# Dissecting the contribution of circulating proteins to multiple myeloma risk: a Mendelian randomization study

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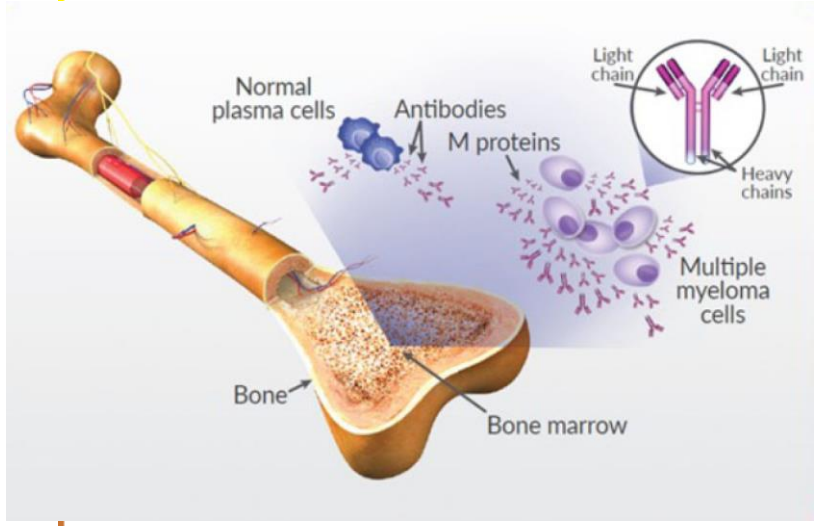
# Multiple myeloma (MM)

## Pathophysiology




- Bone thinning/fractures
- Hypercalcaemia
- Anaemia
- Renal insufficiency

## Statistics

~6000 new cases every year in UK

29% 10+ year survival

No cure

## Research question

Are circulating proteins involved in the development of multiple myeloma?

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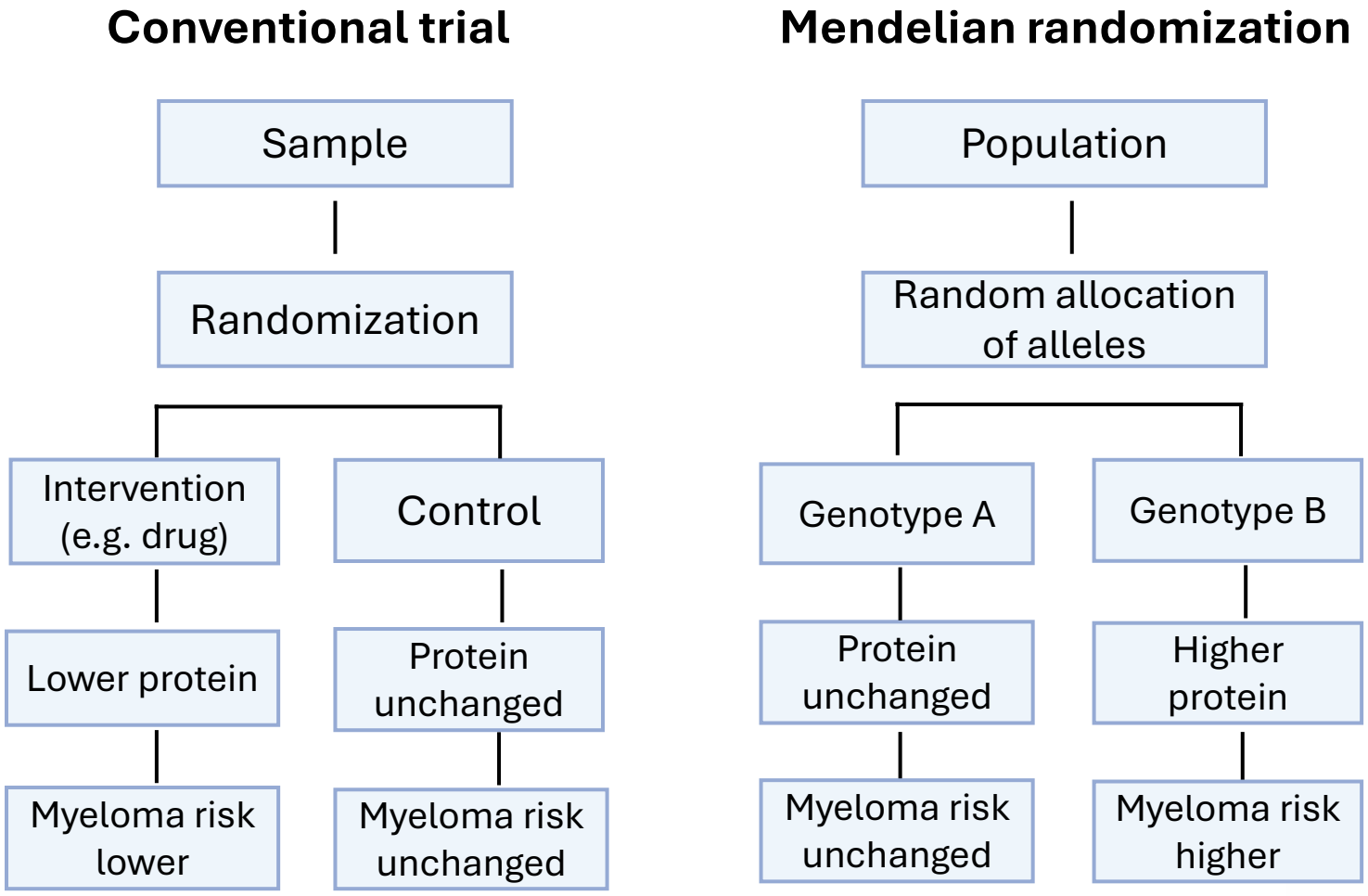
Image: Multiple Myeloma Research Foundation, statistics: Cancer Research UK

# What is Mendelian randomization (MR)?

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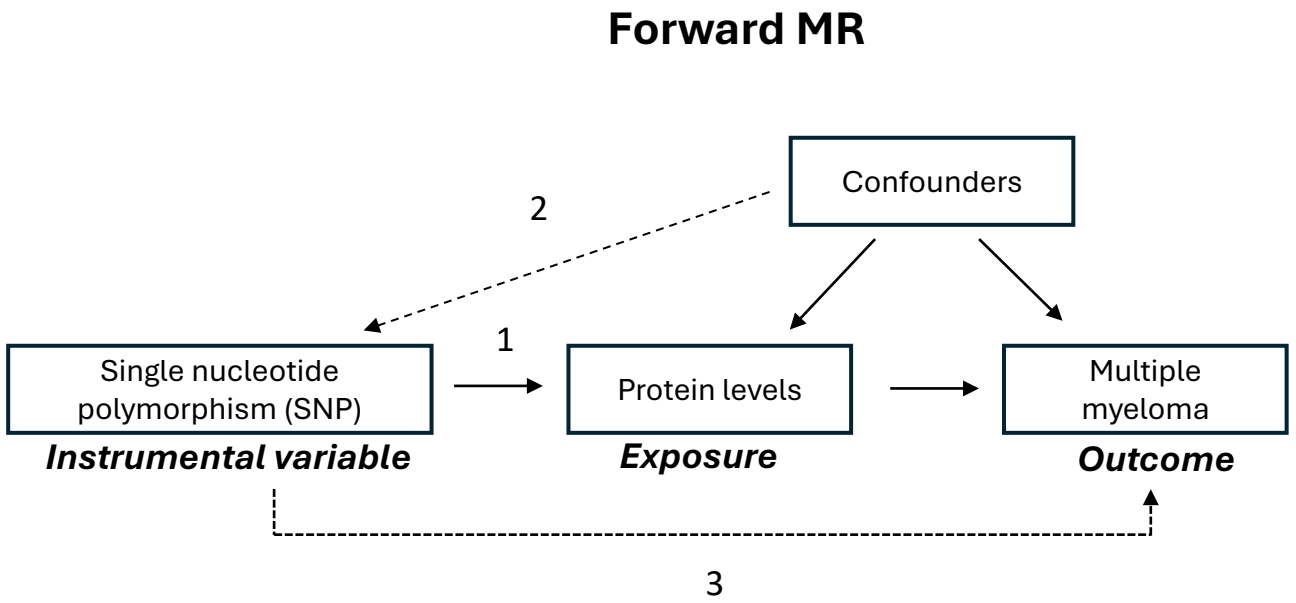
# Aim & Methods

**Aim:** Use two sample MR to identify proteins with evidence for a causal relationship with multiple myeloma




**Assumptions:** (1) relevance, (2) independence, (3) exclusion restriction.

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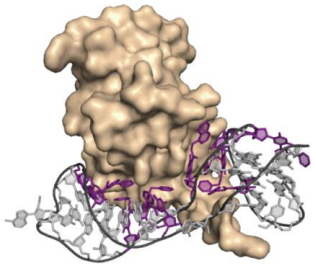
# Methods – GWAS data used for MR analyses

**Exposure**

**Outcome**

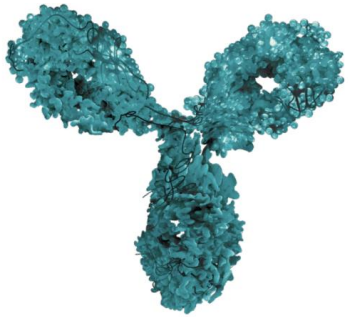
***Modified single stranded DNA***



deCODE
(35,559 Icelanders)

4,907 proteins measured by SomaLogic

***Antibody***



UK Biobank
(34,557 participants)

2,923 proteins measured by Olink Explore 3072

UK Biobank

564 multiple myeloma cases, 455,784 controls

FinnGen

1,085 multiple myeloma cases, 271,463 controls

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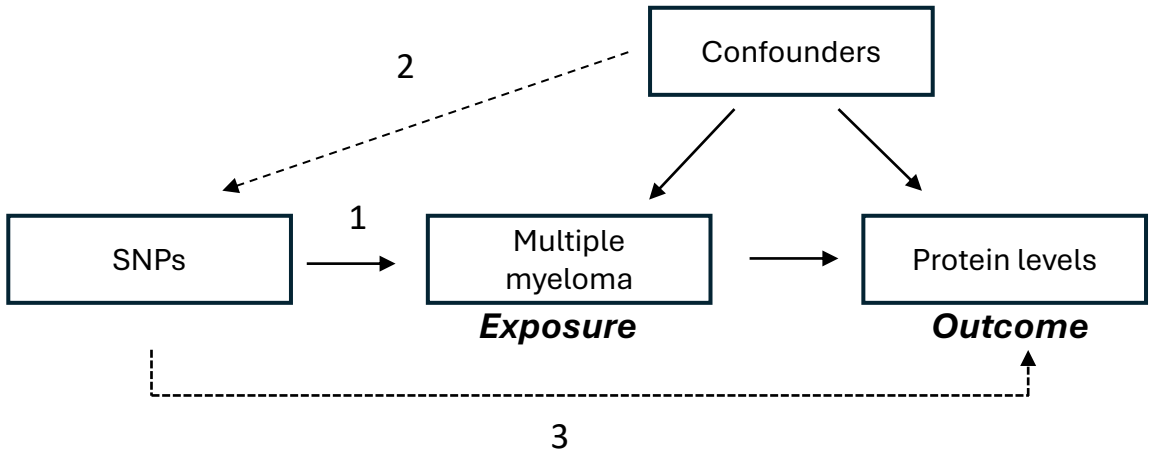
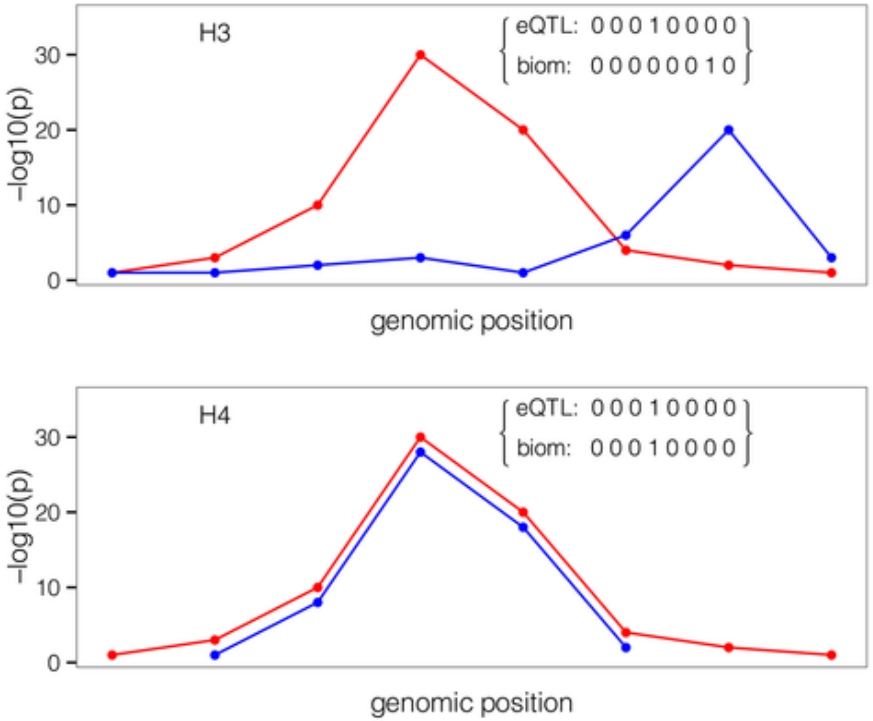
# Sensitivity analyses

## Reverse MR




## Colocalization




***Criteria for detecting effects***

(1) 95% confidence intervals don't overlap with null in the forward MR analyses
(2) No evidence for effect in reverse direction (95% CIs do overlap the null)
(3) Evidence of genetic colocalization

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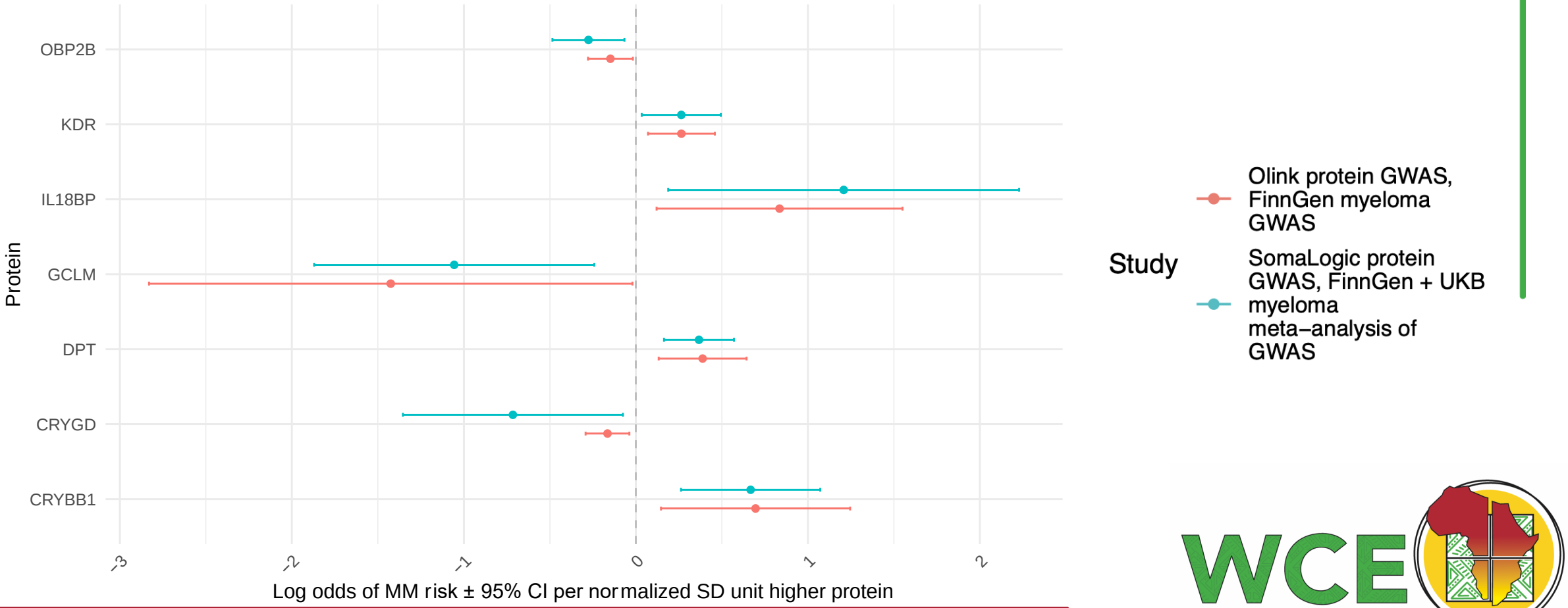
# Results

- 440 proteins measured across both protein datasets
- Circulating levels of 7 proteins may have a causal influence on multiple myeloma risk

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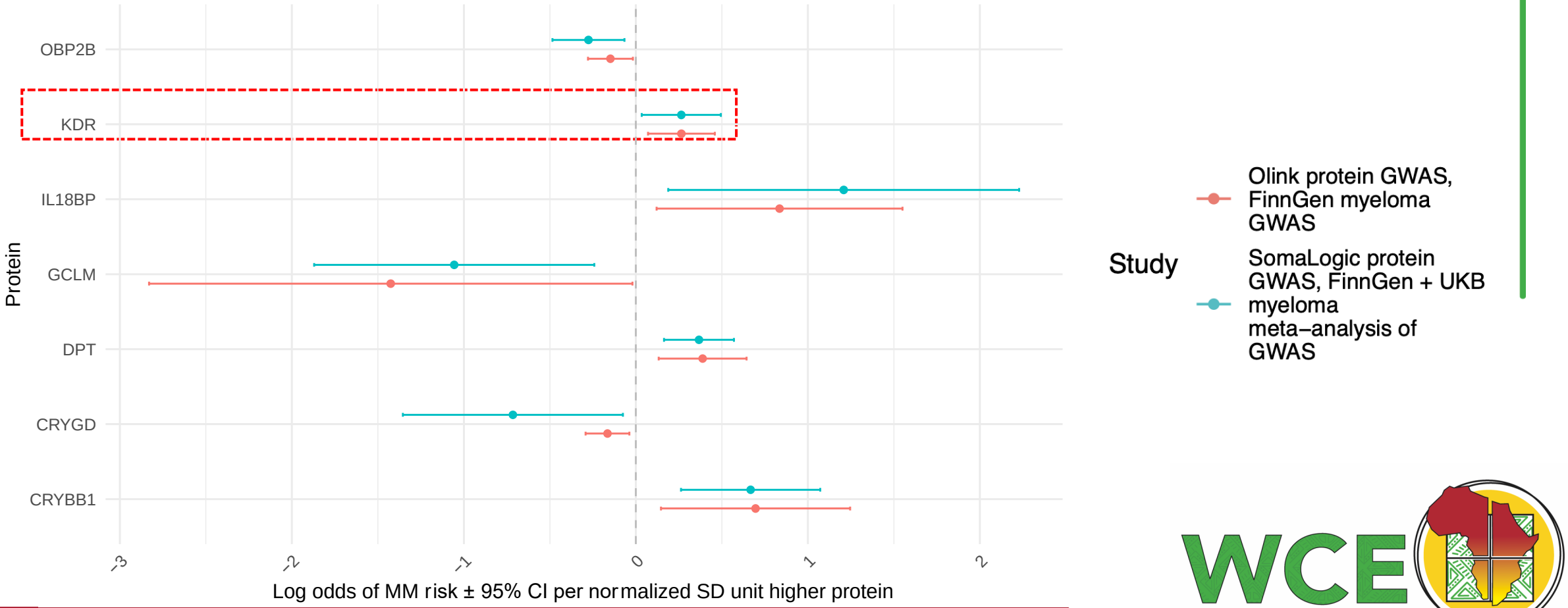


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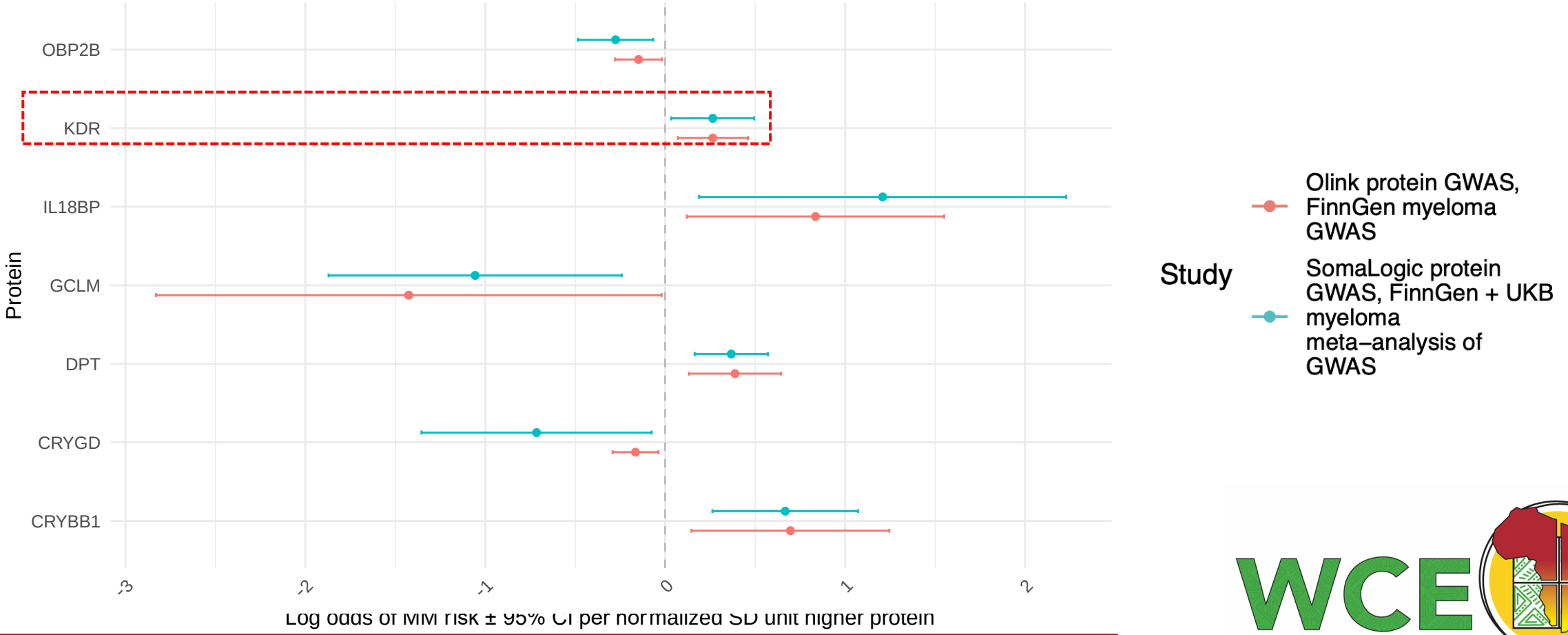
# Results

- 440 proteins measured across both protein datasets
- Circulating levels of 7 proteins may have a causal influence on multiple myeloma risk
- Lack of evidence for colocalization for these proteins.

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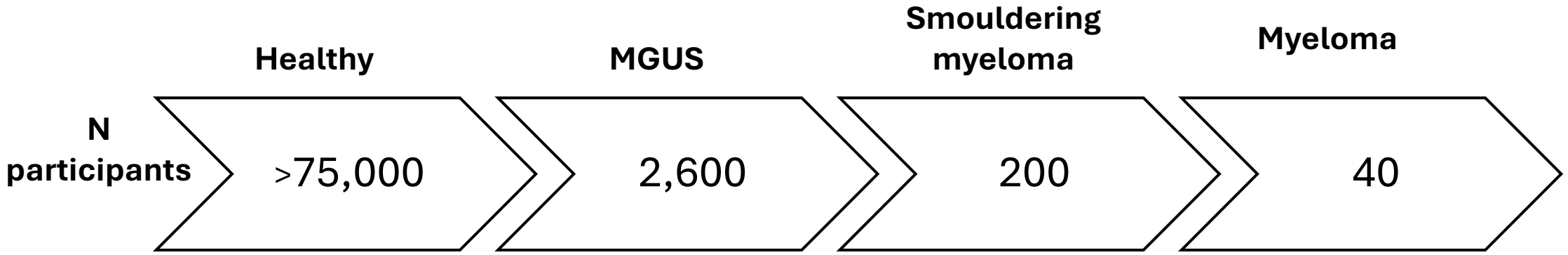
# Next steps

- Use samples from the Iceland screens, treats or prevents multiple myeloma (iStopMM study)




- Characterise the proteomic signature of the progression to myeloma.
- Are we able to replicate effects seen in MR using patient samples?

# Conclusions

- MR can be a useful hypothesis generating tool to explore the involvement of circulating proteins in myeloma.
- Initial MR results indicates 7 proteins for further exploration (e.g. KDR/VEGFR2).
    - Results limited to European ancestry individuals.
    - However, colocalization did not provide sufficient evidence for a shared causal variant.
- MR has limitations; triangulation is important in exploring protein changes in myeloma.

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