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BACKGROUND

- Polygenic risk scores (PRSs) have improved breast cancer (BC) risk assessment by analyzing multiple genetic variants.
- Ashkenazi Jewish individuals have a unique genetic background despite their European descent; therefore, most PRS models optimized for European–ancestry populations may still have limited predictive accuracy for this group.
- Ancestry-specific adjustments are necessary to enhance PRS models and ensure more accurate BC risk prediction for diverse populations.
- This study evaluates the performance of three PRS models—PRS313, caPRS, and caPRSx—to improve BC risk assessment in AJ women.
- caPRSx includes a dedicated AJ ancestry reference panel alongside other ancestry groups to effectively address gaps in existing models in existing models.

OBJECTIVE

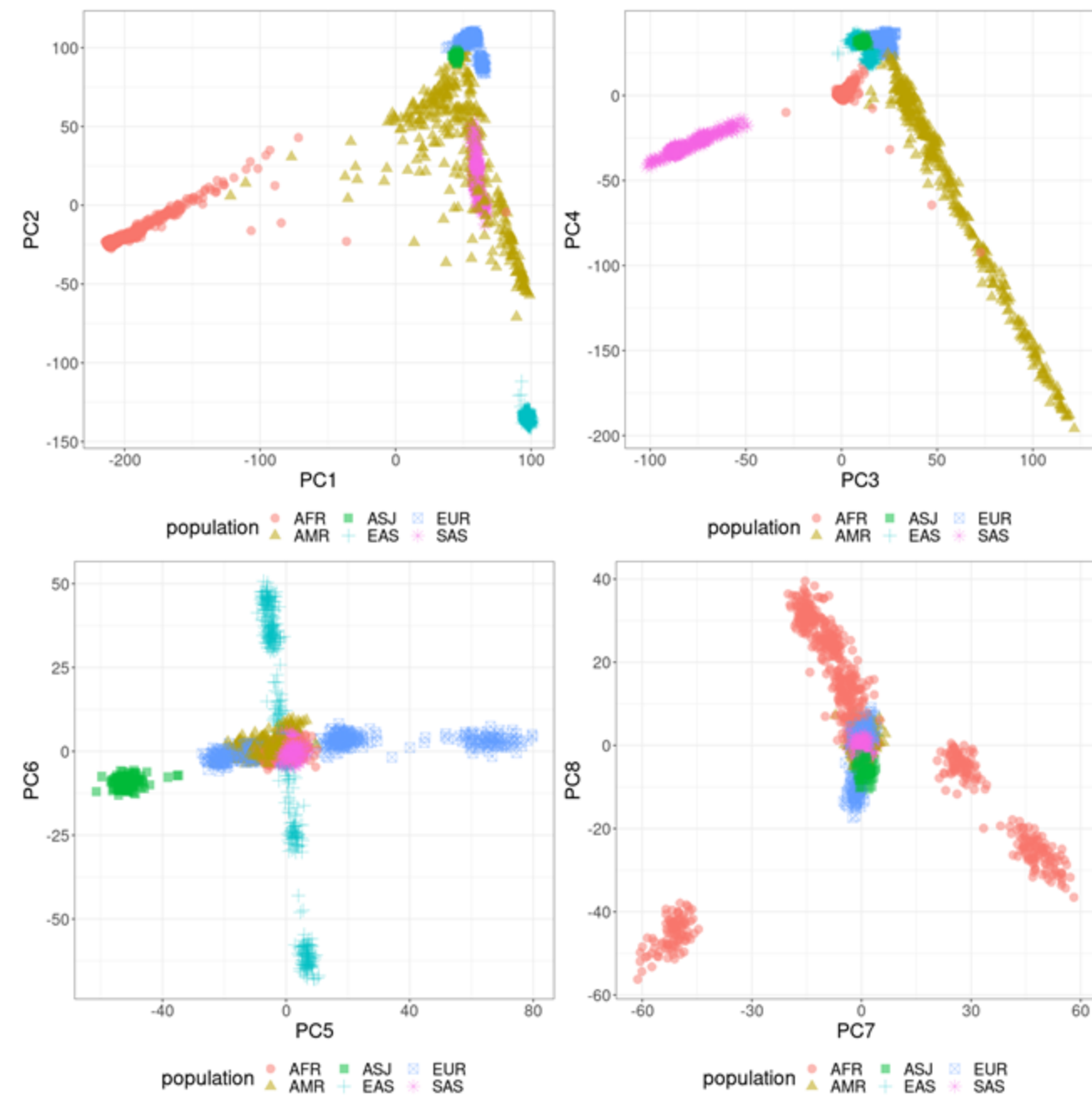
- To assess the performance of PRS313, caPRS, and caPRSx in predicting BC risk among AJ women.
- To determine whether incorporating an AJ ancestry group improves PRS model accuracy and risk assessment.
- To analyze the effect of ancestry-specific PRS adjustments on lifetime BC risk estimates.
- To provide insights into the clinical implications of ancestry-adjusted PRS models for BC prevention and risk stratification.

METHODS

- **Study Design:**
 - Comparative evaluation of three PRS models in predicting BC risk in AJ women.
- **PRS Models Evaluated:**
 - PRS313: A 313–SNP PRS model developed by Mavaddat et al.
 - caPRS: A cross–ancestry PRS model adjusted for five ancestry groups including African, Admixed American, East Asian, European and South Asian.
 - caPRSx: An enhanced cross–ancestry PRS model incorporating an AJ ancestry group alongside the ancestry groups adjusted for in the caPRS.
- **Data Sources:**
 - UK Biobank and Women’s Health Initiative cohorts.
 - Ancestry-specific principal components (PCs) calculated using 1000 Genomes Project data and 100 additional AJ samples for caPRSx.
- **PRS Adjustment:**
 - Each ancestry-specific PRS was adjusted by subtracting the PRS predicted from a linear regression model using the first five principal components (PCs) in unaffected individuals and then normalized using the standard deviation (SD) of the corresponding population in the reference set (Figure 1).
- **Cross–Ancestry PRS:**
 - The best-performing PRS for each ancestry was linearly combined and weighted by fractional ancestry.
- **Statistical Analysis:**
 - Association between BC risk and PRS models were evaluated using multivariable logistic regression with adjustments made for age, ovarian cancer history, family history of BC, and cohort.
 - Model performance was assessed through:
 - PRS skewness analysis.
 - Odds ratio (OR) per SD.
 - Changes in remaining lifetime risk when integrating each PRS with the Tyrer–Cuzick clinical model.

Adjusting for Ashkenazi Jewish ancestry within PRS models significantly improves breast cancer risk prediction, highlighting the need for ancestry-adjusted PRS models for more accurate and equitable genetic risk assessments.

Figure 1. Adjustment of Breast Cancer PRSs for Population Structure.



RESULTS

- caPRSx outperformed PRS313 and caPRS in predicting BC risk in AJ women, with ORs per SD of 1.53 (95% CI: 1.45–1.62) for PRS313, 1.66 (95% CI: 1.57–1.75) for caPRS, and 1.67 (95% CI: 1.58–1.77) for caPRSx (Table 1).
- Skewness reduction in caPRSx suggests better calibration and improved predictive power, with Pearson skewness coefficients of 0.050 (95% CI: –0.09 to –0.19) for PRS313, 0.039 (95% CI: –0.1 to 0.18) for caPRS, and 0.0022 (95% CI: –0.13 to 0.14) (Figure 2 and Table 1).
- Failing to include an AJ ancestry group leads to an overestimation of risk, while incorporating this adjustment significantly improves PRS accuracy (Figure 3).
- Adjusting PRS using an AJ reference panel reduced lifetime BC risk estimates by an average of 2.5% (range: 0.04% to 14.2%) across 2,068 AJ women (Figure 3).

Figure 2. Comparison of PRS Distribution across Models.

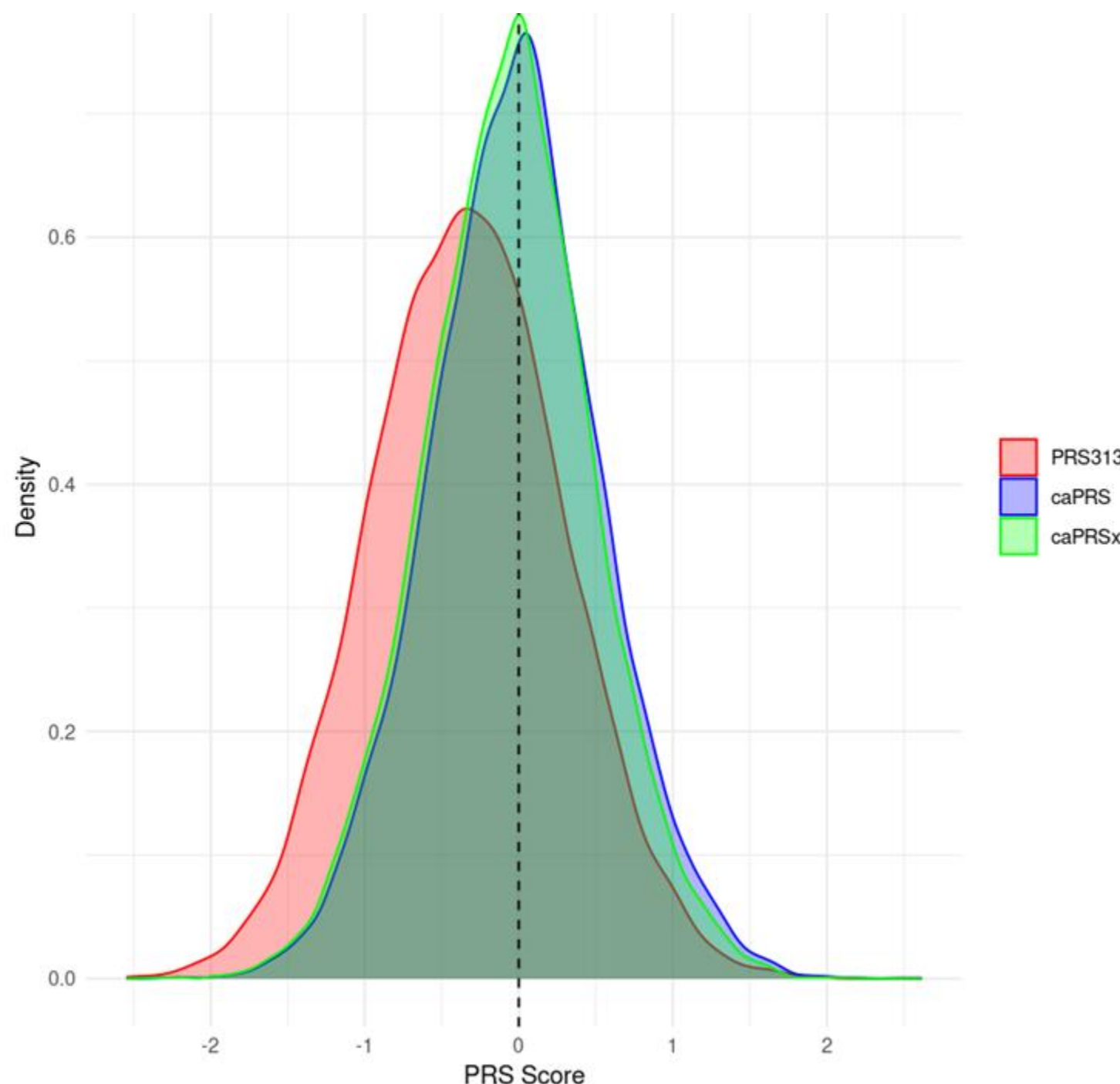
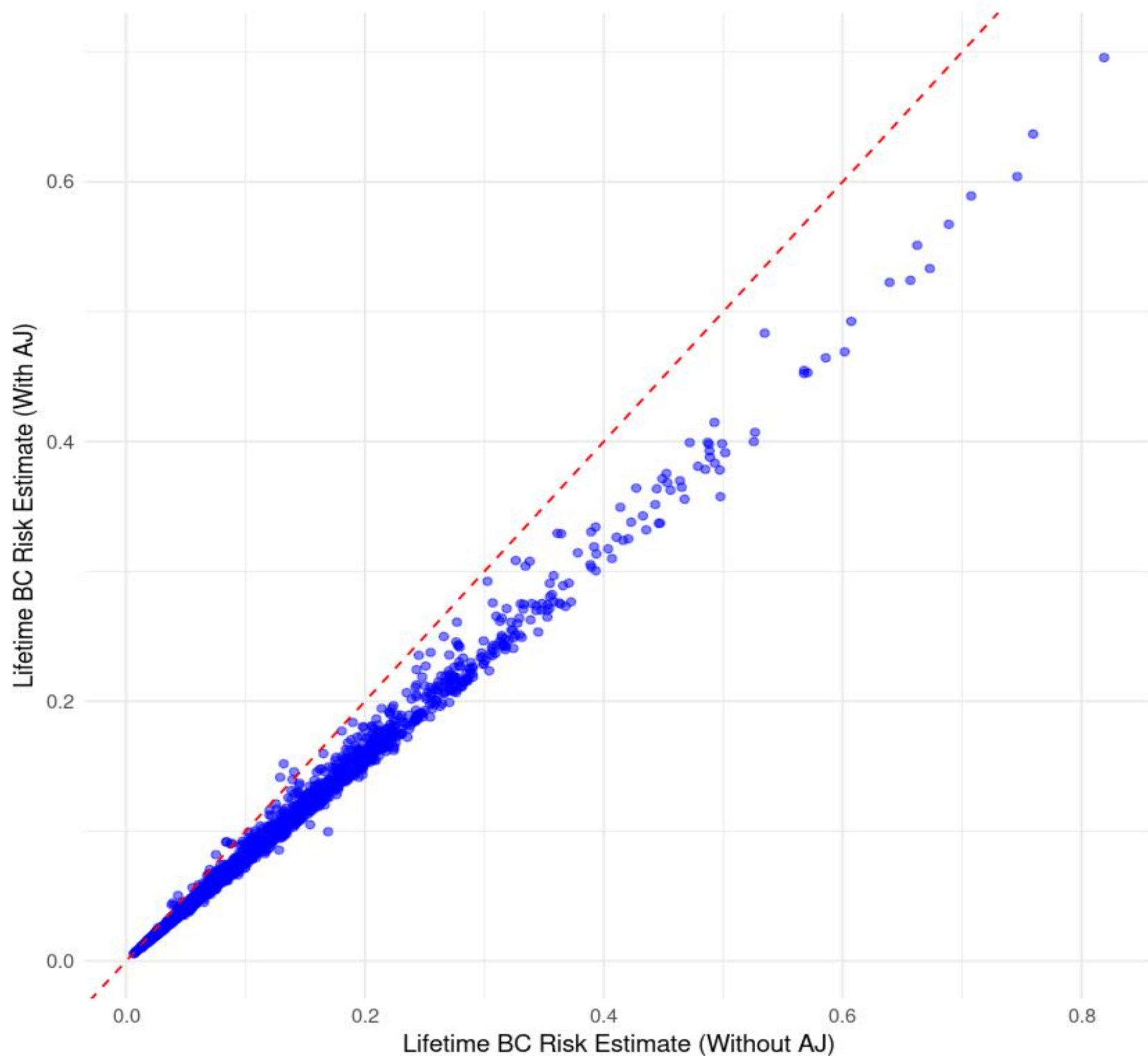


Table 1. PRS Model Performance Metrics.

PRS Model	Skewness (95 % CI)	OR per SD (95% CI)
PRS313	0.050 (–0.09 – 0.19)	1.53 (1.45 – 1.62)
caPRS	0.039 (–0.1 – 0.18)	1.66 (1.57 – 1.75)
caPRSx	0.0022 (–0.13 – 0.14)	1.67 (1.58 – 1.77)

Figure 3. Impact of Ashkenazi Jewish Ancestry Inclusion on Lifetime Breast Cancer Risk Estimates (PRS + Tyrer–Cuzick Score).



CONCLUSIONS AND FUTURE DIRECTIONS

- The caPRSx model demonstrated superior performance in predicting BC risk among AJ women compared to PRS313 and caPRS.
- Adjusting PRS models with ancestry-specific reference panels significantly improved accuracy and reduced bias in risk estimation.
- Ancestry-adjusted PRS models like caPRSx can enhance personalized BC risk prediction and support targeted screening strategies.
- These findings reinforce the necessity of expanding genomic reference panels to include underrepresented populations for more equitable and accurate risk assessments.
- Next, we will use longitudinal studies to assess the long-term predictive power of ancestry-adjusted PRS models in real-world clinical settings.