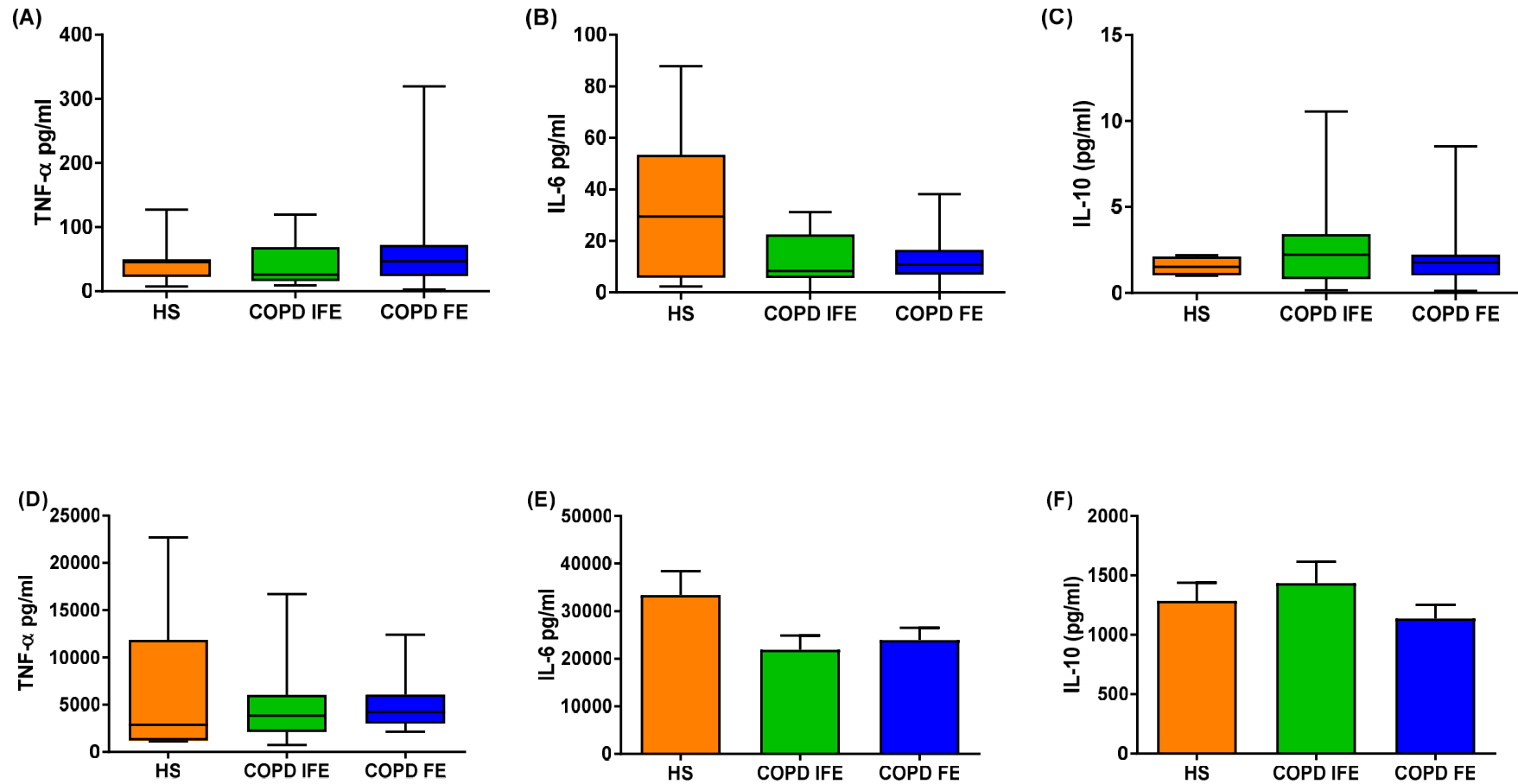
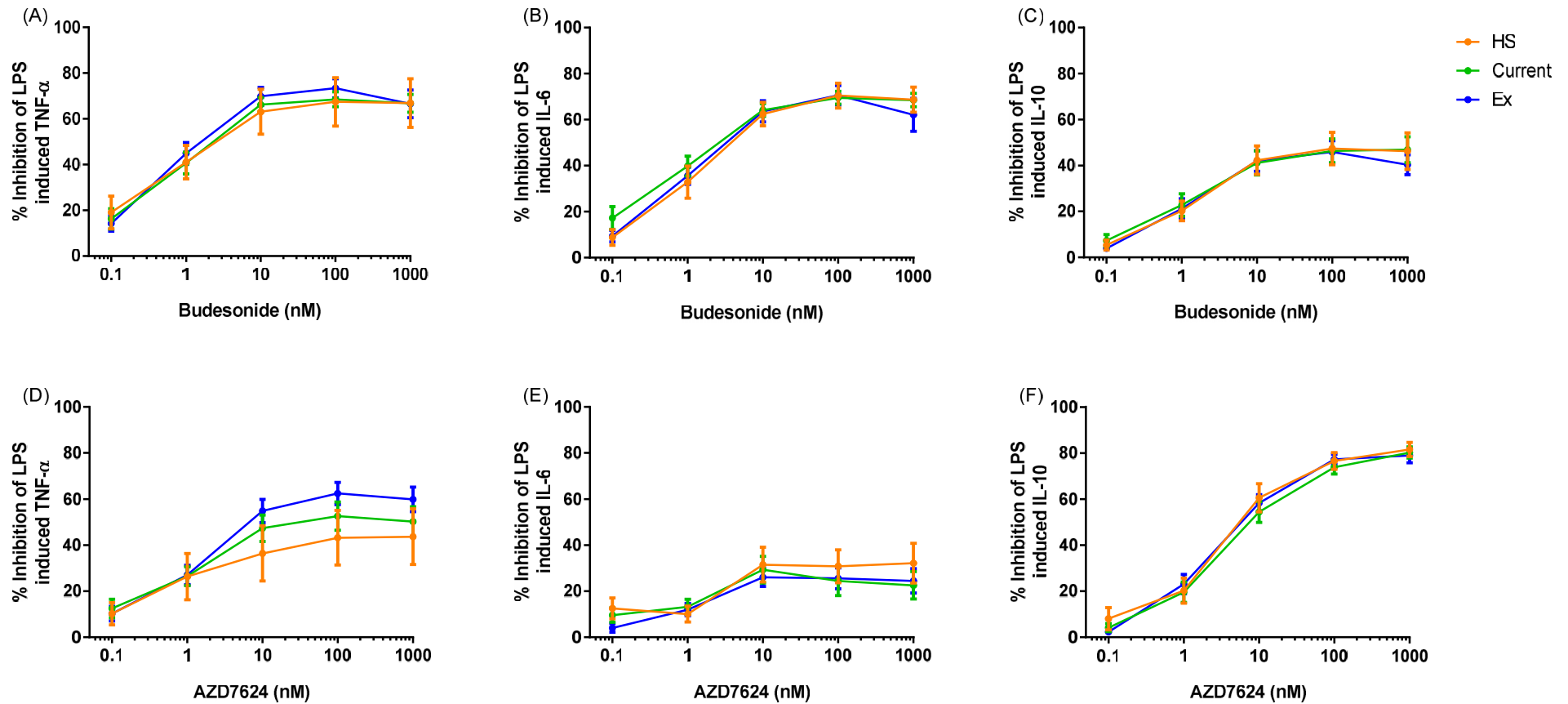


Supplementary Figure 1



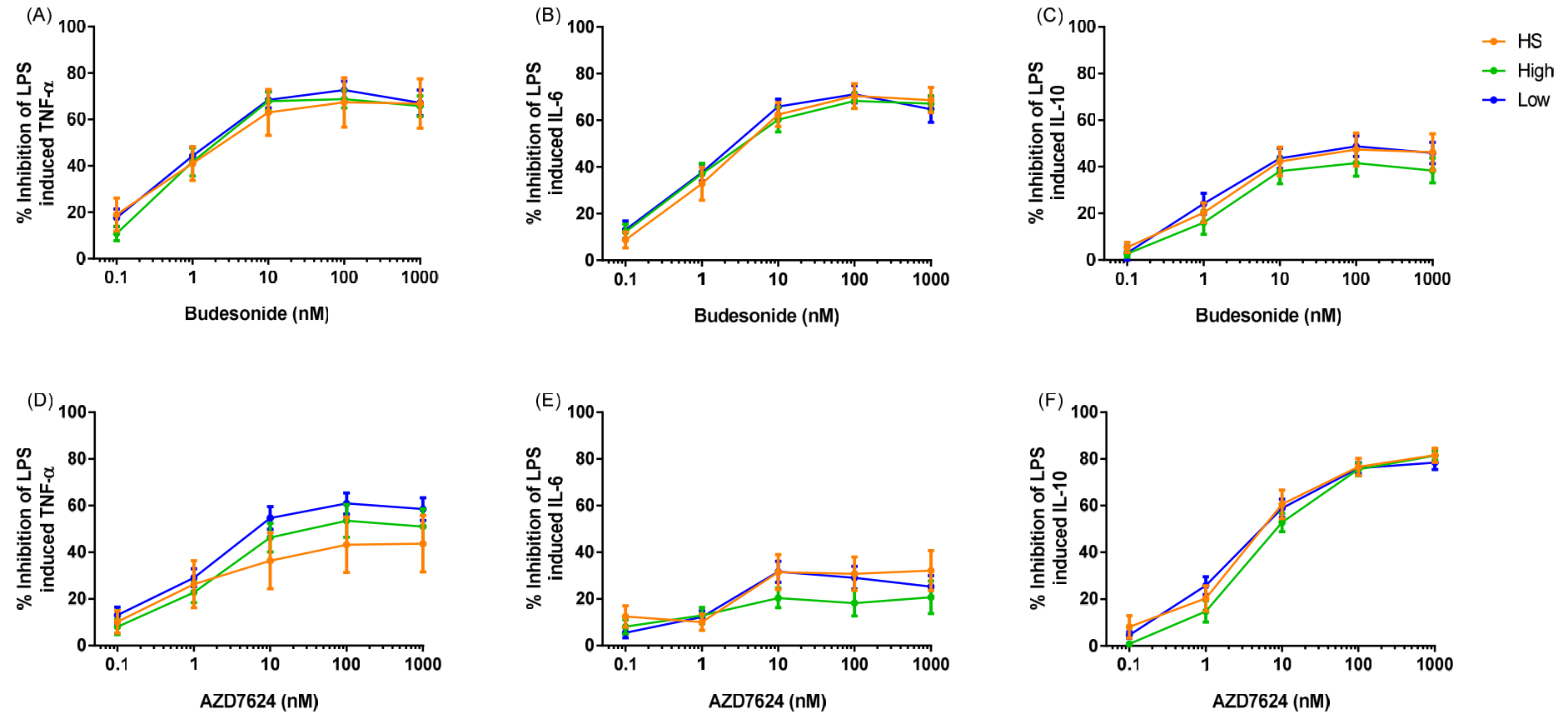
Supplementary figure 1. Baseline and LPS-stimulated cytokine release from peripheral blood mononuclear cells. The levels of TNF- α (A and D), IL-6 (B and E) and IL-10 (C and F) were analysed in the supernatants of untreated (A – C) or LPS stimulated (D – F) PBMCs from healthy smokers (HS; orange), COPD infrequent exacerbators (COPD IFE; green) and COPD frequent exacerbators (COPD FE; blue). Data shown are mean \pm SEM (E and F) and median with range (A – D).

Supplementary Figure 2



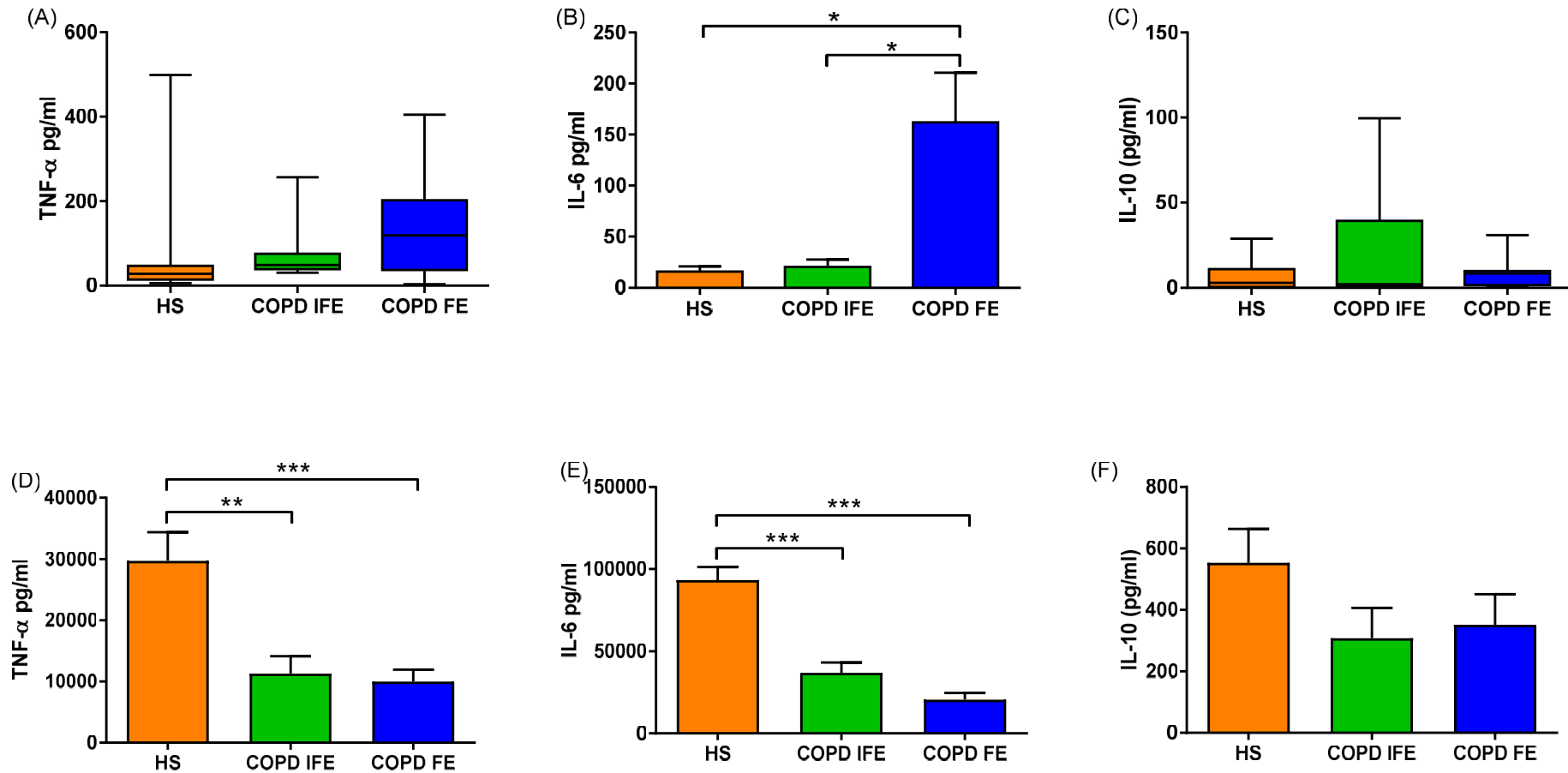
Supplementary figure 2. Group mean budesonide and AZD7624 concentration curves in peripheral blood mononuclear cells, according to smoking status. The group mean data for inhibition of TNF- α (A and D), IL-6 (B and E) and IL-10 (C and F) by budesonide (A – C) and AZD7624 (D – F) are shown for healthy smokers (HS; orange plot), COPD current smokers (green plot) and COPD ex-smokers (blue plot). Data shown are mean \pm SEM.

Supplementary Figure 3



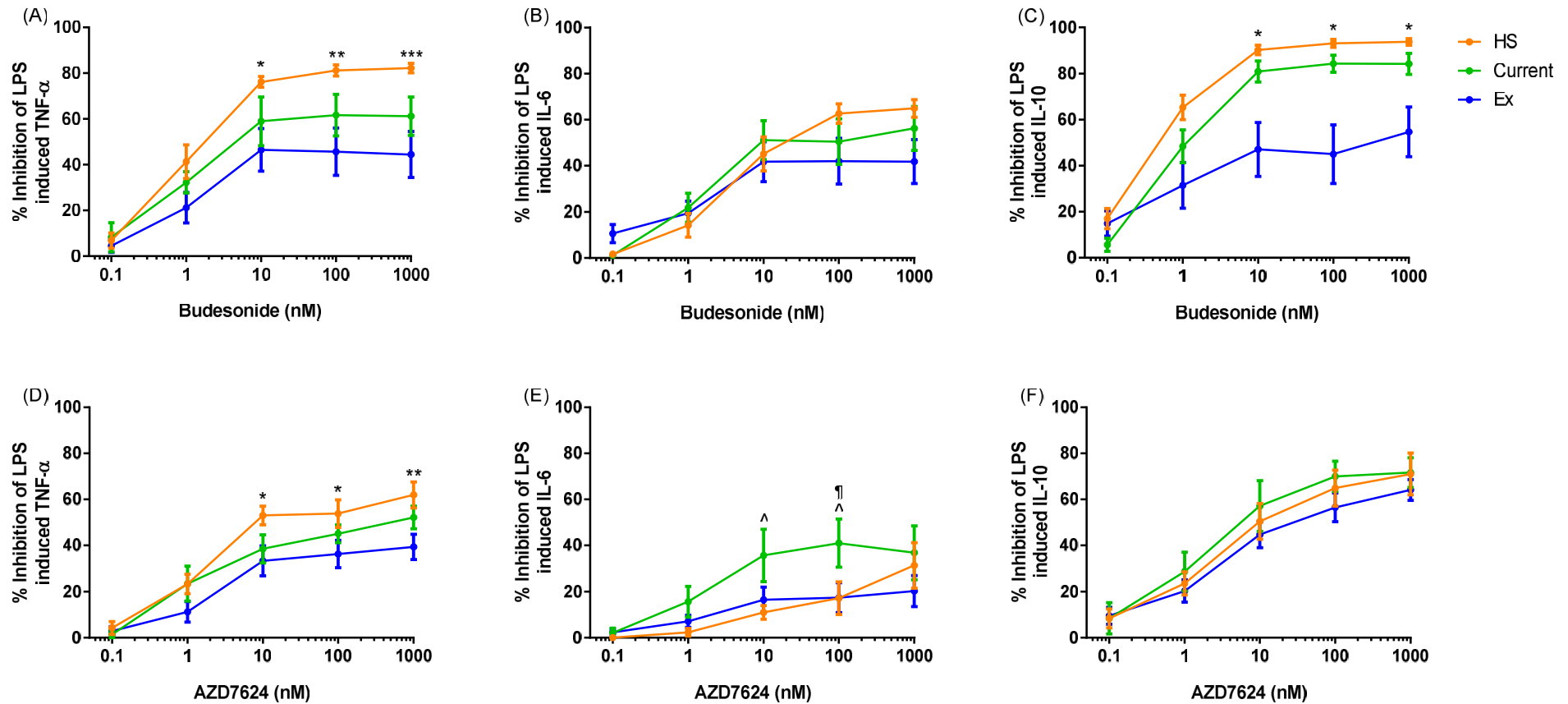
Supplementary figure 3. Group mean budesonide and AZD7624 concentration curves in peripheral blood mononuclear cells, according to blood eosinophil count. The group mean data for inhibition of TNF- α (A and D), IL-6 (B and E) and IL-10 (C and F) by budesonide (A – C) and AZD7624 (D – F) are shown for healthy smokers (HS; orange plot), COPD high blood eosinophils (green plot) and COPD low blood eosinophils (blue plot). An eosinophil threshold of 300 cells/ μ l was applied for purposes of high/low analysis. Data shown are mean \pm SEM.

Supplementary Figure 4



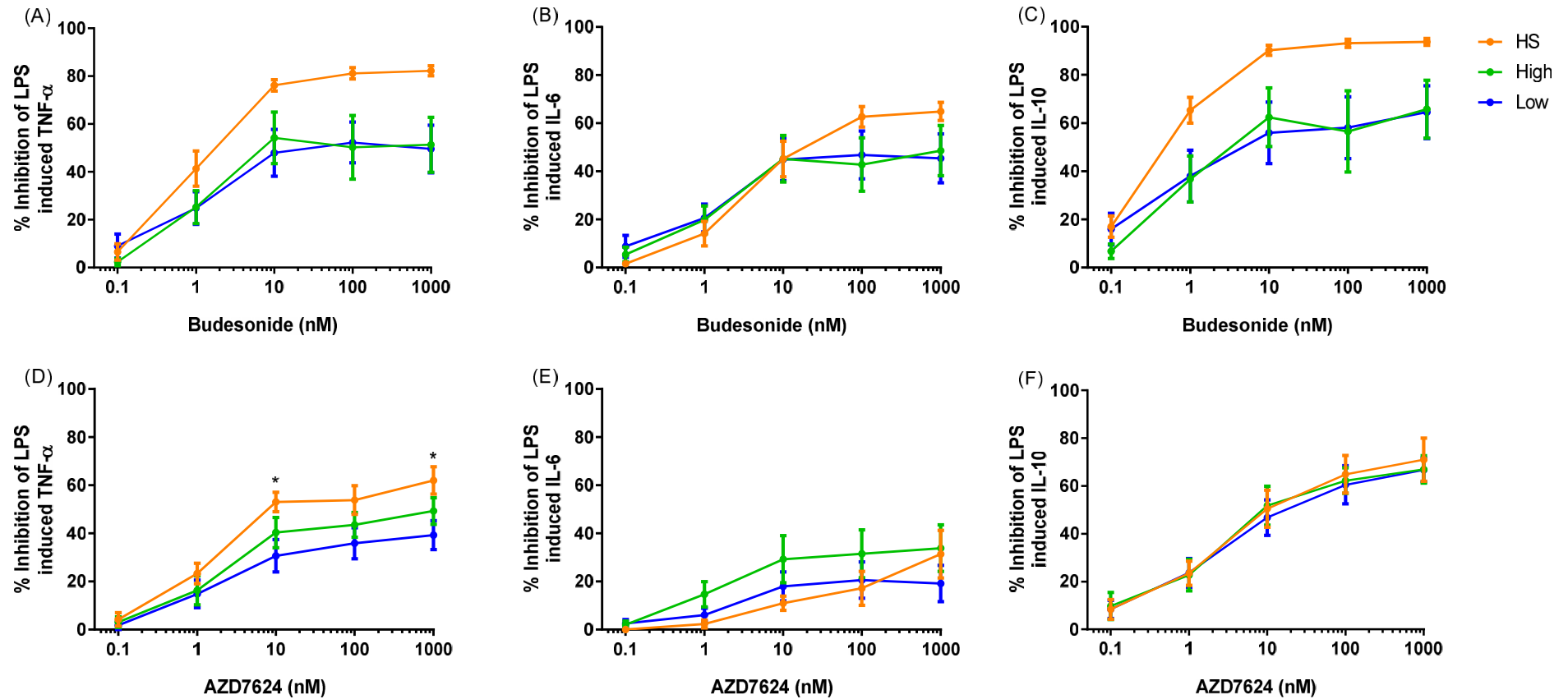
Supplementary figure 4. Baseline and LPS-stimulated cytokine release from alveolar macrophages. The levels of TNF- α (A and D), IL-6 (B and E) and IL-10 (C and F) were analysed in the supernatants of untreated (A – C) or LPS stimulated (D – F) alveolar macrophages from healthy smokers (HS; orange), COPD infrequent exacerbators (COPD IFE; green) and COPD frequent exacerbators (COPD FE; blue). Data shown are mean \pm SEM (B, D – F) and median with range (A and C). *, **, *** = significant difference where $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively.

Supplementary Figure 5



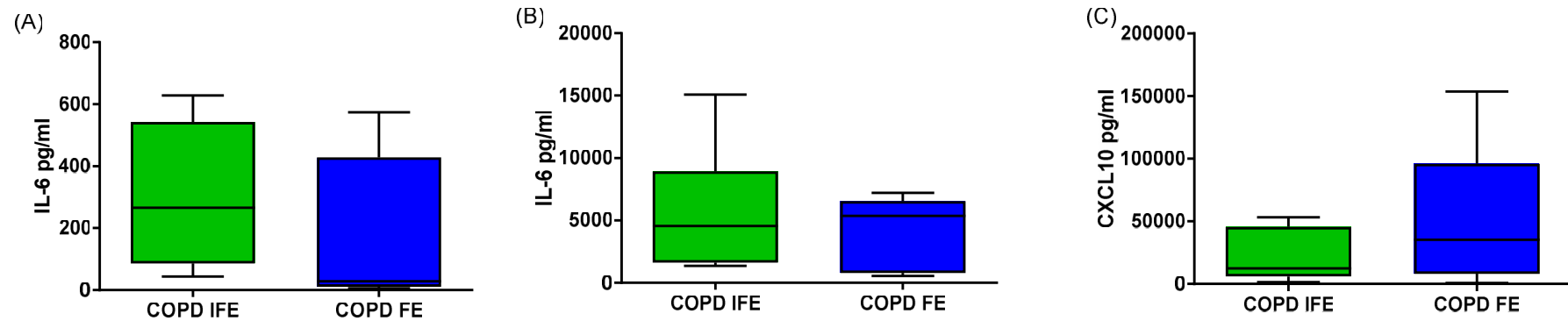
Supplementary figure 5. Group mean budesonide and AZD7624 concentration curves in alveolar macrophages, according to smoking status. The group mean data for inhibition of TNF- α (A and D), IL-6 (B and E) and IL-10 (C and F) by budesonide (A – C) and AZD7624 (D – F) are shown for healthy smokers (HS; orange plot), COPD current smokers (green plot) and COPD ex-smokers (blue plot). Data shown are mean \pm SEM. *, **, *** = significant difference between HS and COPD ex-smokers where $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively. ^ = significant difference between HS and COPD current smokers where $p < 0.05$. ¶ = significant difference between COPD current smokers and COPD ex-smokers where $p < 0.05$.

Supplementary Figure 6



Supplementary figure 6. Group mean budesonide and AZD7624 concentration curves in alveolar macrophages, according to blood eosinophil count. The group mean data for inhibition of TNF- α (A and D), IL-6 (B and E) and IL-10 (C and F) by budesonide (A – C) and AZD7624 (D – F) are shown for healthy smokers (HS; orange plot), COPD high blood eosinophils (green plot) and COPD low blood eosinophils (blue plot). An eosinophil threshold of 300 cells/ μ l was applied for purposes of high/low analysis. Data shown are mean \pm SEM. *, = significant difference between HS and COPD ex-smokers where $p < 0.05$.

Supplementary Figure 7



Supplementary figure 7. Baseline and poly I:C stimulated cytokine release from bronchial epithelial cells. The levels of IL-6 (A – B) and CXCL10 (C) were analysed in the supernatants of untreated (A) and poly I:C stimulated (B and C) BECs from COPD infrequent exacerbators (COPD IFE; green) and COPD frequent exacerbators (blue). Data shown are median with range.

Supplementary table 1. Sputum and BAL and blood characteristics of the study population.

	Healthy Smokers	COPD Patients	
		Infrequent Exacerbators	Frequent Exacerbators
Sputum			
Absolute neutrophil count (x10 ⁶ /g sputum)	10.4	14.7	15.6
Absolute macrophage count (x10 ⁶ /g sputum)	2.3	2.1	3.0
Absolute eosinophil count (x10 ⁶ /g sputum)	0.03	0.2	0.6
Absolute lymphocytes count (x10 ⁶ /g sputum)	0.03	0.01	0.05
Absolute epithelial cell count (x10 ⁶ /g sputum)	0.07	0.2	0.3
Neutrophil (%)	69.8	70.9	74.2
Macrophage (%)	27.7	17.1	19.7
Eosinophil (%)	0.7	2.5	2.4
Lymphocyte (%)	0.8	0.06**	0.3
Epithelial cell (%)	1.0	1.9	3.4
BAL			
Neutrophil (%)	0.5	4.8	13
Macrophage (%)	96	87	80
Eosinophil (%)	0.1	0.5	0.4
Lymphocyte (%)	1.8	3.2	2.2
Epithelial cell (%)	1.4	4.5	4.4
Blood			
WBC x 10 ⁹ /l	7.3	7.3	6.5
Neutrophils x 10 ⁹ /l	3.8	4.1	3.6
Lymphocytes x 10 ⁹ /l	2.6	2.2	2.0
Monocytes x 10 ⁹ /l	0.7	0.7	0.6
Eosinophils x 10 ⁹ /l	0.23	0.3	0.26
Basophils x 10 ⁹ /l	0.04	0.06	0.05

Data presented as mean where * = significant difference compared to healthy smokers.

Supplementary table 2. Maximal inhibitions of budesonide and AZD7624 on LPS-induced cytokine release from peripheral blood mononuclear cells.

Subject Group	Maximum Inhibition					
	TNF- α		IL-6		IL-10	
	Budesonide	AZD7624	Budesonide	AZD7624	Budesonide	AZD7624
HS	67**	44	68***	32	46	82 †††
COPD IFE	70**	57	64***	23	42	84 †††
COPD FE	68***	60	72***	32	44	76 †††

Data presented as means. *, **, *** = significantly above AZD7624 (two-way ANOVA followed by Tukey's post-hoc test where $p < 0.05$, 0.01 and 0.001 respectively). †, ††, ††† = significantly above budesonide (two-way ANOVA followed by Tukey's post-hoc test where $p < 0.05$, 0.01 and 0.001 respectively).

FE: frequent exacerbators; HS: healthy smokers; IFE: infrequent exacerbators.

Supplementary table 3. Maximal inhibitions of budesonide and AZD7624 on LPS-induced cytokine release from alveolar macrophages.

Subject Group	Maximum Inhibition					
	TNF- α		IL-6		IL-10	
	Budesonide	AZD7624	Budesonide	AZD7624	Budesonide	AZD7624
HS	80***	59	65***	31	94***	71
COPD IFE	56	50	51	42	64	69
COPD FE	45	39	43***	11	66	65

Data presented as means. *, **, *** = significantly above AZD7624 (two-way ANOVA followed by Tukey's post-hoc test where $p < 0.05$, 0.01 and 0.001 respectively). †, ††, ††† = significantly above budesonide (two-way ANOVA followed by Tukey's post-hoc test where $p < 0.05$, 0.01 and 0.001 respectively).

FE: frequent exacerbators; HS: healthy smokers; IFE: infrequent exacerbators.

Supplementary table 4. Maximal inhibitions of budesonide and AZD7624 on poly I:C induced cytokine release from bronchial epithelial cells.

Subject Group	Maximum Inhibition			
	IL-6		IP-10	
	Budesonide	AZD7624	Budesonide	AZD7624
COPD IFE	23	49 ‡‡‡	20	39
COPD FE	14	64 ‡‡‡	4	19

Data presented as means. *, **, *** = significantly above AZD7624 (two-way ANOVA followed by Tukey's post-hoc test where $p < 0.05$, 0.01 and 0.001 respectively). ‡, ‡‡, ‡‡‡ = significantly above budesonide (two-way ANOVA followed by Tukey's post-hoc test where $p < 0.05$, 0.01 and 0.001 respectively).

FE: frequent exacerbators; IFE: infrequent exacerbators