

# Do Metabolic Risk Factors Mediate the Genetic Risk for Coronary Heart Disease?

## Background

- Family history of coronary heart disease (CHD) and genetic predisposition as assessed by a genetic risk score (GRS) both predict CHD independently of established cardiometabolic risk factors.
- Though independent, risk assessment through family history or GRS may be partially explained by (mediated through) cardiometabolic risk factors.
- **Objectives:** The investigators evaluated the association between incident CHD and 1) self-reported family history and 2) GRS. They also evaluated what fraction of the association between CHD and family history or GRS is mediated by cardiometabolic risk factors.

## Method

- The study population was 23,595 men and women aged 45 to 73 years recruited between 1991 and 1996 for the Malmö Diet and Cancer study.
  - During a median follow-up of 14.4 years, 2,213 participants experienced a first CHD event.
- The GRS was calculated using a 50-variant score (GRS50).<sup>1</sup>
- Total effects were calculated, as were the effects mediated by:
  - apolipoprotein B (apoB)
  - apolipoprotein A-I (apoA-I)
  - blood pressure
  - diabetes mellitus (DM)

## Results

- Family history and elevated GRS50 were both associated with incident CHD; hazard ratios (highest vs lowest quintile) for CHD were 1.52 (95% CI, 1.39-1.65) for family history and 2.01 (95% CI, 1.76-2.30) for GRS50.
- Approximately 20% of CHD risk assessed by family history was mediated through established cardiometabolic risk factors.
- Approximately 11% of CHD risk assessed by GRS50 was mediated through established cardiometabolic risk factors.
- CHD risk, whether assessed through family history or GRS50, was mediated through ApoB (6.0% to 8.3%) and blood pressure (3.5% to 8.5%). DM did not mediate CHD risk as assessed by family history or GRS50.

## Conclusions

- A small proportion (11% to 20%) of incident CHD risk as assessed by family history or GRS50 is mediated through established cardiometabolic risk factors; most of the risk is independent of these factors.
- Thus, CHD risk assessment by family history or GRS50 in addition to established cardiometabolic risk factors may be warranted.

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### References

1. Tada H, Melander O, Louie JZ, et al. *Eur Heart J*. 2016;37:561-567.