Abstract 1165: Utility of Polygenic Risk Scores for Prediction of Incident Type 2 Diabetes

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Background

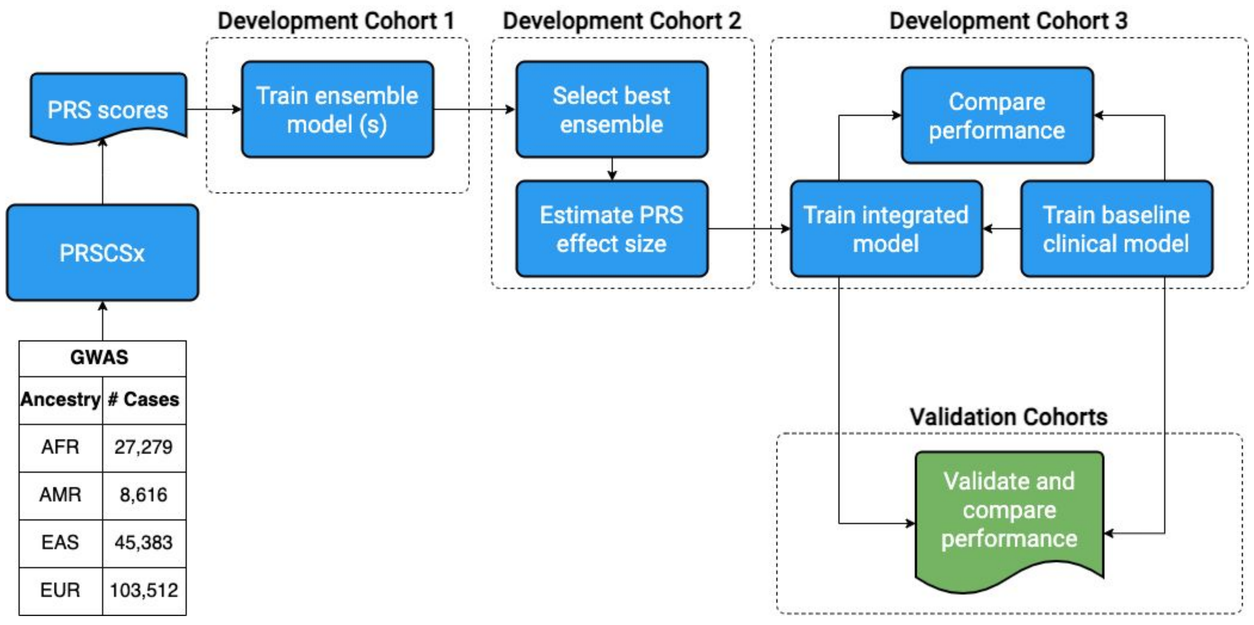
- Diabetes is the leading cause of kidney failure, new onset blindness among adults and a major risk factor for coronary artery disease.
- Identification of asymptomatic individuals at risk of type 2 diabetes (T2D) may enable earlier preventive intervention and ultimately improve health outcomes.
- The clinical utility of genetic information in assessing T2D risk remains uncertain. Our study evaluates the added value of T2D polygenic risk scores (PRS) compared to established, non-genetic risk factors in T2D risk assessment.

Objective

- Develop cross-ancestry PRS (caPRS) model for T2D.
- Evaluate added value of the caPRS in the estimation of 10-year risk of T2D when combined with established risk factors.

Methods

Figure 1. Schematic development and validation workflow for the caPRS and integrated model(s).



Cross-ancestry Polygenic Risk Score (caPRS):

1. We constructed internal PRS models using multi-ancestry GWAS summary statistics which were processed with PRS-CSx using a range of hyperparameter values.
2. To train ancestry-specific ensemble models we linearly combined individual model PRS scores via elastic net regression (**Development Cohort 1**).
3. Using an independent development cohort (**Development Cohort 2**) we selected the best ensemble score for each (continental) ancestry and estimated ancestry-specific effect sizes for best ensemble score.
4. Finally, we calculated the **caPRS** as a linear combination of the best performing ensemble score weighted by the product of the ancestry-specific effect size and fractional ancestry estimate:

$$caPRS = \sum_{i=1}^{5} f_i * \beta_i * ensemblePRS_i$$

Baseline and Integrated risk score models:

1. Using a separate longitudinal cohort (**Development Cohort 3**) we trained 2 baseline models which included established risk factors for T2D:
   a. The **simple model** includes: **age, sex, BMI, waist circumference, systolic blood pressure, 1st degree family history of T2D and PCS 1-6**.
   b. The **clinical model** additionally includes: **fasting glucose, HDL-C and triglycerides**.
2. To construct the corresponding **integrated models** we retrained the **simple** and **clinical** models after adding the **caPRS**.
3. Finally, we assessed model performance in 3 independent , ancestrally-diverse validation cohorts.

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A PRS modulates risk for individuals at elevated clinical risk of developing T2D.

Results

- The caPRS was significantly associated with incident T2D across all 3 validation cohorts, including non-European ancestry groups after accounting for non-genetic risk factors (**Figure 2**).
- Inclusion of the caPRS showed some improvement in the discrimination of risk prediction models based on established, non-genetic risk factors, especially in the absence of clinical measurements (**Figure 3**).
- The difference in absolute risk across caPRS strata was most pronounced for individuals in the highest clinical risk quartile, but negligible for those in the lowest clinical risk quartile (**Figure 4**).

Figure 2. Association of the caPRS with incident T2D after accounting for established risk factors included in the *simple* and *clinical* models.

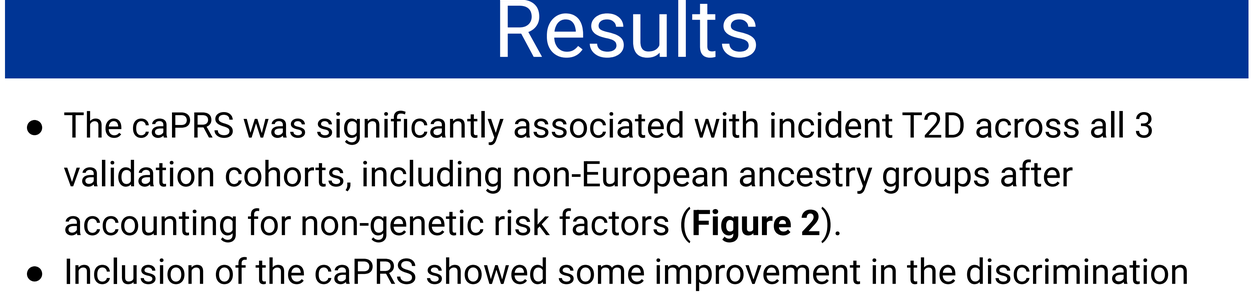


Figure 3. The improvement in model discrimination (over 10-years of follow up) upon adding the caPRS to risk prediction models based on established risk factors.

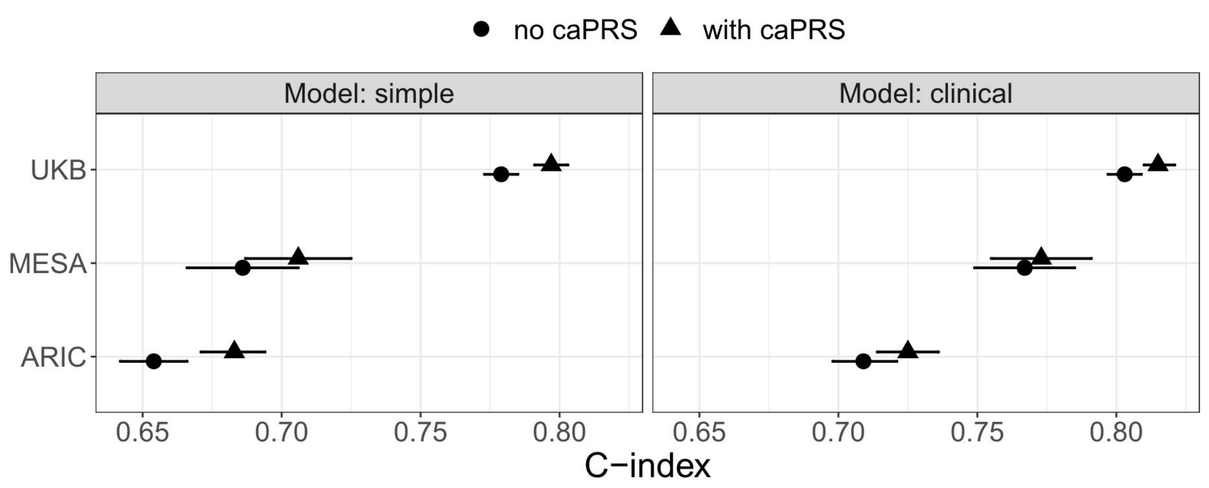
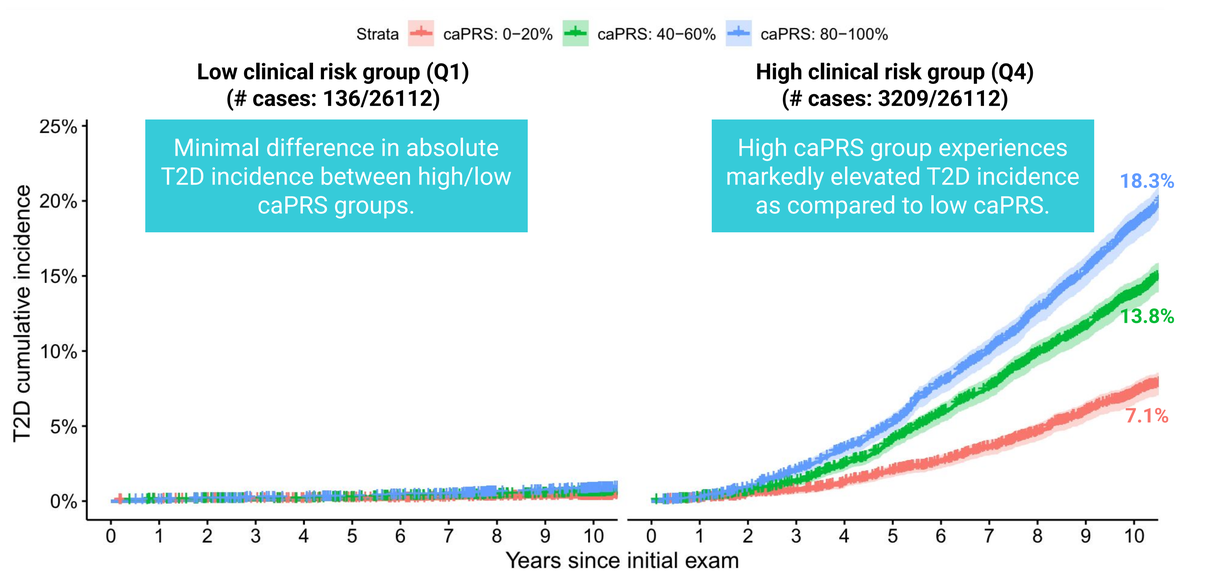


Figure 4. T2D risk stratification with caPRS among individuals at low (1st quartile) and high (4th quartile) clinical risk.



Conclusions

- Accounting for the caPRS in the assessment of T2D risk can provide more accurate risk prediction compared to models based on established, non-genetic risk factors.
- Incorporating a caPRS into T2D risk assessment would be particularly informative for individuals at moderate/elevated clinical risk, leading to significant differences in absolute risk prediction.