# Genetic contribution to Gestational Diabetes in South Asian Women: Analysis from the START-Canada Birth Cohort study

Presented by Jayneel Limbachia
Supervisor: Dr. Sonia Anand

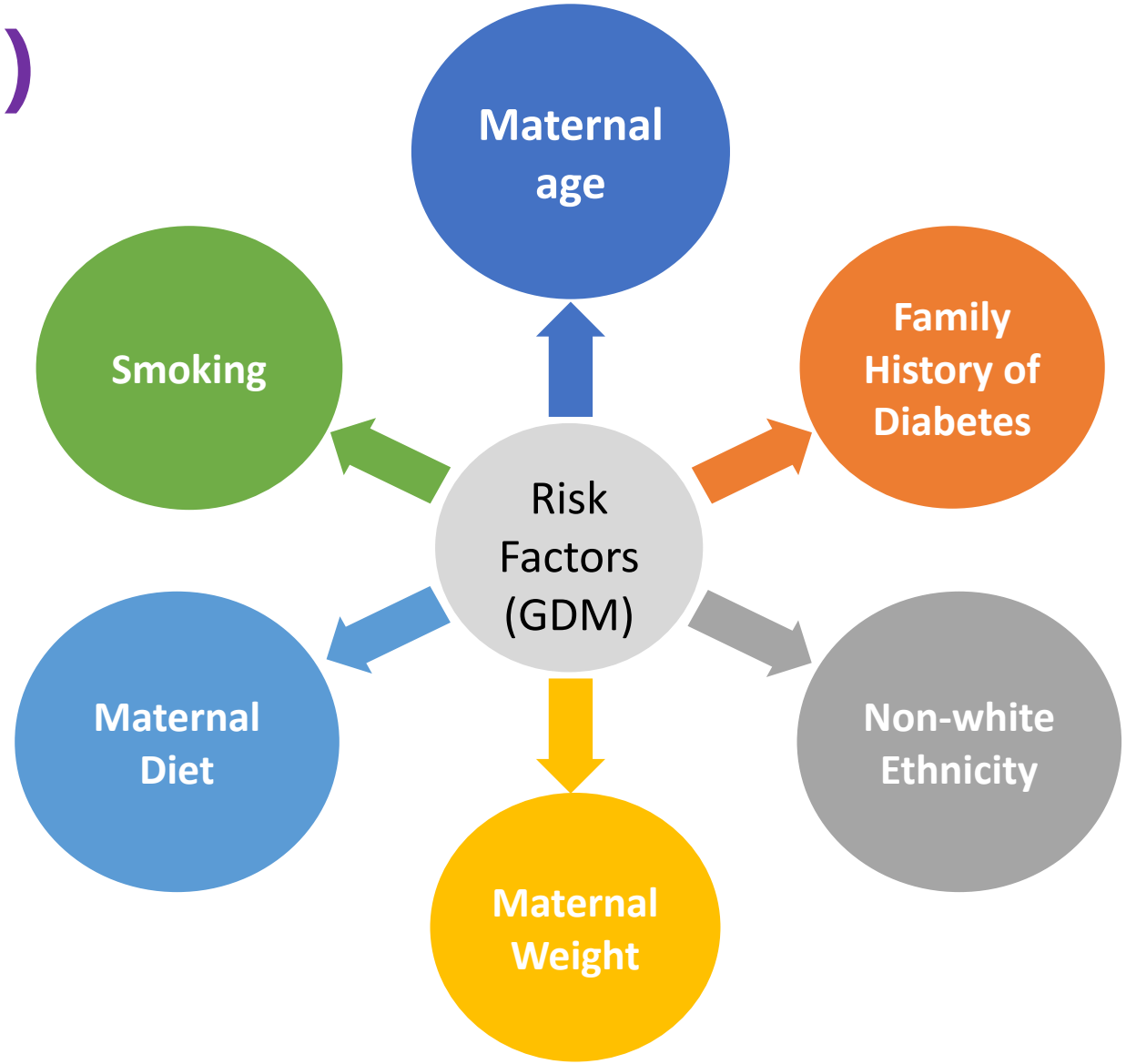
# Background

- South Asians are at an increased risk of Gestational Diabetes (GDM)
- GDM increases the likelihood of developing type 2 Diabetes and other co-morbid conditions such as CVD later in life in mothers and newborns
- Reasons for risks in South Asians are not well understood

# Background (Cont'd)

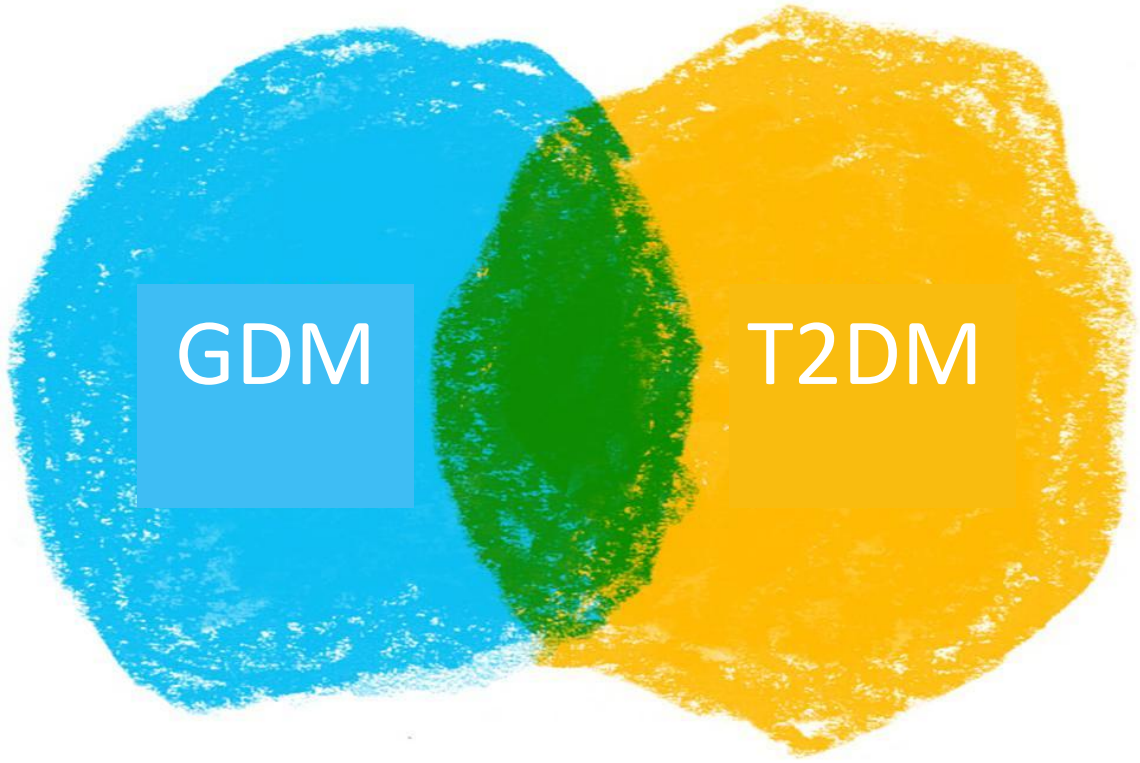
Previous analysis (Anand et. al., CMAJ open)

- Pre-pregnancy weight
- Low diet quality
- Advanced maternal age
- Maternal height
- Family History of T2DM



# Background (Cont'd)

- Family history of T2DM may be a crude surrogate for the genetic component of GDM
  - Large GWAS and GWAMA studies have confirmed more than 1500 loci associated with glycemic traits
    - A) MAGIC, B) DIAGRAM
  - Several T2DM loci have been shown to be associated with GDM



# Purpose/Objective

1) Test the association of a T2DM GRS with GDM in South Asians
2) Determine the extent of the contribution of our GRS in explaining the family history of T2DM (association with GDM)

# Research Question

**Among South Asian pregnant women part of START, is maternal GRS a significant predictor of GDM and to what extent does it change the effect size of family history of T2D as a predictor of GDM in this population**

# METHODS

# Study design – START

Longitudinal prospective birth cohort

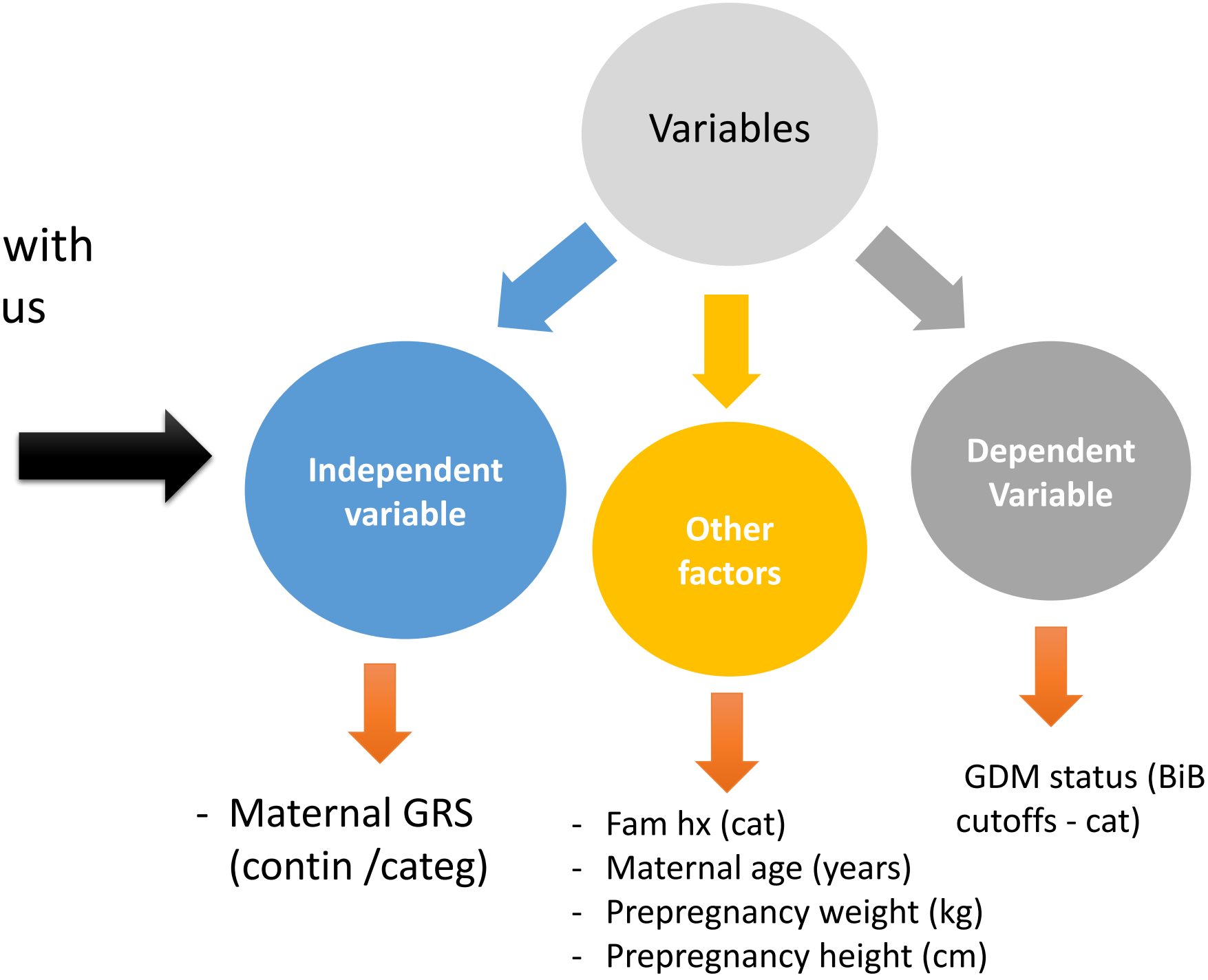
- examines early determinants of health in South Asians
- conducted among 1012 SA pregnant women from the Peel Region.

Ref: Anand, S. S., Gupta, M., Teo, K. K., Schulze, K. M., Desai, D., Abdalla, N., . . . Gerstein, H. (2017). Causes and consequences of gestational diabetes in South Asians living in Canada: results from a prospective cohort study. *CMAJ Open,5*(3), 604-611. doi:10.9778/cmajo.2017002

# Derived Variables

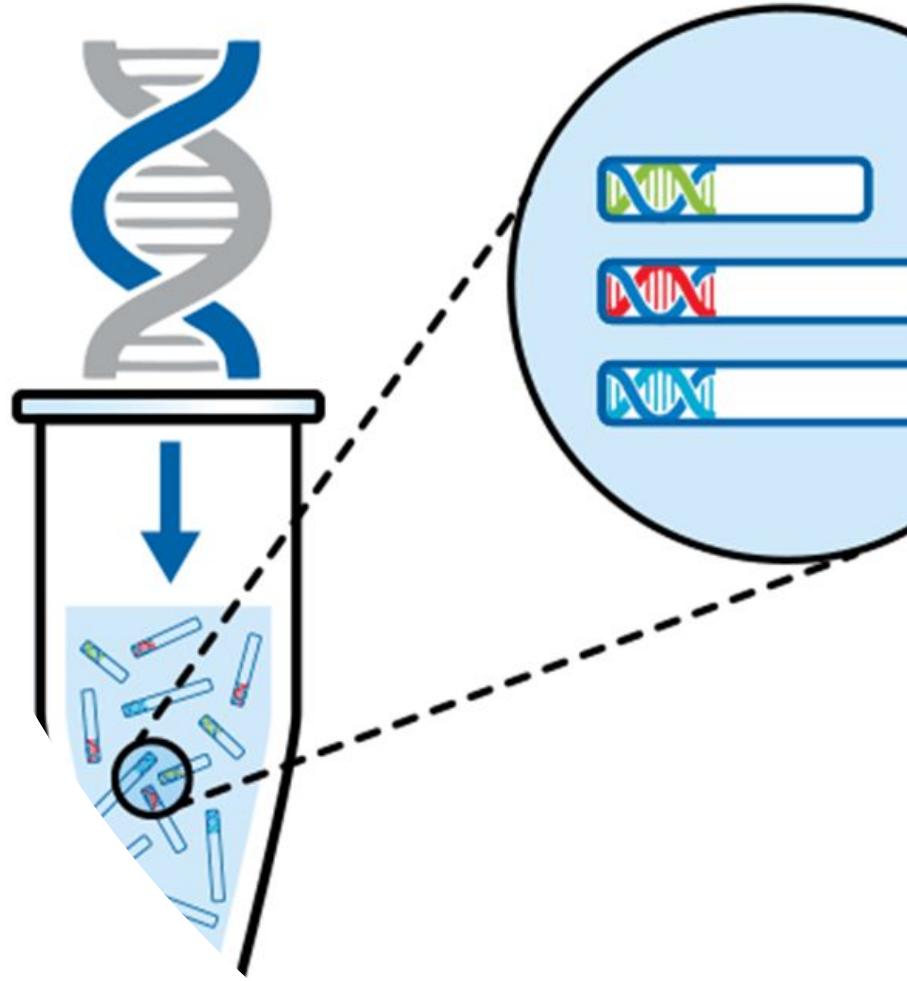
n = 832 mothers with known GDM status

Predictor of interest



# Building the GRS

- Summary statistics from DIAGRAM (Mahajan 2014)
  - SNPs tested in South Asians only
  - SNPs tested in >= 95% of samples only
- Genotyped data from 867 samples from START was used
- 837 samples passed QC
- Variants with an info score of $\geq$ 0.7 were kept for analysis
- A pruning and thresholding (PT) method was used to build the optimal GRS
  - START data use as LD template
  - P value threshold =0.2



# Statistical Analysis

- Analyses were conducted using SPSS v.24.
- Continuous GRS was transformed into a dichotomous category (T1 vs T2+T3)
- Binomial logistic regression: Single and multivariable models (including previously identified predictors of GDM)
- IRAP: calculate the population attributable risks (PAR) – frequency and disease exposure
  - Age was divided into categories (29-31, 32-43, vs 19-28)
  - BMI was divided into 3 categories (<18.5, 18.5-23, >23)

# RESULTS


regression
independent
outcome
coefficient
multiple
analysis
effect
confounding
variable
linear
coefficients
variables
association
Regression
modification
Multiple
Analysis
correlation
squares
logistic
Correlation
Linear
factors
risk
dummy
adjusting
equation
weighted
estimates
least
stratum
Cochran-Mantel-Haenszel
dependent
Y-intercept

# Table 1: Characteristics of START participants

| | No GDM (n= 531) | GDM (n=301) | p value |
|---|---|---|---|
| **Maternal Age, yr** | 30 (4) | 31 (4) | <0.001 |
| **Genetic Risk Score, cont.** | 0.01353 | 0.01356 | <0.001 |
| **Maternal Height, cm** | 162.71 (6.22) | 161.50 (6.18) | 0.007 |
| **Pre-pregnancy weight, kg** | 61.38 (11.71) | 64.89 (12.19) | <0.001 |
| **Pre-pregnancy BMI, kg/m$^2$** | 23.17 (4.21) | 24.89 (4.61) | <0.001 |
| **Low diet quality, n (%)** | 123 (23.5%) | 96 (32.2%) | 0.006 |
| **Family history of diabetes, n (%)** | 180 (34.0%) | 154 (51.2%) | <0.001 |
| **Maternal Genetic Risk Score, n (%)** | | | |
| **Tertile 1** | 118 (22.2%) | 41 (13.4%) | 0.002 |
| **Tertile 2+3** | 413 (77.8%) | 260 (86.4%) | |

# Univariable model - odds for GDM

- Continuous GRS: **OR = 1.09**, [95% CI: 1.06-1.13, p = <0.001]
- Categorical GRS (T1 vs T2+T3): **OR = 1.82**, [95%CI: 1.23-2.67, p = 0.003]

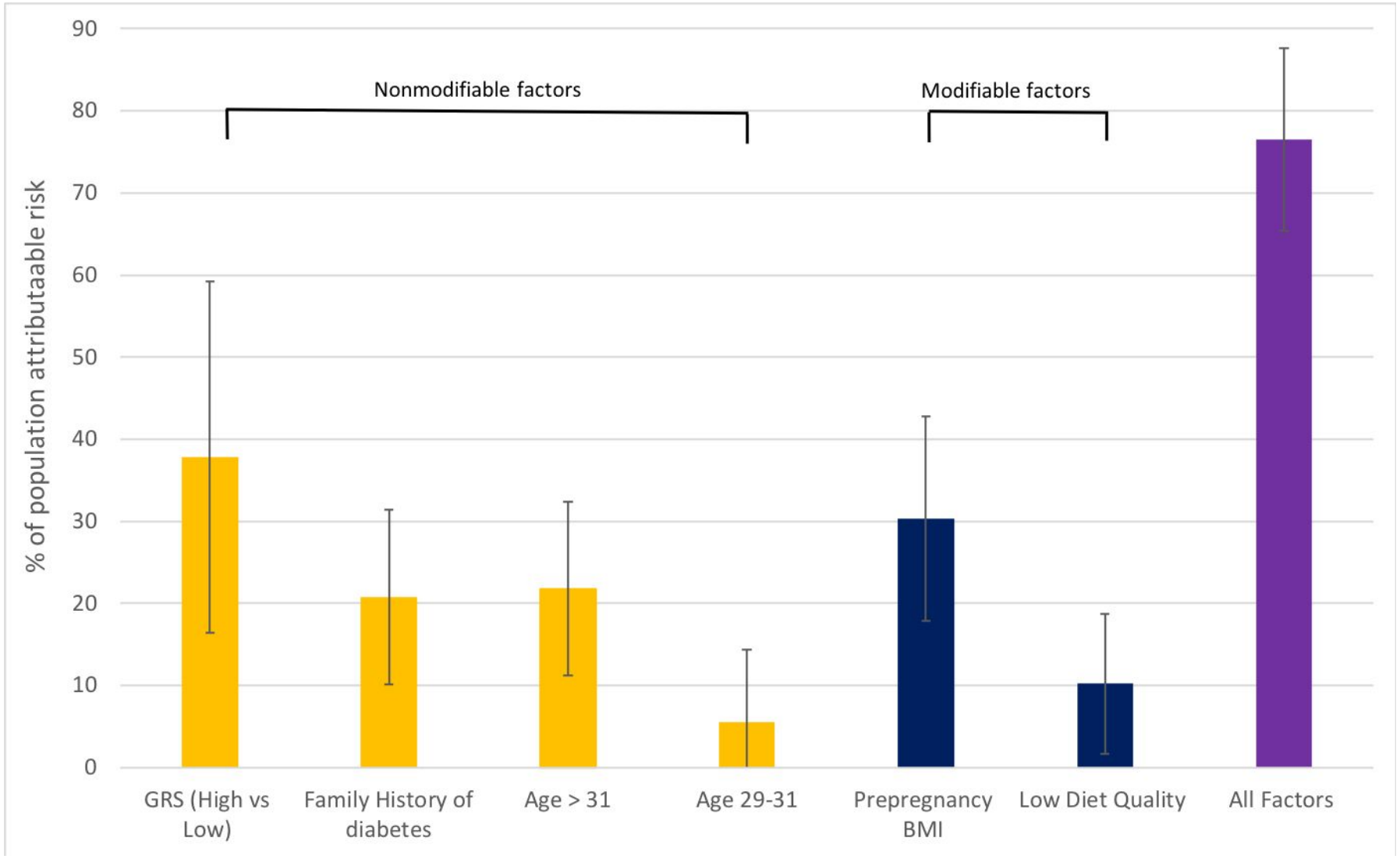
# Table 2: Multivariable model with all risk factors associated with GDM

| Risk Factor | OR [95%CI] * | P-value* |
|---|---|---|
| **GRS** | | |
| **Continuous** | 1.002 [ 1.001- 1.003] | $7.67e^{-08}$ |
| **Tertile 2 + 3** | 1.71 [1.14 - 2.57] | 0.01 |
| **Maternal Age** | 1.08 [1.04 - 1.12] | <0.001 |
| **Pre-pregnancy weight, kg** | 1.03 [1.01 - 1.04] | <0.001 |
| **Maternal Height, cm** | 0.96 [0.94 - 0.99] | 0.004 |
| **Diet quality (low vs medium + high)** | 1.44 [1.04 - 2.01] | 0.03 |
| **Family history of diabetes** | 1.65 [1.21 - 2.23] | 0.001 |

# Table 3: PARs for maternal GDM risk factors

| Risk Factor | OR (95%CI) from multivariable model | Prevalence % | Population attributable risk % (95% CI) |
|---|---|---|---|
| **GRS Tertile 2 + 3 vs 1** | 1.77 (1.18 to 2.67) | 80.1 | 37.8 (16.4 to 59.2) |
| **Age 32-43 yr v. < 29 yr** | 1.89 (1.32 to 2.70) | 36.6 | 21.80 (11.2 to 32.4) |
| **Age 29-31 yr v. <29 yr** | 1.27 (0.86 to 1.87) | 27.7 | 5.6 (-3.2 to 14.4) |
| **Body Mass index >23 v. ≤ 23** | 1.90 (1.40 to 2.58) | 48.2 | 30.3 (17.9 to 42.8) |
| **Low diet quality** | 1.46 (1.05 to 2.04) | 26.7 | 10.2 (1.7 to 18.7) |
| **Family history of diabetes** | 1.68 (1.24 to 2.28) | 40.4 | 20.8 (9.7 to 31.9) |
| **All factors** | | | 76.5 (65.5 to 87.5) |

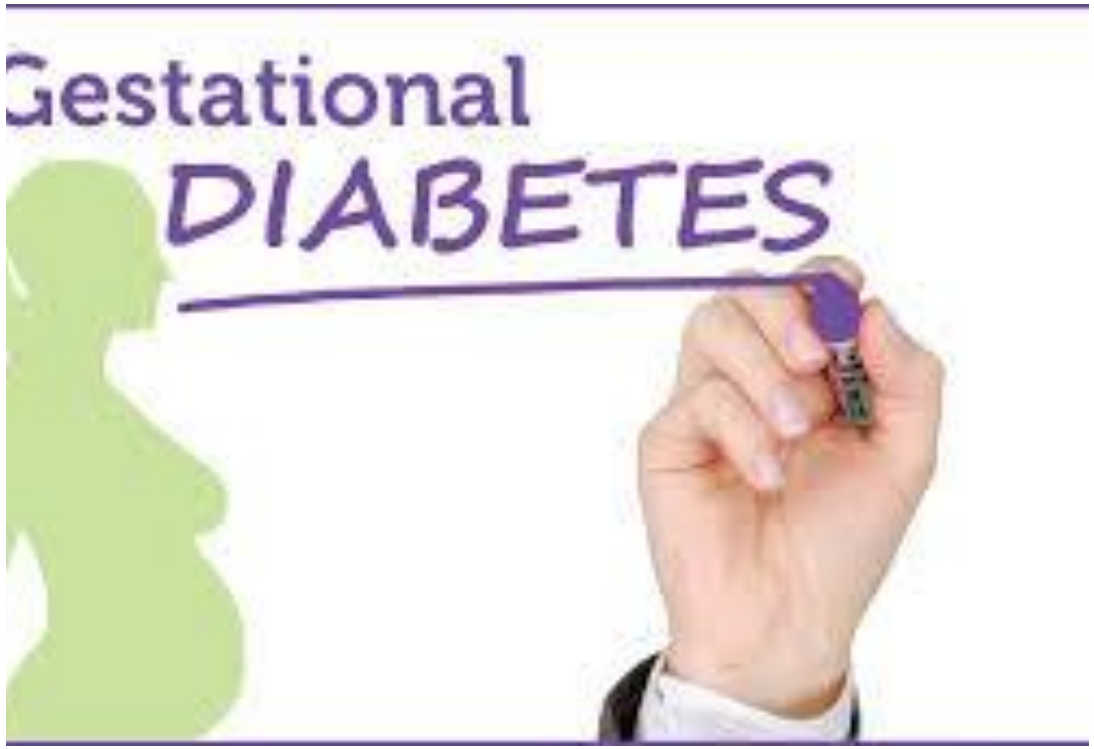
# Figure 1: PARs for individual risk factors



# DISCUSSION

# Interpretation

- Maternal GRS is an independent predictor of GDM in South Asian women
- Accounts for a substantial component of the PAR for GDM
- Family history remains significant even though GRS may be a better predictor



# Interpretation and Clinical Significance

- Inquiring about family history is the only way to identify genetic predisposition to GDM
- GRS can serve as a good screening tool to identify people at risk
- Promote healthy behaviour in people with higher genetic loads

# Support from other studies

T2D GRS has been associated with GDM in other populations

GRS and Family history were better predictors of colorectal cancer risk stratification – Weigl et. al., (2018)

Shared lifestyle factors involved in PH's effect on MI risk – Chow et. al., (2011)

# Strengths and limitations

## Strengths

- Optimized GRS to target South Asian population using a multi-ethnic GWAMA
- Used whole genome genotypes to build the GRS
- GDM status was determined using validated South Asian cutoffs and objective measures (OGTT)

## Limitations

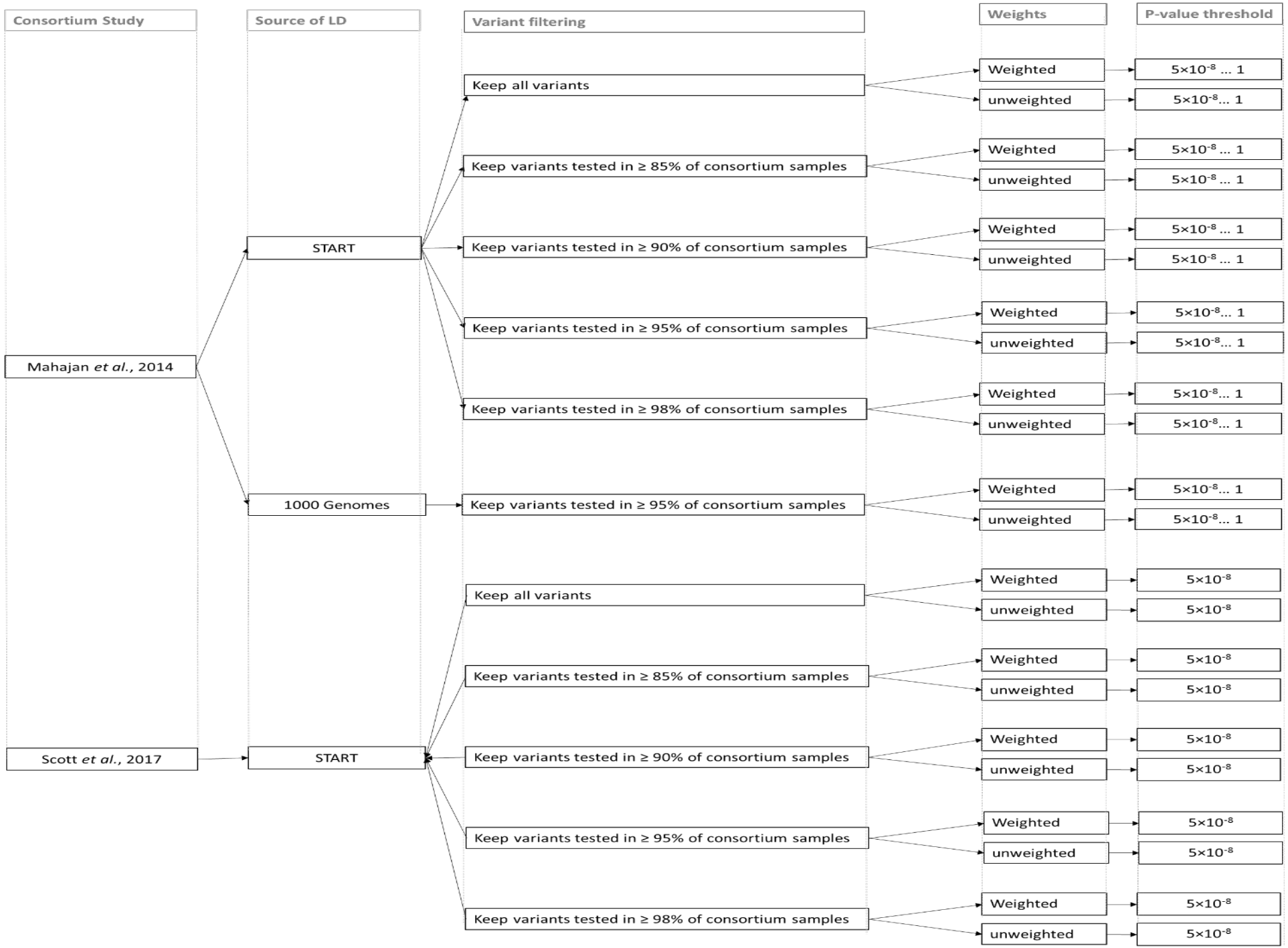
- Mahajan et. al.,'s data was not exclusive to South Asian samples (20%)
- Our GRS is based on T2D loci not GDM specific loci

# Conclusion

A T2D GRS is a strong and independent predictor of gestational diabetes in South Asians

The GRS is more informative and complementary to self-reported family history of diabetes


THANK YOU


Consortium Study
Source of LD
Variant filtering
Weights
P-value threshold
Mahajan et al., 2014
START
1000 Genomes
Scott et al., 2017
START
Keep all variants
Keep variants tested in ≥ 85% of consortium samples
Keep variants tested in ≥ 90% of consortium samples
Keep variants tested in ≥ 95% of consortium samples
Keep variants tested in ≥ 98% of consortium samples
Keep variants tested in ≥ 95% of consortium samples
Keep all variants
Keep variants tested in ≥ 85% of consortium samples
Keep variants tested in ≥ 90% of consortium samples
Keep variants tested in ≥ 95% of consortium samples
Keep variants tested in ≥ 98% of consortium samples
Weighted
unweighted
5×10-8 ... 1
5×10-8... 1
5×10-8