EVALUATING THE PREDICTIVE ABILITY OF POLYGENIC RISK SCORES FOR INTRAHEPATIC CHOLESTASIS OF PREGNANCY IN THE ESTONIAN BIOBANK

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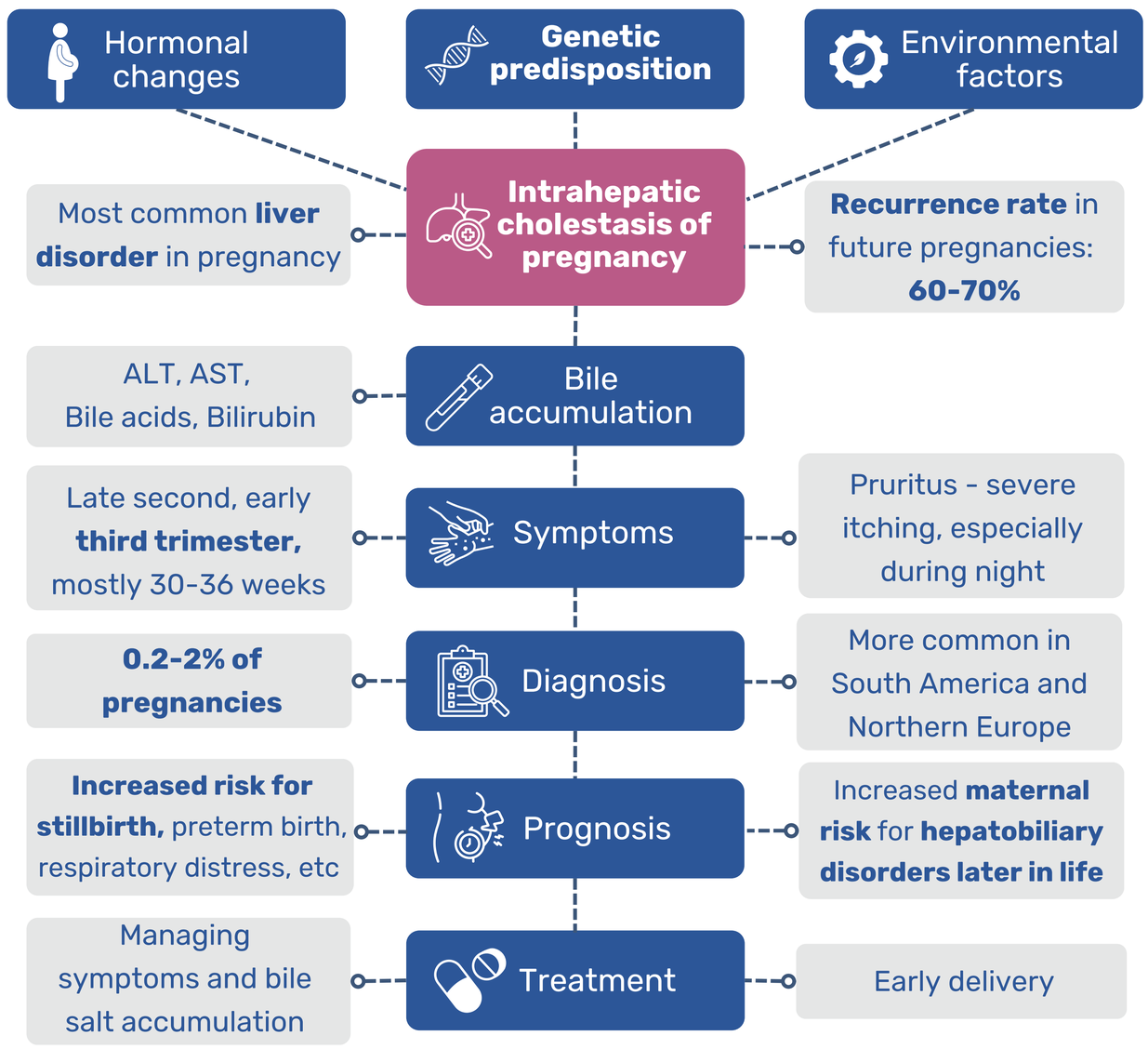


OBJECTIVE

Recent studies have identified genetic factors underlying intrahepatic cholestasis of pregnancy (ICP), enabling **evaluation of polygenic risk score (PRS) as a predictive tool for ICP**.

METHODS

ICP PRS was calculated for **Estonian Biobank participants** using **independent genome-wide association study (GWAS)** meta-analysis summary statistics (1,138 ICP cases and 153,642 European ancestry controls; Dixon et al., 2022).

The following analyses were carried out:

- Logistic regression, to assess the **association between ICP risk and PRS**, adjusted for birth year and first 10 genetic principal components (PCs); **validated in the Trøndelag Health Study (HUNT, Norway).**
- **Time-to-event** analysis (Cox proportional hazards), to evaluate the **risk for ICP onset**, adjusted for age at pregnancy, birth year, and first 10 PCs; one pregnancy per woman, with gestational weeks to ICP diagnosis (cases) or delivery (controls) as time-to-event.
- **Phenome-wide association study (PheWAS)** to explore the **association between the ICP PRS and other phenotypes;** conducted separately for women and for men and women combined, using ICD-10 main category codes.

ASSOCIATION BETWEEN PRS AND ICP RISK

Estonian Biobank:

Cases: 1,152 (women with ICD-10: O26.6)
Controls: **47,775** (women with delivery-related ICD-10 codes, no ICP)

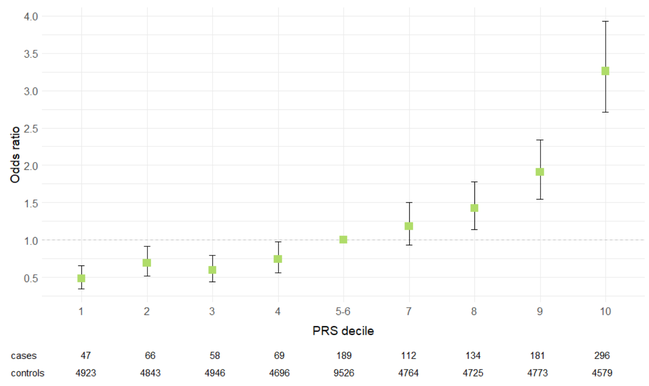
PRS association (per SD increase):

- OR = **1.9** (95% CI: 1.8-2.0, $p=3.8\times10^{-91}$)

Prevalence: **6.1%** (highest PRS decile) **vs. 0.9%** (lowest decile)

Odds Ratios by PRS deciles:

- Highest vs. Lowest: OR = **6.7** (95% CI: 5.0–9.3, $p=1.9\times10^{-33}$)
- Highest vs. Middle: OR = **3.3** (95% CI: 2.7–3.9, $p=1.4\times10^{-35}$)



Predictive performance (AUROC):

- With PRS: **0.66**
- Without PRS: 0.55

HUNT Study (Replication):

Cases: 71
Controls: 10,073

PRS association (per SD increase):

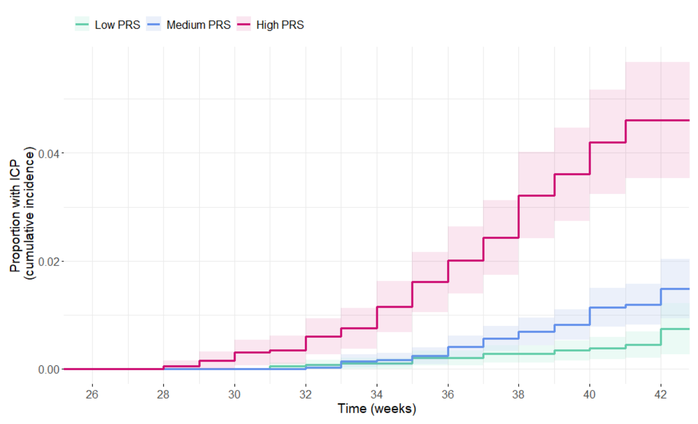
- OR = **1.7** (95% CI: 1.3-2.1, $p=2.8\times10^{-5}$)

TIME-TO-EVENT ANALYSIS

Cases: 138
(ICP diagnosis confirmed by elevated liver enzymes)
Controls: 10,073

Hazard Ratio (per PRS SD increase):

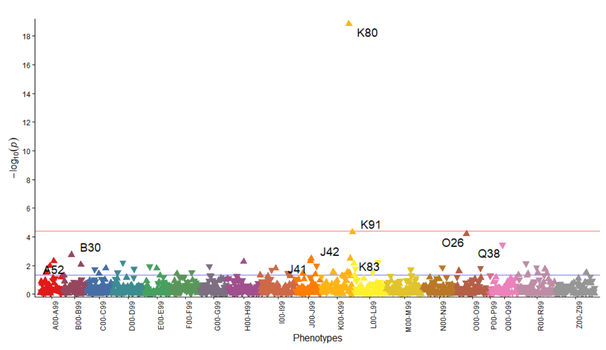
- HR = **2.5** (95% CI: 2.1-2.9, $p=1.9\times10^{-23}$)



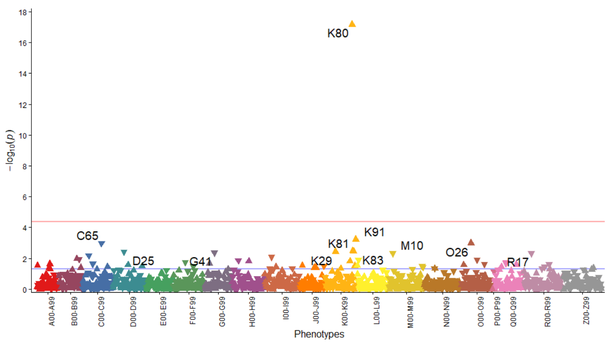
PHENOME-WIDE ASSOCIATION STUDY

Significant association identified: **Cholelithiasis** (ICD-10: K80)

Women only: $p=1.4\times10^{-19}$



Combined: $p=6.7\times10^{-18}$



KEY MESSAGE:

PRS is a valuable tool for predicting ICP risk and identifying high-risk women for enhanced monitoring strategies to improve maternal and fetal outcomes

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