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Title: Greater risk of wheeze in young female compared to male smokers – Results from the Swedish GA2LEN survey

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Body: Smoking has greater negative impacts on lung function and COPD risk in females. However, sex-related differences in smoking burden, body composition and exposures confound this association. We studied wheeze in relation to smoking and sex in a large well-characterised population. In 2008 the GA2LEN questionnaire was mailed to 45.000 Swedish adults (16-75 yrs), and 60% participated. Respiratory symptoms, smoking and other exposures were analysed by multivariate regression. Asthmatic wheeze: wheeze with breathlessness and without a cold. Females reported more wheeze and asthmatic wheeze, 17.3% vs. 15.8% and 7.1% vs. 6.1%, all $p < 0.01$. 39% of both sexes were ever-smokers, and more females were current smokers, 14.5% vs. 13.3%, $p < 0.01$. Males had higher mean age, BMI and pack-years, all $p < 0.01$. Twice as many males were exposed to gas, dust or fumes, and fewer had university education. Females had more traffic exposure and employment in healthcare and cleaning. Adjusted for all these factors, female current smokers aged 16-52 yrs had higher risk of wheeze and asthmatic wheeze, OR 1.28 vs. males (interaction $p = 0.04$) and OR 1.52 ($p = 0.02$). Each pack-year increased the risk of wheeze more in women, OR 1.01 ($p < 0.01$). The interactions were independent of weight, height and age at smoking initiation, and less consistent in subjects aged > 52 yrs. In this large, population-based study female compared to male smokers had higher risk of wheeze after adjustment for important confounders. This

increased susceptibility was greater in pre-menopausal ages, and was not explained by differences in body composition or smoking habits. This points toward biological, possibly hormonal, underlying mechanisms.