

Genes, Lifestyle and Coronary Heart Disease Risk Epidemiological Interaction Studies

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien,
Göteborgs Universitet, kommer att offentligen försvaras i hörsal Arvid Carlsson,
Academicum, Medicinaregatan 3, fredag den 27 mars 2015 kl. 9:00

av

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Fakultetsopponent:

Professor Marju Orho-Melander
Institutionen för kliniska vetenskaper
Lunds Universitet

Avhandlingen baseras på följande arbeten:

- I. Jaana Gustavsson, Kirsten Mehlig, Karin Leander, Elisabeth Strandhagen, Lena Björck, Dag S. Thelle, Lauren Lissner, Kaj Blennow, Henrik Zetterberg, Fredrik Nyberg.
Interaction of apolipoprotein E genotype with smoking and physical inactivity on coronary heart disease risk in men and women.
Atherosclerosis 2012; 220: 486-492
- II. Jaana Gustavsson, Kirsten Mehlig, Karin Leander, Lauren Lissner, Lena Björck, Annika Rosengren, Fredrik Nyberg.
FTO genotype, physical activity and coronary heart disease risk in Swedish men and women.
Circulation Cardiovascular Genetics 2014; 7: 171-177
- III. Jaana Gustavsson, Kirsten Mehlig, Karin Leander, Christina Berg, Gianluca Tognon, Elisabeth Strandhagen, Lena Björck, Annika Rosengren, Lauren Lissner, Fredrik Nyberg.
FTO gene variation, macronutrient intake and coronary heart disease risk: a gene-diet interaction analysis.
European Journal of Nutrition doi:10.1007/s00394-015-0842-0
- IV. Jaana Gustavsson, Kirsten Mehlig, Elisabeth Strandhagen, Karin Leander, Kaj Blennow, Henrik Zetterberg, Annika Rosengren, Dag S. Thelle, Fredrik Nyberg, Lauren Lissner.
FTO and GHRL gene-gene interaction on body mass index.
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ABSTRACT

Coronary heart disease (CHD) has multifactorial background involving both genetic and lifestyle factors, but much is still unknown about their interactions. The aim of this thesis was to study interactions focusing on apolipoprotein E (*APOE*), fat mass and obesity-related (*FTO*) and ghrelin/obestatin prepropeptide (*GHRL*) genes, as well as smoking, physical activity and diet. The study sample included 1831 cases with CHD (myocardial infarction or unstable angina) and 5175 population controls from two population-based studies: SHEEP, Stockholm and INTERGENE, Gothenburg. Interaction was assessed on the relative risk (RR) and risk difference (RD) scales.

APOE-smoking interaction was found both on the RR and RD scales, so that subjects carrying the $\epsilon 2$ allele had lower smoking-related CHD risk, adjusted OR 1.35 (95% CI 0.92-1.97) than non-carriers, with OR 2.17 (95% CI 1.82-2.59) in subjects with common genotype $\epsilon 3\epsilon 3$ and OR 2.43 (95% CI 1.88-3.14) in $\epsilon 4$ carriers. Women carrying the $\epsilon 4$ allele had particularly high smoking-related CHD risk with OR 3.69 (95% CI 2.33-5.83). A potential *APOE*-physical activity interaction was also observed, where the $\epsilon 2$ allele counteracted while the $\epsilon 4$ allele (vs $\epsilon 3\epsilon 3$) potentiated CHD risk from physical inactivity.

Carriers of the *FTO* single nucleotide polymorphism (SNP) rs9939609 A allele (TA/AA vs TT) had increased CHD risk with OR 1.20 (95% CI 1.06-1.37), independent of body mass index (BMI). No evidence of interaction between *FTO* and physical activity was found, indicating that *FTO*-related CHD risk is not counteracted by increased physical activity. No clear interactions between *FTO* and macronutrients were found with a dichotomous variable of below/above median energy% intake. With a continuous energy% variable, excluding subjects reporting diet change, however, interaction was observed on the RR scale for *FTO*-fat and *FTO*-saturated fatty acids, suggesting slightly increased *FTO*-related CHD risk with lower energy% of fat or saturated fatty acids.

Finally, a gene-gene interaction was found for SNPs *FTO* and *GHRL* rs35680 in a subsample of 420 INTERGENE controls, where the minor alleles had synergistic effects on BMI, supporting a mechanistic *FTO*-*GHRL* link behind obesity.

To conclude, identification of gene-lifestyle interactions may contribute to enhanced understanding of mechanisms causing CHD.

Keywords: Coronary heart disease, gene-lifestyle interaction, *APOE*, *FTO*, *GHRL*, smoking, physical activity, diet, obesity

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