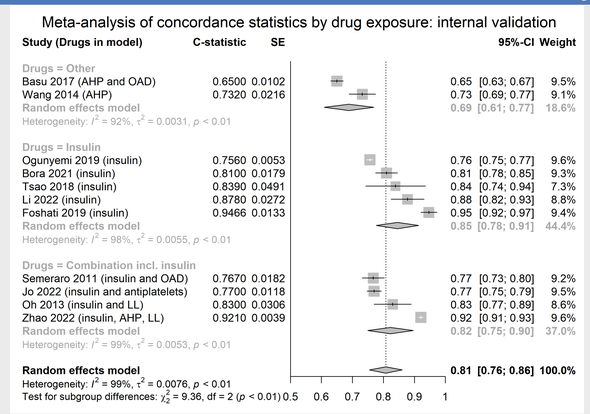
Insulin was associated with an increased risk of DR (OR= 3.09; 95%-CI:1.66, 5.76).

Drug handling

Drugs included in the models were: insulin (n=15), antihypertensives (n=3), oral antidiabetics (n=6), lipid-lowering drugs (n=5), antiplatelets (n=1).

14 studies handled drug exposure as a categorical variable, 2 as a continuous variable, and 3 included both a categorical and continuous component.

Meta-analysis of C-statistic



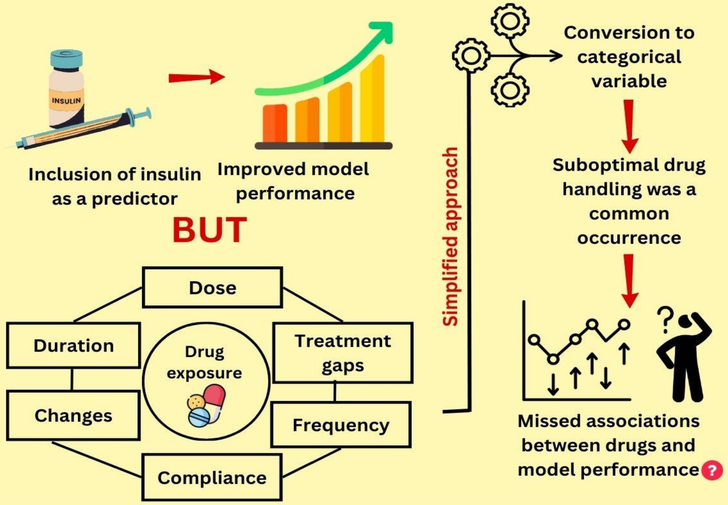
Models that included insulin (n=5) had a higher pooled C-statistic (C-statistic= 0.85, 95%-CI: 0.78, 0.91).

These findings were consistent in the external validation meta-analysis (n=3).

Limitations include high risk of bias (high= 14, unclear=2, and low risk of bias =3) and heterogeneity.

Figure 2: Forest plots of C-statistic in internal validation by drug exposure. CI; Confidence Interval, DR; diabetic retinopathy, SE; Standard Error, OAD; oral antidiabetic drug, AHP; antihypertensive, LL; lipid-lowering drug.

Conclusion



Recommendations

- Avoid converting drug exposure into a never/ever categorical variable
- Perform routine evaluation of drug exposure as a variable in prediction models
- Consider employing time-varying methodologies
- Consider the dosage, frequency, treatment duration and treatment gaps

Improving drug exposure handling could potentially unveil novel variables capable of significantly enhancing the predictive capability of prediction models.