SUPPLEMENTARY MATERIAL

Enhanced airway sensory nerve reactivity in non-eosinophilic asthma

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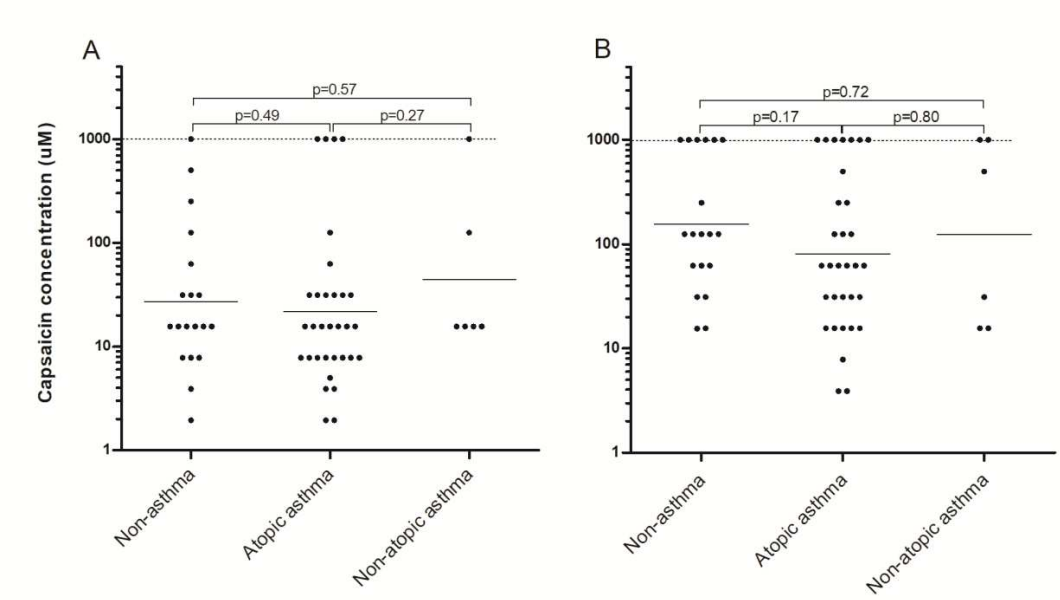
SUPPLEMENTARY RESULTS

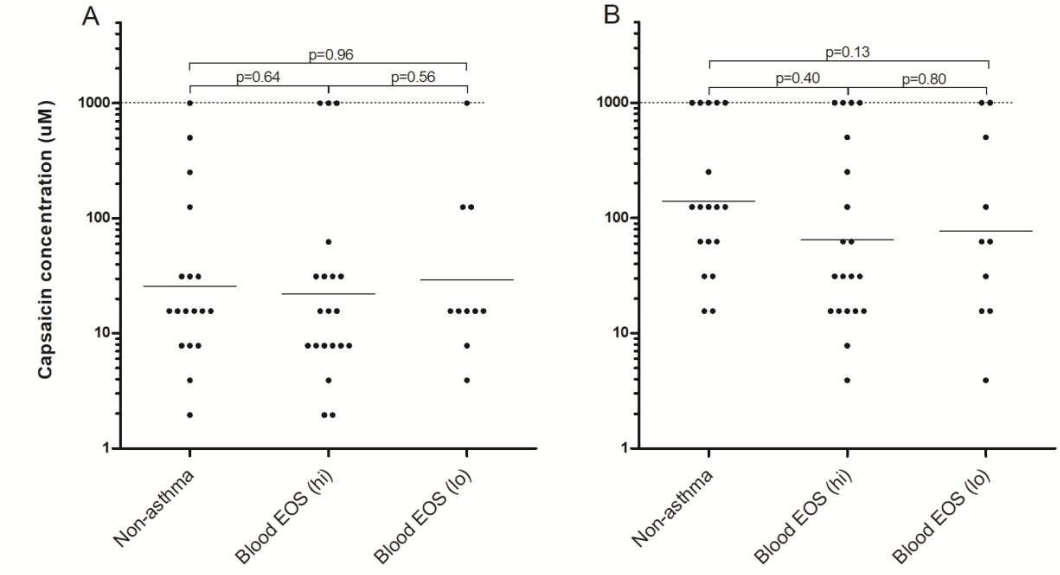
After conducting sensitivity analyses examining the association with atopy (Supplementary Fig 1) and blood eosinophils (Supplementary Fig 2), further sensitivity analyses were conducted examining capsaicin response in only participants with FEV_1% predicted <95% or excluding participants with high FeNO in NEA. Similar results were found between NEA and non-asthma (Supplementary Fig 3A and 3B). To exclude the possibility that NEA was in fact EA with ICS-suppressed eosinophilia, we conducted an analysis excluding all NEA who received ICS in the last 14 days (n=4). This did not have an appreciable effect on the main findings (although results were no longer statistically significant, Supplementary Fig 3C). Finally, as females have previously been shown to have enhanced capsaicin sensitivity, we also conducted a sensitivity analysis excluding males (n=20). This analysis showed significantly increased sensitivity in NEA (41.7 µM, 13.2-131.7) compared with EA (222.7µM, 81.3-610.5); a borderline statistically significant difference was also found comparing NEA with non-asthmatics (146.6µM, 57.3-375.2; Supplementary Fig 4A and B).

Supplementary Figure 1- *Capsaicin response and atopy*



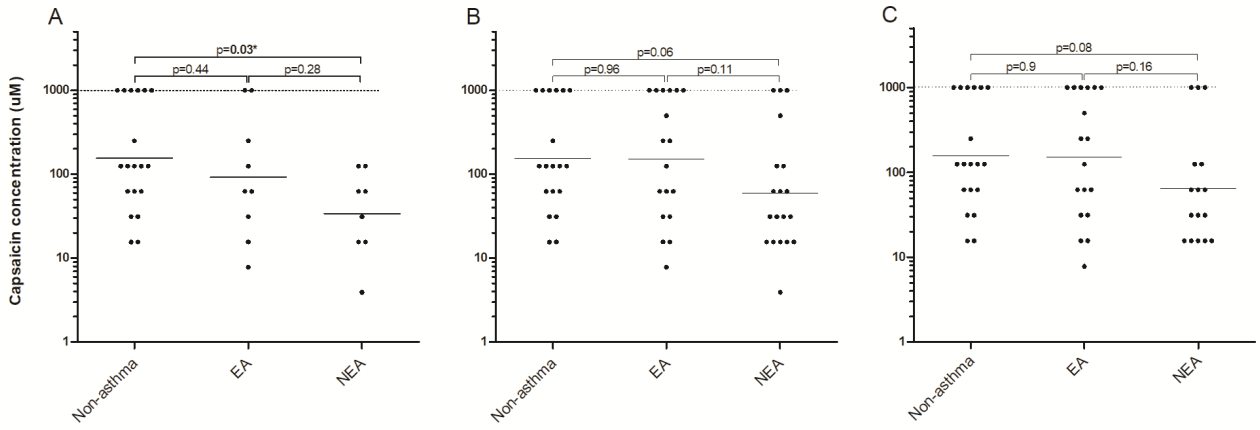
Concentrations (μM) of capsaicin eliciting (A) 2 coughs (C2) or (B) 5 coughs (C5) in non-asthmatics and asthmatics with and without atopy. Dashed lines at 1000 μM represent values assigned to those participants who did not achieve C2 or C5 during testing. Solid line represents geometric mean. Mann-Whitney test was used.

Supplementary Figure 2- *Capsaicin response and blood eosinophils*



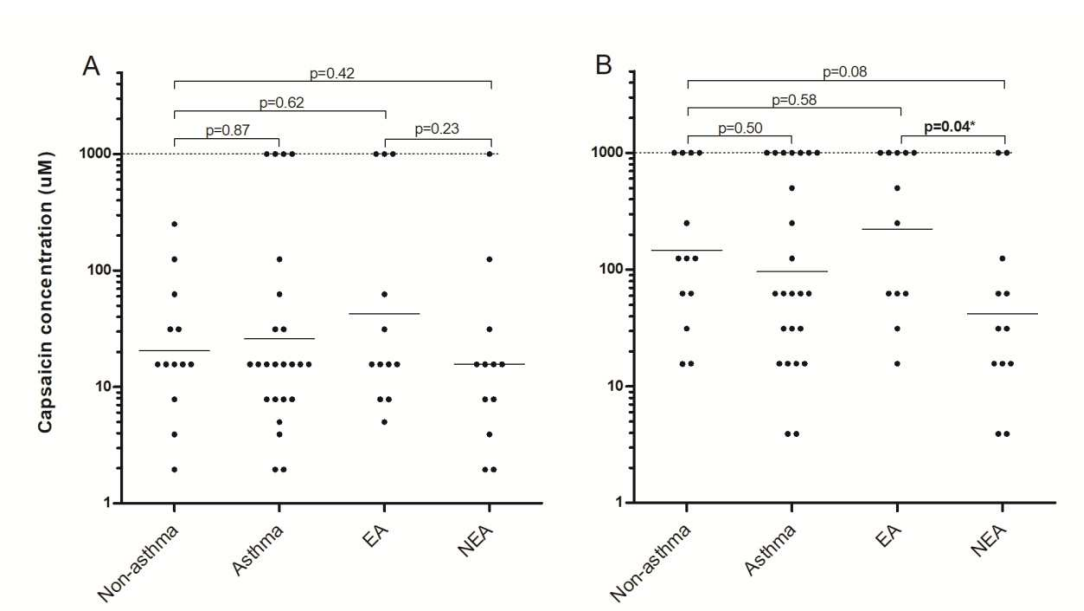
Concentrations (μM) of capsaicin eliciting (A) 2 coughs (C2) or (B) 5 coughs (C5) in participants with and without asthma, and asthmatics identified as blood EOS-high and blood EOS-low. Dashed lines at 1000 μM represent values assigned to those participants who did not achieve C2 or C5 during testing. Solid line represents geometric mean. Mann-Whitney test was used.

Supplementary Figure 3- *Capsaicin response and clinical characteristics*



Concentrations (μM) of capsaicin eliciting 5 coughs (C5) in participants with airflow limitation (FEV_1% predicted <95%) (A), excluding participants with high FeNO (based on the 90th percentile of FeNO levels in non-asthmatics) of in NEA (B) and in NEA participants who did not use ICS in the last 14 days (C). Dashed lines at 1000 μM represent values assigned to those participants who did not achieve C2 or C5 during testing. Solid line represents geometric mean. Mann-Whitney test was used. * p<0.05

Supplementary Figure 4- *Capsaicin response in females*



Concentrations (μM) of capsaicin eliciting (A) 2 coughs (C2) or (B) 5 coughs (C5) in female participants with and without asthma, and asthma stratified into eosinophilic asthma (EA) and non-eosinophilic asthma (NEA). Dashed lines at 1000 μM represent values assigned to those participants who did not achieve C2 or C5 during testing. Solid line represents geometric mean. Mann-Whitney test was used. * p<0.05