

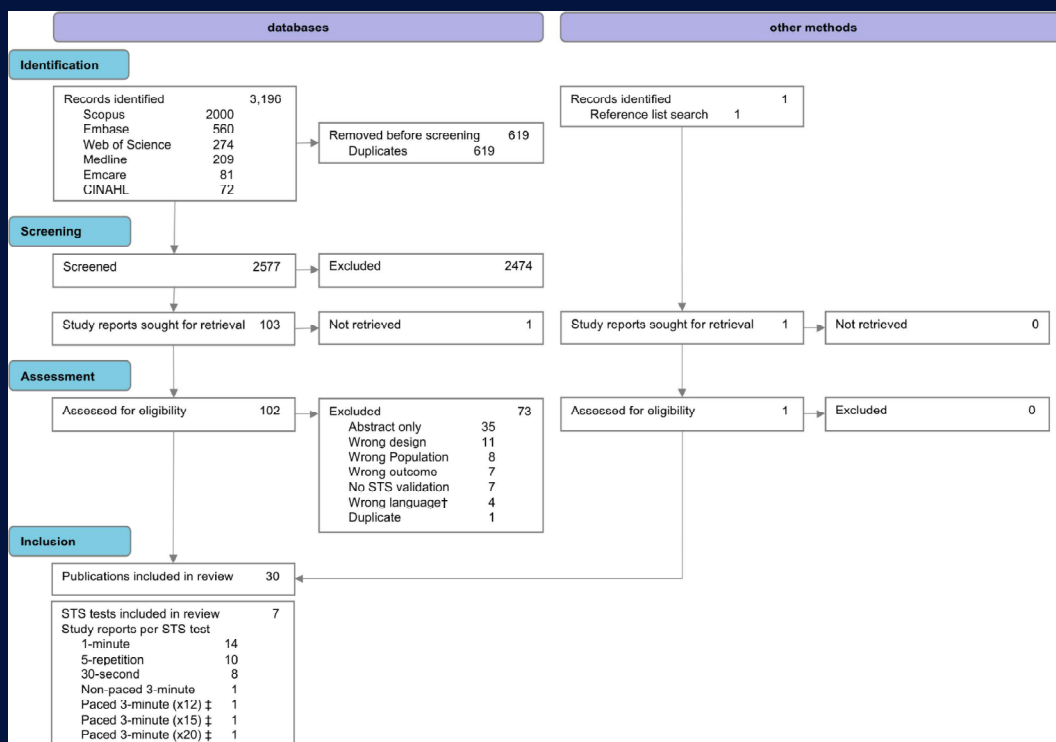
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Rua Bernardo Costa nº127, 1º Esquerdo
2775-809 Carcavelos
Contacto: 938311875
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Archives of Disease in Childhood
BMJ Publishing Group Ltd
BMA House

Tavistock Square
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E: info.adc@bmj.com

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Senior Production Editor

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British Thoracic Society

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Editorial

Este número de Verão de 2026, com uma seleção de artigos das Revistas *Thorax* e *Archives of Diseases in Childhood*, tem uma série de artigos que poderíamos agrupar em:

1. Testes diagnósticos: o aprofundar da interpretação e o agrupamento de testes de diagnóstico, particularmente não invasivos, permitem caminhar no sentido do progresso relacionado com a medicina de precisão, na previsão de doentes de risco e na seleção de doentes para realizar meios de diagnóstico específicos permitindo a melhoria da utilização de recursos de saúde (artigos das páginas 203; 212);
2. Atitudes preventivas: a elevada eficácia de vacinas (tosse convulsa) e anticorpos monoclonais (nirsevimab), com impacto na mortalidade e na utilização de recursos em saúde devem continuar a ser estudadas e divulgadas, pelas lacunas ainda encontradas quando são estudadas (artigos das páginas 205; 260);
3. Registos Clínicos Eletrónicos (RCE): A utilização crescente de modelos estatísticos a partir de dados reais dos RGE favorece a decisão clínica em tempo real antecipando riscos na DPOC (artigo da página 229);
4. Intervenção farmacológica: corticosteróides, durante a gravidez pode modificar os resultados da função respiratória nos lactentes, tornando-os comparáveis com os das crianças filhas de mães saudáveis... (artigo da página 244);
5. Intervenção multidisciplinar, não farmacológica: grupos profissionais em multidisciplinaridade concorrem para a melhoria da dispneia nos doentes com DPOC (artigo da página 220);
6. Determinantes Sociais da Saúde: *last but not least* um comentário para este artigo, na página 251, que permite caracterizar esta publicação da *Thorax* e da *ADC* como uma das mais abrangentes – o conhecimento das fragilidades sociais é fundamental para o desenhar de estratégias de intervenção em saúde... as evidências são crescentes!

Estes comentários não esgotam este número, mas esperamos que possam orientar a sua leitura.

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Quando os biomarcadores discordam: interpretar FeNO e eosinófilos nas doenças das vias aéreas

Angel Almansa-López,¹ Pedro Jose Romero- Palacios,² Bernardino Alcazar Navarrete^{1,2}

A procura de biomarcadores fiáveis de inflamação tipo 2 (T2) ao longo da asma, da doença pulmonar obstrutiva crónica (DPOC) e do *overlap* asma-DPOC (ACO) tem sido um tema central da investigação respiratória na última década. Os eosinófilos no sangue e a fração de óxido nítrico exalado (FeNO) emergiram como marcadores clinicamente acessíveis, com bases biológicas claras e relevância prognóstica e terapêutica demonstrada, particularmente na asma e em populações selecionadas com DPOC.^{1,2}

Contudo, à medida que a investigação em biomarcadores se expande para grandes coortes heterogêneas, a interpretação torna-se cada vez mais desafiante. No seu artigo publicado na *Thorax*, Muiser *et al.*³ exploram as associações entre eosinófilos sanguíneos e FeNO e os desfechos de agudização na asma, DPOC e asma+DPOC na coorte NOVELTY (NOVEL observational longitudinal study on patients with asthma and/or COPD). Embora a dimensão e o alcance internacional da NOVELTY constituam pontos fortes inegáveis, vários dos resultados apresentados — nomeadamente a associação inversa entre FeNO e risco de agudização na DPOC — levantam questões conceptuais e metodológicas importantes que merecem consideração cuidadosa.

A observação de que valores mais elevados de FeNO estão associados a menor risco de agudizações na DPOC contrasta com um corpo crescente de evidência que relaciona FeNO elevado — e particularmente persistentemente elevado — a um aumento do risco de agudizações na DPOC.^{4–7} Do ponto de vista biológico, esta associação inversa é difícil de conciliar com o conhecimento atual sobre inflamação das vias aéreas mediada por T2, produção epitelial de óxido nítrico e resposta aos corticosteroides na DPOC.⁸

Uma explicação mais plausível reside no confundimento residual e nos efeitos do tratamento. Em coortes do mundo real, o FeNO é fortemente influenciado pela exposição a corticosteroides inalados (ICS), pelo estado tabágico e pelo uso recente de corticosteroides sistêmicos. Sem um controlo adequado das alterações na terapêutica com ICS ao longo do tempo, a

causalidade inversa torna-se uma preocupação central: os doentes com FeNO mais elevado podem simplesmente ser aqueles a receber tratamento anti-inflamatório mais intensivo, experienciando assim menos agudizações. Neste contexto, o FeNO pode funcionar mais como marcador de alocação terapêutica do que de biologia subjacente da doença.

Um segundo problema fundamental relaciona-se com a classificação da doença. A coorte NOVELTY baseia-se em diagnósticos atribuídos por médicos, sem confirmação fisiológica sistemática. Num contexto multicêntrico internacional, onde os limiares diagnósticos e as tradições clínicas variam amplamente, a classificação incorreta entre asma, DPOC e ACO não só é possível como provável. Isto é particularmente problemático quando o comportamento dos biomarcadores é comparado entre categorias diagnósticas que são, elas próprias, fluidas e sobrepostas.

Trabalhos anteriores demonstraram que FeNO e eosinófilos se comportam de forma muito diferente consoante a fisiologia das vias aéreas, a exposição ao tabaco e a compartimentalização inflamatória.^{9,10} Quando as categorias diagnósticas são imprecisas, as associações entre biomarcadores e desfechos correm o risco de se tornarem diluídas, distorcidas ou até invertidas. Esta limitação é especialmente relevante quando associações inesperadas são interpretadas mecanisticamente em vez de contextualizadas com cautela.

Embora frequentemente agrupados como biomarcadores T2, FeNO e eosinófilos sanguíneos captam processos biológicos distintos. O FeNO reflete a atividade da óxido nítrico sintase induzível ao nível do epitélio das vias aéreas, enquanto os eosinófilos representam um sinal imunitário sistémico. Na DPOC, as correlações entre estes marcadores são modestas e o seu valor prognóstico parece dependente do contexto.

Estudos prévios sugerem que a avaliação combinada ou longitudinal de biomarcadores T2 oferece maior *insight* clínico do que medições isoladas e transversais.^{6,11} FeNO persistentemente elevado, mais do que um valor basal isolado, tem sido associado ao risco de agudizações na DPOC, apoiando a ideia de que a estabilidade do biomarcador ao longo do tempo pode ser mais informativa do que a sua magnitude absoluta. Em contraste, a presente análise baseia-se sobretudo em medições basais, potencialmente obscurecendo fenótipos inflamatórios dinâmicos que são clinicamente relevantes.

A classificação dos subtipos de agudização com base em padrões terapêuticos (apenas antibióticos vs apenas corticosteroides orais) introduz incerteza adicional. As práticas de prescrição variam amplamente entre sistemas de saúde e podem refletir diretrizes locais, acesso aos cuidados ou preferência do médico, mais do que diferenças biológicas reais no fenótipo da agudização. Sem validação contra critérios clínicos ou biomarcadores objetivos, tais categorias correm o risco de confundir comportamento do sistema de saúde com mecanismos da doença.

Além disso, os tamanhos de efeito reportados são pequenos e frequentemente próximos da unidade. Embora estatisticamente significativos numa coorte grande, a sua relevância clínica é questionável, particularmente na ausência de avaliações formais do valor preditivo incremental ou da melhoria do modelo quando os biomarcadores são adicionados a preditores clínicos estabelecidos, como o historial de agudizações.

Em conjunto, estas considerações sugerem que a aparente discordância entre os resultados atuais e estudos anteriores não deve ser interpretada como evidência contra o papel do FeNO ou dos eosinófilos na DPOC. Pelo contrário, sublinham as limitações de análises transversais e baseadas no diagnóstico numa doença caracterizada por heterogeneidade biológica, modulação terapêutica e variabilidade temporal.

O desafio central daqui em diante não é saber se os biomarcadores T2 “funcionam”, mas sob que condições são informativos. Desenhos longitudinais, medições repetidas de biomarcadores, controlo rigoroso da exposição terapêutica e fenotipagem mais robusta são essenciais para que estes marcadores orientem a medicina de precisão, em vez de gerarem sinais contraditórios.¹²

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¹Departamento de Pneumologia, Hospital Universitario Virgen de las Nieves, Granada, Espanha

²Universidad de Granada, Granada, Espanha
Correspondência: Dr. Ángel Almansa-López
angel.al.98m@gmail.com

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ORCID iDs

Pedro Jose Romero- Palacios <https://orcid.org/0000-0002-9688-2882>
 Bernardino Alcazar Navarrete <https://orcid.org/0000-0003-2356-9366>

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Tosse convulsa, a pandemia e a prevenção de futuras ressurgências

Shamez N Ladhani,¹ Asma Khalil,² Sharif A Ismail,¹ Mary Elizabeth Ramsay,³ Gayatri Amirthalingam¹

Calley e colegas fornecem um lembrete oportuno da elevada morbidade e mortalidade associadas à tosse convulsa (*whooping cough*), que é agora amplamente esquecida devido a um programa de vacinação bem-sucedido que já dura quase sete décadas.¹

Ao longo de um curto período de apenas 7 meses (novembro de 2023 a junho de 2024), 54 lactentes com tosse convulsa confirmada na Grã-Bretanha necessitaram de admissão em cuidados intensivos e ventilação invasiva, principalmente devido a apneia. A idade mediana era de apenas 43 dias e, apesar de uma abordagem terapêutica agressiva, 11 lactentes (20%) morreram.¹

O agente responsável, *Bordetella pertussis*, é um cocobacilo gram-negativo exigente, e os humanos são o único hospedeiro conhecido. A tosse convulsa caracteriza-se por tosse intensa/prolongada. Pode afetar indivíduos de todas as idades, mas o maior risco de morte e de morbidade grave ocorre em lactentes jovens não imunizados, que apresentam o risco mais elevado de complicações, como pneumonia e convulsões. Antes da vacinação de rotina, grandes epidemias ocorriam a cada 3–5 anos, afetando até 150 000 pessoas apenas em Inglaterra e no País de Gales, contribuindo para cerca de 300 mortes por ano, sobretudo em lactentes jovens.²

Em Inglaterra e no País de Gales, a tosse convulsa tornou-se de notificação obrigatória em 1940, e a vacinação infantil de rotina com a vacina de célula inteira contra a tosse convulsa (wP) foi introduzida em 1957, resultando em grandes reduções na incidência da doença em todos os grupos etários. Preocupações sobre o aumento da reatogenicidade e raras complicações neurológicas associadas às vacinas wP levaram a uma diminuição da adesão vacinal na década de 1970, o que resultou num aumento concomitante dos casos de tosse convulsa e das mortes. Em 1990, o esquema infantil do Reino Unido foi alterado de doses aos 3, 4,5–5 e 8,5–11 meses para um esquema acelerado com doses aos 2, 3 e 4 meses, para proporcionar proteção precoce contra a tosse convulsa e reduzir o risco de convulsões febris após a vacinação.

¹ UK Health Security Agency, Londres, Reino Unido

² Serviços de Maternidade, St George's University Hospitals NHS Foundation Trust, Londres, Reino Unido

³ Imunização, Hepatite e Segurança do Sangue, UK Health Security Agency, Londres, Reino Unido

Correspondência: Shamez N. Ladhani
Shamez.Ladhani@ukhsa.gov.uk

Em 1996, uma vacina combinada contra difteria, tétano, tosse convulsa e *Haemophilus influenzae* tipo b (Hib) (DTP-Hib) foi introduzida no programa de vacinação infantil. A adesão vacinal aumentou e, em outubro de 2001, quando 94% das crianças tinham completado o esquema primário até aos 2 anos de idade, foi adicionado um reforço pré-escolar (3,5–5 anos), como vacina combinada com antígenos acelulares de tosse convulsa de três ou cinco componentes (DTaP3 ou DTaP5). Em 2004, a vacina infantil combinada DTP-Hib e a vacina oral contra a poliomielite (OPV) foram substituídas por uma vacina 5-em-1 que incluía a vacina inativada contra a poliomielite (DTaP-Hib-IPV) e, desde 2017, por uma vacina 6-em-1 incluindo hepatite B. Apesar do sucesso do programa de vacinação infantil contra a tosse convulsa, muitos países, incluindo o Reino Unido, continuaram a reportar casos e mortes por tosse convulsa, especialmente durante os picos cíclicos de transmissão de 3–5 anos que tipicamente ocorrem com esta doença.³

A partir de 2011, o Reino Unido e muitos outros países com programas de imunização contra a tosse convulsa bem estabelecidos experienciaram um grande aumento da atividade da doença em todos os grupos etários, incluindo lactentes demasiado jovens para receberem as suas imunizações primárias (figura 1).²

Um surto nacional foi declarado em abril de 2012, levando à introdução de emergência de um programa nacional de vacinação contra a tosse convulsa para mulheres grávidas entre as 28–32 semanas de gestação, em outubro de 2012. A atividade da tosse convulsa atingiu o pico em outubro de 2012 antes de diminuir em todos os grupos etários, em linha com as tendências sazonais habituais.

Desde abril de 2016, as mulheres têm sido convidadas a receber uma vacina contendo antígenos contra a tosse convulsa por altura da ecografia do segundo trimestre (geralmente às 20 semanas), mas podem recebê-la em qualquer momento da gravidez a partir das 16 semanas de gestação, embora idealmente a vacina deva ser administrada antes das 32 semanas para maximizar a probabilidade de o bebé estar protegido desde o nascimento. Esta decisão baseou-se na demonstração de uma transferência transplacentária eficiente de anticorpos maternos após vacinação no segundo trimestre, embora a intenção principal fosse melhorar a adesão, oferecendo mais oportunidades de vacinação.²

O programa de imunização antenatal mostrou-se altamente eficaz na preven-

ção de hospitalizações e mortes por tosse convulsa em lactentes jovens, com as estimativas mais recentes de eficácia vacinal a situarem-se nos 97% (IC 95%: 81% a 100%), incluindo o período após o intervalo de vacinação antenatal ter sido alargado para as 20 semanas de gestação.⁴

A pandemia de COVID-19, no entanto, perturbou significativamente o controlo da tosse convulsa de várias formas.³ Em primeiro lugar, os múltiplos confinamentos e restrições implementados para limitar a propagação do SARS-CoV-2 também reduziram a transmissão de outros agentes respiratórios, incluindo *B. pertussis*. Consequentemente, o pico de atividade da tosse convulsa esperado para 2020/2021 não se materializou, mantendo-se a atividade da doença baixa durante 2021 e 2022.⁵

A partir da segunda metade de 2023, contudo, Inglaterra e outros países observaram um aumento do número de casos de tosse convulsa em todas as regiões e grupos etários, que depois acelerou durante a primeira metade de 2024.⁵ De facto, os 54 lactentes com tosse convulsa que necessitaram de cuidados intensivos, referidos nesta edição, coincidiram com este período de pico de atividade.¹

Em 2024, registaram-se quase 15 000 casos de tosse convulsa confirmados laboratorialmente em Inglaterra (comparados com 856 em 2023), incluindo 893 lactentes e 433 bebés com menos de 3 meses (figura 1).⁵ De forma preocupante, o número de mortes em bebés com menos de 3 meses atingiu 11 em 2024, o segundo valor mais elevado dos últimos 25 anos, ultrapassado apenas por 2012 (14 mortes), quando o programa de vacinação materna foi iniciado.⁵

Consistentemente com anos anteriores, a maioria das mães cujos bebés morreram de tosse convulsa não tinha sido vacinada durante a gravidez.⁵

Vários fatores contribuíram para o aumento recente de casos. A redução do contacto social associada às restrições da pandemia provavelmente aumentou o número de indivíduos suscetíveis durante a ressurgência de 2023/2024 (a chamada “lacuna de imunidade”), o que explica o aumento de casos em todos os grupos etários. As restrições pandémicas também perturbaram os serviços de vacinação para mulheres grávidas e crianças, deixando ambas as populações vulneráveis menos protegidas durante a ressurgência recente.

Isto ocorreu num contexto de um declínio gradual, ano após ano, na adesão à vacinação contra a tosse convulsa durante a gravidez, em Inglaterra, desde um pico de 74,7% em dezembro de 2017 para 58,9% em março de 2024.⁵ Também nos lactentes, a adesão às imunizações de rotina, incluindo a tosse convulsa, tem vindo a diminuir de forma constante, passando de um pico de 94,1% no segundo trimestre de 2014 para 90,7% no terceiro trimestre de 2024.

Embora parte do declínio observado seja provavelmente atribuível à qualidade

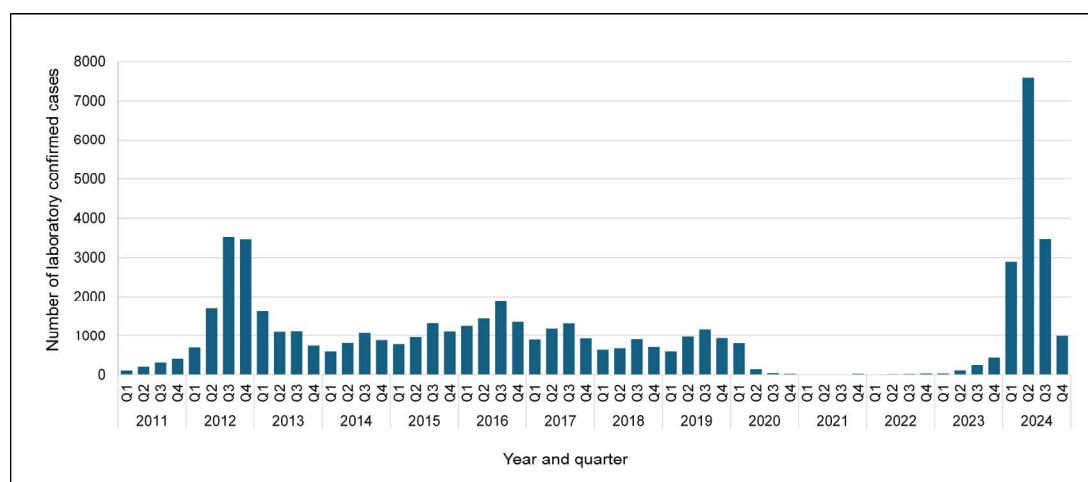


Figure 1 Laboratory-confirmed cases of pertussis by quarter in England, 2011–2024.⁵

dos dados e ao registo, juntamente com o aumento da rotatividade das populações elegíveis para vacinação em diferentes regiões do país, outras razões para a diminuição da adesão vacinal incluem uma combinação de perturbações nos serviços de saúde que levaram a vacinações em falta, barreiras estruturais ao acesso à vacinação, que desencorajam a vacinação, e uma prestação fragmentada dos programas de imunização — afetando particularmente as vacinações antenatais — bem como desinformação sobre vacinas que alimenta a hesitação vacinal e a fadiga vacinal após a pandemia.

Importa salientar também que, ao contrário das vacinas wP, que preveniam tanto a infeção como a transmissão, as vacinas aP são menos eficazes na prevenção da infeção assintomática e, portanto, a transmissão pode continuar a ocorrer mesmo em populações altamente vacinadas com vacinas aP.

A ressurgência de 2023/2024 levou à declaração de um incidente nacional em maio de 2024, resultando em esforços concertados para controlar o surto de tosse convulsa.⁵ As *guidelines* nacionais de saúde pública sobre tratamento antibiótico e quimioprofilaxia, gestão de surtos em contextos educativos e outros ambientes, e vacinação ocupacional de profissionais de saúde foram revistas, com esta última focada especificamente em reduzir o risco de transmissão para mulheres grávidas e lactentes jovens.

Importa destacar que foram feitos esforços intensivos para reforçar a comunicação, incluindo aumentar a sensibilização entre os profissionais de saúde para o reconhecimento clínico precoce e entre o público

para melhorar a adesão às vacinações antenatais e infantis. De forma tranquilizadora, os casos de tosse convulsa começaram a diminuir a partir de maio de 2024 e a adesão à vacinação antenatal aumentou, atingindo 68,2% em dezembro de 2024.

Embora os casos de tosse convulsa tenham diminuído desde a declaração do incidente nacional, trabalhos de modelação sugerem a possibilidade de um nível basal mais elevado de transmissão de tosse convulsa, incluindo durante os anos entre picos, em populações que utilizam vacinas aP. Proteger os mais vulneráveis — nomeadamente os lactentes jovens não vacinados — deve, portanto, continuar a ser a principal prioridade, devido à elevada morbilidade e mortalidade, tal como descrito por Caley e colegas.¹

Idealmente, precisamos de vacinas melhores para prevenir a infeção e a transmissão da tosse convulsa, bem como de uma proteção mais duradoura contra a doença.³ Entretanto, todos os esforços devem ser feitos para melhorar a adesão à vacinação em mulheres grávidas e lactentes jovens, incluindo aumentar a sensibilização pública através de campanhas educativas, com comunicações claras e consistentes, bem como melhorar o acesso à vacinação, tanto em termos de horários como de locais de vacinação.

Os profissionais de saúde, em todas as áreas médicas e afins, têm um papel vital na prestação de recomendações vacinais fortes e proativas, utilizando cada contacto clínico para salientar a importância da vacinação, esclarecer quaisquer dúvidas e facilitar vias de acesso para vacinações atempadas de mulheres grávidas e lactentes.

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ORCID iD

Shamez N Ladhani <https://orcid.org/0000-0002-0856-2476>

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Explorar as perspectivas dos profissionais de saúde sobre a gestão da pieira em idade pré-escolar: um estudo qualitativo

Lubna Mohammed Abdul Wajid,¹ Sejal Saglani,² Prasad Nagakumar,^{1,3} Gemma Heath⁴

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¹Department of Respiratory Medicine, Birmingham Women's and Children's Hospital NHS Trust, Birmingham, UK

²National Heart and Lung Institute, Imperial College London Faculty of Medicine, London, UK

³Department of Inflammation and Ageing, University of Birmingham, Birmingham, UK

⁴Life and Health Sciences, Aston University, Birmingham, UK

Correspondence to

Dr Prasad Nagakumar; p.nagakumar@nhs.net

PN and GH contributed equally.

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RESUMO

Objetivo Este estudo teve como objetivo explorar as perspectivas dos profissionais de saúde sobre a gestão da pieira em idade pré-escolar, incluindo as suas opiniões sobre a utilização de testes para orientar o tratamento de crianças com pieira recorrente.

Desenho Foram utilizados métodos de amostragem intencional (purposive sampling) e em bola de neve (snowball sampling) neste estudo qualitativo para recrutar profissionais de saúde com experiência na gestão de crianças com pieira em idade pré-escolar, provenientes de contextos de cuidados primários e secundários em Inglaterra. Foram realizadas entrevistas semiestruturadas através do Microsoft Teams. As transcrições foram analisadas tematicamente, com o apoio do software NVivo, para identificar temas-chave.

Resultados Participaram 14 profissionais de saúde: quatro médicos de clínica geral, quatro pediatras gerais, quatro enfermeiros hospitalares de asma, um pediatra respiratório de nível terciário e uma enfermeira de cuidados primários. Os participantes concordaram que a pieira em idade pré-escolar continua a ser uma doença significativa. A análise temática identificou quatro temas principais: (1) desafios com a terminologia diagnóstica, em que a falta de terminologia consistente foi considerada prejudicial para a comunicação e gestão; (2) incerteza diagnóstica, em que a ausência de testes objetivos para o diagnóstico precoce de asma contribuiu negativamente para os planos de gestão; (3) prática atual de investigação de crianças com pieira em idade pré-escolar, onde os participantes descreveram a falta de infraestrutura e de abordagens para realizar testes nos cuidados primários e secundários; e (4) considerações terapêuticas, nas quais se considerou que as crenças dos pais sobre a medicação influenciavam a adesão aos tratamentos prescritos. Verificaram-se diferenças nas opiniões sobre a gestão da pieira pré-escolar entre profissionais dos cuidados primários e secundários. **Conclusão** As perspectivas dos profissionais de saúde destacam a utilização inconsistente da terminologia diagnóstica para a pieira em idade pré-escolar, contribuindo para variações na gestão. São urgentemente necessários percursos de cuidados integrados e infraestrutura adequada para melhorar os resultados das crianças com pieira em idade pré-escolar.

INTRODUCTION

Recurrent wheeze, often termed 'preschool wheeze' (PSW), is one of the most common respiratory conditions in children less than 6 years of age. A recent UK study examining wheeze attack rates in a general asthma population between 2007 and 2015 revealed that patients with the most frequent exacerbations were children under 5 years.¹ Wheezing disorders in preschool children constitute one-third of presentations of respiratory disorders in this age group and are associated with significant healthcare costs (estimated at £53 million in the UK in 1998–1999). Frequent hospital admission with PSW exacerbation is associated with parents taking time out of work to

Key messages

What is known about this topic

► One in three children experiences at least one episode of wheeze between the ages of 1 and 5 years. Wheeze attacks requiring unscheduled health utilisation are increasing in prevalence resulting in significant morbidity and healthcare costs.

What this study adds

► This is the first UK study in which health professionals describe the challenges in diagnosing and managing recurrent preschool wheeze.
► Differences in approaches to the management of preschool wheeze between primary care and secondary care professionals are highlighted.

How this study might affect research practice or policy

► There is an urgent need for guidance on uniform terminology to describe preschool wheeze across healthcare systems.
► There is a need for consistent clinical pathways and infrastructure to guide health professionals in the management of preschool wheeze.

care for children, affecting carers' pay, especially for those who are in waged employment.² The UK has the second highest prevalence of wheeze reported during the second year of life in Europe.³ Recurrent wheeze attacks predict long-term diminished lung function and increased morbidity and mortality in early adulthood.⁴ Although many children with PSW outgrow their symptoms by school age, birth cohort studies suggest that children with severe and frequent episodes in the first 5 years develop long-term deficits in lung function by age 6.⁵ Moreover, approximately 30%–50% of children with PSW develop asthma later in life, influenced by factors such as atopy, parental asthma and environmental exposures.⁴

Management of PSW remains a challenge because diagnostic tests such as spirometry or fractional exhaled nitric oxide (FeNO) are not used in routine clinical care, and there are no definitive management pathways. Current guidance relies on expert consensus and symptom patterns with episodic (virus triggered with symptom-free intervals) or multitrigger wheeze (triggered by viruses, activity or allergens with persistent symptoms). Despite heterogeneous pathophysiology, treatments are often extrapolated from asthma pathways in older

children. Inhaled corticosteroids (ICS) and montelukast are commonly prescribed, yet many children continue to experience acute episodes, highlighting the need for more targeted approaches.⁶ The diagnostic uncertainty may lead to inappropriate reliance on salbutamol or oral steroids and a tendency to view virus-induced wheeze as self-limiting. European Respiratory Society guidelines⁷ recommend identifying treatable traits, such as aeroallergen sensitisation or elevated blood eosinophils, to guide therapy. A US study supports this, showing that PSW children with these traits are more likely to respond to ICS.⁸ Evidence regarding healthcare professionals' views of managing recurrent PSW remains unexplored, highlighting a gap in current knowledge. This qualitative study aimed to explore health professionals' perspectives on the management of PSW, including their views on the use of diagnostic tests (eg, full blood count (FBC) and skin prick test (SPT)) for guiding treatment.

METHODS
Sampling and recruitment

Purposeful and snowball sampling were used to recruit health professionals who care for children with PSW but who varied by professional training (eg, nursing and medical) and across traditional care boundaries (eg, primary, secondary and tertiary care). Professionals were recruited via social media and professional networks. Interested professionals who responded to study adverts received a study information pack via email, including an information sheet and consent form. Best practice guidelines for qualitative research were followed throughout.⁹

Data collection

A semistructured interview guide (online supplemental file) was developed for the study, with questions informed by research literature,^{7 10 11} clinical experience and research objectives. Open-ended questions related to professionals' views and experiences of managing PSW, views on investigations and information provided to families of children with PSW. Interviews were conducted by LMAW, a female clinical research fellow and qualified paediatric doctor with training in qualitative research methods. MS Teams was used to conduct a single interview with each participant during April–August 2023. Interviews lasted 30–90 min and were recorded for later analysis. Data collection continued until saturation was achieved, determined by minimal new information emerging during interviews, concurrent data analysis and team discussions.

Data analysis

Interviews were auto-transcribed by MS Teams and manually verified and anonymised by LMAW. Thematic analysis^{12 13} was used to analyse data within an interpretivist framework led by the clinical research fellow (LMAW). Analysis followed the steps of data familiarisation through repeated reading and review, inductively generating and applying codes to salient extracts of data, forming an initial coding framework. A subset of transcripts was double-coded by GH, a female health psychologist, and discussed with PN, a male paediatric respiratory consultant. The coding framework was refined based on these team discussions before being applied to all transcripts. Codes were compared within and across participants and grouped into themes, further discussed by the team (coding tree online supplemental file). NVivo V.12 software was used to support data coding and retrieval, ensuring robust and systematic analysis.¹⁴

RESULTS
Participants

18 healthcare professionals expressed interest in the study. Following receipt of an invitation to interview, four did not respond. Hence, there were 14 participants recruited from across England working in primary, secondary and tertiary centres, all with experience of managing children with PSW. Participants included four general practitioners, four general paediatricians, four hospital-based asthma nurses, one tertiary respiratory paediatrician and

Table 1 Characteristics of participants	
Sex	
Male	7
Female	7
Age range (years)	
40–50	7
50–60	5
60+	2
Ethnicity	
Asian Indian	6
White British	8
Geographical area	
Greater London	1
Southeast England	1
East Midlands	1
West Midlands	5
Northwest	5
East of England	1
HP	
General practitioners (HP 1–4)	4
Paediatric asthma nurse (HP 5–8)	Community: 1 Secondary/tertiary: 3
Primary care nurse (HP 9)	1
Consultant general paediatricians (HP 10–13)	4
Consultant respiratory paediatrician (HP 14)	1
HP, health profession.	

one primary care nurse. Participants were from Northwest England, West Midlands, East Midlands, Greater London, Southeast and East of England (table 1).

RESULTS
Participants
Parents

Of the 95 families enrolled in the TAILOR study, 30 (31.6%) responded t allergen avoidance may be challenging for many families. HCPsd them less feasible due to time, training needs and rare anaphylaxis risks, making implementation dependent on HCPs' readiness.

Thematic findings

Data analysis generated four themes: (1) challenges with diagnostic terminology, (2) diagnostic uncertainty, (3) current practice of investigating children with PSW and (4) treatment considerations. All participants agreed that PSW remains a significant disease without a single diagnostic nomenclature, test or specific treatment. Differences were noted in the views between primary and secondary care professionals. Illustrative quotations for each theme are provided in table 2.

Challenges with diagnostic terminology

Varied terminologies were used by healthcare professionals to describe wheeze in children aged under 5 years of age (eg, PSW, virus-induced wheeze and preschool asthma), revealing terminology preferences and challenges associated with these terms. Primary care professionals and those with limited paediatric experience often preferred 'viral-induced wheeze', recognising that the condition may improve with time. Health professionals based in secondary care, however, were more likely to use terminologies previously recommended by the European Respiratory Society, like 'episodic viral wheeze' and 'multitrigger wheeze/asthma'. In the absence of diagnostic tests, focused history taking for symptom assessment was highlighted by most health professionals in secondary care to differentiate between PSW and asthma. Nearly all health professionals expressed concerns about a lack of uniform terminology and clarity, which was described as negatively impacting communication with parents and management.

Table 2 Illustrative quotations

Challenges with diagnostic terminology	I think it (virus-induced wheeze) is a good initial term to use. It is a good term especially when we are trying to adopt the wait and watch policy, which we do a lot in primary care (HP1, General Practitioner) I think it can be confusing and it would be useful if we had more clarity over what we're describing, but from my experience, most people call it preschool viral wheeze, or viral induced wheeze if it is an episodic virus-related event, whereas if the child does have evidence of allergic asthma markers, interval symptoms, etc, in my experience, people tend to call it Asthma (HP11, General Paediatric Consultant)
Diagnostic uncertainty	That's quite interesting because a lot of families who come have already heard the wheeze because a lot of the time it's audible wheeze as well and they come with the sort of, a preconceived notion that the child is asthmatic because either the mum has asthma or dad has asthma. So, they almost come in looking for the diagnosis of asthma. So, when you tell them it's a viral induced wheeze, there is initially, there's a bit of a disappointment there because we're not actually formalising a diagnosis of asthma and sticking them on inhalers on repeat prescriptions. (HP1, General Practitioner) I think the main concern from parents that I have encountered is that whether this will progress to asthma? That's what they want to know. Is this short-lasting? Is this something that's going to affect the child longer? Do you know if they are going to live with it all their lives? That's what they want to know. So, is there anything that they can do to make it, you know, stop it from getting worse or stop it from progressing to asthma? (HP2, General Practitioner) If you explain it properly, they are happy with it and they understand it, but not everyone explains it fully to them. A lot of them, they just get given a salbutamol inhaler and off they trot and then they label themselves as asthma. So, you've got to take the time. That's part of the process to take the time and explain what you given the inhaler for, when to use it, when not to use it and what to do in an emergency, it, that's, you know, that's a key part of, you know, looking after the child. (HP7, Paediatric Asthma Nurse)
Current practice	I'm aware of suggestions that eosinophil count, for example, could be useful as skin prick testing might come have a place. The main issue is that I find it difficult to see how it would change my management because if I've decided I want to treat them, I'll usually treat them, and I don't really like putting kids through blood tests if it can be avoided. (HP11, Consultant Paediatrician) Top of Form I guess the delay is in actually getting the appointment for the blood test which currently is three to 4 weeks for routine blood test. We have to call the phlebotomy manager in local hospital, speak to them, give them the clinical details and then they do the urgent blood test. Whereas for a routine blood test, you're probably waiting for three or 4 weeks to actually for the patients to get an appointment. Once they get the bloods done, then within a day or two, we have the results (HP1, General Practitioner) The problem is, we don't know when the results will be exactly available because parents phone phlebotomy and make their own appointment and once they make it there, then expect to have the results back to them. But results don't come back on the same day, if we see maybe today, IGE, other results might be available tomorrow (HP14, Respiratory Consultant). I've seen both. Some parents are keen to get to the bottom of it, but some equally don't want children to have blood tests because obviously, it involves pricking them and you know all of that. So, they want treatment to be started straight away. They don't want to wait for longer. (HP2, General Practitioner)
Treatment considerations Top of Form	It's a fear of using steroids basically because I think that's a well-known, well-publicised fact. Most of them are aware, so they're not keen to go on steroid inhalers there. They worry about long-term steroid use. There was a lot of parents are worried about stunting of the growth and recurrent throat infections as well. (HP1, General Practitioner) I think they are OK with the brown Clenil, the steroid inhaler, and obviously it's, as I said, most of the children, I think the parents are happy to try something because they know that this is gonna help their child and obviously hopefully prevent hospital admissions. The Montelukast, I've noticed more parents, and I think people are more aware, can't they, can Google things, about side effects of medication? I mean, we do give them the medication, you know, the children's medication leaflet about the Montelukast and but parents are a little bit reluctant, I've noticed, because they'll say—'Oh the side effects!' (HP8, Community Paediatric Asthma Nurse) Stopping treatment when they're well. That is the most honestly, the most frustrating and then putting enough there's symptoms come back and then they go, 'Then we started the preventer again. It's just basically, I think for them to recognise that actually the preventer is preventing the symptoms'. (HP7, Paediatric Asthma Nurse)

HP, health profession.

Diagnostic uncertainty

Most primary care professionals described uncertainty in diagnosing wheeze symptoms, highlighting the absence of objective tests and diagnostic pathways as key challenges in confirming asthma in young children. Consequently, terms like 'virus-induced wheeze' were preferred. In secondary care, confidence in diagnosing asthma in children aged under 5 years varied; often heavily influenced by the child's proximity to age 5 years, their family history of asthma and signs of atopy. Secondary care professionals were more confident in providing a diagnosis of asthma as the child reached school age, even in the absence of objective tests.

Perceptions of parent/caregiver expectations were highlighted by many health professionals in their experience of managing PSW. Significant disparity was suggested between healthcare professionals' cautious, symptom-based diagnostic approach and parents' expectations for a clear and immediate asthma diagnosis, particularly among families with a strong history of asthma or in children who had frequent wheeze attacks. Diagnostic uncertainty was often described as leading to parental disappointment when a definitive diagnosis was not provided early. Health professionals subsequently emphasised the importance of clearly explaining the nature of PSW to parents, alongside guidance on inhaler use, including its purpose, timing and actions to take in an emergency.

Current practice of investigating children with PSW

Healthcare professionals' approaches to investigation prior to prescribing preventive treatment to prevent wheeze attacks varied significantly. Those in primary care often adopted a conservative approach, preferring observation and treatment trials with salbutamol alone. Investigations (eg, FBC or SPT) were considered only if additional

symptoms such as food allergies or severe eczema were present, or if the child experienced recurrent wheezing episodes. In such cases, referrals to paediatric or allergy specialists in secondary care were common.

Children with recurrent hospital admissions, intensive care admissions or suspected allergies were referred for comprehensive investigations to guide treatment decisions. These investigations were mainly organised by secondary care health providers. Routine investigations in children with milder symptoms were not performed due to concerns about unnecessary distress and the potential for these tests to not significantly alter management plans.

All healthcare professionals in primary care highlighted that blood or allergy tests were not performed in young children in the community due to the lack of availability of paediatric phlebotomy services and were referred to the hospital for investigations. A few general practitioners expressed hesitancy in ordering tests due to the complexity of interpreting results and practical issues related to paediatric phlebotomy.

In secondary care, although ideal, same-day phlebotomy/allergy test services were not always available, leading to a second appointment and significant delay in formulating treatment plans. Staffing challenges were thought to be compounded by post-COVID backlogs, affecting the efficiency of diagnostic processes. Non-availability of phlebotomy appointments also meant that some parents had to take time off work to attend subsequent appointments. Some parents were reported to not attend the scheduled phlebotomy appointment, thus affecting clinicians' decisions on commencing preventive treatment.

Healthcare professionals, both in primary and secondary care, expressed mixed views on parental acceptability of blood/allergy tests. Parents of children with recurrent symptoms/hospital admis-

sions were considered more likely to accept the tests than those at first presentation. A lack of information and timely access to tests, as well as anxieties about painful procedures in young children, were suggested as barriers. Most professionals felt that the availability of point-of-care testing and increased awareness around the utility of tests may improve uptake.

Treatment considerations top of form

Healthcare professionals in primary care felt that the term 'steroid' invoked significant anxiety among parents due to perceived side effects. Misconceptions were therefore considered to persist, despite providing information about the differences between systemic and inhaled steroids. Health professionals also suggested the stigma of having a child labelled as 'asthmatic' contributed to hesitancy. In secondary care, similar concerns were echoed, with additional perceived parental worries about specific medications like montelukast, which some parents were reported to associate with severe side effects (eg, night terrors).

Healthcare professionals, both in primary and secondary care, emphasised the importance of distinguishing between systemic steroids and inhaled forms, which have fewer side effects and the management goal of reducing wheeze attacks in young children. Nurses highlighted the medication adherence challenge of parents stopping preventer medications when children appeared well. Misunderstandings about treatments and inconsistent advice from different healthcare providers exacerbated this issue. To improve adherence to prescribed medications, healthcare professionals suggested integrated approaches, including regular reviews, use of alarm systems and ensuring consistent information about medication use and inhaler techniques.

DISCUSSION

To our knowledge, this qualitative study describes for the first time the views of UK healthcare professionals on diagnosing and managing wheeze in children aged under 5 years. Findings suggest differences in approaches to the management of PSW between primary and secondary care. Health professionals in primary care preferred practical terminology like 'viral-induced wheeze', which allowed for a wait-and-watch approach. In contrast, secondary care professionals opted for more structured terms like 'episodic viral wheeze' and 'multitrigger wheeze' aligned with European Respiratory Society recommendations.¹⁰ Inconsistencies in terminology, however, impacted communication with parents and disease management.

Findings indicated that primary care professionals preferred using straightforward terms, which they suggested facilitated communication with parents and reduced diagnostic procedures. In contrast, secondary care professionals often relied on more precise terms to improve diagnostic clarity. However, using different terminologies across levels of care to describe the same condition was considered confusing for parents. This perception is supported by previous research from the parents' perspective, suggesting that inconsistent terminology presents a barrier to effective management of PSW.¹⁵

In the current study, a lack of objective diagnostic tests (eg, FBC and SPT) in primary care for preschool children resulted in diagnostic uncertainty and inconsistent confidence among clinicians in labelling young children with asthma. Supporting individuals to live well with asthma has previously been recommended to extend beyond biological and pharmacological management to encompass evidence-based tailored support for self-care through the delivery of patient-centred care, including how clinical practice is organised.¹⁶

Our study further describes current approaches to performing investigations to guide the management of PSW. As has been previously highlighted, it was noted that primary care does not always have the infrastructure to perform blood or allergy tests,¹⁷ and health professionals thus preferred symptomatic treatment. Children had to be referred to acute hospitals for blood/allergy tests, which often delayed management decisions. Health professionals in secondary care were aware of the role of the investigations in guiding treatments but described challenges in access to phlebotomy services.

However, many hospitals require routine blood tests to be performed through a booking system and could take days to weeks to get

the tests done, resulting in delays in making treatment decisions. Moreover, in children with recurrent wheezy episodes, health professionals prescribed inhaled steroids without tests, aiming to reduce the wheeze attacks. Health professionals in primary care expressed their reluctance to start inhaled steroids due to the perceived side effects and lack of robust management guidelines. Previous research supports barriers to inhaled steroid prescribing in children. Commonly cited barriers have included unclear guidelines, believing that long-term paediatric medication prescribing is not within their role, and not being able to follow up with patients.¹⁸ Secondary care professionals in our study were more comfortable in prescribing inhaled steroids, perhaps due to the type of patients seen in the hospital setting, who were more likely to have severe or recurrent disease.

The British Thoracic Society and the Global Initiative for Asthma have both provided guidelines for diagnosing and managing asthma in children aged under 5 years. However, these guidelines do not specifically address PSW, leaving health professionals grappling with whether to label every young child with wheeze as having asthma.^{19 20}

Challenges with diagnostic terminology

A strength of this study is the participation of health professionals from across England. General practitioners, asthma nurses working in hospital and community settings, secondary care paediatricians and specialist respiratory paediatricians contributed to the study, providing a unique insight into the multidisciplinary management of PSW. While differences in approaches between primary and secondary care health professionals in this study could be due to the more severe cases being managed in secondary care, others have previously demonstrated a need for upskilling health professionals across the integrated care system.²¹ Two team members (SS and PN) manage children with severe wheeze, potentially influencing analysis. However, the first (LMAW) and lead (GH) authors had no clinical role. Analysis relied solely on professionally provided data, reducing bias. Coding was reviewed collaboratively, ensuring consensus on themes, though not all transcripts were double-coded.

Recommendations

Our study highlights an urgent need for guidance on uniform terminology to describe PSW across healthcare systems. Clinical pathways need to be put in place to guide health professionals in the effective management of PSW. This study suggests an unmet need for developing infrastructure in primary care to perform simple respiratory tests in children. Access to point-of-care testing or setting up diagnostic hubs may help. However, infrastructure should be put in place before recommending tests to be performed in primary care. Finally, there is a need for training and education for health professionals to improve the management of PSW. Upskilling health professionals across healthcare settings and co-producing management plans with parents/carers, as well as providing parent education and support, could significantly impact healthcare utilisation patterns, including emergency department visits, hospital admissions and primary care consultations.

CONCLUSION

Our study demonstrates a need for uniform nomenclature, diagnostic practices and unified guidelines for effectively managing wheeze in young children. Addressing these challenges through standardised terminology and improved diagnostic tools will improve communication, reduce parental anxiety and improve overall care. Future research should prioritise these areas to advance the management of recurrent wheezing in young children.

Correction notice This paper has been updated since it was first published. The affiliations have been amended. **Contributors** LMAW (first author): investigation, formal analysis, writing the original draft and writing the review and editing. SS: conceptualisation and writing the review and editing. PN and GH: conceptualisation, methodology, formal analysis, writing the original draft, writing the review and editing, and supervision. PN is the guarantor. **Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors. **Competing interests** None declared. **Patient consent for publication** Not applicable. **Ethics approval** This study involves human participants. A favourable ethical opinion was obtained from the Wales NHS Research Ethics Committee (#23/WA/0109). Participants gave informed consent to participate in the study before taking part. **Provenance and peer review** Not commissioned; externally peer reviewed.

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ORCID iDs

Lubna Mohammed Abdul Wajid <https://orcid.org/0009-0000-1175-5108>

Sejal Saglani <https://orcid.org/0000-0001-5192-6418>

Prasad Nagakumar <https://orcid.org/0000-0003-0837-0308>

Gemma Heath <https://orcid.org/0000-0002-1569-5576>

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ARTIGO ORIGINAL

A redução desproporcionada da capacidade de difusão prevê hipertensão pulmonar com resistência vascular pulmonar elevada na DPOC

Aparna Balasubramanian,¹ Anna R Hemnes,² Evan L Brittain,³ Jeffrey Annis,³ Ashraf Fawzy,¹ Nirupama Putcha,¹ Anil Singh,⁴ Robert A Wise,¹ Nadia N Hansel,¹ Catherine Simpson,¹ Todd M Kolb,¹ Paul M Hassoun,¹ Meredith C McCormack,¹ Stephen C Mathai¹

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¹Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland, USA

²Division of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

³Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

⁴Division of Pulmonary and Critical Care Medicine, Allegheny Health Network, Pittsburgh, Pennsylvania, USA

Correspondence to

Dr Stephen C Mathai;
smathai4@jhmi.edu

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RESUMO

Contexto As orientações atuais para a avaliação da doença pulmonar obstrutiva crônica (DPOC) não recomendam o rastreio de hipertensão pulmonar (HP), apesar da sua elevada prevalência e impacto nos desfechos clínicos. É urgentemente necessária uma ferramenta de rastreio simples para identificar doentes com resistência vascular pulmonar (PVR) elevada, uma vez que estes podem beneficiar de terapêutica específica para HP e de referência mais urgente para transplante pulmonar.

Questão de investigação Procurámos avaliar se a razão entre o volume expiratório forçado no primeiro segundo (FEV₁) e a capacidade de difusão (DLCO) prevê padrões hemodinâmicos na DPOC.

Desenho do estudo e métodos Foram incluídos indivíduos com DPOC que realizaram cateterismo cardíaco direito em dois centros médicos académicos. Modelos multinomiais ajustados testaram associações entre a razão FEV₁/DLCO e padrões hemodinâmicos. Curvas ROC foram geradas para avaliar o desempenho discriminativo da razão FEV₁/DLCO na previsão de HP com PVR elevada.

Resultados Aproximadamente 40% dos 411 indivíduos incluídos apresentavam HP com PVR elevada. Por cada aumento de 0,1 na razão FEV₁/DLCO, verificou-se um aumento de 12–14% na taxa de HP com PVR elevada, comparativamente à ausência de HP. A razão FEV₁/DLCO apresentou desempenho discriminativo moderado (estatística C 0,68–0,72), que foi reforçado quando combinada num modelo com velocidade elevada do jato de regurgitação tricúspide na ecocardiografia (estatística C 0,78–0,82). Acima de um limiar de 1,4, a razão FEV₁/DLCO demonstrou boa especificidade (75%) na previsão de HP com PVR elevada.

Interpretação Estes resultados sugerem que reduções desproporcionadas da DLCO prevêem HP com PVR elevada numa população com DPOC. A razão FEV₁/DLCO deve ser considerada na avaliação da HP na DPOC.

INTRODUCTION

Pulmonary hypertension (PH) is common in chronic obstructive pulmonary disease (COPD), with a prevalence up to 35%,^{1–3} and is associated with increased morbidity and mortality. Individuals with COPD-PH have a 3-year survival rate from diagnostic right heart catheterisation (RHC) of 41%–66%, worse than other forms of PH, including pulmonary arterial hypertension (PAH)^{4–7} and COPD without PH.⁸ Additionally, studies have demonstrated more frequent severe exacerbations of COPD requiring hospitalisation among those with COPD-PH.^{9,10} Given the substantial morbidity and poor prognosis associated with this condition, it is a priority to identify individuals with COPD who are likely to have PH.

Observed haemodynamic patterns in COPD-PH include elevation in pulmonary vascular resis-

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Though chronic obstructive pulmonary disease-pulmonary hypertension (COPD-PH) is known to confer high morbidity and mortality, there are currently no well-validated tools in COPD that accurately predict haemodynamic patterns that may be most responsive to therapies.

WHAT THIS STUDY ADDS

► This study evaluates the value of a forced expiratory volume in 1 s (FEV₁)/diffusing capacity (DLCO) ratio in predicting PH with an elevated pulmonary vascular resistance (PVR), demonstrating strong associations with PVR. It further demonstrates good discriminative performance in predicting PH with an elevated PVR and improves on traditional echocardiographic screening for PH in this population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► The FEV₁/DLCO ratio is a simple, readily available tool that can help distinguish which individuals should undergo an invasive, limited-resource procedure for diagnosis of a devastating disease and may further identify patients at high risk of severe PH who may benefit from specific therapy.

tance (PVR), pulmonary capillary wedge pressure (PCWP) or both.^{11–14} These distinct patterns warrant different management strategies with only those with an elevated PVR, particularly with severe elevations above 5 Woods units (WU), being potentially responsive to PH-specific therapies.^{15,16} Unfortunately, to date, there are no rigorously validated tools to identify which patients are likely to have COPD-PH with an elevated PVR who may benefit from further evaluation with RHC for diagnosis in anticipation of PH-specific therapy or consideration of study participation in novel therapeutics.

Previous literature has noted associations between diffusing capacity (DLCO) obtained with pulmonary function testing (PFTs) and haemodynamics in COPD-PH and with morbidity and mor-

tality.^{12–21} Based on these associations, guidelines have suggested that the relative impairment in DLCO to airflow obstruction, as measured by forced expiratory volume in 1 s (FEV₁), may be useful in defining COPD-PH phenotypes.^{22,23} However, there has been limited evaluation of the FEV₁/DLCO ratio in COPD-PH to substantiate those recommendations.

This study aimed to better define associations between FEV₁/DLCO ratio and haemodynamic patterns in patients with COPD, with the goal of consideration of this ratio in clinical screening for PH. Leveraging data obtained across two large tertiary care referral centres, this study sought to characterise FEV₁, DLCO and the FEV₁/DLCO ratio as predictors of individual haemodynamic measures and patterns across patients with COPD.

METHODS

Study design and population

This retrospective cohort study used data from the Johns Hopkins Medicine (JHM) COPD Precision Medicine Center of Excellence between July 2016 and April 2023. All individuals over the age of 30 years with an International Classification of Diseases (ICD)-10 diagnosis of COPD, complete spirometry and DLCO data with evidence of airflow obstruction on spirometry by GOLD criteria²⁴ (FEV₁/forced vital capacity (FVC) ratio ≤ 0.7) and complete RHC data were included. An external validation cohort was obtained from the Vanderbilt University Medical Center (VUMC) with clinical data obtained between July 1996 and August 2020. The same inclusion and exclusion criteria were applied to the VUMC cohort. The institutional review board approved this study at both sites with waived consent for minimal risk.

Pulmonary function test data

PFT data included FEV₁, FVC, FEV₁/FVC ratio, DLCO and gas transfer efficiency (carbon monoxide transfer coefficient, KCO) on all individuals. For spirometry data, GLI Global reference equations, and for DLCO, corresponding GLI reference equations were applied.^{25,26} FEV₁/DLCO ratios were calculated using the ratio of FEV₁% predicted divided by DLCO % predicted.

RHC data

Haemodynamic parameters included right atrial pressure (RAP), mean pulmonary artery pressure (mPAP), PCWP, cardiac output

(CO), cardiac index (CI), and PVR. Details on RHC procedures are provided in the online supplemental methods.

For the analyses, haemodynamics were classified into three patterns: (1) PH with an elevated PVR (mPAP > 20 mmHg and PVR ≥ 3 WU), (2) PH without an elevated PVR (mPAP > 20 and PVR < 3) and (3) no PH (mPAP ≤ 20). Applying the 6th World Symposium on Pulmonary Hypertension (WSPH) definitions, PH with an elevated PVR included individuals with pre-capillary (mPAP > 20 mmHg, PCWP ≤ 15 mmHg, PVR ≥ 3 WU), or combined pre and post-capillary PH (mPAP > 20, PCWP > 15, PVR ≥ 3), while PH without an elevated PVR included post-capillary (mPAP > 20 mmHg, PCWP > 15 mmHg, PVR < 3), and individuals with an isolated elevation in mPAP (mPAP > 20 mmHg, PCWP ≤ 15 , PVR < 3).²⁷

Statistical analysis

All analyses were conducted using Stata 18.0, with statistical significance set at a p-value of < 0.05. Further details are provided in the online supplemental file 1. Clinical characteristics at time of RHC and associations between each PFT measure (FEV₁, DLCO, KCO) and haemodynamic patterns were evaluated. Fractional polynomial models examined associations between FEV₁/DLCO ratio and PVR as a continuous variable or categorised as either an elevated PVR (≥ 3 WU), or a severely elevated PVR (≥ 5 WU) as per the 7th WSPH statement.²⁸ Multinomial regressions modelled the probability of having PH with an elevated PVR or PH without an elevated PVR vs no PH as the base outcome. All models were adjusted for age, sex, race, body mass index (BMI) and smoking status. Linear and logistic regression models were further adjusted for mPAP and either N-terminal pro-brain natriuretic peptide (N-T proBNP) or BNP, depending on availability in the specific cohort. Confounders were selected a priori based on clinical knowledge and prior literature. Sensitivity analyses of the multinomial models were performed using the larger cohorts with available PFT data but without restricting for FEV₁/FVC ≤ 0.7 , and the smaller cohorts of individuals with airflow obstruction and PFTs within 1 year, and within 90 days of RHC. Secondary analyses included evaluating the FEV₁ %predicted/KCO %predicted ratio, the FEV₁ z-score/ DLCO z-score ratio, and the absolute FEV₁/DLCO ratio. The ratio of z-scores was calculated using (FEV₁ z-score + 20)/(DLCO z-score + 20) to ensure all values were > 0 and to maintain interpretation of the ratio as consistent with interpretation of the

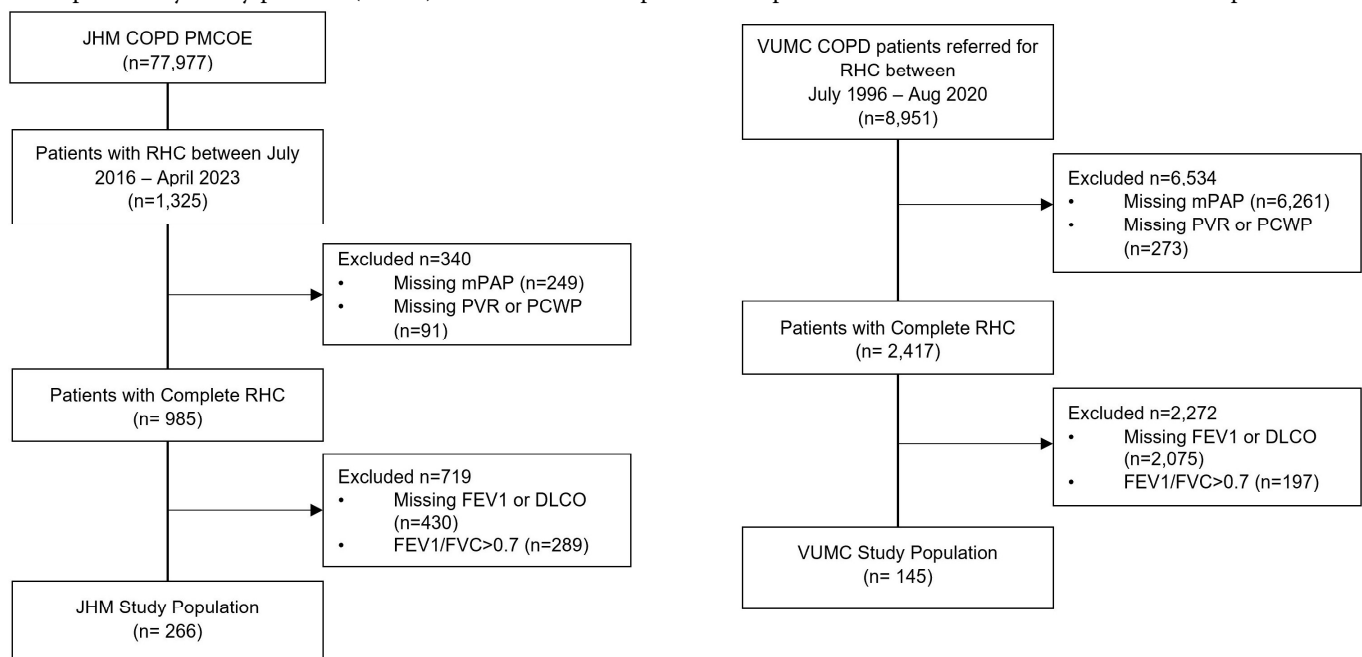


Figure 1 Study populations. COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; JHM, Johns Hopkins Medicine; mPAP, mean pulmonary artery pressure; PMCOE, Precision Medicine Center of Excellence; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RHC, right heart catheterisation; VUMC, Vanderbilt University Medical Center.

percent predicted ratio. Additional analyses included multinomial regressions of haemodynamic patterns divided into pre-capillary, post-capillary, combined pre-post, isolated mPAP elevation and no PH groups. Further, in the JHM cohort where the data were available, multinomial analyses were stratified by the presence or absence of CT emphysema.

To test whether the associations between FEV₁/DLCO ratio and haemodynamic pattern varied across DLCO values, associations were evaluated across four groups, dichotomising FEV₁/DLCO ratio at 1.4 as per prior literature¹⁷: (1) a low ratio and DLCO>50% predicted, (2) a high ratio and DLCO>50% predicted, (3) a low ratio and DLCO≤50% predicted and (4) a high ratio and DLCO≤50% predicted. Logistic regression models tested the probability of PH with an elevated PVR, with the low ratio and DLCO>50% predicted used as the reference group.

Finally, a receiver operating curve (ROC) was generated to define a threshold of FEV₁/DLCO that optimises sensitivity and specificity for PH with an elevated PVR. Statistical comparisons of Harrell's C-statistics for predictors, including FEV₁, DLCO, FEV₁/DLCO and tricuspid regurgitant velocity (TRV) dichotomised at 2.8 cm/s. TRV was selected at this threshold as it is commonly recommended in guidelines for use in screening individuals for PH.²⁹ A model consisting of TRV + FEV₁/DLCO was constructed to assess the additive discriminative value of this combination.

RESULTS

The JHM study population included 266 individuals with COPD and complete PFT and RHC data, and the VUMC cohort included 145 individuals (figure 1). Nearly half of individuals in the JHM cohort (127, 48%) had PFTs within 90 days and 191 (72%) within 1 year of RHC. In the VUMC cohort, 56 individuals (39%) had PFTs within 90 days and nearly half (66, 46%) within 1 year. Clinical characteristics of both cohorts are reported in table 1. Individuals across both samples had an average age in the mid-60s and were predominantly male,

White and overweight with a median BMI of 28.1 kg/m². Approximately three-quarters of individuals in both cohorts were self-reported former or current smokers. Both cohorts had moderately impaired FEV₁ % predicted and severe impairment in DLCO. Forty-one per cent of individuals in the JHM cohort had evidence of emphysema on CT. Most individuals had multiple comorbidities, with over 70% in both cohorts having congestive heart failure and coronary artery disease, and approximately half in both cohorts having sleep apnoea, diabetes and chronic kidney disease. Echocardiograms were available in 258 (97%) and 138 (95%) from the JHM and VUMC cohorts, respectively, with over 80% within 90 days of RHC (JHM 222, 86%; VUMC 112, 81%). From echocardiography, both the JHM and VUMC populations had a high prevalence of left heart diastolic dysfunction with a median E/e' of 13 and 14 respectively, and 52% of individuals in both cohorts having left atrial dilation. Average tricuspid regurgitant velocity was also elevated and similar in both cohorts.

The distribution of haemodynamics was also similar across the JHM and VUMC cohorts (online supplemental table 1). Nearly a quarter of individuals had no PH (18% in JHM vs 25% in VUMC). Twenty per cent had modest elevations in mPAP between 21 and 25 mmHg; similarly, 20% also had modest elevations in PVR between 2–3 WU. The JHM cohort had slightly higher prevalence of PH with an elevated PVR with 113 individuals (43%) having either a precapillary or combined pattern, as compared with 52 individuals (36%) in the VUMC cohort. Using thresholds of 50% predicted, severe impairment in DLCO was associated with higher PVR and mPAP in both cohorts, while severe impairment in FEV₁ was associated with increased CO and CI in the JHM cohort and trended towards the same association in the VUMC cohort (online supplemental table 2). Examining patterns, DLCO≤50% predicted had a higher prevalence of pre-capillary and combined pattern haemodynamics and a lower prevalence of post-capillary haemodynamics (p<0.001 for JHM, p=0.038 for VUMC, online supplemental table 3). There were no significant differences in the proportions of individuals across

haemodynamic patterns based on an FEV₁ above or below 50% predicted (JHM p=0.128, VUMC p=0.766).

FEV₁/DLCO ratio predicts haemodynamic patterns in COPD

Flexible modelling demonstrated that FEV₁/DLCO was associated with PVR independent of demographics and mPAP, with a mostly linear association across both cohorts (figure 2). The probability of having an elevated PVR, and a severely elevated PVR, was also associated with FEV₁/DLCO and observed to increase linearly for ratio values between 1 and 2.5 in both cohorts (online supplemental figure 1).

In multinomial models, FEV₁/DLCO was independently associated with increased probability of having PH with an elevated PVR (figure 3). Specifically, for every 0.1 increase in FEV₁/DLCO ratio, there was an 12–14% higher rate of PH with elevated PVR

Table 1 Clinical characteristics of the JHM and VUMC cohorts

	JHM cohort (N=266)	VUMC cohort (N=145)
Age (years)	66±12	63±10
Female, N (%)	131 (49%)	55 (39%)
African-American, N (%)	72 (27%)	14 (10%)
BMI kg/m ² , median (Q1, Q3)	28.1 (23.6, 33.6)	28.1 (23.9, 31.9)
Smoking status, N (%)		
Never smoker	69 (26%)	34 (24%)
Former smoker	141 (53%)	91 (65%)
Current smoker	56 (21%)	16 (11%)
FEV ₁ % predicted	58±22	53±20
FEV ₁ /FVC ratio	0.59±0.11	0.57±0.12
DLCO % predicted	48±23	46±23
Haemoglobin (g/dL)	12.5±2.3	13.2±2.3
NT-proBNP pg/mL, median (Q1, Q3)	889 (250, 3249)	--
BNP pg/mL, median (Q1, Q3)	--	274 (125, 617)
Left ventricular ejection fraction (%)	60 (40, 60)	55 (30, 60)
Mitral valve E/e', median (Q1, Q3)	13 (9.4, 17)	14 (10.9, 20.2)
LA dilation, N(%)	132 (52%)	75 (52%)
TAPSE	1.97±0.53	1.89±0.51
TRV	3.1±0.8	3.2±0.8
RV dilation, N (%)	129 (51%)	33 (24%)
RV hypokinesis, N(%)	93 (38%)	32 (24%)
6MWD (ft)	933±427	876±242
Emphysema, N (%)	108 (41%)	--
Comorbidities, N (%)		
Congestive heart failure	195 (73%)	116 (80%)
Coronary artery disease	185 (70%)	114 (80%)
Obstructive sleep apnoea	139 (52%)	60 (41%)
Diabetes	130 (49%)	74 (51%)
Chronic kidney disease	146 (55%)	84 (58%)

Continuous variables presented as mean±SD deviation, or median (first quartile, third quartile) as appropriate. When medians are presented, this is labelled. Categorical variables are presented as N with percentages. Missing JHM data: Haemoglobin (N=1), NT-proBNP (N=18), left ventricular ejection fraction (N=10), mitral valve E/e' (N=116), LA dilation (N=13), TAPSE (N=118), TRV (N=72), RV dilation (N=13), RV hypokinesis (N=18), 6MWD (N=141), emphysema (N=5). Missing VUMC data: smoking status (N=4), haemoglobin (N=2), BNP (N=33), left ventricular ejection fraction (N=15), mitral valve E/e' (N=126), TAPSE (N=115), TRV (N=50), RV dilation (N=10), RV hypokinesis (N=14), 6MWD (N=135). BMI, body mass index; BNP, brain natriuretic peptide; DLCO, diffusing capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; JHM, Johns Hopkins Medicine; LA, left atrial; 6MWD, 6 min walk distance; NT-proBNP, N-terminal pro-brain natriuretic peptide; RV, right ventricular; TAPSE, tricuspid annulus plane of systolic excursion; TRV, tricuspid regurgitant velocity; VUMC, Vanderbilt University Medical Center.

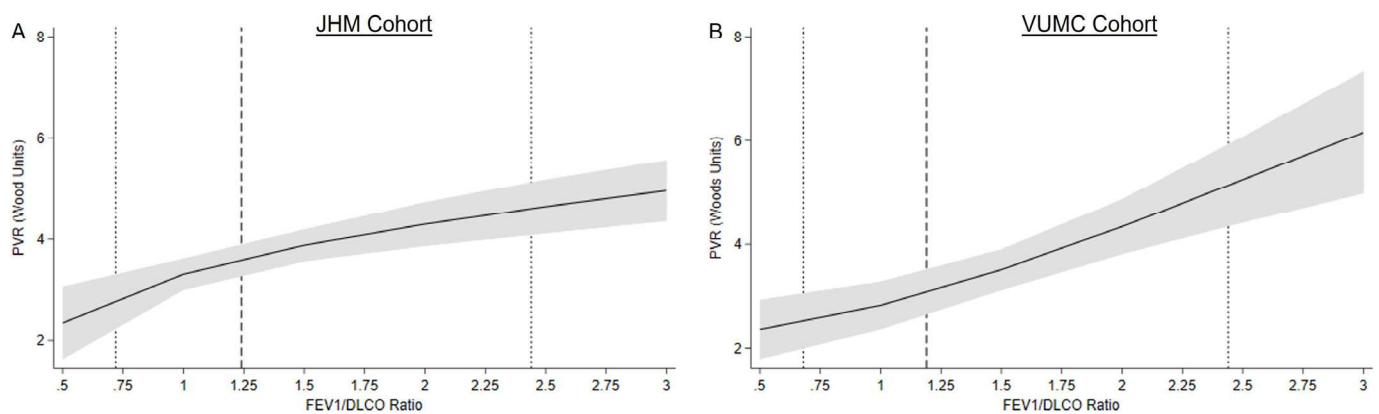


Figure 2 FEV₁/DLCO ratio is associated with pulmonary vascular resistance. Models adjusted for age, sex, race, BMI, smoking status and mean pulmonary artery pressure (mPAP). The models in the (A) JHM cohort were further adjusted for NT-proBNP and in the (B) VUMC cohort for BNP. Dashed lines represent the 10th, 50th and 90th percentile values for FEV₁/DLCO ratios in each cohort. BMI, body mass index; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity; FEV₁, forced expiratory volume in 1 s; JHM, Johns Hopkins Medicine; NT-proBNP, N-terminal pro-brain natriuretic peptide; VUMC, Vanderbilt University Medical Center.

as compared with no PH (table 2). Notably, across both the JHM and VUMC cohorts, above an FEV₁/DLCO ratio of approximately 1.5, the probability of PH with an elevated PVR is higher than the probability of PH without an elevated PVR or no PH (figure 3). When classified into the WSPH five haemodynamic patterns, FEV₁/DLCO ratio was associated with pre-capillary and combined patterns of PH with similar magnitude effect sizes across both cohorts (online supplemental table 4, online supplemental figure 2). Results remained unchanged in sensitivity analyses looking at the sample with complete PFTs regardless of evidence of obstruction by FEV₁/FVC ratio, and the sample with obstructive PFTs within 1 year of RHC (online supplemental table 5). When restricted to a sample with obstructive PFTs within 90 days of RHC, trends remain unchanged but do not achieve statistical significance. Secondary analysis of the FEV₁/KCO ratio, the FEV₁ z-score/DLCO z-score ratio, and the absolute FEV₁/DLCO ratios also demonstrated similar associations (online supplemental table 6). Echocardiographic parameters were also tested as predictors of haemodynamic patterns (online supplemental table 7). While these parameters often were able to predict the presence of PH, only left atrial dilation and mitral E/e' were able to consistently distinguish haemodynamic patterns.

In the JHM cohort, individuals with CT evidence of emphysema had significantly higher FEV₁/DLCO ratios, with an average of 1.8 ± 1.2 as compared with 1.2 ± 0.6 among those without emphysema ($p < 0.001$, online supplemental figure 3).

In adjusted multinomial models stratified by emphysema status, FEV₁/DLCO ratio predicted PH with an elevated PVR similarly regardless of the presence or absence of CT emphysema (online supplemental table 8). Evaluating the associations between groups defined by FEV₁/DLCO ratio and DLCO % predicted and haemo-

dynamic patterns demonstrated that the group with a high ratio and a severely impaired DLCO had a higher proportion of PH with an elevated PVR than any other group, including the group with a high ratio but without severe DLCO impairment (figure 4). In multivariable models, compared with individuals with DLCO $> 50\%$ predicted and FEV₁/DLCO < 1.4 , the odds of identifying PH with an elevated PVR was over five times higher among individuals with DLCO $\leq 50\%$ and FEV₁/DLCO ≥ 1.4 in the JHM cohort (OR 5.01, 95% CI 2.54 to 9.87, $p < 0.001$) and four times higher in the VUMC cohort (OR 4.59, 95% CI 1.72 to 12.32, $p = 0.002$) (table 3). When examining the five WSPH haemodynamic patterns, the high ratio - low DLCO group again was associated with the highest proportion of pre-capillary haemodynamics in both the JHM and VUMC cohorts (online supplemental figure 4).

To assess the performance of FEV₁/DLCO as a predictor of PH with an elevated PVR, ROCs were generated and noted that the FEV₁/DLCO ratio had an AUC of 0.71 and 0.66 in the JHM and VUMC cohorts, respectively (figure 5). Similar ROCs for FEV₁ and DLCO alone demonstrated poor AUCs for FEV₁, while DLCO alone noted an AUC of 0.64 and 0.65 in the JHM and VUMC cohorts, suggesting the ratio of FEV₁/DLCO offers a small amount of additional discriminative performance (online supplemental figure 5). The sensitivity and specificity for threshold values of FEV₁/DLCO in predicting PH with an elevated PVR are reported in table 4. Statistical comparisons of Harrell's C-statistics calculated using a jackknife approach (table 5) demonstrated statistically significant improvement in discrimination between FEV₁/DLCO (C-statistic JHM 0.68, VUMC 0.72) and FEV₁ (C-statistic JHM 0.57, VUMC 0.45; $p < 0.05$ for all comparisons) but was only significantly improved when compared with DLCO alone in the JHM cohort (C-statistic JHM 0.61, VUMC 0.66; $p < 0.05$ for JHM and $p = 0.29$ for

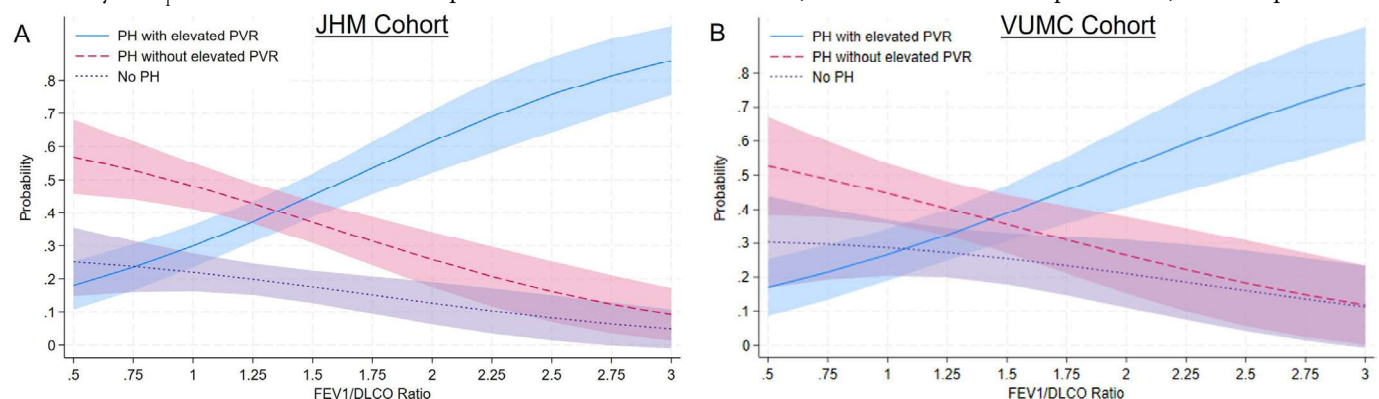


Figure 3 (A and B) Multinomial regression predicted probabilities of haemodynamic patterns. Models adjusted for age, sex, race, BMI and smoking status. N=266 for JHM cohort, N=141 for VUMC cohort. BMI, body mass index; DLCO, diffusing capacity; FEV₁, forced expiratory volume in 1 s; JHM, Johns Hopkins Medicine; NT-proBNP, N-terminal pro-brain natriuretic peptide; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; VUMC, Vanderbilt University Medical Center.

Table 2 FEV₁/DLCO ratio is independently associated with PH with an elevated PVR

	JHM cohort N=266		VUMC cohort N=141	
	RRR (95% CI)	P value	RRR (95% CI)	P value
PH with elevated PVR	1.14 (1.05 to 1.24)	0.001	1.12 (1.04 to 1.21)	0.004
PH without elevated PVR	0.99 (0.91 to 1.08)	0.859	0.97 (0.89 to 1.06)	0.554
No PH	Ref	--	Ref	--

Models adjusted for age, sex, race, BMI and smoking status. Coefficients are relative rate ratios per 0.1 unit change in FEV₁/DLCO ratio.
DLCO, diffusing capacity; FEV₁, forced expiratory volume in 1 s; JHM, Johns Hopkins Medicine; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; Ref, reference group; RRR, relative rate ratio; VUMC, Vanderbilt University Medical Center.

VUMC). When added to a model with TRV, FEV₁/DLCO significantly improved the discrimination for PH with an elevated PVR (JHM C-statistic 0.77, VUMC C-statistic 0.83), and for PH with a severely elevated PVR (JHM C-statistic 0.78, VUMC C-statistic 0.82, online supplemental table 9).

DISCUSSION

In this observational study across two large academic referral centres, we identified the FEV₁/DLCO ratio as predictive of PH with an elevated PVR among patients with COPD, with good discriminative performance. Notably, the FEV₁/DLCO ratio significantly improved discrimination beyond echo-derived measures of PH. The degree of elevation in FEV₁/DLCO ratio associated with haemodynamic phenotypes with a ratio >1.4 predicting precapillary PH and a ratio ≤1 predicting postcapillary PH. Furthermore, for every 0.1 increase in FEV₁/DLCO ratio, there was an 12%–14% increased risk of PH with elevated PVR. These findings highlight simple pulmonary function tests as a useful tool in selecting which patients with COPD may have pulmonary vasculopathy and should undergo RHC to inform treatment strategies and prognosis.

The FEV₁/DLCO ratio conceptually compares the degree of pulmonary vascular involvement to the degree of airflow obstruction by FEV₁. Previous literature in scleroderma has demonstrated an association between a FVC to DLCO ratio in predicting PAH,³⁰ reflecting the relative degree of vascular disease to that of lung parenchymal restriction; as a result, the FVC/DLCO ratio is used in early detection protocols for identifying scleroderma patients at high risk of PH.³² The importance of isolated reductions in DLCO has also been described in postviral illness populations as being associated with clinical outcomes,^{33,34} highlighting the importance of this pulmonary function test particularly when disproportionately reduced. This study adds to these findings, focusing on the FEV₁/

DLCO ratio, conceptually comparing the degree of pulmonary vascular involvement to the degree of airflow obstruction by FEV₁, which is most pertinent to patients with COPD.

Rationale for using an FEV₁/DLCO ratio is supported by the epidemiologic evidence of severe PH in COPD reflecting a 'pulmonary vascular phenotype',^{23,35} which is characterised by severe gas transfer impairment with only mild–moderate reductions in FEV₁. Our findings demonstrate the utility of the FEV₁/DLCO ratio in predicting PH with an elevated PVR, noting a linear relationship between the ratio and PVR across most of the observed range. The strong association with severely elevated PVR and the added discrimination beyond echo-derived TRV in predicting severely elevated PVR is particularly noteworthy as this subgroup is the most likely to be considered a pulmonary vascular phenotype, at highest risk of increased morbidity and mortality related to PH, and most likely to be responsive to PH-specific therapies. Furthermore, echo-derived right ventricular dysfunction was insufficient in discriminating haemodynamic patterns with an elevated PVR from those without, adding evidence to support recommendations that echo, spirometry and DLCO should all be considered in diagnostic evaluation of COPD-PH.^{28,29}

Epidemiologic studies in COPD have demonstrated higher prevalence of PH among those with worse airflow obstruction.³ Yet among registries of PH patients, lower FEV₁ is not associated with worse haemodynamics.^{16,18,35} Our results further demonstrated that FEV₁ alone does not discriminate between individuals with or without an elevated PVR. An increased prevalence of PH with worse airflow obstruction but without increases in PVR may instead reflect PH secondary to left heart failure. Both systolic and diastolic left heart failure are commonly comorbid with COPD,^{13,36} and our findings suggest that patients with COPD referred for RHC with an FEV₁/DLCO ratio less than or equal to 1 (ie, where FEV₁ and DLCO are proportionally decreased), are most likely to have postcapillary PH.

In COPD, the FEV₁/DLCO ratio has been previously assessed in the National Emphysema Treatment Trial (NETT) study, where investigators identified a high specificity (84%) using a cut-off of 1.4 for detecting precapillary PH, defined as an mPAP ≥25 mm Hg and PCWP ≤15 mm Hg.¹⁷ They also demonstrated that the FEV₁/DLCO ratio did not seem to add predictive value to DLCO alone. However, the NETT cohort was restricted to a severely emphysematous population with average FEV₁ and DLCO values roughly half those reported in this study (FEV₁ 27% vs 56%, DLCO 28% vs 47%). Furthermore, the NETT cohort excluded individuals with severe PH. In both the JHM and VUMC cohorts, approximately 40% of individuals had an FEV₁/DLCO ratio greater than 1.4, while in NETT, there were only 13% with a ratio >1.4. The sensitivity of this ratio in NETT was lower than that observed in our results; however, both this analysis and NETT demonstrate that an FEV₁/DLCO of approximately 1.3 to 1.4 has good specificity in predicting PH with an elevated PVR. Our results also demonstrate mod-

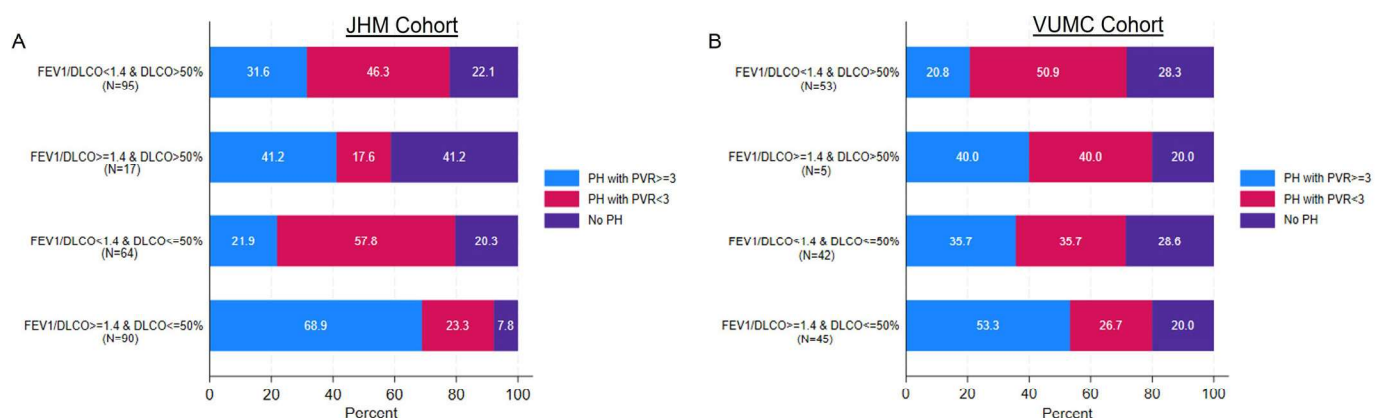


Figure 4 High FEV₁/DLCO ratio and severely impaired DLCO % predicted are associated with PH with elevated PVR. DLCO, diffusing capacity; FEV₁, forced expiratory volume in 1 s; JHM, Johns Hopkins Medicine; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; VUMC, Vanderbilt University Medical Center.

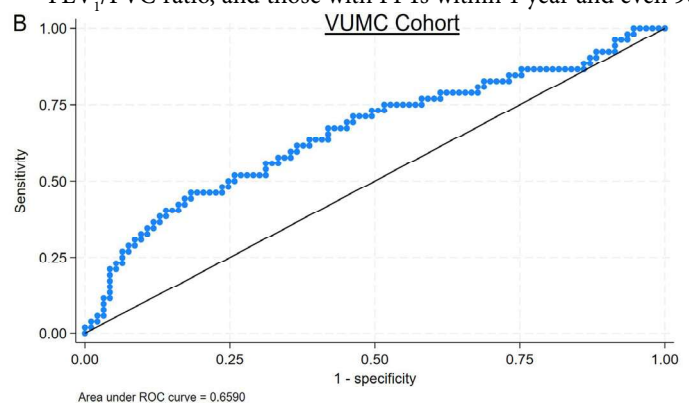
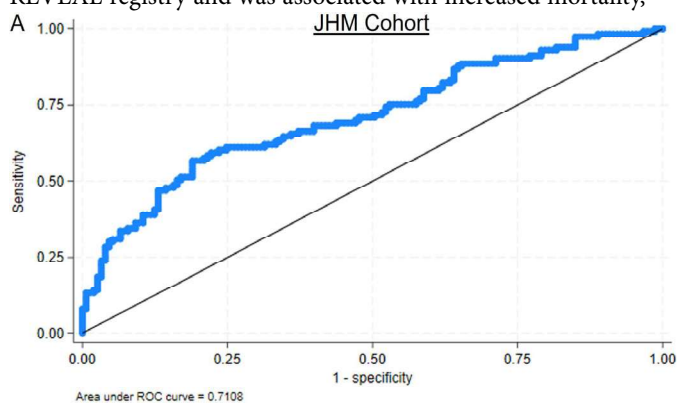
Table 3 High FEV₁/DLCO ratio is associated with PH with an elevated PVR among those with severe impairment in DLCO % predicted

	JHM cohort		VUMC cohort	
	OR (95% CI)	P value	OR (95% CI)	P value
FEV ₁ /DLCO<1.4, DLCO>50%	Ref	--	Ref	--
FEV ₁ /DLCO≥1.4, DLCO>50%	1.57 (0.52 to 4.72)	0.424	3.41 (0.47 to 24.8)	0.226
FEV ₁ /DLCO<1.4, DLCO≤50%	0.54 (0.25 to 1.17)	0.121	1.76 (0.65 to 4.82)	0.269
FEV ₁ /DLCO≥1.4, DLCO≤50%	5.01 (2.54 to 9.87)	<0.001	4.59 (1.72 to 12.32)	0.002

Models are adjusted for age, sex, race, BMI and smoking status. BMI, body mass index; DLCO, diffusing capacity; FEV₁, forced expiratory volume in one second; JHM, Johns Hopkins Medicine; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; Ref, reference group; VUMC, Vanderbilt University Medical Center.

est improvements in discrimination for the FEV₁/DLCO ratio over DLCO alone. Additionally, in the JHM cohort where a crude metric of the presence or absence of emphysema was available, the FEV₁/DLCO ratio showed similar effect magnitude for predicting PH with an elevated PVR across emphysema groups. Together, the presented findings and those from the NETT trial demonstrate across COPD populations with varying degrees of emphysema severity and with different indications for RHC, the FEV₁/DLCO ratio is informative.

Our study population included any patient with COPD who underwent RHC. As such, individuals with idiopathic PAH (IPAH) with comorbid COPD may have been included. COPD was observed in roughly 18% of patients with IPAH from the REVEAL registry and was associated with increased mortality.¹⁴

**Figure 5** (A and B) Receiver operating curves (ROC) for FEV₁/DLCO predicting PH with an elevated PVR. DLCO, diffusing capacity; FEV₁, forced expiratory volume in 1 s; JHM, Johns Hopkins Medicine; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; VUMC, Vanderbilt University Medical Center.**Table 4** Sensitivity and Specificity of FEV₁/DLCO thresholds for predicting PH with an elevated PVR

FEV ₁ /DLCO threshold	JHM cohort			VUMC cohort		
	Sensitivity %	Specificity %	Correctly classified %	Sensitivity %	Specificity %	Correctly classified %
1	79.7	39.2	56.4	76.9	40.9	53.8
1.1	71.7	48.4	58.3	73.1	50.5	58.6
1.2	68.1	59.5	63.2	65.4	58.1	60.7
1.3	65.5	64.1	64.7	57.7	65.6	62.8
1.4	61.1	75.2	68.8	51.9	74.2	66.2
1.5	53.1	81.1	69.2	48.1	76.3	66.2
1.6	47.8	85	69.2	42.3	82.8	68.3
1.7	38.9	88.2	67.3	36.5	87.1	69

DLCO, diffusing capacity; FEV₁, forced expiratory volume in one second; JHM, Johns Hopkins Medicine; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; VUMC, Vanderbilt University Medical Center.

but DLCO was not assessed. In the Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) registry, individuals with IPAH with smoking history and a low DLCO were noted to be a unique cluster,³⁷ with prognosis similar to those with group 3 disease.³⁸ The individuals described as 'IPAH with a lung phenotype', across both the COMPERA and ASPIRE registries, had similar smoking exposure and DLCO % predicted values to individuals with COPD-PH, but higher FEV₁ % predicted values. Our findings corroborate this, looking instead at a population with spirometric and clinically defined COPD rather than IPAH, again demonstrating haemodynamic severity correlates with relatively preserved FEV₁ to significantly impaired DLCO.

A strength of this study is the characterisation of haemodynamic patterns across the spectrum of COPD severity. One other single-centre study examined predictors of severe PH, as defined by mPAP or CI criteria, across a COPD cohort and found no differences in DLCO among severe PH versus mild-moderate PH.³⁹ However, many of the individuals included had elevated PCWP. Our findings note no associations between DLCO and PCWP, and that isolated postcapillary PH was more common at low FEV₁/DLCO ratios. These findings might explain why the prior study saw no associations with DLCO and severe PH.

This study has a few limitations. First, since the indication for RHC was not recorded, selection bias is likely and may limit generalisability of results. However, use of the FEV₁/DLCO ratio even among this select population offers useful information, particularly if considering deferment of RHC on individuals in whom an elevated PVR is unlikely. Furthermore, as noted in the NETT trial, other selected populations of COPD seem to show similar associations between FEV₁/DLCO ratio and PVR. Twenty-eight per cent and 54% in the JHM and VUMC cohorts, respectively, did not have PFT testing within a year of RHC, which could lead to misclassification bias, but our sensitivity analyses of those with any PFTs, with or without airflow obstruction by FEV₁/FVC ratio, and those with PFTs within 1 year and even 90

Table 5 Harrell's C-statistics for predictors of PH with an elevated PVR

Predictor	JHM cohort		VUMC cohort	
	C-statistic	95% CI	C-statistic	95% CI
FEV1	0.57	0.49 to 0.65	0.45	0.33 to 0.57
DLCO	0.61	0.53 to 0.69	0.66	0.55 to 0.77
FEV1/DLCO	0.68*†	0.60 to 0.75	0.72*	0.60 to 0.83
TRV	0.66	0.60 to 0.73	0.73	0.65 to 0.82
TRV+FEV1/DLCO	0.77‡	0.70 to 0.83	0.83‡	0.75 to 0.92

The predictor for TRV was a binary variable for values above or below 2.8 cm/s. For the TRV and TRV+FEV1/DLCO predictions, N=194 in JHM cohort and N=95 in VUMC cohort.

*P<0.05 comparing FEV1/DLCO to FEV1.

†p<0.05 comparing FEV1/DLCO to DLCO.

‡P<0.05 comparing TRV+FEV1/DLCO to TRV.

DLCO, diffusing capacity; FEV1, forced expiratory volume in one second; JHM, Johns Hopkins Medicine; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; TRV, tricuspid regurgitant velocity; VUMC, Vanderbilt University Medical Center.

days of RHC yielded similar inferences. We were unable to assess patients with COPD without PFTs, which could represent individuals who completed testing that did not enter into the medical record or individuals too sick to perform PFTs; either scenario could introduce selection biases. As emphysema is a major contributor to DLCO impairment in COPD, the lack of quantitation of degree of emphysema is a limitation. Although in the JHM cohort, the presence or absence of emphysema, as captured from CT scan, was used to try and address this, the associations between FEV1/DLCO and haemodynamic patterns and how this may vary by degree of emphysema remains an area for future study. The accuracy of both spirometry and RHC data in COPD is challenging, and in this instance, quality of measurements and specifics of cardiac output measurement (direct vs indirect Fick for the individuals in the VUMC cohort without thermodilution CO) was not obtained, which could influence results. However, these results are consistent with the imperfect data used routinely in clinical decision-making. Finally, alternative aetiologies for precapillary haemodynamic profiles were unable to be fully assessed, including objective data on sleep-disordered breathing and/or treatment, concomitant interstitial lung disease or pulmonary embolism.

Given the worldwide prevalence of approximately 200 million people with COPD, there are likely millions of individuals with COPD-PH. With a known devastating prognosis, identifying which individuals should undergo an invasive, limited-resource procedure for diagnosis should be a priority. This study establishes the FEV₁/DLCO ratio as a potentially useful tool in predicting haemodynamic phenotypes in COPD-PH that not only informs the need for RHC but could also identify those most likely to benefit from specific therapy. These findings highlight the need for regular measurement of spirometry and DLCO in COPD, a particular challenge given the disparities in availability of pulmonary function tests across the world,⁴⁰ and also support further screening for COPD-PH and referral for RHC depending on an FEV₁/DLCO ratio. Based on our results, FEV₁/DLCO should be considered in the routine evaluation of PH in patients with COPD.

Social media Stephen C Mathai, X @SteveMathaiMD

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ORCID iDs
Aparna Balasubramanian <https://orcid.org/0000-0002-1854-6672>
Ashraf Fawzy <https://orcid.org/0000-0002-6089-366X>
Robert A Wise <https://orcid.org/0000-0002-8353-2349>

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ARTIGO ORIGINAL

Intervenção multidisciplinar e não farmacológica para a dispneia em doentes com DPOC moderadamente grave a grave: um ensaio clínico randomizado

Tracy A Smith,^{1,2} Mary M Roberts,^{1,2,3,4} Tim Luckett,⁴ Jin-Gun Cho,^{1,2,3} Ester Klimkeit,¹ Heather Stephenson,¹ Nicola McCaffrey,⁵ Adrienne Kirby,⁶ John R Wheatley^{1,2,3}

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¹Department of Respiratory and Sleep Medicine, Western Sydney Local Health District, Wentworthville, New South Wales, Australia

²Faculty of Medicine and Health, Sydney, New South Wales, Australia

³Westmead Institute for Medical Research, Westmead, New South Wales, Australia

⁴Health, University of Technology Sydney, Sydney, New South Wales, Australia

⁵Institute for Health Transformation, School of Health and Social Development, Faculty of Health, Deakin University, Melbourne, Victoria, Australia

⁶NHMRC Clinical Trials Centre, Faculty of Medicine and Health, The University of Sydney, Sydney, New South Wales, Australia

Correspondence to

Dr Tracy A Smith; tracy.smith2@health.nsw.gov.au

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RESUMO

Contexto A doença pulmonar obstrutiva crônica (DPOC) é uma doença respiratória frequentemente progressiva, associada a dispneia incapacitante. Os Breathlessness Intervention Services (BIS), que ensinam os doentes a autogerir a dispneia através de estratégias não farmacológicas, demonstraram eficácia em várias populações, incluindo pessoas com cancro e doenças respiratórias graves. Este estudo teve como objetivo comparar o impacto do Westmead Breathlessness Service em pessoas com DPOC moderada a grave.

Métodos Foram analisados 113 participantes randomizados (1:1) com DPOC moderada/grave (relação FEV₁/CVF <0,70 e FEV₁ ≤60% do previsto) e dispneia incapacitante (pontuação ≥2 na escala modificada do Medical Research Council – mMRC). Os participantes foram distribuídos para uma intervenção de 8 semanas envolvendo técnicas respiratórias, uso de pequena ventoinha portátil a pilhas, exercício, conservação de energia e aconselhamento dietético (n=54), ou para um grupo de controlo em lista de espera durante 8 semanas (n=59). O resultado primário foi a alteração na subescala Mastery da Chronic Respiratory Questionnaire (CRQ), que avalia o controlo da dispneia. Os desfechos secundários incluíram alterações noutras subescalas da CRQ (Fadiga, Emoção e Dispneia), intensidade/desconforto da dispneia ao esforço (escala numérica 0–10), ansiedade e depressão. A diferença na alteração ao longo de 8 semanas entre grupos foi comparada por ANCOVA; p<0,05 considerado estatisticamente significativo.

Resultados Os participantes tinham em média 70,9 (±8,5) anos, 50% eram mulheres, FEV₁ médio de 0,8 L (±0,3 L; 34% do previsto) e pontuação mMRC de 3 (IQR 3–4). A subescala CRQ-Mastery melhorou após a intervenção comparativamente ao controlo (diferença entre grupos: 0,5 unidades; IC 95% 0,2–0,8; p=0,0262), segundo análise por intenção de tratar modificada. Melhorias adicionais foram observadas na CRQ-Dispneia (diferença 0,4 unidades; IC 0,1–0,7; p=0,005) e CRQ-Fadiga (diferença 0,4 unidades; IC 0,1–0,7; p=0,014). A intensidade da dispneia ao esforço (diferença –0,8 unidades; IC –1,4 a –0,2; p=0,013) e o desconforto associado (diferença –1,2 unidades; IC –1,7 a –0,6; p=0,001) também melhoraram.

Interpretação Um BIS de 8 semanas melhorou o controlo da dispneia (CRQ-Mastery), a Dispneia e a Fadiga, bem como a intensidade e o desconforto da dispneia ao esforço em pessoas com DPOC grave.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous respiratory condition characterised by persistent, often progressive, airflow obstruction.¹ Patients with COPD live with a range of disabling symptoms despite treatment, including breathlessness.¹

Disabling breathlessness is associated with high health utilisation costs, including at least some

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Breathlessness intervention services (BIS) have been shown to reduce breathlessness in participants with cancer or those with serious respiratory disease.
- No previous adequately powered randomised controlled trials have been undertaken specifically in patients with COPD.

WHAT THIS STUDY ADDS

- We demonstrate that in participants with severe COPD, a BIS improves breathlessness mastery, dyspnoea and fatigue as measured by the Chronic Respiratory Questionnaire, along with exertional breathlessness intensity and unpleasantness.
- We demonstrate that this improvement is important despite a high rate of exacerbations in both groups.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Our study demonstrates BIS ameliorates breathlessness in patients with severe COPD.
- Further studies are required to determine if this leads to reduced hospitalisations and/or health economic benefits.

acute care presentations that may be preventable.¹ Exacerbations of COPD may be driven by a range of infective and non-infective aetiologies.¹ Increased breathlessness is a hallmark of exacerbations, and these important clinical events drive lung function decline resulting in further worsening of breathlessness.¹ Breathlessness improves with pulmonary rehabilitation; however, not all eligible patients will enrol in or complete the programme.¹ Patients who have recently completed pulmonary rehabilitation may have higher levels of physical activity and may have developed skills in self-management of breathlessness.¹

Breathlessness intervention services (BIS) are holistic models of care that combine a variety of non-pharmacological interventions to relieve breathlessness. These include breathing techniques, use of a handheld fan, use of mobility aids, education, pacing and exercise to address breathlessness.^{2–4} BIS has been shown to alleviate breathlessness-related outcomes in populations

which include patients with cancer.^{2 5 6} A recent meta-analysis combining data from five trials with 80% or more participants with serious non-malignant respiratory disease (including COPD and interstitial lung disease) also concluded that BIS were effective in reducing breathlessness-related outcomes, and a recent European Respiratory Society guideline recommended the use of BIS.^{3 7} The duration of BIS has been between 2 weeks and 6 weeks, though little is known regarding optimal duration or BIS team composition.^{2 8} Published randomised controlled trials (RCTs) of these services have been undertaken in Europe, mostly in England.^{2 5 6} One older RCT, available only as a conference abstract, and therefore perhaps representing preliminary data, is the only RCT to evaluate a BIS designed specifically for people with COPD.⁹ Additionally, a feasibility study of a BIS-like intervention for patients with COPD reported significant improvement in breathlessness measures.¹⁰ However, the efficacy of BIS exclusively in patients with COPD has not been tested in an adequately powered RCT. Furthermore, this type of intervention has not been tested outside of Europe.

We conducted a randomised-controlled trial of the Westmead Breathlessness Service (WBS) in Australia which focused on people with COPD as primary diagnosis and was longer than previous trials (8 weeks compared with 2–6 weeks), as we consider that the behaviour change required as part of a BIS may take some time. Additionally, previous trials have recruited patients with advanced malignancy where a shorter prognosis suggests the need for relatively short trial periods. Further, we incorporated more face-to-face contact and a broader healthcare team than other services evaluated by RCTs in the past. Our team includes doctors, nurses, a physiotherapist, an occupational therapist and a dietitian, making it the most diverse team of health professionals involved in a BIS.

Objective

To assess the impact of WBS on breathlessness and associated symptoms compared with a wait-list control group in people with moderate to severe COPD and disabling breathlessness.

METHODS

Study design

We undertook a single-blind, parallel-group RCT enrolling people with moderate/severe COPD and disabling breathlessness and comparing the WBS intervention to the wait-list controls. Reporting conforms to the Consolidated Standards of Reporting Trials (CONSORT) guidelines,¹¹ including the 2022 updates and patient-reported outcome extension.^{12 13} The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617000499381). All participants gave written informed consent.

Participants

We enrolled participants with moderate to severe COPD (defined as a postbronchodilator forced expiratory volume in 1 s (FEV₁) to forced vital capacity ratio of <0.70 and an FEV₁ ≤60% predicted and disabling breathlessness, defined as a modified Medical Research Council (mMRC) breathlessness score of ≥2). Full details of inclusion and exclusion criteria and a detailed description of the intervention have been previously published.¹⁴ Participants were recruited from a single teaching hospital in western Sydney.

Participants were included in the study if they had confirmation of COPD by spirometry, were willing and able to be an active participant in their care and could provide consent. Participants were excluded if they had a diagnosis of dementia documented in their clinical notes, had an exacerbation requiring hospitalisation within the previous 4 weeks, did not speak sufficient English to understand study procedures or instruments, had a current diagnosis of cancer, lived outside the Westmead catchment area, or were unable to adhere to study procedures. Randomisation was stratified by pulmonary rehabilitation completion (defined as having completed at least 16 supervised sessions) in the prior 12 months. This was undertaken to ensure an equal distribution of participants in

both arms who had completed pulmonary rehabilitation, as it may be a confounder in a trial of a breathlessness intervention.

Recruitment occurred between 01 March 2017 and 01 December 2022 and continued until the sample size was reached. Recruitment was slowed by the COVID-19 pandemic when local restrictions required the temporary suspension of the trial. Additionally, two participants underwent telehealth assessments at 8-weeks, rather than inperson assessments, due to local COVID-related public health restrictions at the time of their assessment.

Prior to randomisation, all participants received general information about COPD from a research nurse, including written information from Lung Foundation Australia, smoking cessation advice, and evaluation and correction of inhaler technique. Additionally, participants were reviewed to ensure they were prescribed guideline-concordant medications for COPD, and comorbidities which may have contributed to breathlessness, such as heart failure, were optimally treated.

Randomisation and masking

Online 1:1 randomisation¹⁵ was performed using permuted blocks of 4, stratified by pulmonary rehabilitation completion in the last 12 months and prepared by an investigator (J-GC) not involved in the clinical administration of the trial. Allocation of participants was concealed in sequentially numbered, opaque, sealed envelopes, which were opened by non-trial research staff after participants were enrolled in the study. The results of randomisation were communicated to administrative staff not involved in the trial who coordinated clinic bookings and assessments, allowing clinicians involved in the trial to remain unaware of the allocation sequence.

Procedures: WBS intervention

Participants were provided with education on individualised, non-pharmacological interventions to relieve breathlessness during an initial outpatient clinic appointment, which involved a clinical nurse consultant and a respiratory physician. Over the subsequent 8 weeks, additional individualised coaching was provided by nursing staff, a physiotherapist, an occupational therapist and a dietitian in the participant's home, supplemented by phone calls. Recommended techniques included use of a battery-operated handheld fan, breathing techniques, exercise prescription, positions to relieve breathlessness, activity prioritisation and pacing, modification of activities to conserve energy, relaxation and nutritional advice. An assessment of the participants' current behaviours to alleviate breathlessness was undertaken at the initial assessment. Participants were then offered additional techniques to relieve breathlessness based on their breathlessness triggers and preferences. A detailed description of the intervention has been published.¹⁴

Procedures: wait-list

The wait-list control group received usual care as provided by their usual care team.

All participants were reassessed at week 8. After 8 weeks, participants allocated to the 8-week wait-list were then offered the WBS intervention.

Outcomes

Our primary outcome was Chronic Respiratory Questionnaire (CRQ) Mastery of breathlessness using the interviewer-administered format with informed follow-up.¹⁶ This outcome was chosen as it reflects participants' sense of being able to control their breathlessness and has been used in previous trials of BIS.¹⁷ The minimal clinically important difference (MCID) for all CRQ subscales is 0.5, with higher scores indicating better health.¹⁸

Prespecified secondary outcomes included other CRQ domains (Dyspnoea, Fatigue and Emotion); the Hospital Anxiety and Depression Scale Anxiety (HADS-A) and Depression (HADS-D) subscales (lower score better; score ≥8 represents a potential case);¹⁹ COPD assessment test (CAT) (lower score better);²⁰ breathlessness intensity and unpleasantness at rest and on exertion measured on a 0–10 Numerical Rating Scale (NRS)²¹ (lower scores better), con-

confidence in managing breathlessness NRS (higher score better) and the EuroQol-5 Dimensions-5 Levels (EQ-5D-5L) (higher score better).²² The MCID of each of these scales, along with reliability, validity and responsiveness, is described elsewhere in detail.¹⁴ Spirometry data were collected on the day of clinical assessment at Westmead Hospital (Care-Fusion Microlab spirometer V3.05) or from spirometry undertaken in the previous 12 months where spirometry could not be undertaken on the day of assessment due to the COVID-19 pandemic. Patient-reported exacerbations were collected at the same time as the final data collection. Accuracy of data in the trial was checked by a separate research assistant prior to locking the trial database.

All outcomes were assessed by a research nurse in participants' homes. The nurse was blinded to participant allocation and had received training in administering the questionnaire instruments. Data were collected at week 0 and week 8 in the participants' homes. Blinding was enabled by the research nurse having an office in a different part of the hospital to the team delivering the intervention and not being involved in the randomising or delivering the intervention.

Statistical analysis

Based on our pilot data,²³ we estimated that 47 participants per group would be required to detect a mean difference in change from baseline of 1.1 ± 1.6 units in CRQ-Mastery of breathlessness, with a two-sided alpha of 0.05 and power of 80%, allowing for a 25% dropout rate. At the height of the COVID pandemic, when it was unclear how we would continue recruitment and when 59 participants had completed the study, our statistician (AK) calculated the mean change from baseline and SD for the primary outcome from the whole group without unblinding any data. The change in the primary outcome was not as large in the study population as it was in the pilot population, resulting in an increase in target recruitment. The target recruitment was revised to 56 participants per group to detect a mean difference in change from baseline of 0.55 ± 1.0 units, with the same alpha and power but allowing for only 5% attrition in line with that observed to that point. This effect size is greater than the MCID for the CRQ.¹⁸ Our primary analysis was performed on complete cases only; however, we conducted a sensitivity analysis using multiple imputation for missing data to assess the robustness of our primary analysis.

We analysed primary and secondary outcomes using a modified intention-to-treat principle, excluding participants who did not have a final visit measurement. Baseline clinical and demographic data were summarised with a count and percentage for categorical variables, and either a mean and SD or median and IQR for continuous variables.

Predefined primary and secondary outcomes were the change from baseline to 8-week values in continuous measurements, and these were analysed with a linear model using analysis of covariance (ANCOVA) adjusting for the baseline value. The assumptions necessary for these analyses were verified using the residuals from the ANCOVA models. The results were reported as the mean difference adjusted for baseline. The proportion of participants achieving the MCIDs was analysed using a linear model with a log link, with the intervention difference being summarised as a mean ratio. CRQ Mastery was analysed for the predefined subgroups (gender, HADS ≥ 8 units for anxiety or depression and FEV_1) using a linear model for each subgroup separately, as well as a model including the baseline variable, the subgroup, the intervention and the subgroup by intervention interaction. Gender was chosen as subgroup analysis as our previous work suggests gender differences in symptom burden.²⁴ Anxiety and depression are common in people with COPD,¹ and their presence may affect the participants' ability to engage in the behavioural change necessary to implement non-pharmacological management of breathlessness. The effect of the intervention was assessed in participants with and without exacerbations during the study period, but as the exacerbations occurred after treatment had begun, these should be regarded as hypothesis-generating. Analysis of participants who had an exacerbation on study compared with those who did not

was undertaken separately as breathlessness is a hallmark of exacerbation, and as such is likely to impact the development of a sense of mastery around breathlessness. All reported values of *p* are two-sided, and values of *p* adjusted for the number of tests, using the Benjamini-Hochberg procedure, have been provided.²⁵ Analyses were completed using SAS V9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

The final analysis population comprised 113 participants. We screened 244 participants, 122 underwent randomisation, with 60 assigned to the intervention group and 62 assigned to the wait-list control group (figure 1). In the intervention group, 6 participants declined to undergo study assessments at week 8, thus not contributing data, leaving 54 participants in the intervention group. In the control group, 1 participant died unexpectedly shortly after enrolment and two declined reassessment at week 8, leaving 59 in this group (see figure 1).

The mean age of all participants was 70.9 ± 8.5 years. Overall, 50% of the participants were female. Mean FEV_1 was $0.84 \text{ L} \pm 0.34 \text{ L}$, equating to a mean FEV_1 of 34% predicted. The group had disabling breathlessness with a median mMRC Breathlessness Score of 3 (IQR 3–4). Further demographic and clinical information is detailed in table 1. Regarding exacerbations, 32 (59%) of the intervention group and 27 (46%) of the control group reported at least one exacerbation during the study period.

Mean CRQ-Mastery increased by 0.1 in the intervention group and fell by 0.4 in the control group (figure 2), achieving a clinically important and statistically significant between-group difference of 0.5 (95% CI 0.2 to 0.8; $p=0.022$). Sensitivity analysis undertaken after multiple imputation for missing data had no effect on this conclusion. See online supplemental table S1.

Both mean CRQ-Dyspnoea and mean CRQ-Fatigue improved in the intervention group and worsened in the control group (between-group difference Dyspnoea 0.4 (95% CI 0.1 to 0.7), $p=0.014$; Fatigue 0.4 (95% CI 0.1 to 0.7), $p=0.015$) (figure 2). Breathlessness intensity and unpleasantness on exertion measured by NRS improved in the intervention group and worsened in the control group (between-group differences: intensity -0.8 (95% CI -1.4 to -0.2); $p=0.0013$; unpleasantness -1.2 (95% CI -1.7 to -0.6); $p=0.001$; MCID ≥ 1.0). No significant between-group difference was noted for anxiety or depression (as measured by HADS), confidence managing breathlessness, or quality of life (as measured by EQ-5D-5L) (see table 2).

Table 3 details relative and absolute difference in the proportion of participants in each group achieving the MCID for each measure. Twice the proportion of participants reported an improvement in CRQ-Mastery exceeding the MCID in the intervention group compared with the control group (15 (28%) vs 8 (14%), relative difference 2.05 (95% CI 0.94 to 4.44)). A higher proportion of participants reported significant improvement in CRQ-Fatigue (18 (33%) vs 10 (17%); relative difference 1.97 (95% CI 1.00 to 3.88)) and CRQ-Dyspnoea (13 (24%) vs 6 (10%); relative difference 2.37 (95% CI 0.97 to 5.79)) in the intervention compared with the control group. In addition, over half of the intervention group (54%) reported a clinically important improvement in breathlessness unpleasantness on exertion compared with 29% in the control group (relative difference 1.86 (95% CI 1.16 to 2.99)).

Predefined subgroup analyses were undertaken by sex, HADS-A, HADS-D and FEV_1 . However, as our study was not powered to detect differences for subgroup analyses, these results should be regarded as exploratory in nature. Having worse anxiety (HADS-A Score ≥ 8), having better lung function ($FEV_1 > 30\%$ predicted) or being female was associated with greater improvement in CRQ-Mastery in participants who undertook the intervention compared with less anxiety, worse lung function and being male, respectively (see table 4). The magnitude of this difference in CRQ-Mastery was greater than the MCID for this scale for both people with HADS-A ≥ 8 and people with $FEV_1 > 30\%$ predicted (between-group differences of 0.6 and 0.5, respectively) but was relatively small for women compared with men (between-group

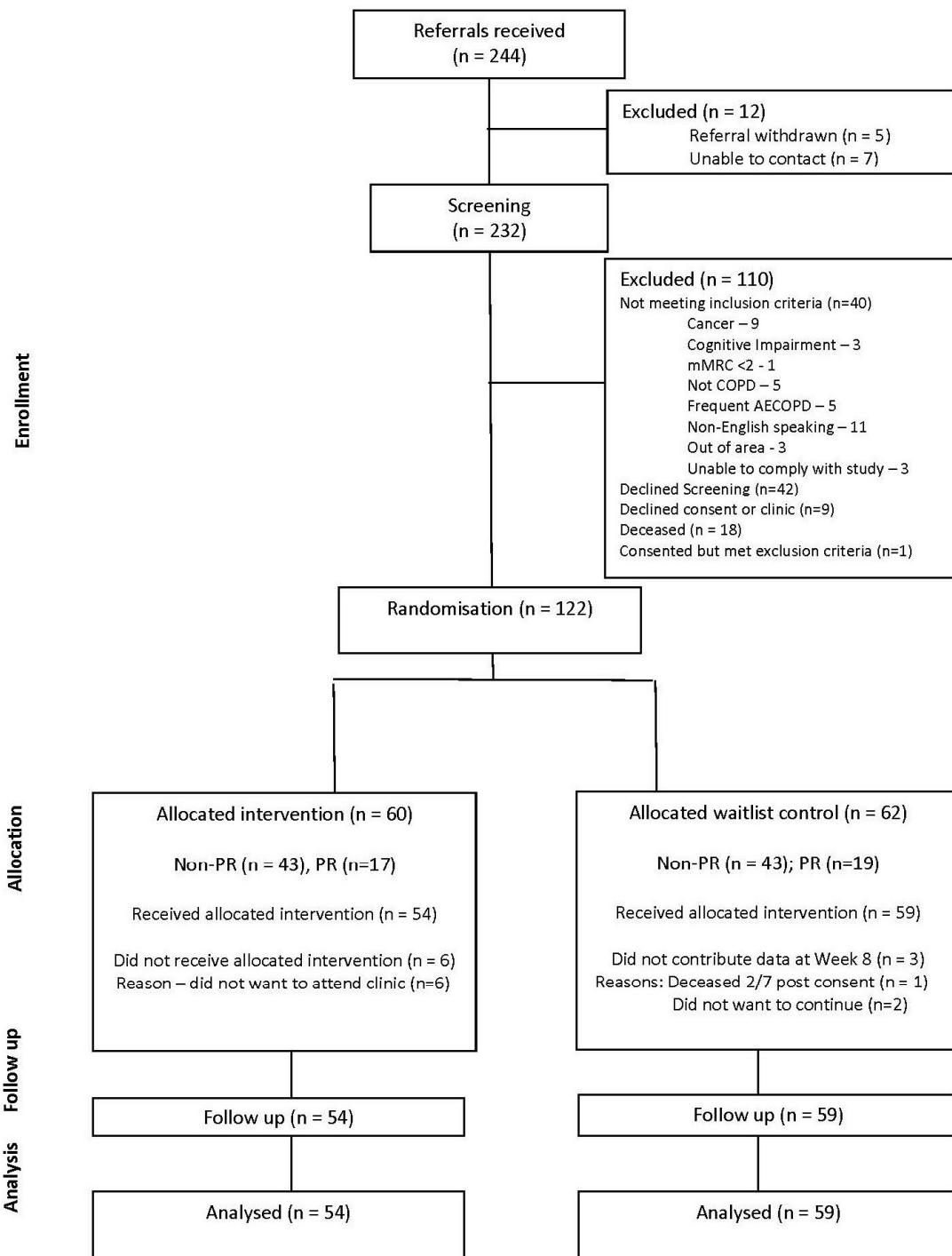


Figure 1 CONSORT diagram including referrals, participants screened, randomisation and follow-up. AECOPD, acute exacerbation of COPD; COPD, chronic obstructive pulmonary disease; mMRC, modified Medical Research Council Breathlessness Score; PR, pulmonary rehabilitation.

difference 0.2). The impact of the intervention appeared to be different for participants who did or did not have an exacerbation during the study period. For participants who did not have an exacerbation, CRQ-Mastery improved with the intervention group compared with the control group (between-group difference 1.0 (95% CI 0.5 to 1.5)) (see table 5). Conversely, where at least one exacerbation was reported, CRQ-Mastery did not improve in either group (see table 5).

DISCUSSION

This is the first RCT of a BIS conducted outside Europe, demonstrating clinical benefit in individuals with severe COPD. We found clinically important and statistically significant between-group differences in change in CRQ-Mastery at 8 weeks following the WBS intervention for people with severe COPD and disabling breathlessness compared with a wait-list control.

Furthermore, we found between-group differences in CRQ-Dyspnoea and CRQ-Fatigue Scores. Additionally, between-group differences in changes in breathlessness intensity and unpleasantness on exertion were statistically significant, with the difference in unpleasantness also being clinically important. The proportion of people reporting change exceeding the MCID in the CRQ-Mastery, Dyspnoea and Fatigue, and NRS breathlessness unpleasantness was higher in the intervention versus control groups. For participants in the intervention arm who did not have an exacerbation during the study period, the change in CRQ-Mastery was greater than those who did experience an exacerbation.

This study adds to the growing evidence that BIS can be helpful for people with disabling breathlessness. A recent meta-analysis focusing on studies that enrolled predominantly people with serious non-malignant respiratory disease reported a statistically

Table 1 Baseline demographic and clinical variables

Characteristic	Value	Breathlessness intervention, n=54	Wait-list control, n=59	Total, n=113
Age (years)		71.8±7.9	70.1±9.0	70.9±8.5
Sex	Female	21 (39%)	36 (61%)	57 (50%)
	Male	33 (61%)	23 (39%)	56 (50%)
Living arrangements	Aged care facility	1 (2%)	·	1 (1%)
	Alone	16 (30%)	17 (29%)	33 (29%)
	With a carer	37 (69%)	42 (71%)	79 (70%)
Country of birth	Australia/New Zealand	44 (81%)	52 (88%)	96 (85%)
	Europe	9 (17%)	7 (12%)	16 (14%)
	Asia	1 (1%)	0 (0%)	1 (1%)
Aboriginal or Torres Strait Islander		1 (1.8%)	2 (3.3%)	3 (2.6%)
Had not completed pulmonary rehabilitation in the previous 12 months		38 (70%)	40 (68%)	78 (69%)
Prescribed supplementary oxygen ≥16 hours/day		8 (15%)	13 (22%)	21 (19%)
Smoking status	Never smokers	2 (4%)	1 (1.7%)	3 (3%)
	Ex-smokers	39 (72%)	47 (78%)	84 (74%)
	Current smokers	13 (24%)	11 (20%)	24 (21%)
Pack years		59.1±40.3	59.5±32.8	59.3±36.4
COPD assessments				
Spirometry				
Mean FEV ₁ (L)		54, 0.9±0.3	47, 0.8±0.3	0.8±0.3
Mean FEV ₁ (% predicted)		54, 34.6±10.3	47, 33.4±14.2	33.7±12.2
Mean FVC (L)		54, 2.1±0.7	47, 2.1±0.9	2.1±0.8
Mean FVC (% predicted)		54, 64.4±14.8	47, 66.4±22.5	65.0±18.2
Mean FEV ₁ :FVC (ratio)		54, 0.4±0.1	47, 0.4±0.2	0.4±0.1
FEV ₁ (% predicted) group				
	50–60%	4 (7)	7 (12%)	11 (10%)
	30–49%	31 (57%)	27 (46%)	58 (51%)
	<30%	19 (35%)	25 (42%)	44 (39%)
Patient-reported exacerbations requiring either prednisone or antibiotics during 8 weeks		32 (59%)	27 (46%)	59 (52%)
Outcome data				
CRQ				
Mastery		4.2±1.3	4.2±1.4	4.2±1.4
Emotion		4.1±1.3	4.2±1.3	4.2±1.3
Fatigue		3.2±1.0	3.2±1.0	3.2±1.0
Dyspnoea		2.9±0.9	2.8±0.9	2.8±0.9
CAT total		23.0 (19.0–26.0)	25.0 (21.0–28.0)	23.0 (19.0–28.0)
mMRC Breathlessness Score		3.0 (3.0–4.0)	4.0 (3.0–4.0)	3.0 (3.0–4.0)
Number of participants reporting any breathlessness at rest		5 (10%)	5 (8%)	10 (9%)
Breathlessness (NRS) on exertion				
Intensity		7.4±1.6	7.6±1.7	7.5±1.6
Unpleasantness		8.0±1.8	8.1±1.8	8.1±1.8
Confidence in managing breathlessness		6.2±2.3	6.5±2.2	6.4±2.2
Median number of exacerbations in the 12 months prior to randomisation		5.0 (4.0–5.0)	5.0 (3.0–5.0)	5.0 (3.0–5.0)
HADS anxiety		7.8±4.4	8.3±4.9	8.1±4.6
HADS depression		7.0±3.8	6.9±3.7	7.0±3.7
EQ-5D-5L VAS		59.9±20.6	56.7±20.2	58.2±20.4
Mean EQ-5D-5L Index		0.5±0.3	0.5±0.3	0.5±0.3

Data are mean±SD, median (IQR) or N (% total). All outcome data scales are in arbitrary units.

CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; CRQ, Chronic Respiratory Questionnaire; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; HADS, Hospital Anxiety and Depression Scale; mMRC, modified Medical Research Council; NRS, Numerical Rating Scale; VAS, Visual Analog Scale.

significant improvement in CRQ-Mastery.⁷ In contrast, an older meta-analysis reported a non-significant change in CRQ-Mastery; however, over 77% of participants included in this study had advanced cancer.² Our results, along with those of Spathis et al⁷ suggest CRQ-Mastery is improved in patients with serious non-malignant respiratory disease by BIS.

Our between-group differences following completion of the WBS extended beyond CRQ-Mastery to also include CRQ-Fatigue and CRQ-Dyspnoea. In contrast with our positive results, a systematic review by Brighton et al and other similar studies, have generally reported no significant differences in other CRQ measures,^{2 17 26} which is possibly due to differences between our

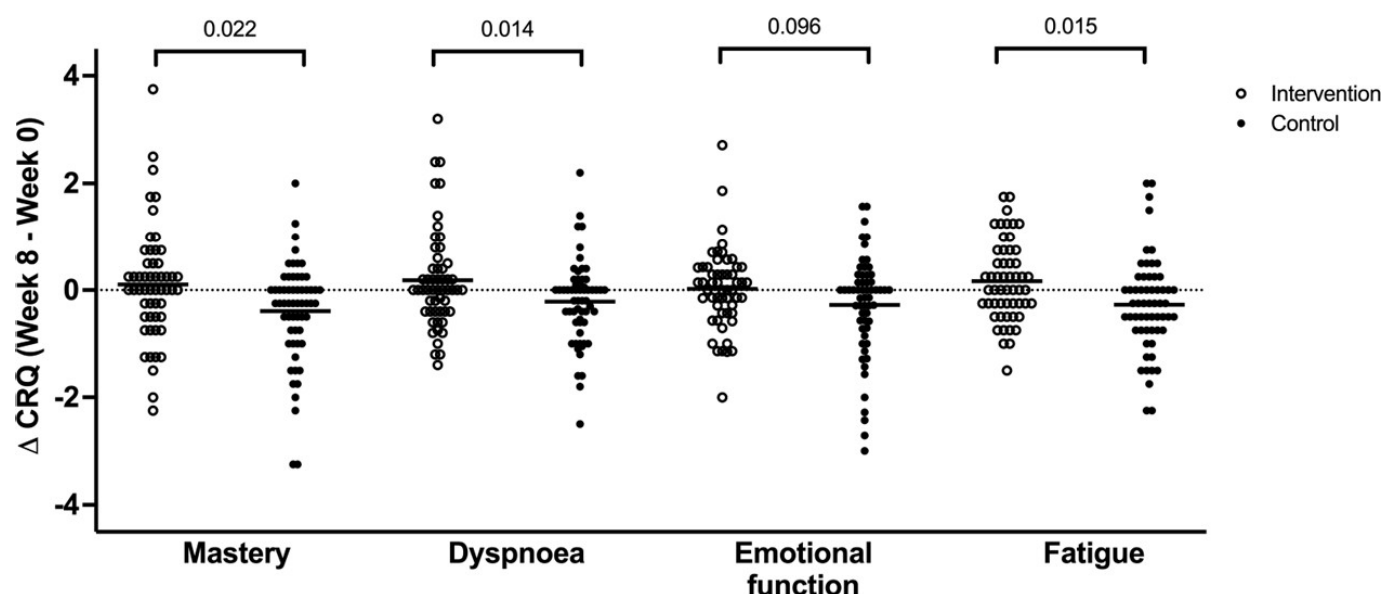


Figure 2 Change in CRQ subscales over an 8-week study period. CRQ, Chronic Respiratory Questionnaire.

study and previous studies, including the recruited population, the longer duration of the intervention and our larger healthcare team.

We report reductions in the intensity and unpleasantness of breathlessness on exertion. While 'distress' and 'unpleasantness' are not synonymous, they are related concepts. The meta-analysis by Brighton et al (which included a significant number of participants with cancer) found superiority in breathlessness-related distress following BIS,² whereas the meta-analysis by Spathis et al (focusing on participants with serious non-malignant disease) reported no impact on distress, though this was based on a single study.⁷ Our finding of improvement in breathlessness intensity on exertion also stands in contrast to the results from Spathis et al, though again this only included a single study.⁷ Taken together, this evidence suggests that BIS can improve outcomes other than CRQ-Mastery for participants with non-malignant respiratory disease, subject to influence from the service and participant characteristics that are as yet unclear. At this stage, we are unable to report the sustainability or otherwise of improvements in outcomes beyond 8 weeks and acknowledge this as a limitation. Data to explore the sustainability or otherwise of changes in this population beyond 8 weeks will be the subject of a forthcoming manuscript.¹⁴

We report some important negative results. Neither anxiety nor depression, as measured by HADS, improved in this population following intervention compared with controls. This is similar to previous meta-analyses.^{2,7} Additionally, there was no improvement in CAT scores following intervention. As yet, no other published BIS has used this tool. The CAT Score assesses eight clinical parameters related to COPD, three of which relate to breathlessness. Given the broad scope of this tool, it is not surprising that an intervention targeting breathlessness did not result in significant change. Finally, while CRQ-Mastery was positive, NRS confidence in managing breathlessness was negative. This interesting finding

may be explained by CRQ-Mastery being derived from the average of four questions which ask about a sense of control over breathlessness as well as emotional responses to it like fear, panic and upset, whereas NRS confidence is a single-item response. Further CRQ-Mastery is derived from a validated tool, whereas NRS confidence has face validity but has not undergone rigorous validity testing.

A recent European Respiratory Society statement about symptoms in respiratory disease called for research aimed at better understanding which patient subgroups benefit more from this type of intervention.³ A pooled analysis of individual participant data from BIS trials enrolling people with varied diagnoses suggested that people with lower baseline CRQ-Mastery may derive more benefit from this type of intervention, whereas other variables, including breathlessness severity, health status, anxiety and lung function, were not predictive.²⁷ In contrast, we found that people with higher anxiety scores and/or better lung function had a greater improvement in CRQ-Mastery of breathlessness in the intervention group. Importantly, given these are subanalyses, they should be regarded as exploratory in nature (due to a lack of power and the risk of a type 1 error related to multiple comparisons). These differences between our results and Brighton et al's²⁷ may be related to differences in analytical technique (using cut points for FEV₁ and HADS, rather than continuous variables). It may be that as lung function declines, this biological limitation becomes a limiting factor, and it becomes more difficult to implement behaviours to alleviate breathlessness. Anxiety and breathlessness are strongly linked for some patients with COPD, and having strategies to address breathlessness may assist both of these symptoms. Both, our work and Brighton et al's, underscore the fact that BIS are 'complex interventions' as per MRC guidance,²⁸ and future research could focus on identifying which patient subgroups benefit

Table 2 Effect of breathlessness intervention on the change (week 0 and week 8), adjusted for baseline, in continuous secondary outcomes

Change in	Mean change (SD)		Difference (95% CI)	Adjusted p value
	Breathlessness intervention	Wait-list control		
HADS anxiety	−0.4 (2.5)	0.1 (3.7)	−0.7 (−1.8 to 0.4)	0.240
HADS depression	−0.1 (3.0)	0.9 (2.8)	−1.0 (−2.1 to 0.0)	0.083
CAT total	−0.3 (6.0)	0.2 (5.0)	−1.2 (−3.1 to 0.7)	0.321
Breathlessness on exertion NRS intensity	−0.3 (1.8)	0.3 (1.9)	−0.8 (−1.4 to 0.2)	0.013
Breathlessness on exertion NRS unpleasantness	−0.9 (2.0)	0.2 (2.0)	−1.2 (−1.7 to 0.6)	0.001
Confidence in managing breathlessness NRS	0.8 (2.6)	0.1 (2.4)	0.5 (−0.2, 1.3)	0.196
EQ-5D-5L	0.045 (0.2)	−0.028 (0.3)	0.1 (0.0 to 0.1)	0.090

Statistical comparison undertaken using ANCOVA.

CAT, COPD assessment test; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; HADS, Hospital Anxiety and Depression Scale; NRS, Numerical Rating Scale.

Table 3 Proportion of participants achieving an improvement at least as large as the MCID

	N (%)			
Improvement as large as MCID	Breathlessness intervention	Wait-list control	Absolute difference (95% CI)	Relative difference (95% CI)
CRQ Mastery	15 (28%)	8 (14%)	14.2 (−5.4 to 33.8)	2.05 (0.94 to 4.44)
CRQ Fatigue	18 (33%)	10 (17%)	16.4 (−2.8 to 35.6)	1.97 (1.00 to 3.88)
CRQ Emotion	10 (19%)	8 (14%)	5.0 (−14.3 to 24.2)	1.37 (0.58 to 3.21)
CRQ Dyspnoea	13 (24%)	6 (10%)	13.9 (−6.3 to 34.1)	2.37 (0.97 to 5.79)
HADS anxiety	16 (30%)	19 (32%)	−2.6 (−20.9 to 15.8)	0.92 (0.53 to 1.60)
HADS depression	13 (24%)	10 (17%)	7.1 (−12.0 to 26.2)	1.42 (0.68 to 2.97)
CAT total	22 (41%)	21 (36%)	4.5 (−14.0 to 23.1)	1.13 (0.70 to 1.80)
mMRC Breathlessness Score	8 (15%)	4 (7%)	8.0 (−12.7 to 28.7)	2.19 (0.70 to 6.85)
NRS breathlessness intensity at rest	1 (50%)	1 (33%)	16.7 (−70.8 to 104.1)	1.50 (0.18 to 12.46)
NRS breathlessness unpleasantness at rest	1 (50%)	1 (33%)	16.7 (−70.8 to 104.1)	1.50 (0.18 to 12.46)
NRS breathlessness intensity on exertion	19 (35%)	18 (31%)	4.7 (−13.9 to 23.2)	1.15 (0.68 to 1.96)
NRS breathlessness unpleasantness on exertion	29 (54%)	17 (29%)	24.9 (6.9 to 42.9)	1.86 (1.16 to 2.99)
NRS confidence	29 (54%)	25 (42%)	11.3 (−7.0 to 29.7)	1.27 (0.86 to 1.87)

CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; CRQ, Chronic Respiratory Questionnaire; HADS, Hospital Anxiety and Depression Scale; MCID, minimal clinically important difference; mMRC, modified Medical Research Council; NRS, Numerical Rating Scale.

under what circumstances, rather than the more binary approach taken by trials to date of whether they work across undifferentiated patient groups.

Our effect size for the primary outcome is similar to a trial that recruited a mixed malignant and non-malignant population¹⁷ and higher than a recent systematic review.²⁷ The change in CRQ-Mastery demonstrated in this study is higher than the MCID, and as such, should be meaningful for patients.²⁹ The effect sizes for our secondary outcomes are also similar to recent trials.^{6 17 26}

The positive result reported in this trial was largely driven by deterioration in the wait-list group rather than improvement in the intervention group. This differs from other comparable trials where there was a greater improvement in the intervention group.^{2 17 26} This intriguing finding requires consideration. We recruited a relatively uniform population with severe COPD, a chronic, progressive, non-malignant disease that tends to deteriorate over time. The deterioration here may be consistent with that seen with severe COPD over 8 weeks, similar to a previously published longitudinal study which reported the majority of patients with COPD fluctuate or worsen over a period of months.³⁰ Further, there was a high rate of exacerbations during the 8-week period in both groups, and evidence of less improvement in CRQ-Mastery in those who exacerbated compared with those who did not exacerbate. Increased breathlessness is almost universal during exacerbations of COPD, and thus a decrease in CRQ-Mastery is expected both during and following an exacerbation.¹ The high rate of exacerbations in the control arm during the study period may, in part, also explain the observed decline in CRQ-Mastery. The stability of CRQ-Mastery

Scores in the intervention group, despite a high rate of exacerbations, further highlights the clinical benefit of the intervention. Future studies could consider adding exacerbation prevention strategies to BIS interventions to leverage further improvements.

Our finding that the WBS maintained rather than improved outcomes is consistent with the aims of tertiary prevention for people with advanced disease, although longer-term follow-up would be informative to appraise the sustainability of the intervention. A recent feasibility study of BIS in people with COPD suggests that at least some outcomes remain improved 6 months after the intervention.³¹ Additionally, patients in the wait-list group knew they were waiting for an intervention that might help their breathlessness, which may contribute to reporting bias. During this waiting period, they may have noted the impact breathlessness has on their quality of life and found it wanting, in a phenomenon known as response shift.³² Compared with other trials that have not observed deterioration in wait-list controls, this response shift may be exacerbated by the use of the informed follow-up version of the CRQ where respondents are told their previous score when the week 8 data were collected.

We recruited people with severe COPD confirmed by spirometry. The applicability to people with less severe disease is unclear. However, those with severe COPD are an important group to target with this type of higher-cost intervention as they suffer the greatest disability and use significant healthcare resources.³³ Future research will explore cost-effectiveness of the intervention over both 8 weeks and 12 months, and provide information about sustainability of outcomes over 12 months.¹⁴ One suggested barrier

Table 4 Effect of the breathlessness intervention on the change in CRQ mastery, in prespecified subgroups

		Breathlessness intervention	Wait-list control	Mean difference (95% CI)	
Subgroup (baseline)	Subgroup	N, mean (SD)	N, mean (SD)	Breathlessness intervention—control	P value, interaction
Sex	Female	21, 0.6 (1.1)	36, −0.1 (0.7)	0.6 (0.1 to 1.1)	0.43
	Male	33, −0.1 (0.7)	23, −0.5 (0.8)	0.4 (−0.0 to 0.8)	
HADS anxiety ≥8	<8	25, −0.1 (0.7)	27, −0.1 (0.9)	0.1 (−0.4 to 0.5)	0.07
	≥ 8	29, 0.4 (1.1)	32, −0.3 (0.7)	0.7 (0.2 to 1.1)	
HADS depression ≥8	<8	31, 0.1 (0.8)	37, −0.2 (0.8)	0.3 (−0.1 to 0.7)	0.44
	≥ 8	23, 0.3 (1.1)	22, −0.3 (0.7)	0.6 (−0.0 to 1.1)	
FEV ₁ %	≤30	21, −0.05 (0.76)	31, −0.1 (0.6)	0.1 (0.5 to 0.3)	0.10
	>30	33, 0.33 (1.01)	28, −0.3 (0.9)	0.6 (1.1 to 0.1)	

CRQ, Chronic Respiratory Questionnaire; FEV₁, forced expiratory volume in 1 s; HADS, Hospital Anxiety and Depression Scale.

Table 5 Effect of the breathlessness intervention on the change in CRQ mastery, adjusted for baseline, for participants with and without exacerbations during the intervention/wait-list period

Change in	Breathlessness intervention (N, mean±SD)	Wait-list control (N, mean±SD)	Difference (95% CI)
CRQ Mastery: no exacerbation	22, 0.7±1.1	32, -0.1±0.7	0.8 (0.3 to 1.3)
CRQ Mastery: one or more exacerbation(s)	32, -0.2±0.6	27, -0.4±0.8	0.2 (-0.1 to 0.6)
CRQ, Chronic Respiratory Questionnaire.			

to implementation of BIS is that breathlessness is often overlooked, and regarded as an inevitable consequence of advanced respiratory disease.⁷ Our results suggest that assessment and management of breathlessness should proceed in parallel with medical optimisation of underlying disease to enable maximal impact on this disabling and distressing symptom. Systems to enable symptom assessment along with disease control should be a priority for both clinicians and policy makers.

The applicability of this intervention to primary care is unknown, though one study suggests patients prefer to have this type of intervention in settings other than primary care.³⁴ It may be difficult for other services to adopt similar interventions with current funding models. Several recent studies have suggested less resource-intensive means of delivering similar interventions including interventions using fewer sessions,^{8 10 35} the use of digital platforms³⁶ and apps,³⁷ although only one of these has been tested in a well-powered RCT.⁸

One strength is the homogeneity of our population compared with previous studies. We recruited only people with COPD and demonstrated a positive impact compared with wait-list controls. Stratification by pulmonary rehabilitation completion in the last 12 months ensures engagement in this important part of COPD care did not confound our results. This is an important consideration that has not been used in previous studies. Participants who complete pulmonary rehabilitation may, first, have better physical activity and less breathlessness and, second, might be more engaged in their healthcare than those who have not. Reporting of pulmonary rehabilitation completion has been absent from previous studies. A further strength is the originality of our study, using a broader healthcare team than other studies and having a slightly longer duration. This allows a broader range of perspectives to enable care and allows patients a longer time to integrate suggested behavioural changes into their daily lives. Additionally, we have collected data regarding exacerbations which has been absent from other studies. Given the importance of exacerbations in driving both lung function decline and healthcare costs, this inclusion adds to the relevance of our data. Finally, we have demonstrated clinical benefit in an Australian population, expanding the evidence base for BIS beyond European settings.

Limitations of this study include that the intervention was undertaken in a single centre limiting generalisability. The intervention lasted 8 weeks, after which the wait-list control participants underwent the intervention. While all efforts were made to ensure the research nurse collecting the data was blinded, this cannot be guaranteed. Future trials might consider checking the success of randomisation by asking data collection staff to report their impressions of whether the participant was intervention or control. Our pilot data suggested a greater primary outcome effect size of 1.1 units, which was subsequently reduced. Effect size in pilot studies is often greater than in RCTs. The final effect size chosen is greater than the published MCID for the primary outcome,¹⁸ and greater than the change reported in recent systematic reviews (which were published after we started this trial) and thus represents a reasonable goal.²⁷ The rate of exacerbations in this population is high, and this may limit the ability of the outcome measures to detect improvements from the intervention compared with other diagnostic groups. Other BIS trials have not reported exacerbations, making comparison of this detail impossible. Finally, we used stratification rather than minimisation as this was a single-centre study with only one stratification factor. Future studies should explore the cost-utility of this intervention and optimal target populations and service characteristics. Ad-

ditionally, consideration should be given to how BIS can be delivered outside of the clinical trial environment so as to provide equity of access, especially given cost-effectiveness to date has been largely positive.²⁷

CONCLUSION

An 8-week non-pharmacological multidisciplinary BIS improves CRQ-Mastery, CRQ-Dyspnoea and CRQ-Fatigue, and exertional breathlessness intensity and unpleasantness in participants with severe COPD compared with wait-list controls. This provides evidence to support using this intervention for patients with moderate/severe COPD and disabling breathlessness. A health economic analysis of this population is planned.

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Contributors TAS: literature search, funding acquisition, project administration, figures, study design, data collection, data analysis, data interpretation, writing—drafting manuscript, writing—editing and reviewing; MMR: literature search, funding acquisition, project administration, figures, study design, data collection, data analysis, data interpretation, writing—editing and reviewing; TL: literature search, funding acquisition, study design, data interpretation, writing—editing and reviewing; J-GC: funding acquisition figures, study design, data interpretation, writing—editing and reviewing; EK: literature search, funding acquisition, project administration, figures, study design, data collection, data interpretation, writing—editing and reviewing; HS: literature search, funding acquisition, project administration, figures, study design, data collection, data interpretation, writing—editing and reviewing; NMCC: funding acquisition, study design, data interpretation, writing—editing and reviewing; AK: funding acquisition, study design, data collection, data analysis, data interpretation, writing—drafting manuscript, writing—editing and reviewing; JRW: funding acquisition, project administration, study design, data interpretation, writing—editing and reviewing. TAS is the guarantor for this manuscript. TAS (the corresponding author) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Competing interests None declared.

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ORCID iDs

Tracy A Smith <https://orcid.org/0000-0002-7729-3820>

Tim Luckett <https://orcid.org/0000-0001-6121-5409>

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ARTIGO ORIGINAL

Desenvolvimento e validação do modelo PRECISE-X: Previsão da primeira agudização grave na DPOC

Mohsen Sadatsafavi,¹ Marc Miravittles,² Jennifer K Quint,³ Valeria Perugini,⁴ Hamid Tavakoli,⁵ Joseph Emil Amegadzie,⁶ Bernardino Alcazar Navarrete,⁷ on behalf of the Respiratory Effectiveness Group (REG)-COPD working group

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For numbered affiliations see end of article.

Correspondence to

Dr Marc Miravittles; marcm@separ.es

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RESUMO

Objetivos Em pessoas com doença pulmonar obstrutiva crônica (DPOC), as agudizações graves (ECOPDs) causam morbidade e mortalidade substanciais. As orientações atuais enfatizam o uso do historial de ECOPD para orientar tratamentos preventivos, mas oferecem pouca orientação para a estratificação do risco da primeira exacerbação grave.

Métodos Desenvolvemos e validamos o PRECISE-X utilizando uma coorte de doentes com diagnóstico recente de DPOC do Clinical Practice Research Datalink do Reino Unido (2004–2022), para prever a primeira ECOPD grave ao longo de 5 anos (resultado primário) e 12 meses (resultado secundário). Os preditores foram selecionados através de conhecimento clínico e métodos orientados por dados. Foi realizada validação cruzada interna-externa entre regiões de prática clínica para avaliar o desempenho fora da amostra do modelo em termos de discriminação (estatística c), calibração e benefício líquido.

Resultados O estudo incluiu 219 015 doentes (idade média 66,0 anos; 42,4% mulheres). O risco observado da primeira ECOPD grave foi de 29,5% aos 5 anos (4,2% ao fim de 1 ano). O modelo final incluiu quatro preditores obrigatórios (sexo, idade, escala de dispneia do Medical Research Council e volume expiratório forçado no primeiro segundo – FEV₁) e 28 preditores opcionais. Na validação cruzada interna-externa, a estatística C média fora da amostra foi: 0,836 (IC 95%: 0,827–0,846) para previsão a 5 anos, 0,756 (IC 95%: 0,746–0,766) para previsão a 1 ano. A calibração entre regiões foi robusta e o modelo apresentou benefício líquido positivo numa ampla gama de limiares de risco. Numa avaliação de validação secundária, entre doentes com espirometria disponível e obstrução confirmada, o modelo manteve boa calibração e apenas um declínio modesto na capacidade discriminativa.

Conclusões O PRECISE-X prevê com precisão a primeira exacerbação grave de DPOC utilizando dados clínicos de rotina, apoiando uma estratificação de risco mais precoce e uma gestão proativa da doença.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive and heterogeneous condition characterised by persistent respiratory symptoms and airflow limitation. Exacerbations of COPD (ECOPD)—defined by an acute worsening of respiratory symptoms with varying severity and clinical impact—play a critical role in the disease's natural history. While mild and moderate exacerbations can often be managed in outpatient settings, severe exacerbations typically require hospital admission, leading to substantial morbidity and mortality.^{1,2} Frequent exacerbations are associated with a steeper decline in lung func-

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Severe exacerbations of chronic obstructive pulmonary disease (COPD) are associated with high morbidity and mortality. Existing tools primarily focus on patients with a history of exacerbations, offering limited guidance for predicting the first severe event.

WHAT THIS STUDY ADDS

► The PRECISE-X model accurately predicts the risk of a first severe COPD exacerbation using routine clinical data. It demonstrates strong performance across UK regions and enables early identification of high-risk patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► This model supports proactive, personalised COPD management by identifying at-risk patients earlier. It may also inform the design of clinical trials targeting first exacerbation outcomes and guide treatment decisions in real-world settings.

tion, reduced health-related quality of life and increased healthcare resource utilisation.² Despite advancements in the pharmacological and non-pharmacological management of COPD,³ the ability to accurately predict and proactively prevent hospital admissions due to severe ECOPDs remains limited.

The consequences of severe ECOPDs extend far beyond the immediate health crisis. Published data indicate that patients requiring hospital admission for ECOPD face markedly elevated short-term and long-term mortality rates,⁴ reflecting both cardiopulmonary complications and broader systemic impact of acute events on disease progression.^{5,6} These patients are also at heightened risk of recurrent exacerbations, establishing a cycle of deterioration that undermines clinical stability and accelerates disease progression.^{7,8} Given the interplay between exacerbations and disease trajectory, accurate risk stratification at the time of COPD diagnosis could transform the current reactive care model into proactive, targeted interventions.⁹

Although several tools exist to estimate ECOPD risk, most rely on prior exacerbation history and



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use specialised biomarkers not routinely available in clinical practice.¹⁰ As such, their value in predicting a patient's first severe ECOPD is limited. There remains a clear need for simple, scalable models that integrate seamlessly into routine clinical workflows. To address this need, we aim to develop a risk prediction model to estimate the likelihood of hospitalisation for a first severe ECOPD at or near diagnosis. Using readily available clinical data, the model will support early risk identification—similar to cardiovascular tools like SCORE and Framingham—by relying on routine variables, with optional predictors if available.^{11,12}

MATERIAL AND METHODS

This manuscript adheres to the Transparent Reporting of a multi-variable model for Individual Prognosis or Diagnosis (TRIPOD) Statement.¹³ We conducted a retrospective observational analysis to develop a risk prediction model for first severe ECOPD following COPD diagnosis, using routinely recorded clinical variables. The model was intended for use at the time of diagnosis in primary care.

Participants

We used the Clinical Practice Research Datalink (CPRD) Aurum (2004–2022),^{14,15} containing electronic medical records from 1491 UK general practices. Eligible patients had a new COPD diagnosis based on a validated code-based algorithm (positive predictive value: 86.5%),^{16,17} detailed in online supplemental section 1.

Inclusion criteria: patients aged ≥ 40 years at diagnosis and current or former smokers. Exclusion criteria: (1) any hospitalisation due to COPD occurring before diagnosis or within the first week after diagnosis; and (2) spirometry results within 1 year before or after diagnosis that were incompatible with COPD (defined as forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) ≥ 0.7). The latter criterion was applied to further improve the accuracy of the case definition (therefore, the positive predictive value of our case definition is likely higher than the original algorithm). We did not exclude patients based on inhaled treatments at diagnosis; instead, treatment history was included as a predictor. Predictions were adjusted for changes in follow-up treatment (see the Statistical Analysis section). The index date—when risk was estimated—was the date of COPD diagnosis. Patients required at least 1 month of follow-up. Variable definitions are detailed in online supplemental sections 1 and 2.

Primary outcome

The primary outcome was the occurrence of a severe ECOPD within 5 years of COPD diagnosis. We used the hospital-based definition of severe exacerbation as evaluated by Whittaker et al.¹⁸ We chose severe exacerbations as they are more accurately verifiable and have a substantially greater impact on long-term outcomes compared with moderate events.¹⁹ Specifically, a severe ECOPD was defined as an episode of hospital admission with (International Classification of Diseases ICD)-10 code recorded in hospital records (ICD10 J44.1, J44.0 or J44.9). The ICD-10 codes had to be in the first position or in the second position if the first was a code for lower respiratory tract infection (J22). This validated algorithm has demonstrated a sensitivity of 87.5% for hospitalised exacerbations.^{20,21} Because this outcome is objectively ascertained based on inpatient records, its accuracy is unlikely to be influenced by practice region or demographic factors. The secondary outcome was the occurrence of severe ECOPD within 12 months since diagnosis, defined using the same criteria as for the primary outcome.

Predictors

We followed a hybrid hypothesis-free and expert-elicited approach to predictor selection, combining data-driven methods with clinical expertise to prioritise variables routinely available at the point of care. Candidate predictors included demographics, symptom score (Medical Research Council (MRC) Dyspnoea Scale), spirometry measures, socioeconomic status, blood eosinophil count and co-existing or comorbid conditions.

The primary spirometric variable was forced FEV₁. The model was designed to accept either raw or percent-predicted FEV₁, with or without bronchodilation. When percent-predicted values were available, we back-transformed them to raw FEV₁ using regression equations incorporating age, sex and body mass index (BMI; see online supplemental section 3). Exploratory analyses showed raw FEV₁ offered better model fit and fewer missing values. Including age, sex and BMI in the model allowed for proper contextualisation of raw FEV₁, effectively adjusting for individual characteristics. Postbronchodilator values were used when available; otherwise, prebronchodilator values were included, reflecting clinical practice.

For most predictors, we used a look-back window of 12 months. For MRC, the look-back window was 2 years, and a look-forward window of 12 months after the index date was also applied. The latter criterion was applied because for some patients the MRC is assessed after a COPD diagnosis is established. Similarly, BMI was assessed using a 5-year look-back and 1-year look-forward windows. All comorbidity conditions were evaluated in the entire available time window up to the index date. An exception was asthma: given that some COPD patients might be initially diagnosed as asthma, we required records >2 years before diagnosis to minimise misclassified cases later re-coded as COPD.

Following preliminary analyses and expert input, sex, age, FEV₁ (raw or % predicted) and MRC Dyspnoea Score were designated essential due to clinical relevance and availability. These are required to generate a prediction, while optional predictors can vary, supporting flexible use across different clinical settings.

Statistical analysis

We did not calculate a formal sample size, given the large, population-based dataset and expected $>20\,000$ events based on prior studies. We adhered to best practice standards for prediction modelling²² and for time-to-event outcomes,²³ and we imputed missing data, adjusted for treatment drop-in and conducted internal-external validation to assess model performance.

Imputation of missing predictors

As it is common in electronic medical records, we anticipated a high level of missingness for some predictors. However, methodological guidelines recommend against removing such predictors based on missingness levels alone (or restricting the sample to complete cases, which causes selection bias) and instead recommend proper imputation methods, followed by out-of-sample validation.²⁴ We followed best practice standards for missing predictor imputation, which recommend different approaches for mandatory and optional predictors.²⁴ For mandatory predictors, we used multiple imputation via chained equations, generating five complete datasets. For non-essential predictors, we applied a regression-based approach, allowing these variables to be imputed at the time of model use based on other predictors. The assumption underlying the imputation of missing values is that conditional on the variables included in the imputation model. There are no systematic differences between the actual value of the missing and non-missing predictors.

Adjustment for treatment drop-in

Because many patients change their medications over the 5-year study period, potentially affecting ECOPD risk, it was important for the model to clearly define the risk it computes.²⁵ The present model reports the expected risk under current treatment (ie, if no change in treatment occurs). We consider this the most relevant prediction, as the 'baseline risk' before any medication changes.

We used Marginal Structural Modelling to adjust for treatment drop-in (ie, the addition of medications to baseline treatment in the future).²⁵ Follow-up time was divided into adjacent 6-month periods for each patient. In each period, we identified the initiation of any of the following medications: long-acting muscarinic agents (LAMA), long-acting beta agonists (LABA), inhaled corticosteroids (ICS) or azithromycin (when used for more than 30

days). We applied inverse probability-of-treatment weighting to calculate, for each patient, a weight that represents their probabi-

Table 1 Baseline characteristics: Predicting ECOPD among patients newly diagnosed with COPD			
Variable*	Male (N=1 26 064)	Female (N=92 951)	Total (N=2 19 015)
Age at diagnosis of COPD, mean (SD)	66.3 (11.2)	65.6 (11. 6)	66.0 (11.4)
Current smoker, N (%)	70 428 (55.9)	57 407 (61.8)	127 835 (58.3)
BMI (kg/m ²), mean (SD)	26.9 (7.9)	26.8 (8.2)	26.9 (8.0)
% missing	57.8	56.8	57.4
Blood eosinophil count (X10 ⁹ /L), mean (SD)	0.123 (0.291)	0.099 (0.213)	0.113 (0.261)
% missing	18.8	16.0	17.6
FEV1, mean (SD)	1.94 (0.75)	1.43 (0.63)	1.73 (0.75)
% missing	70.5	71.3	70.8
FEV1 percent predicted, mean (SD)	63.0 (18.5)	66.2 (18.3)	64.3 (18.5)
% missing	84.0	84.5	84.3
FEV1/FVC ratio, mean (SD)	0.53 (0.12)	0.54 (0.09)	0.53 (0.11)
% missing	45.8	54.1	49.3
FVC, mean (SD)	3.09 (0.98)	2.19 (0.72)	2.72 (0.98)
% missing	42.9	47.0	44.6
MRC scale, N (%)			
1	16 977 (16.8%)	10 290 (13.9%)	27 267 (15.6%)
2	34 251 (33.8%)	25 157 (34.0%)	59 408 (33.9%)
3	26 417 (26.1%)	20 272 (27.4%)	46 689 (26.6%)
4	18 340 (18.1%)	13 688 (18.5%)	32 028 (18.3%)
5	5 341 (5.3%)	4 504 (6.1%)	9 845 (5.6%)
% missing	19.6	20.5	20.0
Socioeconomic status, N (%)			
1	18 420 (14.6)	12 071 (13.0)	30 491 (14.0)
2	22 378 (17.8)	15 881 (17.1)	38 259 (17.5)
3	23 831 (18.9)	16 912 (18.2)	40 743 (18.6)
4	27 544 (21.9)	20 809 (22.4)	48 353 (22.1)
5	33 595 (26.7)	27 049 (29.2)	60 644 (27.8)
% missing	0.2	0.2	0.2
History of all-cause admissions, N (%)	21 451 (17.0)	14 984 (16.1)	36 435 (16.6)
History of all-cause emergency department visits, N (%)	17 305 (13.7)	12 003 (12.9)	29 308 (13.4)
Co-existing conditions, N (%)			
Active rhinitis	3 301 (2.6)	2 368 (2.5)	5 669 (2.6)
Anxiety	59 094 (46.9)	53 150 (57.2)	112 244 (51.2)
Asthma	26 592 (21.1)	25 865 (27.8)	52 457 (24.0)
Arrhythmia	2 819 (2.2)	1 590 (1.7)	4 409 (2.0)
Bronchiectasis	2 630 (2.1)	2 005 (2.2)	4 635 (2.1)
Chronic kidney disease	40 512 (32.1)	36 477 (39.2)	76 989 (35.2)
Diabetes	34 779 (27.6)	22 117 (23.8)	56 896 (26.0)
Gastro-oesophageal reflux disease	1 991 (1.6)	1 821 (2.0)	3 812 (1.7)
Heart failure	8 008 (6.4)	3 643 (3.9)	11 651 (5.3)
Hypertension	21 127 (16.8)	14 958 (16.1)	36 085 (16.5)
Ischaemic heart disease	24 282 (19.3)	9 812 (10.6)	34 094 (15.6)
Osteoporosis	12 540 (9.9)	13 060 (14.1)	25 600 (11.7)

Continued

Table 1 Continued			
Variable*	Male (N=1 26 064)	Female (N=92 951)	Total (N=2 19 015)
Pneumonia	1 572 (1.2)	1 686 (1.8)	3 258 (1.5)
Sleep apnoea	2 528 (2.0)	731 (0.8)	3 259 (1.5)
Stroke	17 482 (13.9)	9 357 (10.1)	26 839 (12.3)
Medication use†			
SABA	71 927 (57.1)	59 763 (64.3)	131 690 (60.1)
SAMA	9 834 (7.8)	7 460 (8.0)	17 294 (7.9)
LABA	30 600 (24.3)	26 388 (28.4)	56 988 (26.0)
LAMA	22 378 (17.8)	16 510 (17.8)	38 888 (17.8)
ICS	40 158 (31.9)	35 405 (38.1)	75 563 (34.5)
Mucolytics	3 711 (2.9)	2 745 (3.0)	6 456 (2.9)
Region, N(%)			
North East	5 087 (4.0)	4 653 (5.0)	9 740 (4.4)
North West	27 929 (22.2)	22 687 (24.4)	50 616 (23.1)
Yorkshire and The Humber	4 416 (3.5)	3 430 (3.7)	7 846 (3.6)
East Midlands	2 843 (2.3)	1 882 (2.0)	4 725 (2.2)
West Midlands	21 940 (17.4)	15 606 (16.8)	37 546 (17.1)
East of England	5 395 (4.3)	3 718 (4.0)	9 113 (4.2)
London	17 530 (13.9)	12 070 (13.0)	29 600 (13.5)
South East	23 802 (18.9)	16 610 (17.9)	40 412 (18.5)
South West	17 122 (13.6)	12 295 (13.2)	29 417 (13.4)
*Variables without % missing value indicator had no missing values. For co-existing conditions, lack of diagnostic code was interpreted as lack of the corresponding condition.			
†Defined by ingredients. For example, an individual on a single-inhaler ICS+LABA therapy would satisfy both ICS and LABA use.			
BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOPD, exacerbations of chronic obstructive pulmonary disease; FEV1, forced expiratory volume at one second; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic agent; MRC, Medical Research Council; SABA, short-acting beta-agonist; SAMA, short-active anti-muscarinic agent.			

lity of initiating any of such treatments. Separate logistic regression models were used within each period.

Model development and validation

We followed the most recent practice recommendations, which emphasise using all the data for development rather than splitting

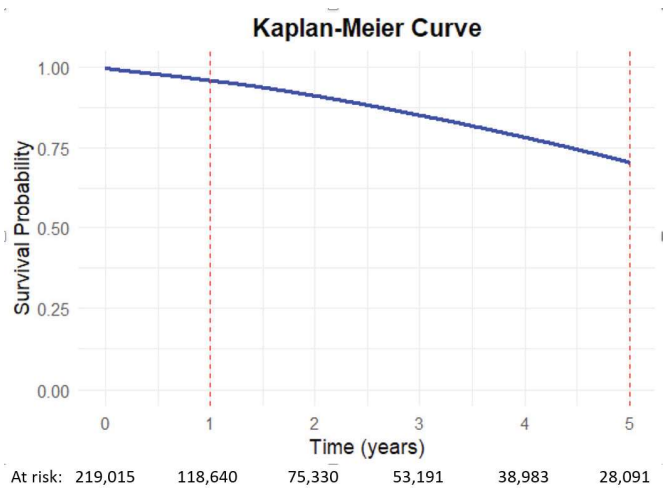


Figure 1 Kaplan-Meier curve (probability of being event-free) for severe exacerbations of chronic obstructive pulmonary disease.

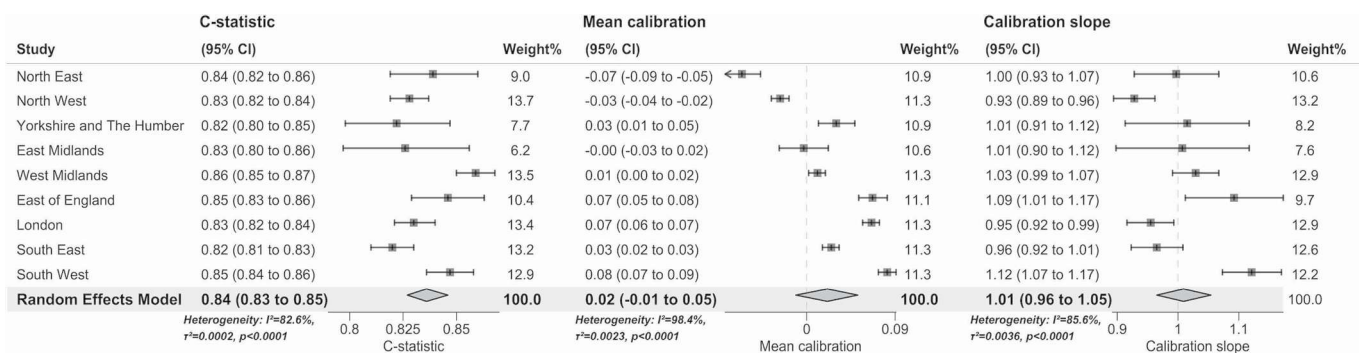


Figure 2 Meta-analysis of the out-of-sample performance of the model for 5-year prediction. Left panel: c-statistic; middle panel: mean calibration; right panel: calibration slope.

data into separate external and internal validation sets.²³ Such recommendations encourage taking advantage of any natural clustering in the data to perform internal-external validation. Accordingly, we used the clustering of the data across the nine health regions in the UK for this purpose. Internal-external cross-validation involved leaving out one region at a time, fitting the model on the remaining eight regions and validating it on the external, left-out region. The final model was based on using the entire dataset. As the model is tested in a sample that is not used for its training, this approach provides the same credibility as an external cross-validation while training the final model on the full data.

We used semiparametric survival (Cox proportional hazards) modelling with least absolute shrinkage and selection operator (LASSO) for prediction. We chose the Cox model due to the flexibility of this platform in separating baseline hazard from predictor effects, thus enabling the model to be adjusted based on outcome prevalence in other settings (as is often required when transporting the model into a new population with different outcome prevalence²⁶). Also, by shrinking predictor coefficients, LASSO prevents model overfitting that would negatively affect its generalisability (especially given the multitude of predictors). The tuning parameter of LASSO was automatically selected based on minimising cross-validated mean-squared error of predictions.

After a preliminary analysis verified the large effective sample size, we included an initial set of 32 predictors, comprising four essential and 28 optional predictors. One-way interaction terms among essential predictors, as well as selected interactions between essential and optional predictors, were included (eg, asthma history by sex) based on clinical judgement. In line with best practice standards, we also considered the missingness of a predictor as a separate binary predictor.²⁴ No rescaling or standardisation of predictors was performed.

Metrics of model performance were the c-statistic (also known as the area under the receiver operating characteristic curve—the closer to one, the better), mean calibration (the difference between the average observed and predicted risk—the closer to zero, the better) and calibration slope (capturing if the calibration plot follows the identity line—the closer to one, the better). We also

evaluated the clinical utility of the model in terms of its net benefit (NB).²⁷ Unlike statistical metrics of model performance, whose relevance to the practical usefulness of a model is not always clear, NB is a utility measure: if a model has a higher NB over not using it, it is expected to provide clinical utility. The NB of a model needs to be evaluated at thresholds of interest for classifying patients into low-risk versus high-risk categories. To the best of our knowledge, such thresholds have not been determined for severe ECOPDs (an example of an established threshold is a 10% 10-year risk of cardiovascular outcomes for initiating statin therapy).²⁸ As such, we evaluated NB at 0.1–0.9 thresholds (with 0.1 increments). C-statistic, calibration plots and NB were calculated as time-dependent metrics for the 5-year time horizon (primary outcome) and 1-year time horizon (secondary outcome).

Because the internal-external cross-validation was repeated nine times (each time leaving one region out), this approach generated nine sets of model performance metrics. We used random-effects meta-analysis to pool these results. We assessed whether the variability across regions was large enough to warrant local adjustments of the model for each jurisdiction. The final model was fitted on the entire dataset.

Secondary validation

While we used a validated case definition with high predictive value for COPD, to examine the validity of predictions among those with spirometrically confirmed COPD, we performed a dedicated validation study in the subset of patients with available spirometry data where $FEV_1/FVC < 0.7$.

RESULTS

A total of 2 19 015 patients were included in the final analytical sample. Table 1 presents the demographic characteristics and the risk factor profile of the sample. Of the total, 42.4% were female. The average age at the time of diagnosis was 66.0 years, with average $FEV_1(\%)$ of 64.3 of percent predicted and an FEV_1/FVC ratio of 0.53.

On average, each patient contributed 1.80 years of follow-up time, during which 23 205 severe ECOPD events were recorded.

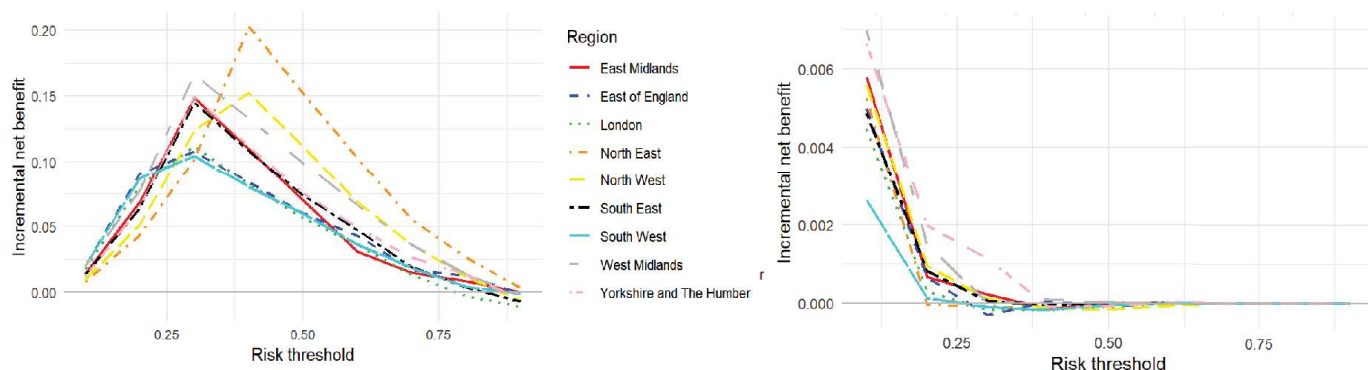


Figure 3 Incremental net benefit of the model over default strategies (treating no one or treating all) for 5-year (left) and 1-year (right) prediction.

Figure 1 provides the Kaplan-Meier curve for survival (not experiencing severe ECOPD). The observed probability of experiencing a severe ECOPD by year 5 was 29.5% (95% CI 29.1% to 29.8%). This probability was 4.2% (95% CI 4.1% to 4.3%) by 12 months.

The final model included the four essential predictors: age, sex, FEV₁ (raw or percent predicted) and MRC score, and the following optional predictors: smoking status, history of all-cause hospital admissions and emergency department visits, BMI, FVC, socioeconomic status (Townsend Score), blood eosinophil count and history of several co-existing conditions (asthma, anxiety, hypertension, heart failure, cerebrovascular disease, ischaemic heart disease, gastro-oesophageal reflux disease, sleep apnoea, chronic kidney disease, bronchiectasis, osteoporosis, pneumonia and active rhinitis), as well as inhaler medications (ICS, LABA, LAMA, short-acting anti-muscarinic agent, short-acting beta-agonist) and the use of mucolytics. Detailed model structure and regression coefficients are provided in the online supplemental section 4.

Figure 2 provides the results of the meta-analyses for c-statistic (left panel), calibration in the large (middle panel) and calibration slope (right panel) of the full model for the primary endpoint (5-year risk prediction). The pooled c-statistic for 5-year prediction was 0.836 (95% CI 0.827 to 0.846). The pooled mean calibration error was not statistically significantly different from 0 (point estimate: 0.021 (95% CI -0.011 to 0.052)). The calibration slope was 1.009 (95% CI 0.965 to 1.054), which was not statistically significantly different from 1.0.

In its simplest form, containing only essential predictors, the model still had a c-statistic of 0.792 (95% CI 0.784 to 0.800) for the primary endpoint and 0.705 (95% CI 0.697 to 0.714) for the secondary outcome.

Online supplemental section 5 reports results for 1-year prediction, with a random-effects pooled c-statistic of 0.756 (95% CI 0.746 to 0.766). Mean calibration error and calibration slope were, respectively, 0.001 and 1.009 (not significantly different from 0 and 1, respectively).

The incremental NB of the model (at 0.1 increments in risk threshold) is provided in figure 3. The performance of the model was evaluated for all nine regions and each of the nine thresholds, resulting in 81 region-threshold combinations. For both 5-year and 12-month predictions, the NB was negative in only one of the 81 region-threshold combinations.

Receiver operating characteristics and calibration plots for the final model on both outcomes are available in online supplemental section 6.

Online supplemental section 7 provides the results of the secondary validation study among those with recorded FEV₁/FVC<0.7. The model was very well calibrated in this subsample, and its discriminatory performance was only modestly lower than in the full sample (pooled c-statistic at 5 years and 12 months of 0.817 (95% CI 0.808 to 0.827) and 0.721 (95% CI 0.705 to 0.737)).

DISCUSSION

We used a large and representative primary care database from the UK to develop and validate a novel prediction model for first severe ECOPD after COPD diagnosis. With easy to obtain demographic and clinical variables, such as age, sex, MRC Dyspnoea Scale and FEV₁, this prediction model provided excellent out-of-sample accuracy for 5-year prediction of this outcome and very good accuracy for 12-month predictions. The out-of-sample calibration was also robust. Critically, while discrimination and calibration varied across regions, the model showed potential for delivering clinical utility (positive net NB) across a wide spectrum of risk thresholds. The model was well calibrated when validation was restricted to those with FEV₁/FVC<0.7.

A history of exacerbations is the strongest known predictor of future COPD exacerbations,²⁹ and models in established COPD populations consistently emphasise its importance.^{30–32} However, this information is often unavailable at the time of diagnosis. As such, assessing the risk of a first hospitalised ECOPD becomes critical. Although some models predict severe ECOPD based on

clinical characteristics, few have been specifically developed or validated for use at diagnosis, when prior exacerbation history is lacking.^{33 34}

Identifying patients at high risk of severe ECOPD at the time of diagnosis can support timely risk reduction strategies,³⁵ especially given the negative impact of early events on disease progression.³⁶ By focusing on diagnosis-time data from real-world primary care, our model addresses a key gap and offers insights that general practitioners can readily apply in everyday clinical settings.

A major strength of our analysis is the use of internal-external cross-validation, which fully used the dataset while enabling robust out-of-sample testing. This method—now a best practice in prediction modelling—helps prevent overfitting and improves generalisability. As a result, our estimates of discrimination and calibration are more reliable than those from conventional split-sample validation. We also used rigorous methods to address missing data and treatment drop-in. Finally, the model's flexible structure—requiring only four core predictors but allowing up to 32—supports broad implementation, whether embedded in electronic records or used in resource-limited settings.

However, several limitations should be acknowledged. Some predictors (including spirometry values) had a high degree of missingness, which is common in electronic medical records. For example, only 28% of the development sample of the widely used QRISK3 model (for 10-year risk of cardiovascular disease) had non-missing essential predictors.³⁸ Current best practices advise against excluding potentially important predictors solely due to missingness. Selection bias by focusing on complete cases is likely to have a more severe impact on the validity of results than the violation of the assumption of missingness at random (conditional on the value of other predictors).²⁴ We also acknowledge that some predictors did not have the desired level of granularity. For example, reliable pack-years calculation in CPRD is not currently feasible. This might have affected the predictive power of the model. While missing or low-resolution data may reduce predictive power, the true measure of performance lies in out-of-sample validation, where our model remained robust.

While the model demonstrated strong predictive accuracy and calibration across UK primary care regions, its generalisability to other healthcare systems, populations and disease patterns remains uncertain. Independent external validation—especially in non-UK settings—is needed to confirm both performance and clinical utility. Additionally, we did not assess all possible predictors or their complex interactions. Incorporating biomarkers, socioenvironmental variables³⁹ or genomic data may further improve risk stratification. Lastly, we did not account for competing risks such as mortality, which is especially relevant in older, multimorbid populations. Future research using joint or multi-state models could provide a more comprehensive understanding of COPD progression and outcomes.

Another key observation is the variability in calibration and predictive accuracy across time horizons and regions. The model showed more consistent calibration over a 1-year prediction window compared with longer-term forecasts (judging by the heterogeneity of c-statistic across regions). This likely reflects the nature of COPD, where short-term risks are more directly influenced by current clinical and demographic factors, while longer-term outcomes are also shaped by differences in healthcare access, socioeconomic status and environmental exposures across regions. Despite regional disparities, our NB analyses indicate that the model retains meaningful clinical utility across different thresholds and geographies. However, independent external validation is essential before applying the model in new populations, particularly outside the UK, to ensure accuracy in settings with different risk profiles.

The strong predictive performance of PRECISE-X for identifying patients at risk of a first severe ECOPD has important clinical implications. Like the Framingham and Systematic Risk Score Evaluation (SCORE) tools used in cardiovascular prevention,⁴⁰ PRECISE-X could support early intervention strategies in COPD. By identifying high-risk individuals at diagnosis, clinicians could

more effectively tailor preventive measures—such as pharmacotherapy, smoking cessation, pulmonary rehabilitation or vaccination. Proactively targeting those at greatest risk may help reduce healthcare burden, improve patient outcomes and slow disease progression.

Beyond direct patient care, this model also has important research applications. It provides a framework for designing clinical trials that prioritise severe ECOPD as a primary outcome—unlike most current COPD trials, where such events are secondary. By using our risk stratification tool during recruitment, trials can identify high-risk individuals more likely to benefit from novel therapies. This enrichment strategy can improve trial efficiency and increase the likelihood of detecting meaningful treatment effects.

In summary, our study shows that the risk of a first severe exacerbation in newly diagnosed COPD patients can be accurately predicted using routinely collected clinical data—even without prior exacerbation history. The model's consistent performance across regions and risk thresholds highlights its potential to support a proactive, prevention-focused approach to COPD care. Integrating the tool into electronic health records could enable early identification of high-risk patients and timely interventions. It may also enhance randomised trial design by facilitating efficient recruitment of high-risk individuals. Further validation and implementation in diverse settings could improve outcomes and COPD care delivery.

Author affiliations

¹Respiratory Evaluation Sciences Program, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, British Columbia, Canada

²Respiratory Department, Vall d'Hebron University Hospital / Vall d'Hebron Research Institute (VHIR), Vall d'Hebron Barcelona Hospital Campus. CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain

³School of Public Health, Imperial College London, London, UK

⁴Respiratory Effectiveness Group, Cambridgeshire, UK

⁵Meta Health Informatics, Vancouver, British Columbia, Canada

⁶Epidemiology and Intelligence Services and Faculty of Pharmaceutical Sciences, British Columbia Centre for Disease Control and The University of British Columbia, Vancouver, British Columbia, Canada

⁷Respiratory Department, Hospital Universitario Virgen de las Nieves, Ibs.Granada, Universidad de Granada, Granada, Spain

Collaborators Respiratory Effectiveness Group (REG)-COPD working group: Nicolas Roche - nicolas.roche@aphp.fr; Joan B Soriano - jbsoriano2@gmail.com; Omar Usmani - o.usmani@imperial.ac.uk; Therese Lapperre - Therese.Lapperre@uza.be; Chin Kook Rhee - chinkook77@gmail.com; Matevz Harlander - matevz.harlander@gmail.com; Alan Kaplan - for4kids@gmail.com.

Contributors MM and BAN conceived the study question. MS, BAN, MM and VP developed the original study protocol. VP was responsible for project management. VP and MS procured the data. JKQ provided expert advice on data elements and shared analysis code from previous studies. MS developed the statistical analysis plan. JEA created the study cohort. HT conducted statistical analyses. JKQ and MS supervised cohort creation and data analysis. MS and BAN wrote the first version of the manuscript. All authors critically commented on the manuscript and approved the final version. MS is the data guardian for this study. MM is the guarantor for this study.

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ORCID iDs

Mohsen Sadatsafavi <https://orcid.org/0000-0002-0419-7862>

Marc Miravittles <https://orcid.org/0000-0002-9850-9520>

Jennifer K Quint <https://orcid.org/0000-0003-0149-4869>

Valeria Perugini <https://orcid.org/0000-0002-9516-4862>

Bernardino Alcazar Navarrete <https://orcid.org/0000-0003-2356-9366>

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ARTIGO ORIGINAL

Propriedades de medição do teste de sentar-levantar em pessoas com doença pulmonar obstrutiva crónica a viver na comunidade: uma revisão sistemática COSMIN

Christopher Farley,¹ Anastasia N L Newman,¹ Stuart M Phillips,² Jenna Smith-Turchyn,¹ Dina Brooks^{1,3}

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¹School of Rehabilitation Science, McMaster University Faculty of Health Sciences, Hamilton, Ontario, Canada

²Department of Kinesiology, McMaster University Faculty of Science, Hamilton, Ontario, Canada

³Respiratory Research, West Park Healthcare Centre, Toronto, Ontario, Canada

Correspondence to

Dr Dina Brooks; brookd8@mcmaster.ca

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RESUMO

Contexto O teste de sentar-levantar (sit-to-stand, STS) pode avaliar a função física em pessoas com doença pulmonar obstrutiva crónica (DPOC); contudo, existem várias versões do teste. Nenhum estudo utilizou as orientações atuais para avaliar as propriedades de medição dos testes STS em pessoas com DPOC.

Métodos Realizámos uma revisão sistemática utilizando as orientações atuais do CONsensus-based Standards for the selection of health Measurement INSTRuments (COSMIN). Foram incluídas publicações completas, revistas por pares, que avaliassem as propriedades de medição (validade, fiabilidade e/ou responsividade) de pelo menos um teste STS em pessoas com DPOC a viver na comunidade. Pesquisámos seis bases de dados e importámos os resultados para o Covidence, onde a triagem de títulos/resumos e a seleção de textos completos foram realizadas de forma independente e em duplicado. A extração de dados foi igualmente conduzida de forma independente e em duplicado, utilizando o ficheiro de extração COSMIN. Avaliámos o risco de viés dos estudos (muito bom, adequado, duvidoso ou inadequado), a qualidade das propriedades de medição (suficiente, indeterminada ou insuficiente) e a certeza global da evidência (alta, moderada, baixa ou muito baixa), utilizando as ferramentas recomendadas pelo COSMIN.

Resultados Foram avaliados 2577 títulos/resumos e 102 textos completos; 30 publicações cumpriram os critérios de inclusão. Identificaram-se sete testes STS distintos, sendo os mais comuns o teste STS de 1 minuto (n=14, 39%), o teste STS de 5 repetições (n=10, 28%) e o teste STS de 30 segundos (n=8, 22%). Quando avaliados, a fiabilidade foi suficiente para os testes STS de 1 minuto, 5 repetições e 30 segundos. Apenas o teste STS de 1 minuto apresentou evidência de alta qualidade quanto à validade de constructo, enquanto o teste STS de 30 segundos foi o único com pelo menos evidência de qualidade moderada quanto à responsividade.

Conclusões O teste STS de 1 minuto apresenta as propriedades de medição mais robustas para avaliações transversais, enquanto o teste STS de 30 segundos é mais robusto para avaliar mudança ao longo do tempo.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive lung condition characterised by shortness of breath, sputum production and chronic cough, with many people also experiencing exercise intolerance.¹ Many individuals with COPD are deconditioned and have decreased muscle strength and impaired physical function.¹ One's ability to move from sitting to standing is a key component to maintaining functional independence.²

The sit-to-stand (STS) test is a performance-based outcome measure that involves a participant per-

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- The sit-to-stand (STS) tests are increasingly used to assess physical function in people with chronic obstructive pulmonary disease.
- A 2017 review summarised some of the measurement properties, but no study has yet used the CONsensus-based Standards for the selection of health Measurement INSTRuments guidelines.

WHAT THIS STUDY ADDS

- We found the 1 min STS has moderate-quality evidence of sufficient reliability and high-quality evidence of sufficient construct validity.
- The 30 s STS test has very low-quality evidence of reliability and moderate quality of sufficient responsiveness.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This study can help researchers and clinicians choose the best STS test for their purposes.

forming the STS movement repeatedly.³ The original design of the STS test had a participant complete 10 STS repetitions as fast as possible to assess lower extremity strength.³ Currently, there are many versions of the STS test which vary by either the duration or the number of repetitions. In the presence of multiple different STS tests, it is unclear which version has the most robust measurement properties and should be used in people with COPD.

The CONsensus-based Standards for the selection of health Measurement INSTRuments (COSMIN) guidelines were created to standardise the methods to assess and select optimal outcome measurement tools.^{4,5} To date, no study has used the COSMIN methods to assess the measurement properties of the STS tests in people with COPD. As such, our primary objective was to determine the measurement properties (reliability, validity and responsiveness) of the STS tests in people with COPD. Furthermore, we aimed to summarise the interpretability (eg, minimal important change) and feasibility characteristics (eg, ease of administration) of the STS tests.

METHODS

A priori, we registered our review with the International Prospective Register of Systematic Reviews (CRD 42024586635). We outlined our methods in our published protocol.⁶ As noted in our protocol, we intended to conduct our review according to the COSMIN guideline (V.1.0).⁵ After the recent publication of the updated COSMIN guidelines, we revised our approach to be consistent with V.2.0.4 This review is published according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses COSMIN guideline (online supplemental table 1).⁷

Eligibility criteria

Peer-reviewed publications were eligible for inclusion if authors assessed the measurement properties (validity, reliability and/or responsiveness) of one or more of the STS test variations (eg, 5-repetition STS, 30 s STS) among community-dwelling people with COPD (≥50% of sample⁴ or reported as a subgroup). Due to inconsistent terminology in the literature, we categorised measurement properties according to the COSMIN taxonomy.⁸ We excluded publications in which participants had a current acute exacerbation of COPD, if STS was used solely as an outcome measure or to validate another instrument,⁴ and if the STS test was conducted remotely or virtually. Additionally, we excluded grey literature, publications that did not have a full text available and review papers.⁴

Information sources

We searched Medline (OVID interface, 1946 onwards), Embase (OVID interface, 1974 onwards), Emcare (OVID interface, 1995 onwards), Cumulative Index to Nursing & Allied Health Literature (EBSCOhost interface, 1981 onwards), Web of Science (Clarivate interface, 1976 onwards) and Scopus (Elsevier interface, 2004 onwards) from their inception to 4 September 2024. We also reviewed the reference lists of all included studies for any other potentially eligible publications.

Search strategy

We developed our search strategy in consultation with a health sciences librarian. Our strategy was built around the following

concepts: (1) Measurement properties, (2) COPD and (3) STS test. The strategy involved combining Medical Subject Headings and keywords using Boolean operators. Where available, we used highly sensitive and validated search strategies to identify measurement property publications.^{5 9} We did not use any limits in our search. Final search strategies for each database are available in online supplemental tables 2–7.

Selection process

Citations identified through our search strategy were exported from their respective databases and imported to EndNote V.21 (2023, Clarivate available from <https://endnote.com/>) for removal of duplicates. Subsequently, we uploaded deduplicated citations to Covidence systematic review (2020, Veritas Health Innovation, Melbourne, Victoria, Australia) where further duplicates were automatically identified and removed. Selection of included publications occurred in two stages: (1) Title and abstract screening and (2) Full text selection. Title and abstract screening was manually completed independently and in duplicate using Covidence. If at least one reviewer deemed a title and abstract potentially eligible, it was assessed in the next stage. Prior to commencing screening, we conducted a calibration exercise of 10 citations to ensure consistency in applying the eligibility criteria among reviewers. Full text selection was also manually conducted independently and in duplicate using Covidence with a third reviewer, as needed. Where studies were excluded, we recorded the most relevant reason for exclusion. Prior to the initiation of full text selection, we conducted a preliminary calibration exercise of five full texts.

Data collection

Data were manually extracted independently by one reviewer using Microsoft Excel for Mac (2024, Microsoft Corporation available from <https://office.microsoft.com/excel>) and verified for accuracy by a second reviewer.⁴ This was a key change from V.1.0 and V.2.0 of the COSMIN guidelines;^{4 5} we originally planned to conduct extraction in duplicate but revised this approach to be consistent with the updated COSMIN guidelines. We used the COSMIN Review Management File (V.27 August 2024) for extrac-

Table 1 Hypotheses for construct validity and responsiveness

Hypotheses		
For construct validity	Criteria	Comparator examples
Comparator instrument that measures a related construct (physical functional capacity)	r ≥0.6 or AUC ≥0.6	► 6 min walk test ⁵⁰ ► Incremental shuttle walk ⁵¹
Comparator instrument that measures largely related constructs (eg, muscle strength, physical activity, balance)	r =0.4–0.7	► Maximal voluntary contraction ► 4 m gait speed test ⁵² ► Berg Balance Scale ⁵³
Comparator instrument that measures a moderately related construct (eg, health-related quality of life, quality of life, dyspnoea, general health)	r =0.3–0.6	► St. George Respiratory Questionnaire ⁵⁴ ► Medical Research Council Dyspnoea Scale ⁵⁵ ► COPD assessment test ⁵⁶
Mortality and exacerbation events will be associated with lower timed STS test scores and higher 5-repetition STS Scores	AUC ≥0.6 or significant HR or significant association via regression	N/A
Relevant subgroups (eg, lower disease severity phenotype vs higher disease severity phenotype) should differ by at least the minimal important change score	N/A	N/A
For responsiveness		
Change scores of comparator instrument that measures a related construct (physical functional capacity)	r ≥0.6 or AUC ≥0.6	► 6 min walk test ⁵⁰ ► Incremental shuttle walk ⁵¹
Change scores of comparator instrument that measures a largely related construct (eg, muscle strength, physical activity, balance)	r =0.4–0.7	► Maximal voluntary contraction ► 4 metre gait speed test ⁵² ► Berg Balance Scale ⁵³
Change scores of comparator instrument that measures a moderately related construct (eg, health-related quality of life, quality of life, dyspnoea, general health)	r =0.3–0.6	► St. George Respiratory Questionnaire ⁵⁴ ► Medical Research Council Dyspnoea Scale ⁵⁵ ► COPD Assessment Test ⁵⁶
Change scores of relevant subgroups should differ by at least the minimal important change score	N/A	N/A
AUC, area under the curve; COPD, chronic obstructive pulmonary disease; N/A, not applicable; r, correlation coefficient; STS, sit-to-stand.		

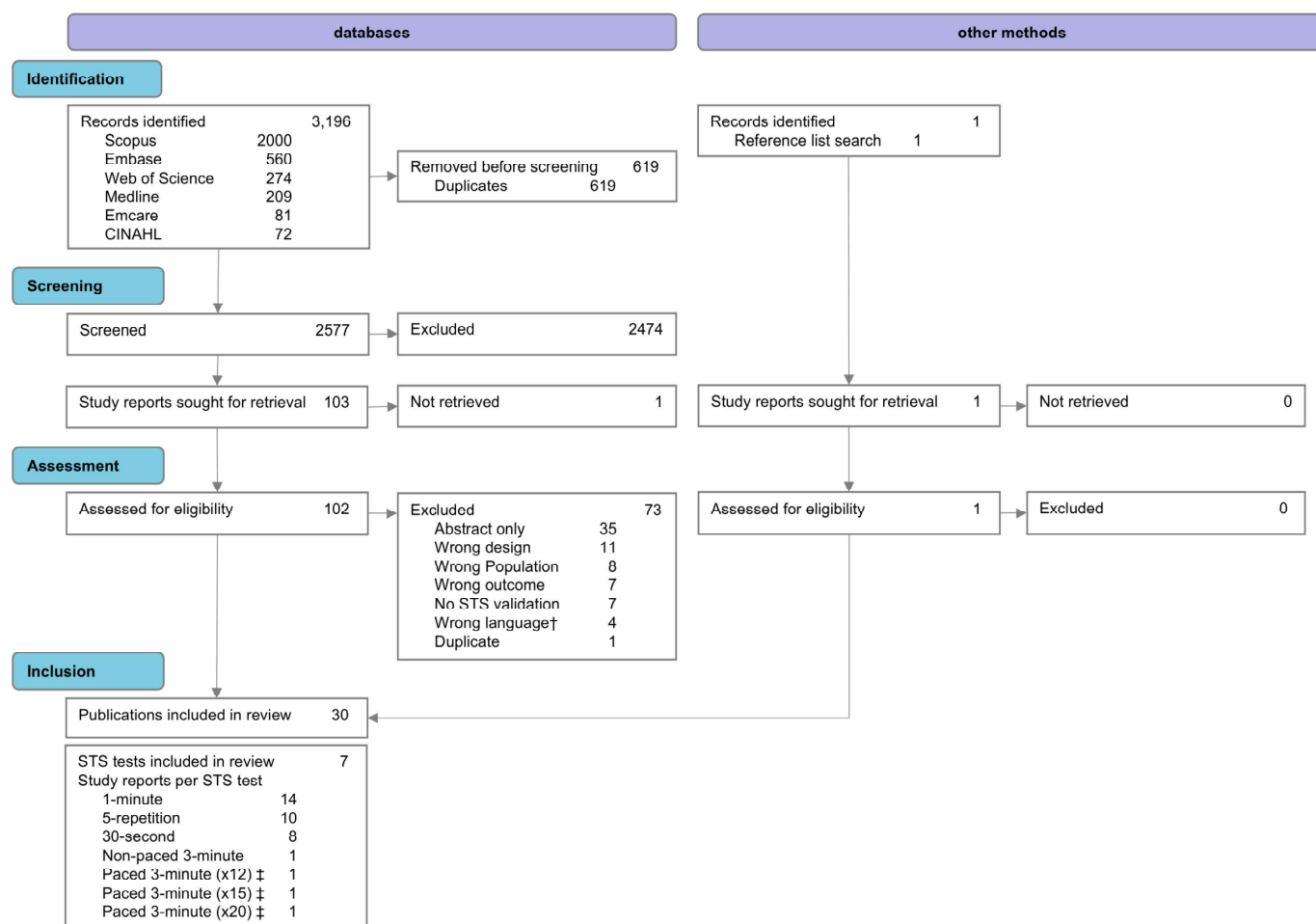


Figure 1 PRISMA-COSMIN flow diagram. † Publications not reported in English were excluded from the analysis due to review team expertise; however, they are listed in online supplemental table 9. ‡ Paced STS tests required participants to complete the indicated number of repetitions during the first minute followed by a self-selected pace for the remaining 2 min. COSMIN, Consensus-based Standards for the selection of health Measurement INstruments; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; STS, sit-to-stand.

tion, which is available at <https://www.cosmin.nl/tools/guideline-conducting-systematic-review-outcomemeasures/>. Extracted data included publication characteristics (eg, study design, country, setting), population characteristics (eg, sample size, eligibility criteria, age, sex, Global Initiative for Chronic Obstructive Lung Disease classification,¹⁰ forced expiratory volume in 1 s (FEV₁), the ratio of FEV₁ to forced vital capacity, smoking history, supplemental oxygen use), STS test characteristics (eg, number of repetitions or duration of the test, description of testing procedure), feasibility characteristics (eg, time to administer, cost; extracted from included studies verbatim and summarised as such), interpretability characteristics (eg, cut-off scores, floor/ceiling effects, minimal important change scores), measurement properties evaluated and their associated results. Prior to the extraction of reported minimal important change scores, we assessed their credibility using the five core credibility criteria presented by Devji et al.¹¹ Consistent with COSMIN guidelines, we did not extract any minimal important change scores which ranked as 'definitely no' on any of the five core credibility criteria.^{4 11} We did not attempt to contact the authors of the included publications throughout the conduct of our study.

Risk of bias

For this review, we adopted language consistent with COSMIN, which considers each analysis of a measurement property to be a unique study.⁴ As such, each publication included in our review could have contributed multiple studies to our synthesis. For example, one publication could have contributed one study of test-retest reliability, one study of intrarater reliability and one study of the responsiveness of a STS test.

We used the COSMIN Risk of Bias tool (V.2.0) to assess the risk of bias of reliability and measurement error studies and the COSMIN Risk of Bias checklist (V.3.0) to assess the risk of bias for construct validity and responsiveness studies.^{4 12} The COSMIN Risk of Bias tool and checklist include a unique set of standards for each measurement property type. For example, when assessing a reliability study, standards that reviewers needed to assess included whether there was evidence of patient stability between timepoints and the appropriateness of the time interval between assessments.¹² Each measurement property study was evaluated by scoring all applicable standards as either inadequate, doubtful, adequate or very good. An overall risk of bias score for each measurement property study was determined as the worst score among the applicable standards. We manually assessed the risk of bias independently and in duplicate and resolved conflicts through discussion or with a third reviewer.

Measurement properties

We used the COSMIN Criteria for good measurement properties (V.2.0) for individual studies and across studies.⁴ Using this tool, each measurement property study was assessed as either sufficient (+), indeterminant (?) or insufficient (-). A sufficient rating indicates that the measurement property has good quality, while insufficient indicates poor quality. An indeterminate rating indicates that the measurement property was assessed, but there was insufficient information reported by authors to evaluate the results. Additionally, summarised results of measurement property studies can be classified as sufficient, indeterminate, insufficient or inconsistent (±). An inconsistent rating indicates that some study results were sufficient while others were insufficient.⁴

Table 2 Description of included STS tests

Instrument name	Description	Scores	Minimal important change	Feasibility*	Measurement properties assessed
5-repetition STS	Score: Time to complete five STS Equipment: Chair seat height of 43 cm, ^{28 42} 46 cm ³⁴ or 48 cm ^{19 27 44} Position: Arms across chest ^{19 27 28 31 34 42 44}	>0 s	1.3 to 1.7 s ²⁷	► Fast to perform^{18 20 27 28 30 44} ► Can be performed in small spaces^{18–20 27 28} ► Low cost and basic equipment^{20 27 28 30 34 44} ► Easy to perform^{20 27 42} ► Simple test^{28–30 34} ► Practical^{34 42} ► No true zero^{26 37} ► Suitable for most healthcare and community settings^{27 28}	► Test-retest reliability ► Inter-rater reliability ► Limits of agreement (test-retest) ► Limits of agreement (inter-rater) ► Convergent validity ► Known-groups validity ► Responsiveness
30 s STS	Score: Number of STSs completed in 30 s Equipment: Chair seat height of 43 cm, ²⁸ 45–47 cm, ²⁵ 46 cm, ³⁴ 47 cm ⁴³ or 48 cm ⁴⁴ that would allow both feet to be flat on the floor ¹⁷ Position: Arms across chest ^{25 26 28 34 44}	≥0 repetitions	Two repetitions ^{25 43}	► Fast to perform^{26 28 29 43 44} ► Can be performed in small spaces¹⁷ ► Low cost and basic equipment^{17 28 29 34 43 44} ► Easy to perform^{26 29 43} ► Simple test^{28–29 34} ► Practical^{28 29 34} ► True zero²⁶ ► Suitable for most healthcare and community settings^{27–29 43} ► Functional test¹⁷ ► Less haemodynamic strain compared with 6MWT²⁶	► Inter-rater reliability ► Intrarater reliability ► Limits of agreement (inter-rater) ► Limits of agreement (intrarater) ► Smallest detectable change (inter-rater) ► Smallest detectable change (intrarater) ► SE of measurement (inter-rater) ► SE of measurement (intrarater) ► Convergent validity ► Known-groups validity ► Responsiveness
1 min STS	Score: Number of STSs completed in 1 min Equipment: Chair seat height of 46 cm, ^{23 33–35 37 39–41} 46–48 cm, ^{36 48 cm} ²⁴ Position: Hands on hips ^{23 24 34–37 40} or arms across chest ⁴⁶	≥0 repetitions	1.9–3.5 repetitions ^{40 57}	► Fast to perform^{23 37–39 41 46} ► Can be performed in small spaces²⁴ ► Low cost and basic equipment^{21 23 24 39–41 46} ► Easy to perform^{23 35 37 46} ► Simple test^{23 32 33 36 38 40} ► Practical^{32 41} ► True zero³⁷ ► Suitable for most healthcare and community settings^{23 36 37 39 40} ► Functional test²⁴ ► Less haemodynamic strain compared with 6MWT⁴¹ ► Well tolerated by patients²³ ► Self-paced³⁷	► Test-retest reliability ► Limits of agreement (test-retest) ► Convergent validity ► Known-groups validity ► Responsiveness
3 min STS (non-paced)	Score: Number of STSs completed in 3 min Equipment: Chair seat height of 46 cm ²² Position: Hands either on hips or arms across chest ²²	≥0 repetitions	Unknown	► Easy to perform²² ► Less haemodynamic strain compared with 6MWT³⁵	► Convergent validity ► Responsiveness
3 min STS-12 (semipaced × 12 repetitions)	Score: Number of STSs completed in 3 min with the first minute of test paced at 12 repetitions ¹⁶ Equipment: Chair seat height of 48 cm ¹⁶ Position: Hands on hips ¹⁶	≥12 repetitions	Unknown	► Fast to perform¹⁶ ► Low cost and basic equipment¹⁶ ► Simple test¹⁶ ► Patients will GOLD I–IV able to maintain pace during the first minute¹⁶	► Test-retest reliability

Continued

Table 2 Continued

Instrument name	Description	Scores	Minimal important change	Feasibility*	Measurement properties assessed
3 min STS-15 (sempaced × 15 repetitions)	Score: Number of STSs completed in 3 min with the first minute of test paced at 15 repetitions ¹⁶ Equipment: Chair seat height of 48 cm ¹⁶ Position: Hands on hips ¹⁶	≥15 repetitions	Unknown	▲ Fast to perform ¹⁶ ▲ Low cost and basic equipment ¹⁶ ▲ Simple test ¹⁶ ▲ Patients will GOLD I-IV able to maintain pace during the first minute ¹⁶	Test-retest reliability
3 min STS-20 (sempaced × 20 repetitions)	Score: Number of STSs completed in 3 min with the first minute of test paced at 20 repetitions ¹⁶ Equipment: Chair seat height of 48 cm ¹⁶ Position: Hands on hips ¹⁶	≥20 repetitions	Unknown	▲ Fast to perform ¹⁶ ▲ Low cost and basic equipment ¹⁶ ▲ Simple test ¹⁶ ▲ Patients with GOLD IV COPD unable to follow pace during the first minute ¹⁶	Test-retest reliability

*Feasibility characteristics were extracted from included studies verbatim and reported as such. COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; 6MWT, 6 min walk test; STS, sit-to-stand.

Reliability

Reliability is the extent to which an outcome measure score is consistent in patients who have not changed and is free from measurement error.⁴ Test-retest reliability involves evaluating a patient on two separate occasions.¹³ Similarly, intrarater reliability involves evaluating a patient on two separate occasions where the focus of the study is the effect of the rater on the reliability.¹³ Inter-rater reliability involves multiple raters assessing a patient.¹³ A reliability study was classified as sufficient if the intraclass coefficient or the Pearson/Spearman correlation coefficient was ≥ 0.70 or insufficient if it was below this threshold.⁴

Measurement error

Measurement error represents the error in outcome measurement scores that are not related to true changes in a patient.⁴ Measurement error is expressed in measurement property studies in three ways: limits of agreement, smallest detectable change and SE of measurement. Limits of agreement represent the range between which 95% of the differences between two measurements are expected to fall.¹⁴ Moreover, the smallest detectable change is a change in score that extends beyond the limits of agreement (ie, measurement error).¹³ SE of measurement quantifies the degree of variation between repeated measures of the same assessment (eg, assessing the 5-repetition STS test on the same patient 10 times).¹³ A measurement error study was classified as sufficient if the smallest detectable change or the limits of agreements were less than the minimal important change and insufficient if not. Minimal important change represents the smallest change on an outcome measure that a patient deems important.¹⁵

Hypothesis testing for construct validity

Testing hypotheses for construct validity examines whether the scores from an outcome measure are consistent with expected results based on the belief that the measure validly assesses the intended construct.⁴ Each publication was deemed sufficient if $\geq 75\%$ of its studies were consistent with our hypotheses and insufficient if not. Our hypotheses are outlined in table 1.

Responsiveness

Responsiveness reflects the ability of an outcome measure to detect change over time.¹³ Each publication is deemed sufficient if $\geq 75\%$ of its studies were consistent with our hypotheses and insufficient if not. Our responsiveness hypotheses are outlined in table 1.

Measurement properties were assessed independently and in duplicate with discrepancies resolved through discussion or by a third reviewer.

Synthesis

Reliability

If reliability studies were either all-sufficient or all-insufficient, we summarised them qualitatively. We planned to calculate a pooled point estimate if studies were sufficiently homogeneous;⁶ we modified this approach because pooled point estimates are not typically reported in systematic reviews because they are not used.⁴ If studies were inconsistent, we attempted to identify a reason for this inconsistency; where a reason was identified, we summarised the studies that were consistent.

Measurement error

If measurement properties were sufficient or insufficient, we summarised the range of the point estimates. Where studies were inconsistent, we attempted to identify reasons for inconsistency; where a reason was identified, we summarised the consistent studies.

Hypothesis testing for construct validity

The number of studies which were consistent and inconsistent with our hypotheses was summarised overall and for each hypothesis.

Responsiveness

The total number of studies which were consistent and inconsistent with our hypotheses was totalled and summarised overall

Table 3 Characteristics of included publications

Included publications, n publications	30
Date of publication, n publications (%)	
2005–2009	2 (7)
2010–2014	4 (13)
2015–2019	10 (33)
2020–2024	14 (47)
Study design, n publications (%)	
Prospective cohort	15 (50)
Cross-sectional	13 (43)
Retrospective cohort	1 (3)
Randomised controlled trial	1 (3)
Country, n publications (%)	
Brazil	3 (10)
France	3 (10)
Spain	3 (10)
India	2 (7)
Portugal	2 (7)
Turkey	2 (7)
Switzerland and the Netherlands	2 (7)
Other*	13 (43)
Participants	
Total, N	3225
Median (first, third quartiles)	70.5 (45, 128)
GOLD classification, n (%)†	
I	138 (4)
II	943 (29)
III	589 (18)
IV	395 (12)
Unspecified	1161 (36)
*Canada (n=1), China (n=1), Croatia (n=1), Denmark (n=1), France and Belgium (n=1), Greece (n=1), Italy (n=1), Sweden (n=1), Switzerland (n=1), Tunisia (n=1), the UK (n=1), USA (n=1), Vietnam (n=1).	
†Total adds to 3226 because Correia <i>et al</i> ²⁰ reported GOLD classification for one more participant than their sample size.	
GOLD, Global Initiative for Chronic Obstructive Lung Disease.	

and by each hypothesis. We did not plan or conduct any subgroup analyses or sensitivity analyses.

Certainty of evidence

We used the modified Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence.⁴ Using the modified GRADE approach, two reviewers considered the risk of bias, inconsistency, imprecision and indirectness independently and in duplicate to rate the synthesised results as high, moderate, low or very low quality. Discrepancies were resolved through discussion or with a third reviewer.

Formulating recommendations

Recommendations for the use of each STS test were determined by considering the quality of evidence and measurement property sufficiency. Where high-quality evidence existed that measurement properties were sufficient, the use of that STS test was recommended. Where high-quality evidence suggested that measurement properties were insufficient, recommendations against the use of that STS test were made. Where no high-quality evidence existed or measurement properties were inconsistent, recommendations for further research were made.

RESULTS

After duplicates were removed, we screened 2577 titles/abstracts and assessed 102 full texts for eligibility (figure 1). Twenty-nine full

text publications identified from our database search met eligibility criteria^{16–44} with one additional citation identified by reference list review.⁴⁵ Publications which met some, but not all, eligibility criteria are summarised in online supplemental table 8. Publications which may meet eligibility criteria that were not published in English are summarised in online supplemental table 9. Across the 30 included publications, there were 36 measurement property assessments of seven STS unique tests; the most frequently assessed STS tests were the 1 min STS (n=14; 39%), the 5-repetition STS (n=10; 28%) and the 30 s STS (n=8; 22%) (table 2).

Of the 30 included publications, most were prospective cohort studies (table 3). The median (first to third quartile) sample size of each publication was 70.5 (45–128) participants. Characteristics and results of individual measurement property studies are summarised in online supplemental tables 10–13.

Reliability

Reliability was assessed in all STS tests except the non-paced 3 min STS test. Where assessed, all STS tests had sufficient reliability; however, aside from moderate evidence quality for test-retest reliability of the 1 min STS, all evidence was very low quality (table 4).

Construct validity

Construct validity was assessed in the 5-repetition, the 30 s, the 1 min and the non-paced 3 min STS tests. When results across all hypotheses were aggregated, there was moderate-to-high quality evidence of inconsistent results (table 4). When combining results for hypotheses that assessed the related constructs and largely related constructs, only the 1 min STS test had high-quality evidence of sufficiency (15+, 5–).

Responsiveness

Responsiveness was assessed in the 5-repetition, the 30 s, the 1 min and the non-paced 3 min STS tests (table 4). When results were combined across all assessed hypotheses, most STS tests had low or very low evidence of inconsistent results; however, the 5-repetition test had high evidence of insufficiency. When considering the related constructs, only the 30 s STS test had moderate evidence of sufficiency.

Recommendations

The 1 min STS test had the most robust evidence of construct validity, while the 30 s STS test had the most robust evidence of responsiveness. The use of these tests should be done in consideration of their limitations; not all reliability components were assessed across tests, and when assessed, no reliability results were of high quality.

DISCUSSION

We conducted a comprehensive synthesis of the measurement properties of the STS tests in community-dwelling people with COPD using methods that were consistent with the COSMIN guidelines.⁴ No STS test had all components of each measurement property assessed across the included studies. Where assessed, reliability was sufficient; however, results were generally limited by low evidence certainty. When considering construct validity with comparator measures which assessed the physical functional capacity, muscle strength, physical activity or balance, there was high-quality evidence for 1 min STS test sufficiency. Similarly, when we considered responsiveness with comparator measures which assessed physical functional capacity, there was moderate evidence certainty that the 30 s STS test was sufficient.

The STS test is a simple,^{16 23 28–30 32–34 36 38 40} low-cost test which only requires basic equipment^{16 17 20 21 23 24 27–30 34 39–41 43 44 46} and can be performed in small spaces.^{17–20 24 27 28} Notably, compared with the 5-repetition STS test, the 30 s and 1 min STS tests have a true zero, meaning even patients who cannot complete a single STS repetition can be assessed according to the validated testing procedure.²⁶ Those who cannot complete a single STS repetition cannot complete the 5-repetition STS test. Where shorter tests (eg, 5-repetition STS, 30 s STS) may be more appropriate to assess constructs

Table 4 Summarised results

	5-repetition STS	30 s STS	1 min STS	3 min STS-NP	3 min STS-12	3 min STS-15	3 min STS-20
Summarised result, summarised rating, quality of evidence							
Reliability							
Test-retest	0.79 to 0.97 Sufficient Very low		0.90 to 0.96 Sufficient Moderate		0.82 Sufficient Very low	0.9 Sufficient Very low	0.9 Sufficient Very low
Inter-rater	0.99 Sufficient Very low	0.92 Sufficient Very low					
Intrarater		0.94 Sufficient Very low					
Measurement error							
Limits of agreement							
Test-retest	−10.9 to 7.00 s Insufficient Low		−5.32 to 6.85 reps Inconsistent Moderate				
Inter-rater		−2.3 to 3.6 reps Insufficient Very low					
Intrarater	−0.41 to 0.40 s Sufficient Very low	−2.0 to 2.5 reps Insufficient Very low					
Smallest detectable change							
Test-retest							
Inter-rater		3.15 reps Insufficient Very low					
Intrarater		2.68 reps Insufficient Very low					
SE of measurement							
Test-retest							
Inter-rater		1.14 reps Insufficient Very low					
Intrarater		0.97 reps Insufficient Very low					
Construct validity	19+, 15− Inconsistent High	16+, 6− Inconsistent High	19+, 11− Inconsistent High	1+, 1− Inconsistent Moderate			
Related constructs*	2+, 3− Insufficient High	2+, 1− Inconsistent High	5+, 4− Inconsistent High	0+, 1− Insufficient Moderate			
Largely related constructs†	5+, 6− Insufficient High	6+, 3− Inconsistent High	10+, 1− Sufficient High				
Moderately related constructs‡	5+, 3− Inconsistent High	2+, 1− Inconsistent High	1+, 2− Insufficient High	1+, 0− Sufficient Moderate			
Mortality and exacerbation	2+, 0− Sufficient High		2+, 2− Inconsistent High				
Subgroups	5+, 3− Inconsistent Moderate	6+, 1− Sufficient Low	1+, 2− Insufficient High				
Responsiveness	0+, 1− Insufficient High	1+, 1− Inconsistent Low	1+, 1− Inconsistent Very low	1+, 1− Inconsistent Very low			

Continued

Table 4 Continued

	5-repetition STS	30 s STS	1 min STS	3 min STS-NP	3 min STS-12	3 min STS-15	3 min STS-20
Related constructs*	0+, 1– Insufficient High	1+, 0– Sufficient Moderate	0+, 1– Insufficient Low	0+, 1– Insufficient Low			
Largely related constructs†			1+, 0– Sufficient Very low				
Moderately related constructs‡		0+, 1– Insufficient Moderate		1+, 0– Sufficient Low			
Subgroups							
Reliability summarised results reported as intraclass correlation coefficients. Construct validity and responsiveness summarised results reported as total study results consistent with our hypotheses (+) and total study results not consistent with our hypotheses (–). Empty spaces indicate measurement property not assessed across included studies.							
*Comparator instruments measuring physical functional capacity.							
†Comparator instruments measuring muscle strength, physical activity or balance.							
‡Comparator instruments measuring health-related quality of life, quality of life, dyspnoea, general health.							
NP, non-paced; reps, repetitions; STS, sit-to-stand.							

such as lower limb strength or power, longer tests (eg, non-paced 3 min STS) may be more suited to aerobic capacity constructs. The inconsistent evidence depth between each STS test limits our ability to compare which constructs are best assessed by which test. Given the current evidence, the 1 min STS demonstrated the most robust measurement properties for situations in which an assessor is aiming to assess either physical functional capacity, muscle strength, physical activity or balance at a single point in time. Conversely, if an assessor is aiming to track physical functional capacity change over time, the 30 s STS test has the most robust evidence of responsiveness.

The STS test was first introduced in 1985 to assess lower extremity strength by counting the time to complete 10 STS movements.³ Given the original design of the STS test, it was surprising that none of the included studies assessed the measurement properties of the 10-repetition STS test. Although the original intent of the STS test was to assess muscle strength, only the 1 min STS test had sufficient construct validity when considering the largely related construct (including muscle strength), whereas the 5-repetition and the 30 s STS tests had insufficient or inconsistent results. Our results are similar to a literature review of 17 studies which was conducted prior to the publication of the COSMIN guidelines.⁴⁷ Among the included studies in which patients with COPD were assessed using the STS tests, the reviewers found sufficient reliability for the 5-repetition, the 1 min and the non-paced 3 min STS tests. However, our review appears to be the first to synthesise the reliability results for the 30 s STS test and the semipaced 3 min STS test among this population. Similar to our results, reviewers found variable associations between physical functional capacity (eg, 6 min walk test), muscle strength and balance outcome measures.⁴⁷ Our review advances their work by using the COSMIN guidelines to summarise the results of measurement property studies in the context of their risk of bias, sufficiency and evidence certainty.

Another systematic review assessed the measurement properties of performance-based functional measures among people with chronic respiratory diseases that did not include COPD.⁴⁸ Similar to our results, all STS tests (5-repetition, 30 s, 1 min STS) assessed had sufficient reliability according to the COSMIN criteria for good measurement properties. The 5-repetition STS test had sufficient construct validity among people with interstitial lung disease, asthma and cystic fibrosis. In contrast, the 30 s and the 1 min STS tests were sufficient among people with interstitial lung disease, pulmonary arterial hypertension and cystic fibrosis but not in people with asthma. Where we separated construct validity hypotheses according to similar constructs (ie, muscle strength, physical activity and balance), Zamboti et al⁴⁸ summarised all construct validity assessments together, which can prove challenging to discern which constructs are and which are not associated with the STS test results.

A 2023 systematic review used the COSMIN guidelines to assess the measurement properties of physical functional outcome

measures in different populations with chronic disease, specifically people with chronic kidney disease across the care continuum.⁴⁹ Although they found sufficient reliability for the 30 s and the 1 min STS tests, they found insufficiency for the 5-repetition STS. Similar to our review, they found inconsistent construct validity across the 5-repetition, the 30 s and the 1 min STS tests. Additionally, they summarised the construct validity of all assessments together, and no included studies assessed responsiveness in the STS tests.

Our review has strengths. We published our protocol a priori and conducted the review with methods consistent with current COSMIN guidelines. The body of evidence is limited by many measurement property components that have not been assessed across all STS tests; however, by highlighting these gaps, this review can guide researchers designing measurement studies among community-dwelling participants with COPD. Consistent with COSMIN guidelines, we combined similar constructs into hypothesis groups with the intent of providing a broad understanding of the construct validity of each test. This approach limited our ability to specifically identify which constructs were most associated with each STS test version. Due to the expertise of our review team, we only synthesised results from English studies; however, in our supplementary material, we did summarise non-English studies which were potentially eligible for inclusion such that other research teams can update our findings in the future.

Future research should focus on clarifying inconsistency and improving the certainty of evidence for the 30 s and the 1 min STS tests. Researchers should include assessments of test-retest reliability for the 30 s STS test and inter-rater and intrarater reliability for the 1 min STS test. More than half of construct validity studies were consistent with our related and largely related construct validity hypotheses; however, these findings were deemed inconsistent because combined results didn't total the 75% threshold required by COSMIN to indicate sufficiency. Given our inconsistent construct validity results, researchers should consider conducting construct validity studies of related and largely related constructs to confirm sufficiency or insufficiency of the 30 s and 1 min STS tests. Similarly, because so few studies have evaluated responsiveness, additional research is recommended to further clarify the inconsistent findings regarding the responsiveness of the 30 s and 1 min STS tests. With the extended duration of the non-paced 3 min STS test, it has the potential to be a sufficient test of aerobic capacity in people with COPD. Given the lack of studies of the non-paced 3 min STS test, we believe future studies are warranted to clarify the sufficiency of its measurement properties in this population.

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ORCID iDs

Christopher Farley <https://orcid.org/0009-0002-4979-9098>

Dina Brooks <https://orcid.org/0000-0001-6080-5052>

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ARTIGO ORIGINAL

A associação entre asma materna e função pulmonar diminuída no lactente é atenuada pelo uso de corticosteroides inalados durante a gravidez

Gabriela Martins Costa Gomes,^{1,2} Adam M Collison,^{1,2} Wilfried J J Karmaus,³ Carla Rebeca Da Silva Sena,^{1,2,4} Vanessa E Murphy,^{1,2} Bronwyn K Brew,^{1,2} Tegan Grace,⁵ Paul D Robinson,⁶ Peter D Sly,⁶ Urs Frey,⁴ Philipp Latzin,⁷ Florian Wyler,⁷ Craig E Pennell,^{2,5,8} Peter G Gibson,^{1,9} Joerg Mattes^{1,2,10}

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For numbered affiliations see end of article.

Correspondence to

Professor Joerg Mattes; joerg.mattes@newcastle.edu.au

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RESUMO

Contexto Os lactentes de mães com asma apresentam uma função pulmonar reduzida no início da vida, por razões que permanecem por esclarecer. A associação entre o uso de corticosteroides inalados (ICS) durante a gravidez e a função pulmonar da descendência não tinha sido previamente investigada.

Objetivos Investigar a associação entre o uso de ICS durante a gravidez e a função pulmonar do lactente.

Métodos Foi realizada uma análise de regressão multivariável da função pulmonar dos lactentes às 4–6 semanas de vida (ciclos de fluxo-volume da respiração corrente e capacidade residual funcional — FRC), associada ao uso de ICS durante a gravidez.

Resultados Entre os lactentes nascidos de mães asmáticas, a razão entre o tempo até ao pico de fluxo expiratório tidal e o tempo expiratório total (tPTEF:tE), corrigida pelo volume pulmonar no final da expiração (FRC), foi superior nos lactentes cujas mães utilizaram ICS durante a gravidez, comparativamente às que não utilizaram (n=161 uso de ICS vs n=25 sem ICS; coeficiente 0,06/mL, IC 95% 0,01–0,11, p=0,014). Comparando com um grupo controlo de lactentes nascidos de mães não asmáticas, observou-se uma razão tPTEF:tE/FRC inferior nos lactentes de mães asmáticas que não usaram ICS (n=46 sem asma vs n=25 asma sem ICS; coeficiente –0,08/mL, IC 95% –0,01 a –0,02, p=0,012), mas não nos lactentes de mães asmáticas que usaram ICS (n=46 sem asma vs n=161 asma com ICS; coeficiente –0,02/mL, IC 95% –0,06 a 0,03, p=0,453).

Conclusões A associação entre asma materna e função pulmonar diminuída no lactente foi atenuada nos bebés cujas mães utilizaram ICS durante a gravidez.

Registo do ensaio Australian New Zealand Clinical Trials Registry ACTRN12613000202763.

INTRODUCTION

Asthma is the most common medical condition during pregnancy, affecting up to 17% of pregnancies,¹ with up to 45% of pregnant women with asthma requiring medical care for an exacerbation.^{2,3} Uncontrolled asthma and asthma exacerbations during pregnancy are associated with an increased risk of complications, including preterm birth and increased perinatal morbidity and mortality.^{2,4,5} Maternal asthma during pregnancy is also associated with lower infant lung function and higher prevalence of severe infant bronchiolitis and childhood asthma.^{6–9}

International guidelines recommend that the treatment of asthma during pregnancy should be the same as for non-pregnant women,¹⁰ including the use of inhaled corticosteroids (ICS) as an effective preventive anti-inflammatory medication for long-term asthma management.^{11,12} A recent analy-

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Infants of asthmatic mothers have reduced early lung function and higher respiratory risk. While inhaled corticosteroid (ICS) is recommended for asthma control, its specific impact on infant lung function remains poorly understood.

WHAT THIS STUDY ADDS

► This study provides novel evidence suggesting that maternal use of ICS during pregnancy may protect against reduced lung function in infants at 4–6 weeks of age. These findings indicate that ICS therapy during pregnancy could play a role in enhancing early respiratory health in offspring, potentially reducing the risk of respiratory complications.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► By demonstrating that ICS use during pregnancy may diminish the association between maternal asthma and reduced infant lung function, this study reinforces current asthma management guidelines, informs clinical practice and highlights the need for further research into long-term respiratory outcomes in offspring.

sis including 238 752 pregnant women of whom 13 509 had asthma suggested that the use of ICS during pregnancy significantly decreased odds of preterm birth and neonatal intensive care unit admissions.¹³ Notably, pregnant women with well-managed asthma have perinatal complication rates that are comparable to those without asthma, and their children have similar rates of developing childhood asthma as those born to non-asthmatic mothers.²

We showed in the Managing Asthma in Pregnancy randomised clinical trial that inflammation-guided asthma management during pregnancy was associated with lower asthma prevalence in offspring at 6 years of age, which was mediated by appropriate ICS use during pregnancy.⁷ Thus, asthma during pregnancy and anti-inflammatory preventer medication may affect the child's future respiratory outcomes.^{7,14,15}



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We have previously shown that lung function is reduced in offspring born to women with asthma during pregnancy;⁶ however, the effect of ICS use during pregnancy is unknown. Notably, lung function tracks throughout life and low lung function predisposes to childhood asthma, chronic obstructive pulmonary disease (COPD) and respiratory mortality.^{16–18} Therefore, here we aimed to investigate the effects of ICS use during pregnancy on infant lung function as it may relate to future lung growth trajectories and respiratory health outcomes.

METHODS

Study participants

Pregnant women with physician-diagnosed asthma enrolled in the Breathing for Life Trial (BLT)^{8,19} (from Newcastle and Sydney, Australia), and those without asthma enrolled in the Newcastle 1000 (NEW1000) study²⁰ (Newcastle, Australia) were invited for a follow-up visit with their offspring when infants were 4–6 weeks old. Both prospective birth cohorts employed fully aligned methodologies (see online supplemental material). The inclusion criteria for infant lung function testing required the absence of major birth defects or perinatal diseases that would prevent performing unsedated lung function tests. Additionally, infants attending the visit who experienced any respiratory illness in the 2 weeks prior to testing were rescheduled.

All participants provided written informed consent before participation. Studies were approved by the Hunter New England Local Health District Human Research Ethics Committee (2019/ETH03856, 2020/ETH02881).

Infant lung function

Lung function was performed in unsedated infants during behaviourally defined quiet natural sleep. Testing was performed with the infant lying supine using an infant mask to maintain a tight face seal (Hommedica, Huenenberg, Switzerland), according to the European Respiratory Society/American Thoracic Society (ERS/ATS) standards of infant lung function testing.²¹ Flow was measured using an ultrasonic flow metre (Spirosen; EcoMedics, Duernten, Switzerland). Software package Spiroware V.2 (EcoMedics AG) was used for signal collection.

Tidal breathing flow volume loops (TBFVL) were measured for 90 s to obtain at least 30 good-quality breaths.^{6,22} TBFVL analyses were performed using Wbreath (V.3.28.0; Ndd Medizintechnik). Data were included only if there was no significant volume drift (defined as less than 3 mL/s) throughout the measurement period, after adjusting for environmental conditions, temperature changes and accounting for the mask's dead space volume. Trials with values exceeding the drift threshold were assumed to contain a leak and were excluded from further analysis. Following the TBFVL test, sulfur hexafluoride (SF6) multiple breath washout (MBW) (Spiroware V.2, ExhalyzerD) was performed. During the wash-in phase, the infant breathed a gas mixture containing 4% SF6, 21% O2 and balance N2 until SF6 reached an equilibrium of 4% within the lungs.²³ MBW analyses were accomplished according to Wyler et al.²⁴

The following parameters were extracted from the lung function analysis a priori, based on relevance: respiratory rate, mean tidal volume, minute ventilation, time to inspiratory flow (tI) and time to expiratory flow (tE), time to reach peak tidal expiratory flow (tPTEF) as a percentage of expiratory time (ratio of time to peak tidal expiratory flow to expiratory time (tPTEF:tE), mean inspiratory flow (MTIF), mean expiratory flow (MTEF), functional residual capacity (FRC). To compare differences between expiratory and inspiratory time and flow, we calculated the ratio of tE to tI (tE:tI), the ratio of the mean-tidal expiratory to inspiratory flow (MTEF:MTIF) and the ratio of the peak tidal expiratory to inspiratory flow (PTEF:PTIF). We further calculated the tPTEF:tE for end-expiratory lung volume using FRC. tPTEF:tE was normalised to FRC to account for inter-subject differences in lung volume. In infants, FRC reflects developmental lung size and serves as the physiological baseline for tidal breathing. Unadjusted tPTEF:tE may conflate true airflow patterns with volume-related variability. FRC normalisation isolates intrinsic

expiratory flow dynamics, aligning with ERS/ATS guidelines for infant pulmonary function testing.^{25,26}

ICS use during pregnancy

Maternal ICS use during pregnancy was defined as: (a) a positive report of ICS use at any pregnancy visit or (b) a positive retrospective report of ICS use during pregnancy at the postpartum interview. In the context of our study, ICS initiation or continuation was guided by clinical guidelines and treatment algorithms.⁸

Statistical analyses

Descriptive statistics and regression analysis were performed using Stata IC V.16.1 (Stata Corporation, College Station, Texas, USA). Differences between groups were assessed using χ^2 tests and independent-samples t-test as appropriate. Visual graphs were created using GraphPad Prism software V.10.1.1 (GraphPad Software, San Diego, California, USA).

For our first analysis, we examined the associations of ICS use during pregnancy on the lung function of infants born to asthmatic mothers. These participants were categorised into two groups: those whose mothers used ICS during pregnancy and those who did not, to determine whether maternal ICS use during pregnancy was associated with less offspring lung function impairment. We also performed an inverse probability weighting (IPW) analysis using stabilised weights from a propensity score model including asthma exacerbations during pregnancy, maternal smoking during pregnancy, male sex, first born child and season of birth. The distribution of weights was stable (mean ≈ 1.0 ; 99% between 0.57 and 1.30), so trimming was not applied. Weighted regressions were additionally adjusted for the same a priori covariates described below to provide a doubly robust estimate.

For our second analysis, we compared these two groups of infants born to asthmatic mothers with a reference group of infants born to mothers without asthma and, consequently, without ICS use during pregnancy, to assess whether maternal ICS use during pregnancy could improve offspring lung function and be comparable to that of infants born to non-asthmatic mothers. Infants born to non-asthmatic mothers from the same geographical population were chosen as a reference group due to their clinical relevance, providing a well-established baseline for comparing the effects of maternal asthma and ICS use on infant lung function. All infant lung function parameter ratios were analysed through regression analysis. Regressions were adjusted for a priori covariates associated with infant lung function,^{6,27} including asthma exacerbation during pregnancy, maternal smoking during pregnancy, caesarean section, preterm birth, season of birth, birth weight, first born child, male sex, weight at time of lung function test, breastfeeding at time of lung function test, and hospital admission due to bronchiolitis before lung function test. To assess the trend across groups, we calculated a linear trend in outcomes starting from the reference group. Analyses were further stratified by the offspring's sex. For all analyses, statistical significance was considered when p value < 0.05 . Additional details on methods are provided in the online supplemental data.

RESULTS

Lung function data analysed in study populations

From May 2014 to December 2019, 590 infants were born to women with asthma during pregnancy and attended lung function follow-ups. Of these, 333 infants successfully completed TBFVL tests and had ICS data, and 186 of those had both TBFVL and FRC data, with ICS data available (online supplemental figure 1).

Infants born to mothers without asthma were included between November 2021 and September 2023, with 129 attending follow-ups. Of those, 92 successfully completed TBFVL tests and 46 with both TBFVL and FRC data (online supplemental figure 1).

In total, we therefore analysed TBFVL data from 425 infants. Of these, 54 (12.7%) were born to women with asthma during pregnancy who did not use ICS and 279 (65.6%) were born to women with asthma during pregnancy who used ICS. Further, 92 infants (21.6%) were born to women without asthma during pregnancy (online supplemental table 1).

Additionally, we separately analysed combined TBFVL and FRC data from 232 infants. Among them, 46 (19.8%) were born to women with asthma during pregnancy who did not use ICS and 161 (69.4%) were born to mothers with asthma during pregnancy who used ICS. 25 (10.8%) were born to women without asthma during pregnancy.

Baseline characteristics of study populations

Characteristics of the 425 infants included in analyses are provided in table 1. Asthmatic women who used ICS during pregnancy had a higher rate of uncontrolled asthma and asthma exacerbations compared with those who did not use ICS (table 1), in line with what is observed in unselected asthma populations.

Univariate analyses and group comparisons investigating the association between infant lung function and ICS use during pregnancy

The tPTEF:tE was not statistically different between infants born to asthmatic women with vs without ICS use during pregnancy

(n=333 with TBFVL data; online supplemental table 2). FRC was also not significantly different between these groups (n=186, table 2). However, when tPTEF:tE was corrected for end-expiratory lung volume using FRC to account for variations in lung volume, a significant difference was observed between ICS use during pregnancy and no ICS use (n=186 with TBFVL and FRC data; coefficient 0.30, 95% CI 0.05 to 0.55, p=0.019) (figure 1, tables 2 and 3). This improved precision aligns with a positive correlation between tPTEF:tE and FRC (p=0.043; online supplemental figure 2).

In a separate analysis using independent t-test comparing infants born to mothers with asthma during pregnancy to those without maternal asthma, tPTEF:tE was significantly different between groups (asthma in pregnancy and no ICS use vs no asthma p=0.0001; asthma in pregnancy and ICS use vs no asthma p=0.00001) (online supplemental table 2). After correcting tPTEF:tE for FRC, no significant difference was found between infants of non-asthmatic mothers and those offspring whose mothers used ICS during pregnancy (p=0.507). In contrast, a significant difference in tPTEF:tE corrected for FRC was observed between infants of non-asthmatic

Table 1 Baseline characteristics of all infants with tidal breathing data and FRC data, born to mothers with and without asthma, stratified by maternal ICS use during pregnancy in the asthma group						
Total cohort with tidal breathing and FRC data (n=232)						
	Maternal asthma (n=186)		P value*	No maternal asthma (n=46)		P value‡
	No ICS use during pregnancy (n=25)	ICS use during pregnancy (n=161)			P value†	
GINA - Uncontrolled maternal asthma at recruitment n (%)	1 (4.0)	75 (46.6)	0.000001	–	–	–
Asthma exacerbation during pregnancy n (%)	2 (8.0)	42 (26.1)	0.048	–	–	–
Maternal smoking during pregnancy n (%)	3 (12.0)	23 (14.3)	0.759	0 (0.0)	0.016	0.007
First born n (%)	14 (56.0)	90 (55.9)	0.993	25 (54.4)	0.894	0.852
Preterm birth n (%)	1 (4.0)	13 (8.1)	0.472	2 (4.4)	0.945	0.390
Male n (%)	15 (60.0)	80 (49.7)	0.337	30 (65.2)	0.663	0.063
Caesarean section n (%)	7 (28.0)	49 (30.4)	0.805	19 (41.3)	0.266	0.166
Season of birth:			0.491		0.030	0.003
Winter n (%)	6 (24.0)	38 (23.6)		1 (2.2)		
Spring n (%)	4 (16.0)	42 (26.1)		10 (21.7)		
Summer n (%)	7 (28.0)	49 (30.4)		19 (41.3)		
Autumn n (%)	8 (32.0)	32 (19.9)		16 (34.8)		
Gestational age in weeks§	39.1 (2.0)	39.4 (1.9)	0.454	39.5 (1.7)	0.355	0.623
Birth weight in kg§	3.3 (0.7)	3.5 (0.7)	0.576	3.4 (0.6)	0.802	0.740
Age at lung function test in weeks§	6.0 (3.0)	6.0 (1.0)	0.993	6.4 (0.6)	0.819	0.715
Weight at lung function test in kg§	4.9 (0.9)	4.8 (0.8)	0.961	4.7 (0.7)	0.213	0.096
Length at lung function test in cm§	56.5 (4.0)	56.5 (3.5)	0.833	56.0 (3.0)	0.682	0.779
Weight gain from birth until lung function test date in kg§	1.5 (0.6)	1.4 (0.7)	0.545	1.3 (0.7)	0.066	0.096
Breastfeeding until test date n (%)	15 (60.0)	117 (72.7)	0.194	44 (95.7)	0.0001	0.001
Bronchiolitis hospitalisation prior to lung function test n (%)	0 (0.0)	2 (1.3)	0.789	1 (2.2)	0.458	0.645
Groups were compared using either a T-test or a χ^2 test as appropriate. P value <0.05 in bold.						
GINA, Global initiative for Asthma. Uncontrolled asthma defined as ≥ 3 of the following in the past 4 weeks: daytime symptoms >2x/week, night waking due to asthma, SABA use >2x/week, or activity limitation due to asthma.						
*Comparison of maternal asthma during pregnancy between those who used ICS versus those who did not.						
†Comparison of no maternal asthma versus maternal asthma without ICS use during pregnancy.						
‡Comparison of no maternal asthma versus maternal asthma with ICS use during pregnancy.						
§Values show median (IQR).						
FRC, functional residual capacity; ICS, inhaled corticosteroid.						

mothers and those whose mothers had asthma but did not use ICS ($p=0.008$) (figure 1, table 2).

Multivariable regression analysis investigating the association between infant lung function and ICS use during pregnancy

In the population of infants that had both TBFVL and FRC data ($n=186$), impaired lung function was less prominent in infants of mothers with asthma who used ICS during pregnancy compared with those who did not (MTEF:MTIF: coefficient 0.07, 95% CI 0.002 to 0.15, $p=0.043$; tE:tl: coefficient -0.12 , 95% CI -0.22 to -0.02 , $p=0.019$; tPTEF:tE: coefficient 4.04, 95% CI 0.38 to 7.71, $p=0.031$; tPTEF:tE:FRC: coefficient 0.06, 95% CI 0.01 to 0.11, $p=0.014$) (table 3). An IPW sensitivity analysis confirmed these findings, showing that ICS use during pregnancy remained significantly associated with less impaired infant lung function (online supplemental table 3).

The data were then stratified by the offspring's sex, and a significant association with less impaired lung function was observed in male offspring born to mothers who used ICS during pregnancy (online supplemental table 4).

Including data from infants born to women without asthma used as the reference group ($n=92$ with TBFVL data only, $n=25$ with FRC data also), there was a significant trend showing less impaired lung function in infants of women who used ICS during pregnancy compared with infants of women who did not use ICS (MTEF:MTIF: trend coefficient -0.03 , 95% CI -0.06 to 0.002 , $p=0.034$; PTEF:PTIF: trend coefficient -0.03 , 95% CI -0.06 to -0.0001 , $p=0.049$; tE:tl: trend coefficient 0.05, 95% CI 0.01 to 0.10, $p=0.022$; tPTEF:tE: trend coefficient -3.44 , 95% CI -5.14 to -1.74 , $p=0.0001$) (online supplemental table 5) as well as within the subgroup with TBFVL and FRC data (tE:tl: trend coefficient 0.07, 95% CI 0.01 to 0.12, $p=0.025$; tPTEF:tE: trend coefficient -4.68 , 95% CI -6.97 to -2.39 , $p=0.0001$) (table 4). In addition, compared with the reference group, there was a significantly lower tPTEF:tE to FRC ratio in infants born to asth-

matic mothers without ICS use (coefficient -0.08 , 95% CI -0.01 to -0.02 , $p=0.012$) but not in infants born to asthmatic mothers with ICS use (coefficient -0.02 , 95% CI -0.06 to 0.03 , $p=0.453$) (table 4).

The data were stratified by the offspring's sex and significant trends towards less impaired lung function were observed in both female and male offspring born to mothers who used ICS during pregnancy, specifically for tPTEF:tE (male: trend coefficient -3.00 , 95% CI -5.27 to -0.72 , $p=0.010$; female: trend coefficient -3.96 , 95% CI -6.61 to -1.32 , $p=0.004$) (online supplemental table 6). The tPTEF:tE corrected for FRC trended significantly towards less impaired lung function only in male offspring (trend coefficient -0.04 , 95% CI -0.08 to -0.01 , $p=0.013$) (online supplemental table 7).

DISCUSSION

We demonstrated that ICS use during pregnancy was associated with significant differences in the offspring's lung function outcomes. Our analysis revealed that, compared with the reference group of babies born to mothers without asthma, infants born to women who did not use ICS during pregnancy exhibited statistically significant lower tPTEF:tE corrected for FRC in univariate and multivariable analyses. Additionally, there were significant trends indicating that the association between maternal asthma and impaired infant lung function was diminished in infants whose mothers used ICS during pregnancy, compared with those who did not use ICS, relative to the reference group without asthma. Notably, there were no significant differences between infants born to mothers without asthma versus those born to mothers with asthma who used ICS during pregnancy for tPTEF:tE corrected for FRC. This suggests that ICS use may improve aspects of infant lung function to a level that is observed in infants born to mothers without asthma. This benefit was predominantly observed in male offspring.

There are limited data on the effects of gestational corticosteroid exposure on respiratory outcomes. Antenatal systemic corticoids

Table 2 Baseline characteristics of lung function parameters in infants with tidal breathing data and FRC data, born to mothers with and without asthma, stratified by maternal ICS use during pregnancy in the asthma group

Total cohort with tidal breathing and FRC data (n=232)					
	Maternal asthma (n=186)		No maternal asthma (n=46)		
	No ICS use during pregnancy (n=25)	ICS use during pregnancy (n=161)		P value*	P value†
TV, mL/kg	7.0 (1.2)	6.7 (1.8)	7.6 (1.2)	0.210	0.00001
V'E, mL/kg	316.6 (94.2)	293.9 (77.9)	323.0 (63.2)	0.763	0.004
RR, min	43.3 (7.7)	45.7 (12.3)	41.9 (11.8)	0.413	0.259
MTEF, mL/s/kg	9.0 (3.2)	8.7 (2.7)	9.6 (2.1)	0.675	0.021
PTEF, mL/s/kg	13.0 (4.2)	12.6 (4.3)	14.0 (4.5)	0.897	0.108
MTIF, mL/s/kg	12.3 (1.9)	11.4 (3.0)	12.5 (2.6)	0.156	0.004
PTIF, mL/s/kg	16.8 (3.0)	16.1 (4.2)	17.3 (3.3)	0.225	0.045
tE, sec	0.8 (0.2)	0.7 (0.3)	0.8 (0.3)	0.311	0.694
tl, s	0.6 (0.1)	0.6 (0.1)	0.6 (0.2)	0.770	0.216
FRC, mL/kg	17.8 (4.8)	17.5 (3.7)	19.1 (2.8)	0.153	0.0002
Ratios					
MTEF:MTIF	0.7 (0.2)	0.8 (0.2)	0.8 (0.2)	0.079	0.934
PTEF:PTIF	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)	0.196	0.964
tE:tl	1.3 (0.3)	1.3 (0.3)	1.2 (0.3)	0.063	0.595
tPTEF:tE	28.9 (9.7)	31.9 (11.3)	36.1 (17.0)	0.045	0.0007
tPTEF:tE corrected for FRC	1.5 (0.6)	1.8 (0.8)	1.9 (0.8)	0.019	0.507

Values show median (IQR). T-test used to compare groups. P value <0.05 in bold.

*Comparison of maternal asthma during pregnancy between those who used ICS versus those who did not.

†Comparison of no maternal asthma versus maternal asthma without ICS use during pregnancy.

‡Comparison of no maternal asthma versus maternal asthma with ICS use during pregnancy.

tPTEF:tE, time to peak tidal expiratory flow divided by total expiratory time. FRC, functional residual capacity; ICS, inhaled corticosteroid; MTEF, mean tidal expiratory flow; MTEF:MTIF, ratio of the mean-tidal expiratory to inspiratory flow; MTIF, mean tidal inspiratory flow; PTEF, peak tidal expiratory flow; PTEF:PTIF, ratio of the peak tidal expiratory to inspiratory flow; PTIF, peak tidal inspiratory flow; RR, respiratory rate; tE, expiratory time; tE:tl, ratio of tE to tl; tl, inspiratory time; TV, tidal volume; V'E, minute ventilation.

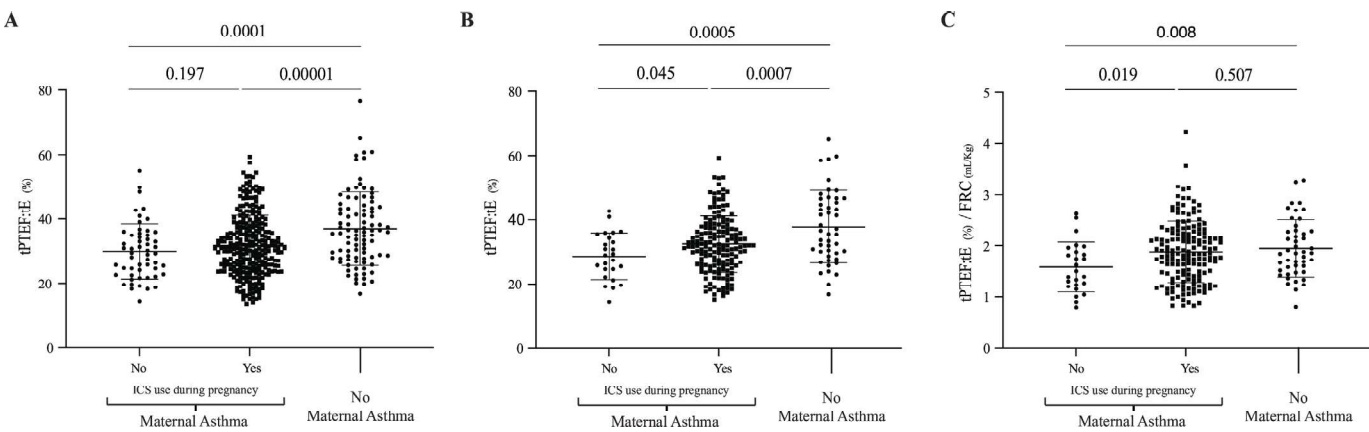


Figure 1 Infant lung function data analysed based on maternal asthma status and ICS use during pregnancy. (A) tPTEF:tE for n=425 infants with TBFVL data available, (B) tPTEF:tE and (C) tPTEF:tE/FRC for n=232 infants with TBFVL and FRC data available. Each data point represents a single participant. Graphs show the median and SD. Statistical significance was assessed using T-test. FRC, functional residual capacity; ICS, inhaled corticosteroids; tE, time to expiratory flow; tPTEF, time to reach peak tidal expiratory flow; tPTEF:tE, ratio of time to peak tidal expiratory flow to expiratory time.

teroid use during pregnancy reduced the incidence and severity of respiratory distress syndrome in preterm infants, primarily by accelerating lung maturation, as these corticosteroids can cross the placenta.²⁸ However, research also indicates that while structural changes from corticosteroid exposure can improve lung function shortly after birth, such exposure may result in fewer but larger alveoli, which can ultimately compromise the total surface area available for effective gas exchange.²⁹ Of note, daily ICS doses used for asthma treatment are much lower in comparison to corticosteroid doses given antenatally with imminent preterm birth. This may explain why no significant effects of ICS on FRC as a surrogate for lung size were observed in this study. ICS maintenance therapy in pregnancy may reduce type 2 and eosinophilic inflammation in the airways, as well as blood eosinophilia.³⁰ Maternal blood eosinophil levels may interfere with lung development and airway function.³¹ In murine models, allergic airway disease during pregnancy promoted fetal eosinophilia through maternal interleukin 5 (IL-5) crossing the placenta, which increased airway sensory innervation and bronchoconstriction in the offspring.³² We therefore speculate that ICS use during pregnancy may directly influence lung function in the offspring through reduced maternal IL-5 crossing the placenta. Other type 2 cytokines may also be relevant, as it has been shown in a murine model that maternal asthma has long-term effects on the activation of fetal lung type 2 innate lymphoid cells (ILC2s).³³ This may be of relevance to lung

development as increased numbers of ILC2s in cord blood correlated with lower infant lung function.³⁴ Furthermore, the levels of a number of protein markers including interferon gamma, matrix metalloproteinase-9, platelet-derived growth factor, beclin-1, sir-tuin 1, ubiquitin-binding protein sequestosome 1 were altered in cord blood plasma from offspring born to women with asthma during pregnancy,¹⁵ and their expression may be modified by ICS use. The measurement of flow variables during naturally occurring sleep in young infants, specifically through tidal breathing, has been extensively studied and validated.²¹⁻³⁵ Clinically, altered tidal breathing flow-volume parameters have been observed in infants with acute viral bronchiolitis admitted to the intensive care unit.³⁶ Lower tPTEF:tE ratios in infancy have been associated with structural airway abnormalities, as assessed by high-resolution CT, including smaller inner and outer diameters, total area, luminal area and wall area at age 26 years.³⁷ Structural and functional lung deficits acquired in early life track into adulthood and predispose individuals to severe infant bronchiolitis, childhood asthma, early-onset chronic obstructive pulmonary disease and premature death.¹⁶⁻¹⁸ This study presents results from two groups: a larger group with only TBFVL data, where some babies did not sleep throughout the entire lung function appointment, limiting the collection of additional data and a smaller group with both TBFVL and FRC measurements, allowing accurate FRC extraction. While both

Table 3 Linear regression analyses of infant lung function parameters in infants with tidal breathing data and combined tidal breathing and FRC data, born to mothers with asthma during pregnancy				
	Total cohort with tidal breathing data (n=333)		Total cohort with tidal breathing and FRC data (n=186)	
	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
ICS use during pregnancy	Crude regression analysis	Multivariable analysis*	Crude regression analysis	Multivariable analysis*
MTEF:MTIF	0.04 (−0.01 to 0.09) 0.080	0.04 (−0.01 to 0.09) 0.104	0.06 (−0.01 to 0.13) 0.079	0.07 (0.002 to 0.15) 0.043
PTEF:PTIF	0.03 (−0.02 to 0.08) 0.194	0.04 (−0.01 to 0.08) 0.153	0.05 (−0.02 to 0.12) 0.196	0.06 (−0.01 to 0.14) 0.097
tE:tl	−0.07 (−0.12 to 0.01) 0.071	−0.06 (−0.13 to 0.01) 0.106	−0.10 (−0.20 to 0.01) 0.063	−0.12 (−0.22 to −0.02) 0.019
tPTEF:tE	1.79 (−0.93 to 4.51) 0.197	1.84 (−0.96 to 4.63) 0.197	3.75 (0.09 to 7.41) 0.045	4.04 (0.38 to 7.71) 0.031
tPTEF:tE corrected for FRC	—	—	0.30 (0.05 to 0.55) 0.019	0.06 (0.01 to 0.11) 0.014
*Multivariable analysis adjusted for asthma exacerbation during pregnancy, maternal smoking during pregnancy, caesarean section, preterm birth, season of birth, birth weight, first born child, male sex, weight at time of lung function test, breastfeeding at time of lung function test and hospital admission due to bronchiolitis before lung function test. P value <0.05 in bold.				
FRC, functional residual capacity; ICS, inhaled corticosteroid; MTEF, mean tidal expiratory flow; MTEF:MTIF, ratio of the mean-tidal expiratory to inspiratory flow; MTIF, mean tidal inspiratory flow; PTEF, peak tidal expiratory flow; PTEF:PTIF, ratio of the peak tidal expiratory to inspiratory flow; PTIF, peak tidal inspiratory flow; tE, expiratory time; tl, inspiratory time; tPTEF:tE, time to peak tidal expiratory flow divided by total expiratory time.				

groups offer valuable insights, the latter allows more precise analysis, accounting for variations in lung volume that could influence respiratory mechanics. Since lung volume differs among infants, this can confound lung function interpretation. While tPTEF:tE is traditionally analysed on its own, we normalised it to FRC to account for potential lung volume confounders, analogous to the use of maximal expiratory flow at FRC (VmaxFRC) in infant pulmonary function testing.^{26 37} By using FRC as a baseline measure of lung capacity and adjusting for it, we aimed to ensure that observed differences in lung function reflect true physiological differences in respiratory flow patterns, rather than disparities in lung size. This improves cross-infant comparisons and clarifies how maternal asthma and ICS use in pregnancy influence infant lung function. Differences in tPTEF:tE corrected for FRC between infants born to mothers who used ICS versus those who did not use ICS during pregnancy can therefore be attributed to the increased precision of combining TBFVL and FRC, likely resulting in more robust results. The approach is further supported by a statistically significant correlation between tPTEF:tE and FRC, reinforcing the validity of the volume-corrected metric.

Interestingly, our earlier studies suggested that infant lung function is lower in male as compared with female offspring of mothers with asthma during pregnancy.⁶ Again, here we show that ICS use during pregnancy is associated with a less impairment in tPTEF:tE corrected for FRC in male infants. The placenta, as a fetal tissue, exhibits sex-specific differences, most notably in the expression of 11 β -hydroxysteroid dehydrogenase type 2 (HSD2), an enzyme that regulates steroid transport to the fetus. Male placentas tend to have lower 11 β -HSD2 expression compared with female placentas, resulting in increased exposure of male fetuses to maternal corticosteroids under equivalent maternal exposure conditions. This finding aligns with previous research showing that antenatal corticosteroid therapy has a more pronounced positive effect in male preterm infants, including reductions in mortality and early respiratory morbidity.³⁸ Research has shown sex-specific alterations in placental 11 β -HSD2 activity following antenatal betamethasone administration, which influenced early postnatal outcomes.³⁹ Similarly, it was reported differential placental 11 β -HSD2 expression in response to maternal glucocorticoid exposure, mediating sex differences in fetal development.⁴⁰ Together, these studies underscore the critical role of placental sex-specific adaptations in shaping fetal responses to maternal steroid therapies. There are several important considerations in our study.

Analyses were based on available participant data from the BLT and NEW1000 cohorts. While no formal sample size calculation was performed, the study included a sufficient number of participants to detect clinically relevant differences in infant lung function across exposure groups. Additionally, the control infants were born between 2021–2023, whereas the index group was recruited between 2014–2019, potentially exposing them to different environmental factors such as respiratory syncytial virus (RSV) circulation. To account for this, hospital admission due to bronchiolitis prior to lung function testing was included in the models to reduce cohort-related bias. Both cohorts followed the same methodology for data collection and infant lung function testing, using standardised protocols and equipment, which helps ensure consistency and comparability between groups. Maternal ICS use during pregnancy was based on self-report, collected either prospectively or retrospectively, which may introduce reporting bias. However, the use of structured clinical assessments and consistency across reports likely minimised misclassification.

In our study, we did not find any direct effects of asthma exacerbations on infant lung function. In addition, asthma exacerbations during pregnancy were more prevalent in the ICS group. This is in line with a recent study showing the highest exacerbation rates in those pregnant women on preventer maintenance therapy who also had favourable pregnancy outcomes.¹³ The observed improvement in infant lung function associated with ICS use was not a direct result of reduced asthma exacerbations but other clinical or biological effects that are influenced by ICS use, including reduced maternal T2 inflammation. Our current study highlights the need

Table 4 Linear regression analyses of infant lung function parameters in infants with tidal breathing data and FRC data, based on maternal asthma status and ICS use during pregnancy

Multivariable analysis*	MTEF:MTIF (n=232)			PTEF:PTIF (n=232)			tE:tI (n=232)			tPTEF:tE (n=232)			tPTEF:tE corrected for FRC (n=232)		
	Coefficient (95% CI)	P value	P value trend	Coefficient (95% CI)	P value	P value trend	Coefficient (95% CI)	P value	P value trend	Coefficient (95% CI)	P value	P value trend	Coefficient (95% CI)	P value	P value trend
Maternal asthma															
No ICS use during pregnancy	-0.07 (-0.15 to 0.02)	0.110	-0.03 (-0.07 to 0.01)	-0.07 (-0.16 to 0.01)	0.099	-0.03 (-0.08 to 0.01)	0.15 (0.03 to 0.26)	0.07 (0.01 to 0.12)	0.07 (0.01 to 0.12)	-9.16 (-13.83 to -4.49)	0.0001	0.07 (0.01 to 0.12)	-0.08 (-0.01 to -0.02)	-0.08 (-0.01 to -0.02)	-0.03 (-0.06 to -0.01)
Maternal asthma ICS use during pregnancy	0.01 (-0.05 to 0.06)	0.833	0.184	-0.01 (-0.07 to 0.05)	0.666	0.129	0.015 (0.003 to 0.026)	0.025 (0.01 to 0.04)	0.025 (0.01 to 0.04)	-5.22 (-8.52 to -1.92)	0.002	0.025 (0.01 to 0.04)	0.012 (-0.06 to 0.03)	0.012 (-0.06 to 0.03)	0.019 (-0.06 to -0.01)
No maternal asthma	0 (Reference)			0 (Reference)			0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)		0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)

*Multivariable analysis included a defined reference group of infants born to mothers without asthma during pregnancy and who did not use ICS and was adjusted for asthma status and ICS use during pregnancy, asthma exacerbation during pregnancy, maternal smoking during pregnancy, caesarean section, preterm birth, season of birth, birth weight, first born child, male sex, weight at time of lung function test, breastfeeding at time of lung function test and hospital admission due to bronchiolitis before lung function test. P value <0.05 in bold. FRC, functional residual capacity; ICS, inhaled corticosteroid; MTEF, mean tidal expiratory flow; MTIF, mean tidal inspiratory flow; PTEF:PTIF, ratio of the peak tidal expiratory to inspiratory flow; tE, expiratory time; tI, inspiratory time; tPTEF:tE, time to peak tidal expiratory flow divided by total expiratory time.

for further investigations into the role of ICS during pregnancy and offspring outcomes, as we lack information on the timing, dosage and cumulative exposure to ICS. Further studies will also be necessary to provide additional mechanistic insights.

Together, we show that the association between maternal asthma and impaired infant lung function is diminished with ICS use during pregnancy, which may positively impact respiratory health in the long term.

Author affiliations

¹Asthma and Breathing Research Program, The University of Newcastle Hunter Medical Research Institute, Newcastle, New South Wales, Australia

²School of Medicine and Public Health, The University of Newcastle, Newcastle, New South Wales, Australia

³School of Public Health, The University of Memphis, Memphis, Tennessee, USA

⁴University Children's Hospital Basel UKBB, University of Basel, Basel, Switzerland

⁵Mothers & Babies Research Program, The University of Newcastle Hunter Medical Research Institute, Newcastle, New South Wales, Australia

⁶Children's Health and Environment Program, Child Health Research Centre, The University of Queensland, South Brisbane, Queensland, Australia

⁷Division of Paediatric Respiratory Medicine and Allergology, Department of Paediatrics, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

⁸Maternity & Gynaecology Department, John Hunter Hospital, Newcastle, New South Wales, Australia

⁹Respiratory & Sleep Medicine Department, John Hunter Hospital, Newcastle, New South Wales, Australia

¹⁰Paediatric Respiratory & Sleep Medicine Department, John Hunter Children's Hospital, Newcastle, New South Wales, Australia

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Contributors GMCG reviewed data quality, prepared and analysed data, prepared figures and tables. JM conceived the project. JM, AMC and WK supervised the analysis. PGG, VM and JM conducted the Breathing for Life Trial (BLT) pregnancy study; CP and TG conducted the NEW1000 study; JM, PDR, PDS, VM, PGG, AMC, GMCG and CRSS conducted BLT and NEW1000 infant follow-up. BB prepared the BLT data set. WK provided epidemiological and statistical guidance. UF, PL and FW analysed multiple breath washout data. GMCG, AMC and JM wrote a draft manuscript and figures; all authors edited the final version of the manuscript. JM is the guarantor and accepts full responsibility for the work, including the data, analysis and decision to publish.

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ORCID iDs

Gabriela Martins Costa Gomes <https://orcid.org/0000-0002-9807-7211>

Adam M Collison <https://orcid.org/0000-0002-3074-3046>

Carla Rebeca Da Silva Sena <https://orcid.org/0000-0002-6424-7796>

Vanessa E Murphy <https://orcid.org/0000-0003-3282-1324>

Paul D Robinson <https://orcid.org/0000-0001-7397-105X>

Peter D Sly <https://orcid.org/0000-0001-6305-2201>

Urs Frey <https://orcid.org/0000-0003-3773-2822>

Florian Wyler <https://orcid.org/0000-0002-1232-1392>

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ARTIGO ORIGINAL

O IMC materno e o tabagismo explicam parcialmente a associação entre a posição socioeconômica materna e a asma na descendência

Cecilia Lundholm,¹ Emma Caffrey Osvald,^{1,2} Samuel Rhedin,^{1,3} Catarina Almqvist^{1,2}

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¹Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

²Astrid Lindgren Children's Hospital, Paediatric Allergy and Pulmonology Unit, Karolinska University Hospital, Stockholm, Sweden

³Sachska Children's and Youth Hospital, Stockholm, Sweden

Correspondence to
Dr Cecilia Lundholm;
cecilia.lundholm@ki.se

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RESUMO

Contexto Numerosos estudos identificaram associações entre a posição socioeconômica (SEP) dos pais e a asma na descendência. A obesidade e o tabagismo durante a gravidez (SDP) são mais prevalentes em grupos com SEP mais baixa e foram identificados como fatores de risco para asma infantil.

Objetivo Explorar e quantificar o papel dos fatores de risco modificáveis — obesidade, índice de massa corporal (IMC) e SDP — na associação entre SEP materna e asma na descendência.

Métodos Este estudo de coorte sueco, baseado em registros, incluiu 1 265 933 crianças nascidas entre 2006 e 2018, com informação sobre asma aos 3 e 6 anos de idade obtida do National Patient Register e do Swedish Prescribed Drug Register. A escolaridade materna foi utilizada como medida de SEP. Utilizamos regressão logística para estimar as associações exposição–resultado e aplicamos a abordagem contrafactual para análise de mediação, de forma a estimar a proporção da associação SEP materna–asma na descendência que poderia ser explicada pela obesidade materna, IMC e SDP, com e sem ajuste para ano de nascimento.

Resultados O OR foi de 1,15 (IC 95% 1,13–1,16) para a associação entre escolaridade materna e asma aos 3 anos, sendo ligeiramente inferior aos 6 anos (OR 1,09; IC 95% 1,07–1,10). Dos riscos acrescidos, 20%–30% puderam ser explicados pela obesidade ou IMC através de mediação e interação mediada, enquanto 15%–20% puderam ser explicados pelo SDP.

Conclusão Os resultados indicam que apoiar mulheres jovens e futuras mães a manter um peso saudável e a abster-se de fumar, especialmente durante a gravidez, pode reduzir a morbidade infantil e melhorar a equidade em saúde na infância.

INTRODUCTION

Social determinants, such as the conditions in which people are born and live, and people's access to power, money and resources influence health outcomes.¹ Moreover, children of parents with low socio-economic position (SEP) have worse health outcomes than those whose parents have higher education and income, also in high-income countries with universal healthcare such as Sweden.² Health inequity is also seen in asthma. Numerous studies have observed an association between parental SEP and childhood asthma.³

SEP has been measured in many different ways in health research, including housing conditions, education, income, occupation and composite measures.^{4,5} There is no SEP indicator that is the preferred measure for all study aims and all settings.⁵ While education can be viewed as a measure of the knowledge-related assets of a person,

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- There is evidence that children of parents with lower socio-economic position have a higher risk of developing asthma than other children.

WHAT THIS STUDY ADDS

- We show that 15%–30% of this excess risk can be explained by the modifiable risk factors of maternal obesity and smoking during pregnancy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Our results indicate that supporting mothers-to-be to healthy weight and smoking cessation has the potential to reduce childhood health inequity regarding asthma.

income reflects the material assets. Income is more volatile than other measures and can change due to health problems and having children. Education is often completed in early adulthood and influenced by parental characteristics, and thereby it can also be viewed as a generic measure of SEP.⁵ We have previously shown evidence of low education being associated with a higher risk of asthma after 1 year of age in Sweden, but not low income.^{6,7}

Social inequalities tend to be persistent also in modern welfare states.⁸ It is therefore important to find downstream factors that can be targeted to reduce common chronic disease such as asthma and other health disparities among children.

The impact of social determinants on a child's health outcomes is present already in pregnancy, through maternal health, environment and lifestyle. In Sweden, as in many other countries, women are monitored by healthcare professionals during the pregnancy. Pregnant women are also usually concerned about the health of the expected child. Therefore, the pregnancy period could be a window of opportunity to intervene on risk factors affecting both the mother and the expected child.

Maternal smoking^{9,10} and obesity^{11,12} in pregnancy have both been identified as risk factors for offspring asthma, both in original articles and systematic reviews. Those are also more commonly

seen in women with low education compared with women with higher education.¹³ Mediation analysis can help in finding what factors to target with interventions, by providing estimates of how large a part of the association between SEP and childhood asthma can be explained by those factors and to what extent they interact with SEP.

Our aim was to investigate the role of the modifiable risk factors such as maternal obesity and smoking during pregnancy (SDP) as mediators in the association between maternal education and offspring asthma.

METHODS

In this population and register-based cohort study, we included all children born in Sweden from 1 January 2006 to 31 December 2018 (n=1 367 272) according to the Register of the Total Population (RTP), which holds information on birth date, death date, sex and parents' identity for all Swedish residents.¹⁴ Since the mediators of interest were retrieved from the Medical Birth Register (MBR),¹⁵ we excluded children not recorded in the register (n=55 953). We also excluded children with missing identity of the mother (n=91), mothers not registered as resident in Sweden (n=121), those with missing information on mother's education (n=30 263), children who emigrated (n=11 453) or died (n=3 458) before age 3 years according to the RTP, leaving us with a cohort of n=1 265 933 children. The registers could be linked unambiguously based on the unique personal identity number given to each person residing in Sweden.¹⁶

All data we retrieved from the registries were pseudonymised by the register holders.

Exposure

We used maternal education as a measure of SEP rather than other measures such as income, since we wanted a generic and stable measure of SEP and since we have previously shown that low education, but not low income, was associated with a higher risk of asthma after 1 year of age.^{6,7} This was defined as the mother's highest attained education registered in the Swedish Longitudinal Integrated Database for Health Insurance and Labour Market Studies (LISA) in the year before the child's birth. LISA is a national database including data on education, social insurance utilisation, income and employment.¹⁷ Education was categorised as low or high education, with low education being upper secondary school or less, and high education being tertiary education. If maternal education information was missing for the year before birth, we used the mother's education from the year the child was born (n=130 667).

Mediators

As mediators, we used maternal body mass index (BMI) and smoking in early pregnancy, both retrieved from the MBR. The MBR includes information on pregnancies and deliveries for almost all children born in Sweden since 1973, including data on maternal smoking, height (in metres), weight (in kilograms), age and birth outcomes.¹⁵ BMI was calculated based on height and weight from the first antenatal care visit ($BMI = \text{weight}/\text{height}^2$), used both as a continuous variable and categorised as obesity yes ($BMI \geq 30 \text{ kg/m}^2$) or no ($BMI < 30 \text{ kg/m}^2$). SDP was reported by the mother at the

first antenatal care visit and categorised as yes (≥ 1 cigarette/day) or no (< 1 cigarette/day). The height, weight and smoking variables in the MBR are all considered to have very good validity.^{18,19}

Outcome

Current asthma during the third and sixth years of life was used as outcomes, to capture both viral-induced wheeze that may be intermittent and a more established asthma phenotype. Asthma

Table 1 Description of the cohort of n=1 265 933 children and their mothers

	Mother's education			
	Secondary education		Tertiary education	
	No.	%	No.	%
N	621 720		644 213	
Maternal obesity				
No	479 466	77.1	546 765	84.9
Yes	98 781	15.9	51 929	8.1
Missing	43 473	7.0	45 519	7.1
Smoking during pregnancy				
No	532 935	85.7	610 845	94.8
Yes	64 473	10.4	7719	1.2
Missing	24 312	3.9	25 649	4.0
Year of child's birth				
2006	52 529	8.4	46 253	7.2
2007	52 376	8.4	48 079	7.5
2008	52 182	8.4	50 208	7.8
2009	51 644	8.3	51 847	8.0
2010	53 143	8.5	55 170	8.6
2011	51 278	8.2	53 573	8.3
2012	51 232	8.2	54 423	8.4
2013	50 732	8.2	55 468	8.6
2014	52 084	8.4	56 374	8.8
2015	51 967	8.4	56 919	8.8
2016	51 591	8.3	57 724	9.0
2017	50 962	8.2	58 175	9.0
Sex				
Male	319 234	51.3	331 661	51.5
Female	302 486	48.7	312 552	48.5
First-born				
No	366 255	58.9	351 881	54.6
Yes	255 465	41.1	292 332	45.4
Offspring asthma during the third year of life				
No	568 292	91.4	595 257	92.4
Yes	53 428	8.6	48 956	7.6
Offspring asthma during the sixth year of life				
No	567 303	91.2	589 718	91.5
Yes	49 200	7.9	47 510	7.4
Excluded*	5217	0.8	6985	1.1
Emigrated before age 6 years				
No	616 682	99.2	637 355	98.9
Yes	5038	0.8	6858	1.1
Dead before age 6 years				
No	621 541	100.0	644 086	100.0
Yes	179	0.0	127	0.0

*Excluded from analyses on asthma during the sixth year of life due to emigration or death before age 6 years.

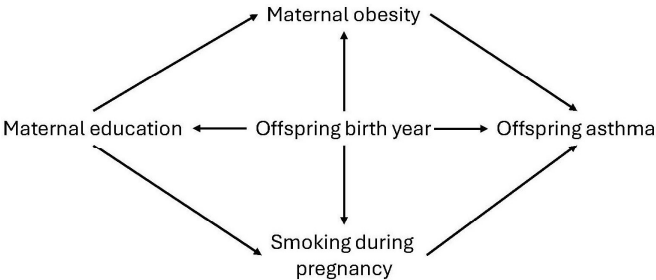


Figure 1 Directed acyclic graph illustrating the research question.



Table 2 ORs and linear regression coefficients (β) with 95% CIs for bivariate associations between exposure, mediators and outcomes

Independent variable	Dependent variable	Unadjusted	Adjusted*
		OR or β (95% CI)	OR or β (95% CI)
Exposure-mediator associations			
Low maternal education	Obesity†	2.17 (2.14 to 2.19)	2.19 (2.16 to 2.21)
Low maternal education	BMI‡	1.39 (1.37 to 1.40)	1.40 (1.38 to 1.42)
Low maternal education	Smoking during pregnancy†	9.57 (9.35 to 9.81)	9.48 (9.26 to 9.71)
Exposure-outcome associations			
Low maternal education	Asthma during third year of life†	1.14 (1.13 to 1.16)	1.15 (1.13 to 1.16)
Low maternal education	Asthma during sixth year of life†	1.08 (1.06 to 1.09)	1.09 (1.07 to 1.10)
Mediator-outcome associations			
Obesity	Asthma during third year of life†	1.33 (1.30 to 1.35)	1.32 (1.30 to 1.34)
Obesity	Asthma during sixth year of life†	1.34 (1.32 to 1.37)	1.33 (1.31 to 1.36)
BMI§	Asthma during third year of life†	1.13 (1.12 to 1.14)	1.13 (1.12 to 1.14)
BMI§	Asthma during sixth year of life†	1.13 (1.13 to 1.14)	1.13 (1.12 to 1.14)
Smoking during pregnancy	Asthma during third year of life†	1.36 (1.32 to 1.39)	1.38 (1.34 to 1.41)
Smoking during pregnancy	Asthma during sixth year of life†	1.13 (1.09 to 1.16)	1.15 (1.12 to 1.18)
*Adjusted for birth year.			
†Logistic regression, OR shown.			
‡Linear regression, regression coefficient shown.			
§Per five units higher BMI.			
BMI, body mass index.			

*Adjusted for birth year.

†Logistic regression, OR shown.

‡Linear regression, regression coefficient shown.

§Per five units higher BMI.

BMI, body mass index.

was defined in accordance with a validated algorithm,²⁰ based on outpatient care specialist diagnoses in the National Patient Register (NPR)²¹ and dispensed prescriptions on asthma medication in the Swedish Prescribed Drug Register (SPDR).²² The NPR includes information on all inpatient hospital visits since 1987 and approximately 80% of all outpatient specialist care visits since 2001, with data on diagnoses by the International Classification of Diseases (ICD), medical procedures and date of visit.²¹ The SPDR started in 2005 to cover all drug prescriptions that are dispensed at pharmacies in Sweden, including prescription and dispense date, Anatomic Therapeutic Chemical code and amount dispensed.²²

According to the asthma algorithm,²⁰ asthma was defined based on the following criteria:

1. ≥ 2 dispenses of asthma controller medication, including inhaled corticosteroids (ICS; R03BA), leukotriene receptor antagonist (R03DC03) and/or fixed combinations of ICS and β_2 -agonists (R03AK06 or R03AK07), regardless of timing for children aged >4.5 years and with ≥ 14 days between the two dispenses for children aged ≤ 4.5 years.
2. ≥ 1 dispensed controller medication and ≥ 2 of short-acting inhaled β_2 -agonists (R03AC02, R03AC03, R03AC12, R03AC13) before the third and sixth birthday.
3. ≥ 3 dispenses of short-acting inhaled β_2 -agonists within any period of 12 months before the third and sixth birthday.
4. ≥ 1 specialist care visit with an asthma diagnosis (ICD V.10: J45-J46) in the NPR.

The validation study showed positive predictive values for each of the four criteria above for children above 4.5 years of age, but less so for children below 4.5 years. For younger children, we therefore required meeting at least one of criteria (1)–(3) in combination with criteria (4), while for children above 4.5 years, fulfilling any one of criteria (1)–(4) was sufficient.

Current asthma during the third year of life was defined as fulfilling the algorithm before 3 years of age, with at least one specialist care diagnosis of asthma or at least one filled prescription on or after the second birthday and before the third birthday. Similarly, current asthma during the sixth year of life was defined as fulfilling the algorithm before the sixth birthday and having at least one filled prescription/asthma diagnosis between the fifth and sixth birthdays. Children who emigrated ($n=11\,896$) or died ($n=306$) before the sixth birthday were excluded from analyses regarding asthma during the sixth year of life.

Other variables

We selected covariates based on a directed acyclic graph (figure 1). We aimed to estimate the effect of education as a generic measure of SEP, rather than the effect of a certain number of years of education. Therefore, we did not include confounders to isolate the effect of education as such, for example, income and grandparental education. Consequently, we only included the year of the child's birth as a covariate. Furthermore, we retrieved parity from the MBR, to be used for sensitivity analysis.

Statistical methods

Bivariate exposure-mediator, exposure-outcome and mediator-outcome associations were estimated using logistic regression for obesity, SDP and asthma as dependent variables and linear regression with robust SEs for BMI as dependent variable.

For mediation analysis, there are two major approaches—the traditional/classical and the counterfactual/causal approach. The traditional approach does not allow for the estimation of indirect (mediated) effects when the mediator is dichotomous or when there is interaction between the exposure and the mediator, whereas the counterfactual approach does.²³ We therefore used the counterfactual approach by VanderWeele²⁴ to estimate the total effect and the decomposition of the total effect into the natural direct effect, the pure indirect effect and the mediated interaction, where the pure mediated effect and the mediated interaction are the components that can be attributed to the mediator. The pure mediated effect is the effect of the mediator on the outcome that is the same for both exposed and unexposed, while the mediated interaction is an effect of the mediator that is there only for the exposed.

To explore the mediated interaction further, we used logistic regression to estimate the interaction between the exposure and the mediator, with interaction terms parametrised to give separate estimates of the mediator-outcome ORs for the different levels of maternal education.

As sensitivity analyses, we repeated all analyses in the subgroups of first-born and non-first-born children, respectively. The mediation analyses were also performed stratified by sex.

Both unadjusted models and models adjusted for birth year as a categorical variable, with each year as a category, were presented. When BMI was used as an independent variable, it was modelled as a linear predictor. The only variables with missing data were maternal BMI/obesity and SDP. Complete case analysis was used

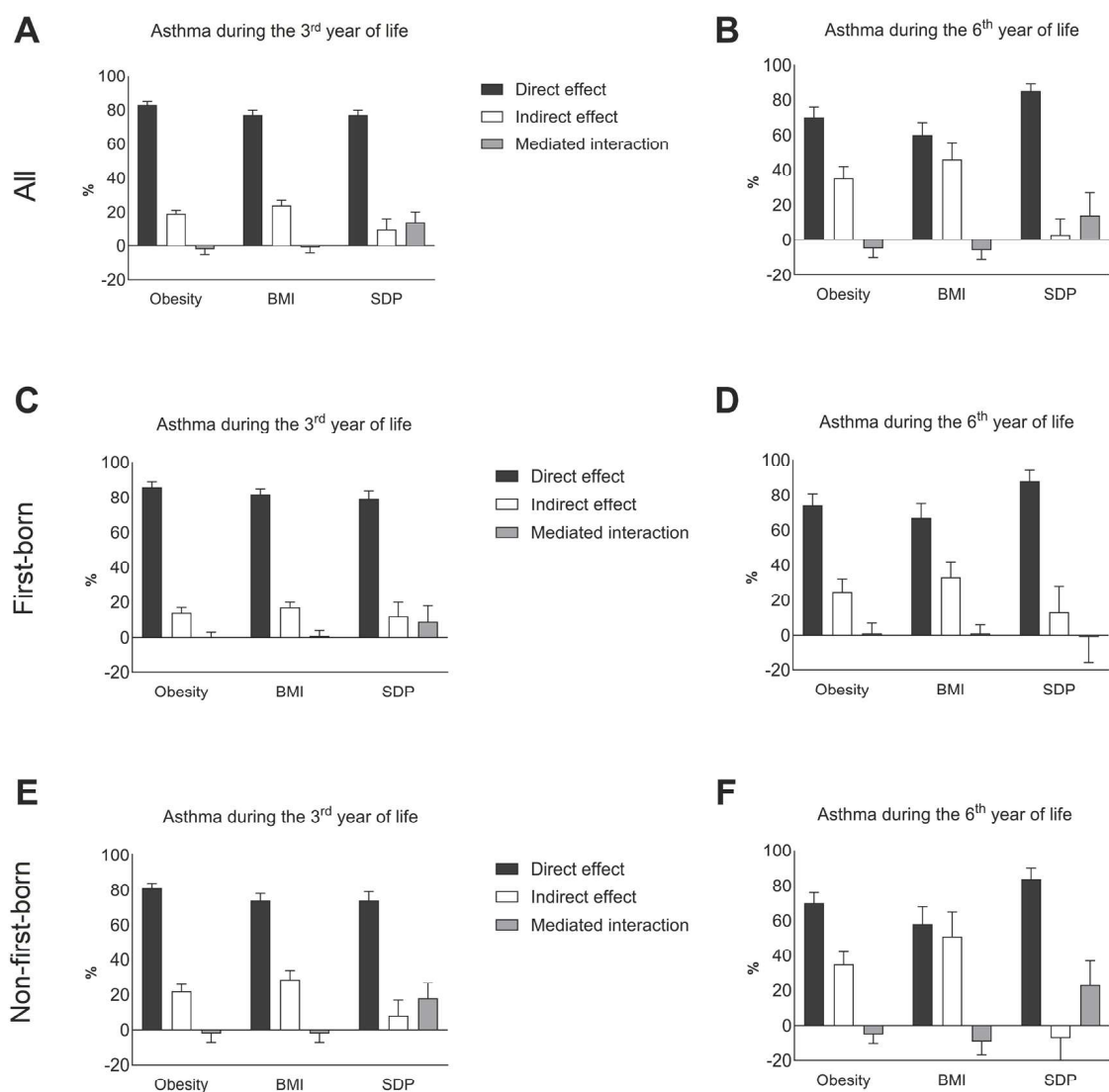


Figure 2 Results of mediation analysis showing percentage of associations between the exposure (maternal education) and the outcome (offspring asthma) during the third (A, C and E) and the sixth (B, D and F) years of life explained by the direct effect, indirect effect of each of the mediators (obesity, BMI and SDP) and the interaction between the exposure and the mediators. Results are shown for all children (A–B), first-born (C–D) and non-first-born (E–F). BMI, body mass index; SDP, smoking during pregnancy.

rather than imputation due to low levels of missingness in combination with no difference in levels of missingness between the exposure groups. The mediation analyses were performed using the SAS procedure CAUSALMED, while Stata V.18.0 was used for bivariate associations and interaction analysis. The statistical analysis plan and analysis code can be retrieved from OSF (osf.io), DOI 10.17605/OSF.IO/KSVPQ.

RESULTS

In this cohort of 1 265 933 children, 49% had mothers with secondary school education or less. This proportion decreased with time. The prevalence of obesity was higher among mothers with secondary versus tertiary education (15.9% vs 8.1%, table 1) and likewise the mean BMI was higher among the mothers with secondary education compared with tertiary (25.5 vs 24.1, data not shown). Similarly, SDP was more common in the secondary education group compared with tertiary education (10.4% vs 1.2%, table 1).

Estimated bivariate associations between the exposure variable maternal education; the mediators maternal obesity, BMI and SDP and the outcome variables asthma during the third and sixth years of life in the child are displayed in table 2. There were strong associations between maternal education and both mediators, for example, unadjusted OR 2.17 (95% CI 2.14 to 2.19) for obesity and OR 9.57 (95% CI 9.35 to 9.81) for SDP. The unadjusted association between the exposure variable maternal education and the outcome during the third year of life (OR 1.14, 95% CI 1.13 to 1.16) was stronger than

the association with the outcome during the sixth year (OR 1.08, 95% CI 1.06 to 1.09). Likewise, the unadjusted ORs with SDP were stronger with asthma during the third year of life (OR 1.36, 95% CI 1.32 to 1.39) than the sixth year (OR 1.13, 95% CI 1.09 to 1.16), while they were very similar for obesity (asthma during the third year: OR 1.33 95% CI 1.30 to 1.35; asthma during the sixth year: OR 1.34, 95% CI 1.32 to 1.37) and BMI (asthma during the third year: OR 1.33, 95% CI 1.12 to 1.14; asthma during the sixth year: OR 1.13, 95% CI 1.13 to 1.14). Adjustment for birth year rendered only marginal changes in estimates. Estimates for the subgroups of first-born and non-first-born were similar, although the association between maternal education and obesity/BMI was slightly weaker in the first-born group (online supplemental table s1).

Results from mediation analyses are displayed in figure 2 and online supplemental table s2. Out of the excess risk of asthma during the third year of life among children whose mothers had low education, 19% could be explained by obesity, 24% by BMI and 10% by SDP. The corresponding figures for asthma during the sixth year of life were 35% (obesity), 46% (BMI) and 3% (SDP). The results also indicated that the association was partly explained by an interaction between the exposure, maternal education and the mediators, particularly for SDP. The interaction between maternal education and SDP explained 14% of the association both during the third and the sixth year of life, while the interaction with obesity/BMI was small and in the opposite direction (–2% with BMI and –1% with obesity for asthma during the third year of life and

Table 3 Interactions between maternal education and the mediators: maternal obesity, BMI and SDP

	Maternal education		P value for interaction
	Low	High	
All			
Asthma during the third year of life			
Obesity	1.27 (1.24 to 1.30)	1.34 (1.29 to 1.38)	0.010
BMI*	1.11 (1.10 to 1.12)	1.13 (1.12 to 1.14)	0.014
SDP	1.33 (1.30 to 1.37)	1.16 (1.07 to 1.25)	0.0008
Asthma during the sixth year of life			
Obesity	1.29 (1.26 to 1.32)	1.36 (1.32 to 1.41)	0.006
BMI*	1.12 (1.11 to 1.13)	1.14 (1.13 to 1.15)	0.002
SDP	1.13 (1.09 to 1.16)	1.02 (0.94 to 1.11)	0.036
First-born			
Asthma during the third year of life			
Obesity	1.31 (1.26 to 1.36)	1.36 (1.30 to 1.43)	0.21
BMI*	1.13 (1.12 to 1.15)	1.14 (1.12 to 1.16)	0.50
SDP	1.31 (1.26 to 1.37)	1.20 (1.07 to 1.35)	0.17
Asthma during the sixth year of life			
Obesity	1.37 (1.32 to 1.42)	1.37 (1.31 to 1.44)	0.88
BMI*	1.15 (1.13 to 1.16)	1.15 (1.14 to 1.17)	0.65
SDP	1.11 (1.06 to 1.16)	1.12 (1.00 to 1.27)	0.83
Non-first-born			
Asthma during the third year of life			
Obesity	1.25 (1.22 to 1.29)	1.32 (1.26 to 1.37)	0.044
BMI*	1.10 (1.09 to 1.11)	1.12 (1.11 to 1.14)	0.034
SDP	1.35 (1.31 to 1.40)	1.12 (1.01 to 1.25)	0.001
Asthma during the sixth year of life			
Obesity	1.27 (1.23 to 1.31)	1.37 (1.32 to 1.43)	0.003
BMI*	1.11 (1.10 to 1.12)	1.14 (1.12 to 1.16)	0.004
SDP	1.14 (1.10 to 1.18)	0.93 (0.83 to 1.06)	0.002
All analyses are adjusted for birth year.			
*Per five units higher BMI.			
BMI, body mass index; SDP, smoking during pregnancy.			

–5% with BMI and –6% with obesity for asthma during the sixth year of life). Results stratified by first-born and non-first-born indicated that a slightly larger proportion of the association was explained by mediation by obesity, BMI and SDP or interaction between those mediators and the exposure in non-first-born than in first-born children. For obesity and BMI, a larger proportion of the association was explained by mediation, whereas for SDP, a larger proportion was explained by interaction between maternal education and SDP (figure 2). Mediation analyses stratified by sex are presented in online supplemental table s3.

Table 3 displays the interaction between the exposure (maternal education) and the mediators (obesity, BMI and SDP), that is, how the associations between the mediators and the outcome differ by maternal education. The associations between obesity or BMI and asthma were slightly stronger for children with highly educated mothers (eg, asthma during the third year of life and obesity OR 1.35, 95% CI 1.30 to 1.39 for high education vs OR 1.28, 95% CI 1.21 to 1.35 for low education). The opposite was found for SDP, with a weaker association for highly educated mothers (eg, asthma during the third year of life OR 1.15, 95% CI 1.06 to 1.24 for high education vs OR 1.32, 95% CI 1.28 to 1.36 for low education). When stratifying by first-born and non-first-born, the results mirror the pattern from the mediation analyses in that the exposure-mediator interaction was more pronounced for non-first-born than for first-born, particularly for SDP (online supplemental table s2).

DISCUSSION

In this population-based cohort study of 1.3 million children, we found that 20%–30% of the excess risk of offspring asthma during the third and sixth years of life among children of mothers with low education was explained by the mediator maternal obesity or BMI and 15%–20% was explained by SDP. This was partly due to interactions between maternal education and the mediators, indicating that obesity and BMI had stronger association with asthma in the offspring if the mother had high education, while the association between SDP and offspring asthma was stronger if the mother had low education. Our results also indicated that for first-born children, there was a slightly larger proportion of the excess risk in the low education group that could be explained by obesity or BMI and SDP as compared with non-first-born children.

Our findings that maternal obesity or BMI and SDP mediate some of the association between maternal SEP and offspring asthma during the third and sixth years of life are supported by findings in two cohort studies with children aged 7–14 years, one showing significant mediation by SDP²⁵ and the other 37% mediation by a block of perinatal factors including, among others, maternal SDP and prepregnancy BMI.²⁶ A study with wheeze as outcome found that the association between SEP and wheeze was partly explained by SDP,²⁷ while another study with breathlessness and wheeze at age 4 years as outcomes found that a block of prenatal factors partly explained the associations between SEP and breathlessness, but not wheeze.²⁸ To our knowledge, we are the first to quantify the role of the modifiable risk factors maternal obesity, BMI or SDP in the association between SEP and asthma. Our results indicate that supporting women of reproductive age with lower SEP to maintain or achieve a healthy weight and to abstain from tobacco smoking could reduce their own morbidity and health inequities in childhood for their offspring.

Our subgroup analyses indicated that maternal obesity or BMI and smoking may be more important in subsequent pregnancies than in the first. Thus, the time after a first pregnancy could be an opportunity to support women with unhealthy weight and tobacco dependency. Future research should focus on intervention programmes targeting women during and between pregnancies.

A major strength of this study is the unique longitudinal registry data covering the entire population, which enabled us to link parental socioeconomic information with information on exposures in pregnancy and offspring respiratory health, ensuring generalisability to the general population. Since the data are registered prospectively by authorities and health professionals, recall bias is avoided. However, using data not collected for research purposes also means that we could not control the way data were collected, for example, the exact timepoint in pregnancy when the women's BMI was measured and the way questions about smoking are asked. Other limitations of this study include the measurement error in the asthma variables. As a consequence of not having information about primary care visits, but only hospital-based specialist care and drug prescription dispenses, we may misclassify mild asthma treated in primary care without or with very few dispensed prescriptions as no asthma. Furthermore, the use of education as a proxy of SEP could be discussed but is generally considered a robust measure of SEP, which is widely used. When focusing on SEP in a broader sense, it also has the advantage of being influenced by the family background and SEP in the previous generation and can thereby be viewed as a generic measure of SEP. Finally, mediation analysis assumes no unmeasured confounding between exposure and mediator, exposure and outcome and between mediator and outcome. We cannot exclude unmeasured confounding from health behaviour, which may increase the risk of obesity and smoking, while its effect on offspring asthma is unclear.

In conclusion, our results showed 15% and 9% increased odds of asthma in children of mothers with low education compared with high education during the third and sixth years of life, respectively. Around 20%–30% of the excess risk of offspring asthma among mothers with low education compared with high education could

be explained by obesity or BMI through mediation or mediator-exposure interaction, while 15%–20% could be explained by SDP. Our results highlight the role of intervention programmes supporting young women and mothers-to-be to healthy weight and to abstain from tobacco smoking, in particular during pregnancy, in order to reduce child morbidity and improve health equity in childhood.

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Ethics approval This study was approved by the Swedish Ethical Review Authority (decision no. 2018/1697-31/1). The Authority waived the requirement for informed consent from study participants due to its register-based nature with data linked using individuals' unique personal identification numbers but pseudonymised for research purposes.

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Data availability statement Data are available on reasonable request. Data may be obtained from a third party and are not publicly available. Original data are held by the Swedish National Board of Health and Welfare and Statistics Sweden. Due to Swedish data storage laws, we cannot make the data publicly available. However, any researcher can access the data by obtaining an ethical approval from the Swedish Ethical Review Authority and thereafter asking the registers for the original data. Pseudonymised data can also be provided from the principal investigator of this study on request after providing a reasonable proposal and if an appropriate data sharing agreement with Karolinska Institutet can be established.

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ORCID iDs

Cecilia Lundholm <https://orcid.org/0000-0002-6546-3650>

Emma Caffrey Osvald <https://orcid.org/0000-0003-3367-694X>

Samuel Rhedin <https://orcid.org/0000-0001-5798-2875>

Catarina Almqvist <https://orcid.org/0000-0002-1045-1898>

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ARTIGO ORIGINAL

Carga negligenciada da apneia obstrutiva do sono: perda de produtividade laboral nos EUA e no Reino Unido

Umar Rehman,¹ Yuju Ahn,¹ Erez Yerushalmi,² Mohamed Abdelwahab,³ Nicholas Eynon-Lewis,⁴ Jacklyn Liu,^{1,5} Liam Sutton,⁶ F Christopher Holsinger,⁷ Robson Capasso,⁷ Marie-Lise Côté,⁸ Ryan Chin Taw Cheong,⁹ Bhik Kotecha,^{10,11} Maurice M Ohayon,¹² Marco Hafner,¹³ Matt Lechner^{1,5}

¹Division of Surgery and Interventional Science, University College London, London, UK

²Birmingham City University, Business School, Birmingham, UK

³Department of Otolaryngology-Head and Neck Surgery, Medical University of South Carolina, Charleston, South Carolina, USA

⁴Department of ENT, The Royal London Hospital, London, UK

⁵UCL Cancer Institute, University College London, London, UK ⁶Department of Paediatric ENT, Great Ormond Street Hospital for Children, London, UK

⁷Department of Otolaryngology-Head and Neck Surgery, Stanford University School of Medicine, Stanford, California, USA

⁸Centre d'Évaluation et de Statistique, Montreal, Quebec, Canada

⁹Royal National ENT and Eastman Dental Hospitals, London, UK

¹⁰Nuffield Health Brentwood, Essex, UK

¹¹UME Health, London, UK

¹²Sleep Medicine, Stanford University School of Medicine, Stanford, California, USA

¹³RAND Europe, Cambridge, UK

Correspondence to
Professor Matt Lechner;
m.lechner@ucl.ac.uk

UR and YA contributed equally.

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RESUMO

Este estudo estima a prevalência e o impacto da perda de produtividade laboral associada à síndrome de apneia obstrutiva do sono (AOS) no Reino Unido e nos EUA, utilizando pausas respiratórias auto-reportadas e sono-lência diurna excessiva como indicadores indiretos. A prevalência da síndrome de AOS foi de 22,8% nos EUA e 19,5% no Reino Unido. As perdas anuais de produtividade foram estimadas em 180,2 mil milhões de dólares nos EUA e 4,22 mil milhões de libras no Reino Unido. Nos dois países, as perdas de produtividade ao nível individual excederam o custo do tratamento com pressão positiva contínua nas vias aéreas (CPAP), sugerindo que uma melhor identificação da AOS, maior acesso ao tratamento e melhor adesão poderiam gerar benefícios económicos significativos.

BACKGROUND

Over the past 30 years, shifts in demographics, lifestyle and healthcare have driven a growing burden of non-communicable diseases, particularly obesity—a major risk factor for obstructive sleep apnoea (OSA), a serious but under-recognised sleep disorder.¹ According to Benjafield et al.,² OSA affects an estimated 1 billion adults worldwide, with prevalence rates of 24.5% in the UK and just over 30% in the USA.² In the UK the Sleep Apnoea Trust (2024) acknowledges there is a lack of accurately reported prevalence estimates specific to the UK working-age population³ and the diagnosis and treatment rates of OSA remain low.^{1–3}

The burden of OSA is further exacerbated by poor adherence to treatment. Recent research shows that 62% of patients discontinue CPAP therapy, compounding both the health and economic impacts.⁴ This non-adherence has also been linked to increased absenteeism due to sick days.⁵

This study aims to estimate the prevalence of OSA in representative samples of the UK and USA populations using self-reported symptom data aligned with diagnostic criteria. It also assesses the societal costs of untreated OSA among working-age adults by applying a productivity-based approach that accounts for both absenteeism (missed work) and presenteeism (reduced on-the-job performance). This pragmatic, policy-relevant perspective complements traditional health economic models and addresses key evidence gaps in both countries to support informed policy reforms.

METHODS

In this study, 4218 subjects from the 2021 US census and 1378 subjects from the 2021 UK census belonging to the non-institutionalised population aged 18 years and above were used as the standard

population. An electronic interview was conducted with this sample of individuals' representative of the USA and UK population via Dynata (Connecticut, USA) during November 2021. Overall, 695 US entries and 538 UK entries were excluded from analysis due to lack of data. This resulted in a total sample of 3523 US and 840 UK subjects for analysis.

OSA syndrome definition

Respondents who reported experiencing breathing pauses at night, along with excessive daytime sleepiness on three or more nights, were used as a proxy for an OSA syndrome diagnosis, as both symptoms form the core criteria for OSA syndrome diagnosis according to the International Classification of Sleep Disorders, Third Edition.⁶

Economic impact analysis

To assess the USA and UK specific workplace productivity burden associated with OSA, a computable general equilibrium (CGE) macroeconomic model was applied. Such models are increasingly applied to estimate the economy-wide burden of health conditions.⁷ The model's technical details are explained in Hafner et al.⁸ The CGE model simulates the workplace productivity burden of OSA syndrome associated with workplace productivity among individuals in the workforce, defined here as those aged 18–64 years. It uses the prevalence of breathing pauses coupled with excessive daytime sleepiness from the survey as a proxy for OSA syndrome (see online supplemental methods, references 1–10). The productivity impairment inputs to the model are based on Stepnowsky et al.^{6,7}

RESULTS

The prevalence of OSA syndrome was 22.8% in the USA and 19.5% in the UK. Nearly 30% of the US working population and 7% of the UK working population aged 18–64 met the study criteria for OSA syndrome (table 1, online supplemental tables 1–3, online supplemental results).

Based on the estimated prevalence of OSA syndrome in the working population, the total annual productivity loss in the USA was calculated at US\$180.2 billion (table 2). At the individual level, this corresponds to an estimated productivity loss of US\$3727.40 per worker with OSA syndrome per year, measured in terms of gross domestic product (GDP). In comparison, the annual cost of CPAP treatment per patient in the USA is estimated at US\$1660.97 (online supplemental reference 11).

The total annual productivity loss due to OSA syndrome in the UK was estimated at £4.22 billion, representing 0.2% of the national GDP (table 3).

Table 1 Demographic characteristics of sample

	Total, USA (n=3625)	Total, UK (n=840)
Age in years		
18–24	155 (4.3%)	109 (13.0%)
25–34	665 (18.3%)	131 (15.6%)
35–44	464 (12.8%)	135 (16.1%)
45–54	613 (16.9%)	120 (14.3%)
55–64	516 (14.2%)	110 (13.1%)
65–74	701 (19.3%)	119 (14.2%)
75 or older	511 (14.1%)	116 (13.6%)
Gender		
Female	1895 (52.3%)	434 (51.7%)
Male	1730 (47.7%)	406 (48.3%)
Marital status		
Single	1000 (27.6%)	289 (34.4%)
Married	1975 (54.5%)	445 (53.0%)
Separated or divorced	418 (11.5%)	70 (8.3%)
Widowed	232 (6.4%)	36 (4.3%)
Ethnicity		
White	2847 (78.5%)	764 (91.0%)
American Indian/Alaska Native	30 (0.8%)	0 (0.0%)
Asian	230 (6.3%)	32 (3.8%)
Hispanic/Latino	111 (3.1%)	0 (0.0%)
Black/African American/black British	294 (8.1%)	27 (3.2%)
Middle Eastern	12 (0.3%)	0 (0.0%)
Native Hawaiian or other Pacific Islander	9 (0.2%)	0 (0.0%)
Mixed race	0 (0.0%)	14 (1.7%)
Prefer not to answer	59 (1.6%)	2 (0.2%)
Unknown	23 (0.6%)	1 (0.1%)
Missing	10 (0.3%)	0 (0.0%)
Smoking status		
Current smoker/chewing tobacco	1062 (29.3%)	246 (29.3%)
Never smoked/chewed tobacco	1845 (50.9%)	353 (42.0%)
Ex smoker/previous tobacco chewing	718 (19.8%)	241 (28.7%)

On an individual level, the annual productivity cost per worker with OSA is approximately £1840. In comparison, the cost of CPAP treatment, including associated healthcare resources and supportive care, is estimated at £1363 per patient (online supplemental reference 12).

DISCUSSION

The economic costs we have estimated in the UK and USA are in accordance with similar reports from Australia which demonstrated a \$A11 billion cost from productivity losses.⁹ Effective identification and treatment of OSA syndrome among the UK and USA working population could yield substantial economic benefits. However, these benefits are unlikely to be fully realised without addressing the widespread issue of poor CPAP adherence, as highlighted by Dielesen et al.³ Enhancing adherence through earlier and more frequent follow-ups after therapy initiation is essential to maximise treatment effectiveness and reduce productivity losses associated with undiagnosed or poorly managed OSA. However, achieving meaningful impact also depends on effective patient education and sustained CPAP adherence. Continued CPAP use has been associated with a reduced proportion of individuals requiring long-term sick leave, thereby reducing absenteeism and the risk of permanent work disability.⁵

Table 2 Workplace productivity burden of OSA in the USA (US\$, 2022)

Prevalence	GDP		Tax revenue			
	US\$ (2022), billion	%	US\$ (2022), per person	US\$ (2022), billion	%	US\$ (2022), per person
1%	6.03	0.03	3739.4	2.02	0.03	1252.9
2%	12.05	0.06	3739.0	4.04	0.06	1252.8
3%	18.07	0.09	3738.6	6.06	0.08	1252.6
4%	24.09	0.13	3738.1	8.07	0.11	1252.5
5%	30.11	0.16	3737.7	10.09	0.14	1252.4
6%	36.13	0.19	3737.3	12.11	0.17	1252.2
7%	42.15	0.22	3736.9	14.12	0.19	1252.1
8%	48.17	0.25	3736.5	16.14	0.22	1252.0
9%	54.18	0.28	3736.1	18.15	0.25	1251.8
10%	60.19	0.31	3735.7	20.17	0.28	1251.7
11%	66.21	0.34	3735.2	22.18	0.30	1251.5
12%	72.22	0.38	3734.8	24.20	0.33	1251.4
13%	78.23	0.41	3734.4	26.21	0.36	1251.3
14%	84.24	0.44	3734.0	28.22	0.39	1251.1
15%	90.24	0.47	3733.6	30.24	0.41	1251.0
16%	96.25	0.50	3733.2	32.25	0.44	1250.8
17%	102.25	0.53	3732.8	34.26	0.47	1250.7
18%	108.25	0.56	3732.3	36.27	0.50	1250.6
19%	114.26	0.59	3731.9	38.28	0.52	1250.4
20%	120.26	0.62	3731.5	40.29	0.55	1250.3
21%	126.26	0.66	3731.1	42.30	0.58	1250.2
22%	132.25	0.69	3730.7	44.31	0.60	1250.0
23%	138.25	0.72	3730.3	46.32	0.63	1249.9
24%	144.24	0.75	3729.9	48.33	0.66	1249.7
25%	150.24	0.78	3729.4	50.34	0.69	1249.6
26%	156.23	0.81	3729.0	52.35	0.71	1249.5
27%	162.22	0.84	3728.6	54.35	0.74	1249.3
28%	168.21	0.87	3728.2	56.36	0.77	1249.2
29%	174.20	0.90	3727.8	58.37	0.80	1249.0
30%	180.19	0.94	3727.4	60.37	0.82	1248.9

GDP, gross domestic product; OSA, obstructive sleep apnoea.

It is important to note that the estimated workplace productivity burden does not account for the impact on healthcare systems due to increased medical expenditures, nor does it include the costs of road traffic or workplace accidents, which can result in elevated morbidity and mortality risks.¹⁰ The exclusion of these additional cost elements likely leads to an underestimation of the true workplace productivity burden of OSA from a societal perspective. Our analysis, though limited to a small subset of OSA-related costs, highlights that the broader workplace productivity burden of OSA syndrome likely exceeds the direct costs of screening and effective treatment in both the UK and USA.

LIMITATIONS

This study has some limitations. OSA was identified using proxy measures, including breathing pauses and excessive daytime sleepiness, based on the International Classification of Sleep Disorders.⁶ Without objective assessment such as the Apnoea-Hypopnoea Index, we cannot confirm OSA severity or exclude alternative causes of sleepiness. Hence, it relies on self-reported symptoms, which introduces potential for recall bias and misclassification. However, while based on estimates rather than confirmed diag-

Table 3 Workplace productivity burden of OSA in the UK (£, 2022)

Prevalence	GDP			Tax revenue		
	£ (2022), billion	%	£ (2022), per person	£ (2022), billion	%	£ (2022), per person
1%	0.61	0.03	1847.0	0.22	0.03	684.0
2%	1.21	0.06	1846.8	0.45	0.06	683.9
3%	1.82	0.09	1846.6	0.67	0.09	683.8
4%	2.42	0.11	1846.4	0.9	0.11	683.8
5%	3.02	0.14	1844.8	1.12	0.14	682.4
6%	3.62	0.17	1842.4	1.34	0.17	680.2
7%	4.22	0.2	1840.6	1.56	0.2	678.6
8%	4.82	0.23	1839.3	1.78	0.23	677.4
9%	5.42	0.26	1838.1	2.00	0.25	676.4
10%	6.02	0.28	1837.2	2.21	0.28	675.7
11%	6.62	0.31	1836.4	2.43	0.31	675.0
12%	7.22	0.34	1835.7	2.65	0.34	674.4
13%	7.82	0.37	1835.1	2.87	0.36	674.0
14%	8.42	0.40	1834.6	3.09	0.39	673.5
15%	9.02	0.42	1834.1	3.31	0.42	673.2
16%	9.61	0.45	1833.6	3.53	0.45	672.8
17%	10.21	0.48	1833.2	3.75	0.48	672.5
18%	10.81	0.51	1832.8	3.97	0.50	672.3
19%	11.41	0.54	1832.4	4.18	0.53	672.0
20%	12.01	0.56	1832.0	4.40	0.56	671.8
21%	12.61	0.59	1831.7	4.62	0.59	671.5
22%	13.20	0.62	1831.4	4.84	0.61	671.3
23%	13.80	0.65	1831.0	5.06	0.64	671.1
24%	14.40	0.68	1830.7	5.28	0.67	671.0
25%	15.00	0.71	1830.4	5.50	0.70	670.8
26%	15.59	0.73	1830.2	5.71	0.73	670.6
27%	16.19	0.76	1829.9	5.93	0.75	670.5
28%	16.79	0.79	1829.6	6.15	0.78	670.3
29%	17.39	0.82	1829.4	6.37	0.81	670.2
30%	17.98	0.85	1829.1	6.59	0.84	670.0
GDP, gross domestic product; OSA, obstructive sleep apnoea.						

noses, the prevalence of OSA in our study aligns with that reported in the literature.²

CONCLUSION

Given the significant yet often-overlooked burden of OSA syndrome and its economic impact, we urge policymakers to allocate resources towards developing an effective screening strategy and implementing targeted public health campaigns and policies. Early identification and treatment of OSA syndrome, along with proactive early follow-up, could result in substantial savings, potentially amounting to billions of dollars/pounds annually in productivity costs.

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Ethics approval This study involves human participants, but it was confirmed that ethical approval was not required for this study (because the survey population consisted of adults aged 18 years and over from non-vulnerable groups). Participation was entirely voluntary, and informed consent was obtained through the completion of the survey. Participants gave informed consent to participate in the study before taking part.

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ORCID iDs

Umar Rehman <https://orcid.org/0000-0002-4856-3414>

Erez Yerushalmi <https://orcid.org/0000-0002-9421-9067>

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Impacto de um programa nacional de nirsevimab no transporte de bebés com bronquiolite para cuidados intensivos: um estudo observacional retrospectivo

ANTECEDENTES

O vírus sincicial respiratório (VSR) é uma das principais causas de bronquiolite, desencadeando epidemias anuais que atingem o pico no outono e inverno e resultam em aproximadamente três milhões de hospitalizações a nível global todos os anos. A bronquiolite grave frequentemente requer admissão numa unidade de cuidados intensivos pediátricos (UCIP), o que pode implicar transferência entre hospitais.

Mais de metade das admissões na UCIP por bronquiolite na Irlanda durante a época de inverno de 2023–2024 foram transferidas de outro hospital.¹ As admissões relacionadas com VSR no *Children's Health Ireland* em 2023–2024 tiveram um custo financeiro estimado superior a 6 milhões de euros.¹

Na Irlanda, sempre que possível, as transferências para UCIP são asseguradas pelo *National Ambulance Service Critical Care Retrieval Service*, composto por equipas médicas e de enfermagem especializadas, com recursos de ambulância dedicados. O *National Neonatal Transport Programme* fornece um serviço 24/7 para bebés com menos de 28 dias de idade corrigida, e o *Irish Paediatric Acute Transport Service* (IPATS) fornece um serviço diurno, 7 dias por semana, para crianças dos 28 dias corrigidos até aos 16 anos. Quando uma criança com mais de 28 dias necessita de transporte fora do horário do IPATS, este é realizado por equipas locais com recursos de ambulância de primeira linha.

O nirsevimab, um anticorpo monoclonal, proporciona 150–180 dias de proteção contra bronquiolite por VSR.² Foi recomendado para todos os recém-nascidos na Irlanda entre setembro de 2024 e fevereiro de 2025, sem custos para os pais, em todas as unidades de maternidade, com uma taxa de adesão global de 83% na primeira época.³ Bebés mais velhos de alto risco foram imunizados através de um serviço domiciliário financiado.

Os dados de vigilância demonstraram: 65% de redução nos casos totais de VSR, 57% de redução nas idas ao serviço de urgência por VSR, 76% de redução nas hospitalizações por VSR e 65% de redução nas admissões na UCIP por VSR.⁴

MÉTODOS

Revimos, com aprovação da comissão de ética, todos os registos de transporte de cuidados intensivos de bebés transferidos durante as épocas pré-nirsevimab e pós-nirsevimab, entre setembro de 2023–fevereiro de 2024 e setembro de 2024–fevereiro de 2025.

RESULTADOS

Na época de VSR de 2023, pré-nirsevimab, 61 bebés foram transportados com diagnóstico de bronquiolite, comparando com 16 bebés na época de VSR de 2024 pós-nirsevimab. Destes bebés, 77% (n=47) na época de 2023 e 63% (n=10) na época de 2024 testaram positivo

Table 1 Babies transported with bronchiolitis

	Pre-nirsevimab (2023–2024)	Post-nirsevimab (2024–2025)
Babies with bronchiolitis transported	61	16
Babies with RSV bronchiolitis transported	47 (77%)	10 (63%)
Babies with RSV who did not receive nirsevimab		8 (80%)
Babies transported on invasive ventilation	24 (39%)	4 (25%)
Babies with RSV requiring invasive ventilation	6 (10%)	1 (6%)
Babies transported on HHFNC	14 (23%)	6 (38%)
Babies transported on CPAP	20 (33%)	5 (31%)
Babies transported on BiPAP	3 (5%)	1 (6%)
Babies who required ventilatory support escalation by transport team	17 (28%)	3 (19%)
Babies who required intubation by transport team	10 (16%)	2 (13%)
Total time spent on transport	388 hours 26 min	101 hours 8 min
BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; HHFNC, humidified high flow nasal cannula; RSV, respiratory syncytial virus.		

Table 2 Age distribution of babies

	2023	2024
Preterm	11 (18%)	4 (25%)
0–1 months	27 (44%)	7 (44%)
1–2 months	11 (18%)	1 (6%)
2–3 months	10 (16%)	2 (13%)
3–4 months	1 (2%)	1 (6%)
4–5 months	1 (2%)	1 (6%)
5–6 months	0	0
Total	61	16

para VSR. Importa salientar que 80% (n=8) dos bebés com bronquiolite VSR-positiva na época pós-nirsevimab não tinham recebido nirsevimab (ver tabela 1). Houve uma distribuição etária semelhante dos bebés em ambas as épocas (ver tabela 2). O tempo total gasto no transporte de bebés com bronquiolite pelas equipas de transporte reduziu-se de 388 horas e 26 minutos na época de 2023 para 101 horas e 8 minutos na época de 2024.

LIMITAÇÕES

Este estudo não inclui bebés transferidos pelo hospital de referência para cuidados intensivos. Comparar apenas duas épocas pode não captar a variação anual na prevalência de VSR.

CONCLUSÃO

Demonstrámos uma redução de 74% no número total de bebés com bronquiolite transportados pelos serviços de transporte de cuidados intensivos na Irlanda após a implementação de um programa nacional de nirsevimab, com uma redução de 79% nos bebés com bronquiolite VSR-positiva transportados. Importa salientar que 80% dos bebés que foram transportados com bronquiolite VSR-positiva não tinham recebido nirsevimab. Devem ser exploradas as barreiras à aceitação parental do nirsevimab.

Tara Moore,^{1,2} Ashfaq Afridi,^{3,4} H Aminudin,^{1,2} Cathy Gibbons,³

Orna Grant,^{3,5} Hana Fucikova,^{1,6} Carmel Maria Moore^{1,7,8}

¹National Neonatal Transport Programme, Dublin, Ireland

²Rotunda Hospital, Dublin, Ireland

³Irish Paediatric Acute Transport Service, Dublin, Ireland

⁴Children's Health Ireland, Dublin, Leinster, Ireland

⁵Children's Health Ireland at Temple Street, Dublin, Leinster, Ireland

⁶Coombe Women and Infants University Hospital, Dublin, Leinster, Ireland

⁷Neonatology, University College Dublin, Dublin, Ireland

⁸Neonatology, National Maternity Hospital, Dublin, Ireland

Correspondence to Dr Carmel Maria Moore; carmel.moore@ucd.ie

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ORCID iDs

Orna Grant <https://orcid.org/0000-0003-1886-7086>

Carmel Maria Moore <https://orcid.org/0000-0003-4164-3195>

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