Nature versus nurture of the puberty: a combined clinical and polygenic risk score to predict pubertal timing in girls

Mojgan Yazdanpanah[a], Nahid Yazdanpanah[a], Sara Moline[b], Ken Ong[c,d], John Perry[c] and Despoina Manousaki[a,b,e]

[a] Research Center of Sainte-Justine University Hospital, University of Montreal, Montreal, Quebec, Canada
[b] Department of Pediatrics, University of Montreal, Montreal, Quebec, Canada
[c] MRC Epidemiology Unit, University of Cambridge School of Clinical Medicine, Institute of Metabolic Science, Cambridge Biomedical Campus, Cambridge, UK
[d] Department of Paediatrics, University of Cambridge, Cambridge, UK
[e] Departments of Pediatrics, Biochemistry and Molecular Medicine, University of Montreal, Montreal, Quebec, Canada

Background

- Precocious or late puberty are common causes of referral to pediatric endocrinology.
- Most of these cases are idiopathic and do not require extensive work-up.
- Pubertal traits are highly heritable.
- Epidemiological risk factors (obesity, socio-economic status etc) have also been linked to pubertal timing.

➢ Objective 1 : to evaluate the impact of genetic and epidemiological factors on age at menarche (AAM) and age at peak height velocity (APHV)
➢ Objective 2: to develop a predictor of early or late AAM

Methods

STUDY COHORT : ALSPAC[2]

- British birth cohort with genotypic and clinical data
- 8,799 children of European ancestry/3,140 girls
- Median AAM : 12.7 years (SD 1,15)
- Mean APHV : 11.8 years (SD 0,82)
- 1.9 % girls with BMI ≥ 25

POLYGENIC RISK SCORE (PRS) for AAM

- Developed from a GWAS in UK Biobank on AAM using LDpred2 (Privé F et al., 2022[1]).
- 854,735 single-nucleotide polymorphims (SNPs) included in the PRS
- 699,499 SNPs (after QC) used to calculate the AAM PRS in ALSPAC

PHENOTYPIC DATA

- Exposure of interest: PRS
- Outcomes:
  - AAM as a continuous outcome
  - Early menarche (AAM ≤ 10.4y); Late menarche (AAM ≥ 15y)
  - APHV evaluated by serial height measurements between ages 8y and 20y
- Covariates : BMI at age 8y, birthweight, gestational age, emotional difficulties score, mother's AAM, BMI and SES, fathers' BMI.

STATISTICAL METHODS

- Linear regression models in univariate and multivariate analyses
- All models with PRS were adjusted for 10 principal components (PC)
- Metrics of performance of each model : R^2 (continuous outcomes), AUROC (binary outcomes)

Results

UNIVARIATE MODELS

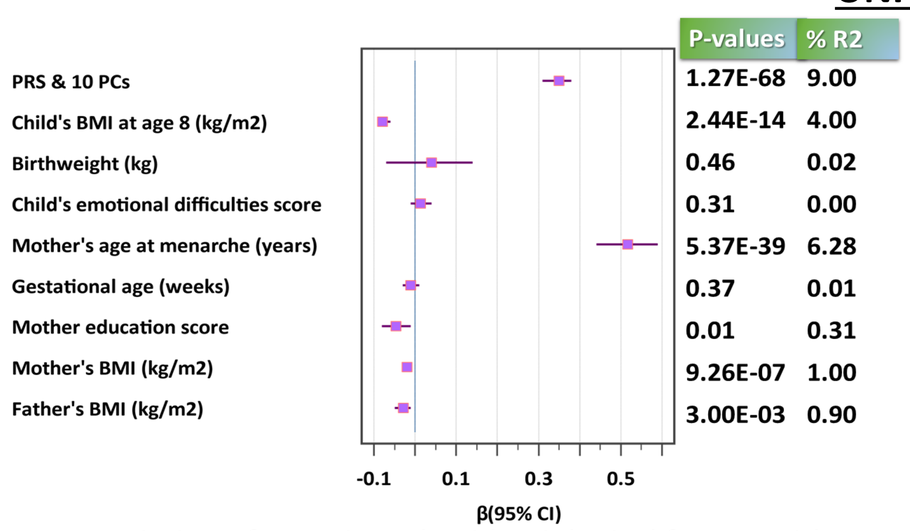

Fig. 1 : Association of genetic and epidemiological factors with AAM

*Betas represent years

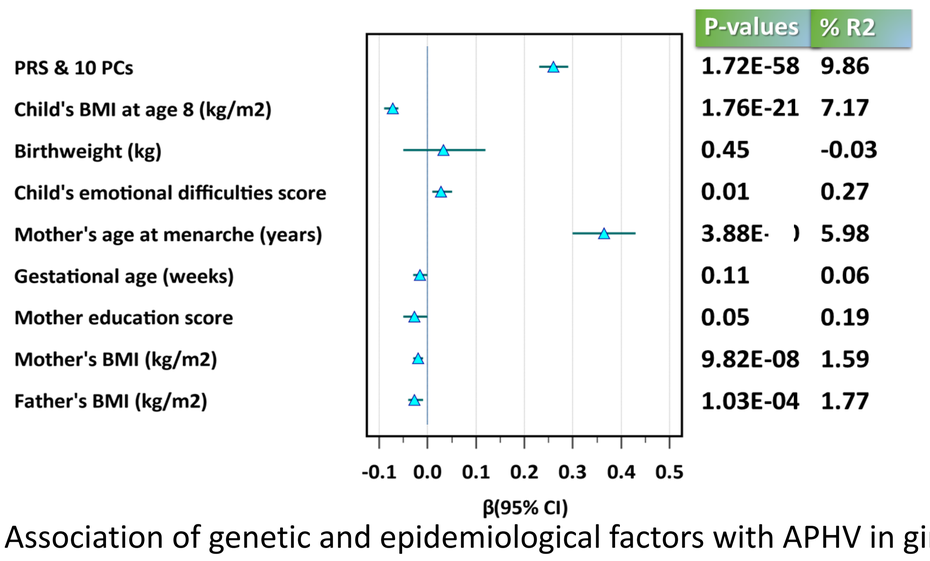

Fig. 2 : Association of genetic and epidemiological factors with APHV in girls

MULTIVARIATE MODELS

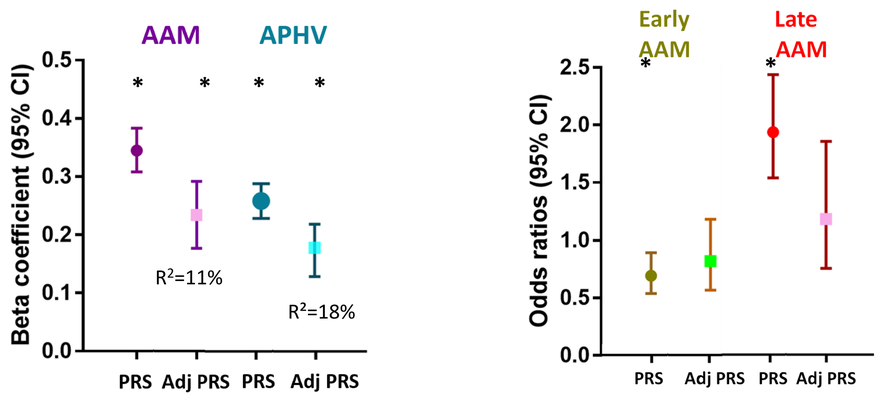

Fig 3: Comparison of the effects of the unadjusted and adjusted PRS
Betas and OR represent changes in the outcomes per 1 SD increase in the PRS
Adj PRS: PRS adjusted for age at menarche of mother and child BMI at age 8 years

AUROC for early and late AAM

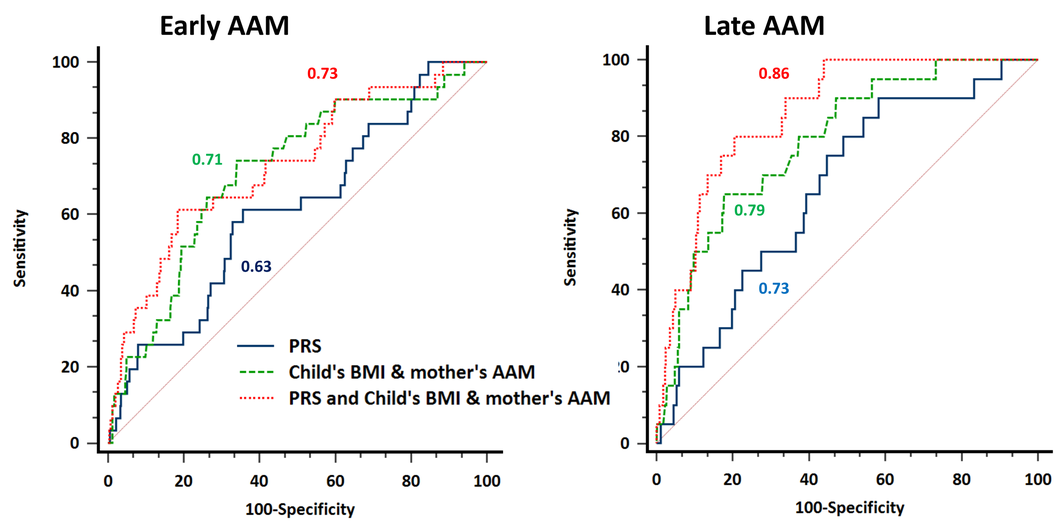

Fig. 4: Comparison of the AUROC of the PRS, clinical predictors, and their combination

Discussion

- We demonstrates the advantage to combine PRS with clinical risk factors to predict pubertal timing, in agreement with a Chinese study[3].
- Such predictors could help clinicians diagnose idiopathic forms of early puberty and avoid unnecessary investigations.
- Next step: replication of our findings in larger cohorts, various ancestries and in boys.

Conclusion

A combined clinical and polygenic risk score could be proposed as a tool to predict (at no risk and low cost) which girls with extreme presentations of their pubertal timing do not warrant further investigations.

References

[1]Privé, F., et al. Portability of 245 polygenic scores when derived from the UK Biobank and applied to 9 ancestry groups from the same cohort. Am J Hum Genet. 2022 Jan 6;109(1):12-23. PMID: 34995502
[2]Fraser, A., et al. Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. Int J Epidemiol. 2013; 42, 97-110.
[3]Zhao, W., et al. Associations between polygenic risk score for age at menarche and menopause, reproductive timing, and serum hormone levels in multiple race/ethnic groups. Menopause. 2021 Apr 19;28(7):819-828.