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**Title:** A low sputum MMP-9 activity/TIMP ratio is associated with CT airway wall thickness in smokers with asthma

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**Body:** BACKGROUND In asthma, smokers have severe symptoms and decreased sensitivity to corticosteroids. A reduced matrix-metalloproteinase (MMP)-9/tissue inhibitors of metalloproteinases (TIMPs) ratio in asthma has been implicated in airway remodelling and steroid resistance. Our hypothesis is that sputum MMP-9/TIMPs are reduced in smokers with asthma and are associated with measures of airway remodelling. METHODS In 98 asthmatics and 44 controls (smokers & non-smokers) we measured sputum MMP-9 activity & concentrations and TIMP1/2 levels, diffusing capacity for carbon monoxide (DLCO) and CT airway wall thickness (RB10% wall area). RESULTS Sputum MMP-9 activity/TIMPs-1 and 2 were lower in smokers with asthma compared with non-smokers and in healthy smokers vs non-smokers (Table 1). Sputum MMP-9/TIMP correlated with sputum % neutrophils, but not with DLCO. In smokers with asthma, reduced sputum MMP-9 activity/TIMP1 was associated with increased RB10 % wall area [correlation coefficient [-0.45 (-0.71, -0.09)].

	Asthma Non-smoker	Asthma Smoker	Control Non-smoker	Control Smoker
MMP-9/TIMP1	1.6 (0.7,2.2)	1.0 (0.5,1.8)	1.3 (0.8,2.4)	1.0 (0.5,2.4)

MMP-9/TIMP2	9.0 (6.0,11.6)	7.5 (3.8,11.4)	6.8 (4.3,11.2)	6.5 (4.3,11.2)
MMP-9 activity/TIMP1	0.4 (0.3,0.6)	0.2 (0.1,0.4)*	0.7 (0.3,1.3)	0.3 (0.1,0.5)*
MMP-9 activity/TIMP2	2.6 (2.0,3.1)	1.4 (0.9,2.3)**	3.1 (2.1,5.0)	1.7 (1.1,3.0)*

Median (IQR); \*=p<0.05, \*\*p=0.001 smokers vs nonsmokers in each group

CONCLUSION A low sputum MMP-9 activity/TIMP1 ratio is associated with airway wall thickness in smokers with asthma, suggesting a potential role for MMP-9 and TIMP in airway remodelling in this group.