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).¹
- 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.

---

[¹] Oral presentation at the 2016 Annual Congress of the European Society of Cardiology

**Authors**
- Josef Fritz,¹ Dov Shiffman,² Olle Melander,³ Hayato Tada,⁴ Hanno Ulmer⁵

**Affiliations**
1. Department of Medical Statistics, Informatics and Health Economics, Innsbruck Medical University, Austria
2. Quest Diagnostics, Alameda, CA, USA
3. Department of Clinical Sciences, Lund University, Malmö, Sweden and Department of Internal Medicine, Skåne University Hospital, Malmö, Sweden
4. Kanazawa University Graduate School of Medicine, Kanazawa, Japan

**Annual Congress of the European Society of Cardiology**
August 27-31, 2016
Rome, Italy
Time: Monday, August 29, 11:18 AM

**Webpage**
http://congress365.escardio.org/Session/19014 (requires ESC login)

**References**