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Institutet för Miljömedicin / Enheten för Miljömedicinsk Epidemiologi

Air pollution, genetic susceptibility and inflammation

*Focusing on cardiovascular effects in adults
and respiratory effects in children*

AKADEMISK AVHANDLING

som för avläggande av medicine doktorexamen vid Karolinska
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av

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ABSTRACT

Air pollution exposure can induce low-grade systemic inflammation with consequences for both cardiovascular and respiratory systems. The overall aim of this thesis was to investigate the effects of air pollutants on the development of complex inflammatory diseases (myocardial infarction and respiratory disease), and genetically determined susceptibility for these effects, using epidemiologic methodology.

The two study populations were drawn from a case-control study of myocardial infarction (SHEEP) and a birth cohort (BAMSE). From SHEEP, the present study population included 1192 first-time myocardial infarction (MI) cases aged 45-70 years identified in Stockholm County during 1992-1994, and 1536 matched population controls from the study base. Participants completed questionnaires and underwent medical examination as well as blood sampling. Their air pollution exposure was assessed retrospectively both long-term (1-30 years) and short-term (12 h - 5 days). NO₂ was used as an indicator of emissions from road traffic and SO₂ as an indicator of emissions from residential heating. From the BAMSE cohort, which recruited 4089 new-born children during 1994-1996 in four municipalities in Stockholm County, this study included 497 wheezers and 485 non-wheezing controls at 4 years, and 198 asthma cases and 192 non-asthma controls at 8 years. Questionnaires were completed by the parents when the children were 2 months, 1, 2, 4, and 8 years of age. The children were also invited for medical examination and blood sampling at 4 and 8 years.

In adults, long-term exposure to both traffic-NO₂ and heating-SO₂ emissions showed an association with IL-6 levels. For instance, 30-year traffic-NO₂ exposure was associated with a 64.5% (95%CI 6.7-153.8%) increase in serum IL-6 per 28.8 µg/m³ (corresponding to the difference between the 5th and the 95th percentile exposure value). There was also suggested association between short-term exposure to traffic-related air pollutants and inflammatory markers (IL-6, TNF-α). Gene-environment interaction was observed for several *IL6* and *TNF* single nucleotide polymorphisms (SNPs) in relation to inflammation blood marker levels. For example, 1-year traffic-NO₂ exposure interacted with *IL6* -174G/C in an additive way, where each additional *IL6*-174C allele was associated with an increased air pollution effect on IL-6 levels, and 1-year heating-SO₂ exposure was associated with higher TNF-α levels in *TNF*-308AA homozygotes but not in -308G carriers. Also short-term air pollution exposure interacted with *IL6* and *TNF* SNPs in relation to marker levels. The risk of MI followed the pattern of effect on blood markers across genotype groups.

In children, interaction with early maternal smoking was seen for 3 *TNF* SNPs with respect to early wheeze. The odds ratio for developing early wheeze related to maternal smoking was 2.4 (95%CI 1.6-3.7) in *TNF* -857C homozygote children, while no tobacco-related risk was seen in children with the rare -857T allele. Suggestive interaction with early maternal smoking was also seen for 3 *GSTP1* SNPs with respect to transient wheeze. SNPs in *TNSI*, *ADAM19*, *THSD4* and *ADCY2* identified through genome-wide analyses on lung function in adults showed association also with lung function in children; *DAAM2* rs2395730 showed suggestive interaction with current tobacco smoke exposure at 8 years.

In summary, the results indicate that air pollutants affect levels of inflammatory blood markers, and this effect appears to be modified by genetic variants, affecting both blood marker levels and consequent MI risk. Polymorphisms in genes related to inflammation (*TNF*) and antioxidant defense (*GSTP1*) seem to modify the effect of early tobacco smoke exposure on childhood wheezing. Several gene variants of importance for lung function in adults also seem to affect lung function in children.