Perinatal exposures and biological ageing markers to predict metabolic syndrome risk in offspring at age 22; Development, validation, and clinical utility of a prediction model.

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Abstract

Background: Metabolic syndrome (MetS) increases the risk of cardiovascular disease, type 2 diabetes and other chronic conditions. Early identification of individuals at high-risk may enable targeted prevention and reduce long-term disease burden. Perinatal exposures including obstetric, behavioural, and demographic factors, and biological ageing markers such as epigenetic ageing and telomere length have been linked to later MetS risk.

Method: Using data from 664 Gen2 participants (age 22 years) in the Raine Study, we developed and internally validated a perinatal risk factor prognostic model (Model 1) and evaluated the incremental predictive value of biological ageing markers in predicting risk for MetS. Predictors were selected using Lasso regression with 10-fold cross-validation. Model performance was evaluated using the area under the receiver operating characteristic curve (AUC) and calibration. The model was internally validated with bootstrapping technique and clinical utility was assessed with decision curve analysis.

Result: MetS prevalence at age 22 years was 9.6%. Model 1 included maternal age, pre-pregnancy BMI, smoking during pregnancy, and preterm birth (AUC = 0.72). Extended models each incorporating biological ageing markers such as DunedinPACE, Hannum age acceleration, and telomere length yielded AUCs of 0.72, 0.73, and 0.73, respectively. All models demonstrated good calibration, and bootstrap validation indicated minimal overfitting. Decision curve analysis showed the Model 1 yielded greater net benefit than a treat-all or treat-none strategies.

Conclusion: Routinely available perinatal variables provide practical and potential cost-effective tool for early MetS risk stratification, however external validation is firstly

Commented [JG1]: correct nomenclature?

Commented [JG2]: we are predicting, not diagnosing. Please check throughout

required. Biological ageing markers provided marginal improvement in some performance metrics and did not meaningfully enhance discrimination.