Abstract T5 Figure 1 Box and whisker plots showing (a) Aerosol number emission rates (aerosol number concentration normalised for ventilation) (b) Aerosol mass emission rates (aerosol mass normalised for ventilation) across the same series of activities, for all 25 participants

high intensity exercise ($0.42\mu\text{g}/\text{m}^3$, $p=0.083$). Rest and exercise demonstrated similar aerosol size distributions, however speaking emitted an additional, larger mode at $2\text{--}3\mu\text{m}$. Mean minute ventilation was 11L/min, 15L/min, 63L/min and 114L/min at rest, speaking, vigorous exercise and high intensity exercise, respectively. Median mass emission rate (aerosol mass concentration normalised for ventilation) produced by speaking, $0.092\text{ng}/\text{s}^{-1}$, was not different to vigorous exercise, $0.207\text{ng}/\text{s}^{-1}$, ($p=0.726$) but was lower than high intensity exercise $0.682\text{ng}/\text{s}^{-1}$, $p<0.001$).

Interpretation The size distribution of airborne particles emitted during exercise, match that of breathing at rest, with increased minute ventilation a primary driver of the increased aerosol mass emissions that occur during exertion. Aerosol mass emission rates during vigorous exercise are not different to speaking at a conversational, to loud conversational volume. These findings enhance our understanding of particle release during the fundamental physiological process of exercise, enabling appropriate mitigations for airborne pathogens, including SARS-CoV-2.

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T6 THERAPEUTICALLY TARGETING PTBP1/PKM2-DRIVEN GLYCOLYSIS IN ENDOTHELIAL CELLS: A NOVEL APPROACH TO TREAT PULMONARY ARTERIAL HYPERTENSION

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Background Pulmonary Arterial Hypertension (PAH) is an often-fatal disease, characterised by the development of apoptosis-resistant, hyperproliferative, and hyper-glycolytic endothelial cells (ECs). Loss-of-function *BMPR2* mutations and metabolic dysfunction are pivotal to PAH EC dysfunction. Enhanced expression of glycolysis enzyme pyruvate kinase M2 isoform (PKM2) and upstream splicing factor poly-pyrimidine

tract binding protein (PTBP1) have been observed regardless of genetic background,¹ suggesting that targeting the PTBP1/PKM2 axis could be a potent therapeutic strategy in PAH. Apigenin has been recognised for its low toxicity and ability to suppress PTBP1 and PKM2-driven Warburg glycolysis and tumorigenesis.² This work investigates apigenin's effects on the PKM2/PTBP1 axis in ECs; whether treatment could correct hallmark characteristics of PAH EC dysfunction; and the influence of *BMPR2* mutations.

Methods Here, we examined the proteomic, metabolic and functional profiles of blood outgrowth endothelial cells (BOECs) obtained from healthy control volunteers and PAH patients with *BMPR2* mutations, following apigenin treatment or *PTBP1/PKM2* knockdown. We hypothesised that, apigenin treatment would reduce glycolysis by inhibiting PTBP1 driven splicing of *PKM* into *PKM2*, and PKM2-dependent expression of glycolytic pathway components, such as lactate-dehydrogenase A (LDHA) and lactate production.

Results In control and *BMPR2* mutant BOECs, apigenin inhibited expression of PTBP1 and tetrameric PKM2. In control and *BMPR2* mutant BOECs, apigenin also suppressed LDHA protein expression and lactate production. Apigenin inhibited cell cycle progression and caspase 3/7 activity in control and *BMPR2* mutant BOECs, suggesting treatment may reduce EC susceptibility to proliferation and apoptosis, hallmarks of PAH ECs.

Conclusions Apigenin treatment may suppress EC glycolysis, possibly through suppression of PKM2-driven glycolytic gene expression and tetrameric activity. This encouraging data suggests apigenin may correct endothelial cell dysfunction observed in PAH, including susceptibility to apoptosis and proliferation.

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The clinical management of acute asthma

S1 OBESE, NON-EOSINOPHILIC ASTHMA: FREQUENT EXACERBATORS IN A REAL-WORLD SETTING

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Introduction In the UK, asthma deaths are at their highest level this century (1). Increased recognition of at-risk patients is needed. This study phenotyped frequent asthma exacerbators, and used machine learning to predict frequent exacerbators. We hypothesised that frequent exacerbators would have more severe peripheral eosinophilia than infrequent exacerbators.

Methods Patients admitted to Watford General Hospital with an asthma exacerbation between 1st March 2018 – 1st March 2020 were included. Patient data was retrospectively collected from

hospital and primary care records. Patients were organised into two groups: “Infrequent Exacerbator” (1 admission in the previous 12 months) and “Frequent Exacerbator” (≥ 2 admissions in the previous 12 months). Good adherence to inhaled corticosteroids (ICS) was defined as medication possession ratio (MPR) ≥ 0.8 ; poor adherence was defined as MPR ≤ 0.5 . Machine learning models were used to predict frequent exacerbators.

Results 200 patients admitted for asthma exacerbations were randomly selected (73% female; mean age 47.8 ± 19.3 years; table 1). Peripheral eosinophilia was uncommon in either group (19% vs 21%). More frequent exacerbators were being treated with high-dose ICS (46.5% vs 23.2%; $P < 0.001$), and frequent exacerbators used more SABA inhalers (10.9 vs 7.40; $P = 0.01$) in the year preceding the current admission. Good adherence to ICS was similarly low between both groups (40.0% vs 48.3%). BMI was raised in both groups (34.2 vs 30.9). Logistic regression classifier was the most accurate machine learning model for predicting frequent exacerbators (AUC = 0.80).

Abstract S1 Table 1 Characteristics of patients admitted for asthma exacerbations

	Infrequent Exacerbators	Frequent Exacerbators	P Value
n	100	100	
Age, years	46.5 $\pm$ 20.9	49.0 $\pm$ 17.5	0.25
Female (%)	69.0	77.0	0.20
Ethnicity (%)			
	Caucasian 82.0	Caucasian 83.0	0.85
	Asian 15.0	Asian 13.0	0.68
	Afro-Caribbean 1.0	Afro-Caribbean 1.0	1.00
Exacerbations managed in primary care in the last 12 months	0.79 $\pm$ 1.15	1.92 $\pm$ 1.83	<0.001***
FEV1/FVC (%)	71.0 $\pm$ 13.4	70.9 $\pm$ 16.8	0.96
Obstructive lung function (%)	34.5	39.1	0.60
FeNO, ppb	42.3 $\pm$ 57.1	24.8 $\pm$ 13.6	0.97
High FeNO (%)	27.3	12.5	0.44
Blood eosinophils, $\times 10^9/L$	0.27 $\pm$ 0.39	0.32 $\pm$ 0.41	0.45
Eosinophilia (%)	19.0	21.0	0.72
Blood neutrophils, $\times 10^9/L$	7.91 $\pm$ 3.87	7.70 $\pm$ 3.11	0.87
Neutrophilia (%)	45.0	49.0	0.57
Total IgE, kU/L	470.3 $\pm$ 870.3	378.9 $\pm$ 755.1	0.18
High IgE (%)	68.2	52.9	0.11
Patients with CT scan changes (%)	78.0	90.2	0.09
ICS-LABA (%)	60.6	88.9	<0.001***
High-dose ICS (%)	23.2	46.5	<0.001***
Long-term OCS (%)	3.03	10.1	0.04*
OCS courses in past year	0.99 $\pm$ 1.21	2.06 $\pm$ 2.34	0.005**
SABA dispensed in past year	7.40 $\pm$ 7.89	10.94 $\pm$ 9.39	0.01*
SABA overuse (%)	64.8	78.6	0.58
ICS MPR	0.72 $\pm$ 0.44	0.72 $\pm$ 0.40	0.66
Good ICS adherence (%)	48.3	40.0	0.35
Poor ICS adherence (%)	36.7	30.8	0.49
Past Medical History			
	COPD (%)	3.03	0.46
	GORD (%)	46.5	0.02*
	Depression (%)	32.3	0.68
Ex or current smoker (%)	64.5	69.9	0.51
BMI	30.9 $\pm$ 6.06	34.2 $\pm$ 9.48	0.14
Obese (%)	63.4	63.6	0.98
Follow-up within 4 weeks (%)	54.0	67.0	0.06

Data presented as mean $\pm$ standard deviation, unless stated differently.

FEV1/FVC: ratio of Forced Expiratory Volume in 1 second to the Forced Vital Capacity. FeNO: fractional exhaled nitric oxide. ICS: inhaled corticosteroid. LABA: long-acting β_2 -agonist. OCS: oral corticosteroid. SABA: short-acting β_2 -agonist. MPR: medication possession ratio. COPD: chronic obstructive pulmonary disease. GORD: gastro-oesophageal reflux disease.

High FeNO defined as FeNO > 40 . Eosinophilia defined as blood eosinophils $\geq 0.5 \times 10^9/L$. Neutrophilia defined as blood neutrophils $\geq 7.2 \times 10^9/L$. High IgE defined as serum IgE ≥ 81 kU/L. Good ICS adherence defined as ICS MPR ≥ 0.8 . Poor ICS adherence defined as ICS MPR ≤ 0.5 . SABA overuse defined as ≥ 3 SABA inhalers per year.