Comparison of the effect of Polygenic Risk Scores (PRSs) on baseline HDL-c levels between white European and Asian Indian type 2 diabetes mellitus population: A pilot study

Mehul K Chourasia[1], Charvi Nangia[1], Simona M Hapca[1] , Moneeza K Siddiqui[1], Sundararajan Srinivasan[1], Ewan R Pearson[1], Pradeepa R[2] , Venkatesan Radha[3], Viswanathan Mohan[2], Colin NA Palmer[1]

1. Division of Population Health and Genomics, Ninewells Hospital, University of Dundee, Dundee, United Kingdom
2. Dr Mohan's Diabetes speciality centre (DMDSC), Chennai, TamilNadu, India
3. Department of Molecular Genetics, Madras Diabetes Research Foundation, Chennai, TamilNadu, India

Introduction

- Type-2 diabetes mellitus (T2DM) patients have a substantially higher risk of cardiovascular morbidity compared to the non-diabetics[1].
- South Asians have a higher prevalence of cardiovascular diseases (CVD) and suffer from early-onset cardiovascular morbidity compared to other ethnic groups[1].
- High-density lipoprotein cholesterol (HDL-c) has a protective effect against CVD[2].
- Previous meta-analysis suggest a number of genetic polymorphisms influence HDL-c levels such as *CETP*, *PCSK9* and *LPL* [3,4].
- Preliminary data suggest that HDL-c profile between the two populations [Scottish (1.20±0.33) and India (1.04±0.23)] were significantly different (p value <0.001)[5].
- This study compared the effect of polygenic variation on HDL-c levels between the two study populations.

Study Objective

- To construct and compare weighted polygenic risk scores (PRSs) from known loci associated with HDL-c in a white European (GoDARTS) and Asian Indian T2DM population.

Study Methodology

Study population	• GoDARTS cohorts* (n = 2,736) • Asian Indian* (n = 1,953)
Exclusion criteria	• Subjects with missing baseline HDL-c measurements
Co-variates	• Age, sex
Study outcome	• Baseline HDL-c (Before lipid lowering drugs)
Study predictor	• Weighted Polygenic risk score (GLGC, Exome wide study)

*Genotyped in Illumina platform

Weighted Polygenic risk score

- All reported SNPs associated with HDL-c were selected from a meta-analysis (~40 SNPs) and exome-wide association study (~200 SNPs) [3,4].
- Weighted PRS were constructed using PRSice - v 2 (Kings College, London)[6].
- PRS were calculated for additive genetic models and on the basis of unfavourable allele (allele associated with lower HDL-c).
- **Weighted PRS formula**

$$wPRS = \sum_i (S_i \times G_i) / M$$

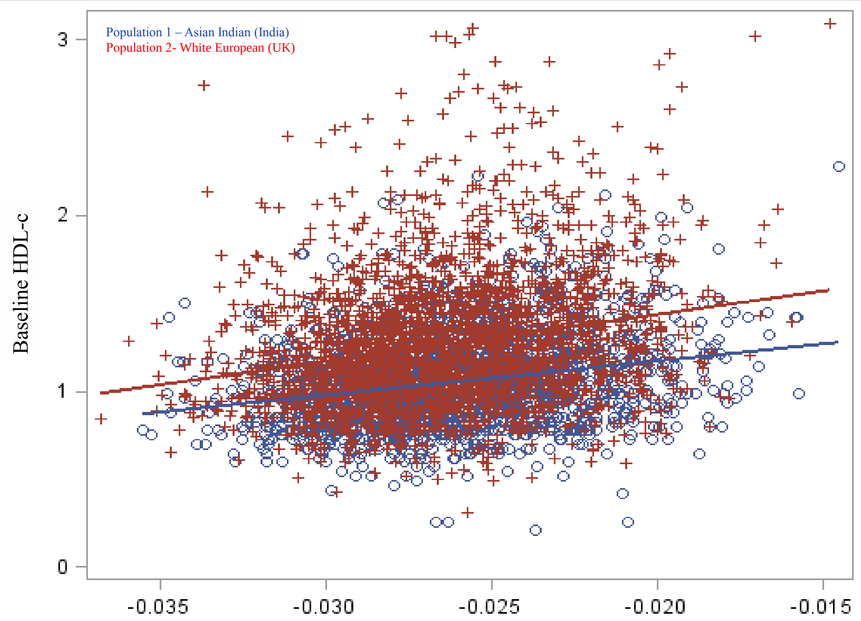
S- beta estimate, G- no of effective allele, M – no of SNPs

Results

Table 1: Characteristics of the study population

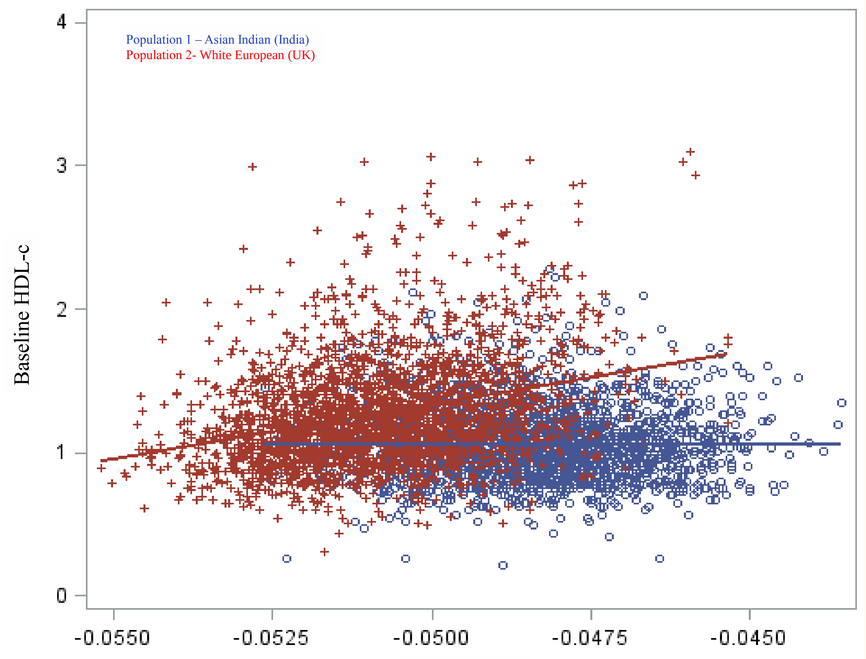
Variable \ Population	Asian Indian (India)	White European (UK)
Age; mean(SD)	63.8(10.5)	62.9(11.5)
Sex; Female(%)	38.4	42.8
Baseline HDL-C; mean(SD)	1.05(0.26)	1.26(0.38)

Graph 1: Regression of Baseline HDL-c (a) with Polygenic risk score (PRS_{40})



	Asian Indian (India)	White European (UK)
Intercept	1.56	1.97
Slope	19.31	26.62

Graph 2: Regression of Baseline HDL-c (a) with Polygenic risk score (PRS_{200})



	Asian Indian (India)	White European (UK)
Intercept	1.07	5.18
Slope	0.39	77.04

Table 2: Comparison of the effect of PRS (40 & 200) on baseline HDL-c in both the study populations

Population	Asian Indian			White European		
Outcome	β(SE)	P value	R^2	β(SE)	P value	R^2
PRS_{40}	19.3(1.7)	<0.0001	**0.06**	26.19(2.2)	<0.0001	**0.05**
PRS_{200}	0.39(3.7)	NS	**0.000**	77.04(4.4)	<0.0001	**0.10**

Results

- Baseline HDL-c and PRS were normally distributed in both the population
- PRS_{40} explained a similar (5- 6%) variance in both populations
- However, PRS_{200} showed a more pronounced effect in the White Europeans (~10% variance) in contrast with the Asian Indians where the effect was almost diminished.
- In both gene scores genetically predicted HDL-c levels were identical between the populations, however the lower observed HDL-c in the Indian population was reflected by a much lower per-allele effect (slope).

Discussion and conclusion

- Genetic loci discovered for HDL-c in Caucasian populations are present at similar frequency in Indian populations, however the level of HDL-c modulated by these variants is lower.
- This suggests that additional genetic variation exists in the Indian population to determine the low HDL levels observed in this population.

Way forward

- Similar PRS will be constructed for baseline HDL-c levels with a larger Asian Indian population
- This PRS will be used in a conditional GWAS to adjust for variants affecting baseline HDL-c levels to evaluate actual pharmacogenetic drug response.

References

1. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007-2017. Cardiovasc Diabetol. 2018;17:83.
2. Kontush A. HDL-mediated mechanisms of protection in cardiovascular disease. Cardiovasc Res. 2014;103:341–9.
3. Willer CJ, Schmidt EM, Sengupta S, Peloso GM, Gustafsson S, Kanoni S, et al. Discovery and refinement of loci associated with lipid levels. Nat Genet. 2013;45:1274–83.
4. Liu DJ, Peloso GM, Yu H, Butterworth AS, Wang X, Mahajan A, et al. Exome-wide association study of plasma lipids in 300,000 individuals. Nat Genet.2017;49:1758.
5. INSPIRED WP1 – Unpublished data provided by MK Siddiqui
6. Euesden J, Lewis CM, O'Reilly PF. PRSice: Polygenic Risk Score software. Bioinformatics. England; 2015;31:1466–8.

Acknowledgements

- We would like to thank Health Informatics Centre at Farr Institute, Dundee, Scotland for their support in data management.
- We would also like to thank entire INSPIRED project staff for their constant support.
- The research was commissioned by the National Institute for Health Research using Official Development Assistance (ODA) funding [INSPIRED 16/136/102].

Contact details

Dr Mehul Kumar Chourasia
Email : mkchourasia@dundee.ac.uk