In young adults, sex-gender modulates the effects of regular smoking on global DNA methylation, endothelial functions, monocytes-derived macrophages function and transsulfuration pathway.

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Cigarettes smoking (CS) kills more then 5 million people much more than AIDS, tuberculosis, malaria combined. CS is more common among men (21.5%) than women (17.3%)[1] but women seem to be at significantly greater risk of developing a smoking related disease than men, as well as being susceptible to sex-gender specific health issues and pregnancy complications[2]. CS alters many functions such as endothelial function, redox state, inflammatory processes and DNA global methylation, which is associated to the one-carbon metabolism and transsulfuration pathway through homocysteine. However, it is not yet known whether the previous alterations are sex-gender-dependent. We therefore analysed a young (median age of 27 years), adult and healthy population of women and men. Women were analysed in the follicular phase and were free from oral contraceptives in order to avoid any bias due to sexual hormones. Men and women were strati?ed according to their smoking habit, so that 28 males and 32 females were regular smokers while 55 males and 53 females were non-smokers. Fasting blood samples were obtained and used for assessments of asymmetric dimethylarginine (ADMA, a marker of endothelial dysfunction), global DNA methylation, transsulfuration pathway, oxidative stress, and human monocytes-derived macrophages (hMDMs) for TNF-alpha release determination as described in Campesi et al, (2012)[4].

Numerous sex-gender differences were found in non-smoker people: men had higher plasma levels of uric acid, total bilirubin, homocysteine, glutamylcysteine, total glutathione, cysteinglycine, higher monocyte number, and released more TNF-alpha from hMDMs in basal conditions. Notably, men had less platelet and lower level of global DNA methylation and their hMDMs released less TNF-alpha after LPS stimulation. MDA, taurine, cysteine, and ADMA levels did not differ between men and women.

Interestingly, CS impacts on the studied parameters in a sex-gender manner. In particular, CS decreased DNA methylation more in women than in men and increased the platelet, monocyte, and lymphocyte counts and the homocysteine, arginine, and ADMA levels only in women, whereas the neutrophil and eosinophil counts were increased only in men. Additionally, CS reduced the sex-gender differences in total bilirubin, basal and LPS-induced TNF-alpha release, total glutathione, and glutamylcysteine, whereas the levels of cysteinylglycine, taurine, MDA, and cysteine were not changed. **Overall,** the present study provides convincing evidences that CS predominantly affects inflammatory response, endothelial function, transsulfuration and global DNA methylation in women than in men. Finally, these findings suggest that cardiovascular risk factors seem to come earlier in young healthy female smokers than in young healthy male smokers.

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