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**Title:** A double blind randomised placebo controlled trial of the PPAR-gamma agonist pioglitazone in mild asthma

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**Body:** Introduction Activation of peroxisome proliferator-activated receptor gamma (PPAR- $\gamma$ ) modulates inflammatory gene transcription, and may be a novel therapeutic target for asthma (Nie et al. J Biol Chem 2005; 280(4):2550-61). To determine whether activating PPAR- $\gamma$  results in measurable clinical effects in asthma, we performed a single centre randomised, parallel group, double blind, placebo controlled trial using the PPAR- $\gamma$  agonist, pioglitazone (PIO). Methods 68 non-smokers with asthma (taking as-required short-acting bronchodilators & 0-800mcg beclometasone) were randomised to PIO (n=34) or placebo (n=34). The primary outcome was the adjusted mean FEV<sub>1</sub> at 12 weeks. Secondary outcomes were adjusted mean morning and evening peak expiratory flow (PEF), asthma control & quality of life questionnaires, exhaled nitric oxide, bronchial hyper-responsiveness, induced sputum cell counts & adverse events (AE) at 12 weeks. Outcomes were adjusted for baseline value and other covariates and compared with ANCOVA. The full analysis (FA) included 55 completed cases & the per-protocol analysis (PPA) 52. Results There was no significant difference in the adjusted mean FEV<sub>1</sub> (-0.014 L, 95 % CI -0.15 to 0.12, p=0.84) or any of the secondary outcomes at 12 weeks in the FA. The PPA replicated the FA, except for a significantly lowered adjusted evening PEF in the PIO group at 12 weeks (-21.33 L/min 95% CI -39.15 to -3.51 p=0.02). There were more reported AEs (40% vs. 32%) & a lower adjusted haemoglobin in the PIO group at 12 weeks (-0.53 g/dL 95% CI -0.96, -0.11, p=0.015). Conclusion PPAR- $\gamma$  agonists are not promising treatments for mild asthma.