Early identification of polycystic ovary syndrome and *associated multimorbidity* — a multi-cohort study

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01 BACKGROUND

A common syndrome, frequently missed.

> *PCOS affects 5–18% of women of reproductive age, yet up to 70% never receive a formal diagnosis.*

PCOS is a heterogeneous, multisystem condition emerging gradually across adolescence and early adulthood — defined by oligo-/anovulation, hyperandrogenism, and polycystic ovarian morphology (Rotterdam, 2003).

Why earlier matters

- 4× increased risk of type 2 diabetes
- Elevated CV risk — hypertension, dyslipidaemia, IHD, stroke
- MASLD, endometrial hyperplasia & cancer
- Adverse obstetric outcomes; high rates of anxiety & depression
- Conventional CV risk scores systematically underestimate risk in younger women

02 AIM & APPROACH

Predict PCOS years before recognition.

Develop and externally validate **TRisk**, a transformer-based survival model on routinely collected EHR, to predict future clinical PCOS diagnosis and identify women at elevated risk of PCOS-related multimorbidity.

03 COHORTS

UK development. USA external validation.

UK · INTERNAL

CPRD Aurum

DEVELOPMENT & VALIDATION

6,507,815	2,046,104
DEVELOPMENT	VALIDATION
37,805	**1.5 yr**
TOTAL PCOS PATIENTS	MEDIAN F/U

USA · EXTERNAL

All of Us

FINE-TUNE & VALIDATION

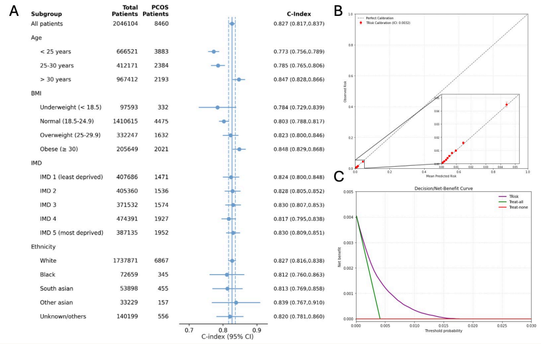
52,834	79,252
FINE-TUNE	VALIDATION
1,966	**2.67 yr**
TOTAL PCOS PATIENTS	MEDIAN F/U

04 RESULTS · MODEL PERFORMANCE

Strong, stable discrimination across systems.

Discrimination, calibration & net benefit

FIG 1 · CPRD AURUM (UK) VALIDATION

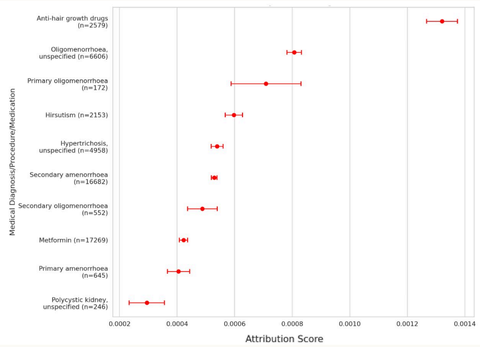


EXTERNAL VALIDATION · ALL OF US (USA)

0.762	79,252	1,183
C-INDEX (0.731–0.792)	WOMEN VALIDATED	PCOS DIAGNOSES

Top contributing feature groups

FIG 2 · UK · INTEGRATED GRADIENTS

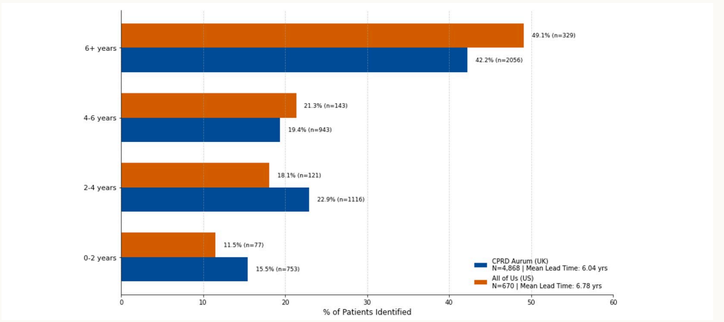


Predictions reflect **established PCOS biology** — anti-hair-growth drugs, oligomenorrhoea, primary oligomenorrhoea, hirsutism, secondary amenorrhoea, and metformin. Attribution distributed across convergent features rather than a single diagnostic code; broadly consistent in All of Us.

05 LEAD TIME & HIGH-RISK PHENOTYPE ANALYSIS

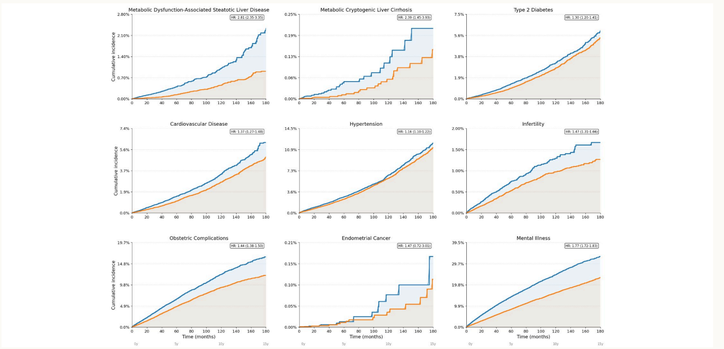
Lead time before clinical diagnosis

FIG 3 · UK & USA · AMONG CAPTURED CASES (~60%)



Cumulative incidence — top decile vs. matched controls

FIG 4 · UK · 15-YEAR FOLLOW-UP (0–180 MONTHS)



HR (95% CI) shown per panel

ALL OF US (USA) · 10-YEAR MATCHED COHORT FOLLOW-UP

Broadly consistent with UK findings across cardiometabolic, reproductive, and mental health outcomes.

↑ Cardiometabolic	↑ Reproductive	↑ Mental health
MASLD · T2D · CVD · HTN	Infertility · obstetric	Consistent with UK finding

INTERPRETATION

A transformer-based survival model on routinely collected EHR can identify women at elevated PCOS risk several years before clinical recognition — and stratify a high-risk group with substantial, modifiable multimorbidity burden currently missed by existing care pathways. Findings are consistent across the UK (15-yr follow-up) and USA (10-yr follow-up) healthcare systems.

IMPLICATIONS

Deployed as a background risk-flagging tool in primary care, this approach could support structured case-finding, earlier metabolic and CV monitoring, and timely fertility planning.

Prospective evaluation is needed to confirm earlier identification reduces diagnostic delay and improves outcomes — alongside equity, clinical acceptability, and cost-effectiveness.

LIMITATIONS

EHR-based outcomes capture *recorded* diagnoses — undiagnosed cases remain censored. UK-trained model required fine-tuning before USA validation. Discrimination lower in younger and underweight subgroups. Calibration deviated mildly at high predicted probabilities in the USA cohort.

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