

1. Background

- Breast cancer** is the most common cancer among women in the UK and the fourth leading cause of cancer death¹.
- Accurate risk prediction** helps identify individuals at highest risk who may benefit from targeted interventions.
- Tyrer-Cuzick (TCv8) model:**
 - Widely used in Family History, Risk and Prevention Clinics (FHRPCs) for risk prediction².
 - Uses detailed questionnaire data on family history and reproductive, hormonal and environmental factors.
 - Optional inputs: **mammographic density (MD)** and **polygenic risk scores (PRS)**³.

Objective: Evaluate risk stratification performance of the TC model in a FHRPC in Manchester, UK.

2. Methodology

Cohort:

- Breast cancer-free women who consented between 2010-2012 at the FHRPC, Manchester.
- Follow-up: until January 2024; censored at breast cancer diagnosis, risk reducing mastectomy, non-breast-cancer-related death, migration or end of follow-up.

Data :

- Questionnaire
- Saliva for genetic testing:
 - BRCA1/2 variants
 - PRS (SNP313 / SNP143 / SNP18)
- Digital mammograms analysed with Volpara for breast density

Tyrer-Cuzick risk models:

- base** (questionnaire only)
- + PRS** (questionnaire + non-BRCA PRS)
- + MD** (questionnaire + mammographic density)
- full** (questionnaire + PRS + MD)

Analysis:

- Stratified by **BRCA status** (BRCA1, BRCA2, non-carrier) and **10-year risk groups** (<3%, 3-5%, 5-8%, 8+%), corresponding to current UK risk-based screening guidance.
- Calibration Assessment:**
 - Absolute:** observed-to-expected (O/E) ratios to compare observed breast cancer diagnoses (O) with expected (E) from each Tyrer-Cuzick model.
 - Relative:** Cox models of log(10-year risk)

3. Results

a) Baseline Characteristics

Characteristics:

- Age: 49 (mean); 8.2 (sd)
- 55% premenopausal
- 80% parous
- 6% on endocrine therapy
- 10% enrolled in IBIS-1/11 trials

PRS availability:

PRS type	Number (%)
SNP313	718 (77%)
SNP143	193 (21%)
SNP18	21 (2%)

Table 1: Number of patients with each PRS type used in the analysis.

b) Breast Cancer, Surgery and Mortality

Women carrying variants in moderate- or high-penetrance genes have an increased risk of breast cancer (moderate: 20-50%; high: >50% lifetime risk).

	Mutation	Number (%)	Breast cancers, n (%)	Non-BC Deaths, n (%)	RRM, n (%)
High	Non-carrier	845 (100%)	34 (4.0%)	13 (1.5%)	10 (1.2%)
	BRCA1	25 (3%)	4 (16.0%)	2 (8.0%)	5 (20.0%)
	BRCA2	39 (5%)	8 (20.5%)	3 (7.7%)	10 (25.6%)
	PALB2	7 (1%)	1 (14.3%)	0 (0.0%)	0 (0.0%)
	CHEK2	11 (1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Moderate	ATM	10 (1%)	2 (20.0%)	0 (0.0%)	0 (0.0%)
	RAD51D	2 (0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	939 (111%)	49 (5.2%)	18 (1.9%)	25 (2.7%)

Table 2: Number of women, breast cancers, non-breast-cancer-related deaths and risk-reducing mastectomies in carriers and non-carriers of breast cancer mutations.

Key observations:

- Median follow-up: 10 years
- Breast cancer incidence was low in non-BRCA (36/868; 4%) and high in BRCA carriers (12/64; 19%)
- Risk-reducing mastectomies (RRMs) and non-breast cancer-related deaths were more common in BRCA carriers.

3. Results

c) Risk Group Reclassification

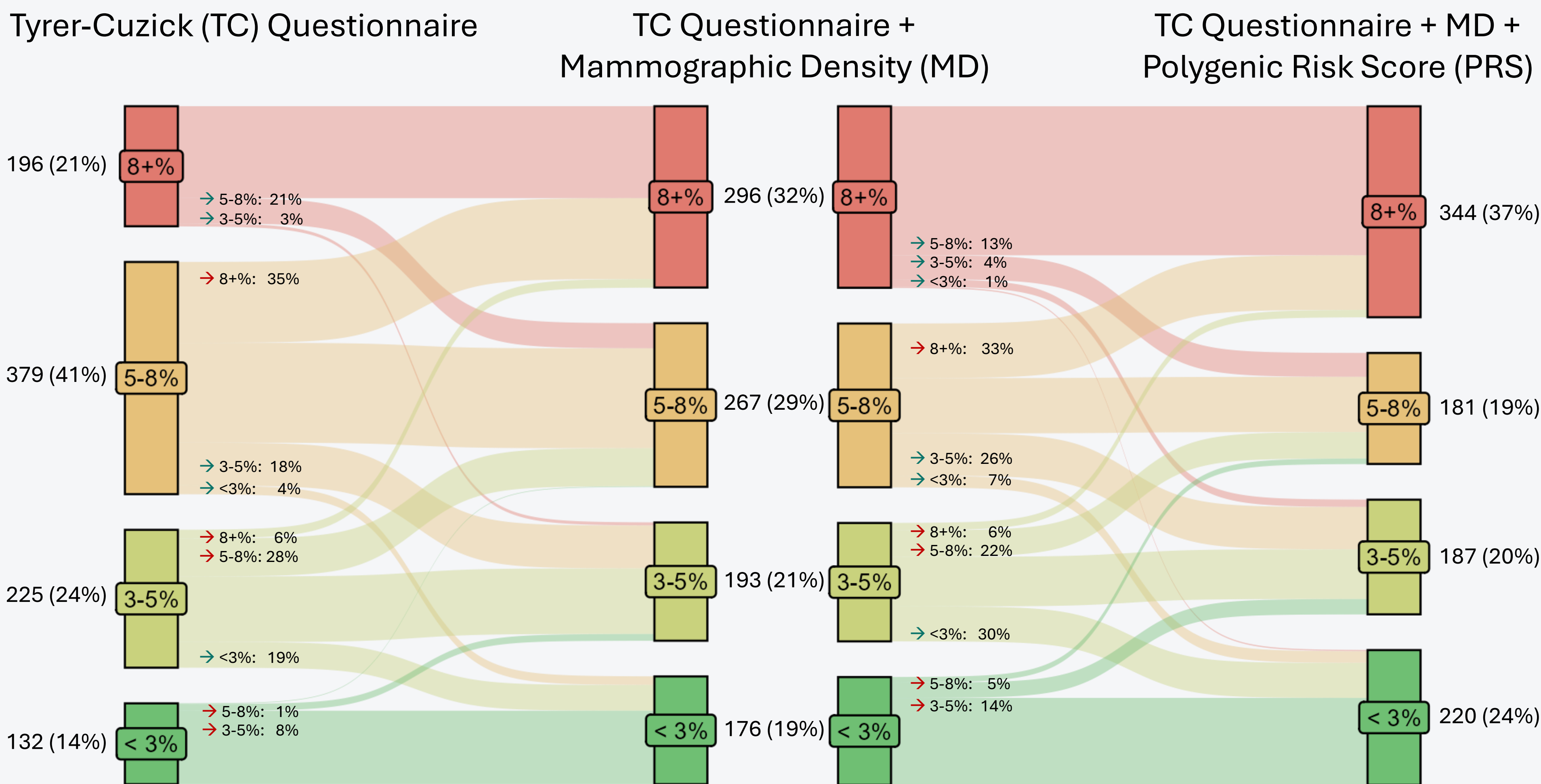


Figure 1: Reclassification of 10-year risk estimated by the Tyrer-Cuzick (TC) model when mammographic density (MD) and polygenic risk scores (PRS) are included in the model.

MD and PRS flatten risk distribution:

- Net increase of +148 individuals into the highest (8+%) category and of +88 into the lowest (<3%) category.
- Net decrease in the middle two categories (3-5%: -5; 5-8%: -198).

d) Calibration Assessment - Absolute

BRCA1/2 calibration (Table 3):

- BRCA1: Observed < Expected => overestimation by the model
- BRCA2: Observed > Expected => underestimation by the model

Mutation Group	TCv8 (base)	+ MD
BRCA1	0.78 (0.21 – 1.99)	0.75 (0.20 – 1.92)
BRCA2	1.31 (0.56 – 2.58)	1.09 (0.47 – 2.15)

Table 3: Number of cases **observed** divided by number **expected** by base Tyrer-Cuzick model and TC + Mammographic Density (MD) in BRCA1/2 carriers.

Non-BRCA subgroup calibration (Figure 2):

Calibration slope < 1 for all models => overestimating high risk and underestimating low risk.

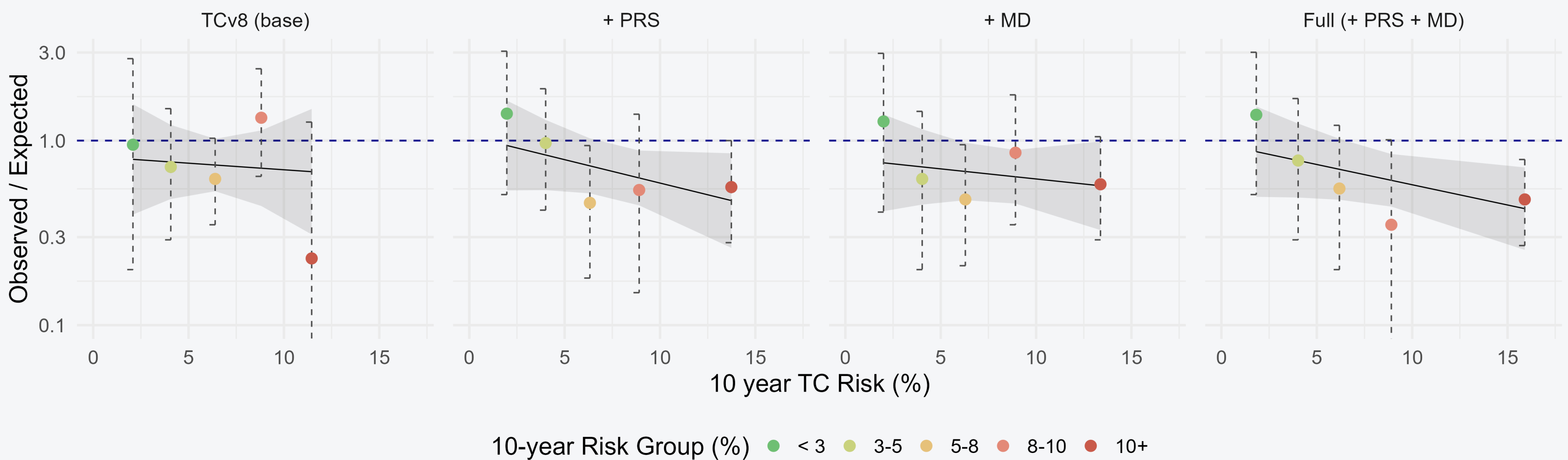


Figure 2: Number of cases **observed** divided by number **expected** within each 10-year risk group predicted by the four Tyrer-Cuzick model variants. Regression line with 95% confidence interval is shown in black and perfect calibration is shown at O/E = 1 with a blue dashed line.

d) Calibration Assessment - Relative

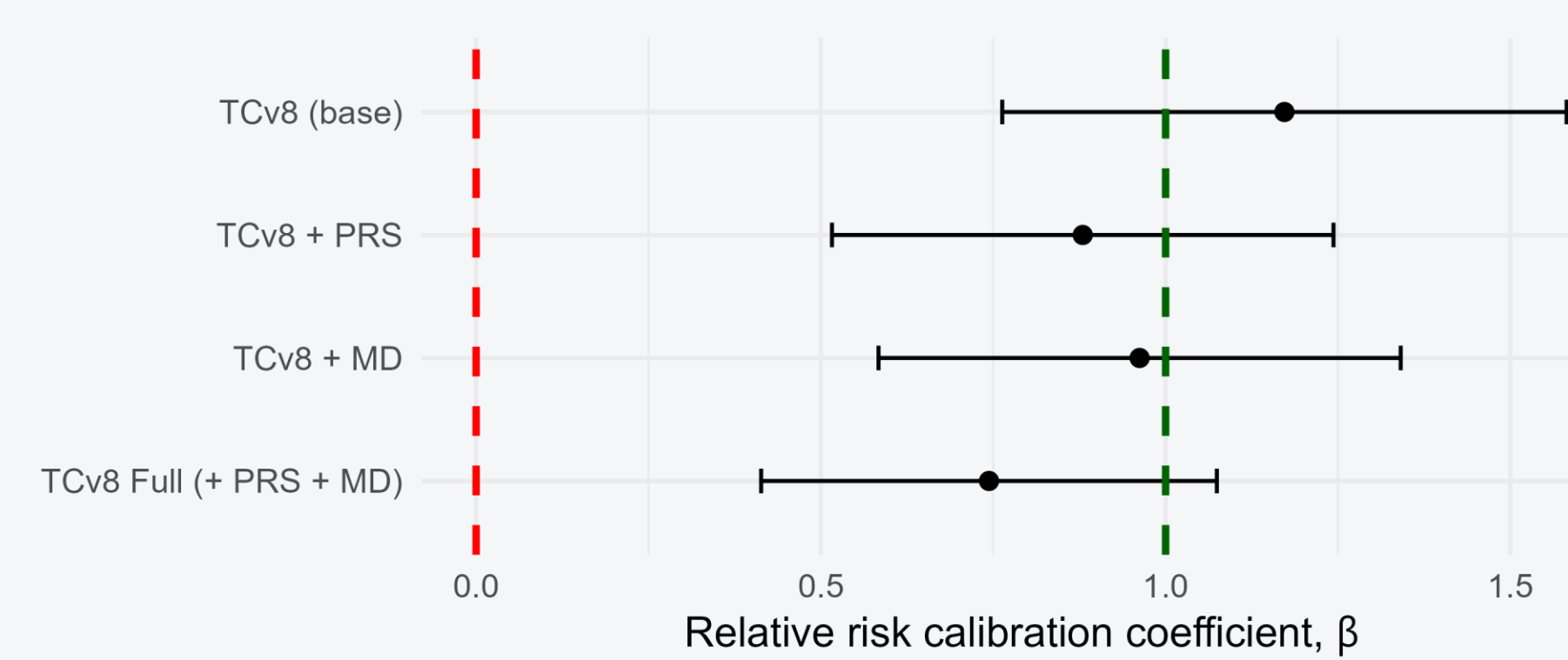


Figure 3: Relative risk calibration of Tyrer-Cuzick (TC) 10-year risk for each model variant (PRS: Polygenic Risk Score; MD: Mammographic Density). Cox regression coefficients for log(10-year TC risk) with 95% confidence intervals are shown.

$\beta = 1$ => perfect relative calibration;
 $\beta = 0$ => no association with breast cancer.

All models have good relative risk calibration.

4. Interpretation & Future Work

- Tyrer-Cuzick v8 model provided reasonable risk stratification in a UK FH clinic**, supporting the potential of current risk models.
- Incorporating breast density and PRS substantially changed the risk profile of the cohort, resulting in a flatter distribution with more individuals put in the extreme risk categories.
- However, **precision of calibration estimates was limited by sample size.**
- Consistency of PRS to be improved by using SNP313 for everybody.
- There is a **need for further validation in larger cohorts.**

References

- Cancer Research UK. [cited 2025 20/05/2025].
- Evans, D.G., et al., *Breast cancer incidence and early diagnosis in a family history risk and prevention clinic: 33-year experience in 14,311 women*. Breast Cancer Research and Treatment, 2021. **189**(3): p. 677-687.
- Evans, D.G.R., et al., *Breast cancer risk stratification in women of screening age: Incremental effects of adding mammographic density, polygenic risk, and a gene panel*. Genetics in Medicine, 2022. **24**(7): p. 1485-1494.