26 September 2024

Comparison of polygenic risk scores for diabetes developed from different ethnic groups: A cross-sectional study in the Japanese population

Takuma Furukawa[1,2]; Megumi Hara[1]; Yuichiro Nishida[1]; Chisato Shimanoe[3]; Chiharu Iwasaka[1,4]; Keitaro Tanaka[1]; J-MICC Study Group

1. *Department of Preventive Medicine, Faculty of Medicine, Saga University, Saga, Japan.*
2. *Clinical Research Center, Saga University Hospital, Saga, Japan*
3. *Department of Pharmacy, Saga University Hospital, Saga, Japan*
4. *Department of Physical Activity Research, National Institutes of Biomedical Innovation, Health and Nutrition, Osaka, Japan*

WCE
WORLD CONGRESS OF EPIDEMIOLOGY 2024

Background

- The Polygenic Risk Score (**PRS**), which is based on hundreds to millions of genetic polymorphisms, is expected to contribute to the prediction of disease risk and the development of tailor-made medicine.

- However, most PRS studies have been conducted in European populations, and knowledge of the specific characteristics and effectiveness of PRS in other ethnic groups is limited.

(Ge T, et al. *Genome Med*. 2022)

WCE
WORLD CONGRESS OF EPIDEMIOLOGY 2024

Background

- In particular, many East Asians have diabetes without obesity, and the factors and mechanisms associated with diabetes might differ from those of Europeans.

(Yeyi Zhu, et al. *Diabetes Care*. 2019)

Objective

Compare the classification accuracy of several PRSs for diabetes developed from different ethnic groups

WCE
WORLD CONGRESS OF EPIDEMIOLOGY 2024

Methods

【Participants】

Japan Multi-Institutional Collaborative Cohort (J-MICC) Study

J-MICC Study is a Japanese large cohort with about 100,000 participants that has been followed up to explore the relationship between lifestyle, genotype, blood composition, and the risk of developing various diseases.

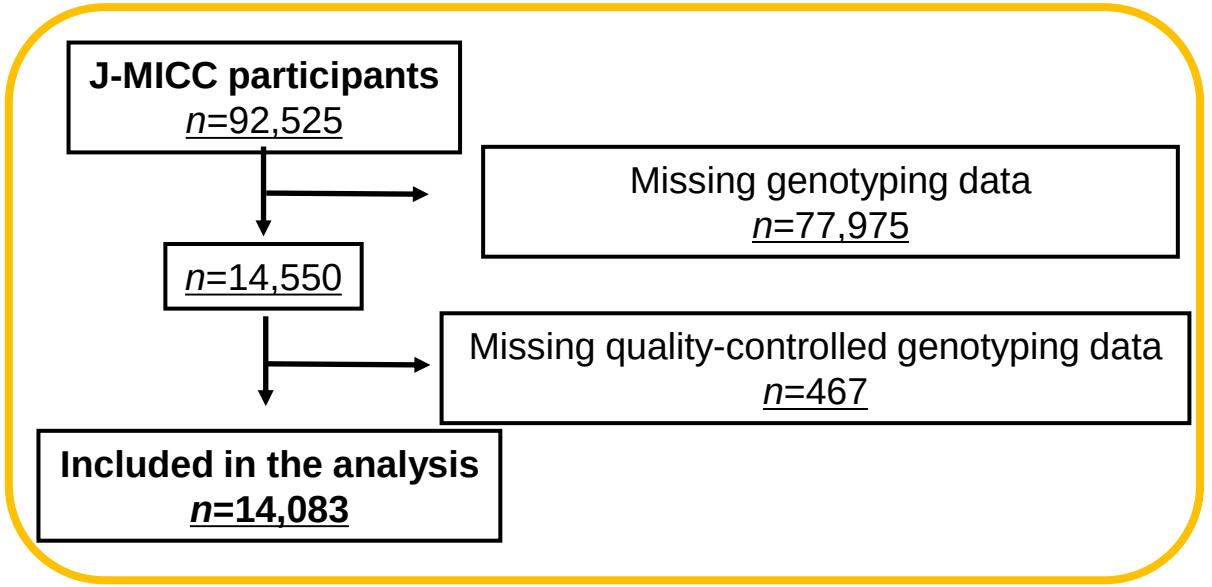


Figure 1. Flowchart of the process for selecting study participants

◆Included in the analysis

n = 14,083

Male: 6,336 (45.0%), Female: 7,747 (55.0%)

[Age]: 54.8 ± 9.4 (mean ± SD)

[**Diabetes**]: **926** (6.6%)

Methods

【PRSs for type 2 diabetes】

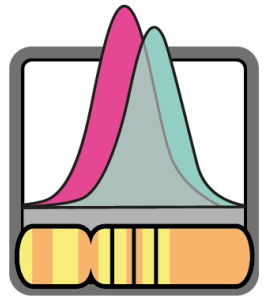
PRS model information is based on the “PGS Catalog”. (https://www.pgscatalog.org)

- **Japanese PRS**

  [ID: PGS002379 / Number of variants: **920,930**]

- **European PRS**

  [ID: PGS002354 / Number of variants: **1,109,311**]



➢ Both PRS models were developed using the same method.

(Weissbrod O et al. *Nat Genet*. 2022)

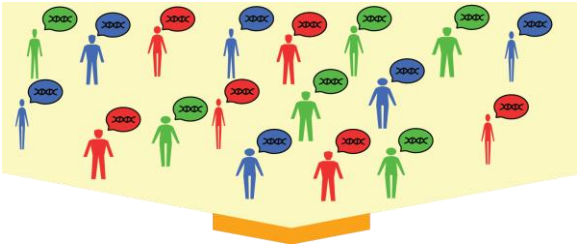
The PRS for each participant was calculated as the weighted sum of each risk allele using previously derived weights.

WCE
WORLD CONGRESS OF EPIDEMIOLOGY 2024

Methods

【Statistical analysis】

■ Association between PRS and diabetes



➢ Logistic regression analysis

Analyzed the odds ratio (OR) of diabetes prevalence

【Outcome】: Diabetes case

【Exposure】: PRS [Covariates]: age, sex, study area, top five principal components

➢ AUC of the ROC curve

Analyzed the classification accuracy for diabetes prevalence

➢ Scatter plots

Visualization of diabetes prevalence per percentile of PRS

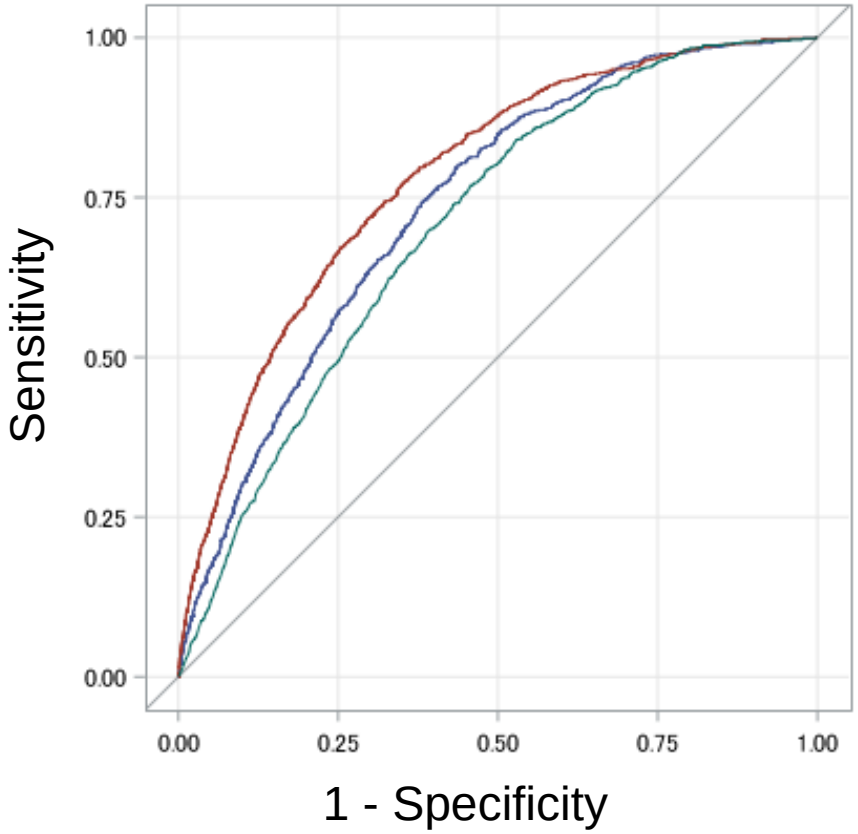
Results

- **Association between PRS and diabetes by quintile or per 1 SD**

PRS developed population	PRS ID	Quintile			Per 1 SD	
			OR	95% CI	OR	95% CI
Japanese PRS	PGS002379	Q1 (Lowest)	1	(reference)	2.18	(2.02 – 2.35)
		Q2	1.68	(1.21 – 2.33)		
		Q3	2.46	(1.81 – 3.34)		
		Q4	4.01	(2.99 – 5.37)		
		Q5 (Highest)	8.08	(6.11 – 10.67)		
European PRS	PGS002354	Q1 (Lowest)	1	(reference)	1.55	(1.45 – 1.66)
		Q2	1.40	(1.08 – 1.83)		
		Q3	1.92	(1.49 – 2.48)		
		Q4	2.40	(1.87 – 3.07)		
		Q5 (Highest)	3.41	(2.69 – 4.33)		

Results

■ ROC curves of PRS and diabetes prevalence



— **Japanese PRS** [PGS002379]
AUC=0.781 (0.767–0.796)

— **European PRS** [PGS002354]
AUC=0.738 (0.723–0.753)

— Base
AUC=0.706 (0.691–0.721)

P <0.001

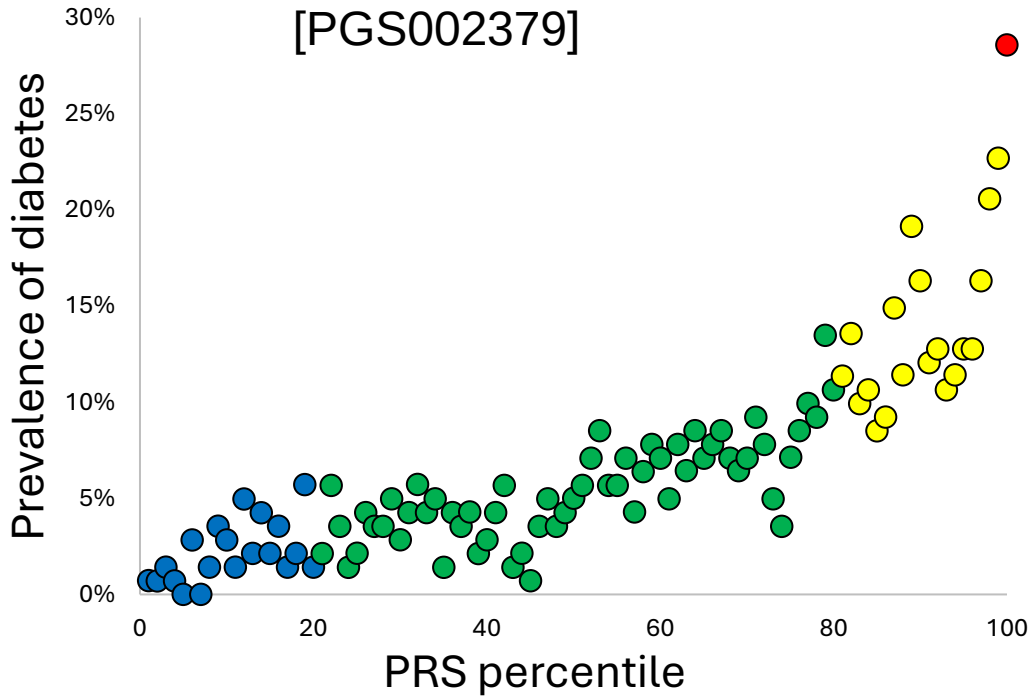
WCE
WORLD CONGRESS OF EPIDEMIOLOGY 2024

Results

- **Scatter plots of diabetes prevalence per percentile of PRS**

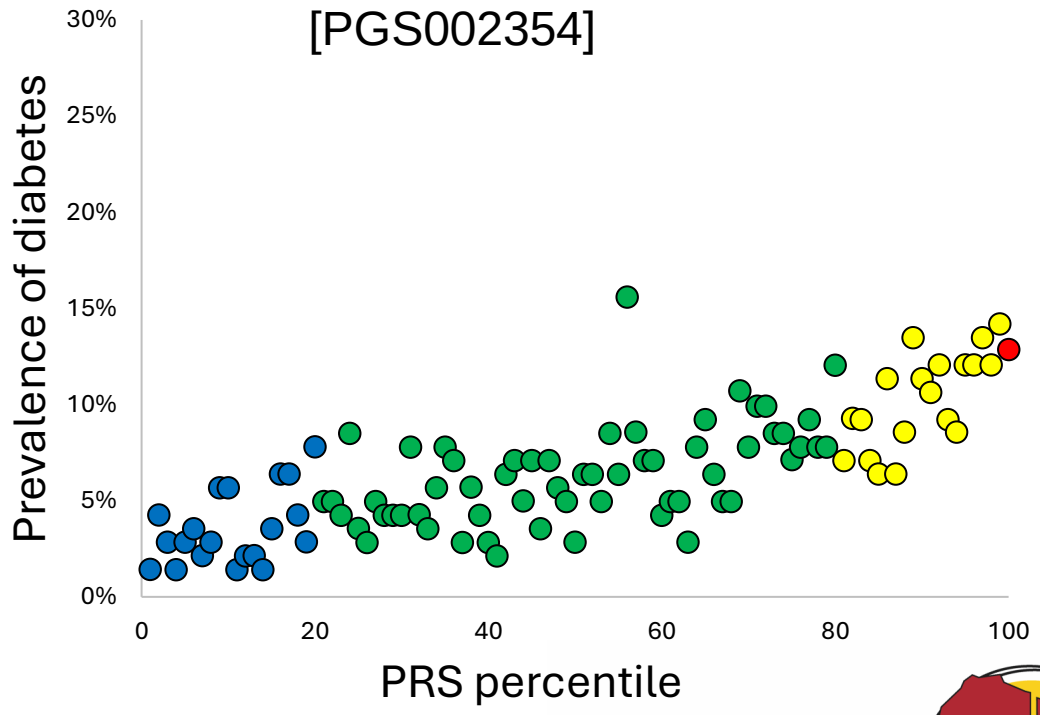
Japanese PRS

[PGS002379]



European PRS

[PGS002354]



WCE
WORLD CONGRESS OF EPIDEMIOLOGY 2024

Results

Association between PRS and diabetes by PRS category based on diabetes prevalence

PRS developed population	PRS ID	PRS category	OR	95% CI
Japanese PRS	PGS002379	Low (1–20%)	1	(reference)
		Medium (21–80%)	2.68	(2.04 – 3.52)
		High (81–99%)	7.54	(5.69 – 9.98)
		Very High (100%)	21.82	(13.67 – 34.82)
European PRS	PGS002354	Low (1–20%)	1	(reference)
		Medium (21–80%)	1.89	(1.52 – 2.36)
		High (81–99%)	3.37	(2.65 – 4.28)
		Very High (100%)	4.11	(2.37 – 7.11)

Discussion

◆ The PRS developed from matched ancestry populations had higher OR and classification accuracy for diabetes

The mechanisms underlying diabetes have ethnic differences, such as insulin secretion and resistance. (Kodama K, et al. *Diabetes Care*. 2019)

Diabetes is not a monogenetic disease but rather a complex combination of many genetic and lifestyle factors. (Griffin S, et al. *Diabetologia*. 2022)

- Lifestyle and physiological functions are different, suggesting that diabetes-related variants and their weightings also differ among ancestry groups.

Ancestry consideration would be important for diabetes PRS

WCE WORLD CONGRESS OF EPIDEMIOLOGY 2024

Discussion

◆ The highest category of PRS showed remarkably high OR of diabetes

Several diseases had particularly high prevalence in populations at the top 10-20% of genetic risk, including diabetes. (Khera AV, et al. *Nat Genet*. 2018)

- PRS could accurately assess the risk and identify individuals with a particularly high risk of diabetes.

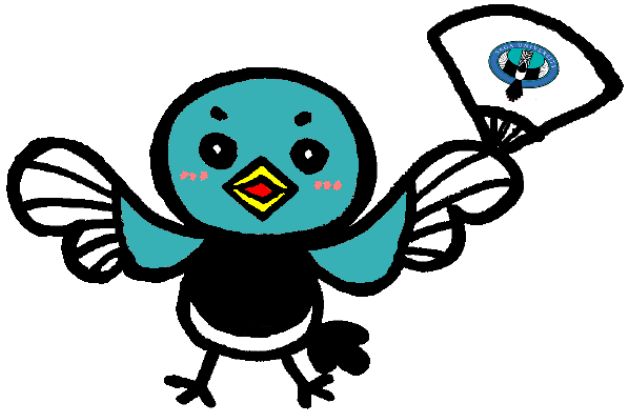
💡 The PRS for diabetes developed from matched ancestry populations would be useful for

- ✓ **Detecting particularly high-risk individuals**
- ✓ **Early prediction and effective prevention**

Conclusion

- The PRS developed from matched ancestry populations had higher ORs and classification accuracy for diabetes prevalence in the Japanese general population.
- The highest category of PRS showed remarkably high OR, detecting individuals with a particularly high risk of diabetes.
- PRSs adjusted to the characteristics of each ancestry group may enhance early prediction and effective prevention of diabetes.

Thank you for your attention



WCE
WORLD CONGRESS OF EPIDEMIOLOGY 2024