“Clarification of the Risk of COPD in Alpha-1 Antitrypsin Deficiency PiMZ Heterozygotes”

Interactions and clarifying group-specific estimates by using stratification

To the Editor –

Personal tobacco smoking has been accepted as the main environmental risk factor for the development of COPD in industrialised countries, with and without emphysema. However, for active smokers who also have the PI*MZ genotype of α-1 antitrypsin deficiency (AATD), the nature of the combined effect on the risk of COPD has been debated (1-4). If PI*MZ heterozygosity augmented the adverse lung function effects of personal smoking, then smoking abstinence could avert the direct smoking effect as well as the extra lung function loss from the interaction itself.

The Irish National Targeted Detection Programme that identifies COPD cases related to AATD, has provided Molloy and colleagues with a unique opportunity to examine the relationship between PI*MZ heterozygosity and spirometrically-defined COPD for first-degree relatives of affected individuals (5). This analysis primarily investigated for an interaction between the effects of PI*MZ heterozygosity and personal smoking on the post-bronchodilator spirometry of individuals who otherwise did not present with clinical disease. The main COPD finding of the abstract may also be interpreted as follows; “for middle-aged-to-older PI*MZ relatives of index cases, the study found with 95% confidence that personal smoking increased the odds of spirometrically-defined COPD by a factor of at least 2.2 (p for interaction p=0.005), as compared with never-smokers”. But, rather than reporting the estimates for never-smokers and ever-smokers separately which is usual in the case of a significant interaction, the abstract highlighted the combined or non-stratified result. This effectively clouded the possibility that there may be no increased risk of COPD for PI*MZ individuals who didn’t smoke, in contrast to the positive association for PI*MZ individuals who did. A similar PI*MZ-smoking interaction was found for continuous lung function outcomes when smoking was stratified into low and high exposure groups (less or more than 20 pack-years), though the statistical basis for this stratification was not explicitly stated in the article.

The prevalence of PI*MZ heterozygosity ranges between 2% and 4% in Western countries (4, 5), with a comparable low clinical expression of AATD that more frequently resembles an emphysematous phenotype. As such, the present study was able to include only 89 PI*MZ relatives of affected individuals and 5 PI*MM smokers and non-smokers with spirometrically-defined COPD (GOLD stage II-IV). These few numbers were reflected by wide confidence intervals, and the limited statistical power might have contributed to the null association for never-smokers.

While the overall negative results for these never-smoking PI*MZ relatives of index cases were acknowledged by the authors, the confirmation of such findings may arguably be more important than quantifying the “COPD risks” for ever-smokers. The Copenhagen General Population Study that measured AAT levels from a subset of over 26,000 never-smokers and without self-reported asthma, essentially found no difference between those with and without COPD, as defined by pre-bronchodilator FEV₁/FVC less than the lower limit of normal (6). As AATD was regarded as an
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unlikely major contributor for never-smokers by this study, together these data might now offer a more positive and definitive message for asymptomatic never-smoking Pi*MZ relatives (1), their health care providers and AATD support groups.

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REFERENCES