Interaction of Genetic Susceptibility and Traffic-Related Air Pollution in Cardiovascular Disease

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Nitric Oxide 39:1-7.

II. Levinsson A, Olin AC, Modig L, Dahgam S, Björck L, Rosengren A, Nyberg F (2014) *Interaction effects of long-term air pollution exposure and variants in the GSTP1, GSTT1 and GSTCD genes on risk of acute myocardial infarction and hypertension: a case-control study*.
PLoS One 9(6): e99043.

III. Levinsson A, Olin AC, Ding B, Björck L, Rosengren A, Nyberg F. *Additive interaction involving a continuous variable: a pragmatic approach*.
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ABSTRACT

This thesis aimed at investigating gene-environment interaction in cardiovascular disease (CVD). A study population of 618 coronary heart disease (CHD) cases (of which 192 first-time acute myocardial infarction (AMI) patients) and 3614 randomly selected population controls was genotyped for genetic variants in genes coding for nitric oxide synthase (NOS) and glutathione s-transferase (GST). Exposure to traffic-related air pollution was assessed using modeled mean annual concentrations of nitric dioxide (NO_2) as a marker for long-term exposure.

Among 58 single nucleotide polymorphisms (SNPs) in the *NOS1*, *NOS2* and *NOS3* genes investigated for risk of CHD and hypertension, several strong associations were found, some of which remained statistically significant after Bonferroni correction for multiple testing. The T-allele of *NOS1* SNP rs3782218 was significantly associated with a protective effect for both CHD (odds ratio (OR) 0.6, 95% confidence interval (CI) 0.44-0.80) and hypertension (OR 0.8, 95% CI 0.68-0.97). A second study investigated SNPs in the genes *GSTP1*, *GSTT1* and *GSTCD* for interaction with traffic-related air pollution on risk of AMI and hypertension. The risk of AMI from air pollution exposure seemed to vary by genotype strata (for example *GSTP1* SNP rs596603 with OR 2.1, 95% CI 1.09-4.10 in the genotype TT+GT stratum; OR 1.4, 95% CI 0.73-2.68 in the genotype GG stratum, although the multiplicative interaction was not significant (p-value =0.27)). Finally, the methodology of estimating additive interaction between a dichotomous (e.g. genetic) variable and a continuous (e.g. air pollution) variable using output from a logistic regression model was investigated in detail. The measure of additive interaction in this setting was shown to be highly sensitive to variation in the parameters defining it, and a pragmatic proposal for controlling this variability when extending estimation of additive interaction to new settings was developed. The proposed method was applied to the *GST* genotype and air pollution exposure data to estimate the additive interaction of these exposures on risk of AMI, finding a sub-additive interaction effect for the *GSTCD* AG+GG genotype.

To conclude, the results of this thesis indicate that *NOS* gene variants are associated with both CHD and hypertension, and that variants in the *GST* genes are of importance regarding the risk of hypertension and the risk of AMI due to air pollution exposure.

Keywords: Cardiovascular disease, genetic variants, air pollution, gene-environment interaction

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