Association of Genetic Predisposition and Physical Activity With Risk of Gestational Diabetes in Nulliparous Women

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Abstract

- **Objective:** To assess the effects of PRS and physical activity on existing GDM risk models and identify patient subgroups who may receive the most benefits from receiving a PRS or activity intervention.
- **Design, Settings, and Participants:** The nuMoM2b cohort was established to study individuals without previous pregnancy lasting 20 weeks (nulliparous) and to elucidate factors associated with adverse pregnancy outcomes. A sub-cohort of 3,533 participants with European ancestry (mean age = 28.6, SD = 4.9 years) were used for risk assessment and performance evaluation. Participants were enrolled from 2010-2013 (Haas et al., 2015) and genotyped from 2019-2021 (Guerrero et al., 2022).
- **Exposures:** Self-reported total physical activity in early pregnancy was quantified as metabolic equivalent of tasks (METs). Polygenic risk scores were calculated for T2DM using contributions of 84 single nucleotide variants, weighted by their association in the DIAGRAM Consortium data.
- **Main Outcomes and Measures:** Prediction of the development of GDM from clinical, genetic, and environmental variables collected in early pregnancy, assessed using measures of model discrimination. Odds ratio (OR) and positive likelihood ratio (LR^+) were used for evaluating the effect of PRS and physical activity on GDM risk.
- **Results:** In high-risk population subgroups (body mass index ≥ 25 or age ≥ 35), individuals with high PRS (top 25^{th} percentile) or low activity (METs < 450) have increased odds of GDM diagnosis between 25 and 75%. Participants with both high PRS and low activity have 3 times higher odds of GDM diagnosis than the population, while those with either low PRS or high activity do not have increased odds of GDM diagnosis.
- **Conclusions and Relevance:** In this cohort study, the addition of PRS resulted in stratified risk of GDM diagnosis among high-risk patient subgroups, suggesting the benefits of targeted PRS ascertainment to encourage early intervention.

Introduction

Polygenic risk scores (PRS) for Type II Diabetes Mellitus (T2DM) can improve risk prediction for Gestational Diabetes Mellitus (GDM), yet the strength of the relationship between genetic and lifestyle risk factors has not been quantified. In this work, we assess the effects of PRS and physical activity on existing GDM risk models and identify patient subgroups who may receive the most benefits from receiving a PRS or activity intervention.

Association of PRS and physical activity with GDM risk

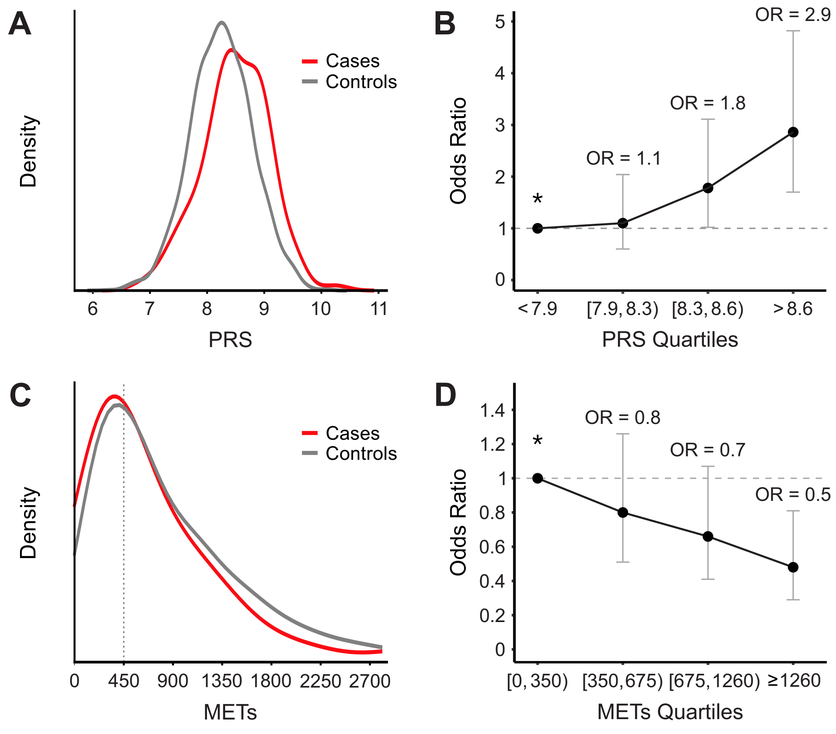

Figure 1: Influence of PRS and METs on GDM risk. (A) PRS Distribution. The distributions of PRS between participants who developed GDM (Cases, red lines) and those who did not (Controls, gray lines). (B) PRS OR Quartiles with 95% confidence intervals. Participants were divided into quartiles based on their PRS, with OR calculated against the reference group Q1, denoted by an asterisk. Quartile ORs are OR = 1.1 (0.6, 2.0) for Q2, OR = 1.8 (1.0, 3.1) for Q3, and OR = 2.9 (1.7, 4.8) for Q4. (C) METs Distribution. The distributions of METs between GDM cases and controls. (D) METs OR Quartiles with 95% confidence intervals. Participants were divided into four separate groups based on their METs, with OR calculated against the reference group Q1, denoted by an asterisk. Quartile ORs are OR = 0.8 (0.5, 1.3) for Q2, OR = 0.7 (0.4, 1.1) for Q3, and OR = 0.5 (0.3, 0.8) for Q4.

Stratification of Risk of GDM diagnosis

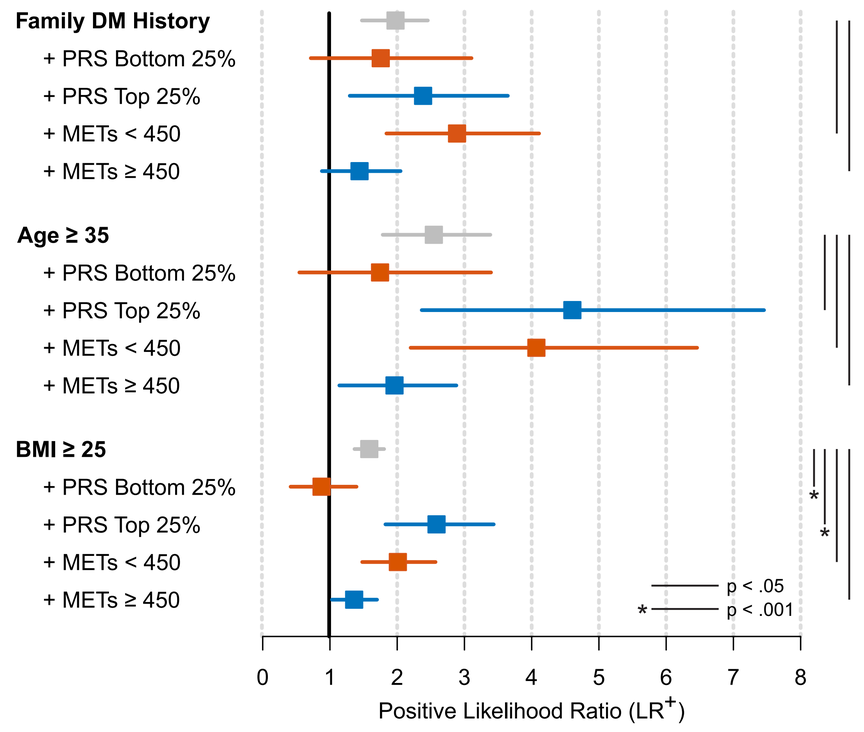

Figure 2: Positive likelihood ratio of GDM risk in the context of key clinical covariates (Family DM History, age, and BMI). The LR^+ values reflect the risk of developing GDM among subgroup participants with the entire cohort used as the reference group. LR^+ p-value against parent subgroup is the bootstrapped p-value of the LR^+, where the reference group is the parent subgroup only.

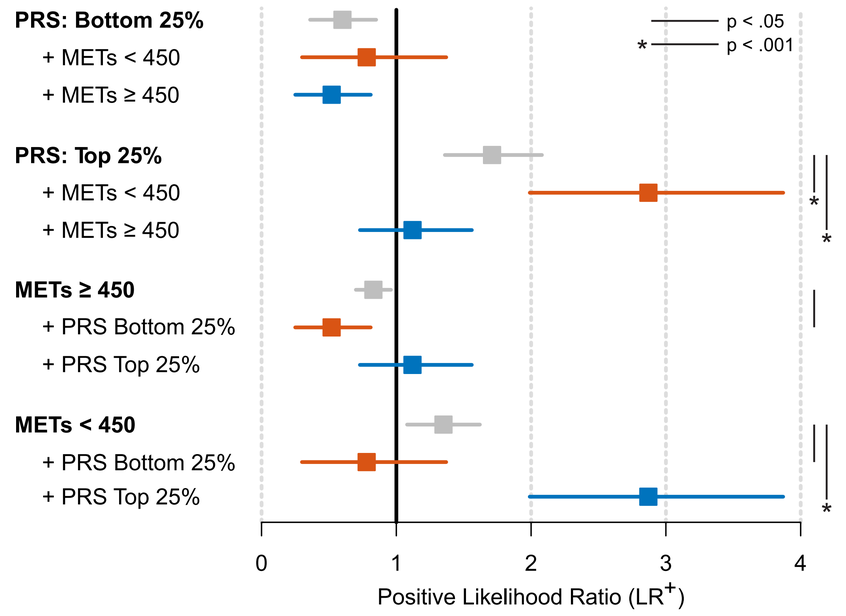

Figure 3: Positive likelihood ratio of GDM risk in the context of the cooperative effects of PRS and METs. The LR^+ values reflect the risk of developing GDM among subgroup participants with the entire cohort used as the reference group. LR^+ p-value was computed as in Figure 2.

A formal test of interaction between PRS and METs was carried out using the logit model with age and body mass index (BMI) as confounders. The data provides evidence of a nonadditive association between the two covariates (Pagel et al., 2022).

Conclusions

The risk of GDM diagnosis increases for women with high PRS as well as those with low level of physical activity. Physical activity in early pregnancy is associated with reduced risk of GDM and reversal of the excess risk in individuals with strong genetic predisposition. Collectively, this work highlights the potential for targeted interventions to mitigate GDM risk among nulliparas who are at risk through genetic predisposition, age, BMI, and family history of diabetes.

References

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