Polygenic Risk Scores for COVID-19 Hospitalization in Spanish and Latin-American Populations

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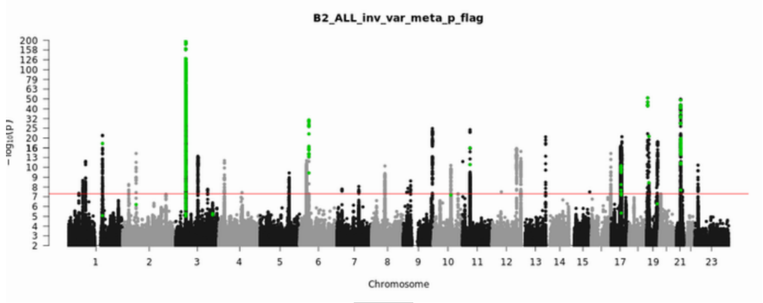
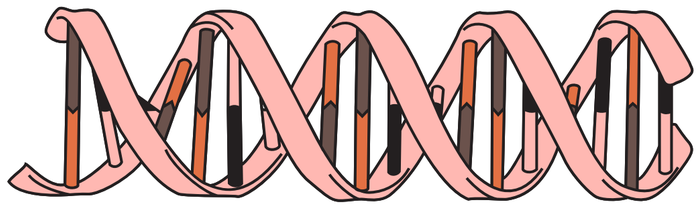
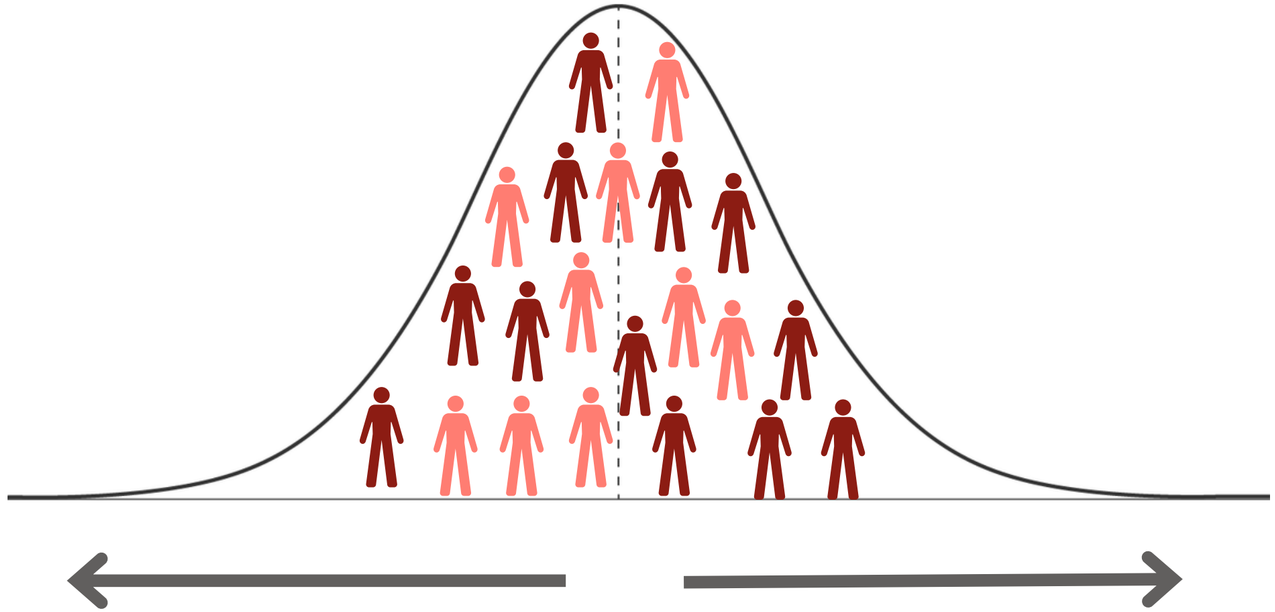
Polygenic Risk Scores

GWAS





AA x 0.03 + TC x 0.1 + CG x -0.2+ GG x 0.04 + GA x -0.12



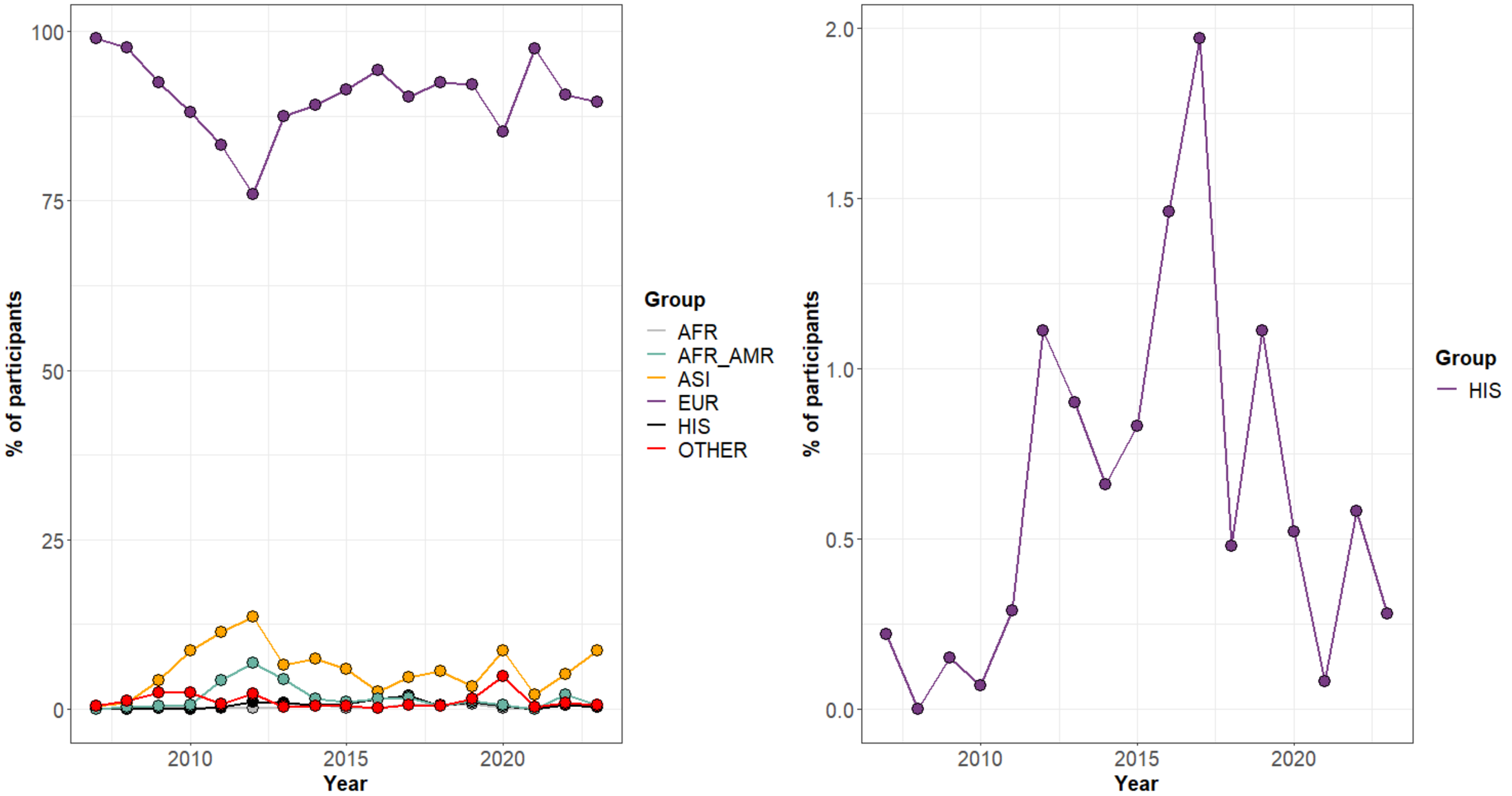
Lower genetic risk

Higher genetic risk

Limitations

- Most PRS are studied on EUR individuals
- Admixed samples are excluded

Lack of diversity in GWAS studies



Data from the GWAS diversity monitor (22/01/2024)

SCOURGE Consortium

Recruited from 2020 to 2021
(pre-vaccines)

+300 variables

Spanish sample

- Recruited all over Spain

5.968 hospitalized cases
3.382 COVID-19+ non hospitalized

Latin-American sample

- LatAm recruiting countries: Brazil, Colombia, Ecuador, Mexico, Paraguay
- Spain (LatAm origin or coherent admixed GIA)

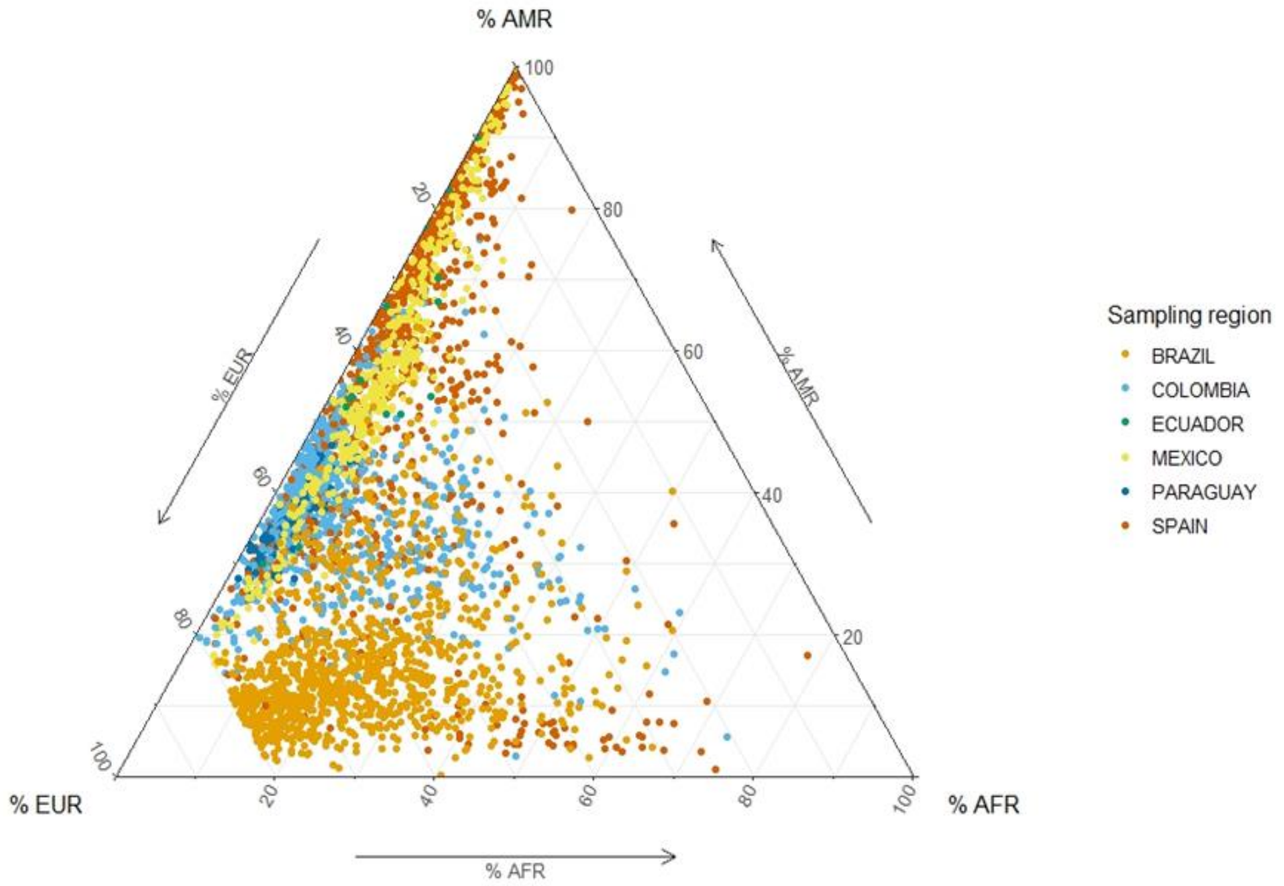
1.625 hospitalized cases
1.887 COVID-19+ non hospitalized

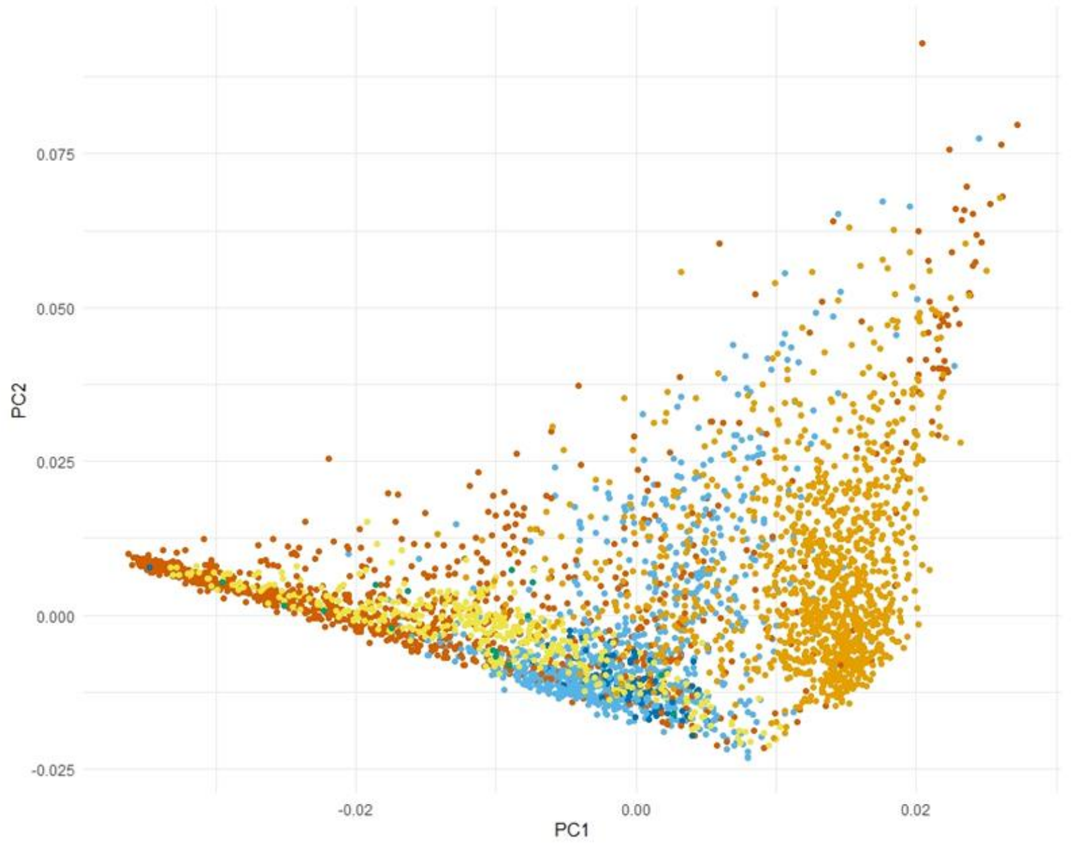
Previous work

Cruz, R., Diz-de Almeida, S., et al (2022). Novel genes and sex differences in COVID-19 severity. Human molecular genetics, 31(22), 3789–3806. https://doi.org/10.1093/hmg/ddac132

Diz-de Almeida, S., Cruz, R., et al (2023). Novel risk loci for COVID-19 hospitalization among admixed American populations. medRxiv 2023.08.11.23293871; doi: https://doi.org/10.1101/2023.08.11.23293871

Ancestry distribution in Latin-American samples





Ternary plot showing the % of AFR, NAM and EUR ancestry in the LatAm sample

PC1 vs PC2 in the LatAm sample

OBJECTIVES

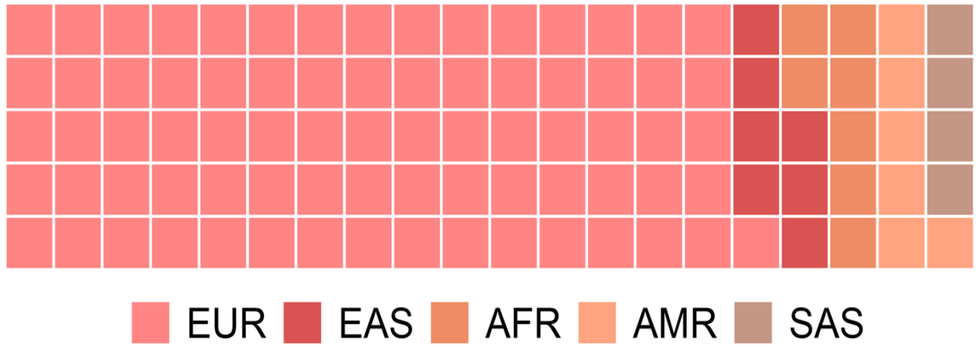
- Development of a PRS for COVID-19 hospitalization
- Explore the PRS in relation to COVID-19 disease outcomes and risk factors
- Identification of high risk individuals

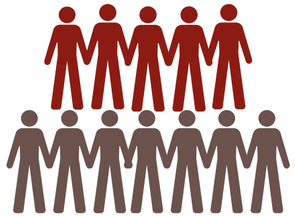
Analysis Stage I

Discovery data

HGI B2 ALL meta-analysis (without SCOURGE): Multi-Pop (MP) and EUR

Hospitalized cases in HGI (v7)





N=39.052

N=2.347.576

Target data

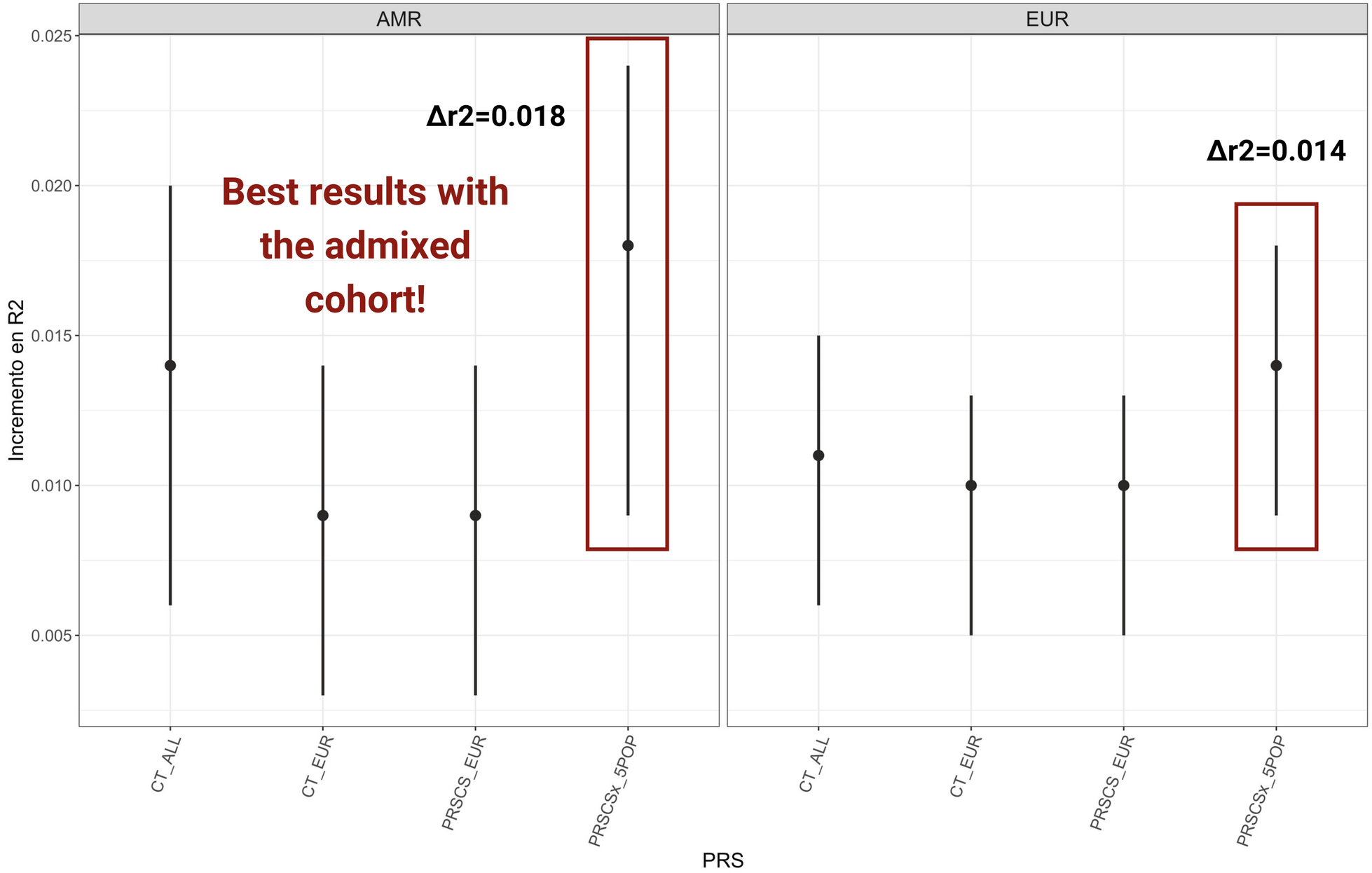
Latin-American sample
Spanish sample

130 PRS were tested for each cohort

SELECT BEST PRS

Bootstrap

Best PRS: PRS-CSx multi-population



Analysis Stage II

Combine samples

Single ancestry-adjusted PRS

N=7.594

N=5.269

Clinical utility of the PRS

Disease outcomes

Modulation by comorbidities

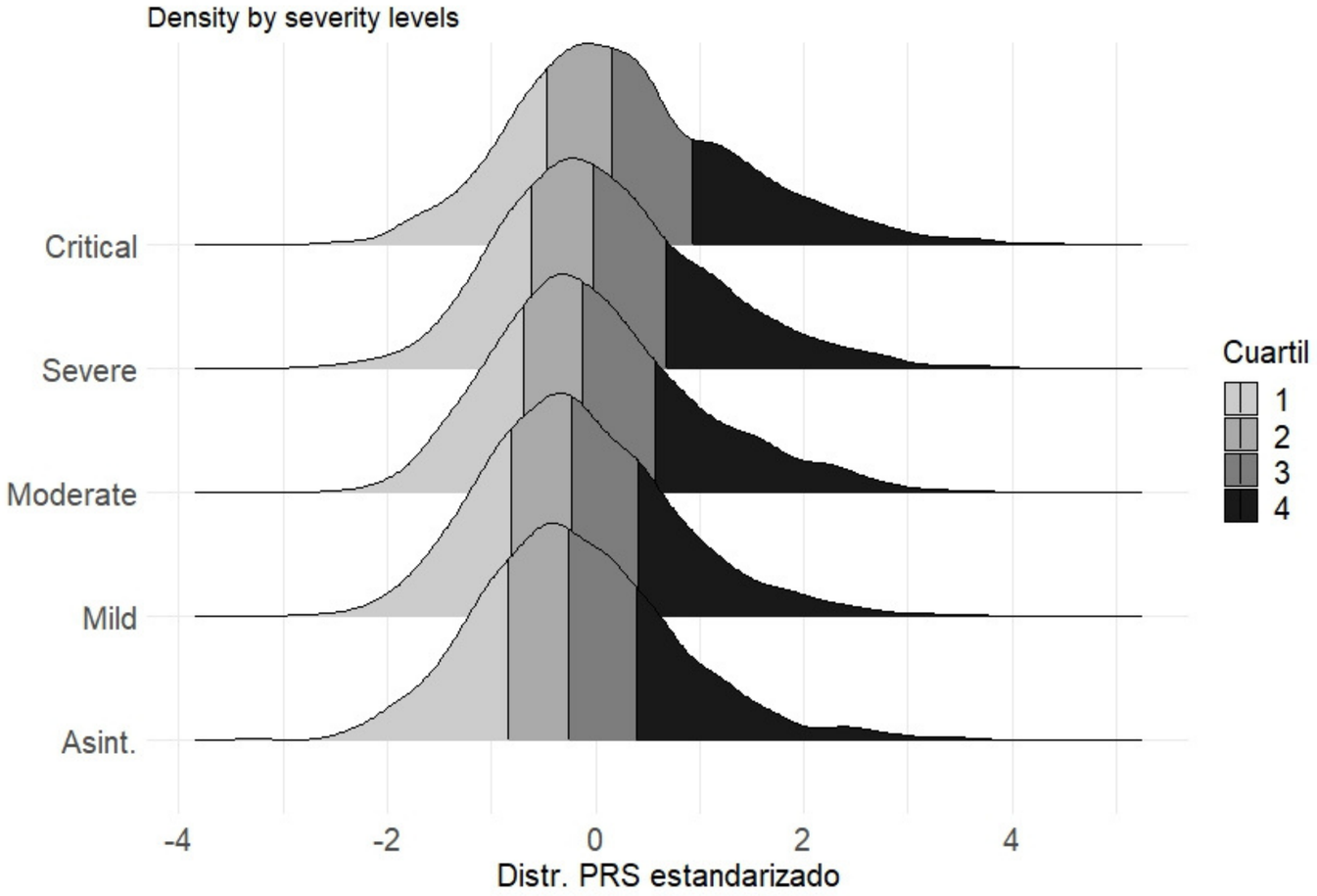
Develop models including common risk factors (CRF)

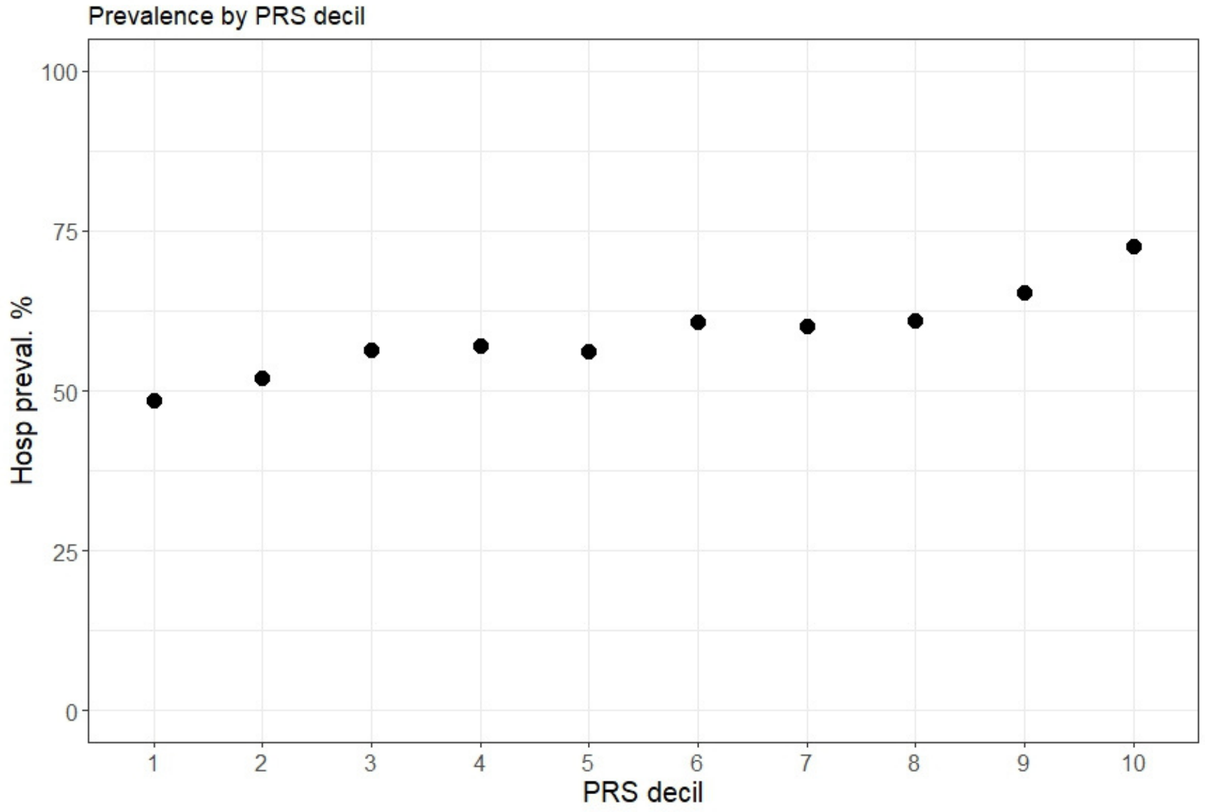
External validation into European cohort

111 cases / 362 controls

Single ancestry-adjusted PRS: Spain + LatAm

- PRS associated pseudo-R2: 0.016
- Model’s AUC: 0.86
- OR (per 1 s.d): 1.42

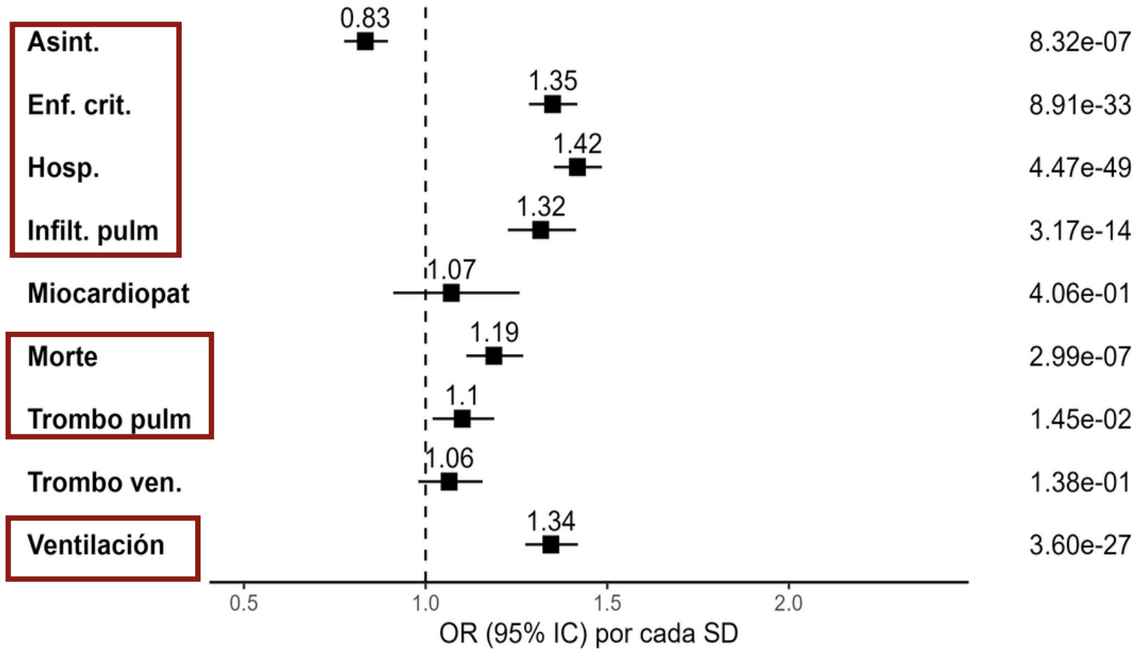




Association with disease outcomes and complications

- PRS was associated with:
  - Asymptomatic and critical disease
  - Death
  - Presence of pulmonary infiltrates
  - Need of mechanical ventilation
  - Pulmonary thromboembolism

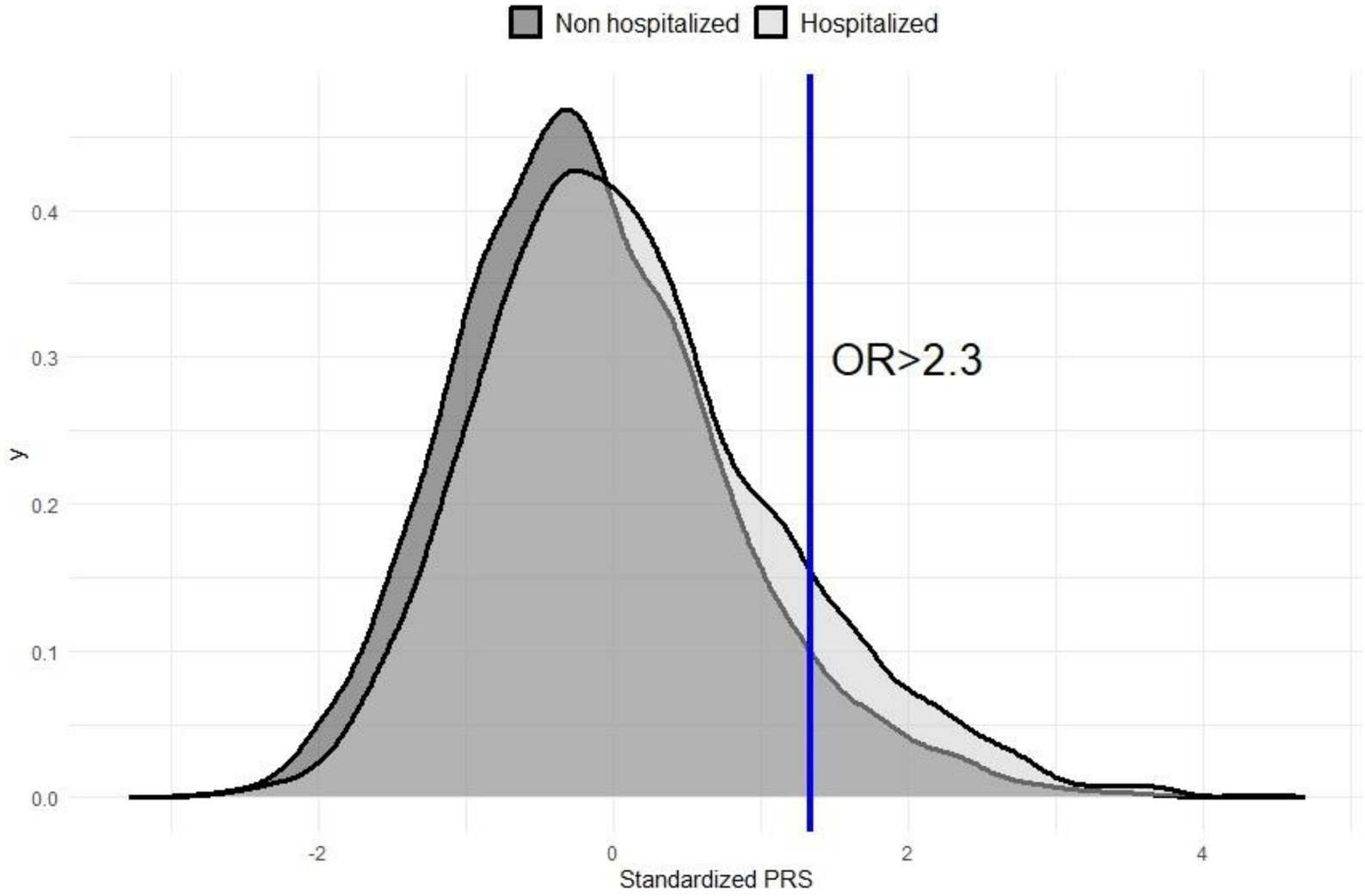
- Effect of PRS <u>modulated by age</u>



Single ancestry-adjusted PRS: Spain + LatAm

Top 10% with 2.3-fold higher risk of hospitalization (compared to average genetic risk).

Value of standardized PRS: 1.33



Modelling risk by including CRF and PRS

Model 0: Hospitalization ~ Age + Sex + Country + PRS_bin

Model 1: Hospitalization ~ Age + Sex + Country + Diabetes + HT + Cardio. C + Resp. C+ obesity

Model 2: Hospitalization ~ Age + Sex + Country + Diabetes + HT + Cardio. C + Resp. C + obesity + PRS_bin

- LR-test between models was significant
- Binarized PRS in model 3 had an OR of 2.23
    - Similar OR to diabetes or chronic respiratory illnesess

Prediction of 473 individuals of European ancestry

- AUC model 0→ 0.859
- AUC model 1→ 0.869
- AUC model 2→ 0.875

Clinical utility of the PRS is unclear

Take-home messages

- Increase diversity in genetic studies and do not exclude admixed samples.
- PRS are not a tool by themselves and should be assessed alongside common risk factors.
- PRS for some outcomes/traits might not worth the cost in comparison to other risk factors.

Thank you for listening!