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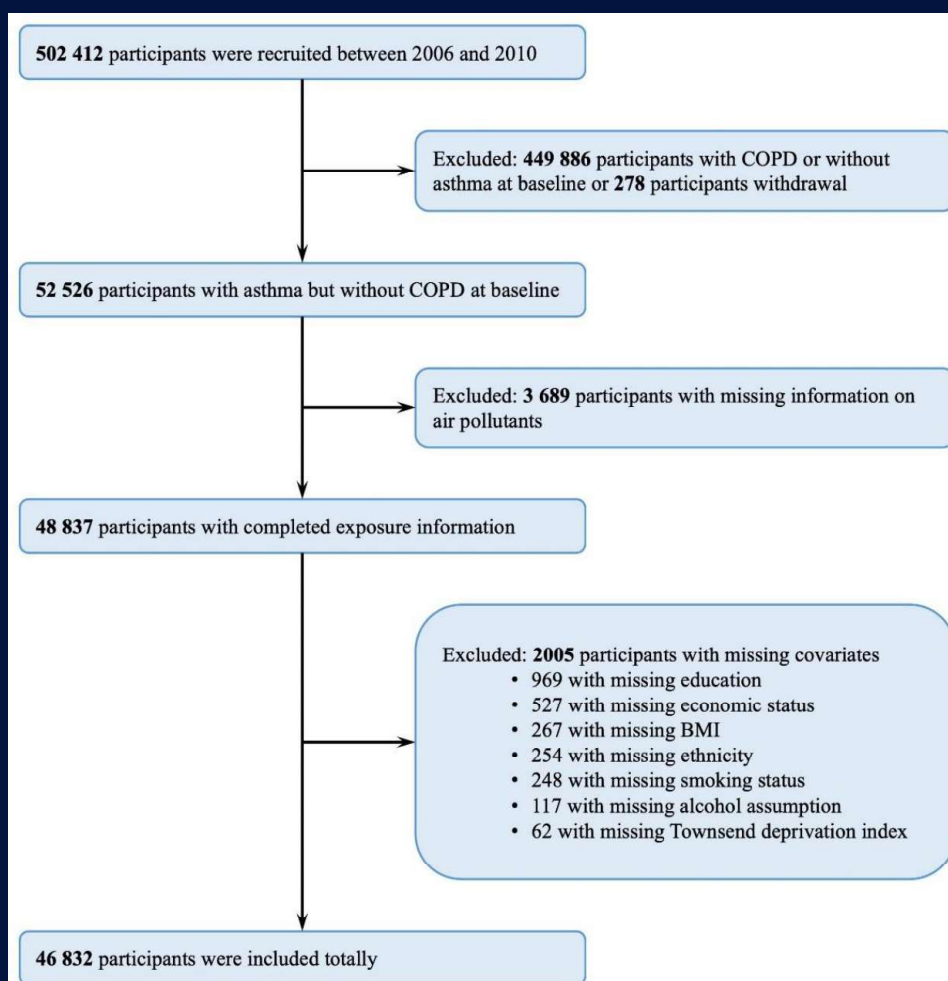


Figure 1 Flow chart of the participants included in the study. BMI, body mass index; COPD, chronic obstructive pulmonary disease.

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Editorial

Esta edição oferece uma visão clara e integrada da doença respiratória como um contínuo ao longo da vida, profundamente moldado por exposições ambientais e decisões clínicas ainda marcadas por alguma incerteza.

Dois editoriais destacam-se pelo seu impacto conceptual. A asma ocupacional mantém-se uma carga relevante e frequentemente subdiagnosticada, representando uma proporção significativa da asma de início no adulto e reforçando a necessidade de integrar sistematicamente a história ocupacional na prática clínica. Em paralelo, emerge com força o conceito de risco intergeracional: a exposição passiva ao fumo dos progenitores antes da puberdade, associa-se a trajetórias de função pulmonar comprometidas na descendência, com implicações até à meia-idade. A saúde respiratória começa, assim, a programar-se e condicionar-se ainda antes do nascimento.

No plano terapêutico, a revisão sobre β 2-agonistas intravenosos na asma aguda pediátrica sugere benefícios clínicos modestos, com redução da gravidade, menor tempo de internamento e menor necessidade de oxigénio. A mensagem é inequívoca: potencial utilidade, mas necessidade de prudência na utilização, devendo aguardar-se por mais evidência.

Outros trabalhos reforçam a importância da identificação precoce de trajetórias de risco e da utilização de ferramentas mais sensíveis e dinâmicas, como a oscilometria, bem como o papel de intervenções comunitárias e fatores ambientais na evolução da doença respiratória.

No seu conjunto, esta edição consolida uma mudança de paradigma: a doença respiratória não começa quando surgem os sintomas; começa muito antes, atravessa gerações e só pode ser verdadeiramente modificada se pensarmos cedo, agirmos cedo e tratarmos melhor.

Estamos na primavera. Intensificam-se os desafios clínicos na patologia alérgica. É o momento de antecipar: otimizar terapêutica de controlo, rever técnica inalatória, melhorar adesão e reduzir exposições, desde os pólenes ao ambiente doméstico. A identificação precoce de doentes em risco, em todos os grupos etário, é determinante para modificar trajetórias de doença. Na patologia respiratória e/ou alérgica, quem antecipa controla. E é essa antecipação que verdadeiramente muda o curso da doença. Boas leituras.

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Asma ocupacional: ainda uma carga subestimada

Filippo Liviero

A asma relacionada com o trabalho continua a ser uma das dimensões mais complexas e subvalorizadas da doença respiratória de início na idade adulta. Estima-se que represente 25% dos casos de início na idade adulta¹ e engloba um conjunto heterogêneo de fenótipos, incluindo asma ocupacional imunológica, asma induzida por irritantes e asma exacerbada pelo trabalho, cada um com mecanismos fisiopatológicos distintos e desafios diagnósticos próprios². Esta diversidade complica não só o diagnóstico e o tratamento, mas também os esforços de vigilância e as estratégias de prevenção em diferentes profissões e contextos. No entanto, os sistemas de vigilância permanecem fragmentados e muitos casos não são reconhecidos na prática clínica, especialmente em contextos não especializados³.

Apesar da crescente consciencialização sobre as exposições ocupacionais como contribuintes para a inflamação das vias aéreas e a sensibilização, continua a faltar evidência longitudinal definitiva que ligue as condições laborais à incidência de asma. Neste contexto, o estudo de Alif e colaboradores⁴, publicado nesta edição do Thorax, representa um avanço significativo. Utilizando dados do *European Community Respiratory Health Survey* (ECRHS), os autores fornecem evidência longitudinal de 20 anos sobre o risco ocupacional persistente de asma na Europa.

Iniciado no início da década de 1990, o ECRHS ajudou a definir o papel das exposições ambientais e ocupacionais na asma do adulto. O ECRHS I incluiu mais de 15 000 adultos em 12 países, avaliando a asma através de questionários e teste de provocação com metacolina. Identificou riscos aumentados em profissões como agricultura, pintura e limpeza, com 5–10% dos casos atribuíveis a exposições ocupacionais⁵. O ECRHS II acompanhou participantes sem sintomas, confirmando papéis significativos para agentes de alto e baixo peso molecular, biocidas e produtos de limpeza, com riscos atribuíveis até 25%⁶. Estes estudos estabeleceram a base para o ECRHS III, um dos mais longos estudos do género.

Este estudo distingue-se pelo rigor metodológico, duração sem precedentes e avaliação longitudinal da exposição. Os autores analisaram dados de 5591 adultos em 13 países, recrutados inicialmente entre 1991–1993 e acompanhados em duas va-

gas subsequentes. Participantes com asma pré-existente foram excluídos para isolar casos incidentes. As exposições ocupacionais foram avaliadas com a versão atualizada da *Occupational Asthma-specific Job Exposure Matrix*, uma ferramenta validada que melhora a especificidade entre profissões⁷. Histórias profissionais completas foram reconstruídas através de calendários de emprego, permitindo uma avaliação cumulativa da exposição ao longo de 20 anos — uma vantagem importante face a estudos transversais anteriores.

A regressão de Poisson com equações de estimação generalizadas foi utilizada para estimar taxas de incidência, considerando medidas repetidas e agrupamento. O ajustamento para fatores de confusão — idade, sexo, tabagismo, estatuto socioeconómico, variação de peso e atopia — reforça a robustez dos resultados. Análises de sensibilidade comparando participantes incluídos e excluídos mostraram estimativas estáveis e sem diferenças relevantes de incidência, apoiando a generalização dos resultados.

Os resultados apoiam fortemente o papel das exposições ocupacionais no desenvolvimento de asma. A incidência global na coorte foi de 15 por 1000 pessoa-anos, superior à de estudos anteriores, que reportaram valores entre 1,4 e 5 por 1000 pessoa-anos^{8–10}. Contudo, os autores adotam uma definição mais ampla de asma, baseada em sintomas e uso de medicação, sem dados funcionais como hiper-responsividade brônquica inespecífica, indisponíveis no seguimento final. Isto, juntamente com diferenças de desenho, população e duração entre estudos, pode explicar a variabilidade observada. Ainda assim, embora alguma variabilidade ou erro de classificação não possa ser excluído, a incidência observada parece superior à de décadas anteriores. Este padrão, também observado noutras coortes, pode indicar uma tendência real de aumento da incidência de asma, merecendo investigação epidemiológica mais aprofundada.

A fração atribuível populacional estimada de 18% para asma relacionada com o trabalho, derivada de análises padronizadas ao nível da coorte, acrescenta peso quantitativo ao argumento de que as exposições ocupacionais continuam a representar uma carga substancial de asma incidente no adulto. Muitos dos agentes implicados continuam presentes em ambientes laborais modernos, sublinhando a urgência de estratégias preventivas atualizadas.

Sensibilizantes de alto peso molecular, irritantes e biocidas estiveram significativamente associados a maior incidência de asma, com rate ratios (RR) de 1,27, 1,21 e 1,28, respetivamente. Associações signifi-

cativas também surgiram para agentes de baixo peso molecular (RR 1,26), ácaros (RR 1,38) e químicos reativos (RR 1,24). Entre substâncias específicas, destacaram-se poeiras de madeira (RR 1,59), produtos de limpeza interiores (RR 1,30) e lixívia (RR 1,40). Estes achados são amplamente consistentes com estudos anteriores³, mas o presente trabalho estende este conhecimento ao demonstrar estas associações num desenho prospetivo, com dados harmonizados e temporalmente detalhados ao longo de duas décadas.

Alguns agentes foram associados à asma apenas em níveis baixos de exposição, desafiando o padrão esperado de relação dose-resposta, especialmente para químicos de baixo peso molecular e alguns agentes biológicos. Em contraste, surgiram gradientes claros para sensibilizantes de alto peso molecular e irritantes. Estas discrepâncias podem refletir erro de classificação da exposição, *healthy worker effect* ou fatores de confusão não medidos, e destacam a necessidade de investigação adicional sobre efeitos limiar e suscetibilidade individual.

Do ponto de vista clínico, os resultados reforçam a necessidade de maior atenção às exposições ocupacionais em doentes com asma de início recente. Apesar da exclusão de participantes com asma conhecida no início, a confirmação diagnóstica foi limitada, particularmente pela ausência de dados de hiper-responsividade brônquica. A distinção entre asma ocupacional imunológica, asma induzida por irritantes e asma exacerbada pelo trabalho permanece complexa. Na ausência de ferramentas diagnósticas de referência, como testes específicos de provocação brônquica, estas classificações devem ser interpretadas com cautela¹¹. Além disso, o estudo destaca a importância de integrar a história ocupacional como componente rotineiro do diagnóstico de asma, especialmente em adultos com sintomas de início tardio ou refratários ao tratamento. Uma abordagem sistemática à identificação de desencadeadores ocupacionais pode alterar significativamente a gestão da doença e melhorar os resultados¹².

Do ponto de vista de saúde pública, as implicações são profundas. Os quadros regulamentares podem necessitar de revisão ou reforço para abordar não só os astmagens tradicionais, como isocianatos e farinhas, mas também agentes cuja relevância emergiu mais recentemente, incluindo produtos de limpeza e exposições microbianas³. Os produtos de limpeza, há muito reconhecidos como desencadeadores de asma por mecanismos irritativos e de sensibilização, continuam amplamente utilizados em ambientes laborais¹³. Notavelmente, alguns casos ocorrem na ausência de hiper-responsividade brônquica, levantando preocupações sobre fenótipos negligenciados e incerteza diagnóstica em populações expostas. A identificação de ácaros de armazenamento e ácaros de plantas como fatores de risco, mesmo em níveis baixos de exposição, sugere ainda que o ris-

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co ocupacional é mais disseminado do que geralmente reconhecido.

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Exposição passiva ao fumo como fator de risco intergeracional para a saúde pulmonar

Giovanni Viegi,¹ Stefania La Grutta²

A OMS, na recente Segunda Conferência Global sobre Poluição do Ar e Saúde, reforçou a necessidade de acelerar a ação para garantir ar limpo¹. A evidência dos efeitos adversos da poluição atmosférica na saúde é esmagadora, incluindo doenças respiratórias em crianças e adultos². A poluição do ar interior inclui o fumo passivo, também conhecido como fumo ambiental do tabaco, que tem impactos silenciosos na saúde de crianças e adolescentes³. Cerca de 31% dos europeus estão expostos ao fumo passivo em casa, enquanto quase um quarto (24%) da população da União Europeia com 15 ou mais anos é fumadora⁴.

Nesta edição da revista, Liu e colaboradores⁵ descrevem como a exposição passiva ao fumo paterno antes da puberdade está associada a trajetórias de função pulmonar prejudicadas, desde a infância até à meia-idade, na descendência. Esta equipa multinacional analisou cerca de 900 pares pai-descendente do *Tasmanian Longitudinal Health Study* (TAHS). Esta é uma das forças do artigo: mesmo na era dos grandes volumes de dados provenientes de estatísticas de saúde de rotina, os estudos epidemiológicos analíticos continuam a ter um papel fundamental.

Os descendentes realizaram espirometrias em seis momentos, entre os 7 e os 53 anos. As trajetórias de função pulmonar (volume expiratório forçado no primeiro segundo (FEV₁), capacidade vital forçada (FVC) e FEV₁/FVC) foram derivadas através de modelos de trajetórias baseados em grupos. Os pais relataram a sua própria exposição passiva ao fumo antes dos 15 anos. Entre os descendentes, 56,5% tiveram exposição passiva ao fumo na infância, 49% tinham historial de tabagismo ativo na meia-idade e 5,1% desenvolveram doença pulmonar obstrutiva crónica (DPOC) definida por espirometria na meia-idade. Embora o conceito de “trajetória da função pulmonar” seja relativamente recente (uma pesquisa no MEDLINE identifica 60 artigos desde 2014), transmite mensagens fortes e úteis para a saúde pública, pois baseia-se em estudos longitudinais — a única ferramenta capaz de descrever a história natural das doenças ao longo da vida.

A relativa escassez de publicações deve-se ao número reduzido de estudos longitudinais comparado com os transversais, aliado à novidade dos métodos estatísticos

sofisticados necessários para derivar estas trajetórias⁶. Mesmo o conceito de “estudo multigeracional em pneumologia” é recente, com apenas 14 artigos identificados no MEDLINE desde 2014. De facto, poucos estudos epidemiológicos conseguem recolher informação sobre avós, pais e irmãos⁷.

Assim, o contributo de Liu *et al*⁵ é oportuno. Os autores descobriram que a exposição passiva ao fumo paterno antes da puberdade estava associada, na descendência, a um aumento de 56% no risco de apresentar uma trajetória de “FEV₁ abaixo da média” e a um aumento de 130% no risco de apresentar uma trajetória de “FEV₁/FVC baixo precoce com declínio rápido”. Estes achados são de enorme importância para a pneumologia e para a saúde pública. De facto, se um indivíduo não atinge a sua função pulmonar máxima na idade adulta jovem, ou apresenta um declínio acelerado nos índices espirométricos, é provável que desenvolva obstrução crónica ao fluxo aéreo na meia-idade^{8,9} — uma condição com elevada morbilidade e mortalidade a nível mundial, cuja prevalência deverá aumentar entre 2025 e 2050¹⁰. Como força adicional, este artigo complementa um estudo anterior do TAHS¹¹, que mostrou que a exposição ao fumo paterno antes da puberdade aumentava o risco de asma na descendência.

Além disso, quando os autores analisaram separadamente as crianças expostas ao fumo passivo de pais fumadores ativos, encontraram uma interação quase significativa entre as duas exposições passivas (do pai e da criança). Por outro lado, tentaram estimar, através de análise de mediação, o contributo de outros fatores de risco, mas verificaram que as associações observadas eram apenas parcialmente mediadas pelo tabagismo e doenças respiratórias em pais e descendentes (cada um contribuindo com <15%), não comprometendo a generalização dos resultados principais.

Liu *et al*⁵ expõem corretamente algumas limitações do estudo. Existe uma possível inconsistência entre as medições da função pulmonar, dado que a espirometria pós-broncodilatador (BD) só foi realizada no último inquérito, enquanto as anteriores utilizaram apenas valores pré-BD. Isto sugere a utilidade de investigar trajetórias pós-BD em estudos epidemiológicos que disponham desses dados. Importa notar que qualquer viés seria conservador, uma vez que os valores pós-BD são superiores aos pré-BD. Contudo, a necessidade de usar um agente terapêutico em estudos populacionais é discutível, tendo em conta a falta generalizada de consciência da doença na população, que na vida real raramente procura cuidados médicos numa fase precoce¹².

Além disso, pais com historial de asma ou pieira podem ter um recordatório diferente da sua exposição passiva ao fumo antes da puberdade, podendo sobrestimar o impacto dessa exposição na função pulmonar da descendência. No entanto, estas limitações são mitigadas pelos resultados das análises de sensibilidade, que não mostraram diferenças entre descendentes não asmáticos e a amostra geral.

Por fim, entre os pais expostos ao fumo passivo antes da puberdade, a maioria teve exposição contínua desde o nascimento até aos 15 anos, impossibilitando isolar os efeitos de janelas específicas de exposição. Isto pode ser relevante para a investigação mecanística, mas é menos importante do ponto de vista da saúde pública.

Assim, esta descoberta inovadora — de que a exposição passiva ao fumo paterno antes da puberdade está associada a trajetórias de função pulmonar prejudicadas na descendência — tem implicações para a investigação. Devem os médicos perguntar apenas se o pai foi exposto ao fumo passivo na infância, ou também alertar que as consequências para a descendência serão muito piores se esta também for exposta? Os médicos devem ainda usar o novo conhecimento derivado de estudos como o de Liu *et al*⁵ para desempenhar um papel de advocacia, alinhado com o tema do Dia Mundial Sem Tabaco 2025 da OMS: “Desmascarar o apelo: Expor as táticas da indústria do tabaco e da nicotina”¹³.

Em conclusão, o artigo de Liu *et al*⁵ reforça o apelo à ação da OMS¹ e a mensagem de Boers e colaboradores¹⁰: para mitigar o substancial impacto económico e sanitário futuro da DPOC, é essencial focar na prevenção, reduzindo fatores de risco como o tabagismo e a poluição do ar.

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Utilização de agonista beta-2 de ação curta por via intravenosa, em complemento ao tratamento de primeira linha padrão, versus placebo em crianças e adolescentes com agudização aguda grave de asma: uma revisão sistemática e meta-análise

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RESUMO

Importância O papel do agonista beta-2 de ação curta (SABA) por via intravenosa na asma aguda na infância permanece pouco claro.

Objetivos Avaliar a segurança e a eficácia do SABA intravenoso versus placebo na asma aguda.

Seleção e extração de dados Foram pesquisadas as bases de dados MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Web of Science e CINAHL até maio de 2024. Apenas ensaios clínicos randomizados (RCTs) foram incluídos, seguindo as diretrizes internacionais para revisões sistemáticas. Os desfechos avaliados foram morbidade, escalada de cuidados, duração da hospitalização, eventos adversos, mortalidade e alterações na função pulmonar.

Resultados Foram incluídos quatro RCTs (total de participantes = 183). O grupo que recebeu SABA intravenoso apresentou melhores pontuações de gravidade da asma (risco relativo (RR)=0,38; IC 95% 0,19 a 0,78; p=0,009), necessidade semelhante de ventilação mecânica (RR=0,13; IC 95% 0,01 a 2,42; p=0,17), escalada semelhante de tratamento intravenoso (RR=1,51; IC 95% 0,60 a 3,82; p=0,38), menor duração da hospitalização (horas) (diferença média (DM)=−18,68; IC 95% −36,76 a −0,61) e menor duração de suplementação de oxigênio (dias) (DM=−1,73; IC 95% −3,01 a −0,45; p=0,008). Os eventos adversos incluíram taquicardia, hipotensão e hipocaliemia. Um estudo relatou um caso isolado de arritmia e um aumento não significativo de troponina I no grupo SABA intravenoso.

Conclusão Esta revisão encontrou evidência de baixa a moderada certeza de que o SABA intravenoso pode melhorar a gravidade da asma aguda, com eventos adversos pouco frequentes. Contudo, esta evidência é limitada devido ao reduzido número de estudos incluídos.

Número de registo PROSPERO:

INTRODUCTION

This is one of a series of systematic reviews commissioned by the WHO to inform consolidated recommendations for managing common childhood illnesses. The recommendations will update the existing guidance in the pocketbook of hospital care for children¹ and integrated management of childhood illness charts.²

Asthma is a common chronic disease, with approximately 262 million people affected in 2019,³ and is a common cause of morbidity and mortality in children.^{3,4} Initial management of asthma exacerbations includes assessment of severity, supportive treatment including oxygen as needed, administration of short-acting beta-2 agonist (SABA), consideration of ipratropium bromide and systemic steroids.⁵ Additional medications

Key messages

What is known about this topic

- Additional medications are added to this first-line treatment in the management of more severe asthma exacerbations with varying levels of supportive evidence.
- Intravenous SABA are increasingly used as a second-line treatment option for acute severe asthma exacerbations.

What this study adds

- This review found that hospital stays were shorter for those who received intravenous short-acting beta-2 agonist (SABA), weaning from supplemental oxygen was faster and symptoms improved quicker.
- The evidence is limited due to limited number of studies included

How this study might affect research practice or policy

- Further research is needed to evaluate the efficacy of the addition of intravenous SABA to the initial management of patients with severe asthma exacerbation recommended, particularly addressing the safety of the treatment, including serious adverse events such as arrhythmias and increased troponin I levels.

are added to this initial treatment of more severe asthma exacerbations with varying levels of supportive evidence.⁵ Intravenous bronchodilators, for example, aminophylline, salbutamol, terbutaline, epinephrine or ketamine, are currently recommended with varying evidence of effectiveness.^{6,7} Intravenous SABA, namely terbutaline and salbutamol, are increasingly used as a second-line treatment option.^{8,9} Travers et al reported that intravenous SABA showed earlier reductions in the need for recurrent SABA, but there were no reductions in the length of intensive care unit (ICU) admission or hospitalisation.¹⁰ However, a retrospective chart review of 120 children found an association between early initiation of intravenous terbutaline and reduced respiratory failure, ICU admission and mechanical ventilation.¹¹ The latest systematic review assessing intravenous SABA was conducted over 10 years ago, and an evidence update was needed.¹⁰

The objective of this systematic review was to assess the safety and efficacy of intravenous SABA, in addition to standard first-line treatment with inhaled/nebulised SABA and systemic steroids, compared with inhaled/nebulised SABA and systemic steroids and placebo in children and adolescents aged 18 years and under with an acute severe asthma exacerbation.

MATERIALS AND METHODS

This study followed the international recommendations for conducting systematic reviews and meta-analyses¹² and was registered with the International Prospective Register of Systematic Reviews, with the registration number CRD42023405119.

Study selection and search strategy

The following databases were searched from inception to April 2023 and updated on 20 May 2024: MEDLINE, Embase, Cumulative Index to Nursing and Allied Health, Web of Science and the Cochrane Central Register of Controlled Trials. Reference lists were inspected from retrieved articles to identify any additional citations the electronic searches may have missed. Furthermore, unpublished ongoing clinical trials were searched on the following websites: www.clinicaltrials.gov and www.controlledtrials.com. We used the standard recommended guidelines for our search strategy. Search terms included (attack or exacerbation or acute severe asthma or episode) AND (SABA, or salbutamol or albuterol or terbutaline). See online supplemental appendix 1 for the full search strategy.

Eligibility criteria and outcomes

We included only randomised controlled trials (RCTs) that assessed the safety and efficacy of intravenous SABA in addition to standard first-line treatment (inhaled/nebulised SABA and systemic steroids) compared with standard first-line treatment and placebo in children and adolescents aged 18 years and under with an acute severe asthma exacerbation. Outcomes measures were:

Primary outcome

Morbidity (symptoms, hospitalisation rate, school absence in days).

Secondary outcomes

- ▶ Escalation of care (ventilation/paediatric intensive care unit (PICU) admission rate).
 - ▶ Length of hospital stay in hours.
 - ▶ Adverse events.
 - ▶ Mortality due to exacerbation.
 - ▶ Lung function (change in forced expiratory volume (FEV₁ in litre or per cent of predicted)) and peak expiratory flow (PEF in L/min).
- No language restriction was applied, and we undertook English translation of relevant studies when needed.

Data collection and analysis

Selection of studies

Two authors (RS, SA, AZZ, AT) reviewed relevant manuscripts in pairs. They independently assessed the eligibility of all identified trials. Discussions and consultations with a third author (ISA and CP) resolved disagreements among authors.

Data extraction and management

The full texts of the included studies were reviewed for inclusion. Two authors (NA, AH) independently extracted data that included the following: risk of bias assessment, demographic information, methodology, intervention details and reported outcomes. They compared the extracted data, and any differences were resolved by consensus and discussion with a third author (ISA) when needed. The extracted data was analysed using the Cochrane Collaboration's Review Manager.¹³

Assessment of risk of bias in included studies

Two review authors (KM, AH) used the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions to assess the risk of bias.¹⁴ They independently evaluated the risk of bias for each study, and any disagreement was resolved through

mutual discussion or involving a third author (ISA, CP) when needed. The risk of bias was assessed according to the following domains:

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.

Each risk of bias was rated as either low, high or unclear.

Data management

The mean difference (MD) was calculated for continuous data when appropriate. We planned to report the risk ratio (RR) for dichotomous data. We highlighted all missing data within the results section. An intention-to-treat basis of analysis was used. The review highlighted and discussed any dropout of included children in the primary studies. We planned to contact authors of published primary studies for further clarification and to provide additional information when needed. The I² statistic was used to measure heterogeneity among the included trials.¹⁴ We considered an I² value of:

- ▶ 0–40% might not be as important.
- ▶ 30–60% represent moderate heterogeneity.
- ▶ 50–90% represent substantial heterogeneity.
- ▶ 75–100% represent considerable heterogeneity.

We planned to explore heterogeneity using sensitivity analyses when appropriate. We planned to investigate potential publication bias using funnel plots for each outcome if there were 10 or more studies.¹⁵

Data synthesis

Studies were pooled for meta-analysis when sufficiently similar data was available. The statistical package Review Manager V.5.4 provided by the Cochrane Collaboration was used for data analysis.¹³ All measures were reported with 95% CIs. A random-effects model was used for data synthesis. The narrative description was used to present trial outcomes' data when data cannot be combined or significant heterogeneity exists.

Sensitivity analysis

Sensitivity analysis was planned to explore the potential impact of missing data and methodological heterogeneity on the overall results.¹⁶ To assess the effect of these, the studies at high risk of bias would be omitted from the meta-analysis, and both random and fixed-effect models of data synthesis would be used.

Summary of findings

The principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system were used to assess the certainty of the body of evidence associated with the following outcomes: morbidity, escalation of care, length of hospital stay, adverse events, mortality and change in FEV₁ and PEF when data was available.¹⁷ We downgraded the quality level of evidence based on the following factors:

1. Methodological quality and risk of bias.
2. The directness of the evidence.
3. The heterogeneity of the data.
4. The precision of effect estimates.
5. The risk of publication bias.

RESULTS

Study selection

After titles and abstracts screening and duplicates were removed, 502 citations were excluded from an initial 612 identified citations. Full-text versions of 27 citations that met the inclusion criteria were accessed. A total of 23 citations were excluded after full-text assessment for the following reasons: 9 citations assessed different research questions and/or outcomes, 7 were non-RCTs, 4 were duplicates and 3 were study protocols. Four RCTs were included in this review, totalling 183 participants with acute severe asthma

Table 1 Characteristics of included studies

Study, country and participants	Intervention	Comparison	Outcomes	Assessment of asthma severity as defined by primary studies and other comments
Browne <i>et al</i> ¹⁸ Australia (High income economy country) ²⁴ Included 29 children aged 1–12 years with acute severe asthma admitted to the paediatric emergency department (ED).	Intravenous salbutamol (15 µg/kg as a single bolus over 10 min).	Placebo— intravenous saline bolus Syringes were prepared and contained either intravenous saline bolus or intravenous salbutamol bolus (15 µg/mL), instructions were to administer 1 mL/kg.	The primary outcomes were recovery time (patients no longer requiring inhaled salbutamol) and persistent moderate-to-severe asthma 2 hours after randomisation. Patients' discharge readiness from ED was defined as when participants were started on hourly inhaled salbutamol therapy; however, data was presented in means and ORs, which could not be included in the data synthesis for this outcome.	The severity of asthma was assessed on a standard clinical assessment scale—National Australian Asthma Campaign guidelines. ²⁵ Patients who had all four features of respiratory distress (wheeze, sternal retraction, accessory muscle use or dyspnoea) or had any of the absolute criteria (cyanosis, pulsus paradoxus, altered consciousness or a silent chest on auscultation) were classified as acute severe asthma and were considered for study inclusion. All children received initial nebulised salbutamol therapy in ED, and if they remained in severe asthma, then received nebulised salbutamol continuously at 30 min, 1 hour, 2 hours, 3 hours and 4 hours, according to need, and intravenous hydrocortisone 5 mg/kg was then given as a bolus over 3 min.
Santana <i>et al</i> ²¹ Brazil (Upper middle-income economy country) ²⁴ Included 50 patients aged 2–13 years old who required hospital admission—who did not respond to the outpatient treatment (three SABA nebulisations that were administered in an hour).	Intravenous salbutamol: 1 µg/kg/min, for 20 min; total dose of 20 µg/kg Or Intravenous magnesium sulfate: 2.5 mg/kg/min, diluted in saline solution for 20 min; total dose of 50 mg/kg, up to a maximum of 2 g. Three arms trial	Intravenous saline solution (placebo), in the drip for 20 min.	Change in blood pressure, respiratory rate, oxygen saturation, the amount of nebulisation with B ₂ -adrenargic drug, number of nebulisations performed per day of hospitalisation, PICU admission, admission to paediatric observation room, changes in serum magnesium, potassium and calcium levels. Authors did not report the criteria for hospital discharge.	The criteria used for the diagnosis of severe asthma were: 1. Wheezing, intercostal, subcostal, sternal retractions. 2. The use of accessory muscles, associated with absolute signs of respiratory insufficiency with hypoxaemia that included cyanosis, altered consciousness and/or silent chest on auscultation. Other treatments used included intravenous hydration, oxygen, nebulised fenoterol or salbutamol (0.15 mg/kg/dose at every 30 min) and intravenous hydrocortisone (5 mg/kg/dose). (Manuscript in Portuguese, English translation was done)
Browne <i>et al</i> ¹⁹ Australia (High income economy country) ²⁴ Included 55 children aged 1–14 years with acute severe asthma who were admitted to paediatric emergency department (ED).	Intravenous salbutamol (15 µg/kg as a single bolus over 10 min), and inhaled placebo (saline) Or Intravenous salbutamol bolus (15 µg/kg as a single bolus over 10 min) plus ipratropium bromide (250 µg every 20 min). Three arms trial	Inhaled ipratropium bromide (250 µg every 20 min), and intravenous saline placebo bolus. Syringes were prepared and contained either intravenous saline bolus or intravenous salbutamol bolus (15 µg/mL), instructions were to administer 1 mL/kg.	The primary outcomes: 1. Recovery time. 2. Discharge time of each group. Other outcomes were: ► Clinical signs of moderate to severe asthma at 2 hours. ► Salbutamol or ipratropium related side effects. ► Means of the quantitative variables (respiratory rate, pulse rate, plasma potassium and plasma glucose) Participants included in the study were discharged from hospital when salbutamol treatment could be spaced to every 3 hours.	The severity of asthma was assessed on a standard clinical assessment scale—National Australian Asthma Campaign guidelines. ²⁵ Patients who had all four features of respiratory distress (wheeze, sternal retraction, accessory muscle use and/or dyspnoea) or had any of the absolute criteria (cyanosis, pulsus paradoxus, altered consciousness or a silent chest on auscultation) were classified as acute severe asthma and were considered for study inclusion. All children who received initial nebulised salbutamol therapy in ED and remained in severe asthma were started on nebulised salbutamol every 20 mins, and intravenous methylprednisolone 1 mg/kg was administered over 3 min.
Bogie <i>et al</i> ²⁰ Italy (High income country) ²⁴ Included 49 children between 2 and 17 years of age who failed acute asthma management and needed intensive care unit admission (PICU).	Intravenous terbutaline. The study drug (whether terbutaline or placebo) was administered as a loading dose of 10 mg/kg per minute given over 10–20 min, followed by a continuous infusion of 1 mg/kg per min. After randomisation, the pharmacy sent two separate syringes to the ED both labelled terbutaline or placebo study 1 mg/mL, with one also labelled loading dose and the other labelled continuous infusion.	Intravenous normal saline as a placebo.	Outcome measures included: 1. Clinical asthma severity score. 2. Duration (hours) on continuous nebulised albuterol. 3. Duration of stay in the paediatric intensive care unit. Authors used the duration of PICU length of stay as a measure of hospital stay. Study protocol stated the addition of intravenous aminophylline to the treatment regimen for any patient who is worsening during intravenous medications from both groups.	Participants were determined to have moderate-to-severe asthma exacerbation when they failed to improve after at least three consecutive nebulised albuterol/ipratropium bromide of 5 mg and 500 mg, respectively, were placed on continuous high-dose nebulised albuterol and needed intravenous B ₂ -agonist. Also, methylprednisolone was provided at a dose of 2 mg/kg loading dose followed by 1 mg/kg every 6 hours. All patients received a normal saline bolus of 20 mL/kg followed by maintenance intravenous fluids. A modified clinical asthma severity score (CASS) was used to determine the level of asthma severity. ²⁶ Three participants from the study were randomised and not included in the final analysis, reasons reported within the manuscript

PICU, paediatric intensive care unit; SABA, short-acting beta 2-agonist.

episodes (table 1). A flow detailing the study's selection process is shown in figure 1.

Effect of interventions

Primary outcomes

Asthma severity scores

Primary studies used asthma severity scores to report morbidity and the severity of symptoms. Table 1 shares the assessment of

asthma severity criteria by primary studies. Brown *et al*¹⁸ used the standard clinical assessment scale to assess asthma severity. Two hours after the interventions, fewer participants in the intravenous SABA group had moderate-to-severe asthma (moderate certainty evidence) (RR=0.38, 95% CI, 0.19 to 0.78, p=0.009, n=29) (online supplemental figure 2).

Moreover, the study done by Bogie *et al*²⁰ used the modified clinical asthma severity score (CASS) to assess asthma severity. They

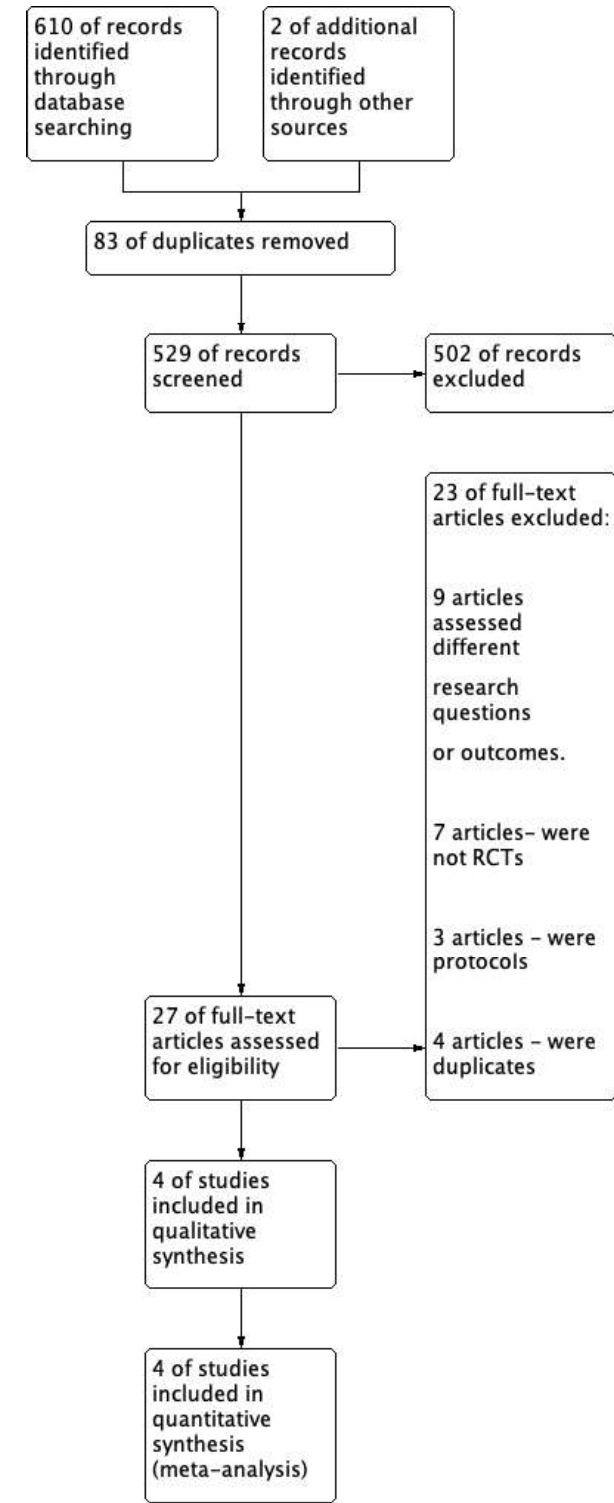


Figure 1 Study flow diagram. RCTs, randomised controlled trials.

reported that after 24 hours, participants on intravenous terbutaline had a non-significant improvement in CASS score (95% CI, 0.20 to 3.50, $p=0.073$).

Secondary outcomes

The need for mechanical ventilation

One study²¹ assessed the need for mechanical ventilation that was not different among the groups (low certainty evidence) (RR=0.13, 95% CI 0.01 to 2.42, $p=0.17$, $n=46$) (online supplemental figure 3).

Escalation of care

In the study by Bogie et al, intravenous aminophylline was used as an escalation of treatment for participants with worsening asthma.²⁰ No significant difference was found among the studied



Figure 2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

groups (moderate certainty evidence) (RR=1.51, 95% CI 0.60 to 3.82, $p=0.38$, $n=46$) (online supplemental figure 4).

Length of hospital stay

All studies reported this outcome. Three studies were included in the meta-analysis.¹⁹⁻²¹ The final study presented the data in means and ORs. Therefore, it was not included in the meta-analysis.¹⁸ One of the three arms of the study done by Browne et al¹⁹ was not included in the meta-analysis and analysed separately, as the intravenous SABA group did not receive ipratropium bromide, which

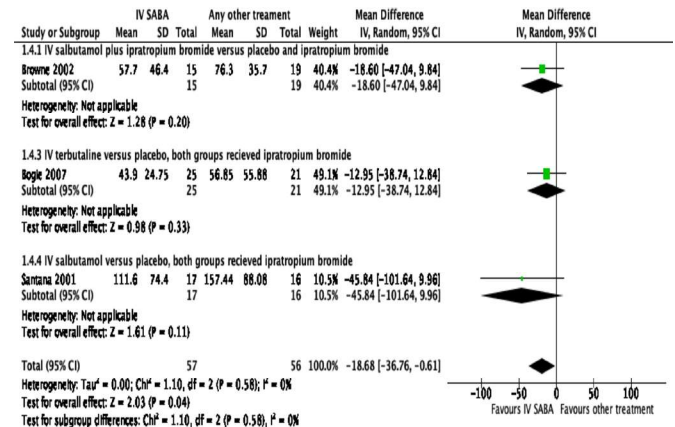


Figure 3 Forest plot of comparison: intravenous SABA for acute severe asthma, outcome: length of hospital stay. SABA, short-acting beta-2 agonist.

Table 2 Summary of findings

Intravenous short-acting-beta2-agonist (SABA) for acute asthma compared with placebo or any other treatment for children 18 years and younger with acute asthma						
Patient or population: children 18 years and younger with acute asthma Setting: studies conducted in high or upper middle income economy countries Intervention: intravenous short-acting-beta2-agonist (SABA) for acute asthma Comparison: any other treatment						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or any other treatment	Risk with intravenous short-acting-beta2-agonist (SABA) for acute asthma				
Asthma severity assessment	933 per 1000	355 per 1000 (177 to 728)	RR 0.38 (0.19 to 0.78)	29 (1 RCT)	⊕⊕⊕○ Moderate†	
The need for mechanical ventilation	188 per 1000	24 per 1000 (2 to 454)	RR 0.13 (0.01 to 2.42)	33 (1 RCT)	⊕⊕○○ Low†‡	
The need for extra intravenous medications	238 per 1000	360 per 1000 (143 to 910)	RR 1.51 (0.60 to 3.82)	46 (1 RCT)	⊕⊕⊕○ Moderate†	
Length of hospital stay		MD 23.44 lower (36.09 lower to 10.8 lower)	–	153 (3 RCTs)	⊕⊕⊕○ Moderate‡	
GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. *The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). †Low sample size of the single included study. ‡There is an unclear risk of bias for both randomisation and allocation concealment in one of the included studies. GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; RCT, randomised controlled trial; RR, risk ratio.						

was deemed a different treatment option compared with other included studies, as all the other studies used ipratropium bromide on both arms as a standard treatment. Overall, there was a significant difference among the groups in the duration of hospital stay in hours, with an average of 18 hours shorter duration of stay for participants who received intravenous SABA, moderate certainty evidence (MD=−18.68, 95% CI −36.76 to −0.61, I² 0%, n=113) figure 3. A separate analysis of the subgroup who received intravenous SABA with no ipratropium bromide showed significantly less duration of hospitalisation in hours among the intravenous SABA group (MD =−28.00, 95% CI −45.70 to −10.30, p=0.002).¹⁹

Browne et al¹⁸ showed that participants who received intravenous SABA were discharged from the ED 9.7 hours earlier than those who received placebo. This difference between the groups was significant (p<0.05).

Adverse events

One study reported no significant differences between the two groups' plasma glucose rise and plasma potassium reduction.¹⁸ Another study reported a statistically but not clinically significant increase in plasma glucose and reduced plasma potassium.¹⁹ Another study reported a higher proportion of tremors in the intravenous SABA group (p<0.02).¹⁸ Santana et al reported tachycardia in 29.4% of participants who used intravenous SABA, compared with none from placebo.²¹ Bogie et al²⁰ reported that 24% of the intravenous terbutaline group had high troponin I values compared with none from the placebo group. One patient who received intravenous terbutaline was removed from the study after developing significant cardiac arrhythmias, and this patient had a normal troponin I value on exit from the study and recovered without complications.²⁰ Hypotension was documented in 42.9% and 32% in the placebo and terbutaline groups respectively.²⁰ Other studies reported no serious adverse events.^{18 19 21}

Oxygen supplementation requirements

Three studies reported this outcome.^{18 19 21} Browne et al¹⁸ reported that fewer participants in the intravenous SABA group were dependent on oxygen supplements at 2 hours postrandomisation. However, the result was insignificant (RR=0.27, 95% CI 0.07 to 1.05, p=0.06, n=29) (online supplemental figure 5).

In the study by Santana et al,²¹ the duration of oxygen supplementation in days was significantly less for the intravenous SABA

group (MD=−1.73, 95% CI −3.01 to −0.45, p=0.008, n=33) (online supplemental figure 6).

Browne et al¹⁹ reported that the need for supplemental oxygen therapy up to 12 hours postrandomisation was similar in all three subgroups (intravenous SABA, nebulised ipratropium or both). At 12 hours, weaning off supplemental oxygen therapy occurred in those children who received intravenous SABA with or without ipratropium bromide (RR=0.35, 95% CI 0.12 to 1.02, p=0.05, n=34) (RR=0.16, 95% CI 0.04 to 0.65, p=0.01, n=40), respectively (online supplemental figure 7).

Other outcomes

Primary studies reported no data for the following outcomes:

Hospitalisation rate, school absence, PICU admission rate, mortality due to exacerbation and change in FEV₁ and PEF.

Quality of evidence

The GRADE certainty of evidence for the outcomes: asthma severity assessment, the need for mechanical ventilation, the need for extra intravenous medication and the length of hospital stay was downgraded to low or moderate due to the risk of bias and the small sample size of the included studies. The methodological quality of the included studies was reported to be good. No heterogeneity was noted, with a low risk of publication bias as none of the studies was pharmaceutically funded. An extensive search for potential unpublished studies has been done, looking for possible non-reported studies (table 2).

DISCUSSION

This review included four RCTs with 183 participants. It showed that the intravenous SABA group had improved asthma severity scores, a shorter hospital stay and had less oxygen supplementation requirements. However, the need for mechanical ventilation and escalation of care was similar in the studied groups. More side effects were noted among intravenous SABA groups, with few reports of tachycardia, hypotension, hyperglycaemia, hypokalaemia, tremors and cardiac ischaemia.

Evidence from other studies has shown that children with acute severe asthma who were refractory to the initial standard therapy would require second-line bronchodilators and additional critical care support, and evidence supporting these interventions in children is sparse.⁶ Travers et al concluded that intravenous

SABA treatment led to earlier reductions in the need for recurrent inhaled/nebulised SABA but no reductions in the lengths of ICU admission or length of hospitalisation.¹⁰ The reported adverse effects of intravenous SABAs include tachycardia, hypotension, hypokalaemia and cardiac ischaemia.²² Several studies report arrhythmias and angina after salbutamol administration⁸ and transient increases in troponins with no clinically significant cardiac injury.²³

The potential for bias in this review is limited. A comprehensive literature search was performed, and two review authors independently assessed the studies for inclusion, extracted data and rated the quality of the included studies. We have identified all the relevant studies in our search up to May 2024. This result applied to the participants who presented with acute severe asthma and were treated with intravenous SABA in addition to the standard treatment. We performed a meta-analysis of the available data. We graded the certainty of evidence for each outcome with a 4-level rating scale using the GRADE classification.

Limitations

The limitation of this systematic review is the number of studies included (four RCTs), which have small-to-modest sample sizes.

CONCLUSIONS

This review found low-to-moderate certainty of evidence that intravenous SABA was associated with improved asthma severity scores, less hospital stay duration and less oxygen supplementation requirement. However, the need for mechanical ventilation and escalation of care was similar in the studied groups. Adverse events of intravenous SABA were low potassium, high glucose levels and hypotension. Moreover, arrhythmias and high troponin I were also reported with no clinical impact on participants on discharge. There was no evidence available to support other outcomes. High-quality RCTs are needed, as it was difficult to reach a firm conclusion about the efficacy and safety of intravenous SABA in addition to the initial treatment of acute severe asthma.

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Contributors CP developed the concept for this review. AH, KM, ISA, AA, AT, AZZ, NA, RS, SA, AKP, selected studies for inclusion and abstracted data. ISA wrote the first draft. ISA, AH, KM, CP did the data analysis, interpretation of data and critically revised the paper for important intellectual content. All authors approved the final version of this article. CP is the guarantor of this work.

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Utilização de sulfato de magnésio intravenoso em complemento ao tratamento padrão de primeira linha com agonista beta-2 de ação curta inalado/nebulizado e corticosteroides sistêmicos na abordagem das agudizações agudas de asma em crianças: uma revisão sistemática e meta-análises de ensaios clínicos randomizados

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RESUMO

Contexto O papel do sulfato de magnésio intravenoso na agudização asmática permanece pouco claro.

Objetivos Determinar a eficácia e a segurança do sulfato de magnésio intravenoso no tratamento de agudizações de asma em crianças.

Métodos Foram pesquisadas as bases de dados MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials e Web of Science até maio de 2024. Incluíram-se ensaios clínicos randomizados, seguindo as diretrizes internacionais para revisões sistemáticas. Os desfechos avaliados incluíram morbidade, escalada de cuidados, duração da hospitalização, função pulmonar, eventos adversos e mortalidade.

Resultados Foram incluídos nove estudos (total de participantes = 473). A taxa de hospitalização e a necessidade de ventilação não invasiva foram menores no grupo que recebeu sulfato de magnésio intravenoso (diferença média (DM)=0,70; IC 95% 0,54–0,90; I²=7%; n=115) e (risco relativo (RR)=0,17; IC 95% 0,15–0,54; p=0,003; n=143), respectivamente. As pontuações de gravidade da asma (DM=–0,18; IC 95% –1,35 a 0,98; I²=2%; n=115), a duração da hospitalização (DM=–78,86; IC 95% –200,37 a 42,66; I²=99%; n=284) e a necessidade de ventilação invasiva (RR=0,35; IC 95% 0,11–1,17; I²=0%; n=237) foram semelhantes entre grupos. Não houve diferença na taxa de admissão em Unidade de Cuidados Intensivos Pediátricos (p=0,43; n=61). O pico de fluxo expiratório melhorou no grupo do sulfato de magnésio intravenoso (p<0.001; n=20). Não foram reportados eventos adversos graves.

Conclusão Encontramos evidência de baixa certeza de que o sulfato de magnésio intravenoso reduz a taxa de hospitalização e a necessidade de ventilação não invasiva. As pontuações de gravidade da asma, a admissão em cuidados intensivos, a ventilação invasiva e a duração da hospitalização foram semelhantes entre grupos. Apesar da base de evidência ser limitada, o perfil de segurança favorável sugere que o sulfato de magnésio intravenoso pode ser considerado como opção terapêutica nas agudizações asmáticas.

Número de registo PROSPERO: CRD42023405261.

INTRODUCTION

This is one of a series of systematic reviews commissioned by the WHO to inform consolidated recommendations for managing common childhood illnesses. The recommendations will update the existing guidance in the Pocket Book of Hospi-

Key messages

What is known about this topic

► Simultaneous administration of intravenous magnesium sulfate and a beta 2-agonist might have an additive bronchodilator effect, with varying supportive evidence.

What this study adds

► Low-certainty evidence that hospitalisation and the need for non-invasive ventilation are less in children with acute asthma exacerbation who receive intravenous magnesium sulfate.

How this study might affect research practice or policy

► The favourable safety profile suggests that intravenous magnesium sulfate can be considered a second-line treatment for acute asthma exacerbation despite current low-level evidence of efficacy.

tal Care for Children and Integrated Management of Childhood Illness charts.^{1,2}

Asthma is one of the most common chronic diseases, with an estimated 262 million people affected in 2019.³ It is a common cause of morbidity in children and adolescents⁴; hence, the acute and long-term management of asthma was identified by WHO as a priority for evidence appraisal and guideline development.^{4,5}

The standard first-line treatment of acute asthma exacerbations includes systemic corticosteroids and inhaled beta 2-agonist medications.^{6,7} Additional medications are added to this first-line treatment in the management of more severe asthma exacerbations with varying levels of supportive evidence.⁸

One of the adjunct treatments for severe asthma exacerbation is intravenous magnesium sulfate, which has a bronchodilator effect.⁹ The mode of action of magnesium sulfate is thought to be related to direct smooth muscle relaxation; however, additional mechanisms may be linked to block-

ing calcium ion influx into smooth muscle cells, thus modulating mast cell histamine release, anti-inflammatory properties and cholinergic neural transmission.⁹ Furthermore, evidence suggests that the simultaneous administration of magnesium sulfate and a beta 2-agonist has an additive bronchodilator effect, perhaps owing to magnesium sulfate augmenting the beta-receptor agonist response.¹⁰ A previous systematic review concluded that intravenous magnesium sulfate significantly improved pulmonary functions with less hospitalisation and less escalation of treatment.¹¹

This review aimed to assess the safety and efficacy of intravenous magnesium sulfate in addition to the standard first-line treatment with inhaled/nebulised short-acting beta 2 agonist (SABA) and systemic steroids compared with the standard first-line treatment of acute asthma attacks in children and adolescents aged 18 years and under.

MATERIALS AND METHODS

This study followed the international recommendations for conducting systematic reviews and meta-analyses¹² and registered with the International Prospective Register of Systematic Reviews, with the registration number CRD42023405261.

Study selection and search strategy

The following databases were searched from inception to April 2023 and updated on 20 May 2024: MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials and Web of Science. We inspected reference lists from retrieved articles to identify any additional citations the electronic searches missed. We also searched unpublished ongoing clinical trials on the websites www.clinicaltrials.gov and www.controlled-trials.com.

Terms for population, interventions and outcomes were included in our search strategy. Search terms used are (acute or severe or asthma) AND (magnesium sulfate). See online supplemental appendix 1 for the complete search strategy.

Eligibility criteria and outcomes

We included randomised controlled trials (RCTs) that assessed the safety and efficacy of intravenous magnesium sulfate in addition to the standard first-line treatment (nebulised/inhaled SABA and systemic steroid) compared with standard first-line treatment in children and adolescents aged 18 years and under with acute asthma exacerbations.

Outcome measures

Primary outcome

- Morbidity (symptoms, hospitalisation rate and school absence in days).

Secondary outcomes

- Escalation of care (ventilation/Paediatric Intensive Care -PICU-admission).
- Length of hospital stay in hours.
- Adverse events.
- Mortality due to exacerbation.
- Lung functions (change in forced expiratory volume (FEV₁) in litres or per cent of predicted, and peak expiratory flow rate (PEFR) in L/min)

We applied no language restriction and planned to translate relevant studies into English if needed.

Assessment of risk of bias in included studies

Two review authors (KM and AH) used the criteria outlined in the Cochrane Handbook for Sysas either low, high or unclear.

Data collection and analysis

Selection of studies

Authors in pairs (SA, RS and AT, AZZ) assessed relevant manuscripts. They independently evaluated the eligibility of all identified trials. Any disagreement among authors was resolved by discussions and consultation with a third author (ISA, CP).

Data extraction and management

The full texts of included studies were reviewed for inclusion in this review. Two authors (NA, AAH) independently extracted data that included demographic information, methodology, intervention details and reported outcomes. They compared the extracted data, and any differences were resolved by consensus and discussion with a third author (AAH) if needed. We analysed the extracted data using the Cochrane Collaboration's Review Manager.¹³

Assessment of risk of bias in included studies

Two review authors (KM, AAH) used the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions to assess the risk of bias.¹⁴ They independently evaluated the risk of bias for each study, and any disagreement was resolved by a mutual discussion or involving a third author (ISA, CP). We assessed the risk of bias according to the following domains:

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.

Each risk of bias will be rated as either low, high or unclear.

Data management

The mean difference (MD) was calculated for continuous data when appropriate. For dichotomous data, we reported the risk ratio (RR). All missing data were highlighted within the results section. We used an intention-to-treat basis of analysis. The review highlighted and discussed any dropout of included children in the primary studies. We planned to contact authors of published primary studies for further clarification and to provide additional information when needed. The I² statistic was used¹⁵ to measure heterogeneity among the included trials. We considered an I² value of:

- 0–40% might not be as important.
- 30–60% represent moderate heterogeneity.
- 50–90% represent substantial heterogeneity.
- 75–100% represent considerable heterogeneity.

The heterogeneity was explored further using sensitivity analyses when appropriate. We planned to investigate potential publication bias using funnel plots for each outcome if there were 10 or more studies.¹⁶

Data synthesis

Studies were pooled for meta-analysis when sufficiently similar data was available. Narrative descriptions were used when data could not be combined, or significant heterogeneity was found. The statistical package Review Manager V.5.4, provided by the Cochrane Collaboration, was used for data synthesis and analysis.¹³ All measures were reported with 95% CIs. A random-effects model was used for data synthesis.

Subgroup analysis

If data were available, the following subgroups were planned to be assessed: severity of asthma using the British Thoracic Society 2019 criteria and timing of administration of intravenous magnesium sulfate.

Sensitivity analysis

We planned to perform a sensitivity analysis to explore the potential impact of missing data and any methodological heterogeneity. To assess this impact on the overall results, we omitted the studies at high risk of bias from the meta-analysis and used both random and fixed-effect models of data synthesis.

Summary of findings

The principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system¹⁷ were used to assess the quality of the body of evidence associated with the following outcomes: morbidity, escalation of care, length of hospital stay, adverse events and mortality. The quality level of a body of evidence was downgraded based on the following factors:

- Methodological quality.
- The directness of the evidence.
- The heterogeneity of the data.
- The precision of effect estimates.
- The risk of publication bias.

RESULTS

Study selection

We identified 842 citations. After duplicates were removed and titles and abstracts were evaluated, the full texts of 24 citations potentially meeting the inclusion criteria were assessed. 15 studies were excluded: 7 were non-RCTs, 3 assessed different interventions and 5 included only adult participants. We included nine RCTs involving 473 children. Figure 1 shows a flowchart detailing the study's selection process.

Study characteristics

We included only nine RCTs (n=473). The characteristics of the included studies are provided in online supplemental table 1. The definition of the severity of bronchial asthma was based on the primary studies included.

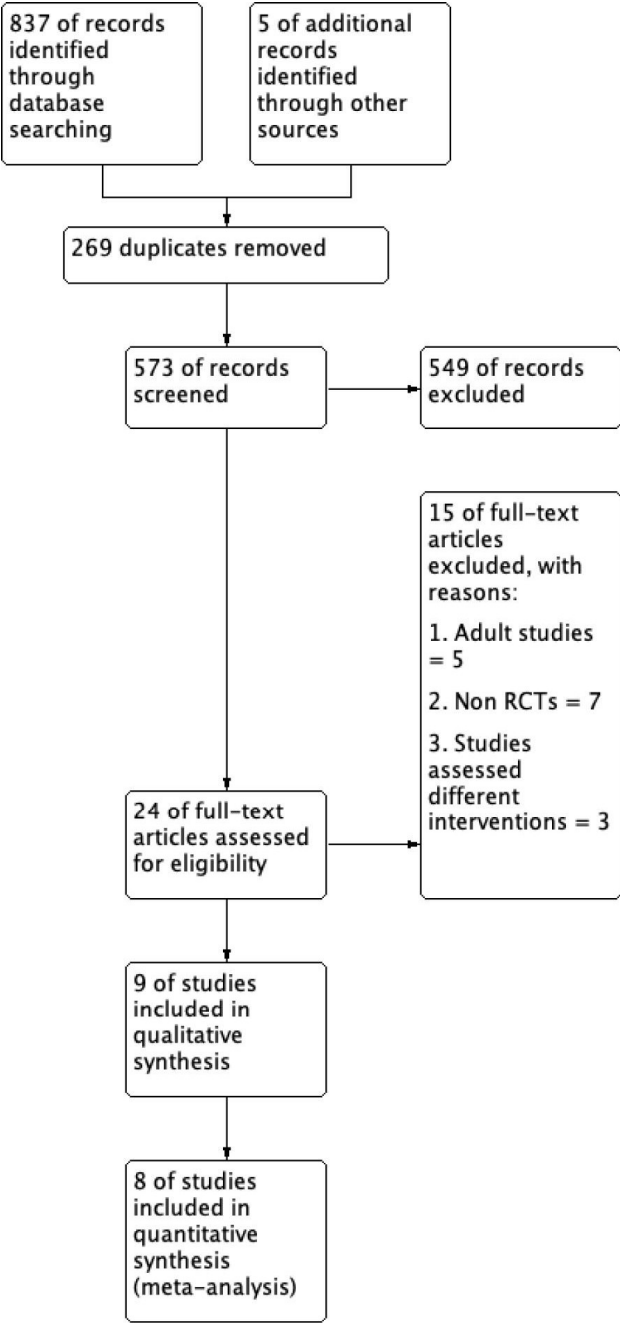


Figure 1 Study flow diagram. RCTs, randomised controlled trials.

Risk of bias

The risk of bias assessment in the nine trials is shown in figure 2, online supplemental figure 1. Four of the included studies were assessed as low risk of bias regarding randomisation,^{18–21} and five studies were classified as unclear risk as no information was provided by the authors.^{22–26} Four studies were assessed as low risk for allocation concealment,^{18 20 21 26} and the remaining studies were classified as unclear risk, with no information shared by the authors.^{19 22–25} Five studies were classified as a low risk of bias with regards to blinding of participants and personnel and outcome assessment,^{18–20 25 26} two unblinded studies were classified as high risk,^{21 24} and two studies had no information regarding blinding. Two studies were classified as unclear bias.^{22 23} All included studies were classified as low risk for incomplete outcome data, selective reporting and other biases.

Effect of the intervention

Primary outcomes

Change in asthma severity score

The primary studies used asthma severity scores to report morbidity symptoms. Two studies were included in this outcome.^{20 26} The asthma severity scores were assessed using Pulmonary Index (PI)²⁷ and the Respiratory Distress Assessment (RDA) scores (table 1, online supplemental material 1). The overall improvement of asthma scores showed no difference when intravenous magnesium

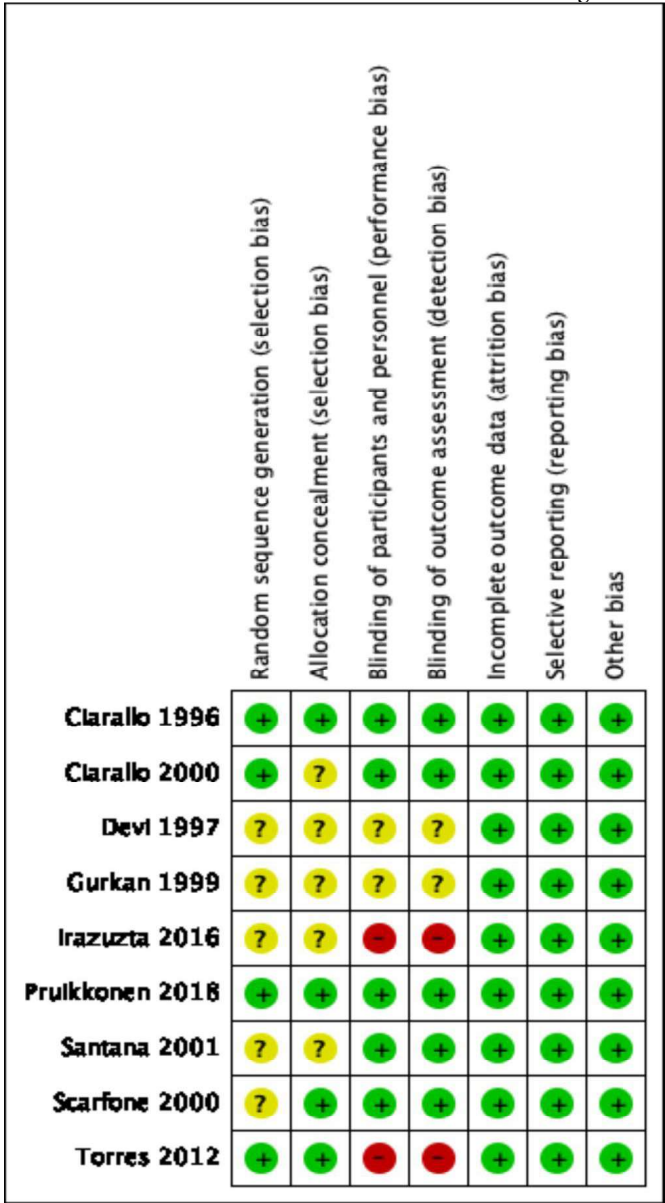


Figure 2 Risk of bias summary: review the authors' judgments regarding each risk of bias item for each included study.

Table 1 Summary of findings

Intravenous magnesium sulfate in addition to the standard first-line treatment compared with placebo or any other treatment for children 18 years and under with acute asthma

Patient or population: children 18 years and under with acute asthma
Setting: high and middle income-economy countries
Intervention: intravenous magnesium sulfate in addition to the standard first-line treatment
Comparison: placebo or any other treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or any other treatment	Risk with intravenous magnesium sulfate in addition to the standard first line treatment				
Change in asthma severity score		MD 0.18 lower (1.35 lower to 0.98 higher)	–	115 (2 RCTs)	⊕⊕○○ Low†‡	
Hospitalisation	767 per 1000	537 per 1000 (414 to 690)	RR 0.70 (0.54 to 0.90)	115 (3 RCTs)	⊕⊕○○ Low‡§	
The need for invasive ventilation	88 per 1000	31 per 1000 (10 to 104)	RR 0.35 (0.11 to 1.17)	237 (3 RCTs)	⊕○○○ Very low‡§¶	
Non-invasive ventilation	239 per 1000	41 per 1000 (12 to 129)	RR 0.17 (0.05 to 0.54)	143 (1 RCT)	⊕⊕○○ Low‡¶	
PICU admission rate	167 per 1000	97 per 1000 (25 to 370)	RR 0.58 (0.15 to 2.22)	61 (1 RCT)	⊕⊕⊕○ Moderate‡	
Length of hospital stay		MD 78.86 lower (200.37 lower to 42.66 higher)	–	284 (4 RCTs)	⊕○○○ Very low‡§¶	

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
All included studies were assessed as low risk of selective reporting. The individual studies reported all prespecified outcomes. A comprehensive search, including grey literature, was conducted, and none of the studies were commercially funded.
Paediatric Intensive Care Unit (PICU)
*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
†Different asthma severity scores measurement tools used.
‡Small sample size.
§Variability of the included studies' designs, including outcomes assessment measures.
¶Non-blinded studies included, and unclear risk of randomisation process and/or blinding on other studies.
GRADE, Grading of Recommendations Assessment, Development and Evaluation; MD, mean difference; PICU, Paediatric Intensive Care Unit; RCT, randomised controlled trial; RR, risk ratio.

sulfate was compared with other treatments (low certainty evidence) (MD=−0.18, 95% CI −1.35 to 0.98, I² 2%, n=115) (figure 3).

Hospitalisation rate

Three studies reported this outcome.^{18 19 26} The hospitalisation rate was significantly lower in children receiving intravenous magnesium sulfate (low certainty evidence) (RR=0.70, 95% CI 0.54 to 0.90, I² 7%, n=115) (online supplemental figure 2).

Secondary outcomes

The need for invasive and non-invasive ventilation

Three studies assessed this outcome.^{20 21 25} Three studies evaluated the need for invasive ventilation^{20 21 25} and reported no statistical difference between the two groups (very low certainty evidence) (RR=0.35, 95%

CI 0.11 to 1.17, I² 0%, n=237) (online supplemental figure 3). One study reported less need for non-invasive ventilation in the intravenous magnesium group²¹ (low certainty evidence) (RR=0.17, 95% CI 0.05 to 0.54 n=143) (online supplemental figure 3).

PICU admission rate

One study reported this outcome.²⁰ The PICU admission rate was not significantly different among both groups (moderate certainty evidence) (RR=0.58, 95% CI 0.15 to 2.22, p=0.43 n=61) (online supplemental figure 4).

Length of hospital stay in hours

Four studies were included.^{20–22 25} There was no difference regarding the length of hospital stay in hours (very low certainty evi-

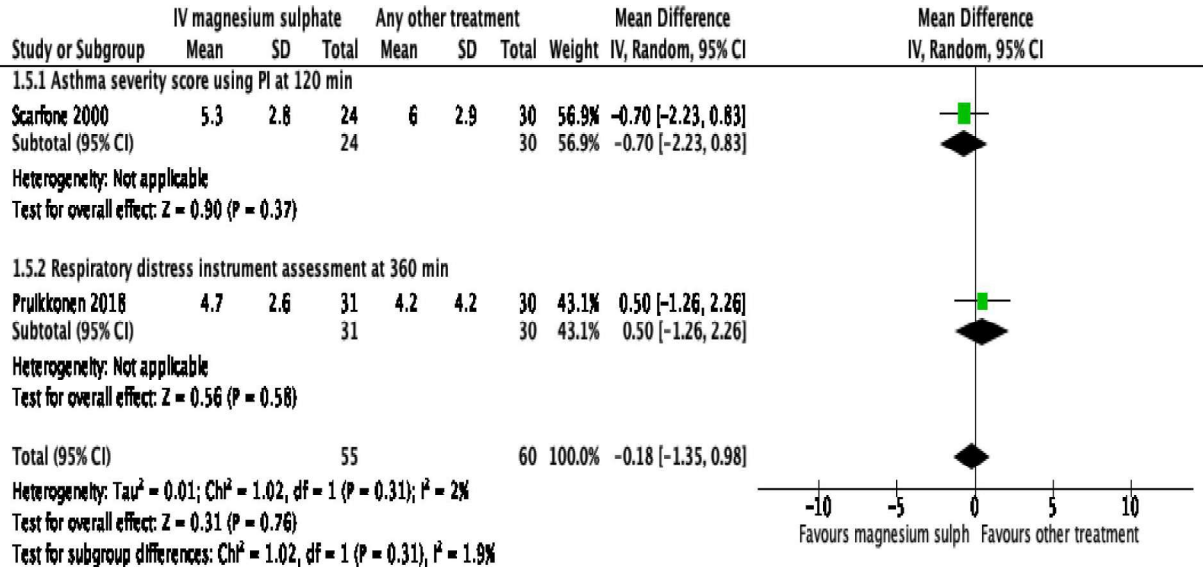


Figure 3 Forest plot of comparison: intravenous magnesium sulfate versus any other treatment, outcome: asthma severity scores.

dence) (MD=−78.86, 95% CI −200.37 to 42.66, I² 99%, n=284) (online supplemental figure 5). Reanalysing the data using the fixed effects model showed a significantly shorter duration of hospital stay among the intravenous magnesium group (MD=−14.03, 95% CI −18.01 to −10.4, I² 99%, n=284). Further sensitivity analysis was done by omitting the study done by Torres et al due to the high risk of blinding, which showed a shorter duration of hospital stay in the intravenous magnesium sulfate group with low heterogeneity (MD=−5.55, 95% CI −9.69 to −1.50, I² 0% n=141).

Improvement in the PEF

One study reported this outcome.²³ The intravenous magnesium sulfate group improved the PEF at 90 min from the baseline (MD=36.60, 95% CI 33.28 to 39.92, p<0.00001, n=20) (online supplemental figure 6).

Adverse events

One patient (3%) in the intravenous magnesium sulfate group had facial redness and redness around the site of the intravenous cannula during the first 15 min of the intravenous infusion.²⁰ One study¹⁸ reported minor side effects like epigastric warmth (12.5%), pain (16.6%) and tingling and numbness (12.5%) at the site of infusion in the intravenous magnesium group. The other studies did not report any other significant adverse events.^{18 19 21 23}

Other outcomes

The supplementary file shares the results of the following outcomes: the need for supplemental oxygen and the duration of the oxygen supplementation in hours including online supplemental figures 7 and 8.

The primary studies reported no data for the following outcomes: symptoms, school absence and mortality due to exacerbation. There was no data to assess the following subgroups: severity of asthma and timing of administration of intravenous magnesium sulfate.

We have included one study that assessed a high-dose infusion versus a bolus dose of intravenous magnesium sulfate. The result is shared in the online supplemental figures 9–11.

Quality of evidence

The GRADE certainty of evidence for the outcome: change in asthma severity scores, hospitalisation rate and non-invasive ventilation was graded as low certainty of evidence. The length of hospital stay and the need for invasive ventilation were downgraded to very low certainty of evidence. The PICU admission rate was graded as moderate certainty of evidence (table 1).

DISCUSSION

In this review, we assessed the safety and efficacy of intravenous magnesium sulfate as an adjunct to the first-line treatment of acute asthma exacerbation. Nine studies were included (n=473). Overall improvement in asthma severity scores, PICU admission rate and the length of hospital stay were similar among both groups. The hospitalisation rate and the need for non-invasive ventilation were less in children who received intravenous magnesium sulfate. The requirement for oxygen supplements was similar in both groups. A study reported that the intravenous magnesium sulfate group improved the PEF from the baseline at 90 min.²²

Overall, there is limited evidence that hospitalisation rate, respiratory support and lung functions were better in the intravenous magnesium sulfate group.

Griffiths and Kew's comparable results revealed a reduction in hospital length of stay in children who received intravenous magnesium sulfate, with an unclear effect on ED treatment time.²⁸ However, a meta-analysis by Cheuk et al showed that intravenous magnesium sulfate probably provides an additional benefit in moderate to severe acute asthma in preventing hospital admission and significantly improving short-term pulmonary function tests and clinical symptom scores.²⁹

One study reported that the hospitalisation rate, length of hospital stay and hospital costs were lower in the group receiving a high intravenous magnesium infusion dose.

A previous systematic review, including adults and children, concluded that intravenous magnesium sulfate might be safe and beneficial in patients with severe acute asthma.³⁰ A recent systematic review of the adult population revealed that intravenous magnesium sulfate benefits FEV₁/PEF and hospital admission rate in treating asthma exacerbations.³¹

To our knowledge, we identified all relevant studies in our search up to May 2024. This result applies to the participants who presented with acute asthma exacerbation and were treated with intravenous magnesium sulfate in addition to the standard treatment. When available, we performed meta-analyses of the data studied. We graded the certainty of evidence for each outcome using the GRADE classification, a four-level rating scale (ie, high, moderate, low and very low).

Limitations

The limitation of this review is due to the number of studies included and the low-to-moderate sample size of the studies.

CONCLUSION

This review showed low certainty of evidence that children who received intravenous magnesium sulfate had a lower hospital admission rate and less need for non-invasive ventilation. Moreover, there was limited evidence that PEF was better in the intravenous magnesium sulfate group. Other outcomes, including improvement in asthma severity scores, the need for invasive ventilation, length of hospital stay and PICU admission rate, were similar among both groups with very low-to-moderate certainty of evidence. No serious adverse events were reported.

Future RCTs are needed particularly to address the suggestion that higher doses of intravenous Mg may be more effective than lower doses.

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Contributors CP developed the concept for this review. ISA, KM, AAH, AT, AZZ, RM, RS, SA, AA and AKP selected studies for inclusion and abstracted data. AAH wrote the first draft. AAH, ISA, KM, CP did the data analysis and interpret the data and critically revised the paper for important intellectual content. All authors approved the final version of this article. CP is the guarantor of this work.

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Fatores de risco para ataques recorrentes de pieira em crianças em idade pré-escolar: um estudo de coorte populacional em Inglaterra

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RESUMO

Objetivo Determinar os fatores associados a ataques recorrentes de pieira aguda em crianças em idade pré-escolar.

Desenho do estudo Estudo de coorte retrospectivo.

Contexto Dados eletrônicos de saúde primária em Inglaterra, provenientes do Clinical Practice Research Datalink, ligados a dados hospitalares do Hospital Episode Statistics.

Participantes 42 820 crianças com 5 anos ou menos, com pelo menos um episódio de pieira aguda entre 1 de janeiro de 2013 e 31 de dezembro de 2014.

Exposições Variáveis demográficas e clínicas, incluindo idade, sexo, etnia, quintil de privação, comorbilidades clínicas, prescrições prévias de medicação para asma e ataques agudos anteriores, foram incluídas nas análises multivariáveis.

Medida principal de resultado Nova procura de cuidados de saúde por pieira/agudização de asma dentro de 12 meses.

Resultados Quase 40% (16 962/42 820) das crianças tiveram um novo ataque dentro de 12 meses. Os preditores mais fortes foram hospitalização no episódio índice (RR 1,42; IC 95% 1,39–1,45) e um ataque no ano anterior (RR 1,27; IC 95% 1,22–1,32). Também se associaram a maior risco de novos ataques: sexo masculino (RR 1,06; IC 95% 1,03–1,08), etnia sul-asiática (RR 1,08; IC 95% 1,04–1,12), atopia (RR 1,21; IC 95% 1,18–1,24), prematuridade (RR 1,09; IC 95% 1,04–1,14), aumento de prescrições de broncodilatadores de alívio (RR 1,04; IC 95% 1,03–1,04), número de ataques prévios (RR 1,03; IC 95% 1,02–1,04) e hospitalização prévia por pieira (RR 1,09; IC 95% 1,05–1,14). Idade mais avançada na apresentação (RR 0,92; IC 95% 0,91–0,93) e número de prescrições de corticosteroides inalados no ano anterior (RR 0,96; IC 95% 0,95–0,97) associaram-se a menor risco de novos ataques.

Conclusões Os nossos resultados podem ser utilizados para apoiar a previsão clínica do risco de novos episódios de pieira em crianças em idade pré-escolar.

BACKGROUND

Wheezing illnesses are common in preschool children, with up to half experiencing wheeze by age 6 years.^{1 2} Most episodes are mild and secondary to viral respiratory infections, but some children experience multiple attacks or symptoms between acute infections resulting in frequent healthcare attendances and poor quality of life.^{3 4} These children are more likely to have asthma and may benefit from regular treatment with inhaled corticosteroids (ICSs). Unlike in older children and adults, objective testing to confirm asthma is not practical in preschool children, leading to hesitance with diagnosis and initiating treatment.⁵

Current guidelines recommend a trial of asthma preventer treatment in preschool children with severe or frequent wheezing, without confirmatory objective testing,^{6 7} with the caveat that a thorough

Key messages

What is known about this topic

- Acute presentations with wheeze are extremely common in preschool children.
- There is limited evidence to inform the risk of further attacks of wheeze in preschool children.
- This is important to inform decisions to initiate regular preventer asthma treatments in this age group.

What this study adds

- This is the first study to report risk factors associated with further attacks of wheeze in preschool children following an index presentation with wheeze to any care setting.

How this study might affect research practice or policy

- Findings from this study can be used to inform clinical decision making and develop a risk stratification tool to personalise initiation and escalation of regular preventative wheeze/asthma treatment in preschool children.

clinical history should be undertaken to exclude alternative causes.

Despite the incidence of unscheduled healthcare attendances for acute wheeze in preschoolers increasing, there has been no evidence of a corresponding increase in ICS prescriptions from routine health data, but instead an overall increase in reliance on short-acting beta-2 agonists (SABAs) and short courses of oral corticosteroids.⁸ This reflects reports of asthma treatment being overly focused on managing acute presentations, with less emphasis on long-term preventative management.^{9 10}

The assessment of future risk of acute attacks is an essential component of asthma care in any age group.^{6 7} In older children, a history of previous attacks, raised fraction of exhaled nitric oxide (FeNO) and increase in SABA use relative to ICS have been associated with increased risk for further attacks.^{11 12} There is limited evidence, however, to inform risk prediction in preschool children. This has been identified as a research need.⁷

We aimed to describe clinically relevant and patient demographic factors associated with further attacks of wheeze in preschool children who have been seen acutely with wheeze in either primary or secondary care.

METHODS

Data source

In this cohort study, we used de-identified routine healthcare data from the Clinical Practice Research

Datalink Aurum (CPRD-A) national primary care database, containing patient information from consenting UK general practices (GPs). The data set is broadly representative of the UK population in terms of age, sex and ethnicity;¹³ and contains coded data on patient demographics, diagnoses, prescriptions, tests and referrals. Data from the May 2022 build¹⁴ were linked via patient residential postcode to small-area level data¹⁵ for socioeconomic deprivation measures and rural–urban classification data.¹⁶ Linkage to secondary care data was available from NHS England’s Hospital Episode Statistics (HES) Admitted Patient Care,¹⁷ Outpatient¹⁸ and Accident and Emergency (A&E)¹⁹ databases.

Population

The study population was children 5 years or under with at least one acute wheeze presentation to primary or secondary care between 1 January 2013 and 31 December 2014; registered with GPs in England contributing data to CPRD-A and eligible for HES linkage. These dates were chosen pragmatically based on the availability of data, which were requested as part of an earlier analysis to explore health inequalities in preschool wheeze as part of the same research programme.²⁰

We excluded children with primary ciliary dyskinesia, cystic fibrosis, bronchopulmonary dysplasia, bronchiolitis obliterans, interstitial lung disease or bronchiectasis.

Outcomes

The index date was defined as the date of the first episode of acute wheeze between 1 January 2013 and 31 December 2014. The main outcome of interest was a subsequent episode of acute wheeze, presenting to any setting within 12 months of the index date. The secondary outcome was a subsequent episode of acute wheeze requiring hospitalisation or critical care within 12 months.

Acute attendances were defined using clinical diagnostic ‘med-codelids’ (derived from Read and SNOMED (Systematized Nomenclature of Medicine Clinical Terms) codes) for primary care, and International Classification of Diseases, 10th Revision/A&E wheeze/asthma diagnostic or treatment codes for secondary care. For primary care data, we developed a broad list of >200 diagnostic and treatment codes to define our outcome, to reflect the large number of Read and SNOMED codes for wheeze and asthma available, and the variable use of these codes between practitioners. Code lists used are available via <https://github.com/dkhl1/ip2am>, and details on how these were created here: <https://github.com/NHLI-Respiratory-Epi/SNOMED-CT-codelists>.

Variables

The following demographic data were extracted from CPRD and HES data sets: age at index date (whole years), sex, socioeconomic status, ethnicity and urban/rural classification of home postcode.

Socioeconomic status was based on the 2019 English Index of Multiple Deprivation (IMD) linked to the patient’s postcode, grouped into quintiles.¹⁵ Ethnicity was defined, from HES data sets, as the most commonly recorded ethnicity value across all healthcare episodes and grouped into five categories.

The rural–urban data set, produced by the UK’s Office for National Statistics using census data, was used to categorise patient residences as either primarily ‘rural’ or ‘urban’ at the patient postcode level. Areas are classified as rural if they fall outside of settlements with more than a 10 000-resident population.²¹

Clinical diagnostic codes were used to define the presence of clinical comorbidities including atopy (defined as the presence of eczema, hay fever, food allergy and/or rhinitis), gastro-oesophageal reflux, prematurity and history of bronchiolitis.

Data on previous healthcare utilisation and wheeze treatment prior to the index date were extracted: number of wheeze attacks ever, any attacks 12 months preindex date, previous hospitalisations with wheeze, setting of index episode (primary care, A&E, hospitalisation/critical care admission), number of reliever (SABA or ipratropium bromide) prescriptions 12 months preindex date and number of ICS prescriptions 12 months preindex date. Medi-

Table 1 Baseline characteristics of cohort

Variable group	Variable categories	Total (n=42 820)
Age at index episode	Median (25th, 75th percentile) age in years	1 (1, 3)
Sex	Female	15 791 (36.9%)
	Male	27 029 (63.1%)
Urban or rural classification of household	Urban	37 567 (87.7%)
	Rural	5215 (12.2%)
	Missing/unknown	38 (0.1%)
2019 English IMD Quintiles (1=least deprived)	1	7568 (17.6%)
	2	7321 (17.1%)
	3	7664 (17.9%)
	4	9107 (21.3%)
	5	11 122 (26.0%)
	Missing/unknown	38 (0.1%)
Recorded ethnicity	White	31 433 (73.4%)
	South Asian	4838 (11.3%)
	Black	2446 (5.7%)
	Other	1102 (2.6%)
	Mixed	1922 (4.5%)
	Missing/unknown	1079 (2.5%)
Comorbidities	History of atopy (including food allergy, eczema, hay fever, rhinitis)	21 445 (50.1%)
	History of prematurity (born at <37 weeks gestation)	2499/42 820 (5.8%)
Medication prescriptions in 12 months prior to index date	Median (25th, 75th percentile) (range) number of relievers	0 (0, 1) (0–33)
	Median (25th, 75th percentile) (range) number of ICS	0 (0, 0) (0–18)
Healthcare setting of index episode	Primary care	25 292 (59.1%)
	Emergency department	4675 (10.9%)
	Hospital admission	12 851 (30.0%)
	Critical care admission	2 (0.0%)
Previous attacks of wheeze	Median number of attacks ever prior to index episode (25th, 75th percentile) (range)	0 (0, 0) (0–58)
	History of at least one hospitalisation ever prior to index episode	4793/42 820 (11.2%)
	History of at least one attack within 12 months prior to index episode	4358/42 820 (10.2%)

ICS, inhaled corticosteroid; IMD, index of multiple deprivation.

cation codes were used to determine reliever and ICS prescriptions from CPRD records.

Statistical analyses

Frequency distributions of cohort characteristics were presented for sex, urban/rural classification, IMD quintile and ethnicity. Age at index episode, number of previous acute wheeze episodes, healthcare attendances within previous year for acute wheeze, previous hospital admissions for wheeze and number of reliever and ICS prescriptions in the previous year were summarised as: mean (SD) or median (25th, 75th percentiles) for continuous variables, and as counts and percentages for categorical and binary variables.

Cross tabulation was performed to present the number (proportion) of children with further attacks by each variable. Separate Poisson generalised linear models with log link and robust standard errors (complete case) were fitted to explore associations between participant characteristics and the outcomes of interest. Potential risk factors were determined based on clinical relevance and existing literature, and only suitable predictors were considered for the analysis.

Adjusted relative risks (RRs) with associated 95% CIs are reported. The variance inflation factor (VIF) was used to check for collinearity between variables (Stata ‘collin’ command), with a value >10 suggesting evidence of collinearity.²² Significant associations

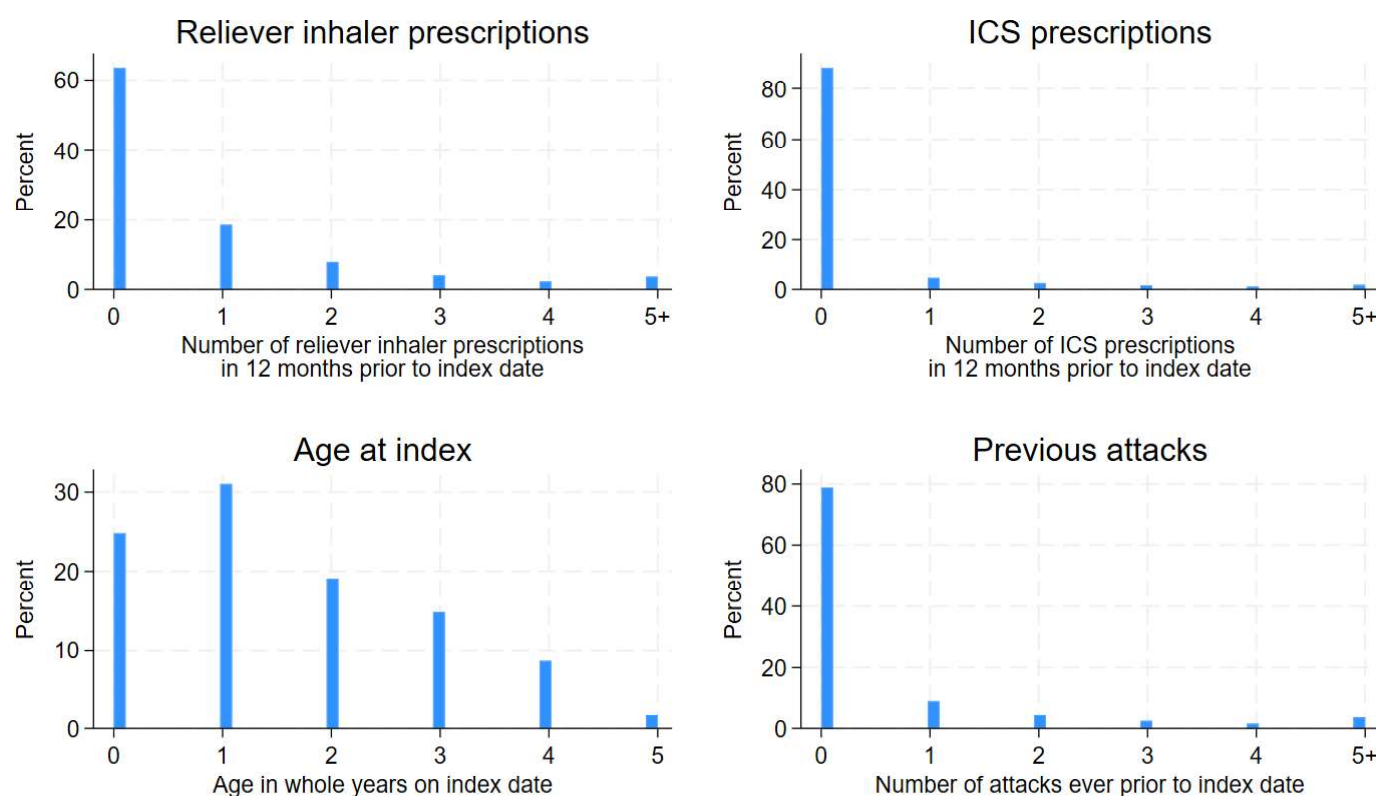


Figure 1 Histogram showing frequency distribution of continuous variables. ICS, inhaled corticosteroids.

should be interpreted in the context that numerous variables were assessed, increasing the probability of a type 1 error.

All analyses were performed using Stata statistical software, V.18.0.

Patient and public involvement

Two patient and public involvement contributors with experience of caring for children with recurrent preschool wheeze were members of the project steering committee. They commented on the study protocol and have been consulted on the contextual interpretation of the study findings and dissemination strategies.

RESULTS

Characteristics of children at index episode

The cohort included 42 820 preschool children and their characteristics are shown in table 1. Children with any missing data were low (2.6%), and the characteristics of children with complete data were similar to the whole cohort (online supplemental table S1).

The majority of children were male (27 029; 63.1%), lived in an urban area (37 567; 87.7%) and were of white ethnicity (31 433; 73.4%). Children from the most deprived two quintiles made up almost half of the cohort (20 229; 47.3%). Half of the children had evidence of atopy (21 445; 50.1%), and 2499 (5.8%) were born preterm (<37 weeks gestation).

Of the index episodes, the majority were managed in primary care (25 292; 59.1%), and around a third were hospitalised (12 851; 30.0%). One-in-10 children (4358; 10.2%) had at least one attack 12 months preindex, and 9041 (21.1%) had at least one attack ever preindex episode (online supplemental table S2).

One-third of the cohort (15 622; 36.5%) had been prescribed at least one reliever inhaler in the year preindex attack, with 1548 (3.6%) prescribed five or more (online supplemental table S3). 4995 (11.7%) children were prescribed at least one ICS inhaler in the year preindex attack (online supplemental table S4). The distribution of children's ages, number of previous attacks and number of prescriptions for reliever or ICS medications are shown in figure 1.

Risk factors for further presentation with acute wheeze

Almost 40% (16 962/42 820) of our cohort had a further attack of wheeze within a year of the index episode. This increased to 61% (944/1553) in children with five or more attacks ever preindex episode, compared with 38% (12 683/33 779) in those presenting with their first attack; and to 58% (2516/4358) in children with at least one attack in the previous year, compared with 38% (14 446/38 462) in those with no attacks in the previous year (table 2).

Figure 2 shows the estimates of association between each variable and the RR of a subsequent wheeze attack within 12 months of the index episode. The strongest predictor for further attacks was hospitalisation at index episode (RR 1.42; 95% CI 1.39 to 1.45) and having at least one attack in the previous year (1.27; 1.22 to 1.32).

Other variables associated with further attacks were: history of atopy (RR 1.21; 95% CI 1.18 to 1.24), index episode treated in emergency department (ED) (1.15; 1.10 to 1.19), prematurity (1.09; 1.04 to 1.14), South Asian ethnicity (1.08; 1.04 to 1.12), previous hospitalisation with wheeze (1.09; 1.05 to 1.14), male sex (1.06; 1.03 to 1.08), increasing number of reliever prescriptions (1.04; 1.03 to 1.04) and increasing number of previous attacks (1.03; 1.02 to 1.04).

Conversely, older age at presentation and prescriptions for ICS were associated with lower risk for further attacks. For each year increase in age at index presentation, there was an 8% lower risk of a further attack (RR 0.92; 95% CI 0.91 to 0.93). Each additional ICS prescription in the year prior to the index attack reduced the risk of a subsequent attack by 4% (0.96; 0.95 to 0.97). Neither deprivation quintile nor urbanicity of home postcode was associated with the risk of further attacks.

Risk factors for further presentation with acute wheeze requiring hospitalisation

Figure 3 shows the estimates of association between each variable and the RR of a severe attack requiring hospitalisation within 12 months of the index episode. Male sex, South Asian ethnicity, atopy, prematurity, increasing number of reliever prescriptions, increasing number of previous attacks, previous hospitalisation with wheeze, an attack within the previous year and care for the index episode

Table 2 Cross-tabulation of primary outcome (further attacks or not 12 months postindex) by each available variable

Variable group	Variable categories	Further attacks 12 months postindex		Total
		Yes n=16 962 (39.6%)	No n=25 858 (60.4%)	
Age at index episode (years)	0	4258 (40.2%)	6339 (59.8%)	10 597
	1	5335 (40.2%)	7947 (59.8%)	13 282
	2	3429 (41.9%)	4761 (58.1%)	8190
	3	2443 (38.6%)	3883 (61.4%)	6326
	4	1306 (35.4%)	2380 (64.6%)	3686
	5	191 (25.9%)	548 (74.1%)	739
Sex	Female	5889 (37.3%)	9902 (62.7%)	15 791
	Male	11 073 (41.0%)	15 956 (59.0%)	27 029
Urban or rural classification of household	Urban	14 853 (39.5%)	22 714 (60.5%)	37 567
	Rural	2098 (40.2%)	3117 (59.8%)	5215
	Missing/unknown	11 (29.0%)	27 (71.0%)	38
2019 English IMD Quintiles (1=least deprived)	1	2958 (39.1%)	4610 (60.9%)	7568
	2	2890 (39.5%)	4431 (60.5%)	7321
	3	3021 (39.4%)	4643 (60.6%)	7664
	4	3654 (40.1%)	5453 (59.9%)	9107
	5	4428 (39.8%)	6694 (60.2%)	11 122
	Missing/unknown	11 (29.0%)	27 (71.0%)	38
Recorded ethnicity	White	12 367 (39.3%)	19 066 (60.7%)	31 433
	South Asian	2082 (43.0%)	2756 (57.0%)	4838
	Black	984 (40.2%)	1462 (59.8%)	2446
	Other	443 (40.2%)	659 (59.8%)	1102
	Mixed	807 (58.0%)	1115 (42.0%)	1922
	Missing or unknown	279 (25.9%)	800 (74.1%)	1079
History of atopy (including food allergy, eczema, hay fever, rhinitis)	Yes	9330 (43.5%)	12 115 (56.5%)	21 445
	No	7632 (35.7%)	13 743 (64.3%)	21 375
History of prematurity (born at <37 weeks gestation)	Yes	1101 (44.1%)	1398 (55.9%)	2499
	No	15 861 (39.3%)	24 460 (60.7%)	40 321
Number of reliever prescriptions 12 months preindex	0	9911 (36.4%)	17 287 (63.6%)	27 198
	1–2	4931 (43.2%)	6472 (56.8%)	11 403
	3–4	1274 (47.7%)	1397 (52.3%)	2671
	5+	846 (54.7%)	702 (45.4%)	1548
Number of ICS prescriptions 12 months preindex	0	14 679 (38.8%)	23 146 (61.2%)	37 825
	1–2	1363 (44.9%)	1671 (55.1%)	3034
	3–4	555 (46.7%)	634 (53.3%)	1189
	5+	365 (47.3%)	407 (52.7%)	772
Healthcare setting of index episode	Primary care	8782 (34.7%)	16 510 (65.3%)	25 292
	Emergency department	1836 (39.3%)	2839 (60.7%)	4675
	Hospital admission	6343 (49.4%)	6508 (50.6%)	12 851
	Critical care admission	1 (50.0%)	1 (50.0%)	2
Number of attacks ever preindex	0	12 683 (37.6%)	21 096 (62.4%)	33 779
	1–2	2444 (42.3%)	3332 (57.7%)	5776
	3–4	891 (52.0%)	821 (48.0%)	1712
	5+	944 (60.8%)	609 (39.2%)	1553
History of at least one hospitalisation ever prior to index episode	Yes	2532 (52.8%)	2261 (47.2%)	4793
	No	14 430 (38.0%)	23 597 (62.0%)	38 027
History of at least one attack within 12 months prior to index episode	Yes	2516 (57.7%)	1842 (42.3%)	4358
	No	14 446 (37.6%)	24 016 (62.4%)	38 462

ICS, inhaled corticosteroid; IMD, index of multiple deprivation.

either in ED or hospital were all associated with increased risk of further attack. The index episode presenting in ED (RR 2.20; 95% CI 2.06 to 2.34) or requiring hospitalisation (2.63; 2.52 to 2.76) was associated with a greater than twofold increase in the risk of hospitalisation with wheeze within a year. Older age at index presentation was also associated with lower risk for further severe attacks, but increased prescriptions of ICS were not associated with a reduction in severe attacks. Neither deprivation quintile nor urbanicity of home postcode was associated with further severe attacks.

In our analysis, the mean VIF was 1.35 (maximum VIF 1.95), indicating no evidence of significant multicollinearity between

variables, including between number of wheeze attacks ever and any attacks within the year preindex date. There was no notable evidence of non-linearity observed for the continuous variables included within the models. A graphical inspection of deviance and Pearson residual distributions against fitted values confirmed suitable model fit for both outcomes.

DISCUSSION

In this analysis of over 40 000 preschool children presenting to any healthcare setting with attacks of wheeze in England, almost 40% presented with a further attack within 12 months. This increased

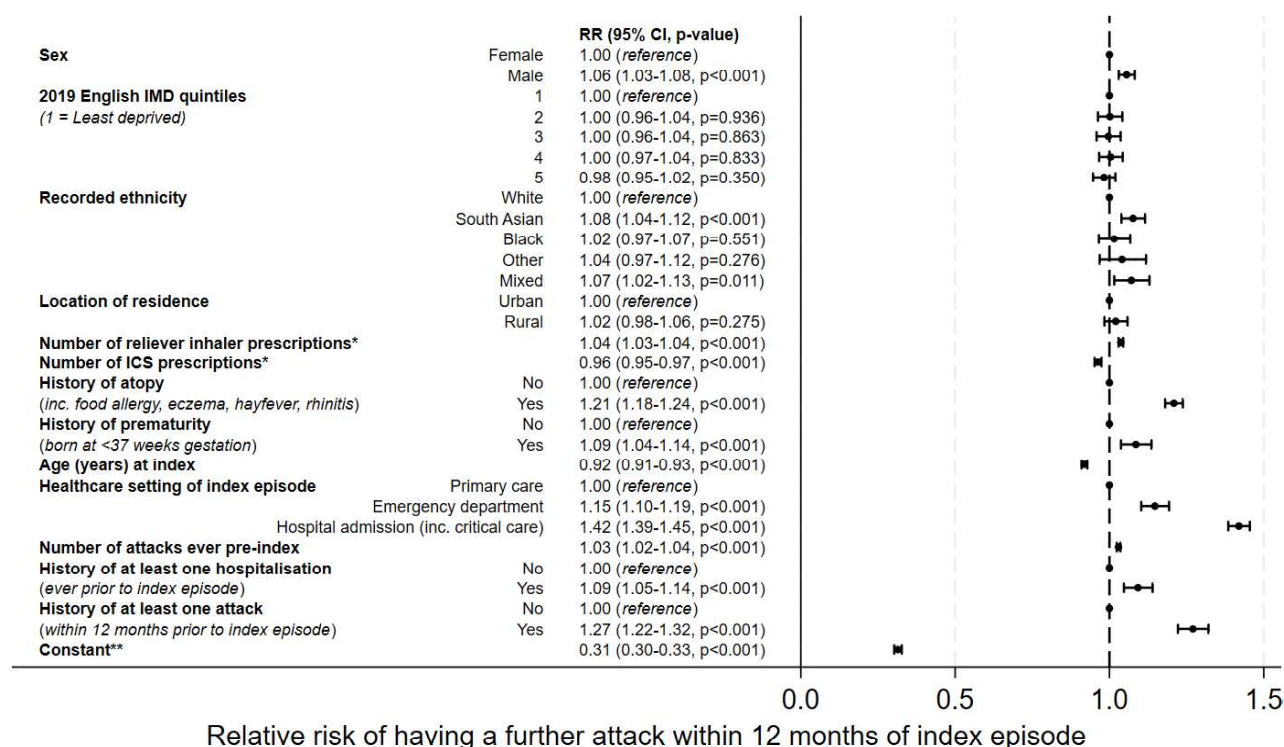


Figure 2 Forest plot of outputs from multivariable regression analysis for primary outcome, adjusted for all covariates presented. The relative risk (RR) is presented adjacent to each variable, followed by the 95% CI and p value. *Number of prescriptions in 12 months prior to index episode. **Constant estimate denotes the baseline risk of an event for an individual with all variables set to the reference level. ICS, inhaled corticosteroid; IMD, index of multiple deprivation.

to almost 50% in children presenting to hospital, and to almost 60% in children with at least one further attack in the previous year. We report multiple factors associated with increased risk for a further attack, including severity of index presentation, history of previous attacks, atopy, premature birth, younger age at presentation, higher reliever inhaler usage and fewer inhaled steroid prescriptions in the previous year.

Our findings are comparable with previous studies in older children and adults.^{11 12 23} A 2018 systematic review of risk factors for asthma attacks in children aged 5–12 years reported the highest risk of further attacks to be in children with a history of previous asthma attacks (ORs between 2.0 and 4.1). In our younger cohort, a previous attack is also associated with further attacks, but the association is less strong compared with older children. This may be

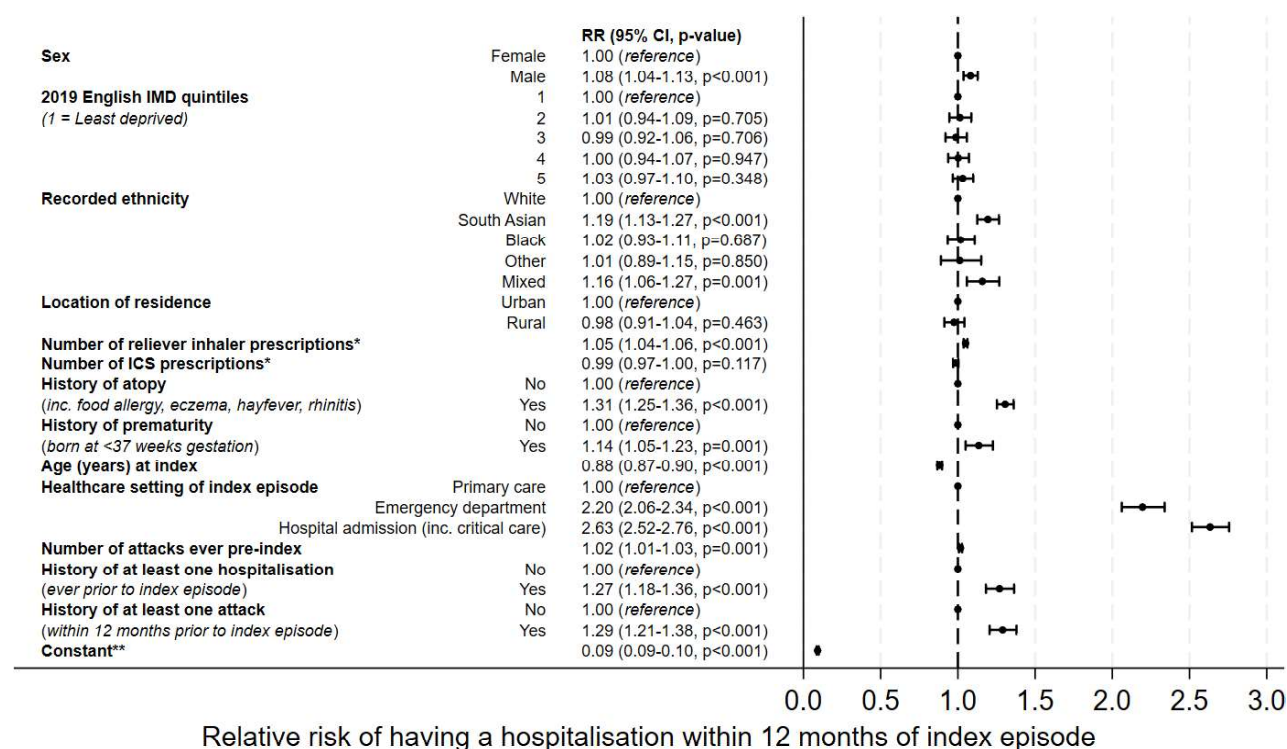


Figure 3 Forest plot of outputs from multivariable regression analysis for primary outcome, adjusted for all covariates presented. The relative risk (RR) is presented adjacent to each variable, followed by the 95% CI and p value. *Number of prescriptions in 12 months prior to index episode. **Constant estimate denotes the baseline risk of an event for an individual with all variables set to the reference level. ICS, inhaled corticosteroid; IMD, index of multiple deprivation.

because asthma is more likely to be the cause for acute wheeze in older children, while in children under 5, wheeze is more commonly a presenting feature of self-limiting viral chest infections; so-called 'viral-induced wheeze'.

In preschool children, we observed the strongest predictor for a further attack was severity of the index presentation. Children requiring hospitalisation for acute wheeze were almost 1.5 times as likely to have a further attack compared with children requiring treatment in primary care only. The severity of the index presentation was also associated with the risk of subsequent hospitalisation with wheeze within 12 months. Preschool children cared for in hospital or the ED have over double the risk of hospitalisation within 12 months compared with children who only required treatment in primary care.

Existing evidence to inform risk prediction in preschool children is limited.⁷ Similar to our study, a previous large UK cohort study using routinely collected healthcare data (n=17 320 preschool children)²⁴ reported the following risk factors for further attacks in preschool children: younger age, atopic disease and male sex. Interestingly, and in contradiction to our findings, their study reported low socioeconomic status and treatment with regular preventer medication to be associated with higher risk of asthma attacks; each increasing British Thoracic Society (BTS) 2016 asthma guideline treatment step was associated with incremental increases in the risk of future attacks. However, their study only included children with a coded diagnosis of asthma, thus likely only including children with better access to GPs (where most diagnoses are made) and excluding children with poor access to primary healthcare services, including those from more deprived backgrounds.²⁰ Asthma treatment step was defined as the highest BTS step (highest asthma medication dosage) based on all medications prescribed in the year prior to study entry. Information on the number of preventer inhalers prescribed (as a surrogate indicator for adherence), reliever prescriptions (symptom control) or history of previous attacks was not available in their analysis. After adjusting for these variables within our analysis, increasing inhaled steroid prescriptions was found to be associated with reduced risk of further attacks, which would intuitively make sense as previous studies have demonstrated a positive response to inhaled steroids in at least a subgroup of preschool children with recurrent wheeze.^{25 26}

We chose not to limit our cohort to include only preschool children with a coded 'asthma diagnosis' within their electronic health records. Symptom overlap with other self-limiting respiratory conditions and the lack of practical objective tests means diagnosing asthma in preschool children is not straightforward. For our analysis, we wanted findings to be generalisable to any preschool child presenting acutely to healthcare with wheeze, and not limit risk prediction to only those with a pre-existing physician diagnosis.

Other key strengths of our study are its large, representative sample size and use of standardised clinical codes for case finding and outcome definitions. Linkage to emergency department and hospital discharge data further allowed us to capture episodes regardless of healthcare setting.

Limitations

Healthcare data is not primarily collected or curated for research purposes. Clinical coding is therefore not standardised between health professionals, which may result in data inaccuracies. To avoid missing potential acute wheeze episodes, we incorporated broad clinical codes for acute wheeze and asthma to account for clinician differences in diagnostic recording.

The number of prescriptions for both inhaled steroids and asthma relievers was likely underestimated as we were only able to include medication prescriptions issued from primary care, and not those from hospital or A&E.

We decided to include the number of ICS prescriptions in our analysis as a surrogate indicator for adherence. However, electronic prescriptions do not necessarily represent what was dispensed by pharmacies or what was used by patients, potentially over-estimating ICS and/or reliever usage.

Predictors included in our analysis were limited to those which were consistently recorded and available in the data sets used. Other previously reported biomarkers for future attacks, such as FeNO or low lung function, were not available to us. Similarly, predictors for response to regular inhaled steroids, such as blood eosinophils, are not routinely performed within the primary care setting in preschool children, and not available from HES.

Finally, the data are from over 10 years ago, due to this being a secondary analysis of data requested for a previous analysis. We are confident, however, that our findings remain valid as the association between our outcomes of interest with the available demographic and predictor variables included is unlikely to have changed since 2013, particularly since there have been no radical changes to asthma guidelines pertaining to preschool children over this time period. Moreover, by using broad clinical codes for attacks (including those for both wheeze and asthma) and linking both primary and secondary care data sets, our findings will remain relevant even if there have been changes in how asthma attacks are coded or which healthcare settings children are taken to for attacks over the past decade.

CONCLUSIONS

The aim of asthma treatment is not only to improve symptom control, but also to reduce the risk of further attacks. In this study, we report clinically relevant risk factors associated with further attacks in children presenting acutely with an asthma/wheeze attack. While no single factor can predict a further attack with complete certainty, children presenting to hospital and those who have had an attack within the previous year have a 40% and almost 30% higher risk respectively for a further attack in the following year, and warrant closer follow-up and monitoring, and consideration for regular asthma medications.

Building on our present analysis, we plan to develop a clinical prediction tool to improve further the accuracy of risk stratification in preschool children with wheeze.

X David Lo @david_lo

Contributors DL conceived the idea of the study and developed the protocol with input from CL, HP, EAG, CG and JQ. SS extracted the data for analysis and developed the codes to identify index dates and generate birth dates. All subsequent data cleaning and analyses were conducted by DL, with support from CL, CG, JB and JQ. All authors interpreted the data. DL drafted and revised the manuscript, with input from all authors. The guarantor (DL) accepts full responsibility for the work and the conduct of the study, had access to the data and controlled the decision to publish. The corresponding author (DL) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Papel da oximetria noturna na avaliação da gravidade da apneia obstrutiva do sono em crianças com síndrome de Down: um estudo bicêntrico

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INTRODUCTION

Obstructive sleep apnoea (OSA) is the most common form of sleep disordered breathing (SDB) in children with Down syndrome (DS), affecting 57–97%.^{1–5} These children are at high risk of SDB due to hypotonia, mid-face shape and relative macroglossia.^{6–8} OSA can have significant long-term effects including cognitive impairment and behavioural difficulties in children with DS.^{9–11} The cardiovascular sequelae of OSA have relevance to children with DS, up to 60% of whom are born with congenital cardiac disease and increased risk of pulmonary hypertension.^{12–14} Children with DS may be more vulnerable to OSA-associated cognitive insult with reduced cognitive reserve at baseline.^{15 16}

Early OSA diagnosis and intervention from 6 months of age have been shown to significantly improve neurocognitive development and behaviour at 36 months in children with DS.¹⁷ The benefits of treatment of OSA for quality of life in children with DS have been shown.^{18 19}

RESUMO

Contexto e objetivo A poligrafia cardiorrespiratória (PCR) é a tecnologia predominante utilizada para diagnosticar apneia obstrutiva do sono (AOS) em centros terciários no Reino Unido. A oximetria noturna (ON) é mais barata e mais acessível. Este estudo avalia a capacidade dos índices de ON para prever AOS em crianças com síndrome de Down (SD).

Métodos Foram comparados índices provenientes de registos simultâneos de ON e PCR em crianças com SD (2–16 anos) referenciadas para avaliação de AOS em dois centros terciários ao longo de um período de 8 anos. Curvas ROC foram usadas para avaliar a precisão diagnóstica dos índices de ON, incluindo ODI3 (Índice de Dessaturações de Oxigênio $\geq 3\%$) e ODI4 ($\geq 4\%$). Tabelas 2×2 determinaram as sensibilidades e especificidades dos valores de corte para prever AOS.

Resultados Foram incluídas 387 crianças com SD submetidas a ON isolada; 177 do sexo feminino (46,7%), idade mediana 6,1 anos (intervalo 2,02–15,97). Havia 265 crianças (68,5%) com Índice de Apneia–Hipopneia Obstrutiva (OAH) ≥ 1 /hora, 164 com OAH ≥ 1 –5/hora (42,4%), 51 com OAH ≥ 5 –10/hora (13,2%) e 50 com OAH ≥ 10 /hora (12,9%). ODI3 e ODI4 demonstraram o melhor valor preditivo para AOS. Um ODI3 ≥ 19 /hora e um ODI4 ≥ 8 /hora estiveram associados às combinações mais elevadas de sensibilidade (59,2% / 63,8%) e especificidade (74,6% / 71,3%), respetivamente.

Conclusão Valores elevados de ODI3 e ODI4 predizem AOS moderada e grave em crianças com SD, com sensibilidade e especificidade moderadas, mas apresentam baixa sensibilidade para detetar AOS ligeira. O fraco desempenho preditivo da oximetria reflete a natureza multifatorial das perturbações respiratórias do sono em crianças com SD. Recomendamos que a oximetria não seja utilizada para diagnóstico de AOS em SD, devendo ser preferida a PCR ou a polissonografia.

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► There is limited evidence regarding the ability of nocturnal pulse oximetry (NPO) to diagnose obstructive sleep apnoea (OSA) in children with Down syndrome (DS). Current guidelines advise NPO can be used as a first-line investigation in typically developing children; however, they do not recommend NPO to be used as a first-line investigation in children with comorbidities.

WHAT THIS STUDY ADDS

► This dual-centre study has evaluated the ability of a range of NPO indices to predict OSA in over 300 children with DS.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► NPO is not a suitable alternative to polysomnography/cardiorespiratory polygraphy for diagnosing OSA in children with DS.

Overnight polysomnography (PSG), which determines sleep stages using electroencephalogram, is considered the gold-standard test for diagnosing OSA in children.^{20 21} Cardiorespiratory polygraphy (CRP), which estimates sleep time, is recognised as a less costly alternative with good diagnostic outcomes in populations with a modest to high pretest probability of OSA.²²

Nocturnal pulse oximetry (NPO) is easier to report, relatively inexpensive, and places less demands on the child in terms of monitoring equipment.^{16 23} The predictive value of NPO for diagnosing OSA in typically developing (TD) children has been explored.²⁴ While NPO is not diagnostic for SDB, many centres have limited access to CRP and rely on NPO for guiding clinical decision making.^{16 20 25 26} The role of NPO in screening for SDB has been acknowledged.^{20 27} These data are not applicable to children with complex medical conditions due to mixed patterns of breathing disorder.²¹ As such, recent guidelines did not recommend NPO as a diagnostic tool in children with comorbidities or genetic syndromes.¹⁶ Previous studies have explored the utility of NPO in mixed populations; however, none to date have focused on DS alone.^{26–30}

This study aimed to determine whether NPO indices exist with high sensitivity and specificity to



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allow NPO to be used as a predictor of OSA in children with DS in clinical practice with acceptable accuracy.

METHODS

Study design

This retrospective study compared simultaneous CRP and NPO recordings of children at two UK tertiary sleep centres (University Hospital Southampton NHS Foundation Trust and the Royal Hospital for Children Glasgow) between May 2016 and May 2024 (inclusive). Although CRP and simultaneous NPO are standard practice in tertiary centres; PSG was not undertaken. Studies (undertaken at home or in hospital) were included for children with DS (aged 2–16 years) referred to evaluate OSA. DS with cyanotic congenital heart disease, haemoglobin disorders and those on oxygen therapy/non-invasive ventilation were excluded. Studies were excluded if less than 4 hours of artefact-free data (from either NPO or CRP) were obtained.

Data collection

CRP was recorded using SOMNOscreen (SOMNOmedics, Germany) and SOMNOtouch (SOMNOmedics, Germany). Respiratory effort was measured using thorax and abdominal respiratory inductance plethysmography (RIP) bands, alongside the derived RIP sum channel for surrogate marker analysis if required. Oxygen saturation (SpO₂) and pulse rate were measured by a Nonin integrated probe. ECG, body position, movement and nasal pressure flow were routinely recorded, while video, audio and transcutaneous carbon dioxide were recorded in some children. The oximeter evaluated as a predictor for OSA was Radical-7/Radical-8/Radical-97 (Masimo, USA) or oxicapnography via transcutaneous monitoring (TCM4 and TCM5; radiometer with inbuilt Masimo oximetry) with a 2-second averaging time. CRP recordings were scored by sleep physiologists according to American Academy of Sleep Medicine (AASM).³¹ Each 30-second epoch was classified as 'estimated sleep' or 'wake'. Oxygen desaturations $\geq 3\%$ were auto-scored and then reviewed manually. Apnoeas were scored if there was $\geq 90\%$ flow reduction from baseline for ≥ 2 breaths. They were classified as 'obstructive' if respiratory effort continued during absent flow, 'mixed' if part of the event had continued and part had cessation of respiratory effort, and 'central' if there was cessation of respiratory effort with an associated $\geq 3\%$ desaturation or if the central apnoea lasted ≥ 20 s. Hypopnoeas were scored if there was a $\geq 30\%$ reduction in baseline flow for ≥ 2 breaths with an associated $\geq 3\%$ desaturation. Physiologists were not blinded.

Outcomes

The following NPO parameters were recorded: mean baseline SpO₂ (%), 3% Oxygen Desaturation Index (ODI3), 4% Oxygen Desaturation Index (ODI4), minimum SpO₂ (%), Delta 12 s Index as a measure of variability over 12 s (D12) and a percentage of analysis time with SpO₂ $< 94\%$, 92% and 90% . Visi-Download software (Stowood Scientific, UK) was used for analysis. For this analysis, we have defined ODI3 as desaturations of $\geq 3\%$ from baseline/hour and ODI4 as desaturations of $\geq 4\%$ from baseline/hour.

Visi-Download software uses artefact rejection software to identify oximetry trace sections of probe disconnection and low signal confidence. These and probable wake sections (from diary cards/live monitoring of studies) were removed.

CRP data were downloaded using Domino software (Somnomedics). In this analysis, the mixed/Obstructive Apnoea–Hypopnoea Index (OAHl) (events/hour) was the outcome of interest.

Definitions

OSA was defined as OAHl ≥ 1 /hour, mild OAHl ≥ 1 – < 5 /hour, moderate OSA as OAHl ≥ 5 – < 10 /hour and severe OSA as OAHl ≥ 10 /hour.²¹

Statistical analysis

Data were stored (Microsoft Excel) and analysed (PRISM 10). Confidence intervals for sensitivity, specificity, positive and nega-

tive predictive values (PPV and NPV) were calculated using MedCalc V.23.2.1. Normally distributed data were summarised by mean and SD, and non-normally distributed data were summarised by 25th –75th percentiles and 95% CI of median. NPO indices from groups were compared using ANOVA test applying Bonferroni correction.

Receiver operating characteristic (ROC) curves were used to assess the diagnostic accuracy of ODI3, ODI4, D12, minimum SpO₂ and % time with SpO₂ $< 94\%$, 92% and 90% to predict OAHl ≥ 1 , ≥ 5 /hour, ≥ 10 /hour, ≥ 1 – < 5 /hour and ≥ 5 – < 10 /hour. The analysis was repeated for Apnoea Hypopnoea Index (AHI). An area under the curve (AUC) of 0.7–0.8 was considered acceptable, 0.8–0.9 as excellent and > 0.9 outstanding. Two-by-two tables were generated for ODI3, ODI4, D12 and minimum SpO₂ predicting OAHl and AHI. Cut-off values for time less than 94, 92 and 90% were derived from ROC curves. PPV and NPV values were calculated for ODI3, ODI4 and D12 predicting OAHl and AHI. Further analysis was not undertaken for variables where AUC was less than 0.7. A sensitivity/ specificity of 65–80% was considered 'moderate', a sensitivity/specificity of 80–90% as 'high' and a sensitivity/ specificity of 90–100% as 'very high'.¹⁶

RESULTS

Participants

387 children with DS were included from Glasgow and Southampton; 177 females (46.7%), median age 6.1 years (range 2.02–15.97). A high prevalence of respiratory events was observed in our population with DS; 94.3% having a total AHI of ≥ 1 /hour and 49.6% having a total AHI ≥ 5 /hour (table 1).

There were 265 children (68.5%) with OSA, 164 with mild OSA (42.4%), 51 with moderate OSA (13.2%) and 50 with severe OSA (12.9%). The median mean baseline SpO₂ of participants with OSA was 95.9% (94.7–96.8) and was similar across severities (table 2). Median ODI3 ranged from 13.85/hour in those without OSA to 18.15/hour in mild OSA ($p < 0.0001$) and 32.96/hour in those with severe OSA ($p < 0.0001$). The median ODI4 was 6.20/hour in children without OSA compared with 9.45/hour in those with OSA ($p < 0.0001$) and 17.60/hour in severe OSA. A summary of NPO indices across AHI categories is provided in online supplemental table S1 with Bonferroni adjusted p values in online supplemental tables S2–S17.

ODI3 as a predictor of OSA

ODI3 demonstrated 'acceptable' predictive potential for OSA in children with DS, with AUC of 0.73 (95% CI 0.68 to 0.78), $p < 0.0001$ with poorer predictive potential for mild OSA (figure 1 and online supplemental figure S1). Excellent predictive potential was demonstrated for severe OSA AUC 0.80 (95% CI 0.73 to 0.82), $p < 0.0001$. AUCs for ODI3 and AHI are provided in online supplemental figure S2.

An ODI3 threshold of ≥ 19 /hour was associated with the highest combined sensitivity/specificity (59.2%/74.6%) for predicting OSA (table 3). For OAHl ≥ 5 /hour and OAHl ≥ 10 /hour, an ODI3 ≥ 23 /hour provided highest combined sensitivity (70.3%, 82.0%) and specificity (79.7%, 73.9%), respectively.

An ODI3 of ≥ 23 /hour predicted AHI ≥ 10 /hour with highest combined sensitivity/specificity (82.3%/82.8%) (online supplemental table S18).

Table 1 Summary of respiratory events in population

Respiratory event type	< 1 /hour	≥ 1 – < 5 /hour	≥ 5 – < 10 /hour	≥ 10 /hour
All (AHI)	5.7% (n=22)	44.7% (n=173)	24.8% (n=96)	24.8% (n=96)
Obstructive/ mixed (OAHl)	31.5% (n=122)	42.3% (n=164)	13.2% (n=51)	12.9% (n=50)
Central (CAHI)	37.5% (n=145)	48.3% (n=187)	9.3% (n=36)	4.9% (n=19)

AHI, Apnoea Hypopnoea Index; CAHI, Central Apnoea Hypopnoea Index; OAHl, Obstructive Apnoea–Hypopnoea Index.

Table 2 Summary of NPO results in study participants, stand-alone oximetry

	All children (n=387)	OAH1 <1/hour (n=122)	OAH1 ≥1<5/hour (mild OSA) (n=164)	OAH1 ≥5<10/hour (moderate OSA) (n=51)	OAH1 ≥10/hour (severe OSA) (n=50)
Mean baseline SpO ₂ (%)†	96.0 (95.0–96.4, 95% CI 95.8 to 96.1)	96.1 (95.4–96.9, 95% CI 95.9 to 96.3)	96.0 (94.9–96.8, 95% CI 95.7 to 96.2) p>0.9999	95.6 (93.5–96.9, 95% CI 94.4 to 96.2) p 0.0009	95.6 (94.5–96.6, 95% CI 95.2 to 96.1) p 0.2435
Minimum SpO ₂ †	86.0 (82.0–89.0, 95% CI 86 to 87)	88.0 (85.8–90.0, 95% CI 87.0 to 88.0)	87.0 (83.0–89.0, 95% CI 86.0 to 87.0) p 0.4000	83.0 (79.0–86.0, 95% CI 81.0 to 84.0) p<0.0001	80.5 (71.0–84.5, 95% CI 75.0 to 84.0) p<0.0001
ODI3 (events/ hour)†	18.33 (12.41–27.60, 95% CI 16.88 to 19.59)	13.85 (9.34–19.48, 95% CI 12.41 to 15.91)	18.15 (12.42–23.20, 95% CI 16.05 to 19.43) p 0.1294	24.68 (18.33–38.60, 95% CI 21.59 to 33.45) p<0.0001	32.96 (25.05–49.50, 95% CI 28.30 to 40.02) p<0.0001
ODI4 (events/ hour)†	8.20 (5.50–13.43, 95% CI 7.65 to 8.84)	6.20 (3.90–8.61, 95% CI 5.50 to 7.32)	7.98 (5.58–10.96, 95% CI 7.19 to 8.55) p 0.2599	14.08 (8.84–21.01, 95% CI 10.52 to 17.90) p<0.0001	17.60 (11.53–31.42, 95% CI 15.40 to 23.00) p<0.0001
Delta 12 Index†	0.52 (0.43–0.65, 95% CI 0.51 to 0.54)	0.46 (0.39–0.55, CI 0.43 to 0.50)	0.51 (0.43–0.59, 95% CI 0.48 to 0.53) p 0.2762	0.64 (0.52–0.79, 95% CI 0.60 to 0.70) p<0.0001	0.81 (0.63–1.06, 95% CI 0.71 to 1.0) p<0.0001
% time with SpO ₂ <94%†	2.24 (0.59–12.94, 95% CI 1.69 to 2.75)	1.26 (0.36–4.27, 95% CI 0.92 to 1.75)	1.82 (0.56–11.61, 95% CI 1.31 to 2.62) p 0.6501	7.15 (1.44–46.69, 95% CI 2.61 to 27.18) p<0.0001	7.94 (2.18–20.22, 95% CI 4.08 to 11.63) p 0.0188
% time with SpO ₂ <92%†	0.29 (0.10–1.43, 95% CI 0.24 to 0.43)	0.16 (0.04–0.40, 95% CI 0.13 to 0.22)	0.27 (0.27–1.03, 95% CI 0.19 to 0.43) p>0.9999	1.47 (0.50–8.86, 95% CI 0.71 to 2.74) p 0.0003	2.7 (0.55–5.42, 95% CI 1.19 to 4.14) p 0.0638
% time with SpO ₂ <90%†	0.09 (0.02–0.40, 95% CI 0.06 to 0.11)	0.04 (0.01–0.11, 95% CI 0.02 to 0.05)	0.27 (0.09–1.03, 95% CI 0.19 to 0.43) p>0.9999	0.38 (0.11–1.19, 95% CI 0.25 to 0.63) p 0.0022	0.96 (0.21–2.67, 95% CI 0.56 to 1.55) p 0.6922

P values refer to comparison of each group with children without OSA (OAH1 <1/hour) using analysis of variance.

*Data reported as mean±SD.

†Data reported as median (25th–75th centiles, 95% CI of median).

NPO, nocturnal pulse oximetry; OAH1, Obstructive Apnoea–Hypopnoea Index; ODI3, 3% Oxygen Desaturation Index; ODI4, 4% Oxygen Desaturation Index; OSA, obstructive sleep apnoea; SpO₂, oxygen saturation.

An ODI3 threshold of ≥19/hour gave a high PPV of 83.5% for OAH1 ≥1/hour and NPV of 45.7%. ODI3 ≥23/hour gave high NPVs for predicting OAH1 ≥5/hour, 88.4%, and OAH1 ≥10/ hour, 96.5%, with lower PPVs observed, 55.0% and 31.8%, respectively (online supplemental table S19). ODI3 ≥23/hour provided higher PPV, 61.2% for AHI ≥10/hour with high NPV of 93.4% (online supplemental table S20).

ODI4 as a predictor of OSA

ODI4 demonstrated 'acceptable' predictive potential for OSA in children with DS (online supplemental figure S3). There was excellent predictive potential for OAH1 ≥5/hour, AUC 0.81 (95% CI 0.77 to 0.87), p<0.0001, and OAH1 ≥10/hour AUC 0.83 (95% CI 0.76 to 0.89), p<0.0001 (figure 1 and online supplemental figure S3). Higher AUC was observed for ODI4 and AHI ≥1/hour and AHI ≥10/hour (online supplemental figure S4).

An ODI4 threshold of ≥10/hour was associated with the highest combined sensitivity and showed moderate sensitivity (76.2%) and specificity (75.2%). For OAH1 ≥10/hour, an ODI4 of ≥13/hour demonstrated moderate sensitivity and high specificity, 72.0% and 80.7%, respectively (table 3). ODI4 threshold of ≥10/hour predicted AHI ≥10/hour with high sensitivity (86.4%) and moderate specificity (77.7%) (online supplemental table S18).

High PPV, 82.8%, was demonstrated for OAH1 ≥1/hour using ODI4 threshold of ≥8/hour, with low NPV, 47.5%, observed. High NPVs were identified for OAH1 ≥5/hour, using an ODI threshold of ≥9/hour for OAH1 ≥10/hour with a lower PPV, 35.8% (online supplemental table S19). ODI4 threshold of ≥23/ hour provided higher PPV of 59.4% for AHI ≥10/hour with high NPV, 92.3% (online supplemental table S20).

D12 as a predictor of OSA

The ability of D12 to predict mild OSA was poor, AUC <0.7. Diagnostic accuracy improved for moderate and severe OSA with AUC 0.82 (95% CI 0.77 to 0.87), p<0.0001 for OAH1 ≥5/hour, and 0.85 (95% CI 0.79 to 0.91), p<0.0001 for OAH1 ≥10/hour (figure 1 and online supplemental figure S5). Higher AUC was observed for D12 and AHI ≥1/ hour and AHI ≥10/ hour (online supplemental figure S6).

D12 ≥0.57 demonstrated the optimum combined sensitivity (70.6%) and specificity (71.7%) cut-off for moderate OSA (table 4). D12 ≥0.62 showed superior performance for severe OSA, with sensitivity and specificity of 80.0% and 77.2%, respectively (table 4). D12 threshold of ≥0.60 and ≥0.61 provided highest combined sensitivity and specificity for predicting AHI ≥5/hour and AHI ≥10/hour, respectively (online supplemental figure S6 and table S21).

PPV was generally low for D12 optimum sensitivity/specificity thresholds. NPV was high for OAH1 ≥5/hour, a D12 of ≥0.62 demonstrated an NPV of 88.1% (online supplemental table S22). D12 threshold of ≥0.61/hour provided higher PPV and NPV for AHI ≥10/hour, 63.0% and 92.2%, respectively (online supplemental table S23).

Minimum saturation (SpO₂) as a predictor of OSA

The diagnostic accuracy of minimum SpO₂ for identifying children with DS and mild OSA was poor with AUC <0.7 (figure 1 and online supplemental figure S7 and table S24). Performance was moderate for ≥5/hour, 0.75 (95% CI 0.68 to 0.82), p<0.0001. Similar AUCs were observed for minimum SpO₂ and AHI (online supplemental figure S8 and table S25).

Percentage of analysis time with saturation (SpO₂) <94%, 92% and 90% as a predictor of OSA

The diagnostic accuracy of percentage time with SpO₂ <94% was poor, with AUC <0.7 (figure 1, and online supplemental figure S9). Diagnostic accuracy improved for time <92% and <90% (figure 1 and online supplemental figures S9–S11 and tables S26 and S27). Higher AUC was observed for SpO₂ and AHI (online supplemental figures S12–S14 and tables S28–S30).

DISCUSSION

To our knowledge, this is the largest study to date exploring the role of NPO in predicting OSA in children with DS. Children with DS are at greater risk of SDB than TD children and can find tolerating CRP challenging.^{8, 27} The use of NPO as a screening or diagnostic tool could increase the accessibility and acceptability of

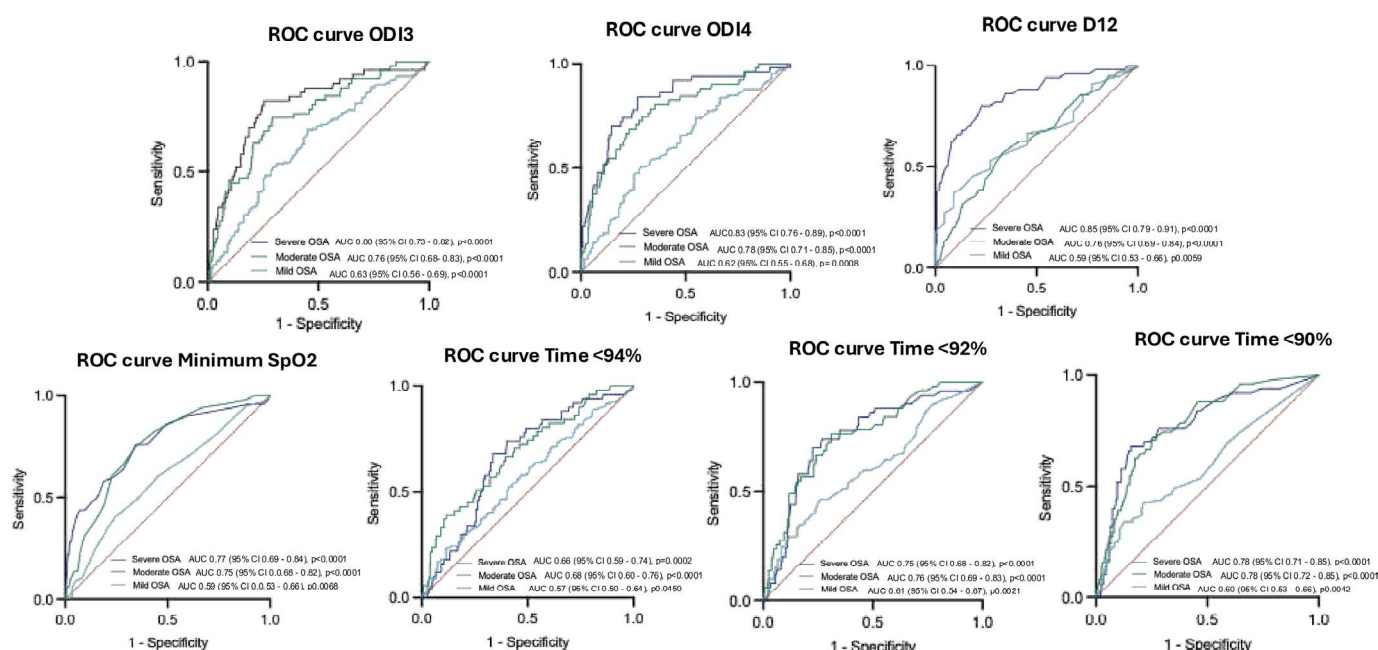


Figure 1 Summary of ROC analysis for nocturnal pulse oximetry index predictive value for OSA in children with Down syndrome. Mild OSA was defined as OAHl ≥ 1 <5/hour, moderate OSA was defined as OAHl ≥ 5 <10/hour, severe OSA was defined as OAHl ≥ 10 /hour. AUC, area under the curve; D12, Delta 12 s Index; OAHl, Obstructive Apnoea–Hypopnoea Index; ODI3, 3% Oxygen Desaturation Index; ODI4, 4% Oxygen Desaturation Index; OSA, obstructive sleep apnoea; ROC, receiver operating characteristic; SpO₂, peripheral oxygen saturation.

SDB evaluation for children and their families.³² Our results suggest raised NPO indices do not provide sufficient sensitivity and specificity to be used as a reliable diagnostic test for OSA.

The British Thoracic Society recommends NPO can be used as a first-line diagnostic test in TD children suspected of having SDB with a high sensitivity and moderate specificity.¹⁶ In studies evaluating populations of children with complex medical conditions, NPO indices were found to have a low sensitivity and high specificity for diagnosing SDB.¹⁶ Evidence is lacking around use of NPO in children with DS who have a unique combination of facial dysmorphology and hypotonia alongside predisposition to pons hypoplasia.³³

Our results suggest a low sensitivity and moderate specificity of NPO for identifying OSA in children with DS, likely reflecting the multifactorial nature of SDB in this population. Based on AUC, we observed ODI3, ODI4 and D12 had the best diagnostic accuracy for OSA. For all indices, AUC was greater as severity of OSA increased. High NPVs in our cohort suggest moderate–severe OSA can be ruled out in 88.0% children with ODI3 <23/hour and 96.5% of children with severe OSA. Similarly, an ODI4 <10/hour rules out 90.0% of children with moderate–severe OSA. High PPV for OAHl ≥ 1 /hour means that OSA can be identified in 83.5% of children with DS with ODI3 ≥ 19 /hour and 82.8% of children with ODI4 ≥ 8 /hour. Low prevalences of moderate–severe OSA in our cohort may explain the low PPV for ODI3 and ODI4 for predicting OAHl ≥ 5 /hour and OAHl ≥ 10 /hour.

The thresholds for NPO indices chosen for diagnosing OSA will reflect the sensitivity/specificity felt clinically appropriate considering risk of false negative and false positive outcomes. ODI3 >7/hour and ODI4 >4/hour are the recommended cut-offs for abnormality in TD children over 2 years of age.^{16–34} We found that ODI3 ≥ 19 /hour and ODI4 ≥ 8 /hour predicted OSA in children with DS with low sensitivity and moderate specificity. This is unsurprising given a high prevalence of central events in children with DS (table 1) when oximetry indices do not discriminate between obstructive and central events. Lower mean SpO₂, 96.0%, may also contribute to higher ODI in DS population compared with 97.2% in a TD population.²⁴ Higher predictive D12 thresholds were identified in our DS cohort compared with a TD cohort. We found D12 of 0.59 to be a superior diagnostic threshold for OAHl ≥ 5 /hour, with a sensitivity and specificity of 74.2% and 76.9%, respectively. Selby

et al identified a lower cut-off, D12 ≥ 0.44 , to be the optimum predictor of OAHl ≥ 5 /hour (sensitivity 73.8%, specificity 79.2%).²⁴ Higher D12 thresholds in our DS cohort compared with the TD children may reflect greater instability and variability in oxygenation.

Predictive performance of minimum SpO₂ and time below 94%, 92% and 90% was poor.²⁴ Physiological functions such as lung capacity and ventilation–perfusion matching are more likely to be impaired in the population with DS.¹⁵

Our findings suggest that the diagnostic potential of NPO for SDB in DS is limited, and CRP/PSG is required for accurate diagnosis. However, NPO may have a valuable role in screening. Hill et al demonstrated the potential for NPO to identify children with DS at high risk of SDB who would benefit from multichannel diagnostic evaluation.²⁷ In an era of novel technology, the sleep diagnostic landscape is changing, and wearable technology is being developed, which has potential to improve tolerability and diagnostic accuracy of SDB evaluation for children.^{35–36}

Limitations

There are limitations to this study: First, CRP was used to diagnose OSA rather than PSG; therefore, total sleep time was estimated and OAHl may have been underestimated due to underscoring of hypopnoeas not associated with desaturation when arousal from sleep could not be detected.²⁸ Stand-alone oximetry total recording time and CRP total sleep time will not be identical, which may influence the accuracy of oximetry indices predicting OAHl. Additionally, high prevalence of central apnoeic events may contribute to higher ODI thresholds and impact the accuracy of predicting OSA. Future evaluation of oximetry and transcutaneous carbon dioxide (TcCO₂) to predict Central Apnoea Hypopnoea Index in the population with DS would be valuable; the absence of TcCO₂ may impact the diagnostic accuracy of using oximetry alone.²⁰

Our findings raise an important question: is the AASM criteria capable of capturing the intricacies of SDB in a complex patient cohort such as DS, where scoring of respiratory events is dichotomous, that is, obstructive or central. Children with DS show lower baseline saturation than TD children, predisposing to desaturations.^{24–34} Raised OAHl may not reflect OSA in children with complex conditions. Centrally driven shallow breathing is scored as obstructive if snoring is detected, although shallow breathing and

Table 3 Sensitivity and specificity values for a range of ODI3 and ODI4 cut-off values for predicting OAH ≥ 1 /hour, ≥ 5 /hour, ≥ 10 /hour, from external Masimo oximetry

	OAH ≥ 1 /hour (all OSA)		OAH ≥ 5 /hour (moderate OSA)		OAH ≥ 10 /hour (moderate and severe OSA)		OAH ≥ 10 /hour (severe OSA)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
ODI3 $\geq$ (events/hour)								
16	69.1% (63.1 to 74.6) (183/265)	59.8% (50.6 to 68.6) (73/122)	82.4% (69.1 to 91.6) (42/51)	49.0% (43.0 to 54.9) (140/286)	85.1% (76.7 to 91.4) (86/101)	49.0% (43.0 to 54.9) (140/286)	88.0% (75.7 to 95.5) (44/50)	44.2% (38.8 to 49.7) (149/337)
17	64.5% (58.4 to 70.3) (171/265)	66.4% (57.3 to 74.7) (81/122)	76.5% (62.5 to 87.2) (39/51)	54.9% (48.9 to 60.8) (157/286)	82.2% (73.3 to 89.1) (83/101)	54.9% (48.9 to 60.8) (157/286)	88.0% (75.7 to 95.5) (44/50)	50.1% (44.7 to 55.6) (169/337)
18	62.6% (56.5 to 68.5) (166/265)	70.5% (61.6 to 78.4) (86/122)	76.5% (62.5 to 87.2) (39/51)	58.4% (52.4 to 64.2) (167/286)	82.2% (73.3 to 89.1) (83/101)	58.4% (52.4 to 64.2) (167/286)	88.0% (75.7 to 95.5) (44/50)	53.1% (47.6 to 58.5) (179/337)
19	59.2% (53.1 to 65.2) (157/265)	74.6% (65.9 to 82.0) (91/122)	74.5% (60.4 to 85.7) (38/51)	62.6% (56.7 to 68.2) (179/286)	80.2% (71.1 to 87.5) (81/101)	62.6% (56.7 to 68.2) (179/286)	86.0% (73.3 to 94.2) (43/50)	57.0% (51.5 to 62.3) (192/337)
20	52.5% (46.3 to 58.6) (139/265)	77.0% (68.6 to 84.2) (94/122)	74.5% (60.4 to 85.7) (38/51)	69.6% (63.9 to 74.9) (199/286)	79.2% (70.0 to 86.6) (80/101)	69.6% (63.9 to 74.9) (199/286)	84.0% (70.9 to 92.8) (42/50)	62.9% (57.5 to 68.1) (212/337)
21	47.5% (41.4 to 53.8) (126/265)	82.0% (74.0 to 88.3) (100/122)	66.7% (52.1 to 79.2) (34/51)	74.5% (69.0 to 79.4) (213/286)	74.3% (64.6 to 82.4) (75/101)	74.5% (69.0 to 79.4) (213/286)	82.0% (68.6 to 91.4) (41/50)	68.2% (63.0 to 73.2) (230/337)
22	44.2% (38.1 to 50.4) (117/265)	83.6% (76.0 to 89.8) (102/122)	62.7% (48.1 to 75.9) (32/51)	77.6% (72.3 to 82.3) (222/286)	72.3% (62.5 to 80.7) (73/101)	77.6% (72.3 to 82.3) (222/286)	82.0% (68.6 to 91.4) (41/50)	71.5% (66.4 to 76.3) (241/337)
23	42.3% (36.2 to 48.5) (112/265)	86.0% (78.6 to 91.7) (105/122)	58.8% (44.2 to 72.4) (30/51)	79.7% (74.6 to 84.2) (228/286)	70.3% (60.4 to 79.0) (71/101)	79.7% (74.6 to 84.2) (228/286)	82.0% (68.6 to 91.4) (41/50)	73.9% (68.9 to 78.5) (249/337)
24	40.8% (34.8 to 46.9) (108/265)	86.1% (78.6 to 91.7) (105/122)	54.9% (40.3 to 68.9) (28/51)	80.1% (75.0 to 84.5) (229/286)	67.3% (57.3 to 76.3) (68/101)	80.1% (75.0 to 84.5) (229/286)	80.0% (66.3 to 90.0) (40/50)	74.8% (69.8 to 79.3) (252/337)
25	37.7% (31.9 to 43.9) (100/265)	87.7% (80.5 to 93.0) (107/122)	49.0% (34.8 to 63.4) (25/51)	81.8% (76.9 to 86.1) (234/286)	62.4% (52.2 to 71.8) (63/101)	81.8% (76.9 to 86.1) (234/286)	76.0% (61.8 to 86.9) (38/50)	77.2% (72.3 to 81.5) (260/337)
26	35.5% (29.7 to 41.6) (94/265)	88.5% (81.5 to 93.6) (108/122)	47.1% (32.9 to 61.5) (24/51)	83.2% (78.4 to 87.4) (238/286)	59.4% (49.2 to 69.1) (60/101)	83.2% (78.4 to 87.4) (238/286)	72.0% (57.5 to 83.8) (36/50)	78.6% (73.9 to 82.9) (265/337)
ODI4 $\geq$ (events/hour)								
5	84.5% (79.6 to 88.7) (224/265)	35.2% (26.8 to 44.4) (43/122)	90.2% (78.6 to 96.7) (46/51)	26.6% (21.6 to 32.1) (76/286)	94.9% (88.5 to 98.3) (93/98)	26.6% (21.6 to 32.1) (76/286)	94.0% (83.5 to 98.8) (47/50)	24.0% (19.6 to 29.0) (81/337)
6	78.1% (72.7 to 82.9) (207/265)	46.7% (37.6 to 56.0) (57/122)	90.2% (78.6 to 96.7) (46/51)	37.4% (31.8 to 43.3) (107/286)	92.1% (85.0 to 96.5) (93/101)	37.4% (31.8 to 43.3) (107/286)	94% (83.5 to 98.8) (47/50)	33.2% (28.2 to 38.5) (112/337)
7	70.6% (64.7 to 76.0) (187/265)	57.4% (48.1 to 66.3) (70/122)	84.3% (71.4 to 93.0) (43/51)	47.9% (42.0 to 53.9) (137/286)	89.1% (81.4 to 94.4) (90/101)	47.9% (42.0 to 53.9) (137/286)	94.0% (83.5 to 98.8) (47/50)	43.0% (37.7 to 48.5) (145/337)
8	63.8% (57.7 to 69.6) (169/265)	71.3% (62.4 to 79.1) (87/122)	80.4% (66.9 to 90.2) (41/51)	59.1% (53.2 to 64.8) (169/286)	86.1% (77.8 to 92.2) (87/101)	59.1% (53.2 to 64.8) (169/286)	92.0% (80.8 to 97.8) (46/50)	53.1% (47.6 to 58.5) (179/92)
9	53.2% (47.0 to 59.3) (141/265)	78.7% (70.4 to 85.6) (96/122)	74.5% (60.4 to 85.7) (38/51)	69.6% (63.9 to 74.9) (199/286)	79.2% (70.0 to 86.6) (80/101)	69.6% (63.9 to 74.9) (199/286)	84.0% (70.9 to 92.8) (42/50)	62.9% (57.5 to 68.1) (212/337)
10	47.5% (41.4 to 53.8) (126/265)	82.0% (74.0 to 88.3) (100/122)	68.6% (54.1 to 80.9) (35/51)	75.2% (69.8 to 80.1) (215/286)	76.2% (66.7 to 84.1) (77/101)	75.2% (69.8 to 80.1) (215/286)	84.0% (70.9 to 92.8) (42/50)	68.5% (63.3 to 73.5) (231/337)
11	41.9% (35.9 to 48.1) (111/265)	86.1% (78.6 to 91.7) (105/122)	60.8% (46.1 to 74.2) (31/51)	79.7% (74.6 to 84.2) (228/286)	69.3% (59.3 to 78.1) (70/101)	79.7% (74.6 to 84.2) (228/286)	78.0% (64.0 to 88.5) (39/50)	73.6% (68.5 to 78.2) (248/337)
12	37.0% (31.2 to 43.1) (98/265)	86.9% (79.6 to 92.3) (106/122)	56.9% (42.3 to 70.7) (29/51)	83.2% (78.4 to 87.4) (238/286)	65.3% (55.2 to 74.5) (66/101)	83.2% (78.4 to 87.4) (238/286)	74.0% (59.7 to 85.4) (37/50)	77.2% (72.3 to 81.5) (260/337)
13	34.3% (28.6 to 40.4) (91/265)	91.8% (85.4 to 96.0) (112/122)	52.9% (38.5 to 67.1) (27/61)	86.7% (82.2 to 90.4) (248/286)	62.4% (52.2 to 71.8) (63/101)	86.7% (82.2 to 90.4) (248/286)	72.0% (57.5 to 83.8) (36/50)	80.7% (76.1 to 84.8) (272/337)
14	34.3% (26.5 to 38.1) (91/265)	91.8% (86.5 to 96.6) (112/122)	52.9% (36.6 to 65.3) (27/51)	86.7% (84.2 to 91.9) (248/286)	60.4% (50.17 to 70.0) (61/101)	86.5% (84.2 to 91.9) (253/286)	70.0% (55.4 to 82.1) (35/50)	82.5% (78.0 to 86.4) (278/337)

Continued

Table 3 Continued

OAHI ≥ 1 /hour (all OSA)		OAHI $\geq 5 < 10$ /hour (moderate OSA)		OAHI ≥ 5 /hour (moderate and severe OSA)		OAHI ≥ 10 /hour (severe OSA)	
Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)

Values with the optimum sensitivity and specificity are highlighted in bold.
 OAHI, Obstructive Apnoea–Hypopnoea Index; OD13, 3% Oxygen Desaturation Index; OD14, 4% Oxygen Desaturation Index.

Table 4 Sensitivity and specificity values for a range of D12 cut-off values for predicting OAHI $\geq 5 < 10$ /hour, ≥ 5 /hour, ≥ 10 /hour

OAHI $\geq 5 < 10$ /hour (moderate OSA)		OAHI ≥ 5 /hour (moderate and severe OSA)		OAHI ≥ 10 /hour (severe OSA)	
D12 $\geq$	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Specificity (95% CI)
0.55	72.6% (58.3 to 84.1) (37/51)	67.8% (62.1 to 73.2) (194/286)	79.2% (70.0 to 86.6) (80/101)	67.5% (62.1 to 73.2) (194/286)	86.0% (73.3 to 94.2) (43/50)
0.56	70.6% (56.2 to 82.5) (36/51)	70.3% (201/286)	78.2% (79/101)	70.3% (201/286)	86.0% (43/50)
0.57	70.6% (56.2 to 82.5) (36/51)	71.7% (64.6 to 75.5) (205/286)	78.2% (68.9 to 85.8) (79/101)	71.7% (64.6 to 75.5) (205/286)	86.0% (73.3 to 94.2) (43/50)
0.58	68.6% (54.1 to 80.9) (35/51)	73.4% (67.9 to 78.5) (210/286)	75.3% (65.7 to 83.3) (76/101)	73.4% (67.9 to 78.5) (210/286)	82.0% (68.6 to 91.4) (41/50)
0.59	66.7% (52.1 to 79.2) (34/51)	76.9% (71.6 to 81.7) (220/286)	74.2% (64.6 to 82.4) (75/101)	76.9% (71.6 to 81.7) (220/286)	82.0% (68.6 to 91.4) (41/50)
0.60	64.7% (50.1 to 77.6) (33/51)	79.4% (74.2 to 83.9) (227/286)	72.3% (62.5 to 80.7) (72/101)	79.4% (74.2 to 83.9) (227/286)	80.0% (66.3 to 90.0) (40/50)
0.61	56.9% (42.3 to 70.7) (29/51)	82.5% (77.6 to 86.7) (236/286)	68.3% (58.3 to 77.2) (69/101)	82.5% (77.6 to 86.7) (236/286)	80.0% (66.3 to 90.0) (40/50)
0.62	56.9% (42.3 to 70.7) (29/51)	83.2% (78.4 to 87.4) (238/286)	68.3% (58.3 to 77.2) (69/101)	83.2% (78.4 to 87.4) (238/286)	80.0% (66.3 to 90.0) (40/50)
0.63	51.0% (36.6 to 65.3) (26/51)	84.3% (79.5 to 88.3) (241/286)	63.4% (53.2 to 72.7) (64/101)	84.3% (79.5 to 88.3) (241/286)	76.0% (61.8 to 86.9) (38/50)
0.64	51.0% (36.6 to 65.3) (26/51)	85.0% (80.3 to 88.9) (243/286)	62.4% (52.2 to 71.8) (63/101)	85.0% (80.3 to 88.9) (243/286)	74.0% (59.7 to 85.4) (37/50)
0.65	49.0% (34.8 to 63.4) (25/51)	87.1% (82.6 to 90.7) (249/286)	60.4% (50.2 to 70.0) (61/101)	87.1% (82.6 to 90.7) (249/286)	72.0% (57.5 to 83.8) (36/50)

Values with the optimum sensitivity and specificity are highlighted in bold.
 D12, Delta 12 s Index; OAHI, Obstructive Apnoea–Hypopnoea Index.

desaturation may arise from other factors such as muscular weakness, inadequate central respiratory control, closure of lower airways or less compliant ribcage.³⁷ Snoring in these situations may be an epiphenomenon and a consequence of multiple contributing factors. A dichotomous scoring system fails to delineate the underlying pathophysiology.

We did not collect information on ethnicity; however, we acknowledge NPO has potential to overestimate SpO₂ in black compared with other races, which is accentuated as SpO₂ decreases.³⁸ The use of DS-specific growth charts could allow for separate analyses for individuals with obesity, and subgroup analyses could include treatment intervention.

AASM guidelines were used for scoring across all centres; however, different scorers in each site may account for differences. A mixture of home and sleep lab studies was included, which represents current practice. Data were collected retrospectively, and investigators analysing the data were not blinded.

The findings of this study can only be applied to data obtained from TCM Masimo, Masimo oximeters and analysed using Visi-Download software, which is a commonly used software in the UK. Further analyses could examine the predictive potential of combining oximetry parameters such as ODI3/ODI4 and D12.

Summary

This study provides data on the diagnostic accuracy of stand-alone NPO to predict OSA in children with DS. Sensitivity and specificity values for a range of cut-off values for NPO indices have been provided. Raised ODI3 and ODI4 have a low sensitivity and moderate specificity for detecting mild OSA in children with DS and a moderate sensitivity and specificity for predicting moderate and severe OSA. The poor predictive performance of oximetry likely reflects the multifactorial nature of SDB in children with DS. Oximetry alone does not provide a reliable diagnostic tool for evaluating OSA in children with DS; therefore, we recommend CRP/PSG should be performed. Further studies should reassess if current scoring systems for OSA adequately capture the complexity of SDB in the population with DS.

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Contributors Study design and conception: HJE, MS, AS and RoL. Data acquisition: EB, ReL, TLW, HV, MA and JJ. Data analysis and interpretation: HV, HJE, MS, EB, PB, DY and RoL. Drafting of the manuscript: HV, HJE, MS and RoL. All authors reviewed/critiqued the manuscript and approved the final version. RoL is responsible for the overall content of the work as guarantor.

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Avaliação do impacto de um modelo de “parent champion” nas taxas de hospitalização por bronquiolite: um estudo de diferença-em-diferenças

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RESUMO

Contexto A bronquiolite e os seus desfechos têm determinantes socioeconômicos marcados. Em Liverpool, uma cidade com elevados níveis de privação e taxas de hospitalização por bronquiolite acima da média, foi implementada a intervenção Respiratory Parent Champions in the Community. Os Parent Champions receberam formação de pediatras e organizações comunitárias e prestaram apoio entre pares e educação sobre bronquiolite e fatores de risco modificáveis nos centros infantis locais.

Métodos Utilizando registos eletrônicos de saúde anonimizados e ligados de crianças nascidas em Cheshire e Merseyside entre 2016–2023, aplicaram-se métodos de diferença-em-diferenças ponderados por probabilidade inversa de tratamento para comparar a variação mensal nas admissões por bronquiolite após a introdução da intervenção, entre o grupo de intervenção e crianças residentes noutros wards da região que não receberam a intervenção, ajustando para diferenças populacionais.

Resultados Oito Respiratory Parent Champions realizaram 18 050 contactos familiares em 16 wards de Liverpool ao longo de 24 meses. A intervenção associou-se a uma redução de 128 admissões de emergência por 100 000 crianças por mês (IC 95% 43 a 214; $p < 0,01$), comparativamente ao grupo sem intervenção. Isto corresponde a uma redução de 23,8% nas admissões, ou 107 admissões evitadas por ano (IC 95% 36 a 179) no grupo de intervenção. A estimativa preliminar do custo anual das admissões evitadas foi de £219 243, com uma poupança líquida de £101 283 por ano (intervalo –£44 196 a +£248 811), após contabilizar o custo de contratação dos Parent Champions.

Interpretação Este estudo demonstra o potencial de uma intervenção comunitária dirigida e co-produzida para reduzir a carga sobre os serviços de saúde e mitigar desigualdades socioeconômicas nas doenças respiratórias infantis.

INTRODUCTION

Early childhood exposures and illness are increasingly recognised as important determinants of long-term respiratory health, particularly among those experiencing socioeconomic disadvantage.^{1,2} These early-life inequalities contribute to persistent health disparities and represent a significant burden for healthcare systems. In the UK, where child health outcomes are poorer than in many comparable countries,³ inequality in hospitalisation across the life course costs the National Health Service (NHS) approximately £4.8 billion each year.⁴

One common and clinically significant illness in early childhood is bronchiolitis, a viral respiratory infection in infancy which is commonly caused by respiratory syncytial virus (RSV) and can lead to lasting damage to the developing lungs.⁵ In England, one in three infants will develop

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► We searched PubMed, Web of Science and Google Scholar for the following search terms: ‘peer support’ AND “bronchiolitis”, “bronchiolitis” AND “inequalities”, peer support AND (“child health” OR “infant health”) and (“place based” OR “community initiative”) AND (“child health” OR “infant health”). We searched for all article types published in the years 2000–2024 with no language restrictions. We also searched reference lists of identified articles and Google and UK government websites for UK health policy reports and public health data. We found no previous studies on peer support and bronchiolitis outcomes. However, there is evidence demonstrating the impact of peer support for other preventive measures, including breastfeeding and smoking cessation, and studies highlighting the benefits of peer support on self-reported well-being for long-term conditions, including HIV and mental health disorders. Most studies assessing the impact of place-based or community-level interventions on child health and health inequalities were set in low- and middle-income countries. Systematic reviews collating data for place-based interventions for young children in high-income countries found insufficient evidence for place-based interventions due to the heterogeneity of interventions and mixed outcomes for child health.

WHAT THIS STUDY ADDS

► This difference-in-differences study evaluated the impact of a Respiratory Parent Champions programme on monthly bronchiolitis hospitalisation rates for intervention wards, finding that it led to a 23.8% reduction in monthly bronchiolitis hospitalisation rates. This reduction occurred in socioeconomically deprived areas at a time when inequalities in health were widening across the UK due to the effects of the COVID-19 pandemic and the subsequent cost-of-living crisis. Our findings contribute to evidence that

place-based and peer-led interventions can improve child health outcomes in deprived areas.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This study demonstrates the impact of community-based, co-produced interventions such as Respiratory Parent Champions in the Community in reducing infant emergency respiratory admissions and health service pressures. This is, to our knowledge, the first evaluation of a community peer support intervention aimed at reducing bronchiolitis hospitalisations, using causal methods. Similar approaches should be considered in comparable populations, alongside research to explore long-term impacts and cost-effectiveness to inform broader policy implementation.

bronchiolitis,⁶ with well-described socioeconomic disparities in both outcomes and risk factors.^{7 8} Using an adapted Diderichsen model,⁹ these disparities can be understood as pathways linking broader social determinants, such as political and community structures and living conditions, to health outcomes. Risk factors for bronchiolitis hospitalisation, including premature birth, formula feeding and exposure to adverse environments,^{5 8 10–12} illustrate how these pathways contribute to inequalities (see figure 1).

Bronchiolitis hospitalisation rates had been rising steadily until the COVID-19 pandemic in 2020,¹³ when they sharply declined.¹⁴ Following the easing of pandemic restrictions in 2021–2022, many countries, including England, experienced a ‘viral surge’ marked by atypical seasonality and increased healthcare demand for bronchiolitis and related illnesses.^{14–16} This was expected to disproportionately affect children from the most socioeconomically deprived backgrounds, given the exacerbation of pre-existing social inequalities during the cost-of-living crisis that emerged in the later stages of the pandemic.

The adapted Diderichsen model in figure 1 can also be used to identify key points for intervention to mitigate the risk of widening

inequalities in bronchiolitis outcomes. The model emphasises the importance of addressing broader structural drivers of social stratification, as well as differential exposures and vulnerabilities at individual and community levels.⁹ Historical place-based initiatives like Sure Start¹⁷ exemplify efforts to address these determinants. The programme successfully reduced inequalities in infant mortality and child development, although results for service utilisation and other health outcomes were mixed.^{17–22} Currently, local authority-funded children’s centres serve as community hubs offering free services to families with children under five. Targeted peer support has also been effective in addressing differential exposures, vulnerabilities and consequences for chronic conditions^{23–25} and behaviours such as smoking cessation²⁶ and breast-feeding.²⁷ However, to our knowledge, such strategies have not been evaluated for their potential to reduce inequalities in bronchiolitis hospitalisation.

OBJECTIVES

Liverpool experiences high levels of deprivation²⁸ and persistently higher than average rates of bronchiolitis hospitalisations and associated risk factors.¹³ In anticipation of a postpandemic viral surge, we implemented a parent-led intervention embedded within the existing children’s centre infrastructure. The Respiratory Parent Champions in the Community programme aimed to empower parents with knowledge about child respiratory health, rapidly and at scale, and was well received by parents and community stakeholders.²⁹ This study evaluates whether the programme reduced emergency hospitalisation rates for bronchiolitis and related illnesses.

Intervention

The Respiratory Parent Champions initiative employed local mothers to provide advice and peer support aimed at improving infant lung health.^{29 16} electoral wards were selected as intervention areas based on hospital utilisation and socioeconomic geographic data (figure 2). Wards were also used as the unit of analysis, as smaller geographic areas could not be easily aligned with children’s centre catchment populations. To minimise problems of geographical boundary leakage, all data were analysed at the ward level.

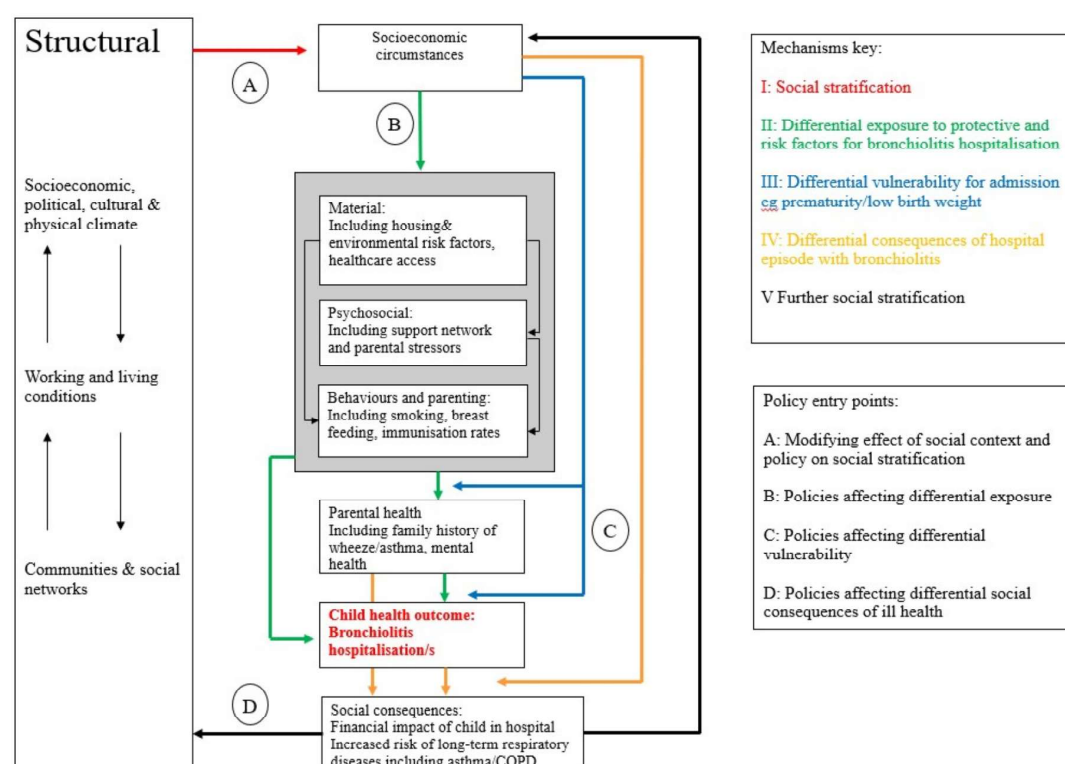


Figure 1 Adapted Diderichsen conceptual model demonstrating pathways to inequalities in bronchiolitis admission.⁹ COPD, chronic obstructive pulmonary disease.

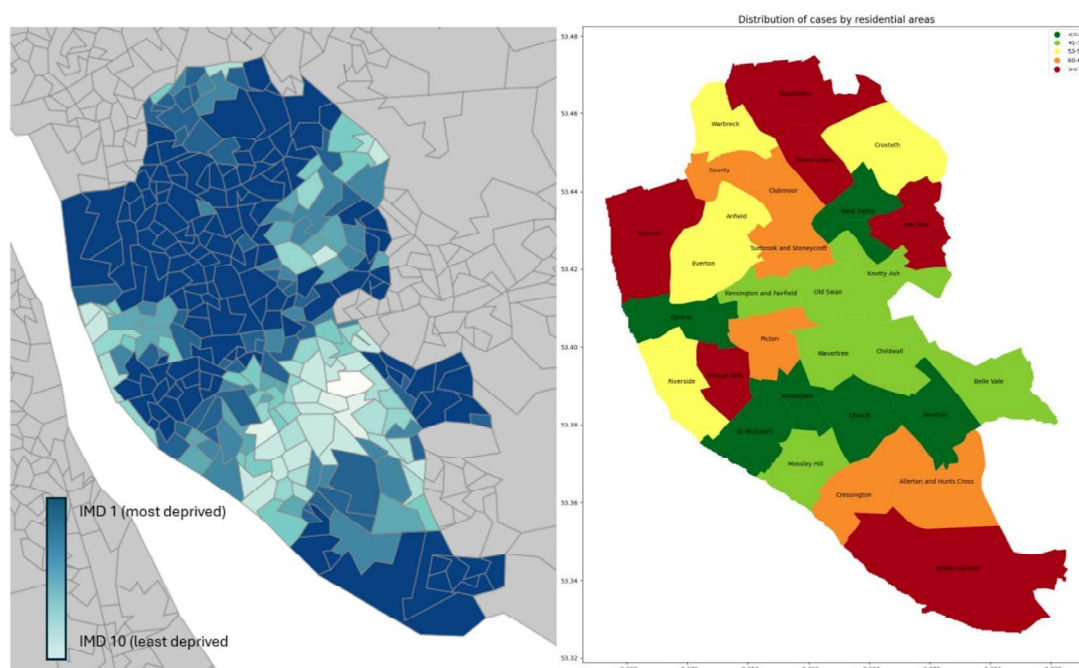


Figure 2 (A) Map of Index of Multiple Deprivation across Liverpool from the Ministry of Housing, Communities and Local Government and (B) Heat map for bronchiolitis hospitalisations 2017–2019 (taken preintervention and pre-COVID).

The intervention aimed to address key pathways linking social determinants to bronchiolitis outcomes, as outlined in the adapted Diderichsen model. It targeted Pathway I by addressing social stratification, supporting families to access poverty reduction schemes such as the Citizen's Advice on Prescription programme³⁰ and providing monetary vouchers for essentials like fuel and food. It also addressed Pathway II, reducing differential exposure to risk through education, peer support and social prescribing. This included promoting breastfeeding, smoking cessation and immunisation uptake, offering psychosocial support, and signposting families to housing assistance and healthcare services. Parent Champions also worked to raise community awareness of bronchiolitis, providing education on prevention, self-management and navigating healthcare services (see the TIDieR tool in online supplemental file 2 for further details).

Eight Parent Champions—mothers reflective of the local community (50% non-white British; 50% multilingual)—were recruited from among recent children's centre service users and employed by Alder Hey Children's Hospital on NHS Band 3 contracts. The intervention launched in January 2022.

Parent Champions deliver the intervention through existing children's centre infrastructure, offering individual and group support via home visits, children's centre activity groups and clinics, and community outreach events. The programme and accompanying educational materials were co-produced by Parent Champions, clinicians and children's centre staff. Parent Champions were trained, in response to their self-identified needs, by healthcare professionals and community organisations, including breastfeeding charities, advocacy and fire services.

Design

The evaluation of the Respiratory Parent Champions programme was conducted as an opportunistic quasi-experimental study, using routinely collected data to generate timely insights.

Data sources

A population cohort for healthcare utilisation was built in the Combined Intelligence for Population Health Action (CIPHA) Secure Data Environment, now known as Data into Action (<https://dataintoaction.cheshireandmerseyside.nhs.uk>). CIPHA holds near real-time, pseudonymised general practitioner (GP), inpatient, outpatient, community and emergency care data for the Cheshire and Merseyside Integrated Care System (an NHS region comprising 2.6 million of the general population) from 2010 onwards for the purposes of care, planning and research.

Perinatal Hospital Episode Statistics (HES) data were used to identify children born between 2016 and 2023 in Cheshire and Merseyside. Records were linked with HES data for emergency hospitalisations (inpatient stays) between January 2018 and December 2023, as well as GP and community service datasets for relevant independent variables. As the cohort was defined through HES, children without a recorded perinatal hospital episode were excluded from the analysis.

Intervention cohort

The intervention cohort was defined as children aged 0–24 months living in the 16 intervention wards during the intervention period (January 2022–December 2023). The control cohort was defined as children aged 0–24 months living in the other 220 non-intervention wards across Cheshire and Merseyside.

Outcome measures

Our primary outcome was the monthly rate of emergency hospitalisation for bronchiolitis and bronchiolitis-type illnesses. Monthly data intervals were chosen to capture seasonal variation as well as improve statistical power for analysis. International Classification of Diseases 10th edition (ICD-10) codes for acute bronchiolitis, viral lower respiratory tract infection and viral wheeze were chosen for our health outcomes (online supplemental file 1). We included ICD-10 codes beyond 'acute bronchiolitis' to recognise common diagnostic uncertainties, particularly between bronchiolitis and viral wheeze for infants aged 1–2 years.

Statistical analysis

To assess the average treatment effect on the treated (ATT) for infants living in our intervention wards, we used a difference-in-differences model with inverse probability of treatment weighting.

Difference-in-differences (DID)

The DID approach estimates the causal effect of an intervention by comparing the change in outcomes in the intervention cohort relative to the change in the control cohort. By using a comparison both within and between groups, DID isolates the intervention effect by accounting for both trends over time that affect both groups (eg, the COVID-19 pandemic) and time-invariant differences between groups that could otherwise confound findings.³¹

The parallel trends assumption (PTA), which is a fundamental assumption for DID analyses, was that the difference in rates of hospitalisation between our intervention and control cohorts would have remained constant without the intervention.

Table 1 Population demographics for Cheshire and Merseyside infants

	Intervention areas	Non-intervention areas	P value*
Group	n=25 565	n=179 413	
Sex			
Male	51%	51%	0.2
Female	49%	49%	
Deprivation			
Index of Multiple Deprivation Deciles†	1 (1, 1)	4 (2, 8)	<0.001
Ethnicity			
White British	52%	69%	<0.001
Prematurity			
Premature (<37 weeks)	8.40%	7.60%	<0.001

* χ^2 test; Mann-Whitney test
†%; median (quartiles 1 and 3).

We used linear regression models within a DID framework to evaluate the intervention's impact on monthly bronchiolitis admission rates. The regression model formula for our analysis was as follows: $Y_{it} = \beta_0 + \beta_1 \text{time_period}_t + \beta_2 \text{intervention_status}_i + \beta_3 (\text{time_period}_t \times \text{intervention_status}_i) + \varepsilon_{it}$, where Y_{it} is the observed value (admission rate) for unit i at time t , β_3 captures the ATT, and ε_{it} represents unexplained variability. Clustered SEs accounted for within-group/individual and time-related correlations.

Inverse probability of treatment weighting (IPTW)

IPTW was used to adjust for potential confounding by balancing observed differences between the two groups that could have influenced admission trends in the absence of the intervention. As intervention exposure was assigned by electoral ward, IPTWs were also calculated at the ward level. Propensity scores were derived from a logistic regression predicting the probability of being in an intervention ward, using predictors of preintervention hospitalisation trends, percentage of white British ethnicity and population characteristics associated with bronchiolitis admissions (Index of Multiple Deprivation score, percentage of premature births at <37 weeks gestation; online supplemental file 1). These scores were used to calculate IPTWs for the control cohort, which were incorporated into the DID model.³² By balancing these covariates between intervention and control groups, this approach reduces bias from differential pre-intervention admission trends related to these factors.

We conducted sensitivity analyses to evaluate the robustness of our model choice and data input selection (online supplemental file 1). For model choice, we ran two further DID models: one without IPTW and another using a Poisson regression, comparing the marginal effects to those of the linear regression outputs. In our main analysis, we used patient-level data to capture variability and heterogeneity across individuals within cohorts and used the full dataset to maximise statistical power and precision. To assess sensitivity to data granularity, we reran the model using aggregated data. Robustness checks included fidelity to the PTA by (1) visual inspection and (2) statistical analysis for trends in differences of hospitalisation rates between the two groups in the preintervention period (online supplemental file 1). Visual trends during the COVID-19 pandemic confirmed that our data do not violate the common shocks assumption. Results are presented as main effects with 95% CI unless otherwise stated. All statistical analyses were computed using R V.4.2.1.

Preliminary cost analysis

As our admission data were not disaggregated by severity, we calculated a weighted mean unit cost using national data that capture the distribution of admission severity for each ICD-10 diagnostic code. This method ensures that cost estimates reflect national variation in case complexity and length of stay, providing a representative estimate of unit costs across the country.

Each ICD-10 code corresponds to multiple currency codes within the NHS National Schedule of Reference Costs, accounting for differences in complexity and duration of hospital stays for the same diagnosis.³³ We calculated the weighted mean unit cost by aggregating costs across all relevant currency codes. For each currency code, we recorded the number of finished consultant episodes (FCEs) and the national average unit cost. The total cost per code was obtained by multiplying the number of FCEs by the unit cost. Summing these total costs across all codes and dividing by the total number of FCEs yielded a weighted mean unit cost.

This analysis is intended as a pragmatic, indicative assessment of potential cost implications for a hospital employing the Parent Champions, rather than a complete health economic evaluation. Our aim was to provide context on the possible financial impact from the provider's perspective, based on estimated reductions in admissions. Net annual savings were calculated as:

Net annual savings = (weighted mean cost per admission × estimated reduction in admissions) – yearly cost of employing Parent Champions

RESULTS

Our intervention cohort was significantly more socioeconomically deprived and ethnically diverse than the Cheshire and Merseyside

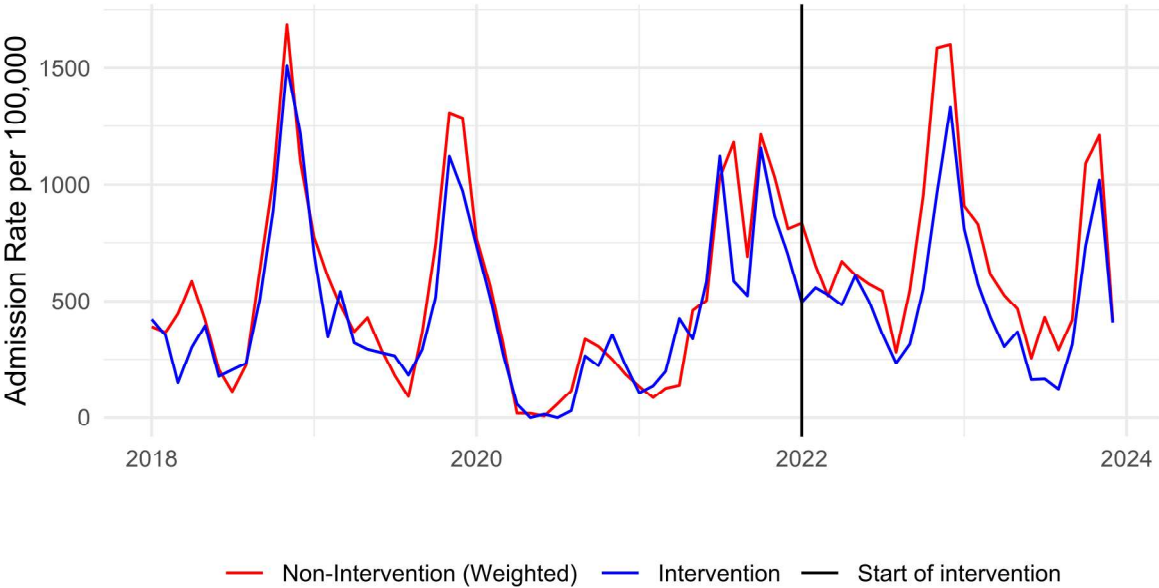


Figure 3 Monthly hospitalisation rates for bronchiolitis and bronchiolitis-type illnesses in toddlers aged 0–2 years in intervention and inverse probability weighting-adjusted non-intervention cohorts in Cheshire and Merseyside, January 2018–December 2023

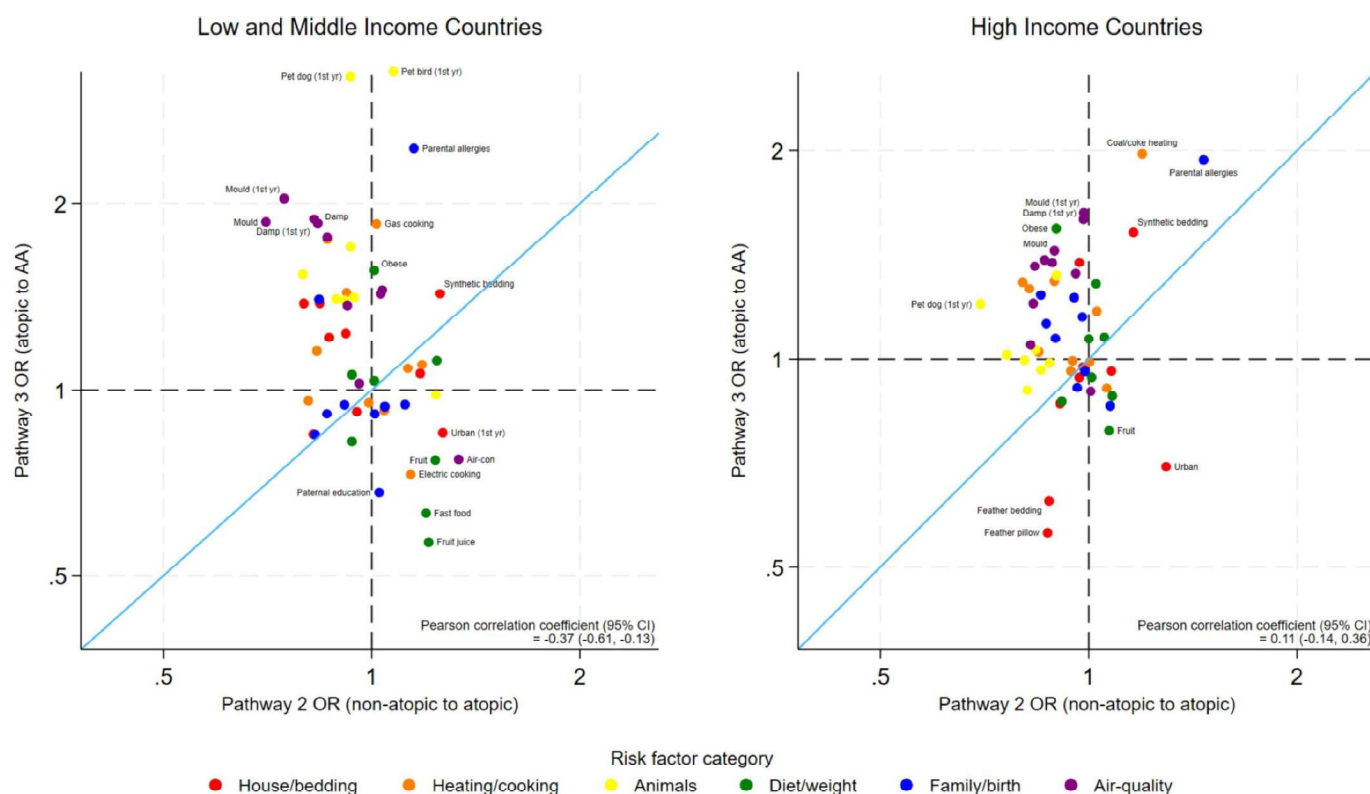


Figure 5 Estimated ORs of risk factors for asthma (in atopic individuals) compared with atopy (pathway 3 vs pathway 2) stratified by country affluence. Axes are shown on the natural log scale. AA, atopic asthma.

average, with a higher rate of prematurity. However, when weighting for IPT, these differences were accounted for (table 1 and online supplemental file 1). Between January 2022 and the end of December 2023, the Parent Champions had 18 050 contacts with families in these wards through direct outreach or Children's Centre sessions.

Comparison of bronchiolitis hospitalisation rates

Monthly hospitalisation rates for our intervention cohort and IPTW-adjusted rates for the non-intervention cohort between January 2018 and December 2023 are shown in figure 3. There were a total of 21 903 hospitalisations for bronchiolitis and related illnesses across Cheshire and Merseyside, with 7.5% of children having ≥ 1 hospitalisation in the first 2 years of life. The mean age at hospitalisation was 41 weeks, and the most common age at hospitalisation was 8 weeks. The average monthly rate of hospitalisation for both groups was 579 per 100 000, with expected seasonal variation. Hospitalisation rates dropped to 11 per 100 000 in June 2020 after the introduction of pandemic restrictions on mixing, with a summer and winter peak in 2021 before returning to prepandemic patterns in 2022. DID analysis for hospitalisation rates in the preintervention period showed no significant difference in trend between our intervention and non-intervention cohorts (online supplemental file 1). From the introduction of Parent Champions in January 2022, the intervention cohort had persistently lower monthly hospitalisation rates, with an average monthly hospitalisation of 524 per 100 000 (95% CI 473 to 574) in comparison to an average of 691 per 100 000 (95% CI 668 to 714) in the non-intervention wards.

Our IPT-weighted DID model demonstrated a reduction in bronchiolitis hospitalisations following the introduction of the intervention, relative to the change in the non-intervention cohort. The interaction coefficient for intervention $\times$ time, representing the ATT, showed a reduction in hospitalisation rates of 128 per 100 000 (95% CI -43 to -214, $p < 0.005$). SEs were clustered by individuals and date.

To aid interpretability, this result can be presented as a 23.8% (95% CI 8% to 39.9%) change relative to the average preintervention monthly rates in the treatment group (537 per 100 000). The baseline rate excludes the COVID-19 period (from February 2020 onwards), as including this period would artificially lower the mean

and inflate the estimated per cent reduction. This is equivalent to a total of 107 (95% CI 36 to 179) fewer admissions per year than would have otherwise been the case in the absence of the intervention. Additional analyses using aggregated data, unweighted data and sensitivity tests employing Poisson regression yielded similar results (online supplemental file 1).

Cost analysis

The weighted mean unit cost as per our ICD-10 codes was £2049. Estimated net annual savings were calculated by multiplying the DID-derived estimate of admissions avoided by the weighted mean unit cost and subtracting the annual cost of employing the parent champions.

Based on an estimated 107 (95% CI 36 to 179) admissions prevented per year, the gross savings total £219 243 (£73 764–£366 771). The cost of running the model was £117 960 per year. After accounting for this, the average estimated net yearly savings to the NHS amounts to £101 283 (–£44 196 to +£248 811).

DISCUSSION

Our study shows that the Respiratory Parent Champions in the Community programme was associated with a 23.8% reduction in monthly bronchiolitis hospitalisation rates in the target population. This reduction occurred in socioeconomically deprived areas of the region at a time when (1) health inequalities were widening across the UK following the COVID-19 pandemic and cost-of-living crisis and (2) national rates of bronchiolitis admissions were elevated compared with prepandemic levels.³⁴

Our study demonstrates the impact of a place-based, co-produced preventive intervention—targeting the pathways to early childhood respiratory health inequalities identified in the adapted Diderichsen model in figure 1—in reducing hospitalisation rates for bronchiolitis. This is, to our knowledge, the first study showing a multifaceted (and multiply targeted) peer support correlating to reduced hospitalisation rates in an infant population. It is, however, in keeping with previous work demonstrating the effectiveness of peer support for chronic conditions.^{18 19} Our findings also demonstrate a rapid impact on healthcare utilisation when deploying a community-based initiative, in comparison to previous evidence which has yielded mixed

results for the impact of such interventions in high-income countries.^{24–26} Similar programmes could be adapted and implemented in other settings by leveraging existing community services that influence the social determinants of health and through meaningful co-production with local communities.

Given the quasi-experimental design of this study, there are inherent limitations to causal inference. However, while the possibility of unmeasured individual-level confounding cannot be fully excluded, we employed IPTW to adjust for population-level differences, particularly in socioeconomic deprivation and preintervention hospitalisation trends. Additionally, the DID approach mitigates bias from time-invariant confounders and from external shocks or trends that would have similarly affected both groups. At the small-area (electoral ward) level, there were no concurrent interventions or events that could explain the observed reductions in admission rates, and sensitivity analyses yielded consistent results.

Considering financial constraints in the NHS, a complete health economics analysis is important for an accurate assessment of cost-effectiveness. We adopted a pragmatic approach to provide a preliminary cost analysis, guided by available data, rather than conducting a full economic evaluation. Our analysis provides indicative insight but excludes potential benefits such as reductions in other health-care utilisation (eg, emergency department attendances), parental work absences, long-term health outcomes and social return on investment. Longitudinal data would enable evaluation of the intervention's impact on long-term respiratory health outcomes, particularly in the context of the recent introduction of the maternal RSV vaccine. Likewise, we did not account for all costs associated with the programme, such as increased costs to community services or initial materials. No additional training costs were included; Parent Champions' time was accounted for as an ongoing employment cost, reflecting 'on the job' training, while training provided by healthcare professionals and community organisations occurred within existing structures without charge. We acknowledge that these assumptions may not hold in other regions or settings.

CONCLUSION

In a context where health inequalities and system pressures from acute respiratory illnesses represent major challenges for the NHS, our findings suggest that community-based interventions co-produced between the NHS and local community structures can reduce paediatric healthcare utilisation and alleviate service pressures among targeted populations. This approach warrants consideration in policy strategies addressing winter pressures and health inequalities. While the intervention was delivered through existing children's centre infrastructure, highlighting the importance of such place-based assets, its core components could be adapted for scale in areas with equivalent community platforms. Further research is needed to assess long-term impacts on respiratory health, and data-driven implementation can support evaluations of cost-effectiveness and guide resource allocation. If replicated elsewhere, maintaining co-production with communities will be essential to ensure contextual relevance and maximise effectiveness.

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ARTIGO ORIGINAL

Índices de variabilidade dia-a-dia melhoram a utilidade da oscilometria na asma pediátrica

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RESUMO

Contexto A oscilometria pode constituir uma ferramenta viável e sensível para a monitorização remota e objetiva da asma pediátrica.

Métodos Estudo observacional envolvendo crianças em idade escolar saudáveis, com asma bem controlada e mal controlada, que realizaram oscilometria diária em casa durante 3–4 meses, juntamente com medidas objetivas de controlo da asma (Asthma Control Questionnaire semanal e Asthma Control Test mensal), utilização de medicação e agudizações. A variabilidade dia-a-dia foi calculada como coeficiente de variação (CV) para a resistência a 5 Hz (R5), reatância a 5 Hz (X5) e área sob a curva de reatância (AX). O objetivo foi avaliar a viabilidade, determinar se a variabilidade diária estava aumentada na asma e analisar correlações com controlo da asma e carga de agudizações. Padrões clínicos de agudização foram explorados através de análise de componentes principais e k-means clustering de oscilometria, sintomas, parâmetros respiratórios e adesão terapêutica.

Resultados A viabilidade foi de 74,9±16,0% no grupo saudável (n=13; 93,7±16,2 dias) e 80,6±12,9% no grupo com asma (n=42; 101,6±24,9 dias; 17 bem controlados e 27 mal controlados). Observou-se aumento da variabilidade diária em todos os índices de oscilometria na asma comparativamente ao grupo saudável (todos p<0,002), sendo o CV R5 o melhor discriminador (AUC 0,88; p<0,001). O CV R5 aumentou durante agudizações e correlacionou-se com todas as medidas de controlo da asma e com a carga de agudizações. Estas correlações mantiveram-se mesmo quando analisados apenas dados de períodos sem agudização. Foram identificados dois padrões de agudização com base nos dados de oscilometria no período pré-agudização, caracterizados pela gravidade da alteração de R5, X5, AX e CV R5 (n=12, padrão mais grave). Resultados semelhantes foram observados utilizando dados do período pós-exacerbação (n=8, padrão mais grave). Os sintomas não diferiram entre os padrões de agudização.

Conclusões A monitorização domiciliária por oscilometria mostrou elevada viabilidade durante períodos prolongados em crianças com asma em idade escolar. A variabilidade diária da oscilometria estava aumentada na asma em comparação com crianças saudáveis, refletiu o controlo da doença e a carga de agudizações e permitiu identificar diferentes padrões de exacerbação.

INTRODUCTION

Disease burden of asthma for society is significant, affecting 10% of children and adults¹ with huge annual healthcare costs (>\$A24 billion in Australia and >US\$80 billion in USA).² 50% of children with asthma have inadequately controlled symptoms,¹ accounting for almost 3% of US paediatric emergency department visits and hospitalisations annually.³ Asthma deaths remain a significant concern because many are preventable, with the strongest

Key messages**WHAT IS ALREADY KNOWN ON THIS TOPIC**

- Results of paediatric home monitoring studies in asthma have been disappointing to date.

WHAT THIS STUDY ADDS

- Oscillometry provided a highly feasible home-based monitoring tool over extended periods in school-aged asthmatics. Day-to-day variability in oscillometry indices, in contrast to conventional single occasion assessments, revealed high discrimination of asthma from health, based on increased variability in asthma, compared with health. Day-to-day variability increased during exacerbation, correlated with objective measures of asthma control and exacerbation burden, and revealed differing patterns of exacerbations within our cohort.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- These data outline the exciting potential of oscillometry to fill an urgent unmet need for an objective remote monitoring solution in paediatric asthma.

risk factors being poor asthma control and ongoing exacerbations.⁴ Conventional symptom-based guideline approaches to obtaining good asthma control continue to be inadequate, limited by factors such as poor symptom perception or reporting by children and parents.⁵ Furthermore, it is increasingly recognised that asthma exacerbations can be highly heterogeneous, and better phenotyping may facilitate better targeted, more effective treatment.⁶ The 2022 GINA (Global Initiative for Asthma) report recognised the rapid increasing use of digital technology, telemedicine and telehealthcare but highlighted that greater research is required to outline how these can be beneficial.⁷

Asthma is characterised by chronic airway inflammation and variable airway obstruction. Yet current objective lung function-based tools, such as peak expiratory flow (PEF) or spirometry have limited utility, especially in children.⁸ It is difficult to obtain consistent technically acceptable forced expired volume in 1 s (FEV₁) and PEF data in children due to its effort-dependent nature. The value of adult PEF variability to predict exacerbations or loss of control⁹ does not translate to children. Written daily PEF diaries are unreliable in children,¹⁰ and PEF variability correlates poorly with asthma



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severity.⁸ In addition, there is limited sensitivity to detect this variable airflow obstruction: FEV₁ lies within the normal range in the majority of asthmatics and may remain so during acute exacerbation.¹¹ In contrast, oscillometry is an effort-independent tidal breathing test which addresses these issues. It has strong feasibility in children down to preschool age and enhanced sensitivity, in comparison to FEV₁, to detect bronchodilator response¹² and airway hyper-responsiveness.¹³ We have previously shown that in a 1 week asthma camp setting, under physician supervision, measurement of day-to-day variability in oscillometry indices differentiated asthmatics from healthy controls, and differentiated between levels of asthma severity and asthma control.¹⁴ FEV₁ and PEF failed to do this within that cohort.

There are currently no studies in children outlining feasibility and utility of daily monitoring with oscillometry, under parental supervision, in the home setting. In this study, the primary aim was to determine the feasibility of measurement in this setting over a prolonged period of up to 4 months. Secondary aims were to determine whether day-to-day variability in oscillometry-derived respiratory system resistance and reactance at 5 Hz (R5 and X5, respectively) (1) is increased in asthma compared with healthy controls, (2) correlates with objective validated measures of asthma control and exacerbation frequency and finally (3) provides additional clinical utility in identifying different patterns of asthma exacerbation. We hypothesised that oscillometry-based home monitoring would be highly feasible, that day-to-day oscillometry variability would be higher in asthmatics, in those with worse asthma control and higher exacerbation frequency and would identify differing exacerbation patterns over and above conventional measures including symptoms.

METHODS

Subjects and study design

Recruitment occurred across two studies with written informed consent/assent obtained from all parents/guardians and children. Children, aged 8–18 years, with a physician diagnosis of asthma were recruited from a tertiary paediatric chest and asthma clinic at The Children's Hospital at Westmead, New South Wales. Asthmatics within the first study were enrolled in an observational study and underwent home monitoring for 3–4 months, specifically recruiting those with a history of 'poorly-controlled asthma', defined as a history of reported exacerbations in the preceding 12 months, to increase the potential to capture exacerbations during the monitoring period. The second study enrolled subjects with a treating physician's assessment of 'well-controlled asthma' based on reported good asthma control for ≥6 months and the treating physician's intention to step down preventer therapy in line with international GINA guidelines. Home monitoring was performed for a similar period prior to the step-down. To define normal day-to-day variability, healthy control subjects were recruited from families participating in these studies and staff members and defined as those with no known history of preterm birth, chronic respiratory condition or previous admission to hospital for respiratory illness or regular respiratory medication use.

Baseline assessment

Detailed assessment of baseline lung function was performed at study entry, consisting of Multiple and Single Breath Washout (MBW and SBW, respectively), oscillometry and spirometry in all subjects. Nitrogen-based MBW and SBW (Exhalyzer D, Spiroware V.3.1.6, ECO MEDICS, Switzerland, reanalysed in V.3.3.1) were performed in triplicate according to European Respiratory Society (ERS)/ American Thoracic Society (ATS) consensus recommendations.¹⁵ Outcomes reported for MBW were Lung Clearance Index (LCI), functional residual capacity (FRC) and concentration-normalised phase III slope parameters Scond and Sacin, which represent ventilation inhomogeneity arising within more proximal conducting airway and more distal acinar airway regions of peripheral airways, respectively. SBW outcomes reported were phase III slope (S_{III}), S_{III} normalised for vital capacity (S_{III}*VC) and clo-

sing volume (CV). Oscillometry training and baseline assessment were performed as triplicate 60 s recordings using a pseudorandom 5–37 Hz waveform (tremoFlo C-100 Airwave Oscillometry System, THORASYS, Canada, V.1.04 build 43) according to ERS technical standards.¹⁶ Outcomes reported were R5, X5 and area under reactance curve (AX). Z-scores were calculated using recently published paediatric reference data.¹⁷ Spirometry was performed using JAEGER equipment (Vyntus Masterscreen PNEUMO, Germany, Sentry-Suite software V.3.0) with outcomes (FEV₁, FEV₁/forced vital capacity (FVC) and forced expiratory flow between 25% and 75% of vital capacity per cent predicted (FEF_{25–75}) reported as z-scores.¹⁸ Validated questionnaires performed were the Asthma Control Questionnaire (ACQ)19 and Asthma Control Test (ACT).^{20 21}

Home monitoring period

Following oscillometry training and device setup in the subjects' home, families were instructed to perform triplicate measurements once a day (at a time convenient for the family) for ≥3–4 months. Where suitable electronic medication data loggers existed for the medications used (SmartInhaler, Adherium, New Zealand), these were installed onto both preventer and reliever asthma medications. Subjects completed an electronic daily questionnaire immediately prior to measurement and were contacted weekly by videoconferencing to review oscillometry technique and SmartInhaler technique proficiency, perform an ACQ and record details of any exacerbations. Asthma exacerbations were defined according to Virchow et al²² as described in the online supplemental file 1. ACT was recorded monthly. Oscillometry data were reviewed by research staff at completion of the monitoring period. Technically acceptable test occasions were defined as those with three recordings each containing at least five breaths free of technical artefact.¹⁶ Breaths containing artefacts were excluded. Only test occasions with technically acceptable data were included in analyses.

Data analyses

Descriptive statistics were used to describe patient demographics and clinical characteristics: frequencies and percentages for categorical variables; symmetric data reported as mean and SD and skewed data as median and quartiles. Home monitoring feasibility was characterised as percentage of days with technically acceptable measurements, expressed as percentage of total monitoring period, and percentage of total 'eligible' monitoring period excluding days where family/child were away from the home where equipment had been installed. Day-to-day variability of oscillometry indices was calculated as the coefficient of variance (CV%) of data from the entire monitoring period. To avoid the contribution of lung function behaviour during exacerbations, 'stable' day-to-day variability indices were also calculated by excluding oscillometry data collected during defined exacerbation periods (eg, 'R5 CV stable'). Exacerbation burden was explored as the number of exacerbations experienced and the per cent of monitoring days spent in exacerbation. Categorical data were compared using Fisher's exact tests. For continuous data, based on whether the distribution of data was normal or not, differences between groups were compared using t-tests or Mann-Whitney U test, or when more than two groups were compared, by one-way analysis of variance (ANOVA) or Kruskal-Wallis tests, respectively. Post-hoc analyses were performed using Tukey-Kramer Honestly Significant Difference (HSD) or Steel-Dwass All Pairs tests for those variables found to be statistically significant between the three groups (healthy, well-controlled asthma, poorly-controlled asthma) on one-way ANOVA or Kruskal-Wallis tests, respectively. As all assessing variables were not normally distributed, we used Spearman's correlation coefficients to identify associations between oscillometry indices and asthma burden. After confirming that data met the fundamental assumptions required for the test, univariable logistic regression was used to evaluate the performance of day-to-day variability in oscillometry indices in differentiating asthma from healthy con-

Table 1 Baseline demographics and asthma characteristics of the cohort

	Healthy (n=13)	Asthmatics		P value
		Well-controlled (n=17)	Poorly-controlled (n=25)	
Demographics				
Male – n (%)	5 (39)	11 (64)	16 (64)	0.260
Age at study entry (years) – mean±SD	12.3±2.4	13.21±2.56	13.05±2.56	0.617
Height z-score – mean±SD	0.75±1.12	0.12±0.89	−0.01±0.87	0.061
Weight z-score – mean±SD	0.54±1.12	0.31±0.88	0.44±1.05	0.819
BMI – mean±SD	0.75±1.12	0.12±0.89	−0.01±0.87	
Overweight (85.0–94.9 centile)	0	4 (24)	7 (28)	0.112
Obesity (≥95.0 centile)	2 (15)	1 (6)	4 (16)	0.594
Asthma characteristics				
Age of asthma diagnosis (years)* – mean±SD	–	3.49±1.74	3.15±2.16	0.587
Asthma duration (years)* – mean±SD	–	9.69±2.85	9.89±3.54	0.855
Atopy (positive skin prick test) – n (%)	0	15 (88)	23 (92)	<0.001
Allergy rhinitis – n (%)	0	15 (88)	17 (68)	<0.001
Eczema – n (%)	0	11 (65)	14 (56)	<0.001
Persistent asthma – n (%)	–	17 (100)	24 (96)	0.404
Asthma exacerbations				
Total exacerbations in last 12 months – median (IQR)	0	0 (0–1)	4 (2.5–8.5)	<0.001
OCS courses in last 12 months – median (IQR)	0	0 (0–1)	3 (2–7)	<0.001
Hospital admissions in last 12 months – median (IQR)	0	0	1 (0–3)	<0.001
Asthma medication				
GINA stage – n (%)				
Stage 3	–	8 (47)	5 (20)	0.063
Stage 4	–	4 (24)	11 (44)	0.174
Stage 5	–	1 (6)	6 (24)	0.122
Asthma control				
Asthma Control Questionnaire – median (IQR)	0	0.33 (0–0.67)	0.67 (0.17–1.64)	<0.001
Asthma Control Test – median (IQR)	25	20 (19–24.5)	20 (17–22.75)	<0.001

Variables compared across three groups (healthy control, well-controlled and poorly-controlled) were analysed using ANOVA or Kruskal Wallis, as appropriate. Fisher's exact test was used for categorical data.

*Asthma-specific variables (where between group comparisons were limited to the well-controlled and poorly-controlled asthma groups) were analysed using t-test or Mann-Whitney U test, as appropriate. Statistically significant values ($p<0.05$) displayed in bold. All variables with a numerical value were based on completion of questionnaires/questions specific to that variable. Post hoc analyses are summarised in section 4.2 of the online supplemental file 1.

ANOVA, analysis of variance; BMI, body mass index; GINA, Global Initiative for Asthma; OCS, Oral Corticosteroid.

trols. Area under receiver operating characteristics curve (AUC) values were used to compare performance of day-to-day variability in oscillometry indices with conventional single session oscillometry variable values, collected at baseline lung function assessment with effect size outlined by ORs and 95% CIs. Best cut-off values for sensitivity and specificity were determined using Youden's index. Multivariable logistic regression models were used to establish added predictive power of oscillometry values over established predictors (age, sex, height and weight). Significance level was set as $p<0.05$. All data were analysed using JMP, V.16 Pro (SAS Institute, Cary, North Carolina, USA).²³

We explored differing patterns of exacerbation based on oscillometry indices (including mean and CV%), breathing parameters, symptoms and medication adherence data in 7-day time windows in the weeks surrounding each exacerbation. Principal component analysis (PCA) was used to reduce the number of potential explanatory variables into a smaller number of principal components (linear combinations of original variables), minimising collinearity.²⁴ This was followed by k-means clustering to determine the presence of any data-driven clusters.²⁵ Optimum number of k-means clusters was chosen based on maximising the silhouette coefficient (a measure of mean between-cluster distance proportionate to the within-cluster size), as a metric of goodness of clustering. Clusters represent groupings based on symptoms,

oscillometric lung function and medication adherence pre-onset and post-onset of exacerbation. Input variables and patient baseline characteristics were then compared across clusters. Effects of varying number of clusters, window size and timing were also examined in sensitivity analyses. PCA and k-means clustering were conducted using custom code written in Python on the Jupyter platform within the Anaconda environment (Anaconda, Austin, Texas, USA)²⁶ using scikit-learn library V.0. Further details of data preprocessing, PCA and cluster analyses are provided in the online supplemental file 1.

RESULTS

Study population

13 healthy and 42 asthmatic subjects participated. Five families were approached to participate but declined. In addition, one child with poorly controlled asthma was recruited but sadly died from an asthma exacerbation prior to her baseline visit. Baseline demographics differed in sex and body mass index but were otherwise well matched between healthy and asthma (table 1, online supplemental tables E1 and E2). Almost all asthmatic subjects were sensitised to aeroallergens, with the majority having other diagnosed atopic disease. Asthmatics had worse lung function at enrolment than healthy controls (table 2, online supplemental table E2).

Table 2 Baseline lung function of the cohort

	Healthy (n=13)	Asthmatics		P value
		Well-controlled (n=17)	Poorly-controlled (n=25)	
Spirometry – mean±SD				
FEV ₁ (% Pred)	98.5±8.6	87.7±19.4	95.6±15.0	0.140
FVC (% Pred)	100.0±11.6	98.2±14.9	104.6±14.6	0.333
FEV ₁ /FVC (%)	86.4±7.0	76.8±9.9	80±9.2	0.024
FEF _{25–75} (% Pred)	94.3±14.7	67.1±28.7	77.7±26.6	0.023
Spirometry – mean±SD				
FEV ₁ (z-score)	−0.12±0.74	−1.41±1.63	−0.37±1.27	0.037
FEV ₁ /FVC (z-score)	−0.01±1.00	−2.03±0.93	−1.03±1.21	<0.001
FEF _{25–75} (z-score)	−0.27±0.69	−2.24±1.34	−1.07±1.35	0.002
Multiple breath washout				
LCI (turnovers) – median (IQR)	6.11 (5.98–6.46)	6.65 (6.40–8.96)	6.5 (6.21–7.62)	0.014
S _{cond} (L) – mean±SD	0.026±0.011	0.054±0.024	0.048±0.020	0.002
S _{acin} (L) – median (IQR)	0.057 (0.050–0.081)	0.069 (0.050–0.094)	0.062 (0.047–0.084)	0.672
Single breath washout – median (IQR)				
S _{III} (%/L)	1.26 (1.03–1.69)	1.66 (0.89–1.86)	1.47 (0.82–2.10)	0.698
S _{III} *VC (%)	4.08 (2.60–4.47)	4.31 (2.85–5.30)	3.79 (2.76–5.12)	0.738
CV (L)	0.230 (0.080–0.362)	0.176 (0.073–0.321)	0.23 (0.14–0.40)	0.474
Oscillometry – median (IQR)				
R5 (z-score)	0.03 (−1.00 to 0.67)	0.10 (−0.97 to 1.30)	−0.40±0.90	0.382
X5 (z-score)	0.70 (−0.90 to 1.18)	0.30 (−1.44 to 0.85)	0.63 (−0.28 to 1.00)	0.393
AX (z-score)	−1.17 (−3.20 to 0.46)	−0.43 (−1.78 to 5.03)	−0.82 (−1.59 to 0.51)	0.238

Variables compared across three groups (healthy control, well-controlled and poorly-controlled) used ANOVA or Kruskal Wallis where appropriate. Statistically significant values (p<0.05) displayed in bold. Post hoc analyses are summarised in section 4.2 of the online supplemental file 1.

ANOVA, analysis of variance; AX, area under the reactance curve; CV, closing volume; FEF_{25–75}, forced expiratory flow between 25% and 75% of vital capacity percent predicted; FEV₁, forced expired volume in 1 s; FVC, forced vital capacity; LCI, Lung Clearance Index; %Pred, per cent predicted; R5, resistance at 5Hz; Sacin, contribution of the more distal acinar airways to the ventilation inhomogeneity; Scond, contribution of the more proximal conducting airways to the ventilation inhomogeneity; SIII, phase III slope; VC, vital capacity; X5, reactance at 5Hz.

Feasibility of home monitoring

Overall, 55 monitoring periods were completed by 13 healthy subjects and 42 asthmatic subjects (17 recruited as well-controlled asthma and 27 as poorly-controlled asthma). Strong feasibility was observed across groups (table 3) based on both percentage of total days enrolled or as percentage of eligible days. Feasibility results were similar between groups. Across all subjects, all test occasions attempted achieved technical acceptability.

Comparing health versus asthma

At baseline, asthmatic subjects had higher rates of atopy (online supplemental table E1), lower flow-based spirometry indices, higher MBW-based LCI and S_{cond} but no difference in SBW indices (online supplemental table E2). Significantly higher day-to-day variability in all oscillometry indices was observed in asthmatic subjects, compared with healthy subjects (online supplemental table E3). In contrast, baseline oscillometry indices' z-scores were not different (online supplemental table E2). Univariable logistic regression analyses are summarised in online supplemental table E4. Receiver operating characteristic analysis showed high predictive values (defined as AUC≥0.80) for CV R5 (AUC 0.88, OR (95% CI) 1.52 (1.17 to 1.97), p<0.001), CV X5 (AUC 0.85, OR (95% CI) 0.82 (0.71 to 0.95), p<0.001) and CV R5 stable (AUC 0.85, OR (95% CI) 1.48 (1.14 to 1.93), p<0.001). Highest sensitivity and specificity were observed for CV R5 at 0.80 and 1.00, respectively. AUC values of baseline oscillometry indices (0.47–0.61) were not statistically significant. These findings persisted on multivariable logistic regression adjusting for age, sex, height and weight (online supplemental table E4).

Relationships with asthma control

Across the three groups of healthy, well-controlled and poorly-controlled asthmatics, a progressive increase in day-to-day varia-

bility was observed, with significant differences across groups in all indices regardless of whether data was from the entire monitoring period or only from stable periods (figure 1, table 3). Statistically significant differences were observed with R5 CV (all p<0.001), X5 CV (p≤0.005) and AX CV (all p≤0.026). Post-hoc analyses (online supplemental tables E5 and E6) revealed both well-controlled and poorly controlled asthmatics differed from healthy subjects in all variables, apart from some/all AX CV based indices and spirometry-based indices (excluding FEV₁/FVC). Poorly-controlled asthma differed from well-controlled asthma in total exacerbations experienced, days spent in exacerbation, objective measures of asthma control and length of home monitoring. Lower FEV₁/FVC and FEF_{25–75} (as z scores, online supplemental table E5) were observed in the well-controlled group, compared with those with a history of increased exacerbations. At the time of baseline assessment, no statistical difference in asthma control was observed in ACQ and ACT scores (ACQ p=0.056, online supplemental table E6).

Specific to oscillometry day-to-day variability indices, differences between group pairs were most apparent when subjects were classified as 'well-controlled' or 'poorly controlled' based on validated thresholds applied to mean ACQ or ACT scores across all questionnaires performed during home monitoring (online supplemental tables E7–E12): all day-to-day variability indices differed between healthy subjects and those with poor asthma control; X5-based indices differed between health and each of the two asthma classifications; and R5 CV during non-exacerbation periods was the only variability index found to significantly differ between all group pairs, with highest R5 CV day-to-day variability occurring in poorly-controlled asthmatics.

Significant correlations between day-to-day variability oscillometry indices and asthma control during monitoring (mean val-

Table 3 Data collected during home monitoring

	Healthy (n=13)	Asthmatics		P value
		Well-controlled (n=17)	Poorly-controlled (n=25)	
Demographics				
Length of monitoring period (days) – mean±SD	93.7±16.2	83.8±21.2	113.7±19.7	<0.001
Home oscillometry feasibility measured over eligible oscillometry days (%) – mean±SD	74.9±16.0	78.2±14.0	82.3±12.0	0.286
Home oscillometry feasibility measured over all monitoring days (%) – mean±SD	74.9±16.0	72.9±15.8	74.9±12.8	0.896
Children that suffered an asthmatic exacerbation – n (%)	0	10 (59)	25 (100)	<0.001
Total exacerbations – median (IQR)	0	1 (0–2.5)	3 (2–4)	<0.001
Days spent in exacerbation – median (IQR)	0	3 (0–20.5)	23 (16.5–46.5)	<0.001
Oscillometry indices				
R5 CV (%) – mean±SD	8.75±2.11	14.32±5.11	17.84±6.71	<0.001
Non-exacerbation periods (%)	–8.75±2.11	14.03±5.26	16.96±6.72	<0.001
Exacerbation periods (%)*	–	15.56±5.29	19.10±8.25	0.182
X5 CV (%) – median (IQR)	–16.0 (–17.5 to –11.7)	–20.4 (–29.6 to –17.6)	–28.9 (–42.3 to –19.9)	<0.001
Non-exacerbation periods (%)	–16.0 (–17.5 to –11.7)	–20.1 (–30.9 to –17.6)	–21.8 (–38.6 to –16.9)	0.005
Exacerbation periods (%)*	–	–22.7 (–29.2 to –14.4)	–32.4 (–49.1 to –20.3)	0.093
AX CV (%) – mean±SD	33.4±16.81	43.32±17.80	57.75±26.58	0.006
Non-exacerbation periods (%)	33.4±16.81	42.67±19.05	51.74±21.03	0.026
Exacerbation periods (%)*	–	44.74±22.33	60.48±28.62	0.125
Questionnaires				
Asthma Control Questionnaire (ACQ) – median (IQR)	0	0.20 (0.22–0.51)	0.48 (0.28–1.28)	<0.001
Asthma Control Test (ACT) – median (IQR)	25	22.7 (21.25–23.75)	21 (17.8–22.7)	<0.001
All variables compared across the three groups (healthy control, well-controlled and poorly-controlled) were analysed using ANOVA or Kruskal-Wallis, as appropriate. All variables with a numerical value were based on completion of questionnaires/questions specific to that variable. ACQ and ACT values reported as mean score across all questionnaires during monitoring.				
*Asthma-specific variables (where between group comparisons were limited to the well-controlled and poorly-controlled asthma groups) were analysed using Mann-Whitney U test or t-test, as appropriate. Statistically significant values (p<0.05) displayed in bold. Post hoc analyses are summarised in sections 4.2 and 4.3 of the online supplemental file 1.				
ANOVA: analysis of variance; AX: area under the reactance curve; CV: coefficient of variation; R5: resistance at 5Hz; X5: reactance at 5Hz				

All variables compared across the three groups (healthy control, well-controlled and poorly-controlled) were analysed using ANOVA or Kruskal-Wallis, as appropriate. All variables with a numerical value were based on completion of questionnaires/questions specific to that variable. ACQ and ACT values reported as mean score across all questionnaires during monitoring.

*Asthma-specific variables (where between group comparisons were limited to the well-controlled and poorly-controlled asthma groups) were analysed using Mann-Whitney U test or t-test, as appropriate. Statistically significant values ($p<0.05$) displayed in bold. Post hoc analyses are summarised in sections 4.2 and 4.3 of the online supplemental file 1.

ANOVA, analysis of variance; AX, area under the reactance curve; CV, coefficient of variation; R5, resistance at 5Hz; X5, reactance at 5Hz.

ues across all questionnaires performed) were observed (figure 2). Examining all home monitoring data, the strongest correlations were observed with CV R5. X5-based and AX-based indices also correlated with ACQ but not ACT. Restricting day-to-day variability data to that collected during ('stable') non-exacerbation periods retained these patterns of correlation with ACQ and resulted in statistically significant, but weak, correlation with ACT for X5 and AX, decreasing the p value from borderline significance to be just below $p=0.05$.

Relationships with exacerbation burden

Within the monitoring period, exacerbation burden was significant across the cohort with mean±SD 2.3±1.7 exacerbations experienced and 24.3±22.3% days spent in exacerbation despite a monitoring period of only 101.6±24.9 days. Exacerbation burden differed between groups, with both metrics larger in the poorly controlled group (table 3, both $p<0.001$ online supplemental table E6). Among all asthmatics, higher day-to-day variability values in R5 during exacerbation trended toward statistical significance, in comparison to non-exacerbation periods, but reached statistical significance in the poorly controlled group: 19.10±8.25 versus 16.96±6.72, $p=0.037$, respectively (online supplemental table E13). This may reflect the higher number of exacerbations observed (table 3). All day-to-day variability indices correlated with measures of exacerbation burden, both expressed as exacerbation number or per cent days spent in exacerbation (figure 2). The strongest correlations were again observed with CV R5, and correlations were retained when examining oscillometry behaviour during ('stable') non-exacerbation monitoring periods.

Exacerbation cluster analysis

78 exacerbations were identified across the home monitoring periods and included in clustering analysis. When considering the pre-exacerbation period, the optimum window for clustering (ie, yielding the highest silhouette coefficient of 0.513, see online sup-

plemental file 1) began 10 days prior to exacerbation onset (online supplemental figure E1). Two clusters of exacerbations were identified on the basis of principal component 1 (online supplemental table E14 and figure E2), with a smaller cluster (Cluster 2 'higher impedance and variability', $n=12$) typified by higher R5, X5 and AX and higher R5 and X5 day-to-day variabilities compared with the larger cluster (Cluster 1 'lower impedance and variability', $n=53$), but no differences in symptom scores (online supplemental table E15). Cluster 2 was associated with participants who had more abnormal Scond, and more participants used long-acting beta-agonists (LABA) and leukotriene receptor antagonists (LTRA) at study entry (online supplemental table E16). A similar pattern was observed for the post-exacerbation onset period, where the optimum window began 2 days after exacerbation onset (silhouette coefficient: 0.593). Again, two clusters were identified on the basis of principal component 1 (online supplemental table E17 and figure E3), whereby a smaller cluster (Cluster 2, $n=8$) had higher R5, X5, AX and also day-to-day variability across all these indices compared with the larger cluster (Cluster 1, $n=65$), but no differences in symptoms scores (online supplemental table E18). Here also, Cluster 2 was associated with participants with more abnormal Scond, and more of them used LTRA at study entry (online supplemental table E19). Note the difference in the number of exacerbations between the pre-exacerbation and post-exacerbation onset periods is due to different windows excluded on the basis of missing data points.

Importantly in all cases, including symptoms, controller adherence or breathing data in the cluster analyses decreased the silhouette coefficient, indicating a less good fit of the clustering. This suggests oscillometry was the most significant classifier of differing exacerbation patterns.

DISCUSSION

This study provides evidence that daily parent-supervised oscillometry monitoring is highly feasible in school-aged children, in

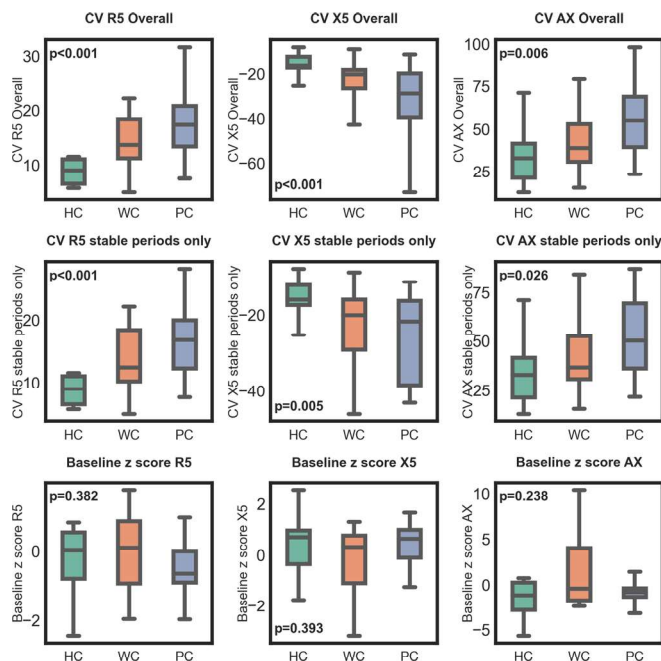


Figure 1 Comparison of day-to-day variability in oscillometry indices and baseline oscillometry indices across healthy, well-controlled and poorly-controlled asthma subjects. Box and whisker plots display median, first and third quartiles and range for each parameter. All variables were compared across the three groups (healthy control, well-controlled and poorly-controlled) using ANOVA or Kruskal-Wallis tests, where appropriate. Post hoc analyses are summarised in sections 4.2 and 4.3 of the online supplemental file 1. ANOVA, analysis of variance; AX, area under the reactance curve; CV, coefficient of variation; HC, healthy controls; PC, poorly-controlled; R5, resistance at 5Hz; WC, well-controlled; X5, reactance at 5Hz.

the home setting for prolonged periods. In this study, this was achieved in homes as far away as 700 km from the managing tertiary hospital. Day-to-day variability in oscillometric resistance was raised in asthma, compared with health, and correlated with asthma symptom control and risk of flares in those symptoms ('asthma exacerbations'). Of all oscillometry parameters, day-to-day variability in R5 had the most significant correlations, in this regard. Finally, day-to-day variability in R5, combined with clinical characteristics, allowed identification of two distinctly different patterns of exacerbation; one having more severe physiologic derangement with worse day-to-day variability in CV R5 and CV X5, both when clinically stable as well as during the exacerbation period. Importantly, symptoms did not differ between the two patterns of exacerbation, but those who had worse day-to-day variability also had worse conductive airway function (Scond) and greater preventer medication requirement.

The present study provides further evidence that lung function variability is increased in asthma, and that this can be accurately captured in children using remote oscillometry-based monitoring. Increased day-to-day variability of lung function, measured by PEF, is characteristic of adult asthma, reflects asthma control,²⁸ loss of control with inhaled corticosteroid withdrawal,⁹ and is a marker of severity and exacerbation risk.²⁹ Increased variability in asthma has not been consistently evident within adult oscillometry literature, but the time scale of assessment is an important consideration: Diba et al, comparing recordings over 1 min,³⁰ did not report the same increased within-session variability found by Que et al in recordings over 15 min.³¹ Within our study, a highly feasible remote-based approach (based on the same 1 min recordings performed in triplicate by Diba et al³⁰) enabled us to examine variability day-to-day over a much longer time scale in children, where PEF is both problematic¹⁰ and less sensitive⁸ compared with adults. Increased day-to-day variability in oscillometry in asthma was not only present but

showed high predictive value to differentiate health from disease in all oscillometry indices, but highest for CV R5 (AUC 0.88, OR (95% CI) 1.52 (1.17 to 1.97), $p<0.001$). This was completely missed by baseline oscillometry assessments (mimicking a hospital clinic-based assessment), highlighting limitations of single lung function measurements for disease characterisation. This study was not designed to assess diagnostic utility, nor are we proposing day-to-day variability should be, but demonstrating increased variability in asthma was an important initial goal prior to exploring relationships within this dataset with asthma control and exacerbation burden. By outlining its ability to correlate with questionnaire-based assessments of asthma control, we both confirm and extend the findings from our pilot study conducted onsite within an asthma camp over a 1-week period¹⁴: the period of monitoring in the current study was much longer, was conducted under parental rather than physician supervision and used a commercial rather than an in-house oscillometry device. Since the pathophysiological basis of asthma is intermittent bronchoconstriction, regular monitoring to detect it is logical and avoids reliance on symptoms and recall.

Exacerbations were prominent in our cohort. Detection was optimised through the prospective longitudinal cohort study design, use of daily electronic diaries, electronic medication monitoring and weekly remote follow ups, which likely meant greater sensitivity in detecting flares in symptoms and also better detail within those flares (guideline defined exacerbations are exclusively symptoms based). In addition, rigorous training to self-administer oscillometry with regular contact ensured high-quality data and high adherence rates. Day-to-day variability of oscillometry, even that collected during periods excluding exacerbations, correlated with both frequency of asthma exacerbations and exacerbation duration. This is an important finding because it supports the notion that uncontrolled and frequent bronchoconstriction is a physiological characteristic of uncontrolled and/or severe asthma. Because frequent monitoring to measure frequency and severity of bronchoconstriction in children has been difficult, there has been little to no published data to support this notion until now. We also found evidence of increased day-to-day variability within exacerbation, within those at greater risk, and this dataset will provide an important opportunity to explore the ability of variability in oscillometry to provide an early warning signal of impending exacerbation, which, if shown, would be highly significant for clinical care. We also need to better understand factors that may affect variability, such as variation in time of testing, given the enhanced circadian variation in airway calibre and lung volume described in asthma,^{32,33} and the impact of preventer medication adherence.

Asthma exacerbations are highly heterogeneous, and better understanding is critical, since the simplistic, symptom-based definitions result in them being viewed and consequently treated as a single entity.⁶ It possibly or even probably explains why a single management strategy of quintupling inhaled corticosteroids was ineffective in reducing prednisone use for paediatric exacerbations,³⁴ where different strategies may be needed depending on their pattern of exacerbation. In our study, despite optimised accuracy in symptom recording, symptoms did not differ between patterns of exacerbation, suggesting that symptoms do not differentiate those going onto exacerbation or not in the weeks prior to exacerbation. Our cluster analysis provides insight into the presence of differing patterns of exacerbation. Using four characteristics—day-to-day variability in impedance parameters, symptoms, respiration (rate and tidal volume) and inhaled corticosteroid adherence—suggested that there were two patterns of exacerbations. One pattern being more severe, based on worse mean impedance and greater day-to-day variability, despite symptoms being similar between the two patterns. Association with worse conductive ventilation heterogeneity (more abnormal Scond) provides pathophysiological plausibility for the more severe pattern of exacerbation. In both adults³⁵ and children,³⁶ increased Scond is associated with greater airway hyper-

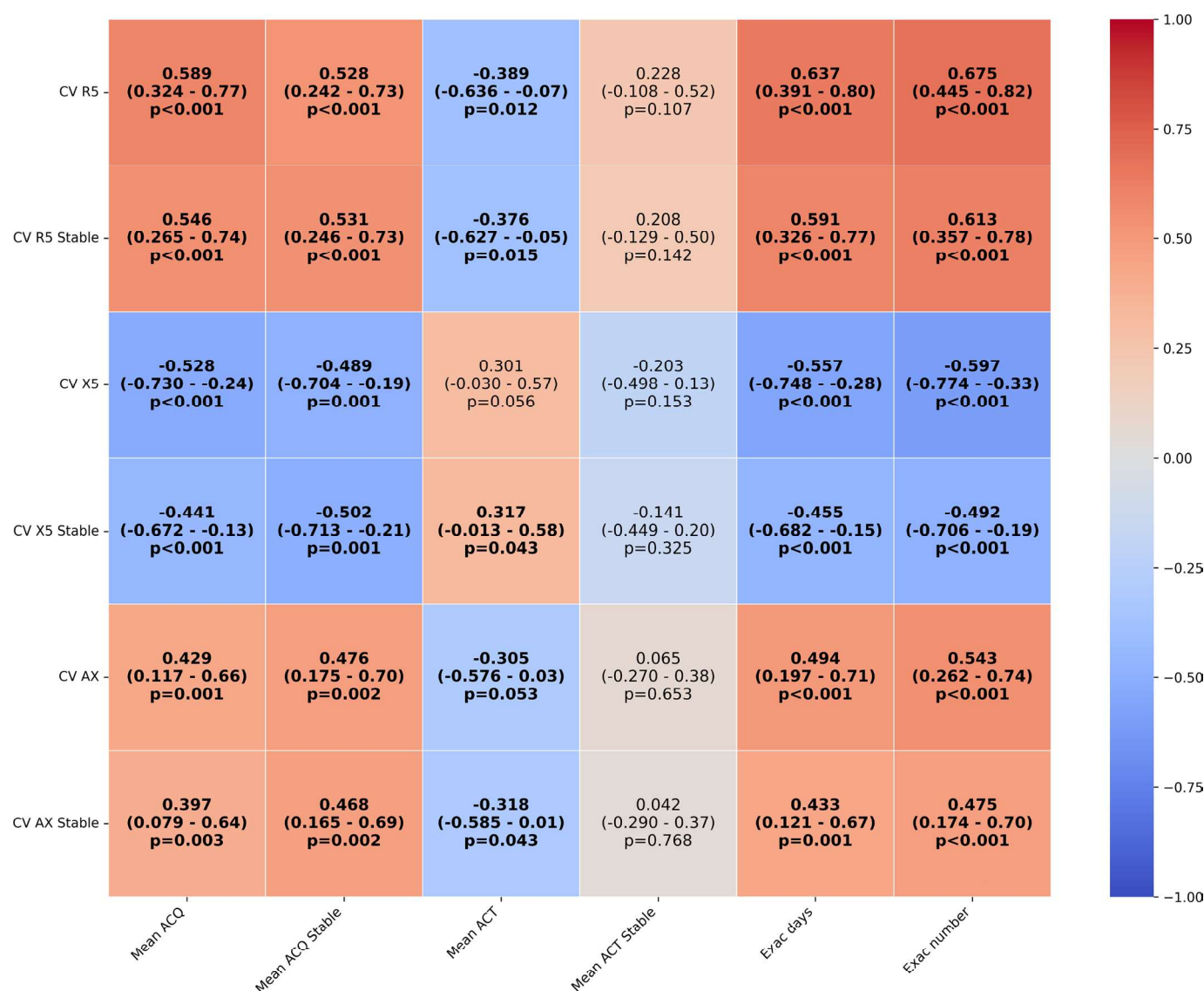


Figure 2 Heat map summarising Spearman correlation between indices of day-to-day variability in oscillometry and objective measures of asthma control and exacerbation burden in the cohort. The association between day-to-day variability in oscillometry indices with asthma burden is shown with Spearman's coefficient ρ and its 95% CI. Asthma burden is represented by ACQ and ACT. Exacerbation (Exac) burden is represented by Exac days and Exac number. Statistically significant values ($p<0.05$) displayed in bold. ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; AX, area under the reactance curve; CV, coefficient of variation; R5, resistance at 5Hz; X5, reactance at 5Hz.

responsiveness. Additionally, in adults, Scond is associated with airway closure,³⁷ while increased phase III slopes from SBW are associated with greater exacerbation risk.³⁸ It is possible or likely that those with more frequent and severe airway narrowing are at risk of longer-term complications, or conversely, those with less severe bronchoconstriction might be more appropriately treated non-pharmacologically or do not require oral corticosteroids. The possibilities raised by these initial, exploratory analyses deserve further study, including confirmation of the consistency of our findings within other cohorts (including those outside of the tertiary hospital setting) and whether these differing patterns of exacerbation represent true differing phenotypes of exacerbation by including additional important measures such as inflammation among others. Future planned analyses within our cohort will explore the impact of preventer medication adherence on the finding that lung function was better in the poorly controlled group (for all lung function techniques except oscillometry). GINA stages were higher in the poorly-controlled group, although this did not reach statistical significance and could represent a sample size issue. Finally, the signal for day-to-day variability within our paediatric dataset was more consistent with R5 than X5 or AX, in contrast to the reactance-based signals observed in adult oscillometry data,³⁹ which may reflect the fact that higher chest wall compliance in

children than adults yields a weaker signal for change in X5 when airway narrowing or heterogeneity occurs (ie, less change in respiratory system stiffness), thus mainly affecting R5.

In conclusion, the results of this study suggest that remote home monitoring under parent supervision using oscillometry is highly feasible in school-aged children. These results suggest that assessing day-to-day variability of lung function using oscillometry shows that variability is increased (1) in asthma, compared with healthy subjects, (2) during exacerbation, in those at risk of exacerbation and (3) as asthma control worsens and exacerbation burden increases. Importantly, remote monitoring detected this better than single assessments of lung function as would be performed at a clinic visit. Future studies will need to confirm the generalisability of our findings in other cohorts, the clinical utility of this approach to direct treatment and improve important patient-reported outcome measures such as asthma control, exacerbation burden and exacerbation severity, to reduce the enormous health cost of asthma. The sad death from an asthma exacerbation of one of the participants recruited to this study prior to her baseline visit serves as an ongoing reminder of the importance of this line of research.

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Poluição atmosférica, suscetibilidade genética e risco de progressão de asma para DPOC

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RESUMO

Contexto No Reino Unido, estima-se que 15% dos doentes com asma tenham também doença pulmonar obstrutiva crônica (DPOC), embora as causas e mecanismos subjacentes permaneçam pouco compreendidos. Este estudo teve como objetivo investigar o papel da poluição atmosférica e da suscetibilidade genética na progressão de asma para DPOC.

Métodos Foram recrutados 46 832 participantes com asma do UK Biobank durante o período basal (2006–2010). As concentrações de partículas finas com diâmetro $\leq 2,5 \mu\text{m}$ ($\text{PM}_{2,5}$) e dióxido de azoto (NO_2) foram estimadas no endereço de residência utilizando modelos de regressão de uso do solo. Foi criado um índice de exposição à poluição atmosférica refletindo a exposição conjunta aos poluentes. O score de risco poligênico foi calculado com base em novos sinais genéticos identificados para coexistência de asma+DPOC. Modelos de regressão de riscos proporcionais de Cox foram utilizados para quantificar o risco associado à poluição atmosférica e ao risco genético no desenvolvimento de DPOC entre indivíduos asmáticos, ajustando para covariáveis.

Resultados Ao longo de um seguimento mediano de 10,84 anos, 3759 participantes com asma desenvolveram DPOC. Por cada aumento de um intervalo interquartil (IQR) em $\text{PM}_{2,5}$ e NO_2 , o risco de desenvolver DPOC foi: $\text{PM}_{2,5}$: HR 1,07 (IC 95% 1,02–1,11), NO_2 : HR 1,10 (IC 95% 1,04–1,15). Efeitos adversos foram observados em concentrações tão baixas quanto $8 \mu\text{g}/\text{m}^3$ para $\text{PM}_{2,5}$ e $12 \mu\text{g}/\text{m}^3$ para NO_2 . Foi identificada uma interação multiplicativa significativa entre poluição atmosférica e suscetibilidade genética. Indivíduos com maior risco genético apresentaram o risco mais elevado, com HR 1,13 (IC 95% 1,05–1,22) por aumento de um IQR no índice de poluição (p de interação $<0,05$).

Conclusões A poluição atmosférica está fortemente associada à progressão de asma para DPOC, especialmente entre indivíduos com elevado risco genético.

INTRODUCTION

In 2019, it was estimated that over 260 million people across the world were living with asthma, the most prevalent chronic respiratory disease affecting both children and adults.¹ Both asthma and chronic obstructive pulmonary disease (COPD) are characterised by airway obstruction of varying reversibility and airway inflammation, with similar symptoms and diagnostic criteria.² However, they are two different respiratory diseases, which can coexist in a patient particularly among older patients and smokers. A growing literature has shown that patients with both diseases experienced poorer prognosis including frequent exacerbations and shorter life expectancy as compared with those patients with either condition alone.³ The prevalence of this particular group of patients, sometimes being referred to as having 'asthma+COPD', ranges from 2% in the general population⁴ up to 60% among patients with asthma,⁵ depending on the use of varying diagnostic criteria across studies. Although asthma+COPD is a sizeable patient group with potentially more

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Across the world, there is a sizeable group of asthmatic patients who have developed chronic obstructive pulmonary disease (COPD) over time (asthma-COPD overlap, ACO), with aetiology being largely unknown. Air pollution could be a potential risk factor, according to only one previous study which yielded uncertain effect estimates due to the use of relatively coarse air pollution data at regional or neighbourhood level. It is not yet known whether the association between long-term exposure to air pollution and occurrence of ACO could be seen at individual patient level, and to what extent genetic risk is playing a role.

WHAT THIS STUDY ADDS

► To date, this is the largest study at individual patient level by using outcome, exposure and covariate data from the UK Biobank cohort. We found that long-term exposure to either fine particles (particulate matter with a diameter of $2.5 \mu\text{m}$) or nitrogen dioxide was significantly linked to the occurrence of COPD among patients with asthma at baseline. Moreover, for the first time, we have investigated the interactions between air pollution and genetic risk scores specifically for ACO. We found that asthmatic patients with high genetic risk scores were particularly vulnerable to developing COPD during the 10-year follow-up period.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► Findings of this study will inform the clinical guidelines on asthma management with regard to development of other respiratory morbidity due to long-term air pollution exposure. The study will also inform caregivers and asthma patients who can take measures to minimise their air pollution exposure and prevent asthmatic patients from developing COPD over time. Overall, adverse effects were even seen at relatively low concentrations of air pollution, indicating that stringent, societal-wide air quality policies are urgently needed to protect the public and patients' health.

severe clinical outcomes, research into its risk factors remains few apart from studies of tobacco smoking.⁶ Therefore, it is important to identify other novel risk factors and prevent those at-risk asthma patients from developing into asthma+COPD, which may signal changes in therapy as well as prognosis.

It is well established that air pollution is associated with acute exacerbation and new onset of asthma or COPD.^{7–9} However, whether, and the extent to which, air pollution exposure may contribute to the development of asthma+COPD among asthma patients is still largely unknown. Moreover, to our best knowledge, no studies to date have investigated the gene–air pollution interactions on the development of asthma+COPD, representing a major knowledge gap in disease prevention at individual level.

We hypothesised that patients with asthma who are chronically exposed to higher concentrations of air pollution could develop a certain degree of fixed obstruction over time. In this prospective cohort study, we aim to investigate the associations of long-term exposure to ambient air pollution and incident COPD among patients with asthma, and the role of gene–air pollution interactions on these associations.

METHODS

Study population and design

The data used in this study were from the UK Biobank, a large-scale prospective biomedical database that enrolled over 500 000 participants aged 40–69 years from 22 assessment centres across England, Scotland and Wales between 2006 and 2010.¹⁰ On baseline recruitment, data on sociodemographic characteristics, lifestyles and health information were collected through touch-screen questionnaires, physical and biological measurements, with follow-up of disease morbidity and mortality via record linkages.

This is a prospective study, in which only participants with asthma but without COPD at baseline (identified either through the first occurrence medical records or self-reported answers, see online supplemental eMethod for ICD code list) were included in the analysis. These participants were then followed up to 29 February 2020, for the first occurrence of COPD. Individuals withdrawing or with missing information on air pollutants and covariates in the main analysis were subsequently excluded.

Ambient air pollution assessment

Air pollution estimates for particulate matter (PM) with aerodynamic diameter of 2.5 µm or less (PM_{2.5}), PM with aerodynamic diameter between 2.5 µm and 10 µm (PM_{2.5–10}), nitrogen dioxide (NO₂) and nitrogen oxides (NO_x) were modelled for each participant's residential address using land use regression models. Since the air pollution levels in UK Biobank were only available at the baseline when the participants were enrolled, annual average air pollution concentrations of the baseline year 2010 were used. Geographical information system-derived variables, mainly including traffic intensity, population density and land use, were used to model the spatial variation of mean annual air pollution concentrations. Ambient air pollution concentrations were assigned to the participants using their geocoded residential address on a 100×100 m grid.¹¹ The median model-explained variance (R²) for PM_{2.5}, PM_{2.5–10}, NO₂ and NO_x was 71%, 68%, 82% and 78%, respectively.^{12–13} Nitric oxide (NO) concentrations were derived by subtracting NO₂ from NO_x.¹⁴ An air pollution score was subsequently developed using principal component analysis, considering high correlations among multiple air pollutants.^{15–16} Considering the fluctuations of temporal trends of most air pollutants were generally stable during the study period,¹⁷ the average values of ambient air pollution in the year 2010 used as a surrogate measure of long-term exposure, as most previous environmental epidemiological studies.^{18–20}

Follow-up and outcome identification

Participants were followed from the time of enrolment until the occurrence of COPD diagnosis, loss to follow-up, death or the end of follow-up on 29 February 2020, whichever occurred first. Incident COPD cases were ascertained from algorithmically defined

outcomes in the UK Biobank, which incorporated information from baseline assessment data, along with linked data from primary care, hospital inpatient admissions, death records and self-reports (see online supplemental eMethod for the International Classification of Diseases code list).

Polygenic risk score calculation

In the UK Biobank, genotyping was conducted using high-density single-nucleotide polymorphism (SNP) arrays, following protocols established in previous genomic studies.²¹ In the present study, we included eight SNPs for asthma+COPD, as reported in a recent GWAS study using UK Biobank data.²² These SNPs were selected based on their demonstrated relevance to the genetic aetiology of asthma+COPD, providing comprehensive coverage of the genetic variants of interest. All eight SNPs were available in the UK Biobank imputed database, ensuring accurate representation and reliability of the genetic data. Each SNP was recoded as 0, 1 or 2 based on the number of risk alleles. Polygenic risk score (PRS) was calculated using a weighted sum approach, incorporating the effect sizes from the selected SNPs.²³ The formula used for the PRS calculation was: $PRS = \sum_{j=1}^M \beta_j \times SNP_j$, where M is the total number of SNPs, and j is per allele log OR for asthma+COPD associated with SNP_j.^{24–25} The ORs were taken from the previous study.²³ Furthermore, the PRS was categorised into three risk groups based on tertiles: low (tertile 1), intermediate (tertile 2) and high (tertile 3) genetic risk.

Covariates

Based on prior literature, sociodemographic characteristics, socioeconomic status and lifestyle factors were considered as covariates, and an illustrative directed acyclic graph was drawn to discern which covariates are confounders (online supplemental figure S1).²⁶ Sociodemographic characteristics included age, sex, ethnicity, body mass index (BMI), length of time at residence and assessment centre. Socioeconomic status contained area-level Townsend Deprivation Index, and participant's education level, as well as economic status. Lifestyle factors included smoking status and alcohol consumption. The detailed information of covariates is provided in online supplemental eMethods.

Statistical analyses

Characteristics of the study population were presented as means with SDs for continuous variables and as numbers with percentages for categorical variables.

Cox proportional hazards regression models were performed to estimate the associations of ambient air pollution and genetic susceptibility with incident COPD among asthmatics. Crude model (model 1) was adjusted for age, sex, ethnicity, assessment centre, smoking status and alcohol consumption. Main model (model 2) was further adjusted for Townsend Deprivation Index, education level, BMI, economic status and length of time at residence. Schoenfeld residuals were used to test the assumption of proportional hazards.

The analysis incorporated air pollution exposure as both categorical variables stratified into quartiles and continuous variables, for the latter HR was presented as per IQR increase of each exposure. Exposure-response curve between air pollution and incident COPD in all asthmatics as well as divided by different PRS scores was depicted using restricted cubic spline functions with three knots, based on the Akaike information criterion.

Further analysis to investigate the potential multiplicative and additive interactions between air pollution exposure and genetic risk was conducted. The interactions in the multiplicative scale were estimated by adding the cross-product term in the Cox model. The additive interactions were evaluated by the relative excess risk due to the interaction (RERI) and the attributable proportion due to the interaction (AP). The corresponding 95% CIs of the RERI and AP were generated by drawing 2000 bootstrap samples from the estimation dataset. If there were no additive interactions, the 95% CIs would include 0. Subgroup analysis was performed based on the hypothesis that the associations of air pollution and incident COPD

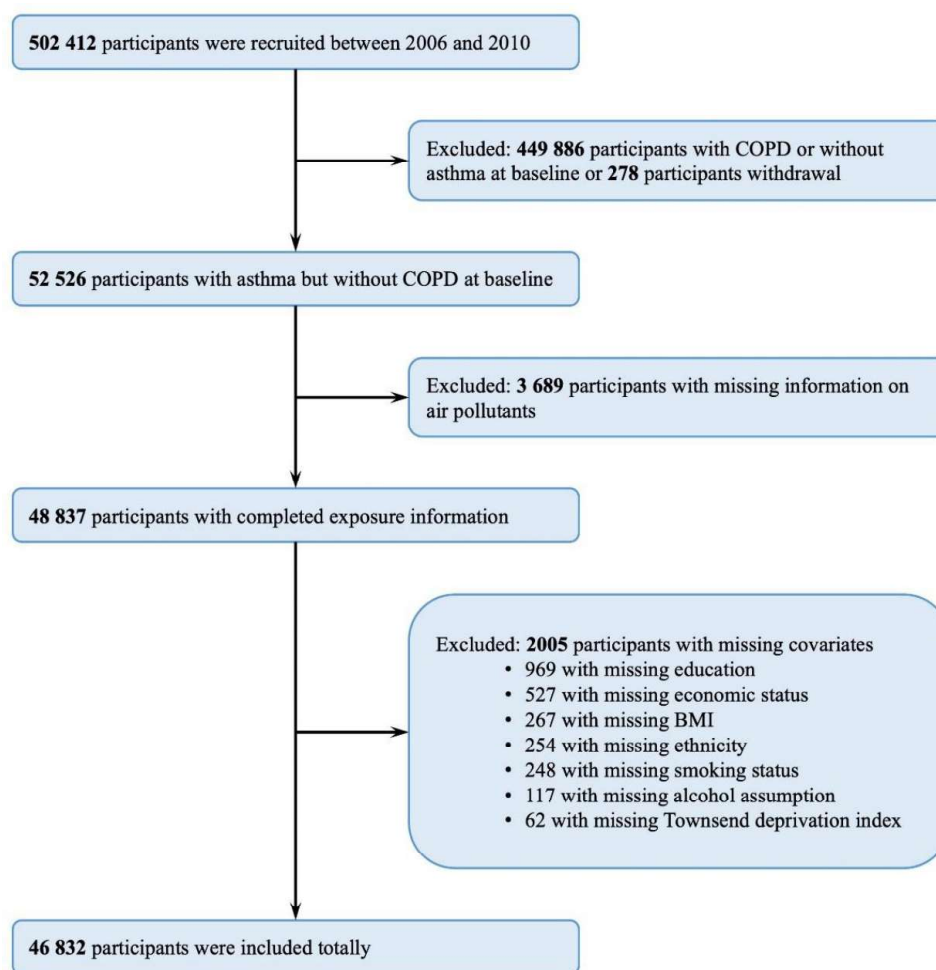


Figure 1 Flow chart of the participants included in the study. BMI, body mass index; COPD, chronic obstructive pulmonary disease.

in the asthmatics may be modified by age, sex, education level, economic status, smoking status as well as BMI. Group comparisons were assessed by P-interaction value, and a Bonferroni-corrected two-sided p value of 0.008 was used as the significance threshold for the six interaction analyses due to multiple comparisons.

Furthermore, several sensitivity analyses were conducted to examine the robustness of the results. First, considering the competing risk of mortality, a Fine-Gray model which takes into account the informative censoring nature of the competing risk events was used.²⁷ The Fine-Gray model can be fit using `crmmulti()` function shipped with the `finalfit` package (https://argoshare.is.ed.ac.uk/healthyr_book/competing-risks-regression.html). Considering that the mortality rate is less than 5%, the above-mentioned analysis was added as an important sensitivity analysis in the Online supplemental material. Second, comorbidities including hypertension and type 2 diabetes mellitus were further adjusted in the main model. Third, multiple imputation using chained equations by exposures and covariates was conducted considering the potential bias of missing data. Fourth, the analysis was restricted to individuals who had resided at the same address throughout the follow-up period to minimise misclassification of long-term air pollution exposures. Fifth, participants who were diagnosed with COPD within the first 5 years of follow-up were excluded to evaluate the stability of the observed associations. Sixth, PRS were calculated using two different approaches to assess different PRS estimations (PRS1 and PRS2) on the results (further details are provided in online supplemental table S1). Last but not least, as greenness is also related to the risk of respiratory disease, sensitivity analysis was added to consider the influence of greenness.

All analyses were performed with R software, V.4.2.2.

RESULTS

Descriptive statistics

A total of 46 832 participants with asthma were included in the final analysis after excluding those with COPD or without asthma

at baseline, the withdrawal participants as well as those with missing information (figure 1). Among whom 3759 developed COPD during follow-up, while 43 073 did not over a median follow-up of 10.84 years. The mean age of participants was 55.6 years, and 57.9% were female. Participants with incident COPD were significantly more likely to be younger, with 35.1% under 65 years compared with 15.4% in the non-COPD group ($p<0.001$) and male (48.5% vs 41.5%, $p<0.001$). Socioeconomic differences were also evident, as the COPD group exhibited higher levels of deprivation according to the Townsend Deprivation Index ($p<0.001$), had lower education levels ($p<0.001$) and were more likely to have an inactive economic status ($p<0.001$). The median (SD) concentrations of air pollutants were: $PM_{2.5}$, 10.00 (1.06) $\mu\text{g}/\text{m}^3$; $PM_{2.5-10}$, 6.43 (0.90) $\mu\text{g}/\text{m}^3$; NO_2 , 26.67 (7.63) $\mu\text{g}/\text{m}^3$ and NO , 17.45 (9.11) $\mu\text{g}/\text{m}^3$. The COPD group was exposed to higher median levels of $PM_{2.5}$, NO_2 and NO compared with the non-COPD group (table 1). The Spearman correlations between air pollutants are presented in online supplemental table S2.

Association between air pollution and COPD incidence among participants with asthma

Figure 2 illustrates the exposure-response curves of air pollution and incidence of COPD. We found a positive association between air pollution score and increased HR for COPD, indicating a higher risk of progression from asthma to asthma+COPD as the air pollution scores increase. For $PM_{2.5}$, significant effects were observed at concentrations as low as 8 $\mu\text{g}/\text{m}^3$, which highlights the risk that can be posed by even relatively low concentrations of $PM_{2.5}$. The curve for NO_2 showed a slightly steeper gradient as compared with that of $PM_{2.5}$, with notable adverse effects starting from around 12 $\mu\text{g}/\text{m}^3$ and a more pronounced rise in HR at higher concentrations. A similar trend was observed for NO as well, while no associations were found with coarse particles. Exposure to air pollution significantly increased the risk of COPD among participants with

Table 1 Demographic characteristics of the asthma population with and without the progression to COPD

	All participants	COPD	Non-COPD	P value
Number	46832	3759	43 073	
Follow-up years, mean (SD)	10.42 (2.03)	6.16 (3.07)	10.79 (1.39)	
Age, years, mean (SD)	55.59 (8.28)	55.16 (8.25)	60.60 (6.85)	<0.001
Age, N (%)				<0.001
<65 years	7942 (17.0)	1320 (35.1)	6622 (15.4)	
≥65 years	38890 (83.0)	2439 (64.9)	36 451 (84.6)	
Sex, N (%)				<0.001
Female	27 117 (57.9)	1936 (51.5)	25 181 (58.5)	
Male	19 715 (42.1)	1823 (48.5)	17 892 (41.5)	
Ethnicity, N (%)				<0.001
White	44 210 (94.4)	3619 (96.3)	40 591 (94.2)	
Others	2622 (5.6)	140 (3.7)	2482 (5.8)	
Length of time at residence, N (%)				
≥10 years	30 714 (65.6)	2474 (65.8)	28 240 (65.6)	0.769
<10 years	16 118 (34.4)	1285 (34.2)	14 833 (34.4)	
Townsend deprivation index, N (%)				<0.001
Quartile 1	9261 (19.8)	495 (13.2)	8766 (20.4)	
Quartile 2	9115 (19.5)	558 (14.8)	8557 (19.9)	
Quartile 3	9188 (19.6)	597 (15.9)	8591 (19.9)	
Quartile 4	9689 (20.7)	825 (21.9)	8864 (20.6)	
Quartile 5	9579 (20.5)	1284 (34.2)	8295 (19.3)	
Education level, N (%)				<0.001
University or college degree	16 139 (34.5)	586 (15.6)	15 553 (36.1)	
Others	30 693 (65.5)	3173 (84.4)	27 520 (63.9)	
Economic status, N (%)				<0.001
Active	27 809 (59.4)	1225 (32.6)	26 584 (61.7)	
Inactive	19 023 (40.6)	2534 (67.4)	16 489 (38.3)	
Smoking status				
Former or current smokers	20 562 (43.9)	2769 (73.7)	17 793 (41.3)	<0.001
Never-smokers	26 270 (56.1)	990 (26.3)	25 280 (58.7)	
Alcohol assumption				
Never	4136 (8.8)	449 (11.9)	3687 (8.6)	<0.001
Special occasions only	5888 (12.6)	658 (17.5)	5230 (12.1)	
One to three times a month	5473 (11.7)	378 (10.1)	5095 (11.8)	
Once or twice a week	11 695 (25.0)	845 (22.5)	10 850 (25.2)	
Three or four times a week	10 429 (22.3)	652 (17.3)	9777 (22.7)	
Daily or almost daily	9211 (19.7)	777 (20.7)	8434 (19.6)	
BMI, kg/m ² , median (SD)	28.13 (5.28)	29.33 (5.89)	28.02 (5.21)	<0.001
PM _{2.5} , µg/m ³ , median (SD)	10.00 (1.06)	10.22 (1.11)	9.98 (1.06)	<0.001
PM _{2.5-10} , µg/m ³ , median (SD)	6.43 (0.90)	6.44 (0.88)	6.43 (0.90)	0.466
NO ₂ , µg/m ³ , median (SD)	26.67 (7.63)	27.97 (7.66)	26.56 (7.61)	<0.001
NO, µg/m ³ , median (SD)	17.45 (9.11)	18.91 (9.70)	17.32 (9.05)	<0.001

BMI, body mass index; COPD, chronic obstructive pulmonary disease; NO₂, nitrogen dioxide; NO, nitric oxide; PM_{2.5}, particulate matter with aerodynamic diameter ≤2.5 µm; PM_{2.5-10}, PM with aerodynamic diameter between 2.5 and 10 µm.

asthma (table 2). Specifically, after adjusting for all covariates in model 2, each IQR increase in PM_{2.5} was associated with an HR of 1.07 (95% CI 1.02 to 1.11; p=0.003). The HR was 1.18 (95% CI 1.07 to 1.31; p<0.001) for fourth quartile compared with the lowest quartile. Notably, exposure to NO₂ demonstrated relatively stronger effects. Each IQR increase in NO₂ was associated with an HR of 1.10 (95% CI 1.04 to 1.15; p<0.001). The HRs were 1.15 (95% CI 1.04 to 1.27; p=0.006), 1.19 (95% CI 1.07 to 1.32; p=0.001) and

1.22 (95% CI 1.09 to 1.37; p<0.001) for second to fourth quartile compared with the lowest quartile, respectively. Similar associations were found for NO as well.

The first principal component which contributed to 85.4% of the total variance was chosen to represent the air pollution score. Each IQR increase in the air pollution score was associated with an HR of 1.07 (95% CI 1.03 to 1.11; p=0.001). Compared with the lowest quartile of the air pollution score, the HRs of COPD were 1.14 (95% CI 1.03 to 1.26; p=0.012) and 1.17 (95% CI 1.05 to 1.30; p=0.004) in 3rd and 4th quartiles, respectively. In sensitivity analyses, the associations presented in the main models remained robust including taking the competing risk of mortality as well as the influence of greenness into consideration, etc (online supplemental tables S3–S8). Additionally, in subgroup analyses, we observed that among asthma cases, individuals who were older, female, had a BMI greater than 30 kg/m², attained higher education levels and had a history of smoking tended to exhibit a higher incidence of COPD. However, no significant effect modification by any of these factors was detected (online supplemental table S9).

Association between air pollution and COPD by different genetic risk

We observed a joint effect of genetic risks and air pollution on COPD risk among patients with asthma. As depicted in figure 3, the exposure-response curves illustrate that participants with a high genetic risk exhibited the highest risk of developing incident COPD as concentrations of air pollution increased, compared with those with a low genetic risk.

Table 3 further elucidates the interaction effects of air pollution and PRS on incident COPD. Specifically, for PM_{2.5}, the HRs were 1.06 (95% CI 0.97 to 1.15; p=0.200), 1.06 (95% CI 0.98 to 1.15; p=0.155) and 1.12 (95% CI 1.04 to 1.22; p=0.004) in the low, intermediate and high PRS groups, respectively. Furthermore, exposure to NO₂ demonstrated even stronger associations, particularly in the high PRS group, with an HR of 1.19 (95% CI 1.08 to 1.31; p<0.001). For NO, the HR in the high PRS group was 1.08 (95% CI 1.02 to 1.15; p=0.007), and the interaction effect between NO exposure and PRS was significant in the high PRS group (Pinteraction=0.042). However, no significant associations were observed for PM_{2.5-10} across any PRS groups. For the air pollution score, the HR in the high PRS group was 1.13 (95% CI 1.05 to 1.22; p=0.001), which was higher than those seen in the low and intermediate PRS groups (Pinteraction=0.045), further suggesting a joint effect of genetic risks and air pollution on incident COPD risk among asthmatics. The results remained significant when including the competing risk of mortality as well as the influence of greenness into consideration (online supplemental tables S10 and S11), and using PRS 1 and PRS 2 separately (online supplemental tables S12, S13 and figures S2, S3). No additive interaction was observed between air pollution and PRS on the risk of incident COPD among participants with asthma (online supplemental table S14).

DISCUSSION

This is a large population-based prospective cohort study with over a decade of follow-up for incident COPD among patients with asthma. We here reported that higher exposure to air pollution, particularly that is closely related to road traffic (PM_{2.5} and NO₂), is a significant risk factor for developing COPD among patients with asthma. Notably, such associations appear to be only observed among those patients who carry high PRSs for asthma+COPD. These findings are novel to inform current clinical guidelines in managing asthma with comorbidities, specifically COPD, by taking into account both environmental exposures and individual genetic risks.

Our study is an important addition to current knowledge as the evidence base on this investigated topic is weak. A previous study in Ontario, Canada was the first, and the only one to date, to report the effects of air pollution on asthma progression to COPD.²⁸ The study included a sample of 6040 adults from the Canadian Community Health Survey who had asthma between 1996 and 2009, and were followed until 2014 for asthma+ COPD.

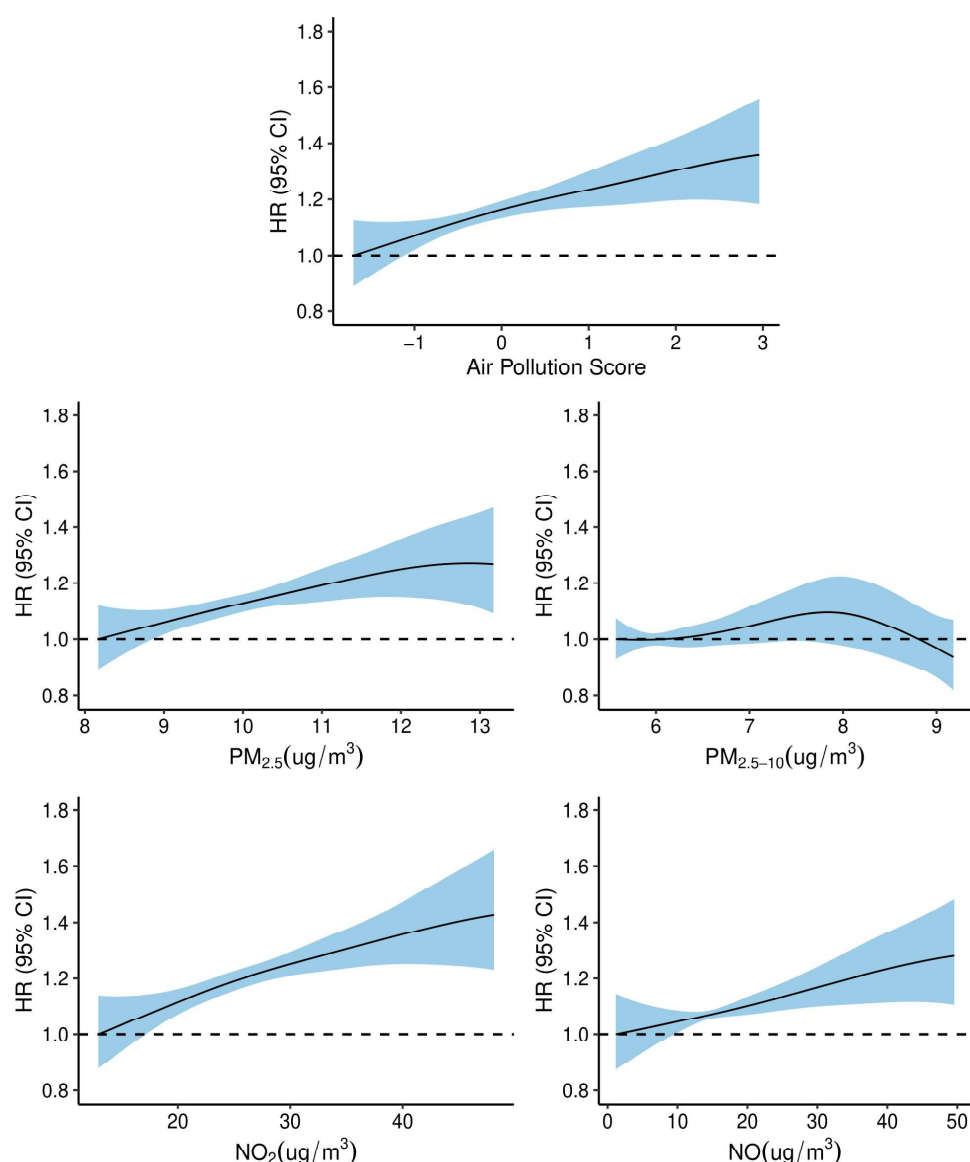


Figure 2 Exposure-response curves between air pollution and incidence of chronic obstructive pulmonary disease in the asthma population. The results were based on the main model, which was adjusted for age, sex, ethnicity, BMI, length of time at residence, assessment centre, Townsend Deprivation Index, education level, economic status, smoking status and alcohol consumption. Air pollution level ranges from the 0th to 99th percentiles. BMI, body mass index; NO_2 , nitrogen dioxide; NO, nitric oxide; $\text{PM}_{2.5}$, particulate matter with aerodynamic diameter $\leq 2.5 \mu\text{m}$; $\text{PM}_{2.5-10}$, PM with aerodynamic diameter between 2.5 and $10 \mu\text{m}$.

630 asthma+COPD cases were identified at the end of follow-up. It was found that for every $10 \mu\text{g}/\text{m}^3$ increase in annual average $\text{PM}_{2.5}$, the adjusted HR was 2.78 (95% CI 1.62 to 4.78). This effect size is much higher than what we found for $\text{PM}_{2.5}$ in the UK Biobank for the same unit increase. Some notable differences between the two studies may have explained this discrepancy. First, the Canadian study adopted a crude exposure assessment for each study participant. Same concentrations, derived using inverse distance-weighted interpolation method from fixed-site monitors, were assigned to all participants living within the same census division, the size of which varies considerably within Ontario (between 663 and 439 000 km^2).²⁹ In our study, we adopted an individualised modelling approach in assessing air pollution exposures with relatively good predictive performances. The extent of exposure misclassification, therefore, is expected to be much less than that of the approach used in the Canadian study. Second, our study sample size was larger than the Canadian study by a factor of eight, and we were able to consider more individual-level factors such as ethnicity, education and income, which may further refine the effect estimates we reported. However, in our study, we could not co-adjust NO_2 for $\text{PM}_{2.5}$ estimates given the high correlation, whereas in the Canadian study the effect of $\text{PM}_{2.5}$ seemed to be independent from that of ozone. Consistent

with previous studies,^{30,31} our findings suggest that NO_2 may exert a more pronounced effect on COPD risk compared with $\text{PM}_{2.5}$. While long-term exposure to $\text{PM}_{2.5}$ has been associated with reduced lung function, emphysematous changes and chronic airway inflammation,³² NO_2 may have a stronger impact due to its properties as a reactive gaseous pollutant that can penetrate deep into the airways, directly irritate the respiratory epithelium and subsequently trigger inflammatory responses.³³

A recent study by Wang et al using the same UK Biobank resource investigated the effects of air pollution on disease progression of chronic respiratory disease using multistate models.³⁴ However, this study is not directly comparable to our study given the completely different study designs and research questions. One of their study subgroups was those participants who were free from asthma at baseline ($n=265\,493$), but during the follow-up period (median 11.9 years) these participants first developed asthma ($n=6317$), and then went on to develop either COPD or lung cancer ($n=490$), a state the authors coined as 'chronic lung multimorbidity'. Among these 6317 incident asthma cases during the follow-up, for every $5 \mu\text{g}/\text{m}^3$ increase in annual average $\text{PM}_{2.5}$ and NO_2 , respectively, the HRs for developing into 'chronic lung multimorbidity' state were 2.01 (95% CI: 1.32 to 3.08) and 1.12 (95% CI: 1.06 to 1.18), respectively. From a clinical perspective,

Table 2 Associations of incidence of chronic obstructive pulmonary disease in the asthma population with exposure to multiple air pollutants

Air pollutants	Number of cases/person-years	Model 1*		Model 2†	
		HR (95% CI)	P value	HR (95% CI)	P value
PM _{2.5}					
Quartile 1	722/122 918	ref		ref	
Quartile 2	867/121 300	1.15 (1.04 to 1.27)	0.007	1.06 (0.96 to 1.17)	0.237
Quartile 3	945/121 613	1.24 (1.13 to 1.37)	<0.001	1.07 (0.96 to 1.18)	0.213
Quartile 4	1225/122 212	1.53 (1.39 to 1.69)	<0.001	1.18 (1.07 to 1.31)	0.001
Per IQR	3759/488 043	1.20 (1.16 to 1.25)	<0.001	1.07 (1.02 to 1.11)	0.003
PM _{2.5-10}					
Quartile 1	831/118 533	ref		ref	
Quartile 2	949/124 821	1.02 (0.93 to 1.12)	0.619	1.00 (0.91 to 1.10)	0.960
Quartile 3	996/122 566	1.13 (1.03 to 1.25)	0.009	1.04 (0.95 to 1.14)	0.407
Quartile 4	983/122 123	1.14 (1.03 to 1.25)	0.009	1.05 (0.95 to 1.15)	0.357
Per IQR	3759/488 043	1.02 (0.99 to 1.04)	0.300	1.00 (0.97 to 1.03)	0.949
NO ₂					
Quartile 1	687/124 001	ref		ref	
Quartile 2	936/122 450	1.28 (1.16 to 1.41)	<0.001	1.15 (1.04 to 1.27)	0.006
Quartile 3	1035/121 400	1.42 (1.29 to 1.57)	<0.001	1.19 (1.07 to 1.32)	0.001
Quartile 4	1101/120 192	1.62 (1.46 to 1.80)	<0.001	1.22 (1.09 to 1.37)	<0.001
Per IQR	3759/488 043	1.25 (1.20 to 1.31)	<0.001	1.10 (1.04 to 1.15)	<0.001
NO					
Quartile 1	742/123 188	ref		ref	
Quartile 2	895/121 690	1.15 (1.04 to 1.27)	0.005	1.06 (0.96 to 1.17)	0.213
Quartile 3	966/121 470	1.22 (1.11 to 1.34)	<0.001	1.06 (0.96 to 1.17)	0.234
Quartile 4	1156/121 695	1.40 (1.27 to 1.54)	<0.001	1.11 (1.00 to 1.22)	0.047
Per IQR	3759/488 043	1.10 (1.07 to 1.13)	<0.001	1.04 (1.01 to 1.07)	0.020
Air Pollution Score					
Quartile 1	710/123 877	ref		ref	
Quartile 2	875/122 280	1.17 (1.06 to 1.29)	0.002	1.07 (0.97 to 1.18)	0.182
Quartile 3	1009/120 712	1.35 (1.23 to 1.49)	<0.001	1.14 (1.03 to 1.26)	0.012
Quartile 4	1165/121 175	1.54 (1.39 to 1.70)	<0.001	1.17 (1.05 to 1.30)	0.004
Per IQR	3759/488 043	1.18 (1.14 to 1.23)	<0.001	1.07 (1.03 to 1.11)	0.001
IQR for PM _{2.5} :1.27 µg/m ³ , IQR for PM _{2.5-10} :0.80 µg/m ³ , IQR for NO ₂ :9.97 µg/m ³ , IQR for Air Pollution Score: 1.13. Bold indicates the associations with statistical significance in the fully adjusted model.					
*Model 1 was adjusted for age, sex, ethnicity, assessment centre, smoking status and alcohol consumption.					
†Model 2 was adjusted for age, sex, ethnicity, BMI, length of time at residence, assessment centre, Townsend Deprivation Index, education level, economic status, smoking status and alcohol consumption (main model).					
BMI, body mass index; NO, nitric oxide; NO ₂ , nitrogen dioxide; PM _{2.5} , particulate matter with aerodynamic diameter ≤2.5 µm; PM _{2.5-10} , PM with aerodynamic diameter between 2.5 and 10 µm.					

IQR for PM_{2.5}:1.27 µg/m³, IQR for PM_{2.5-10}:0.80 µg/m³, IQR for NO₂:9.97 µg/m³, IQR for Air Pollution Score: 1.13. Bold indicates the associations with statistical significance in the fully adjusted model.

*Model 1 was adjusted for age, sex, ethnicity, assessment centre, smoking status and alcohol consumption.

†Model 2 was adjusted for age, sex, ethnicity, BMI, length of time at residence, assessment centre, Townsend Deprivation Index, education level, economic status, smoking status and alcohol consumption (main model).

BMI, body mass index; NO, nitric oxide; NO₂, nitrogen dioxide; PM_{2.5}, particulate matter with aerodynamic diameter ≤2.5 µm; PM_{2.5-10}, PM with aerodynamic diameter between 2.5 and 10 µm.

it is difficult to interpret these findings as both incident cases of COPD and lung cancer were combined as a study outcome. In addition, the follow-up period for either incident COPD or lung cancer among these asthmatic patients was relatively short. This might be particularly problematic for lung cancer, as some cases may be undiagnosed in early stages before asthma occurrence during the follow-up. Pathogenies of COPD and lung cancer due to air pollution among asthmatic airways are not necessarily identical.³⁵ Asthma and COPD are two of the most common chronic respiratory diseases and the coexistence of both chronic conditions in the same patient is being increasingly recognised. Therefore, it is important that our analysis provided direct, interpretable findings for the air pollution risk on development of asthma+COPD only, a notable health condition for which risk factors are currently poorly understood.

To our best knowledge, this is the first study looking into gene–air pollution interactions of asthma+COPD susceptibility. A novel finding of our study is that the risk of air pollution on asthma progression to asthma+COPD seems to be only found among participants who carry high PRS. This finding has en-

hanced our understanding of biological mechanisms underlying asthma+COPD development by studying gene by environment interactions. It will potentially inform future clinical guideline development in the context of personalised medicine, which will help earlier identification and targeted treatment for those at-risk patient groups.

Strengths of this study include a relatively large sample size with individual-level covariate and genetic risk data, and the findings indicated that asthma populations with high genetic risk should be paid attention to develop COPD comorbidity under ambient air pollution exposure. Furthermore, adverse effects could be observed at concentrations as low as 8 µg/m³ for PM_{2.5} and 12 µg/m³ for NO₂ in our study, which indicated the necessity of stricter regulations of air pollution. In the latest WHO global air quality guidelines 2021, the annual concentrations for PM_{2.5} reduced from 10 µg/m³ to 5 µg/m³, and the annual concentrations for NO₂ reduced from 40 µg/m³ to 10 µg/m³. Considering that many countries' air quality standards are still well above the latest WHO global air quality guidelines 2021, stricter standards or regulations for air pollution control should be implemented

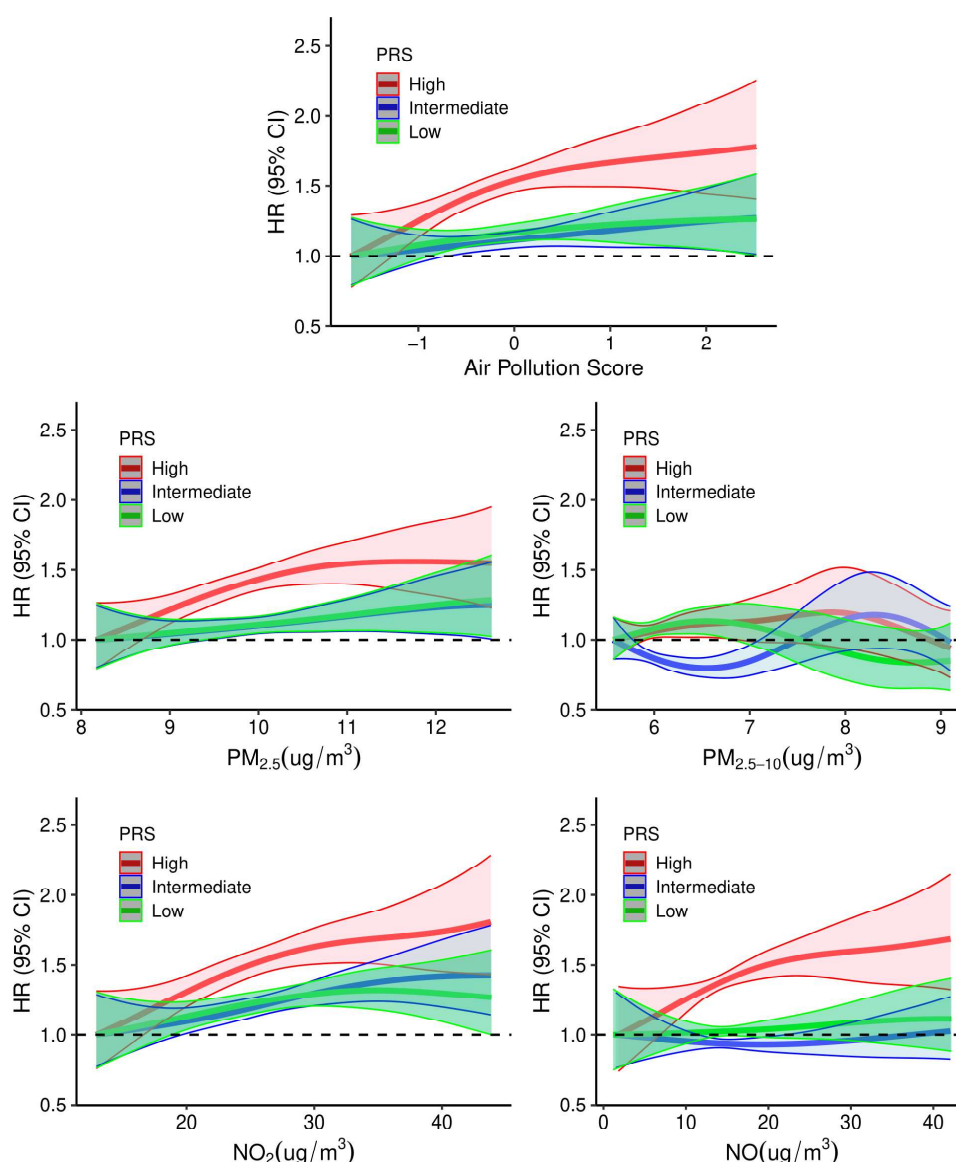


Figure 3 Exposure-response curves between air pollution and incidence of chronic obstructive pulmonary disease in the asthma population with different polygenic risk scores. The results were based on the main model, which was adjusted for age, sex, ethnicity, BMI, length of time at residence, assessment centre, Townsend Deprivation Index, education level, economic status, smoking status and alcohol consumption. BMI, body mass index; NO₂, nitrogen dioxide; NO, nitric oxide; PM_{2.5}, particulate matter with aerodynamic diameter ≤2.5 µm; PM_{2.5-10}, PM with aerodynamic diameter between 2.5 and 10 µm; PRS, Polygenic Risk Score.

to alleviate the disease burden of COPD among asthma populations.

However, this study has several limitations. First, there are two main sources of ‘measurement error’ in the analysis. About the ‘measurement error’ for exposure to ambient air pollution, we used 1-year average air pollution concentrations to capture the long-term exposure as most previous environmental epidemiological studies.^{18–20} Such choice might induce exposure misclassification, though the temporal trends of the air pollution remained stable during the study period. Furthermore, indoor air pollution and occupational exposure to air pollution were not measured in this study, which would lead to potential residual confounding. Further analysis would be performed if the related data were available. About the ‘measurement error’ for PRS, a real challenge is that the research community has not adopted any universal best practices for reporting PRS, and there are inconsistencies in how PRS are calculated and reported. These differences threaten to compromise the adoption of PRS in epidemiological studies. A 22-item framework which was created by the National Human Genome Research Institute has identified the minimal PRS-related information that scientists should include in their studies.³⁶ This framework would help to promote the validity, transparency

and reproducibility of PRS in future studies. Second, there is a possibility of outcome misclassification. For example, it might be difficult to differentiate the diagnosis between asthma and COPD, particularly among older participants, or clinicians may be reluctant to diagnose, or less likely to suspect, COPD among non-smokers.³⁷ Third, we cannot capture changes in some time-varying individual-level factors such as tobacco smoking habits or BMI during the follow-up, which might bias the effect estimates of incident COPD. Fourth, it is impossible for our study to obtain detailed clinical information to characterise different phenotypes of heterogeneous asthma-COPD overlap condition, and to study their respective associations with air pollution exposure. Fifth, study participants in UK Biobank are predominantly white population, which limits the generalisability of the study findings to other ethnic groups.

CONCLUSIONS

In conclusion, this study found that long-term exposure to ambient air pollution, indicated by PM_{2.5} or NO₂, was significantly associated with development of COPD among asthma patients. However, such associations were only evident among participants who carry high polygenic risk scores for asthma+ COPD. Our

Table 3 Associations of multiple air pollutants exposure with incidence of chronic obstructive pulmonary disease in the asthma population with different PRS

Air pollutants	PRS	Number of cases/person-years	HR (95% CI)	P value	P interaction
PM _{2.5}	Low	965/12 741	1.06 (0.97 to 1.15)	0.200	--
	Intermediate	1029/12 741	1.06 (0.98 to 1.15)	0.155	0.877
	High	1022/12 741	1.12 (1.04 to 1.22)	0.004	0.104
PM _{2.5-10}	Low	965/12 741	0.98 (0.92 to 1.04)	0.500	--
	Intermediate	1029/12 741	1.02 (0.97 to 1.08)	0.412	0.292
	High	1022/12 741	1.01 (0.96 to 1.07)	0.612	0.464
NO ₂	Low	965/12 741	1.06 (0.96 to 1.17)	0.255	--
	Intermediate	1029/12 741	1.10 (1.00 to 1.21)	0.052	0.684
	High	1022/12 741	1.19 (1.08 to 1.31)	<0.001	0.054
NO	Low	965/12 741	1.01 (0.95 to 1.08)	0.786	--
	Intermediate	1029/12 741	1.03 (0.97 to 1.09)	0.376	0.634
	High	1022/12 741	1.08 (1.02 to 1.15)	0.007	0.042
Air pollution score	Low	965/12 741	1.04 (0.96 to 1.13)	0.336	--
	Intermediate	1029/12 741	1.06 (0.98 to 1.14)	0.130	0.716
	High	1022/12 741	1.13 (1.05 to 1.22)	0.001	0.045

The results were based on the main model, which were adjusted for age, sex, ethnicity, assessment centre, smoking status and alcohol consumption, Townsend Deprivation Index, education level, economic status, BMI and length of time at residence. The HRs were estimated by an IQR increase in multiple air pollutants. Bold values indicate statistical significance. BMI, body mass index; NO, nitric oxide; NO₂, nitrogen dioxide; PM_{2.5}, particulate matter with aerodynamic diameter ≤2.5 µm; PM_{2.5-10}, PM with aerodynamic diameter between 2.5 and 10 µm; PRS, polygenic risk score.

findings provide novel evidence for gene by environment interactions of asthma+COPD susceptibility and hence important clinical implications, enabling targeted prevention and treatment of asthma+COPD in the future.

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Contributors JH and GL has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: JH and YSC; Acquisition, analysis or interpretation of data: GL, JH, KZ and TY; Drafting of the manuscript: JH, YSC, KZ and GL; Critical revision of the manuscript for important intellectual content: all authors; Statistical analysis: GL, JH, TY and JJ; Obtained funding: JH and YSC; Administrative, technical or material support: JH; Supervision: JH and YSC. As the guarantor (JH) accepts full responsibility for the finished work and/or the conduct of the study, had access to the data and controlled the decision to publish.

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Ethics approval This study involves human participants. The UK Biobank has approval from the North West Multi-centre Research Ethics Committee (21/ NW/0157), and participants have provided written consent.

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Segurança, viabilidade e eficácia do exercício como técnica de desobstrução brônquica na fibrose quística: um ensaio piloto randomizado de viabilidade

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RESUMO

Objetivos Testar a viabilidade e a segurança do exercício como técnica de desobstrução brônquica (Exercise as Airway Clearance Technique — ExACT) para pessoas com fibrose quística (pwCF), em comparação com os cuidados habituais (UC).

Métodos Ensaio piloto randomizado, de dois braços, realizado em dois centros. Foram recrutadas 50 pessoas com fibrose quística (≥ 10 anos, FEV₁ $\geq 40\%$ do previsto), clinicamente estáveis sob Elexacaftor/Tezacaftor/Ivacaftor; 48 foram aleatorizadas (1:1, com minimização) para ExACT diário (suspensão de todas as outras técnicas de desobstrução brônquica) ou UC. A viabilidade foi avaliada através de recrutamento, retenção e adesão, comparados com critérios de progressão pré-definidos. As principais medidas de segurança e sinais de eficácia incluíram espirometria (FEV₁), lung clearance index (LCI_{2.5}), agudizações pulmonares, atividade física, carga terapêutica e qualidade de vida ao longo de 28 dias. Foram ainda recolhidos dados qualitativos de entrevistas e dados preliminares de economia da saúde.

Resultados O ExACT foi seguro ao longo de 28 dias, evidenciado pelas alterações em: LCI_{2.5}: ExACT $-0,1$ (0,6) vs UC $+0,2$ (0,8), média (DP) FEV₁ (% previsto): ExACT $+2,1$ (6,6) vs UC $-0,8$ (5,5). As diferenças relativas (ExACT/UC) de $0,97$ ($0,92-1,02$) para LCI_{2.5} e as diferenças absolutas de $+3,2\%$ ($-0,6$ a $6,9$) para FEV₁ sugerem potencial eficácia da intervenção. Poucos eventos adversos foram reportados; nenhum grave. Os dados de viabilidade apoiam a progressão para um ensaio definitivo: 48/117 (41%) dos abordados foram randomizados, 45/48 (92%) completaram o estudo. Adesão global de 60%.

Discussão O teste da hipótese primária num ensaio de viabilidade demonstrou que o ExACT é uma intervenção segura, aceitável e viável para pessoas com fibrose quística. Estes resultados apoiam o avanço para um ensaio definitivo, multicêntrico e de maior duração, para avaliar segurança, eficácia e custo-efetividade do ExACT, após pequenos ajustes.

Número de registo do ensaio: NCT05482048.

INTRODUCTION

Cystic fibrosis (CF) is an inherited disorder characterised by thick mucus accumulation in vital organs. Clearing secretions from the lungs through airway clearance techniques (ACTs), such as chest physiotherapy, combined with mucoactive agents, is essential to prevent recurrent infections and airway inflammation that may lead to airway obstruction and mucus plugging,¹ airway damage, loss of respiratory function² and eventual respiratory failure. ACTs employ various methods and devices to remove excess mucus secretions, aiming to alleviate airway obstruction and prevent respiratory tract infections, as well as to re-expand atelectatic areas, improve gas exchange and reduce inflammation.³

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Chest physiotherapy airway clearance techniques (ACTs) are essential for people with cystic fibrosis (CF) but are time-consuming and burdensome. Intense aerobic exercise that incorporates forced expiratory techniques offers a promising alternative to ACT, but its safety and effectiveness need evaluation.

WHAT THIS STUDY ADDS

► People with CF were open to participating, and trial processes were feasible. Exercise as an ACT (ExACT) appeared safe and may be as effective as chest physiotherapy over 28 days, but a larger, longer trial is needed to definitively establish safety and efficacy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► ExACT could ease treatment burden, offer greater flexibility and better align with patient preferences. A larger trial could confirm efficacy and, if established, subsequently demonstrate effectiveness and support its integration into CF care.

For over 60 years, performing regular chest physiotherapy has been central to CF care.⁴ Standard practice globally involves at least daily chest physiotherapy,⁵ increasing during exacerbations. To meet the diverse needs of people with CF (pwCF),⁶ chest physiotherapy as 'usual care' for airway clearance encompasses a variety of techniques, including positive expiratory pressure, oscillating devices, active cycle of breathing techniques and autogenic drainage. Despite the range of available options, chest physiotherapy is often performed with low quality.⁷ Many pwCF find it both time-consuming⁸ and burdensome,⁹ leading to poor adherence.^{10,11} The landscape of CF has changed with widespread availability of highly effective modulator therapy (HEMT), which reduces exacerbations¹² and improves life expectancy,^{13,14} prompting exploration of alternative approaches to reduce treatment burden.⁹

Exercise is emerging as a potential alternative to ACT, acting to enhance mucociliary clearance and facilitate secretion removal.¹⁵ Structured exercise is already a recommended component of 'usual care' for pwCF,⁵ with aerobic exercise capacity being an important survival predictor.^{16,17} While current



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usual care recommendations advocate exercise in addition to chest physiotherapy,⁵ pwCF are already changing their approach based on preference to either incorporate exercise into their airway clearance regimens¹⁸ or to omit chest physiotherapy if they exercise.¹⁹ This preference underscores the need to investigate exercise as a primary ACT, engaging with patient priorities to address the question of whether exercise could replace chest physiotherapy, a priority highlighted by the James Lind Alliance.²⁰

Whether exercise alone can serve as an effective ACT remains unknown.¹⁵ A recent UK Delphi consensus²¹ defined a bespoke exercise as an ACT (ExACT) intervention, proposing it as a potential substitute for chest physiotherapy during stable periods, that warranted further study. ExACT involves >20 minutes of aerobic exercise inducing deep breathing^{21 22} and is performed by predominantly weight-bearing exercise types that incorporate vibration.²² Huffing and coughing (forced expiratory techniques) are integral to ExACT,²³ with pre- and post-session breaths to check for, and remove mucus. ExACT is self-administered, promoting independence and flexibility.²⁴ Combining daily exercise and ACT recommendations as 'ExACT' could yield significant time savings and health benefits. With the widespread availability of HEMT, such as Elexacaptor/Tezacaptor/Ivacaftor (ETI), realigning treatment burden is now a top priority in CF care.⁶ High-quality evidence is needed to guide clinical practice.

Aims

The 'Exercise as an Airway Clearance Technique in CF (ExACT-CF)' randomised pilot trial aimed to test the primary hypothesis of the feasibility and acceptability of the ExACT intervention when compared with usual care, together with safety and early signals of efficacy.

METHODS

The study was designed to establish the feasibility and acceptability of recruitment (target $n=50$), randomisation and retention for a 28 day trial comparing usual care with ExACT. The acceptability and feasibility of the ExACT intervention, for participants and trial delivery staff, were also established. Process evaluation, including intervention fidelity assessment, was undertaken, along with testing of the feasibility of collecting healthcare service resource use. Criteria for progression to a definitive trial were preset for recruitment, retention and adherence using traffic light criteria²² (table 1); green denoting 'proceed' - no concerning issues threatening success of definitive trial, amber denoting modification required for a larger trial, and red denoting likely non-progression.

A brief methods overview is provided in accordance with guidance for reporting pilot trials,²⁵ with further details in the published protocol.²² The safety of stopping chest physiotherapy and replacing it with ExACT was also evaluated through changes in lung function, rates of pulmonary exacerbations and adverse

events over the 28 day trial period. Additionally, a variety of candidate primary and secondary outcomes (physical activity (PA), treatment burden, quality of life (QoL) and sleep outcomes) were assessed for signals of efficacy, as well as for their associated burden, levels of completeness and estimates of outcome variance (to inform the sample size of a definitive trial).

In brief, lung clearance index (LCI2.5) was measured at baseline and day 28 by nitrogen-multiple breath washout (N2-MBW, Exhalyzer-D device, EcoMedics) and most recent software (Spiroware V3.3.1). Spirometry (Spirobank Smart, Intermedical UK, Kent, UK) was performed either in hospital or at home, at baseline and days 7, 14, 21 and 28. Data for forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were converted to % predicted values in accordance with Global Lung Initiative reference values.²⁶

Study design

A two-arm, parallel-group, dual-site randomised pilot trial, with mixed-methods process and economic evaluations, was conducted at two UK sites. Eligible participants were randomised to ExACT or usual care arms. Statistical analysis and health economics analysis plans were developed a priori. An embedded qualitative sub-study (ExACT-Q) explored participant and trial staff experience, though these data will be predominantly presented elsewhere. Study duration (28 days) and the requirement for all participants to be on ETI were informed by our community involvement and in order to undertake the study safely.

Participants

PwCF (≥ 10 years, $FEV_1 \geq 40\%$ predicted; table 2), stable on ETI, were eligible, with target recruitment $n=50$.²² Two participants withdrew prior to randomisation. Comprehensive inclusion/exclusion criteria are published.²² Potential participants were screened by clinicians and research nurses at consecutive clinics. Clinical records were reviewed to confirm eligibility, and potential participants were approached in person during routine clinic visits or via telephone/email. Clinical stability was assessed by the participant's treating clinician. Participants were not excluded due to any pathogen, if clinically stable. All participants provided fully informed written consent, with parental consent and participant assent for childhood participants.

Intervention

In accordance with the Medical Research Council's framework for the development and evaluation of complex interventions,²⁷ and considerable Patient and Public Involvement and Engagement (PPIE),²¹ we designed the ExACT intervention.²² Briefly, ExACT is aerobic exercise lasting > 20 minutes, at an intensity sufficient to be out of breath, and into which are incorporated forced expiratory techniques, specifically huffs and coughs. Participants were asked to stop all chest physiotherapy ACTs and instead undertake ExACT at least once a day for 28 days. All other CF treatments, including mucolytic and mucoactive agents, were continued. This was unsupervised following initial instruction.

Usual care

Participants continued chest physiotherapy ACTs at least once a day. Exercise and PA were encouraged and advised to be maintained, but no specific instructions were provided. A chest physiotherapy refresher was offered, given knowledge that adherence and quality of chest physiotherapy are frequently suboptimal.²⁸

Adherence

As outlined in our published protocol,²² adherence was monitored in both study arms using a combination of self-report and objective measures. Participants recorded daily sessions via a purpose-built, participant-facing study database, including details of both ExACT and traditional chest physiotherapy ACTs, as well as any additional PA. They also rated their perceived exercise intensity. In addition, participants were instructed to start and stop each

Table 1 Performance against pre-defined trial progression criteria

	Green	Amber	Red
Recruitment/randomisation	$\geq 60\%$	30–59%	< 30%
Number randomised/number approached			
Stop-go study outcome	48/117, 41% (amber)		
Retention	> 85%	70–84%	< 70%
Number providing primary clinical outcome data/number randomised			
Stop-go study outcome	45/48, 92% (green)		
Adherence	$\geq 80\%$	60–79%	< 60%
Number undertaking satisfactory* airway clearance/number randomised			
Stop-go study outcome	29/48, 60% (amber)		

*Adherence was defined as undertaking airway clearance on ≥ 5 days out of 7 for both the usual care chest physiotherapy arm and the exercise as an airway clearance technique (ExACT) intervention arm. Details regarding the predefined trial progression criteria are available in the published protocol.²²

Table 2 Baseline participant demographics at randomisation

	Usual care	ExACT	Overall
Randomised participants, n	24	24	48
Age, years	19.1 (10.4)	21.8 (12.8)	20.5 (11.6)
Adults ≥ 16 years, n	11	14	25
Children <16 years, n	13	10	23
Sex (M/F), n	14/10	14/10	28/20
Height, m	161.7 (15.3)	162.8 (13.6)	162.3 (14.3)
Weight, kg	53.5 (16.6)	63.0 (18.9)	58.2 (18.2)
BMI, kg/m ²	20.1 (3.9)	23.2 (4.5)	21.7 (4.4)
Ethnicity, n (%)			
White – UK	22 (92)	22 (92)	44 (92)
White – European	2 (8)	2 (8)	4 (8)
CFTR genotype, n			
F508del/F508del	15	13	28
F508del/other	9	11	20
Dornase alfa, n (%)	20 (83)	13 (54)	33 (69)
Hypertonic saline, n (%)	1 (4)	2 (8)	3 (6)
Nebulised antibiotics, n (%)	8 (33)	5 (21)	13 (27)
Colistin	3 (13)	2 (8)	5 (10)
Tobramycin	4 (17)	2 (8)	6 (13)
Aztreonam	1 (4)	0 (0)	1 (2)
Meropenem	0 (0)	1 (4)	1 (2)
Prophylactic antibiotics, n (%)	7 (29)	6 (25)	13 (27)
Azithromycin	5 (21)	3 (13)	8 (17)
Flucloxacillin	2 (8)	1 (4)	3 (6)
Cotrimoxazole	0 (0)	1 (4)	1 (2)
Coamoxiclav	0 (0)	1 (4)	1 (2)
CFRD, n (%)	4 (17)	5 (21)	9 (19)
Pancreatic insufficient, n (%)	22 (92)	20 (83)	42 (88)
LCI _{2.5}	8.3 (3.2)	7.9 (2.0)	8.3 (3.2)
FEV ₁ , % predicted	84.1 (19.9)	90.2 (16.0)	87.1 (18.1)
FVC, % predicted	92.3 (14.2)	95.9 (11.2)	94.1 (12.7)

Values are means (SDs) unless otherwise stated.
Two participants withdrew prior to randomisation.
BMI, body mass index; CFRD, cystic fibrosis-related diabetes; CFTR, cystic fibrosis transmembrane conductance regulator; ExACT, exercise as an airway clearance technique; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; LCI, Lung Clearance Index.

session – whether ExACT or chest physiotherapy ACTs – using their Garmin device, enabling capture of session duration and physiological response (eg, heart rate). Informed by our PPIE, adherence was defined as undertaking airway clearance on ≥ 5 days in each week for both arms of the trial. These procedures were designed to assess the feasibility and acceptability of capturing adherence through a mixed-methods approach across both arms of the trial.

Randomisation and blinding

The randomisation sequence was computer generated within a bespoke study database, hosted by Edinburgh Clinical Trials Unit. Randomisation was at the individual level, with a 1:1 allocation ratio, and minimised (with a random element) by age (< 20 and > 20 years), lung function (FEV₁ < 70% predicted and >70% predicted²⁶) and baseline device-measured (Garmin Vivosmart 4) PA (< 3 and > 3 hours of moderate to vigorous intensity physical activity (MVPA) / week). The randomisation algorithm for each participant (other than the first) allocated them with a probability of 0.8 to the group that minimised the difference between the two arms of the trial with respect to the minimisation variables. The

study was, in effect, ‘open label’, with neither participant nor treating clinicians blinded to the study allocation.

Outcome measures

Feasibility

Feasibility was assessed through recruitment, retention and adherence over 28 days, against pre-defined criteria for progression to a definitive trial (table 1), as laid out in the study protocol.²² More specifically, green (good to proceed); amber (proceed with modifications); and red (not recommended to proceed) progression criteria were devised for the proportion of pwCF randomised, completing the study and submitting necessary data at 28 days, and adhering to the intervention. In addition, we quantified (by exit questionnaire) the proportion that would choose the ExACT intervention over usual care (chest physiotherapy) in the future.

Safety and efficacy

The safety and potential efficacy of replacing chest physiotherapy with ExACT were assessed via adverse events and change from baseline to day 28 in spirometry (FEV₁), LCI_{2.5} by N2-MBW and rates of pulmonary exacerbations (defined as increased respiratory symptoms that required antibiotic treatment).

Health economic evaluation

A health economic evaluation was conducted in accordance with best practice guidance for clinical trials,²⁹ in order to pilot data collection methods. Descriptive statistics and an assessment of the completeness of self-report surveys/questionnaires, along with preliminary cost-utility estimates, were provided. Data are presented in accordance with guidance for Consolidated Health Economic Evaluation Reporting Standards.³⁰ Where suitable/deemed viable, exploratory, within-trial analysis was undertaken to provide provisional cost-utility estimates and quality-adjusted life years (QALYs) and understand the main cost-effectiveness drivers.³¹

Additional outcomes

Other secondary clinical outcomes included changes in PA, sleep, mood, QoL and treatment burden. Fidelity was assessed through independently scored role-play videos of selected trial staff explaining the study and intervention (online supplemental table S1), as well as intensity of sessions being recorded via activity monitors.

Data analysis

As this was a feasibility pilot trial, analysis was primarily descriptive, with participant flow, screening, recruitment and attrition rates summarised with exact 95% CI (figure 1) displayed alongside. Means and SDs were reported for exploratory outcomes at baseline and 7, 14, 21 and 28 days for each group. Intention-to-treat analyses were performed. To facilitate power calculations of a future trial, linear regression models were fitted on outcome variables regressed on treatment adjusting for baseline. Where appropriate, log transformations were performed to adhere to the assumption of normality. Models adjusting for baseline and minimisation variables gave similar results (data not shown).

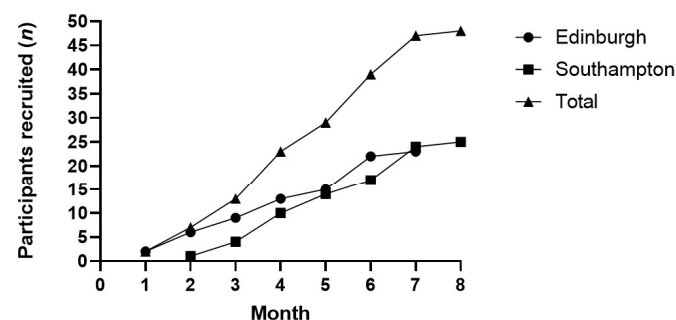


Figure 1 Recruitment trajectory for the ExACT-CF trial for the overall cohort and by site. ExACT-CF, Exercise as an Airway Clearance Technique in CF; FEV₁, forced expiratory volume in 1 s.

RESULTS

Recruitment took place from February to September 2023. The baseline demographics of study participants in each arm are displayed in table 2. Baseline airway clearance is summarised in table 3. Recruitment was on target and on time (figure 2).

Feasibility and acceptability of recruitment, randomisation, retention, and adherence to the ExACT intervention, processes and outcome measures

We screened/approached 117 pwCF, of whom 48 (41% of those approached) were randomised (figure 1); amber for trial progression (table 1). One individual became ineligible ($FEV_1 < 40\%$ predicted) between consent and randomisation, and another withdrew consent. In total, 45/48 (92%) randomised participants provided data at day 28, supporting progression (green) to a definitive trial. Adherence through 28 days for the ExACT intervention was 60% (amber for trial progression; table 1). Adherence data for both the ExACT intervention and usual care chest physiotherapy ACTs are presented in online supplemental table S5. It is noted that in those completing the study, adherence to ExACT exceeded that of usual care at all time points.

Safety and clinical impact of replacing routine chest physiotherapy with ExACT

The study identified no safety concerns with regard to the impact of stopping chest physiotherapy on lung health over a 28-day period. LCI2.5 was similar in both groups at each time point (table 4). Mean (SD) changes in FEV_1 (% predicted) from baseline to day 28 were +2.1 (6.6) in the ExACT arm and -0.8 (5.5) in the usual care arm. Exploratory linear regression models suggested trends towards estimated mean (95% CI) between group (ExACT vs usual care) differences for change in both LCI2.5 and FEV_1 from baseline to day 28, in favour of ExACT. Data for LCI2.5 showed a relative difference (ExACT/usual care) of 0.97 (95% CI 0.92 to 1.02—back-transformed results from analyses on log normal data), while FEV_1 absolute difference (ExACT—usual care) was 3.2% predicted (95% CI -0.6% to 6.9%).

Inter-individual variation was, however, noted (figure 2), with the majority of the observed changes being lower than the accepted within-subject variability (<8%) for FEV_1 .³² 11 of the 14 greatest observed falls in FEV_1 (% predicted) were in the usual care group, while six of the seven biggest increases were in the ExACT group (figure 3). Post hoc analyses revealed similar height, weight and BMI over the 28-day period in both treatment allocation groups (table 4).

A total of 51 adverse events were recorded for 25 different trial participants, none of which were 'Serious' (table 5). There was a higher proportion of exercise-related injuries in the ExACT group, none being severe. Injuries included a bicycle fall, groin strain, painful coccyx related to a bicycle seat and pain in the knee, shin,

hip and foot. All were managed with rest and/or simple analgesia, while five were coded as 'possibly related' and two 'unrelated'. No participant had to stop ExACT and resume their previous ACT regimen. Self-reported weekly changes in sputum volume or colour are reported in online supplemental table S4.

Additional outcomes

Physical activity

Exploratory analyses of device-measured PA revealed higher step counts at day 28 in the ExACT arm, although a potential between-group difference at baseline is noted. Although MVPA (table 6) at day 28 was similar between the groups, the ExACT arm increased by 60 minutes/week (mean) from baseline versus an increase of 5 minutes (mean) in MVPA for those receiving usual care. Habitual Activity Estimation Scale questionnaire data suggested that ExACT participants spent more time active across weekdays and weekends from baseline to day 28 with a reduction in activity over the 28 days in the usual care arm (table 6).

Treatment burden

No additional treatment burden at 28 days is suggested (online supplemental table S2), although Cystic Fibrosis Questionnaire-Revised (CFQ-R) treatment burden subscale scores increased in both study arms. More weekly sessions of exercise were undertaken when ExACT was used for airway clearance (table 6).

Sleep, mood and QoL

Sleep duration was similar between the groups over 28 days (table 5). Slight reductions in anxiety and depression scores were noted in both study arms (online supplemental table S2). Scores for the CFQ-R domains at baseline and day 28 are presented in online supplemental table S2, with QoL domains that were similar between groups over the 28-day trial period.

Health economics

Health-related QoL data (using the EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L) questionnaire) were collected with high levels of completeness. No large differences between trial arms were seen in respect of healthcare utilisation, EQ-5D-5L scores or QALYs.

All clinical trial outcome data were collected with high levels of completeness through 28 days (online supplemental table S3). For each outcome measure, we exceeded the number of cases recommended for pilot studies to estimate outcome variance.³³

Acceptability of the ExACT intervention, study outcomes and aspects of trial delivery

Fidelity

The approach and explanation of the trial scored highly across both sites (online supplemental table S3). Explaining the ExACT

Table 3 Reported methods of airway clearance at randomisation (n = 48)

	Usual care (n=24)	ExACT (n=24)	Overall (n=48)
Chest physiotherapy (n, %)	21/24, 88%	16/24, 67%	37/48, 77%
Chest physiotherapy, type (n, %)			
PEP mask	10/21, 48%	4/16, 25%	14/37, 38%
Aerobika	4/21, 19%	4/16, 25%	8/37, 22%
Acapella	3/21, 14%	2/16, 13%	5/37, 14%
Active cycle breathing techniques	1/21, 5%	1/16, 6%	2/37, 5%
Autogenic drainage	4/21, 19%	6/16, 38%	10/37, 27%
Exercise (n, %)	10/24, 42%	10/24, 42%	20/48, 42%
Mixture of exercise and chest physiotherapy (n, %)	8/24, 33%	6/24, 25%	14/48, 29%
Only undertaking exercise as airway clearance (n, %)	3/24, 13%	6/24, 25%	9/48, 19%
No regular airway clearance being undertaken (n, %)	0/24, 0%	2/24, 8%	2/48, 4%
No participant reported using high-frequency chest wall oscillation devices, cough assist or non-invasive ventilation devices for airway clearance. ExACT, exercise as an airway clearance technique.			

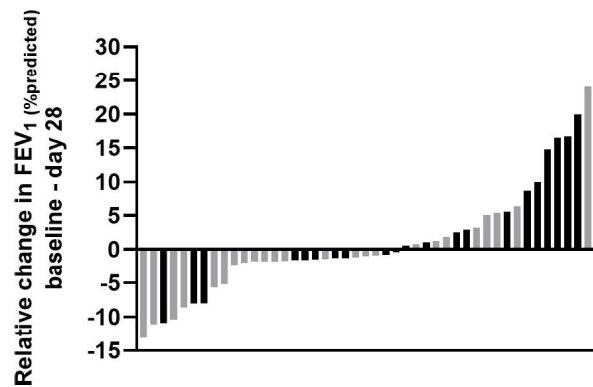


Figure 2 Waterfall plot delineating change in FEV₁ for participants in the ExACT (● black) and chest physiotherapy (● grey) trial arms over 28 days. ExACT, exercise as an airway clearance technique; FEV₁, forced expiratory volume in 1 s.

intervention was less consistent, suggesting that additional resource (videos, a web-based resource for participants and further role-play) may be required in a larger trial. Central over-reading of LCI2.5 data scored 44/45 (98%) as successful in Edinburgh and 46/49 (94%) in Southampton, with an overall acceptability rating of 96%.

Preference

In total, 44 participants completed the end of study questionnaire establishing their preferred ACT going forward. Only three people (7%, 1 ExACT) chose chest physiotherapy as their preferred ACT, with 12 (27%, 6 ExACT) selecting ExACT only, and 29 (66%, 13 ExACT) selecting interchangeable use of ExACT and chest physiotherapy.

Qualitative interviews

In this embedded study, 32 online/phone interviews were conducted with participants receiving ExACT (n=5) and usual care (n=5), parents/caregivers (n=5), decliners/dropouts (n=5) and health professionals (n=12). Two main themes emerged: facilitators and barriers to participation and trial delivery, and appetite for airway clearance regimes other than daily chest physiotherapy. Not a single interviewee wished to perform chest physiotherapy as their only ACT. The data confirmed the acceptability of most trial processes and the intervention, while identifying areas for improvement to enhance a definitive trial. Qualitative data will be published separately (under review).

DISCUSSION

The ExACT-CF pilot feasibility trial represents the first dual-site randomised controlled pilot trial to test the feasibility and acceptability of recruiting pwCF, stable on ETI, into a trial examining exercise as a form of airway clearance to replace traditional ACT, to inform whether a definitive randomised controlled trial focused on establishing efficacy and safety is possible. Meeting all pre-stated safety and feasibility criteria,²² this trial lays a strong foundation for a larger, definitive study. No clinical respiratory safety signals

were identified in those who stopped traditional ACTs over 28 days in this feasibility trial. The findings suggest, from LCI_{2.5} and FEV₁ changes over 28 days, that ExACT is at least as good as usual care, although signals towards efficacy of ExACT now warrant further investigation. Feasibility data demonstrate that pwCF are receptive to trials exploring ExACT, showing acceptable recruitment and retention, high levels of adherence and promising preliminary safety data.

The ExACT intervention, trial design and processes were well received by both participants and staff. Minimal participant burden and high outcome measure completion further support the acceptability of ExACT as an alternative to chest physiotherapy. The trial also effectively rehearsed health economic evaluation and trial governance procedures. Diary entries noted different levels of PA from that measured directly (using Garmin device) and suggest that cross-validation with a widely used measure (accelerometry) may be important for a larger trial. Qualitative feedback from participants and healthcare professionals indicated that the ExACT intervention was safe, enjoyable and less time-consuming than chest physiotherapy. While full findings will be reported separately, early insights highlight that many found integrating daily exercise feasible and flexible, though some faced challenges with routine or fatigue — suggesting the need for realistic adherence targets in future trials.

Exercise-related injuries were more commonly reported in pwCF undertaking ExACT (table 4). These were generally mild and self-resolving; however, they would require a modified training approach within a definitive trial to reduce this safety signal. With some modifications, progressing to a larger, more pragmatic trial, assessing the efficacy and cost-effectiveness of the ExACT intervention is feasible and justified.

In line with our published Delphi consensus,²¹ we demonstrated that a sufficient number of pwCF were willing to be randomised into an exercise-based airway clearance trial. However, competing CF trials impacted recruitment. Our study highlights the importance of effective collaboration with stakeholders, including robust PPIE mechanisms. Both trial sites were members of the UK CF Trust Clinical Trials Accelerator Platform, with ExACT-CF being one of the top-recruiting trials in their portfolio despite involving only two sites. A definitive trial will seek to ensure equitable access for pwCF across a wider range of sites.

This trial enabled us to evaluate the ExACT intervention and optimise the design for a definitive study. Patient preference from exit questionnaires and qualitative interviews demonstrated strong support for ExACT as a treatment modality—either stand-alone or interchangeable with usual care. The need for a pragmatic trial to confirm that ExACT is safe and non-inferior to usual care is therefore suggested, facilitating the integration of exercise into the airway clearance toolkit for pwCF. Further work to evaluate the safety, acceptability and efficacy of ExACT in other causes of bronchiectasis³⁴ should also be considered.

The ExACT-CF feasibility study has several limitations. First, it was conducted across two UK centres (Edinburgh and Southampton) only, which may limit the generalisability of the findings. Second, the study exclusively included patients established on ETI (guided by our intervention development work with physiothera-

Table 4 Lung function and anthropometric changes from baseline to day 28 by treatment allocation

Parameter	Usual care (n=24)			ExACT (n=21)		
	Baseline	Day 28	Difference	Baseline	Day 28	Difference
LCI _{2.5}	8.3 (3.2)	8.5 (3.3)	0.2 (0.8)	7.9 (2.0)	7.8 (1.9)	−0.1 (0.6)
FEV ₁ , % predicted	84.1 (19.9)	83.3 (20.6)	−0.8 (5.5)	89.9 (17.2)	92.1 (16.6)	2.1 (6.6)
FVC, % predicted	92.3 (14.2)	90.0 (13.5)	−2.3 (5.8)	95.7 (11.8)	96.4 (12.4)	0.8 (7.5)
Height, m	1.62 (1.53)	1.62 (1.51)	0.0 (0.69)	1.62 (1.37)	1.63 (1.34)	0.0 (1.09)
Weight, kg	53.5 (16.6)	53.7 (16.3)	−0.2 (0.9)	62.3 (18.7)	61.9 (18.5)	0.3 (1.2)
BMI, kg/m ²	20.1 (3.9)	20.1 (3.7)	−0.1 (0.4)	23.1 (4.5)	23.0 (4.6)	0.1 (0.4)

Values are means (SDs) for complete cases, unless otherwise stated.
BMI, body mass index; ExACT, exercise as an airway clearance technique; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; LCI, Lung Clearance Index.

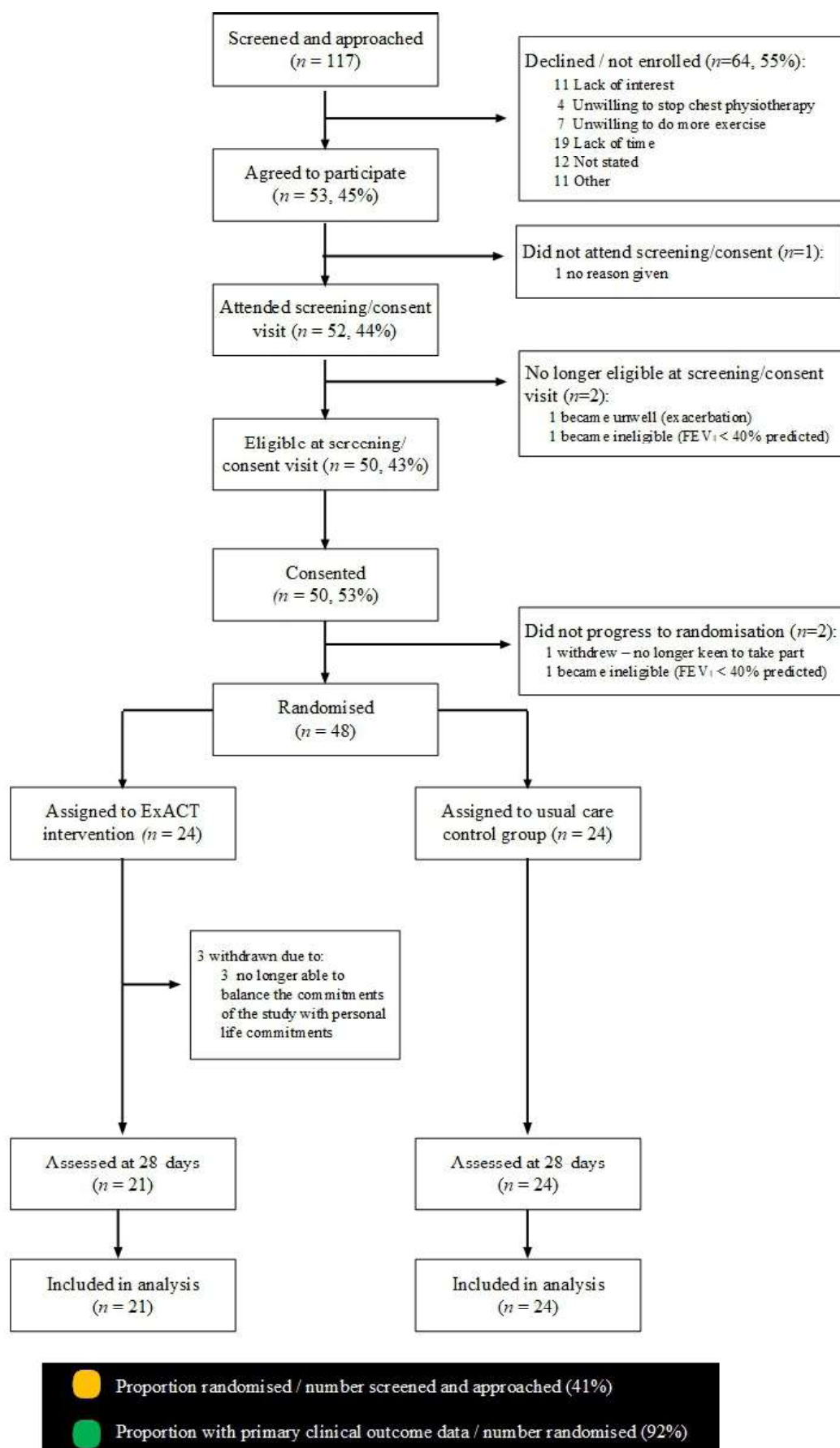


Figure 3 CONSORT flow diagram for the ExACT-CF study. CONSORT, Consolidated Standards of Reporting Trials; ExACT-CF, Exercise as an Airway Clearance Technique in CF.

Table 5 Summary of adverse events in the ExACT-CF pilot trial (n=25 experienced)

Adverse event	ExACT (n, number coded as possibly related to ExACT)	Usual care (n)
Respiratory		
Pulmonary exacerbation	2, 1	2
Antibiotic treatment for chest	4, 2	4
Cough	4, 0	5
Nasal congestion	1, 0	0
Sore throat	2, 0	0
Tight chest/breathlessness	2, 2	1
Coryza	1, 0	1
Hay fever	0, 0	1
Ear infection	1, 0	1
Sports injuries		
Knee pain	3, 3	0
Foot pain	1, 1	0
Shin pain	1, 0	0
Painful coccyx	1, 1	0
Groin pain	1, 1	0
Hip pain	1, 0	1
Other		
Hypoglycaemic episode	1, 1	0
Abdominal pain	1, 0	0
Fatigue	4, 1	2
Headache	1, 0	0
Fever	1, 0	0
Vomiting	1, 0	0
Nasal injury	1, 0	0

ExACT, exercise as an airway clearance technique; ExACT-CF, Exercise as an Airway Clearance Technique in CF.

pists, pwCF and their families, and clinicians²¹), potentially affecting the applicability of results to all pwCF. However, this criterion was implemented to ensure participant stability and homogeneity within this small-scale feasibility trial. Third, the study was not powered to assess clinical efficacy; thus, any observed differences in clinical outcomes should be interpreted with caution. This aligns with the primary aim of feasibility studies, which is to assess the practicality of study procedures rather than to evaluate treatment effects. Additionally, the open-label design, while common in feasibility studies, may introduce bias, although blinding was not feasible given the nature of the intervention. Lastly, while adherence to the intervention was monitored, adherence to concurrent therapies, such as mucolytic and mucoactive agents and antibiotics, was not assessed, though broadly similar baseline usage was reported (table 2). Future studies should consider monitoring these factors, as changes in airway clearance regimens could influence adherence to other treatments, potentially impacting clinical outcomes.

This pilot trial identified areas needing refinement in design and management, essential for optimising the effectiveness of the ExACT intervention in future trials. Given the adherence being amber (60%), a more rigorous application of the behaviour change wheel³⁵ and techniques such as motivational interviewing, which have shown promise in enhancing engagement and adherence to PA in pulmonary rehabilitation,³⁶ are key considerations. Furthermore, incorporating injury prevention strategies and providing enhanced training resources for participants and trial staff are important areas for improvement.

The flexible, home-based delivery of trial interventions and some study visits was well received and aligns with prior quali-

Table 6 Physical activity and sleep in the ExACT-CF study

Outcome measure	Data collection time point					
	Baseline		Day 7*		Day 14*	
	ExACT (n=24)	UC (n=24)	ExACT (n=22)	UC (n=24)	ExACT (n=21)	UC (n=24)
Device-based PA						
Total steps, steps/day	10 331 (5246)	8859 (3640)	10 646 (5249)	9196 (3773)	10 714 (4564)	9503 (5955)
MVPA, min/week	420 (350)	469 (310)	550 (398)	450 (363)	456 (232)	340 (308)
Sleep time, hours/day	8.2 (1.8)	7.9 (1.8)	8.0 (1.7)	8.2 (1.4)	8.0 (1.8)	8.3 (1.5)
PA data from patient-facing exercise diary						
Exercise sessions, sessions/week	–	–	9.1 (3.7)	4.5 (2.8)	8.1 (3.2)	3.9 (8.1)
Weekly PA, minutes/week	–	–	356 (213)	325 (220)	430 (651)	348 (200)
Time spent active or somewhat active (HAES questionnaire)						
Weekday, minutes/day	441.6 (168.0)	470.6 (184.6)	–	–	–	–
Weekend, minutes/day	439.4 (186.9)	483.9 (177.9)	–	–	–	–

*Poststratification. Values are expressed as numbers, means and (SD) as a function of trial arm and measurement time point for PA and sleep. ExACT, exercise as an airway clearance technique; ExACT-CF, Exercise as an Airway Clearance Technique in CF; HAES, Habitual Activity Estimation Scale; MVPA, moderate to vigorous intensity physical activity; PA, physical activity; UC, usual care.

tative insights from adults with CF, who expressed a preference for PA interventions that are enjoyable, foster autonomous motivation, have personal outcomes and can be performed at home.³⁷ This highlights opportunities to leverage digital health technologies to support pwCF.³⁸ Participant and staff experiences, along with lessons learnt from this trial, will be detailed in a forthcoming qualitative article.

Recent withdrawal studies, such as CF-STORM and SIMPLIFY,³⁹ have focused on reducing treatment burden. However, whether chest physiotherapy can be safely modified or discontinued in the era of HEMT remained unclear.⁴⁰ Our adaptive approach to realign ACTs to periods of clinical stability and instability may provide patients with an efficient method of self-care. Preliminary findings from the embedded health economic evaluation within the ExACT-CF pilot trial suggest that ExACT may be deliverable without significant additional cost, while the broader health benefits of structured aerobic exercise,⁴¹ such as maintaining health in an ageing CF population,⁵ may be being accrued.

ExACT aligns with the European CF Society Standards of Care for Maintaining Health in PwCF,⁵ which recently recognised exercise as a viable option in personalised, preference-based ACT regimens. While this validation of ExACT is cautiously welcomed, it is recognised that there is not yet a definitive trial to support such a statement.

Given the burden for pwCF who are currently being asked to undertake both ACT and exercise, ExACT may simplify treatment burden by combining both exercise and ACT together. Notably, although weekly exercise time was similar between groups, ExACT participants engaged in more moderate to vigorous-intensity exercise, likely conferring greater long-term fitness and health benefits.

A larger, definitive trial is needed to rigorously test the efficacy, cost-effectiveness and safety of the ExACT intervention. Insights from this could influence clinical practice and potentially extend to other respiratory diseases, for example, primary ciliary dyskinesia and other causes of bronchiectasis. Bronchiectasis, affecting > 2 000 000 people in the UK,⁴² poses a significant burden,⁴³ and similar to CF also poses challenges with long-term adherence to ACT and exercise.³⁴ This could lead to a programme of research that may offer a more manageable and effective approach to airway clearance applicable across chronic suppurative lung diseases of differing aetiology.

In conclusion, ExACT is feasible, acceptable and appears safe for pwCF over 28 days. Its adoption as a recommended ACT, alone or in combination with chest physiotherapy, could enhance CF management by increasing flexibility and reducing treatment burden, and aligning with the needs and preferences of pwCF. A definitive trial is needed to confirm its clinical effectiveness and cost-effectiveness, supporting broader integration into CF care and potentially other chronic respiratory conditions. This work addresses key priorities for pwCF and has the potential to significantly influence clinical practice.

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