

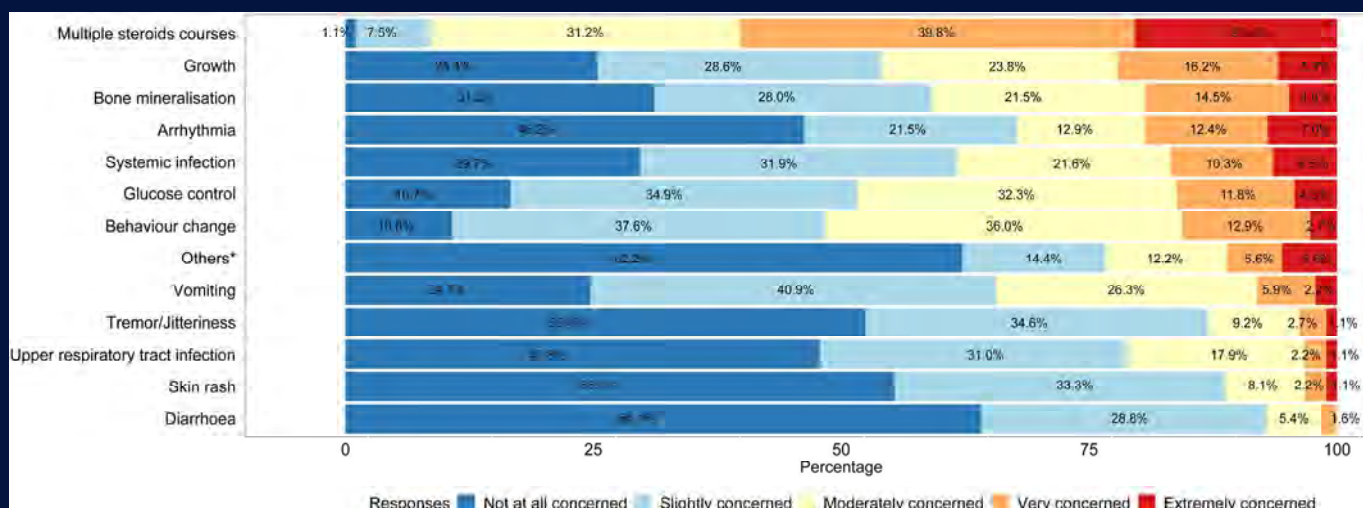
Thorax

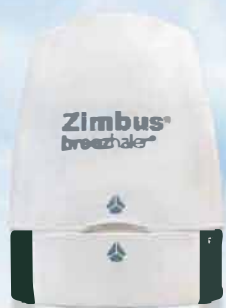
ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

com artigos do

ARCHIVES OF
DISEASE IN
CHILDHOOD

Edição Portuguesa





**1ª associação
LABA/LAMA/ICS**
indicada na ASMA⁴
Dose fixa diária¹

1 vez dia¹

**Zimbus®
breezhaler®**

Indacaterol, glicopirrônio, furoato de mometasona
pó para inalação, cápsulas



**NOVA
ASSOCIAÇÃO
LABA/LAMA
/ICS¹**

Dá ritmo à vida^{2,3*}

Para adultos com ASMA moderada a grave não controlados adequadamente com LABA/ICS.¹

1. Zimbus® Breezhaler®, Resumo das Características do Medicamento, última atualização 12/11/2021. Disponível em https://www.ema.europa.eu/en/documents/product-information/zimbus-breezhaler-epar-product-information_pt.pdf. Consultado a 12/01/2022. Terapêutica inalada, 1x/dia, combinação de dose-fixa de acetato de indacaterol, brometo de glicopirrônio e furoato de mometasona. Mistura de lactose em pó para inalação, doses únicas, através do dispositivo BREEZHALER® que permite a confirmação de doses¹. *Entende-se por 'dá ritmo à vida' que o doente ao tomar Zimbus® Breezhaler® poderá obter melhorias de função pulmonar, controlo de sintomas, qualidade de vida e redução de exacerbações vs terapêuticas padrão. 2. Gessner C, et al. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON). Respir Med. 2020 Aug-Sep;170:106021. 3. Kerstjens HAM, et al. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. Lancet Respir Med. 2020 Oct;8(10):1000-1012. 4. EPAR: European public assessment report. https://www.ema.europa.eu/en/documents/assessment-report/zimbus-breezhaler-epar-public-assessment-report_en.pdf; consultado em 21/05/2021. LABA: Agonista Beta2 de longa duração de ação; LAMA: antagonista muscarínico de longa duração de ação; ICS: corticosteroides inalados.

Zimbus Breezhaler 114 microgramas/46 microgramas/136 microgramas pó para inalação, cápsulas

NOTA: Antes de prescrever consulte o RCM do medicamento. **APRESENTAÇÃO:** Pó para inalação, cápsula (pó para inalação). Cada cápsula contém 150 microgramas de indacaterol, 50 microgramas de glicopirrônio e 160 microgramas de furoato de mometasona. Cada dose libertada (a dose libertada através do aplicador bucal do inalador) contém 114 microgramas de indacaterol (na forma de acetato), 8 microgramas de brometo de glicopirrônio equivalente a 46 microgramas de glicopirrônio e 136 microgramas de furoato de mometasona. **Excipiente(s) com efeito conhecido:** Cada cápsula contém 25 mg de lactose mono-hidratada. **INDICAÇÕES:** Zimbus Breezhaler está indicado como terapêutica de manutenção da asma em doentes adultos não controlados adequadamente com uma associação de um agonista beta, de ação prolongada e uma dose alta de corticosteroide inalado em regime de manutenção que experimentaram uma ou mais exacerbações da asma no ano anterior. **POSOLOGIA: Adultos:** A dose recomendada é uma cápsula inalada uma vez por dia. A dose máxima recomendada é de 114 µg/46 µg/136 µg uma vez por dia. **Doentes pediátricos (< 18 anos):** Não recomendado em doentes com menos de 18 anos de idade. **Populações especiais: População idosa:** Não é necessário ajuste de dose em doentes idosos (65 anos de idade ou mais). **Compromisso renal:** Não é necessário ajuste de dose em doentes com compromisso renal ligeiro a moderado. Deve ter-se precaução em doentes com compromisso renal grave ou doença renal terminal que necessitem de diálise. **Compromisso hepático:** Não é necessário ajuste de dose em doentes com compromisso hepático ligeiro a moderado. Não existem dados disponíveis sobre a utilização deste medicamento em doentes com compromisso hepático grave, como tal deve ser utilizado nestes doentes apenas se o benefício esperado superar o risco potencial. **Modo de administração:** Apenas para utilização por via inalatória. As cápsulas não podem ser engolidas. Os doentes que não sintam melhorias na sua respiração devem ser questionados se estão a engolir o medicamento em vez de o inalar. As cápsulas têm de ser administradas usando apenas o inalador Zimbus Breezhaler. O tratamento deve ser administrado à mesma hora do dia todos os dias. Pode ser administrado independentemente da hora do dia. Após a inalação, os doentes devem lavar a boca com água sem engolir. Se for omitida uma dose, esta deve ser tomada assim que possível. Os doentes devem ser instruídos a não tomarem mais do que uma dose por dia. As cápsulas de Zimbus Breezhaler devem ser sempre conservadas no blister para proteger da luz e humidade, e só podem ser removidas do blister imediatamente antes da utilização. **CONTRAINDICAÇÕES:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **ADVERTÊNCIAS/PRECAUÇÕES:** ♦ **Asma Aguda:** não deve ser utilizado para tratar sintomas agudos de asma, incluindo episódios agudos de broncoespasmo, para os quais é necessário um broncodilatador de curta ação. ♦ **Hipersensibilidade:** Se ocorrer uma reação de hipersensibilidade, Zimbus Breezhaler deve ser descontinuado imediatamente e deverá ser instituída terapêutica alternativa. ♦ **Broncoespasmo paradoxal:** Tal como com outra terapêutica inalatória, a administração deste medicamento pode resultar em broncoespasmo paradoxal, o qual pode colocar a vida em risco. Se tal ocorrer, o tratamento deve ser interrompido imediatamente e deverá ser instituída terapêutica alternativa. ♦ **Efeitos cardiovasculares:** Tal como outros medicamentos contendo agonistas adrenérgicos beta, este medicamento pode produzir um efeito cardiovascular clinicamente significativo em alguns doentes conforme avaliado através de aumentos na frequência cardíaca, pressão arterial e/ou sintomas, alterações do electrocardiograma (ECG). Este medicamento deve ser usado com precaução em doentes com patologias cardiovasculares (doença arterial coronária, enfarte agudo do miocárdio, arritmias cardíacas, hipertensão, suspeita ou confirmação de prolongamento do intervalo QT, distúrbios convulsivos ou tirotóxicose e em doentes com resposta aumentada aos agonistas adrenérgicos beta). ♦ **Hipocalcemia:** Os agonistas adrenérgicos beta, podem causar uma hipocalcemia significativa em alguns doentes, o que potencialmente pode levar a reações adversas cardiovasculares. Em doentes com asma grave, a hipocalcemia pode ser potenciada pela hipoxia e pela terapêutica concomitante, o que pode aumentar a suscetibilidade a arritmias cardíacas. ♦ **Hiperglicemia:** A inalação de doses elevadas de agonistas adrenérgicos beta, e corticosteroides pode produzir um aumento da glicose plasmática. Nos doentes diabéticos, ao iniciar o tratamento, a glicose plasmática deve ser monitorizada mais cuidadosamente. ♦ **Efeitos anticolinérgicos:** Tal como com outros medicamentos anticolinérgicos, este medicamento deve ser utilizado com precaução em doentes com glaucoma de ângulo fechado ou retenção urinária. ♦ **Doentes com compromisso renal grave:** Nos doentes com compromisso renal grave (taxa de filtração glomerular estimada inferior a 30 ml/min/1,73 m²), incluindo aqueles com doença renal terminal que necessitam de diálise, deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. ♦ **Prevenção de infeções orofaríngeas:** De modo a reduzir o risco de infeção orofaríngea por *Candida albicans*, os doentes devem ser aconselhados a lavar a boca ou a gargarejar com água, sem a engolir, ou a lavar os dentes após inalarem a dose prescrita. ♦ **Efeitos sistémicos dos corticosteroides:** Podem ocorrer efeitos sistémicos dos corticosteroides inalados, principalmente no caso de doses elevadas prescritas por períodos prolongados. Os efeitos sistémicos possíveis podem incluir: síndrome de Cushing, manifestações Cushingóides, supressão adrenal, atraso do crescimento em crianças e adolescentes, diminuição da densidade mineral óssea, cataratas, glaucoma e, mais raramente, uma série de efeitos psicológicos ou comportamentais incluindo hiperatividade psicomotora, distúrbios do sono, ansiedade, depressão ou agressão (especialmente em crianças). Como tal, é importante que a dose de corticosteroide inalado seja titulada para a dose mais baixa na qual o controlo efetivo da asma é mantido. Podem ser notificados distúrbios visuais como o uso de corticosteroides sistémicos ou tópicos (incluindo intranasais, inalados ou intraoculares). Doentes que apresentem sintomas como visão turva ou outros distúrbios visuais, devem ser considerados para encaminhamento a um oftalmologista para avaliação de possíveis causas dessas perturbações visuais, as quais podem incluir cataratas, glaucoma ou doenças raras como a coriorretinopatia central serosa (CRCS), que foram notificadas após o uso de corticosteroides sistémicos ou tópicos. Este medicamento deve ser administrado com precaução em doentes com tuberculose pulmonar ou em doentes com infeções crónicas ou não tratadas. ♦ **Gravidez:** Este medicamento deve ser utilizado durante a gravidez apenas se o benefício esperado para o doente justificar o potencial risco para o feto. ♦ **Amamentação:** Tem que ser tomada uma decisão sobre a descontinuação da amamentação ou a descontinuação/abstenção da terapêutica, tendo em conta o benefício da amamentação para a criança e o benefício da terapêutica para a mulher. ♦ **Trabalho de parto:** Como outros medicamentos contendo agonistas adrenérgicos beta, o indacaterol pode inibir o trabalho de parto devido a um efeito relaxante no músculo liso uterino. **INTERAÇÕES:** ♦ **Bloqueadores adrenérgicos beta:** este medicamento não deve ser administrado com bloqueadores adrenérgicos beta (incluindo gotas para os olhos) a menos que existam razões importantes para a sua utilização ♦ **Medicamentos conhecidos por prolongarem o intervalo QTc:** este medicamento deve ser administrado com precaução a doentes que estejam a ser tratados com inibidores da monoamina oxidase, antidepressivos tricíclicos ou medicamentos conhecidos por prolongar o intervalo QT. ♦ **Tratamento hipocalcémico:** O tratamento hipocalcémico concomitante com derivados da metilxantina, esteróides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocalcémico dos agonistas adrenérgicos beta. ♦ **Interação com inibidores do CYP3A4 e da glicoproteína P:** A inibição do CYP3A4 e da glicoproteína P (gp-P) não tem impacto na segurança de doses terapêuticas de Zimbus Breezhaler. ♦ **Outros antimuscarínicos de ação prolongada e agonistas adrenérgicos beta, de ação prolongada:** A coadministração deste medicamento com outros medicamentos contendo antagonistas muscarínicos de ação prolongada ou agonistas adrenérgicos beta, de ação prolongada não foi estudada e não é recomendada. ♦ **Cimetidina ou outros inibidores do transporte de catiões orgânicos:** Não é esperada qualquer interação medicamentosa clinicamente relevante. **EFEITOS INDESEJÁVEIS:** ♦ **Frequentes (≥1% a <10%) e potencialmente graves:** hipersensibilidade. ♦ **Muito frequentes:** asma (exacerbação), nasofaringite. ♦ **Frequentes (≥1% a <10%):** infeção do trato respiratório superior, candidíase, infeção do trato urinário, cefaleia, taquicardia, dor orofaríngea, tosse, disfonia, gastroenterite, dor musculoesquelética, espasmos musculares, piroxia. ♦ **Pouco frequentes (≥0,1% a <1%):** hiperglicemia, cataratas, boca seca, erupção cutânea, prurido, disúria. Para mais informações, consultar o titular de autorização de introdução no mercado ou o representante local do titular de autorização de introdução no mercado. Medicamento sujeito a receita médica. **Escala de comparticipação:** Escalão B. **Titular da AIM:** Novartis Europharm Limited. **Representante local:** Laboratório Medifar - Produtos Farmacêuticos, S.A. - Rua Henrique de Paiva Couceiro, N° 29, Venda Nova, 2700-451 Amadora Informações Essenciais Compatíveis com o Resumo das Características do Medicamento (ZIM_RCM20210422_IEC_v2).



Journal of the British Thoracic Society
Impact Factor: 10.8
Editors-in-Chief
Mark Griffiths (UK)
Jennifer Quint (UK)
Cecilia O’Kane (UK)
Deputy Editor
Alex Bottle (UK)
Rachel Chambers (UK)
Associate Editors
Mona Bafadel (UK) Georgios Kaltsakas (UK)
Kevin Blyth (UK) David Kiely (UK)
HJ Bogaard Bruce Kirenga (Uganda)
(The Netherlands) Onn Min Kon (UK)
Matthew Callister (UK) David Lo (USA)
Nazia Chaudhuri (UK) Refloe Masekela (S. Africa)
Bronwen Connolly (UK) Patrick Murphy (UK)
Michael Crooks (USA) Vidya Navaratnam (Aus)
Philip Crosbie (UK) Marko Nikolic (UK)
Charlotte Dean (UK) Jean-Louis Pepin (France)
Raja Dhar (India) Mike Polkey (UK)
David Dockrell (UK) Joanna Porter (UK)
Francis J Gilchrist (UK) Sejal Saglani (USA)
Rob Hallifax (UK) Maor Sauler (USA)
Nick Hopkinson (UK) Chris Scotton (UK)
David Jackson (UK) Anand Shah (UK)
Christer Janson (Sweden) Sheetu Singh (India)
Colin Solomon (UK) Claire Wainwright (Aus)
Robert Stevens (USA) Hannah Whittaker (UK)
Katia Verhamme (Ned)
Guidelines Associate Editor
I Du Rand (UK)
Statistical Editors
N Beckley-Hoelscher (UK)
A Douiri (UK)
C Flach (UK)
C Jackson (UK)
S Nevitt (UK)
L Stanberry (USA)
S Stanojevic (USA)
I Stewart (UK)
R Szczesniak (USA)
B Wagner (USA)
Y Wang (UK)
Journal Club Editor
P Murphy (UK)
Multimedia Editor
R Moses (UK)
President, British Thoracic Society
Rachael Moses
Editorial Office
Thorax, BMJ Journals, BMA House,
Tavistock Square, London, WC1H 9JR, UK
T: +44 (0)20 7383 6373
E: thorax@bmj.com
Twitter: @ThoraxBMJ
ISSN: 0040-6376 (print)
ISSN: 1468-3296 (online)
Disclaimer: Thorax is owned and published by the British Thoracic Society and BMJ Publishing Group Ltd, a wholly owned subsidiary of the British Medical Association. The owners grant editorial freedom to the Editor of Thorax. Thorax follows guidelines on editorial independence produced by the World Association of Medical Editors and the code on good publication practice of the Committee on Publication Ethics. Thorax is intended for medical professionals and is provided without warranty, express or implied. Statements in the Journal are there sponsibility of their authors and advertisers and not authors’ institutions, the BMJ Publishing Group Ltd, the British Thoracic Society or the BMA unless otherwise specified or determined by law. Acceptance of advertising does not imply endorsement. To the fullest extent permitted by law, the BMJ Publishing Group Ltd shall not be liable for any loss, injury or damage resulting from the use of Thorax or any information in it whether based on contract, tort or otherwise. Readers are advised to verify any information they choose to rely on.
Copyright © 2025 BMJ Publishing Group Ltd and the British Thoracic Society. All rights reserved; no part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without the prior permission of Thorax. Thorax is published by BMJ Publishing Group Ltd, typeset by Exeter Premedia Services Private Ltd, Chennai, India and printed in the UK on acid-free paper. Thorax (ISSN No: 0040–6376) is published monthly by BMJ Publishing Group and distributed in the USA by Air Business Ltd. Periodicals postage paid at Jamaica NY 11431 POSTMASTER: send address changes to Thorax, Air Business Ltd, c/o Worldnet Shipping Inc., 156-15, 146th Avenue, 2nd Floor, Jamaica, NY 11434, USA

Índice Volume 9 Número 5

Thorax com artigos do Archives of Disease in Childhood

setembro / outubro 2025

Edição Portuguesa N.º 5 setembro / outubro 2025 - Volume 9

265	Editorial nacional	296	Asma
269	Editorial	296	O impacto do horário de administração de corticosteroides inalatórios na asma: um ensaio randomizado cruzado com três vias
269	Esta é a guideline unificada sobre asma que estávamos esperando?	303	Doença pulmonar obstrutiva crónica
271	Construindo hipóteses para compreender os efeitos sinérgicos da exposição ao calor e à poluição num clima em mudança	303	Diferenças entre os sexos na DPOC em relação à exposição ao tabagismo: um estudo de coorte baseado na população
272	Artigo original	310	Variabilidade na sensibilidade à inflamação nos músculos e pulmões de doentes com DPOC pode estar relacionada à suscetibilidade à perda da função pulmonar
272	Resultados consensuais entre profissionais de saúde e pais sobre corticosteroides orais no tratamento da sibilância em idade pré-escolar: um estudo multinacional com inquérito e técnica de grupo nominal	318	Revisão do estado arte
278	Resumo de guidelines	318	Pneumonia grave adquirida na comunidade (sCAP): avanços no tratamento e direções futuras
278	Guideline conjunta BTS/NICE/ SIGN sobre asma: diagnóstico, monitorização e gestão da asma crónica (novembro de 2024) – resumo das recomendações	327	Desafios e controvérsias na medicina respiratória
286	Epidemiologia respiratória	327	Cuidados respiratórios sustentáveis: o que realmente importa
286	Incidência e prevalência de asma, doença pulmonar obstrutiva crónica (DPOC) e doença pulmonar intersticial (DPI) entre 2004 e 2023: análises harmonizadas de coortes longitudinais na Inglaterra, País de Gales, Sudeste da Escócia e Irlanda do Norte	330	Ponto de vista
		330	Atenção à lacuna (dos prematuros): a desigualdade na atual abordagem de imunização contra o VSR no Reino Unido deixará muitos bebés prematuros desprotegidos contra o vírus neste inverno
		332	Novo programa para prevenir bronquiolite em bebés

Thorax

com artigos do
**Archives of
Disease in Childhood**

Edição bimestral em língua portuguesa
Editada por:

Medjournal

Rua Bernardo Costa nº127, 1º Esquerdo
2775-809 Carcavelos
Contacto: 938311875
Email: geral@medjournal.pt
www.medjournal.pt
NIF: 510 542 719

General Manager
António Gonçalves

Diretores Médicos
Carlos Robalo Cordeiro
Jaime Correia de Sousa
Mário Morais de Almeida
Teresa Bandeira

A Medjournal não se responsabiliza pela opinião expressa dos autores.
Proibida a reprodução total ou parcial sob qualquer forma, sem autorização prévia do BMJ Publishing Group.



Editor in Chief
Nick Brown
Senior Editor
Rachel Agbeko
Deputy Editors
Claire Lerner (Commissioning)
Ben Stenson (Fetal & Neonatal)
Neelam Gupta (Education & Practice)
Editorial Office
Archives of Disease in Childhood
BMJ Publishing Group Ltd
BMA House
Tavistock Square
London WC1H 9JR, UK
E: info.adc@bmj.com
Twitter: @ADC_BMJ
Senior Production Editor
Malcolm Smith
E: production.adc@bmj.com
ISSN: 0003-9888 (print)
ISSN: 1468-2044 (online)
Impact factor: 3.2
Journal of the Royal College of Paediatrics and Child Health
Disclaimer: ADC is published by BMJ Publishing Group Ltd (a wholly owned subsidiary of the British Medical Association) and the Royal College of Paediatrics and Child Health. The owners grant editorial freedom to the Editor of ADC. ADC follows guidelines on editorial independence produced by the World Association of Medical Editors and the code on good publication practice of the Committee on Publication Ethics. ADC is intended for medical professionals and is provided without warranty, express or implied. Statements in the journal are the responsibility of their authors and advertisers and not authors’ institutions, the BMJ Publishing Group Ltd, the Royal College of Paediatrics and Child Health or the BMA unless otherwise specified or determined by law. Acceptance of advertising does not imply endorsement. To the fullest extent permitted by law, the BMJ Publishing Group Ltd shall not be liable for any loss, injury or damage resulting from the use of ADC or any information in it whether based on contract, tort, or otherwise. Readers are advised to verify any information they choose to rely on.
Copyright © 2025 BMJ Publishing Group Ltd and Royal College of Paediatrics and Child Health. All rights reserved; no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise without prior permission. ADC is published by BMJ Publishing Group Ltd, typeset by Nova Techset Private Limited, Bengaluru & Chennai, India and printed in the UK on acid-free paper from sustainable forests. ADC (ISSN No: 0003-9888) is published monthly by BMJ Publishing Group Ltd and is distributed in the USA by Air Business Ltd. Periodicals postage paid at Jamaica NY 11431 and additional mailing offices. POSTMASTER: send address changes to Archives of Disease in Childhood, Air Business Ltd, c/o Worldnet Shipping Inc., 156-15, 146th Avenue, 2nd Floor, Jamaica, NY 11434, USA

Thorax

ORIGINALITY, RIGOUR AND EXCELLENCE
IN RESPIRATORY MEDICINE

Impact Factor: 9.203

Journal of the
British Thoracic Society

Editorial Board

H Aranibar (Chile)
R Beasley (New Zealand)
J Brown (UK)
J Celedon (USA)
T Fardon (UK)
P Gibson (Australia)
J Grigg (UK)
ML Han (USA)
F Holguin (USA)
I Janahi (Qatar)
A Jones (UK)
A Knox (UK)
F Maltais (Canada)
D Mannino (USA)
S Nathan (USA)
I Pavord (UK)
F Ratjen (Canada)
J Scullion (UK)
J Simpson (UK)
M Steiner (UK)
A Torres (Spain)
Z Udwadia (India)
D Warburton (USA)
M Whyte (UK)

President, British Thoracic Society

Rachael Moses

Publisher

Claire Rawlinson

Associate Publisher

Henry Spilberg

Guidelines for Authors and Reviewers

Full instructions are available online at <http://thorax.bmj.com/pages/authors/>. Articles must be submitted electronically <https://mc.manuscriptcentral.com/thorax>. Authors retain copyright but are required to grant *Thorax* an exclusive licence to publish <https://thorax.bmj.com/pages/authors/>

Aims and Scope: *Thorax* aims to cover all areas of respiratory medicine from paediatric to adults through publishing original papers, systematic reviews and meta-analyses, trial protocols, state of the art reviews, invited editorials, case-based discussions and images. The priorities are originality, rigour and excellence.

Editors-in-Chief

M Griffiths (UK)
C O'Kane (UK)
J Quint (UK)

Deputy Editors

A Bottle (UK)
R Chambers (UK)
M Shankar-Hari (UK)
C Wainwright (Australia)

Associate Editors

M Bafadel (UK)
D Baldwin (UK)
B Blackwood (UK)
K Blythe (UK)
HJ Bogaard (The Netherlands)
F Brimms (Australia)
B Connolly (UK)
GJ Criner (USA)
C Dean (UK)
D Dockrell (UK)
A Floto (UK)
J Honda (USA)
N Hopkinson (UK)
D Jackson (UK)
C Janson (Sweden)
G Kaltsakas (UK)
D Kiely (UK)
B Kirenga (Uganda)
M Knauer (UK)
O M Kon (UK)
G Lee (Australia)
W Lenney (UK)
M Loebinger (UK)
I Mudway (UK)
M Nikolic (UK)
J Park (UK)
J-L Pepin (France)

M Polkey (UK)

J Porter (UK)
R Riha (UK)
L Rose (UK)
J Rylance (UK)
S Saglani (UK)
E Sapey (UK)
M Sauler (USA)
C Scotton (UK)
A Shah (UK)
S Singh (India)
R Stevens (USA)
M Toshner (UK)
K Verhamme (Netherlands)
P Wark (Australia)

Guidelines Associate Editor

I Du Rand (UK)

Statistical Editors

A Douiri (UK)
E Gecili (USA)
M Taghavi Azar Sharabiani (USA)
S Stanojevic (USA)
I Stewart (UK)
R Szczesniak (USA)
Y Wang (UK)

Journal Club Editor

P Murphy (UK)

Social Media Editors

K Diomedes (UK)
P Mehta (UK)

Education Editors

J Park (UK)
S Chatterjee (USA)

Multimedia Editor

Nick Hopkinson (UK)

Contact Details

Editorial Office

Thorax, BMJ Journals, BMA House, Tavistock Square, London, WC1H 9JR, UK
E: thorax@bmj.com
Twitter: @ThoraxBMJ

British Thoracic Society

17 Doughty Street, London WC1N 2PL, UK
T: +44 (0)20 7831 8778
E: bts@brit-thoracic.org.uk
W: <https://www.brit-thoracic.org.uk/>

Customer Support

For general queries and support with subscriptions:
T: +44 (0)20 7111 1105
E: support@bmj.com
W: <https://myaccount.bmj.com/myaccount/customerservice/support-home.html>

Self-archiving and permissions

E: bmj.permissions@bmj.com
W: bmj.com/company/products-services/rights-and-licensing/

Advertising

W: bmj.com/company/for-advertisers-and-sponsor/

Display Advertising ROW

Sophie Fitzsimmons
T: +44 (0)20 3655 5612
E: sfittsimmons@bmj.com

Online Advertising ROW

Marc Clifford
T: +44 (0)20 3655 5610
E: mclifford@bmj.com

Display & Online Advertising Sales Americas

American Medical Communications (AMC)
T: +1 973 214 4374
E: rgordon@americanmedicalcomm.com

Author Reprints

BMJ Reprints Team
E: admin.reprints@bmj.com

Commercial Reprints ROW

Nadia Gurney-Randall
M: +44 (0)7866 262344
E: ngurneyrandall@bmj.com

Commercial Reprints Americas

Ray Thibodeau
T: +1 267 895 1758
M: +1 215 933 8484
E: ray.thibodeau@contentednet.com

Production Editor

Tasnia Nizam
E: production.thorax@bmj.com

For all other journal contacts:

<https://thorax.bmj.com/pages/contact-us/>

Subscription Information

Thorax is published monthly (subscribers receive all supplements)

Institutional Rates 2025

Print
£1019

Online

Site licences are priced on FTE basis and allow access by the whole institution. Details available online at <http://www.bmj.com/company/bmj-for-institutions/> or contact Subscription (see above right).

Personal Rates 2025

Print (includes online access at no additional cost)
£422

Online only

£227
ISSN 0040-6376 (print)
ISSN 1468-3296 (online)

Personal print or online only and institutional print subscriptions may be purchased online at <http://thorax.bmj.com/pages/subscribe/> (payment by (MasterCard/Visa only).

Residents of some EC countries must pay VAT; for details call us or visit <http://www.bmj.com/company/eu-vat-rates/>

Editorial

Nesta edição é apresentado um retrato do momento actual da medicina respiratória, em que se conjuga maturidade científica, inovação terapêutica e urgência ambiental.

Alguns contributos merecem particular destaque. O primeiro, da autoria de Hitasha Rupani, apresenta a nova guideline conjunta BTS/NICE/SIGN sobre asma, como uma resposta consensual às inconsistências históricas nesta área. Esta guideline propõe uma reformulação paradigmática de três domínios críticos: diagnóstico baseado em biomarcadores inflamatórios (FeNO e eosinófilos), terapêutica universal de alívio e de manutenção sempre com fármaco anti-inflamatório, e encaminhamento precoce para especialistas com base em risco biológico. Marca assim um alinhamento inédito com uma prática clínica realista e baseada em valor. Para sistemas como o português, que enfrentam desafios de adesão, capacitação e equidade, esta abordagem integrada oferece ensinamentos práticos.

O segundo editorial, de Sarah Chambliss et al., expande o foco clínico para o impacto das alterações climáticas e da poluição atmosférica, explorando interações complexas e sinérgicas entre temperaturas extremas e poluentes menos estudados, como o formaldeído. Ao demonstrar efeitos de interação específicos entre calor e poluentes em hospitalizações pediátricas por doença respiratória, este estudo reforça a necessidade de métricas ambientais ajustadas, modelos regionais e sistemas de alerta adaptativos, com potencial aplicabilidade à Saúde Pública em Portugal.

Por fim, o artigo original publicado no Archives of Disease in Childhood, conduzido por Bohee Lee et al., destaca o valor do consenso estabelecido entre profissionais de saúde e pais na definição de desfechos relevantes para ensaios clínicos na sibilância pré-escolar tratada com corticosteroides orais. Este estudo internacional, representa um modelo de investigação participativa e centrada no doente, promovendo não apenas a robustez metodológica, mas também a pertinência clínica e ética da investigação pediátrica.

Ao integrar estas três vertentes (1. prática clínica orientada por biomarcadores; 2. resposta ambiental sistémica e 3. Envolvimento de doentes e cuidadores), propõe-se um reposicionamento das nossas especialidades enquanto disciplinas sentinelas da saúde planetária. Na era do Antropoceno, onde os determinantes ambientais e sociais da saúde respiratória se entrelaçam de forma inédita, esta convergência entre guidelines baseadas em evidência, investigação ecológica integrativa e construção participada de valor clínico, representa não apenas um avanço, mas uma exigência ética e científica para as próximas décadas.

Finalmente, é este um momento em que a “luta” anti-infecciosa está muito presente na nossa agenda clínica, pelo que a leitura dos 2 artigos finais sobre imunização ao VSR, ganha ainda maior relevância...

Mário Morais de Almeida

Editor in Chief
Nick Brown
Senior Editor
Rachel Agbeko
Deputy Editors
Claire Lemer (Commissioning Editor)
Ben Stenson (Fetal & Neonatal)
Neelam Gupta (Education & Practice)

Drug Therapy Editor
Dan Hawcutt
Global Child Health Editor
Trevor Duke
Advocacy Editor
Heather Burris
Paediatric Emergency Medicine Editor
Cynthia Mollen
Health Policy Editor
John Puntis
Images Editor
Mark Tighe
Quality Improvement Editor
Claire Lemer
Adolescent Health Editor
Dougal Hargreaves
Social Media and Archimedes Editor
Bob Phillips
Archivist and Lucina Editor
Colin Powell

Voices Editor
Robert Scott-Jupp
Associate Editors
Karel Allegaert
Diana Baralle
Martin Bellman
Sophie Bennett
Frances Bu'lock
Ronny Cheung
David Cottrell
Louise Fleming
Hadeel Hassan
Peter Hoyer
Fyezah Jehan
Vic Larcher
Anne Kelly
Uzma Khan
Daniel Lumsden
Catherine Peters
Colin Powell
Philippa Prentice
A V Ramanan
Andrew Riordan
Helen Sammons
Natasha Saunders
Robert Tasker
Indi Trehan
Paul Turner
Sunitha Vimalasvaran

Guidelines for Authors and Reviewers

Full instructions are available online at <https://adc.bmj.com/pages/authors/>. Articles must be submitted electronically <https://mc.manuscriptcentral.com/adc>. Authors retain copyright but are required to grant *ADC* an exclusive licence to publish (<https://adc.bmj.com/pages/authors/>)

Archives of Disease in Childhood focuses on all aspects of child health and disease from the perinatal period through adolescence

Statistical Editor

Tim Cole

Statistical Advisors

Emmanouil Bagkeris
Mario Cortina Borja
Sarah Donegan
Sara Godward
Marlous Hall
Katie Harron
Eirini Koutoumanou
Sarah Nevitt
Snehal Pinto Pereira
Deborah Ridout
Andrea Sherriff
Lesley Smith
Angie Wade

International Advisors

Zulfi A Bhutta
Leyla Namazova-Baranova

Education & Practice Section Editors

Best practice
Amanda Gwee

Problem solving in clinical practice
Mark Anderson, Mark Tighe

Interpretations
Sam Behjati, Thomas Waterfield

Epilogue
Mark Tighe, Lisa Brown

Guidelines
Philippa Prentice, Emma Dyer

Picket
Giordano Perez-Gaxiola, Rebecca Dalrymple, Amanda Friend

Equipped and Equipment
Alice Roueche, Jane Runnacles

Public Health
Ronny Cheung, Rakhee Shah

Research in Practice
Bob Phillips, John Apps

Medicines update
Amanda Gwee



The Journal of the Royal College of Paediatrics and Child Health



ADC is the official journal of NPPG. NPPG members receive online access to *ADC* via the NPPG website.



Don't wait to read the latest *ADC* articles

Most articles accepted for publication in *ADC* are published online well before they appear in a print issue

- Read the latest articles by following the Online First link at the top right of the homepage (adc.bmj.com)
- Sign up for an email alert to be notified when new content is added (adc.bmj.com/cgi/alerts/etoc)
- Comment on the articles in the *ADC* Blog (<http://blogs.bmj.com/adc/>)

Subscription information

Archives of Disease in Childhood is published monthly plus *Fetal & Neonatal* Edition bimonthly and *Education & Practice* Edition bimonthly (subscribers receive all editions and supplements)

Institutional rates 2025

Print
£1451

Online

Site licences are priced on FTE basis and allow access by the whole institution. Print is available for online subscribers; details available online at <http://group.bmj.com/subscribe?adc> or contact the Subscription Manager in the UK (see above right)

Residents of some EC countries must pay VAT; for details, call us or visit support@bmj.com

Personal rates 2025

Print (includes online access at no additional cost)
£625

Online only
£240

ISSN 0003-9888 (print); 1468-2044 (online)

Personal print or online only and institutional print subscriptions may be purchased online at <https://adc.bmj.com/pages/subscribe/> (payment by Visa/Mastercard only)

Contact Details

Editorial Office

Archives of Disease in Childhood
BMJ Publishing Group Ltd
BMA House, Tavistock Square
London, WC1H 9JR, UK
E: info.adc@bmj.com

Customer Support

For general queries and support with existing and new subscriptions:

T: +44 (0)20 7111 1105

<https://myaccount.bmj.com/myaccount/customerservice/support-home.html>

Self-archiving and Permissions

W: bmj.com/company/products-services/rights-and-licensing/
E: bmj.permissions@bmj.com

Publisher

Christiane Notarmarco

Associate Publisher

Richard Sands

Publishing Executive

Joshua McAlpine
E: jmc Alpine@bmj.com

Senior Production Editor

Malcolm Smith
E: production.adc@bmj.com

Supplement enquiries

E: rsands@bmj.com

Subscriptions (except USA)

For all subscription enquiries and orders

T: +44 (0)20 7111 1105

<https://adc.bmj.com/pages/subscribe/>

Display Advertising Sales – Rest of World

Sophie Fitzsimmons
T: +44 (0)20 3655 5612
E: sfztsimmons@bmj.com
<https://www.bmj.com/company/for-advertisers-and-sponsor/>

Online Advertising Sales

Marc Clifford
T: +44 (0)20 3655 5610
E: mclifford@bmj.com
<http://group.bmj.com/advertising/>

Display & Online Advertising Sales – North America

American Medical Communications (AMC)
T: +1 973 214 4374
E: rgordon@americanmedicalcomm.com

Author Reprints

BMJ Reprints Team
E: admin.reprints@bmj.com

Commercial Reprints – Rest of World

Nadia Gurney-Randall
T: +44 (0)20 8445 5825
M: 07866 262344
E: ngurneyrandall@bmj.com

Commercial Reprints – North America

Ray Thibodeau
T: +1 267 895 1758 (toll free in the USA)
T: +1 215 933 8484 (outside the USA)
E: ray.thibodeau@contentednet.com

Royal College of Paediatrics and Child Health

5–11 Theobalds Road
London WC1X 8SH
T: +44 (0)20 7092 6000
E: enquiries@rcpch.ac.uk
www.rcpch.ac.uk

For all other *Archives* journal contacts

<http://adc.bmj.com/site/help/index.xhtml>

**PROTEJA
O SEU DOENTE
EM TODAS AS FASES
DA DPOC^{1,2}**

**TRAVA
antes que
seja tarde**

**1 em cada 5 doentes
morre no período de 1 ano*
após a primeira exacerbação com
necessidade de hospitalização.³
Não perca mais tempo.**

*após alta hospitalar



**BEVESPI
AEROSPHERE®**

(glicopirrónio/fumarato de formoterol)
Suspensão Pressurizada para Inalação

DPOC, doença pulmonar obstrutiva crónica

Referências: 1. Riltrava Aerosphere 5 microgramas/7,2 microgramas/160 microgramas, suspensão pressurizada para inalação [Resumo das Características do Medicamento]. AstraZeneca AB, SE-151 85 Södertälje Suécia; outubro 2023. Acedido em www.infarmed.pt em novembro 2023. 2. Bevespi Aerosphere 5 microgramas/7,2 microgramas, suspensão pressurizada para inalação [Resumo das Características do Medicamento]. AstraZeneca AB, SE-151 85 Södertälje Suécia; setembro 2023. Acedido em www.infarmed.pt em novembro 2023. 3. Ho TW, Tsai YJ, Ruan SY, Huang CT, Lai F, Yu CJ. In-Hospital and One-Year Mortality and Their Predictors in Patients Hospitalized for First-Ever Chronic Obstructive Pulmonary Disease Exacerbations: A Nationwide Population-Based Study. *Bai C, editor. PLoS ONE*. 2014 Dec 9;9(12):e114866.

Informações essenciais compatíveis com o Resumo das Características do Medicamento

Bevespi Aerosphere 7,2 microgramas/5 microgramas, suspensão pressurizada para inalação. Cada dose única (dose libertada, a dose que sai do aplicador bucal) contém 9 microgramas de brometo de glicopirrónio, equivalente a 7,2 microgramas de glicopirrónio, e 5 microgramas de fumarato de formoterol di-hidratado. Isto corresponde a uma dose calibrada (isto é, a dose que sai da válvula) de 10,4 microgramas de brometo de glicopirrónio, equivalente a 8,3 microgramas de glicopirrónio, e 5,8 microgramas de fumarato de formoterol di-hidratado. **Indicações terapêuticas:** Bevespi Aerosphere é indicado como tratamento broncodilatador de manutenção para o alívio de sintomas em doentes adultos com doença pulmonar obstrutiva crónica (DPOC). **Bevespi Aerosphere** pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, só deve ser utilizado se o benefício esperado for superior ao risco potencial. **Compromisso hepático:** Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Não existem dados relevantes sobre a utilização de Bevespi Aerosphere em doentes com compromisso hepático grave e o medicamento deve ser utilizado com precaução nestes doentes. **População pediátrica:** Não existe utilização relevante de Bevespi Aerosphere em crianças e adolescentes (com idade inferior a 18 anos) para a indicação de DPOC. **Modo de administração:** Utilização por via inalatória. **Instruções de utilização:** Ao acionar Bevespi Aerosphere, um volume de suspensão é expelido do recipiente pressurizado a alta velocidade. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes devem ser instruídos sobre a técnica de inalação correta. É importante instruir o doente para: Ler com atenção as instruções de utilização no folheto informativo, que se encontra dentro da embalagem de cada inalador. Não utilizar o inalador se o agente excicante, contido na bolsa de alumínio, tiver vazado da sua embalagem. Preparar o inalador agitando-o e acionando-o quatro vezes para o ar antes da primeira utilização ou duas vezes quando o inalador não tenha sido utilizado há mais de sete dias, tenha sido exposto a temperaturas baixas ou tenha caído. Para obter uma deposição pulmonar adequada das substâncias ativas, o carregamento da dose tem de ser coordenado com a inalação. Doentes com dificuldade em coordenar o carregamento da dose com a inspiração podem utilizar Bevespi Aerosphere com uma câmara expansora para garantir a administração adequada do produto. Foi demonstrada compatibilidade com a câmara expansora Aerochamber Plus Flow-Vu. **Contraindicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** Não indicado para utilização em situações agudas. Bevespi Aerosphere não é indicado para o tratamento de episódios agudos de broncospasma, isto é, como terapêutica de alívio. **Asma:** Bevespi Aerosphere não deve ser utilizado no tratamento da asma. **Broncospasma paradoxal:** Tal como com outra terapêutica inalatória, a administração deste medicamento pode resultar em broncospasma paradoxal, o qual pode colocar a vida em risco. Se ocorrer broncospasma paradoxal, o tratamento com o medicamento deve ser interrompido e devem ser considerados outros tratamentos. **Efeitos cardiovasculares:** Podem ser observados efeitos cardiovasculares, após a administração de antagonistas dos receptores muscarínicos e simpaticomiméticos, incluindo glicopirrónio ou formoterol. Bevespi Aerosphere deve ser utilizado com precaução em doentes com doenças cardiovasculares graves, tais como cardiopatia isquémica, taquiarritmias ou insuficiência cardíaca grave. Recomenda-se também precaução em doentes com tireotoxicose ou com prolongamento do intervalo QTc conhecido ou suspeito. **Hipocalcemia:** Os agonistas β_2 -adrenérgicos podem causar hipocalcemia significativa, o que pode aumentar a suscetibilidade para arritmias cardíacas. A diminuição do potássio sérico é normalmente transitória, não necessitando de suplementação. Em doentes com DPOC grave, a hipocalcemia pode ser potenciada por hipoxia e tratamento concomitante. **Hiperglicemia:** A inalação de doses elevadas de agonistas β_2 -adrenérgicos pode provocar o aumento da glucose plasmática. **Atividade anticolinérgica:** Devido à sua atividade anticolinérgica, Bevespi Aerosphere deve ser utilizado com precaução em doentes com hiperplasia da próstata sintomática, retenção urinária ou glaucoma de ângulo fechado. **Doentes com compromisso renal grave:** Como o glicopirrónio é excretado predominantemente por via renal, os doentes com compromisso renal grave (depuração de creatinina <30 ml/min), incluindo aqueles com doença renal em fase terminal com necessidade de diálise, apenas devem ser tratados com Bevespi Aerosphere se o benefício esperado superar o risco potencial. **Doentes com compromisso hepático grave:** Em doentes com compromisso hepático grave, Bevespi Aerosphere só deve ser utilizado se o benefício esperado superar o risco potencial. Estes doentes devem ser monitorizados para potenciais reações adversas. **Interações medicamentosas e outras formas de interação:** **Interações farmacocinéticas:** O potencial para interações metabólicas é considerado baixo. Como o glicopirrónio é eliminado principalmente por via renal, podem ocorrer potencialmente interações com medicamentos que afetam os mecanismos de excreção renal. **Interações farmacodinâmicas:** **Outros antimuscarínicos e simpaticomiméticos:** A coadministração de Bevespi Aerosphere com outros medicamentos contendo anticolinérgicos e/ou agonistas β_2 -adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas β_2 -adrenérgicos inalados. Não existe evidência clínica de interações quando utilizado concomitantemente com outros medicamentos para a DPOC, incluindo broncodilatadores β_2 -adrenérgicos de curta duração de ação, metilxantinas e esteroides orais e inalados. **Hipocalcemia induzida por fármacos:** O tratamento concomitante com derivados da metilxantina, esteroides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocalcémico inicial dos agonistas β_2 -adrenérgicos, pelo que se recomenda precaução na sua utilização concomitante. **Bloqueadores β -adrenérgicos:** Os bloqueadores β -adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito dos agonistas β_2 -adrenérgicos, tal como o formoterol. O uso simultâneo de bloqueadores β -adrenérgicos não seletivos ou seletivos deve ser evitado, a não ser que existam razões determinantes para a sua utilização. Se forem necessários bloqueadores β -adrenérgicos (incluindo colírios), dá-se preferência a bloqueadores β -adrenérgicos cardiosseletivos, embora também estes devam ser administrados com precaução. **Outras interações farmacodinâmicas:** Bevespi Aerosphere deve ser administrado com precaução em doentes que estejam a ser tratados com medicamentos conhecidos por prolongar o intervalo QTc. **Fertilidade, gravidez e aleitamento:** **Gravidez:** Não existem dados sobre a utilização de Bevespi Aerosphere em mulheres grávidas. Bevespi Aerosphere só deve ser utilizado durante a gravidez se os benefícios esperados superarem os potenciais riscos. **Amamentação:**

Não é conhecido se o glicopirrónio ou o formoterol são excretados no leite humano. A administração de Bevespi Aerosphere a mulheres que estão a amamentar só deve ser considerada se o benefício esperado para a mãe for superior a qualquer possível risco para o bebé. **Fertilidade:** Considera-se pouco provável que Bevespi Aerosphere, administrado na dose recomendada, afete a fertilidade no ser humano. **Efeitos indesejáveis:** *Frequentes:* Ansiedade, Cefaleia, Tonturas, Boca seca, Náuseas, Espasmos musculares, Infecção do trato urinário, Dor torácica. *Pouco frequentes:* Reações de hipersensibilidade, incluindo erupção cutânea e prurido, Hiperglicemia, Agitação, Irrequietude, Insônia, Tremor, Taquicardia, Palpitações. Arritmias cardíacas (fibrilhação auricular, taquicardia supraventricular e extra-sístoles), Retenção urinária. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaoam> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel.: +351217987373; Linha do Medicamento: 800222444 (gratuita); E-mail: farmacovigilancia@infarmed.pt). **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado:** Tecnimed - Sociedade Técnico-Medicinal, S.A., Rua da Tapada Grande, n.º 2, Abrunheira, 2710-089 Sintra. Informações revistas em outubro 2023. **Para mais informações deverá contactar o representante local do Titular da Autorização de Introdução no Mercado. Medicamento sujeito a receita médica. Medicamento compartilhado pelo Escalão B (69% de participação no regime geral e 84% de participação no regime especial). Versão 2.0 (outubro 2023).**

Informações essenciais compatíveis com o Resumo das Características do Medicamento

Riltrava Aerosphere 5 microgramas/7,2 microgramas/160 microgramas, suspensão pressurizada para inalação. Cada dose única (dose libertada que sai do aplicador bucal) contém 5 µg de fumarato de formoterol di-hidratado, 9 µg de brometo de glicopirrónio, equivalente a 7,2 µg de glicopirrónio e 160 µg de budesonida. Isto corresponde a uma dose calibrada de 5,3 µg de fumarato de formoterol di-hidratado, 9,6 µg de brometo de glicopirrónio, equivalente a 7,7 µg de glicopirrónio e 170 µg de budesonida. **Indicações terapêuticas:** Riltrava Aerosphere é indicado como tratamento de manutenção em doentes adultos com DPOC moderada a grave, que não estão adequadamente tratados com uma associação de um corticosteroide inalado e um agonista beta2 de longa duração de ação ou uma associação de um agonista beta2 de longa duração de ação e um antagonista muscarínico de longa duração de ação. **Posologia e modo de administração:** *Posologia:* A dose recomendada é máxima de 2 inalações 2x/dia (2 inalações de manhã e 2 inalações à noite). Se for omitida uma dose, esta deve ser tomada assim que for possível e a dose seguinte deve ser tomada no horário habitual. Não se deve tomar uma dose a dobrar para compensar uma dose esquecida. *Populações especiais:* **Idosos:** Não é necessário qualquer ajuste de dose em doentes idosos. **Compromisso renal:** Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, apenas se o benefício esperado for superior ao risco potencial. **Compromisso hepático:** Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso hepático grave, o medicamento deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. **População pediátrica:** Não existe utilização relevante deste medicamento em crianças e adolescentes (com idade inferior a 18 anos) para a indicação da DPOC. **Modo de administração:** Para utilização por via inalatória. **Instruções de utilização:** De forma a assegurar uma administração correta do medicamento, o médico ou outro profissional de saúde deve demonstrar ao doente como utilizar corretamente o inalador, e deve monitorizar regularmente a técnica de inalação do doente. O doente deve ser aconselhado a ler com atenção o Folheto Informativo e seguir as instruções de utilização conforme indicado no mesmo. Ao acionar Riltrava Aerosphere, um volume de suspensão é expelido do recipiente pressurizado. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes que têm dificuldade em coordenar o acionamento com a inalação podem utilizar Riltrava Aerosphere com uma câmara expansora para garantir a administração adequada do medicamento. Pode ser utilizado com câmaras expansoras incluindo o Aerochamber Plus ou FlouVu. **Contraindicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** Não indicado para utilização em situações agudas. Este medicamento não é indicado para o tratamento de episódios agudos de broncospasmo, isto é, como terapêutica de alívio. **Broncospasmo paradoxal:** A administração de formoterol/glicopirrónio/budesonida pode produzir broncospasmo paradoxal com sibilos e dispnéia imediatamente após a administração e pode ser potencialmente fatal. O tratamento com este medicamento deve ser imediatamente interrompido se ocorrer broncospasmo paradoxal. O doente deve ser avaliado e instituído tratamento alternativo, se necessário. **Deterioração da doença:** Recomenda-se que o tratamento com este medicamento não seja interrompido abruptamente. Se os doentes não considerarem o tratamento eficaz, devem manter o tratamento, mas tem de se procurar aconselhamento médico. O aumento da utilização de broncodilatadores de alívio indica um agravamento do quadro clínico subjacente e justifica uma reavaliação da terapêutica. A deterioração rápida e progressiva nos sintomas da DPOC é potencialmente fatal e o doente deve ser submetido a avaliação médica urgente. **Efeitos cardiovasculares:** Podem ser observados efeitos cardiovasculares, tais como arritmias cardíacas, p.ex. fibrilhação auricular e taquicardia, após a administração de antagonistas dos receptores muscarínicos e simpaticomiméticos, incluindo glicopirrónio e formoterol. Este medicamento deve ser utilizado com precaução em doentes com doença cardiovascular grave não controlada e clinicamente significativa, tal como cardiopatia isquémica instável, enfarte agudo do miocárdio, cardiomiopatia, arritmias cardíacas, e insuficiência cardíaca grave. Recomenda-se também precaução ao tratar doentes com prolongamento do intervalo QTc (QTc > 450 milissegundos para homens ou > 470 milissegundos para mulheres), conhecido ou suspeito, quer seja congénito ou induzido por medicamentos. **Efeitos sistémicos com corticosteroides:** Podem ocorrer efeitos sistémicos com qualquer corticosteroide inalado, particularmente em doses elevadas prescritas por longos períodos de tempo. Estes efeitos são muito menos prováveis de ocorrer com o tratamento por inalação do que com corticosteroides orais. Os efeitos sistémicos possíveis incluem síndrome de Cushing, manifestações Cushingoides, supressão suprarrenal, diminuição da densidade mineral óssea, cataratas e glaucoma. Devem ser considerados efeitos potenciais na densidade óssea especialmente com a administração de doses elevadas durante longo período de tempo em doentes com fatores de risco coexistentes para osteoporose. **Perturbações visuais:** Podem ser notificadas perturbações visuais com a utilização sistémica e tóxica de corticosteroides. Se um doente apresentar sintomas tais como visão turva ou outras perturbações visuais, o doente deve ser encaminhado para um oftalmologista para avaliação de possíveis causas que podem incluir cataratas, glaucoma ou doenças raras, tais como CRSC, que foram notificadas após a utilização de corticosteroides sistémicos e tópicos. **Transferência de terapêutica oral:** Recomenda-se atenção especial nos doentes que fazem a transição de esteroides orais, uma vez que podem continuar em risco de compromisso da função suprarrenal durante um período de tempo considerável. Os doentes que necessitam de terapêutica com doses elevadas de corticosteroides ou tratamento prolongado com a dose mais elevada recomendada de corticosteroides inalados, podem estar igualmente em risco. Estes doentes podem apresentar sinais e sintomas de insuficiência suprarrenal quando expostos a stress grave. Deve ser considerada cobertura adicional com corticosteroides sistémicos durante períodos de stress ou cirurgia eletiva. **Pneumonia em doentes com DPOC:** Tem sido observado um aumento na incidência de pneumonia, incluindo pneumonia que requer hospitalização, nos doentes com DPOC a receberem corticosteroides inalados. Existe alguma evidência de risco aumentado de pneumonia com o aumento da dose de esteroide, não tendo sido demonstrado de forma conclusiva nos diversos estudos. Não existe evidência clínica conclusiva para diferenças dentro da mesma classe na magnitude do risco de pneumonia entre os medicamentos contendo corticosteroides inalados. Os médicos devem continuar alerta para o possível desenvolvimento de pneumonia em doentes com DPOC pois as características clínicas de tais infeções sobrepõem-se aos sintomas das exacerbações da DPOC. Os fatores de risco para pneumonia em doentes com DPOC incluem tabagismo atual, idade avançada, IMC baixo e DPOC grave. **Hipocalcemia:** A hipocalcemia potencialmente grave pode resultar da terapêutica com agonistas-β. Estes têm o potencial de produzir acontecimentos cardiovasculares adversos. Recomenda-se precaução especial na DPOC grave, pois esse efeito pode ser potencializado pela hipoxia. A hipocalcemia também pode ser potencializada pelo tratamento concomitante com outros medicamentos que podem induzir hipocalcemia, tais como derivados de xantinas, esteroides e diuréticos. **Hiperglicemia:** A inalação de doses elevadas de agonistas β-adrenérgicos pode provocar o aumento da glicose plasmática. A glicemia deve ser monitorizada durante o tratamento de acordo com as orientações estabelecidas para doentes com diabetes. **Condições coexistentes:** Este medicamento deve ser utilizado com precaução em doentes com tirotoxicose. **Atividade anticolinérgica:** Devido à sua atividade anticolinérgica, este medicamento deve ser utilizado com precaução em doentes com hiperplasia da próstata sintomática, retenção urinária ou glaucoma de ângulo fechado. Os doentes devem ser informados sobre os sinais e sintomas do glaucoma de ângulo fechado e devem ser informados para interromper a utilização deste medicamento e contactar o seu médico imediatamente, caso algum destes sinais ou sintomas se desenvolvam. Não é recomendada a administração concomitante deste medicamento com outros medicamentos contendo anticolinérgicos. **Compromisso renal:** Como o glicopirrónio é excretado predominantemente por via renal, os doentes com compromisso renal grave (depuração de creatinina <30 ml/min), incluindo aqueles com doença renal em fase terminal com necessidade de diálise, apenas devem ser tratados com este medicamento se o benefício esperado superar o risco potencial. **Compromisso hepático:** Em doentes com compromisso hepático grave, este medicamento só deve ser utilizado se o benefício esperado superar o risco potencial. Estes doentes devem ser monitorizados para potenciais reações adversas. **Interações medicamentosas e outras formas de interação:** **Interações farmacocinéticas:** Prevê-se que o tratamento em associação com inibidores potentes do CYP3A, por exemplo itraconazol, cetoconazol, inibidores de prótese do VIH e medicamentos que contêm cobistatado, aumente o risco de efeitos indesejáveis sistémicos, e deve ser evitado, a não ser que o benefício seja superior ao risco aumentado de reações adversas aos corticosteroides sistémicos, nesse caso os doentes devem ser monitorizados para reações adversas aos corticosteroides sistémicos. Este facto é de relevância clínica limitada em tratamentos de curta duração (1-2 semanas). Como o glicopirrónio é eliminado principalmente por via renal, podem ocorrer potencialmente interações medicamentosas com medicamentos que afetam os mecanismos de excreção renal. **Interações farmacodinâmicas:** **Outros antimuscarínicos e simpaticomiméticos:** A administração concomitante deste medicamento com outros medicamentos contendo anticolinérgicos e/ou agonistas β-adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas β-adrenérgicos inalados. A utilização concomitante de outros medicamentos beta-adrenérgicos pode ter efeitos potencialmente aditivos; portanto é necessário precaução quando outros medicamentos beta-adrenérgicos são prescritos concomitantemente com formoterol. **Hipocalcemia induzida por medicamentos:** A hipocalcemia pode aumentar a disposição para arritmias em doentes que são tratados com glicosídeos digitálicos. **Bloqueadores β-adrenérgicos:** Os bloqueadores β-adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito do formoterol. O uso simultâneo de bloqueadores β-adrenérgicos deve ser evitado, a não ser que o benefício esperado ultrapasse o risco potencial. Se forem necessários bloqueadores β-adrenérgicos, dá-se preferência a bloqueadores β-adrenérgicos cardioseletivos. **Outras interações farmacodinâmicas:** O tratamento concomitante com quinidina, disopiramida, procainamida, anti-histamínicos, inibidores da monoamina oxidase, antidepressivos tricíclicos e fenotiazinas pode prolongar o intervalo QT e aumentar o risco de arritmias ventriculares. Além disso, L-dopa, L-tirosina, oxitocina e álcool podem prejudicar a tolerância cardíaca aos beta-2-simpaticomiméticos. O tratamento concomitante com inibidores da monoamina oxidase, incluindo medicamentos com propriedades semelhantes como furazolidona e procabazina, pode dar origem a reações hipertensivas. Existe um risco elevado de arritmias em doentes a receberem anestesia concomitante com hidrocarbonetos halogenados. **Fertilidade, gravidez e aleitamento:** A administração deste medicamento a mulheres grávidas só deve ser considerada se o benefício esperado para a mãe justificar o potencial risco para o feto. A administração deste medicamento a mulheres que estão a amamentar só deve ser considerada se o benefício esperado para a mãe for superior a qualquer possível risco para a criança. Considera-se pouco provável que este medicamento administrado na dose recomendada, afete a fertilidade no ser humano. **Efeitos indesejáveis:** *Frequentes:* Candidíase oral; Pneumonia; Hiperglicemia; Ansiedade; Insônia; Cefaleia; Palpitações; Disfonia; Tosse; Náuseas; Espasmos musculares; Infecção do trato urinário. *Pouco frequentes:* Hipersensibilidade; Depressão; Agitação; Irrequietude; Nervosismo; Tonturas; Tremor; Angina de peito; Taquicardia; Arritmias cardíacas (fibrilhação auricular, taquicardia supraventricular e extrasístoles); Irritação da garganta; Broncospasmo; Boca seca; Equimose; Retenção urinária; Dor torácica. *Muito raras:* Sinais ou sintomas de efeitos sistémicos de glucocorticóides, por exemplo supressão suprarrenal; Comportamento anormal. **Desconhecida:** Angioedema; Visão turva; Cataratas; Glaucoma. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaoam> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel.: +351 21 798 73 73; Linha do medicamento: 800 222 444 (gratuita); E-mail: farmacovigilancia@infarmed.pt). **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado:** Tecnimed - Sociedade Técnico-Medicinal, S.A., Rua da Tapada Grande, n.º 2, Abrunheira, 2710-089 Sintra. Informações revistas em abril 2022. **Para mais informações deverá contactar o representante local do Titular da Autorização de Introdução no Mercado. Medicamento sujeito a receita médica. Medicamento compartilhado pelo Escalão B (69% de participação no regime geral e 84% de participação no regime especial). Versão 1.1 (abril 2022).**

Promovido e comercializado por:

Titular de AIM e comercialização:

tecnimede

TECNIMÉDE - Sociedade Técnico-Medicinal, S.A. - Rua da Tapada Grande, n.º 2 2710-089 ABRUNHEIRA, PORTUGAL
Tel.: +351 210 414 100 | Fax: +351 219 412 157
Nif: 500 626 413

PT-M0331 aprovado em 12/2023, revalidado anualmente



AstraZeneca

AstraZeneca Produtos Farmacêuticos, Lda
R. Humberto Madeira n.º 7 | Queluz de Baixo |
2730-097 Barcarena | Contribuinte N.º PT 502 942 240
Capital Social: 1.500.000€ | Mat. Cons. Reg. Com.
Cascais sob o N.º 502942240
Telefone: +351 214 346 100
PT-17303 aprovado em 12/2023

Esta é a *guideline* unificada sobre asma que estávamos esperando?

Hitasha Rupani^{1,2,3}

As *guidelines* da *British Thoracic Society* (BTS), do *National Institute for Health and Care Excellence* (NICE) e da *Scottish Intercollegiate Guidelines Network* (SIGN) para o diagnóstico, monitorização e tratamento da asma crónica, publicadas em novembro de 2024 na revista *Thorax*,¹ representam o primeiro conjunto de recomendações. Durante muitos anos, a existência de múltiplas *guidelines*, frequentemente contraditórias e desalinhas entre si e com orientações internacionais, foi apontada como um dos principais obstáculos à melhoria dos resultados nacionais em asma.² Esta inconsistência também foi associada ao uso subótimo de inaladores anti-inflamatórios (corticosteroides inalados – ICS) e à dependência excessiva de inaladores de alívio. Por isso, estas *guidelines*, desenvolvidas com base em conhecimento clínico, avaliação económica rigorosa e o contributo de um comité experiente, são amplamente bem recebidas e servirão de base para melhorar os resultados da asma no futuro.

Três aspetos fundamentais destas *guidelines* irão transformar a prática clínica. Primeiro, o algoritmo de diagnóstico é o primeiro a incorporar biomarcadores inflamatórios como passo inicial. Dado que a asma é uma doença inflamatória, é surpreendente que nenhuma *guideline* anterior tenha recomendado o uso de biomarcadores no seu diagnóstico. Daqui em diante, em doentes com sintomas sugestivos de asma, níveis elevados de óxido nítrico exalado (FeNO) ou contagem de eosinófilos no sangue (BEC) serão suficientes para estabelecer o diagnóstico. Os clínicos há muito defendem a inclusão de biomarcadores no diagnóstico da asma, e as análises económicas realizadas durante o desenvolvimento destas *guidelines* demonstraram, finalmente, uma convergência entre as recomendações clínicas e a relação custo-eficácia.

¹Department of Respiratory Medicine, University Hospital Southampton NHS Foundation Trust, Southampton, UK

²Clinical and Experimental Sciences, School of Medicine, University of Southampton, Southampton, UK

³NIHR Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

Correspondence to Dr Hitasha Rupani; h.rupani@nhs.net

Segundo o algoritmo de diagnóstico, se os biomarcadores inflamatórios não estiverem elevados, recomenda-se o teste de reversibilidade com broncodilatador. Se este não fornecer um diagnóstico, o próximo passo é o teste de provocação brônquica (BCT). Espera-se que cerca de 50% dos doentes necessitem de encaminhamento para BCT, o que levanta preocupações válidas sobre a capacidade dos cuidados secundários para gerir o volume de encaminhamentos. Ao incorporar a variabilidade do pico de fluxo no processo, se o teste de reversibilidade for adiado, a necessidade de BCT reduz-se para menos de 20%, enquanto não realizar biomarcadores pode aumentar essa necessidade para 70%.³

Como *guideline* do NICE, cada etapa do percurso diagnóstico, juntamente com as várias combinações possíveis dessas etapas, foi submetida a avaliações rigorosas de eficácia clínica e económica. Apesar disso, é provável que surjam questões sobre a implementação do percurso diagnóstico. Estimativas de há alguns anos indicavam que cerca de 50% dos cuidados primários tinham acesso ao FeNO.⁴ As *guidelines* ajudarão a impulsionar a criação de centros comunitários de diagnóstico e, se acompanhadas de investimento em equipamento e formação de pessoal, permitirão um diagnóstico mais rápido e preciso, reduzindo a pressão sobre os cuidados secundários para realizar BCT.

O segundo aspeto fundamental da *guideline* é o algoritmo de tratamento, que recomenda a combinação de ICS com broncodilatador de ação rápida (formoterol) em todas as etapas do tratamento para pessoas com 12 anos ou mais. No momento do diagnóstico, pode ser usado conforme necessário (também conhecido como anti-inflamatório de alívio – AIR) e, se os doentes permanecerem descontrolados, o tratamento é escalado para uso como terapia de manutenção e alívio (MART) com o mesmo inalador. Isto está alinhado com *guidelines* internacionais^{5,6} e tem várias vantagens. Principalmente, garante que todos os doentes com asma recebam ICS, o que está comprovado que reduz a morbilidade e mortalidade relacionadas com a asma.^{7,8} Embora 80% dos doentes com asma no Reino Unido recebam prescrição de ICS,⁹ 55% recolhem menos de cinco inaladores por ano,¹⁰ o que indica níveis elevados de não adesão ao ICS e consequente

monoterapia com inalador de alívio. A estratégia AIR garante perfeita concordância entre o uso de ICS¹¹⁻¹⁴ e inalador de alívio, e os ensaios clínicos mostram que resulta em riscos de exacerbação semelhantes ou inferiores aos da terapia tradicional com ICS em dose baixa regular e, importante, também reduz a inflamação das vias aéreas (medida por FeNO).¹² Além disso, simplifica o tratamento, reflete o comportamento dos doentes (usando mais quando têm sintomas e menos quando estão bem) e tem uma pegada de carbono mais baixa.¹⁵

A implementação do algoritmo de gestão recomendado apresentará desafios. Os doentes estão habituados a transportar consigo o inalador de alívio “azul”. A mudança para longe do “inalador azul” exigirá tempo e educação. Atualmente, apenas certos inaladores estão licenciados para terapia AIR e MART, mas o seu papel destacado nas diretrizes deverá incentivar a indústria farmacêutica a avançar com a aprovação regulamentar de mais inaladores.

O terceiro aspeto fundamental é a orientação clara sobre quando encaminhar doentes adultos para um especialista em asma. Mais uma vez, as *guidelines* enfatizam a importância dos biomarcadores inflamatórios (FeNO e BEC) na gestão da asma. Se os doentes em MART com dose moderada permanecerem descontrolados e apresentarem biomarcadores elevados, recomenda-se o encaminhamento. Esta é uma recomendação importante, pois esses doentes têm elevado risco de exacerbações,¹⁶⁻¹⁸ e o encaminhamento precoce permite uma intervenção atempada, incluindo tratamentos biológicos. Mais de 50% dos doentes que iniciam biológicos no Reino Unido estão descontrolados há mais de dois anos,¹⁹ e espera-se que a recomendação clara nas novas *guidelines* melhore esta situação. Se nenhum biomarcador estiver elevado, são apropriadas e recomendadas tentativas sequenciais com antagonistas dos recetores de leucotrienos e antagonistas muscarínicos de longa duração. As *guidelines* também recomendam especificamente contra o uso de ICS em dose elevada sem supervisão especializada. Os riscos dos ICS em dose elevada são bem reconhecidos,²⁰ e apesar das recomendações de que devem ser prescritos apenas a 5–10% dos doentes com asma grave, 20% de todas as prescrições de ICS na Inglaterra são de dose elevada.¹⁰

Para responder à pergunta colocada no título, a resposta é “sim”. As recomendações arrojadas e transformadoras destas *guidelines* são um desenvolvimento bem-vindo. Embora a implementação exija tempo e investimento, a inclusão de avaliação económica em cada etapa oferece uma garantia valiosa às equipas clínicas e aos responsáveis pelos serviços. Ao melhorar o diagnóstico, facilitar a adesão ao ICS e garantir o encaminhamento atempado de doentes de alto risco para especialistas, estas *guidelines* representam uma abordagem custo-eficaz para melhorar os resultados da asma a nível nacional.

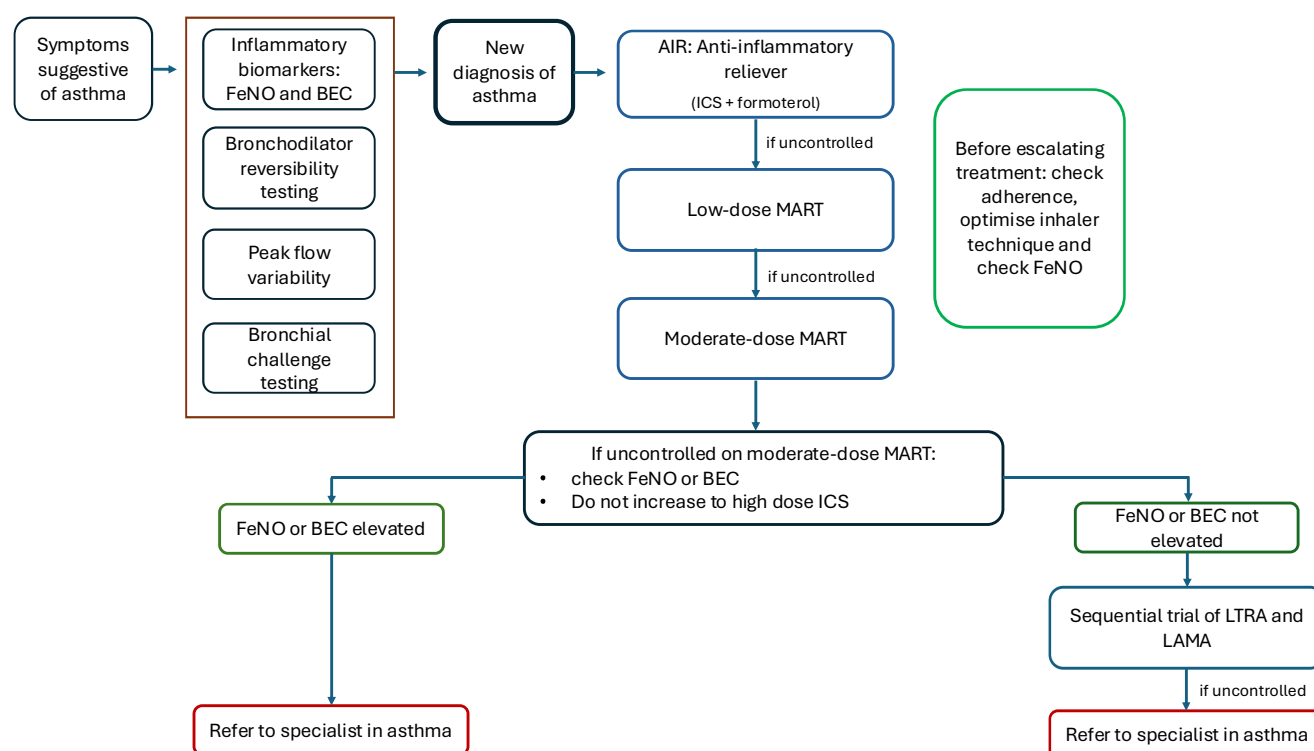


Figure 1 Diagnosis and management of asthma in adults, adapted from BTS/SIGN/NICE Joint Guideline for the Diagnosis, Monitoring and Management of Chronic Asthma.¹ BEC, blood eosinophil count; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; MART, maintenance and reliever therapy.

X Hitasha Rupani @tasha_rupani

Contributors HR conceived and wrote the manuscript.

Funding HR is supported by a Research Leaders Fellowship from University Hospital Southampton

Competing interests HR has received advisory board and speaker fees from GSK, Chiesi, AstraZeneca, Sanofi and Boehringer Ingelheim; conference support from AZ and Sanofi and grant funding to her institution from AZ and GSK.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

© Author(s) (or their employer(s)) 2025. No commercial re-use.

See rights and permissions. Published by BMJ Group.



To cite Rupani H. Thorax 2025;80:403–405.

Accepted 17 February 2025

Published Online First 24 April 2025



→ <https://doi.org/10.1136/thorax-2024-222910>
Thorax 2025;80:403–405.

doi:10.1136/thorax-2025-223056

ORCID iD

Hitasha Rupani <http://orcid.org/0000-0002-0150-138X>

REFERENCES

- 1 BTS/sign/nice joint guideline for the diagnosis, monitoring and management of chronic asthma. 2024 Available: <https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma>
- 2 All Party Parliamentary Group for Respiratory Health. All party parliamentary group for respiratory health, improving asthma outcomes in the uk. Available: <https://edwebcontent.ed.ac.uk/sites/default/files/atoms/files/appg-asthma-report-2020.pdf> [Accessed Feb 2025].
- 3 Asthma: diagnosis, monitoring and chronic asthma management. Cost-utility analysis: most cost-effective sequence or combination of tests to diagnose asthma. 2024. Available: <https://www.nice.org.uk/guidance/ng245/evidence/costutility-analysis-mostcosteffective-sequence-or-combination-of-tests-to-diagnose-asthma-pdf-13558289293> [Accessed Feb 2025].
- 4 NHS. NHS accelerated access collaborative: fractional exhaled nitric oxide (feno). Available: <https://healthinnovationwessex.org.uk/img/projects/FeNO%20-%20national%20programme%20impact%20report%20-%20FINAL-1689322592.pdf> [Accessed Feb 2025].
- 5 Global Initiative for Asthma. Global strategy for asthma management and prevention. 2024. Available: www.ginasthma.org [Accessed Jan 2025].
- 6 Reddel HK. Updated Australian guidelines for mild asthma: what's changed and why? *Aust Prescr* 2020;43:220–4.
- 7 Suissa S, Ernst P, Benayoun S, et al. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:332–6.
- 8 Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. *Thorax* 2002;57:880–4.
- 9 Bloom CI, Saglani S, Feary J, et al. Changing prevalence of current asthma and inhaled corticosteroid treatment in the UK: population-based cohort 2006–2016. *Eur Respir J* 2019;53:1802130.
- 10 NHS. NHS business services authority dashboard. Available: <https://www.nhs.uk/accessour-data-products/epact2/dashboards-and-specifications/respiratory-dashboard> [Accessed Feb 2025].
- 11 O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. *N Engl J Med* 2018;378:1865–76.

- 12 Beasley R, Holliday M, Reddel HK, et al. Controlled Trial of Budesonide-Formoterol as Needed for Mild Asthma. *N Engl J Med* 2019;380:2020–30.
- 13 Bateman ED, Reddel HK, FitzGerald JM. As-Needed Budesonide-Formoterol in Mild Asthma. *N Engl J Med* 2018;379:898.
- 14 Hardy J, Baggott C, Fingleton J, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet* 2019;394:919–28.
- 15 Hatter L, Holliday M, Eathorne A, et al. The carbon footprint of as-needed budesonide/formoterol in mild asthma: a post hoc analysis. *Eur Respir J* 2024;64:2301705.
- 16 Kraft M, Brusselle G, FitzGerald JM, et al. Patient characteristics, biomarkers and exacerbation risk in severe, uncontrolled asthma. *Eur Respir J* 2021;58:2100413.
- 17 Pavord ID, Holliday M, Reddel HK, et al. Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. *Lancet Respir Med* 2020;8:671–80.
- 18 Couillard S, Laugerud A, Jabeen M, et al. Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide. *Thorax* 2022;77:199–202.
- 19 Rupani H, Rose J, Cumella A. P145 What is the severe asthma patient journey to biologic initiation in uk severe asthma centres? British Thoracic Society Winter Meeting 2022, QEII Centre, Broad Sanctuary, Westminster, London SW1P 3EE, 23 to 25 November 2022, Programme and Abstracts; 2022
- 20 Bloom CI, Yang F, Hubbard R, et al. Association of Dose of Inhaled Corticosteroids and Frequency of Adverse Events. *Am J Respir Crit Care Med* 2024;211:54–63.

Construindo hipóteses para compreender os efeitos sinérgicos da exposição ao calor e à poluição num clima em mudança

Sarah Chambliss,¹ Ifeanyichukwu C Nduka,² Geeta G Persad²

O aumento da intensidade, frequência e duração dos eventos climáticos extremos devido às alterações climáticas representa uma ampla gama de riscos para a saúde.¹ Os efeitos sinérgicos de temperaturas extremas combinadas com outras exposições perigosas, como a poluição do ar, podem resultar em riscos mais elevados de mortalidade por todas as causas e de morbilidade cardiovascular e respiratória do que a exposição a cada fator isoladamente.^{2,3} Existem vários mecanismos hipotéticos para esse efeito de interação, incluindo maior suscetibilidade aos efeitos do calor em condições crônicas influenciadas pela poluição do ar, agravamento dos efeitos da poluição devido ao stresse induzido pela temperatura e vias fisiopatológicas partilhadas (por exemplo, inflamação sistêmica), embora os mecanismos fisiológicos específicos ainda não sejam bem compreendidos.²

Neste editorial, discute-se esse aspeto com base num estudo publicado por Cheng *et al.* neste número intitulado “Exposição combinada a formaldeído ambiente e altas temperaturas e admissões por doenças respiratórias em crianças: um estudo de séries temporais em várias cidades”.⁴

A expansão das tecnologias de monitorização ambiental fornece dados de temperatura e poluição com elevada resolução espacial e temporal e cobertura global, o que facilita a investigação dos impactos na saúde de múltiplas coexposições a temperatura e poluição.² No entanto, a riqueza desses dados também apresenta desafios metodológicos: quando a exposição pode ser quantificada em várias dimensões, os investigadores devem considerar cuidadosamente quais métricas escolher para responder a hipóteses específicas sobre os mecanismos biológicos subjacentes ao efeito de interação.

No estudo discutido, os autores aplicaram a abordagem de risco relativo por interação para examinar possíveis interações entre exposição a altas temperaturas e formaldeído (HCHO), um poluente raramente considerado em estudos de poluição atmosférica. Cheng *et al.* analisaram 12 cenários

de exposição, combinando quatro variações de intensidade e três variações de sequência temporal. A única situação com interação estatisticamente significativa foi aquela em que um período de ≥ 48 horas com temperaturas acima do percentil 95 precedeu, mas não coincidiu com, um período de ≥ 24 horas com HCHO acima do percentil 90. Não foram observados riscos de interação em períodos com temperaturas mais baixas, concentrações menores de HCHO ou outras sequências temporais. Embora esta observação possa sugerir um possível efeito de sensibilização da temperatura elevada na suscetibilidade à morbilidade respiratória relacionada com HCHO, as métricas utilizadas não foram escolhidas especificamente para investigar esse mecanismo, que merece estudo adicional noutras populações.

Outros estudos recentes também demonstraram que a escolha da métrica de temperatura (por exemplo, temperatura horária, média diária ou medidas de variabilidade térmica) afeta a magnitude dos efeitos estimados, e que considerar a variação horária pode capturar efeitos cardiovasculares que as médias diárias não conseguem. Os autores destacam a necessidade de selecionar métricas específicas para cada hipótese testada.^{5,6}

Outro aspeto crítico dos efeitos sinérgicos da coexposição é que as variáveis climáticas não são independentes. Temperatura, humidade relativa e velocidade do vento apresentam covariância temporal significativa, influenciando tanto o clima como a qualidade do ar. Por exemplo, inversões térmicas sazonais e condições de ar estagnado no inverno podem aprisionar poluentes, levando a concentrações mais elevadas de partículas finas (PM_{2.5}) e dióxido de azoto,^{7,8} enquanto a elevada humidade e temperatura podem intensificar a formação de poluentes secundários como ozono e PM_{2.5} através de reações fotoquímicas.⁹ Devido a essas conexões mecanísticas, a possibilidade de fatores de confusão deve ser cuidadosamente considerada, e a escolha das métricas para resumir essas variáveis também exige atenção rigorosa.

Embora os autores tenham controlado as concentrações médias diárias de PM_{2.5}, não conseguiram incluir a composição das partículas, os extremos diários ou as concentrações de alguns precursores de PM. Como a covariância entre parâmetros meteorológicos e poluição varia significativa-

mente entre zonas climáticas, é útil examinar questões de interação em várias regiões geográficas.

A observação de que os efeitos na saúde de poluentes como o HCHO são amplificados após períodos de altas temperaturas pode ajudar a informar sistemas de alerta de risco, mesmo sem um conhecimento completo dos mecanismos fisiológicos subjacentes. No entanto, uma compreensão biológica mais profunda dos efeitos de interação entre calor e poluição atmosférica pode melhorar as intervenções — especialmente à luz do aumento dos eventos extremos de temperatura e poluição associados às alterações climáticas.

Contributors SC (guarantor): conceptualisation, writing—original draft, writing—review and editing. IN: writing—review and editing. GP: writing—review and editing.

Funding This study was funded by the National Institute of Environmental Health Sciences 1R01ES034803-01, U.S. Department of Energy DE-SC0023216

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

© Author(s) (or their employer(s)) 2025. No commercial re-use.

See rights and permissions. Published by BMJ Group.



To cite Chambliss S, Nduka IC, Persad GG. Thorax 2025;80:412–413.
Accepted 2 April 2025
Published Online First 16 April 2025



→ <https://doi.org/10.1136/thorax-2025-222709>
Thorax 2025;80:412–413.

doi:10.1136/thorax-2025-222323

ORCID iD

Sarah Chambliss <http://orcid.org/0000-0002-6170-1789>

REFERENCES

- 1 Ebi KL, Vanos J, Baldwin JW, et al. Extreme Weather and Climate Change: Population Health and Health System Implications. *Annu Rev Public Health* 2021;42:293–315.
- 2 Anenberg SC, Haines S, Wang E, et al. Synergistic health effects of air pollution, temperature, and pollen exposure: a systematic review of epidemiological evidence. *Environ Health* 2020;19:130.
- 3 Rahman MM, McConnell R, Schlaerth H, et al. The Effects of Coexposure to Extremes of Heat and Particulate Air Pollution on Mortality in California: Implications for Climate Change. *Am J Respir Crit Care Med* 2022;206:1117–27.
- 4 Cheng Y, Zhang M, Zheng H, et al. Ambient formaldehyde combined with high temperature exposure and respiratory disease admissions among children: a time-series study across multiple cities. *Thorax* 2025;80:457–65.
- 5 Rowland ST, Boehme AK, Rush J, et al. Can ultra short-term changes in ambient temperature trigger myocardial infarction? *Environ Int* 2020;143:105910.
- 6 Rowland ST, Parks RM, Boehme AK, et al. The association between ambient temperature variability and myocardial infarction in a New York-State-based case-crossover study: An examination of different variability metrics. *Environ Res* 2021;197:111207.
- 7 Rowland OE. Comparative analysis of meteorological parameters and their relationship with NO₂, PM₁₀, PM_{2.5} and O₃ concentrations at selected urban air quality monitoring stations in Krakow, Paris, and Milan. *Discov Environ* 2024;2:75.
- 8 Wallace J, Kanaroglou P. The effect of temperature inversions on ground-level nitrogen dioxide (NO₂) and fine particulate matter (PM_{2.5}) using temperature profiles from the Atmospheric Infrared Sounder (AIRS). *Sci Total Environ* 2009;407:5085–95.
- 9 Nguyen D-H, Lin C, Vu C-T, et al. Tropospheric ozone and NO_x: A review of worldwide variation and meteorological influences. *Environ Technol Innov* 2022;28:102809.

¹Department of Population Health, The University of Texas at Austin Dell Medical School, Austin, Texas, USA

²The University of Texas at Austin Jackson School of Geosciences, Austin, Texas, USA

Correspondence to Dr Sarah Chambliss; sechambliss@utexas.edu

ARTIGO ORIGINAL

Resultados consensuais entre profissionais de saúde e pais sobre corticosteroides orais no tratamento da sibilância em idade pré-escolar: um estudo multinacional com inquérito e técnica de grupo nominal

Bohee Lee,^{1,2,3} Stephen W Turner,⁴ Jasmine Hine,^{1,3} Ann McMurray,^{1,5} Damian Roland,^{6,7} Meredith Louise Borland,^{8,9} Peter Csonka,^{10,11} Jonathan Grigg,¹² Theresa W Guilbert,^{13,14} Tuomas Jartti,^{15,16} Abraham Oommen,¹⁷ Steff Lewis,^{1,18} Steve Cunningham¹⁹

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/archdischild-2024-327696>).

For numbered affiliations see end of article.

Correspondence to
Dr Bohee Lee; blee5@ic.ac.uk

Received 16 July 2024 Accepted 17 December 2024
Published Online First 15 January 2025

RESUMO

Objetivo: Obter consenso prioritário sobre medidas de resultado no tratamento com corticosteroides orais para sibilância em idade pré-escolar, representando os grupos de interesse.

Desenho: (1) Revisão sistemática para identificar medidas de resultado; (2) Inquérito internacional com profissionais de saúde e reunião nominal com pais; (3) Reunião final de consenso com investigadores clínicos, médicos de urgência pediátrica e o mesmo grupo de pais.

Principais medidas dos resultados: Prioridade consensual das medidas de tratamento, diferenças mínimas clinicamente importantes (MCIDs) e nível de preocupação com efeitos adversos.

Resultados: Após processo interativo com profissionais de saúde e pais, o consenso final sobre o desfecho primário foi o Índice de Gravidade da Sibilância (WSS). Os desfechos secundários priorizados foram: nova visita ao médico ou urgência, reinternamento, duração da hospitalização, tempo até retorno ao normal, número de doses de beta-agonistas de curta duração e necessidade de novo curso de corticosteroides. Comparado com placebo, os clínicos consideraram como MCID mediana uma mudança de 40% no WSS às 4 horas e 50% às 12 horas; 5 horas para duração da hospitalização e 2 dias para retorno ao normal. Os pais identificaram MCIDs frequentemente superiores aos efeitos fisiológicos observados nos ensaios. A maior preocupação foi com múltiplas doses de corticosteroides.

Conclusões: Os participantes priorizaram a mudança no WSS como principal medida de resultado. O estudo demonstrou o potencial do envolvimento de pais e doentes na co-criação de desfechos clínicos. Incorporar esses resultados em futuros ensaios clínicos permitirá uma avaliação mais holística do impacto do tratamento, garantindo desfechos relevantes.

INTRODUCTION

Short courses of oral corticosteroids (OCS) are commonly used to treat acute severe wheeze in children aged 12–71 months (preschool wheeze, aPSW). In recent decades, several clinical trials have assessed the efficacy of OCS for this age group, but evidence has been inconsistent.^{1–4}

Currently, outcome measures and endpoints for treatment with OCS for preschool wheeze vary across the trials, limiting the ability of evidence synthesis that could inform guidelines. A systematic review including 10 studies in 2016 was able to use fewer than five studies for each outcome measure, reducing the power of overall evidence.⁵

Additionally, it has been unclear whether clinically relevant outcome measures are meaningful to patients or caregivers/parents. Parents may offer valuable perspectives that may be different from those prioritised by clinicians or healthcare

Key messages

What is known about this topic

- Acute wheezing episodes are very common for preschoolers, that is, aged 12–71 months, and oral corticosteroids (OCS) are widely used.
- Evidence on the efficacy of OCS is inconsistent, and trials used different outcomes to assess the efficacy of OCS as a treatment for preschool wheeze.
- There is no consensus on outcome measures of OCS treatment.

What this study adds

- This study co-created consensus outcome measures for OCS treatment agreed on by healthcare professionals and parents of children who have lived experience of acute preschool wheeze.
- Healthcare professionals and parents prioritised change in Wheezing Severity Score as the most favourable outcome measure.

How this study might affect research practice or policy

- Our study demonstrated that parent/patient engagement is key to ensuring relevant patient research outcomes.
- Our findings can be used in the design of future clinical studies to provide a more holistic assessment of the impact of treatment.



© Author(s) (or their employer(s)) 2025. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Lee B, Turner SW, Hine J, et al. Arch Dis Child 2025;110:521–527.

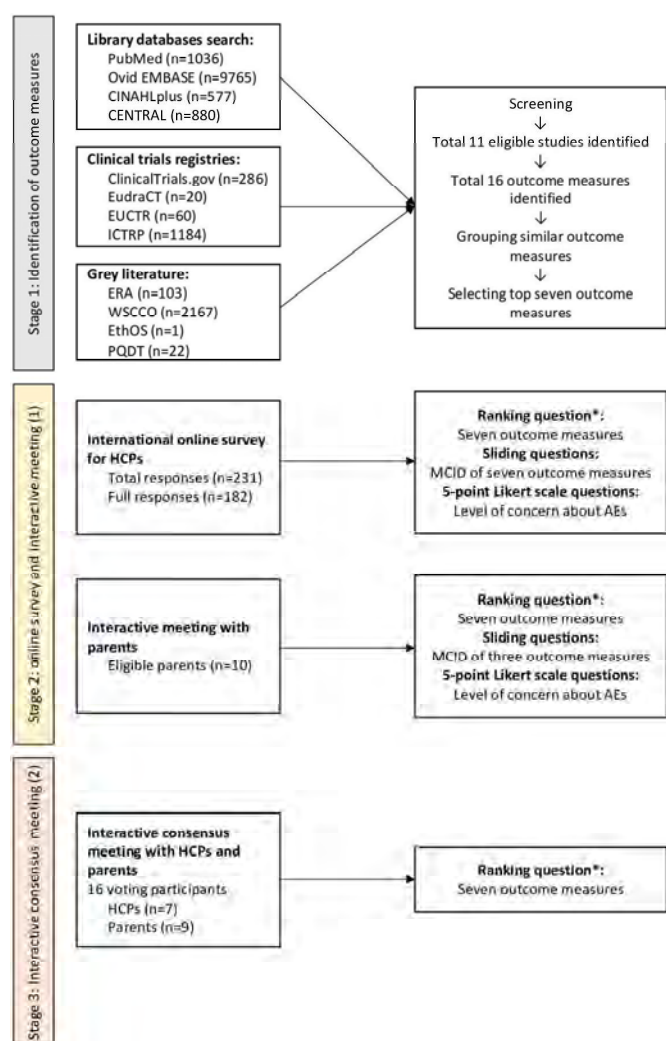


Figure 1 Overview of the consensus outcome. *Primary outcome. AEs, adverse events; HCPs, healthcare professionals; MCID, minimal clinically important difference.

(healthcare professional (HCP) group and parent group), (b) the minimal clinically important difference (MCID) of each outcome measure and (c) perspectives on adverse events (AEs) (stage 2); and (3) to determine final prioritisation of outcome measures (stage 3) (figure 1).

In stage 1, systematic searches for trials, published between 1994 and 2020, examining the efficacy of OCS for aPSW were performed in eight databases and clinical trials, along with grey literature and citation screening (online supplemental document p1). Details of the search strategy are published elsewhere as part of a systematic review and individual patient meta-analysis of randomised clinical trials of OCS for aPSW.⁷ We identified a preliminary list comprised of outcome measures reported ≥ 2 across the included trials. Similar outcome measures were grouped into one to simplify the list. The final set of outcome measures was selected for the next stages (online supplemental table 1).

In stages 2 and 3, a hypothetical scenario was provided to help participants understand the background for OCS prescription and standardise various situations where preschool children with acute wheezing episodes present to a hospital and might be considered for, or receive, OCS (online supplemental table 2). A nominal group technique (NGT) was employed in all group meetings. Meetings were held online for 1 hour, involving a two-round voting system using mentimeter.⁸ Details for the NGT process are described in online supplemental figure 1.

In stage 2, HCPs and then parents were invited to participate separately and sequentially. We used both convenience and snowball sampling methods to identify potential participants.

International HCP survey

An online single survey was delivered via the Qualtrics platform⁹ from 12 January 2022 to 7 March 2022. Any board-certified clinicians who prescribe OCS for acute preschool wheeze were invited regardless of nationalities, hospital settings, specialities or years of work experience. They were identified through mailing lists of national or international networks of our research team, including the international membership of the European Respiratory Society; the UK Royal College of Paediatrics and Child Health; Asthma UK Centre for Applied Research; Paediatric Emergency Research UK and Ireland; General and Adolescent Paediatric Research in UK and Ireland; and local hospital networks.

Parents-only NGT meeting

Parents were identified through the study advertisement in local communities, personal invitations in clinics and flyers in waiting rooms in the Royal Hospital for Children and Young People in Edinburgh, UK.

Parents who had lived experience of their children receiving OCS for the treatment of one or more acute wheezing episodes when they are/were 12 to 71 months of age were invited to an interactive online meeting convened via Zoom on a single occasion.

Both groups were asked to answer questions in three sections (online supplemental table 3). The first section asked to rank the outcome measures derived from stage 1 in order of importance based on their experience. The second section asked to demarcate an MCID for several outcome measures compared with a placebo. In the final section, 5-point Likert scale questions were used to express different levels of concern for potential AEs (1=not-at-all to 5=extremely). A list of AEs was based on the medication patient information leaflet¹⁰ and a recent systematic review.¹¹ We added 'multiple uses of OCS due to recurrent wheeze' to encompass longer-term AEs associated with repeated treatment. For parents, questions for MCID and AEs were slightly modified to support focused engagement, asking MCIDs only for the top three priority outcome measures selected from the HCP survey (for this reason, the meeting with parents was subsequent to the online survey completion), three most concerning AEs for the short-term OCS course and their perception of the longer-term risks/AEs associated with multiple OCS courses.

In stage 3, we invited the same parents from stage 2 and 'key HCPs' to a consensus meeting. We used a convenience sampling method and invited key HCPs who agreed to participate in the study. These key HCPs included the chief investigators of the clinical trials identified from the systematic review, who conducted trials in the UK, USA, Australia and Finland. To increase input from paediatric emergency medicine where OCS for children are most frequently prescribed in a hospital setting, we invited a clinician who agreed to participate and contribute to this study.

All analyses were done using R (V.4.2.2). Descriptive analyses were performed to explore and characterise the survey and group meeting results. The average ranking for each outcome measure was calculated by applying weights in reverse for a ranking question. For the Likert scale questions, a total score for each item was calculated and compared. Qualitative contents during the discussion in stage 3 were obtained to summarise key arguments of stakeholders.

RESULTS

Stage 1: a set of outcome measures from literature

After the screening, 11 trials were retained^{1–4 12–18} and seven outcome measures were identified: length of hospital stay (LOS), change in Wheezing Severity Score (WSS—we used this term to encompass the various symptom scoring systems employed across the studies⁷), time back to normal, doses of short-acting beta-agonists (SABA), rehospitalisation, revisit to general practice (GP)/emergency department (ED) and additional steroid course. The frequency of the outcome measures is summarised in online supplemental figure 2.

Stage 2: (a) priority of outcome measures

Analysis generated four themes: (1) pathway to diagnosis, (2) medication management, (3) living with PSW and (4) improving PSW healthcare. Illustrative quotations are presented in table 3.

Stage 2: (a) priority of outcome measures

In total, 253 HCPs from 44 countries consented to participate in the survey, of which 231 responses were obtained, including 182 completed responses (table 1). Respondents were most prominently from the UK (93, 40.3%) and non-UK European countries (84, 36.4%). Specialist respiratory paediatricians/pulmonologists accounted for most responses (117, 50.6%). No difference was found in participant characteristics between incomplete and complete responses.

Ten parents participated in the interactive meeting, with one parent per household. Characteristics of their children are summarised in online supplemental table 4.

Figure 2 summarises the priority results for outcome measures from each group. According to 231 HCPs (231/253, 91.3%), the highest rank was LOS, followed by ‘Change in WSS’ and ‘Time back to normal’. In contrast, the parent group (n=10) assigned the highest rank to ‘Change in WSS’, followed by ‘Rehospitalisation’ and ‘Time back to normal’. LOS remained among the bottom three outcomes.

Stage 2: (b) minimal clinically important difference

The MCIDs reported by each stakeholder group were summarised (online supplemental table 5). For HCPs, the MCID for LOS was a median of 5.0 hours (IQR 4.0–6.0 hours) compared with the non-treatment group. For the change in WSS, the MCIDs were a median reduction of 40.0% (IQR 29.0–51.0%) and 50.0% (IQR 37.0–62.5%) at 4 and 12 hours, respectively. However, parents perceived 6.5 hours (IQR 5.3–8.0 hours) as a median MCID for LOS and median 88.5% (IQR 78.3–100.0%) and 80.5% (IQR 76.3–92.8%) reduction at 4 and 12 hours for the change in WSS.

Stage 2: (c) level of concern about AEs

Among AEs, those associated with the most clinical concern (very or extremely concerned) was ‘Multiple steroid use’ (60.2%) (figure 3, online supplemental table 6). When parents were asked about the most concerning short-term AEs, the majority selected multiple steroid use and their associated AEs (8/10, 80.0%) and vomiting (4/10, 40.0%) (online supplemental table 7).

Stage 3: consensus outcome measures

In stage 3, seven key HCPs and nine of the 10 same parents participated in the NGT group meeting. After two votes and discussion, ‘Change in WSS’ was agreed as a consensus primary outcome measure (figure 4).

Change in rankings of outcome measures between the first and the second vote is summarised in online supplemental table 8. During the discussion, clinical study investigators initially gave the highest rank to LOS. However, conflicting opinions were expressed regarding LOS. Some clinicians commented that LOS was most clinically relevant and would allow families to go home sooner. Furthermore, a shorter LOS may be an indicator of how fast OCS attenuates the duration of symptoms, with reducing LOS a priority in clinical practice to ensure patients are discharged from the hospital without unnecessary delay. Others argued that LOS may be an unreliable measure as it is affected by additional factors such as the hospital organisation, timing of clinical review or social factors relating to transport home. Parents expressed a perspective that once in the hospital, life had been disrupted and their wish was to see their child’s wheeze improve to a more stable position more quickly. The discussion coalesced around the observation that the parent perspective (more rapid reduction in WSS) could be consistent with the clinician perspective (reduction in LOS), but because of the additional factors determining LOS the converse may not necessarily be true. For this reason, the group consensus was a preference to have measurable tools of disease severity, such as Paediatric Respiratory Assessment

Table 1 Demographic characteristics of HCPs participated in the online international survey

Category	Total responses (N=231)	Complete responses (N=182)
Mean years of experience* (SD)	17.9 (9.6)	18.2 (9.7)
Regions (N, %)		
European	177 (76.7)	147 (80.8)
UK	93 (40.3)	81 (44.5)
Europe	84 (36.4)	66 (36.3)
Western Pacific	19 (8.3)	13 (7.1)
Australia	17 (7.4)	11 (6.0)
New Zealand	2 (0.9)	2 (1.1)
America	15 (6.5)	10 (5.5)
South America	8 (3.5)	4 (2.2)
North America	7 (3.0)	6 (3.3)
South-East Asian	9 (3.9)	7 (3.8)
Eastern Mediterranean	6 (2.6)	3 (1.6)
Caribbean	1 (0.4)	0 (0.0)
Africa	3 (1.3)	0 (0.0)
Not answered	2 (0.9)	2 (1.1)
Job title (N, %)		
Specialist respiratory paediatrician/pulmonologist	117 (50.6)	89 (48.9)
General paediatrician with a special interest in respiratory medicine	36 (15.6)	29 (15.9)
Emergency medicine doctor	29 (12.6)	26 (14.3)
General paediatrician	11 (4.8)	10 (5.5)
General practitioner	9 (3.9)	8 (4.4)
Respiratory nurse specialist	8 (3.5)	5 (2.7)
Advanced nurse practitioner	8 (3.5)	5 (2.7)
Trainee	8 (3.5)	6 (3.3)
Allergist	4 (1.7)	3 (1.6)
Clinical research nurse	1 (0.4)	1 (0.5)

HCPs, healthcare professionals; SD, Standard deviation.

Measure (PRAM), as they could be more robust in assessing the efficacy of the treatment for resolving symptomatology.

Readmission to the hospital and revisit to GP/ED were considered almost equally important tools to measure the preventative effects of OCS. Some remarked that these two are critical for families because revisiting hospitals or GPs can be a distressing and disruptive event for them. The majority did not agree that additional steroid course and doses of SABA could be considered a reliable outcome measurement given the infrequent need for additional steroids and high variance in practice for the use of SABA post-discharge.

DISCUSSION

This is the first study using co-creation to identify consensus outcome measures of OCS treatment for aPSW by examining the key stakeholders’ perspectives. The priority of outcome measures for OCS treatment on aPSW was different between clinical trials and between the HCPs and the parent group. The HCPs and parents agreed on ‘change in WSS’ as a key outcome measure. There was also a consensus for focus on potential medium-term impacts on airway inflammation from OCS, that is, revisit to GP/ED and re-hospitalisation. Greater reductions in LOS and WSS were meaningful for parents compared with HCPs. Regarding AEs, concerns about multiple steroid use and potential longer-term AE were most prevalent. Our findings demonstrated the potential of parent/patient engagement in delivering research outcomes relevant to parents. These results should be incorporated into the design of future clinical trials of OCS in aPSW and also quality improvement.

Although our stakeholders prioritised WSS as the most desired outcome measure, relatively few studies currently use sco-

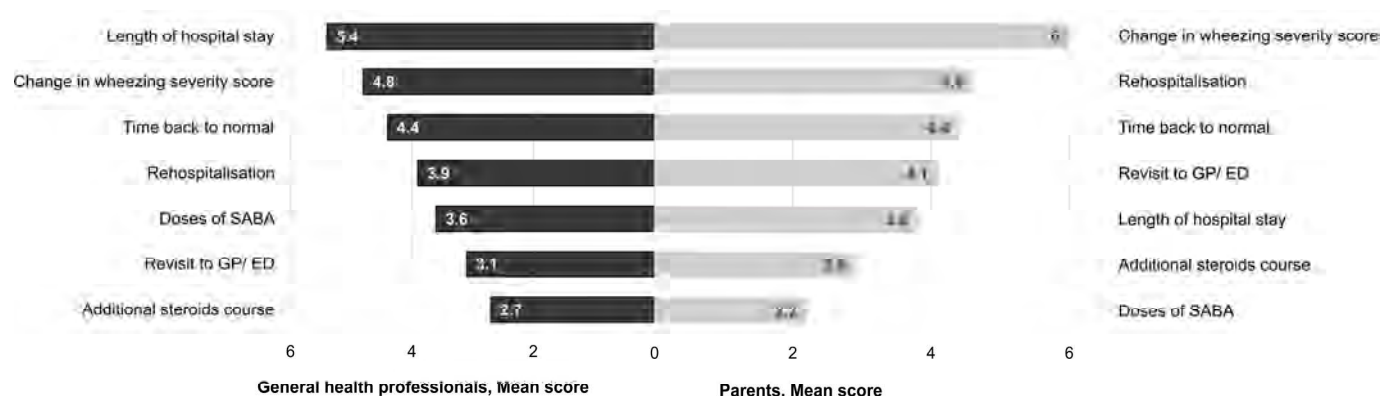


Figure 2 Outcome measure rankings by healthcare professionals (n=232) and parents (n=10) at stage 2. ED, emergency department; GP, general practice; SABA, short-acting beta-2 agonists.

ring tools. Within our systematic review, those studies measuring WSS at presentation, frequently used different scoring tools in which the measuring components and scales were inconsistent (online supplemental table 9). The PRAM tool was popular and validated for preschoolers.^{19 20} However, it is not perfect for evaluating dyspnoea²¹ and other aspects (eg, mental status or appearance).²² Also, there is no agreement on the timing to predict hospitalisation or home discharge using the PRAM.^{23 24}

Furthermore, many scoring tools, including PRAM, have not been validated for use across various settings, leading to challenges in their integration into clinical care and infrequent use in the ED.²⁵ We did not investigate underlying difficulties in using WSS in clinical practice, so research evaluating scoring tools capable of overcoming obstacles in use and demonstrating good validity in preschool children should be continued. A study to compare and optimise clinical scoring tools for children with acute wheeze is underway.²⁶

We obtained MCIDs for each outcome measure; however, achieving agreement between HCPs and parents was not possible. Parents selected a much higher potential impact of OCS on MCID for WSS that was considerably beyond that observed in clinical trials of OCS in asthma (even in older children). Helping to provide context to parents without introducing bias was a challenge within MCID research. Extreme scores from patients can result from previous experience rather than the potential impact from a therapeutic intervention.²⁷ Although parents were provided with data to inform their initial decision, we recognised that it may not have been sufficient to provide perspective. When baseline changes observed with placebo treatment were subsequently provided, we observed adjustments in expectations closer to that of clinicians who would have a wider experience of

potential placebo effects (online supplemental table 10). We did not investigate the consensus MCIDs between the stakeholders in the final stage as time was limited.

Despite a high level of concerns about AEs associated with multiple courses of OCS treatment, none of the included studies examined this AE. One cross-sectional study involving children aged 2–17 years found no cases of bone metabolism or adrenal suppression with frequent short courses of OCS.²⁸ A small body of evidence also suggests that short-term use of OCS (<14 days) is unlikely to cause long-term AEs or serious AEs, such as immune suppression or suppression of the hypothalamic-pituitary-adrenal axis.^{29 30} Bone mineralisation or osteopenia were observed in few studies,³¹ but a small body of evidence found no associations with growth or adrenal suppression by multiple OCS courses.^{28,32} Longitudinal data to assess the safety of frequent OCS use for recurrent wheezing episodes will still be required.

Strengths and limitations

Our study is the co-created delivery of outcomes related to OCS treatment for aPSW by HCPs and parents with lived experience. Using an international survey allowed us to gather HCPs' perspectives from diverse healthcare settings. Moreover, the successful adoption of the NGT facilitated the efficient attainment of a consensus outcome while ensuring a balanced power distribution among stakeholders, thereby enhancing the scientific rigour of the study. Our findings represent the first step in mitigating the heterogeneities observed in the published literature and can guide future studies on this subject.

The participation rate of the online survey was biased towards the UK and Europe, potentially undermining the applicability of our findings in non-native English-speaking countries or

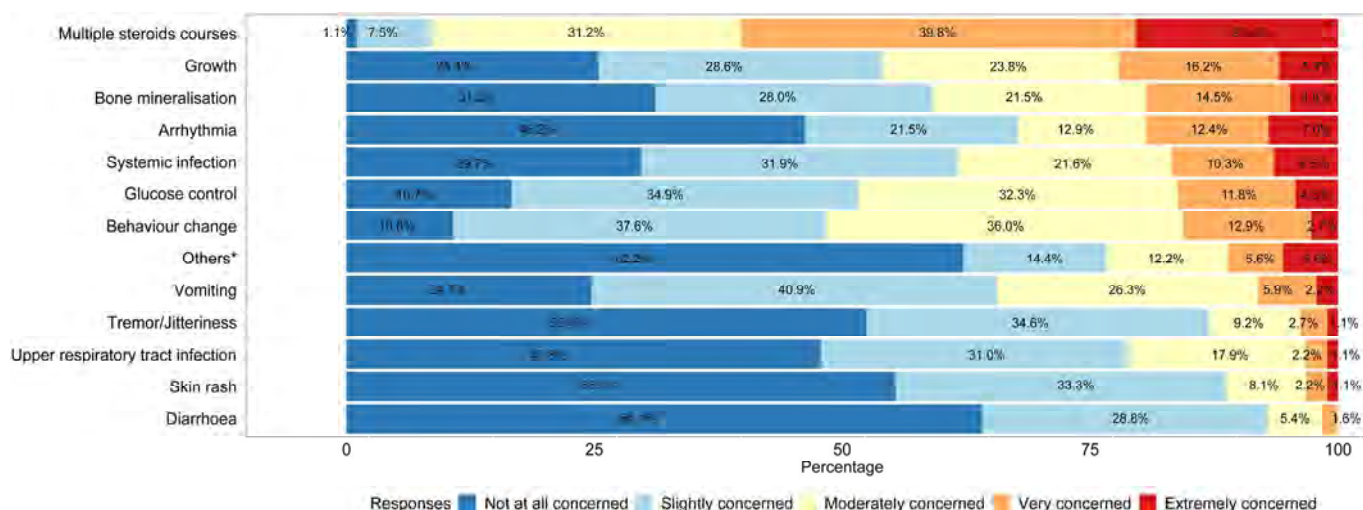


Figure 3 Level of concern for each risk when balancing against the potential benefits of OCS in health professionals (n=186). Note: N, number; values in bold indicate mode values for clarity; Others*: adrenal suppression, overuse or misuse of OCS, Cushing syndrome, gastritis, virus infection, peptic ulcer, high blood pressure and immunological maturation. OCS, oral corticosteroids.

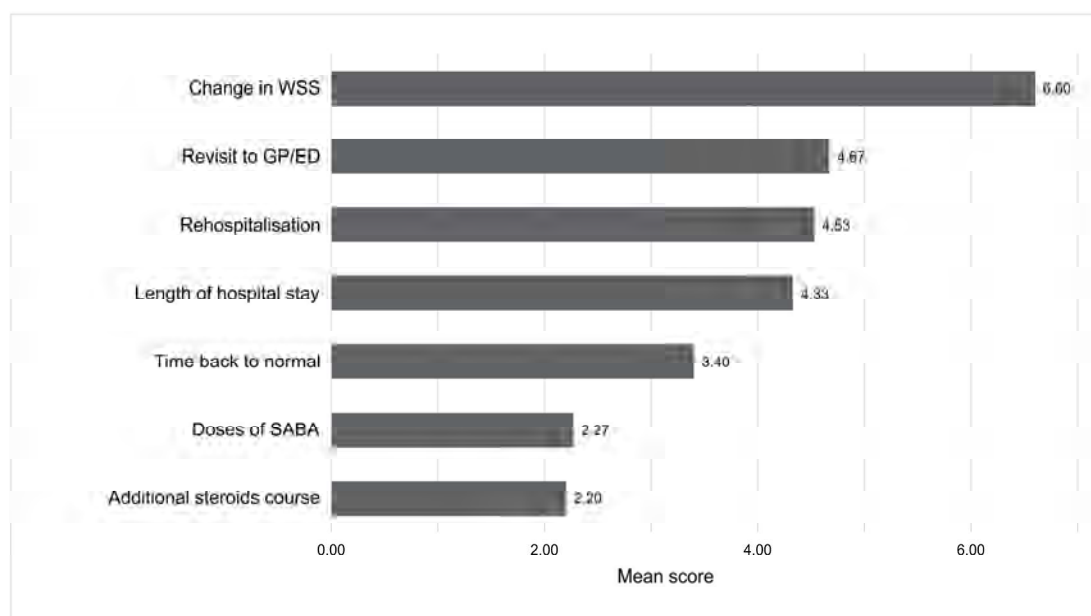


Figure 4 Consensus ranking of outcome measures by mean scores by healthcare professionals (n=7) and parents (n=9). WSS, Wheezing Severity Score; ED, emergency department; GP, general practice; SABA, short-acting beta-2 agonist

non-EU countries. General practitioners and ED physicians are more likely to consider prescribing OCS for preschool wheeze; however, most of the respondents were specialist respiratory paediatricians. Therefore, our findings may not fully apply to all settings. Further research to incorporate input from diverse regions/countries as well as from more general practitioners and ED physicians would be needed.

Additionally, MCIDs for severity symptoms from parents were not free from potential bias. As we did not want to overwhelm parents by explaining wheezing severity tools or current evidence, it was challenging to explain to parents the context in which MCIDs should be considered without overtly influencing their viewpoints. Future research should consider how best to provide informative context while minimising the unintended risk of bias.

CONCLUSIONS

In conclusion, we co-created consensus outcome measures for OCS treatment agreed on by HCPs and parents of children who have lived experience of aPSW. We found that change in WSS was the most favoured outcome measure. The engagement of parents/patients in this study demonstrated the potential to produce concrete research that is of high relevance to parents/families.

Author affiliations

- ¹Asthma UK Centre for Applied Research, Edinburgh, UK
- ²Centre for Population Health Sciences, University of Edinburgh, Edinburgh, UK
- ³National Heart and Lung Institute, Imperial College London, London, UK
- ⁴Royal Aberdeen Children's Hospital, Aberdeen, UK
- ⁵Royal Hospital for Sick Children, Edinburgh, UK
- ⁶SAPPHIRE Group, Health Sciences, University of Leicester, Leicester, UK
- ⁷Paediatric Emergency Medicine Leicester Academic (PEMLA) Group, University Hospitals of Leicester NHS Trust, Leicester, UK
- ⁸Emergency Medicine, Perth Children's Hospital, Nedlands, Western Australia, Australia
- ⁹Divisions of Paediatrics and Emergency Medicine, The University of Western Australia - Perth Campus, Perth, Western Australia, Australia
- ¹⁰Center for Child, Adolescent, and Maternal Health Research, Tampere University, Tampere, Finland
- ¹¹Paediatrics, Terveystalo Healthcare Services, Tampere, Finland
- ¹²Centre for Child Health, Blizard Institute, Queen Mary University of London, London, UK
- ¹³Division of Pulmonology Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA
- ¹⁴Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio, USA
- ¹⁵Department of Pediatrics, TYKS Turku University Hospital, Turku, Finland
- ¹⁶Department of Pediatrics, University of Turku, Turku, Finland
- ¹⁷Department of Paediatrics, Milton Keynes University Hospital NHS Foundation Trust, Milton Keynes, UK
- ¹⁸Edinburgh Clinical Unit, University of Edinburgh, Edinburgh, UK
- ¹⁹Department of Child Life and Health, University of Edinburgh Institute for Regeneration and Repair, Edinburgh, UK

Acknowledgements This study was funded by Asthma UK Centre for Applied Research. We thank all healthcare professionals who participated in the survey and 10 parents in Edinburgh. We thank all patient/public advisory members from Asthma UK Centre for Applied Research for reviewing the study advertisement materials.

Contributors SC, SL, SWT and BL conceived the study and wrote the initial protocol. SC, AM, and BL recruited parent participants and reviewed meeting materials. JH led nominal group technique meetings and BL, AM and SC helped participants understand the terminologies. BL conducted data analyses. SC, SL, SWT and BL interpreted the results. DR, MLB, PC, JG, TWG, TJ and AO helped to identify consensus outcome measures and provided relevant data. All authors provided critical feedback and approved the final version of the manuscript. SC is the guarantor of this study.

Funding BL has received a PhD studentship from AUKCAR programme (AUK-AC-2018-01) funded by Asthma + Lung UK. Competing interests BL received a PhD studentship from AUKCAR programme (AUK-AC-2018-01) funded by Asthma + Lung UK. SC received institutional grants for BL's PhD studentship via AUKCAR. PC reports grants from Juhani Aho Foundation for Medical Research, Allergy Research Foundation, Tampere Tuberculosis Foundation, the Research Foundation of the Pulmonary Diseases, The Finnish Medical Foundation and The Jalmari and Rauha Ahokas Foundation; consulting fees from ALK, Sanofi and Thermo Fisher; payments for expert testimony from Sanofi; supports for attending meetings or travel from ALK and Orion Pharma; and participation on a Data Safety Monitoring Board or Advisory Board from ALK and Sanofi. TWG reports grants from GSK, Sanofi, Regeneron, Amgen, AstraZeneca, and OM Pharma; royalties and licenses from UpToDate; consulting fees from Sanofi, Regeneron, AstraZeneca, Genentech, Polarean and OM Pharma; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Sanofi, Regeneron, AiCME, PlatformQ Health and Advent; supports for attending meetings or travel from AiCME, PlatformQ Health and Advent; and participation on a Data Safety Monitoring Board or Advisory Board from Best Pharmaceuticals for Children Act. JG is an NIHR Senior Investigator and reports research grants from OM Pharma and Marinomed, honoraria from AstraZeneca, payment from OM Pharma as an Advisory Board member, gift of asthma equipment from Omron, donation of Investigational Medicinal Product from Marinomed and OM Pharma, and was commissioned by Hodge Jones & Allen Solicitors to provide medical evidence related to the inquest on an asthma death. All other authors declare no competing interests.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Edinburgh Medical School Research Ethics Committee (21-EMREC-050). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed.

Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs

- Bohee Lee <http://orcid.org/0000-0002-9671-386X>
 Stephen W Turner <http://orcid.org/0000-0001-8393-5060>
 Damian Roland <http://orcid.org/0000-0001-9334-5144>
 Meredith Louise Borland <http://orcid.org/0000-0002-5326-5008>
 Peter Csonka <http://orcid.org/0000-0003-0819-7875>
 Jonathan Grigg <http://orcid.org/0000-0003-3109-6028>
 Steve Cunningham <http://orcid.org/0000-0001-7342-251X>

REFERENCES

- 1 Panickar J, Lakhanpaul M, Lambert PC, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med* 2009;360:329–38.
- 2 Oommen A, Lambert PC, Grigg J. Efficacy of a short course of parent-initiated oral prednisolone for viral wheeze in children aged 1–5 years: randomised controlled trial. *Lancet* 2003;362:1433–8.
- 3 Foster SJ, Cooper MN, Oosterhof S, et al. Oral prednisolone in preschool children with virus-associated wheeze: a prospective, randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2018;6:97–106.
- 4 Wallace A, Sinclair O, Shepherd M, et al. Impact of oral corticosteroids on respiratory outcomes in acute preschool wheeze: a randomised clinical trial. *Arch Dis Child* 2021;106:339–44.
- 5 Castro-Rodriguez JA, Beckhaus AA, Forno E. Efficacy of oral corticosteroids in the treatment of acute wheezing episodes in asthmatic preschoolers: Systematic review with meta-analysis. *Pediatr Pulmonol* 2016;51:868–76.
- 6 Heidi M, Emily K, Benjamin H, et al. Patient reported outcomes for preschool children with recurrent wheeze. *NPJ Prim Care Respir Med* 2019;29:7.
- 7 Lee B, Turner S, Borland M, et al. Efficacy of oral corticosteroids for acute preschool wheeze: a systematic review and individual participant data meta-analysis of randomised clinical trials. *Lancet Respir Med* 2024;12:444–56.
- 8 Mentimeter. Mentimeter:interactive presentation software. 2023.
- 9 Qualtrics. Qualtrics™ 2024. Available: www.qualtrics.com [Accessed 10 Jan 2022].
- 10 EMC. Prednisolone 1mg&5mg tablets. 2023. Available: <https://www.medicines.org.uk/emc/medicine/18752#grf> [Accessed 07 Jun 2023].

- 11 Fernandes RM, Wingert A, Vandermeer B, et al. Safety of corticosteroids in young children with acute respiratory conditions: a systematic review and meta-analysis. *BMJ Open* 2019;9:e028511.
- 12 Connett GJ, Warde C, Wooler E, et al. Prednisolone and salbutamol in the hospital treatment of acute asthma. *Arch Dis Child* 1994;70:170–3.
- 13 Ho L, Landau LI, Le Souëf PN. Lack of efficacy of single-dose prednisolone in moderately severe asthma. *Med J Aust* 1994;160:701.
- 14 Fox GF, Marsh MJ, Milner AD. Treatment of recurrent acute wheezing episodes in infancy with oral salbutamol and prednisolone. *Eur J Pediatr* 1996;155:512–6.
- 15 Jartti T, Lehtinen P, Vanto T, et al. Evaluation of the efficacy of prednisolone in early wheezing induced by rhinovirus or respiratory syncytial virus. *Pediatr Infect Dis J* 2006;25:482–8.
- 16 Jartti T, Nieminen R, Vuorinen T, et al. Short- and long-term efficacy of prednisolone for first acute rhinovirus-induced wheezing episode. *J Allergy Clin Immunol* 2015;135:691–8.
- 17 Csonka P, Kaila M, Laippala P, et al. Oral prednisolone in the acute management of children age 6 to 35 months with viral respiratory infection-induced lower airway disease: a randomized, placebo-controlled trial. *J Pediatr* 2003;143:725–30.
- 18 Grant CC, Duggan AK, DeAngelis C. Independent parental administration of prednisone in acute asthma: a double-blind, placebo-controlled, crossover study. *Pediatrics* 1995;96:224–9.
- 19 Ducharme FM, Chalut D, Plotnick L, et al. The Pediatric Respiratory Assessment Measure: a valid clinical score for assessing acute asthma severity from toddlers to teenagers. *J Pediatr* 2008;152:476–80.
- 20 Thaweerujirot C, Daengsuwan T. Comparison between pediatric respiratory assessment measure (PRAM) score and Wood's asthma score to assess acute asthma exacerbation. *Asian Pac J Allergy Immunol* 2019;37:123–9.
- 21 Eggink H, Brand P, Reimink R, et al. Clinical Scores for Dyspnoea Severity in Children: A Prospective Validation Study. *PLoS One* 2016;11:e0157724.
- 22 Nayani K, Naeem R, Munir O, et al. The clinical respiratory score predicts paediatric critical care disposition in children with respiratory distress presenting to the emergency department. *BMC Pediatr* 2018;18:339.
- 23 Alnaji F, Zemek R, Barrowman N, et al. PRAM score as predictor of pediatric asthma hospitalization. *Acad Emerg Med* 2014;21:872–8.
- 24 Judge P, Tabeshi R, Yao RJ, et al. Use of a standardized asthma severity score to determine emergency department disposition for paediatric asthma: A cohort study. *Paediatr Child Health* 2019;24:227–33.
- 25 Chacko J, King C, Harkness D, et al. Pediatric acute asthma scoring systems: a systematic review and survey of UK practice. *J Am Coll Emerg Physicians Open* 2020;1:1000–8.
- 27 Copay AG, Subach BR, Glassman SD, et al. Understanding the minimum clinically important difference: a review of concepts and methods. *Spine J* 2007;7:541–6.
- 28 Ducharme FM, Chabot G, Polychronakos C, et al. Safety profile of frequent short courses of oral glucocorticoids in acute pediatric asthma: impact on bone metabolism, bone density, and adrenal function. *Pediatrics* 2003;111:376–83.
- 29 Price J, Hindmarsh P, Hughes S, et al. Evaluating the effects of asthma therapy on childhood growth: what can be learnt from the published literature? *Eur Respir J* 2002;19:1179–93.
- 30 Dolan LM, Kesarwala HH, Holroyde JC, et al. Short-term, high-dose, systemic steroids in children with asthma: the effect on the hypothalamic-pituitary-adrenal axis. *J Allergy Clin Immunol* 1987;80:81–7.
- 31 Kelly HW, Van Natta ML, Covar RA, et al. Effect of long-term corticosteroid use on bone mineral density in children: a prospective longitudinal assessment in the childhood Asthma Management Program (CAMP) study. *Pediatrics* 2008;122:e53–61.
- 32 Saha MT, Laippala P, Lenko HL. Normal growth of prepubertal nephrotic children during long-term treatment with repeated courses of prednisone. *Acta Paediatr* 1998;87:545–8.

Guideline conjunta BTS/NICE/SIGN sobre asma: diagnóstico, monitorização e gestão da asma crónica (novembro de 2024) – resumo das recomendações

British Thoracic Society (BTS), National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN)

Correspondence to

British Thoracic Society (BTS), National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN); asthmaenquiries@nice.org.uk

OVERVIEW

This is a summary of the recommendations of the joint guideline on Asthma: diagnosis, monitoring and chronic asthma management, which was published in November 2024. This new collaborative guideline was developed jointly by the British Thoracic Society (BTS), National Institute for Health and Care Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN).

The guideline covers diagnosing, monitoring and managing asthma in adults, young people and children. It aims to improve the accuracy of diagnosis, help people to control their asthma and reduce the risk of asthma attacks. It does not cover managing severe asthma or acute asthma attacks.

The recommendations in this guideline represent the view of BTS, NICE and SIGN, arrived at after careful consideration of the evidence available.

Last reviewed: November 2024

It updates and replaces NICE guideline 80 (published November 2017) and parts of BTS/SIGN British guideline SIGN 158 (published July 2019).

Next review: This guidance will be reviewed if there is new evidence that is likely to change the recommendations.

BTS, NICE and SIGN have developed an asthma pathway, which brings together recommendations on diagnosing, monitoring and managing asthma in adults, young people and children. It aims to improve the accuracy of diagnosis, help people to control their asthma and reduce the risk of asthma attacks. It also covers managing difficult and severe asthma and acute asthma attacks. The pathway can be linked via Health Improvement Scotland's Right Decision Service here, or via the NICE website here.

Who is it for?

- Healthcare professionals in primary care and the community secondary care and tertiary asthma services
- Commissioners and providers
- People with suspected or diagnosed asthma, their families and carers

RECOMMENDATIONS

Initial clinical assessment

Clinical history

Obtain a structured clinical history in people with suspected asthma. Specifically, check for:

- reported wheeze, noisy breathing, cough, breathlessness or chest tightness, and any variation (for example, worse during the night or early morning, or seasonal) in these symptoms
- any triggers that make symptoms worse

→ a personal or family history of asthma or allergic rhinitis

→ symptoms to suggest alternative diagnoses (see the tables on alternative diagnoses in wheezy children and alternative diagnoses in adults in the BTS/SIGN British guideline on the management of asthma SIGN 158.) [NICE 2017, BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

Do not confirm a diagnosis of asthma without a suggestive clinical history and a supporting objective test. Code as suspected asthma until the diagnosis is confirmed. [NICE 2017, amended BTS/NICE/SIGN 2024]

If the diagnosis of asthma is confirmed, record the basis for this in the person's medical records, alongside the coded diagnostic entry. [NICE 2017, amended BTS/NICE/SIGN 2024]

Physical examination

Examine people with suspected asthma to identify expiratory polyphonic wheeze and signs of other causes of respiratory symptoms but be aware that even if examination results are normal, the person may still have asthma. [NICE 2017]

Initial treatment and objective tests for acute symptoms at presentation

Treat people immediately if they are acutely unwell or highly symptomatic at presentation, and perform objective tests that may help support a diagnosis of asthma (for example, eosinophil count, fractional exhaled nitric oxide (FeNO), spirometry or peak expiratory flow (PEF) before and after bronchodilator) if the equipment is available. [NICE 2017, amended BTS/NICE/SIGN 2024]

If objective tests for asthma cannot be done immediately for people who are acutely unwell or highly symptomatic at presentation, carry them out when acute symptoms have been controlled, and advise people to contact their healthcare professional immediately if they become unwell while waiting to have objective tests. [NICE 2017, amended BTS/NICE/SIGN 2024]

Be aware that the results of spirometry and FeNO tests may be affected in people who have been treated with inhaled corticosteroids (the test results are more likely to be normal). [NICE 2017]

Objective tests for diagnosing asthma in adults, young people and children aged 5 to 16 with a history suggestive of asthma

Adults

See also algorithm A for a summary of objective tests for diagnosing asthma in adults and young people (aged over 16 years) with a history suggesting asthma.



► <https://doi.org/10.1136/thorax-2025-223056>



© Author(s) (or their employer(s)) 2025. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Thorax 2025;80:416–424.

Measure the blood eosinophil count or fractional exhaled nitric oxide (FeNO) level in adults with a history suggestive of asthma. Diagnose asthma if the eosinophil count is above the laboratory reference range or the FeNO level is 50 ppb or more. [BTS/NICE/SIGN 2024]

If asthma is not confirmed by eosinophil count or FeNO level, measure bronchodilator reversibility (BDR) with spirometry. Diagnose asthma if the FEV₁ increase is 12% or more and 200 mL or more from the pre-bronchodilator measurement (or if the FEV₁ increase is 10% or more of the predicted normal FEV₁). [BTS/NICE/SIGN 2024] If spirometry is not available or it is delayed, measure peak expiratory flow (PEF) twice daily for 2 weeks. Diagnose asthma if PEF variability (expressed as amplitude percentage mean) is 20% or more. [BTS/NICE/SIGN 2024]

If asthma is not confirmed by eosinophil count, FeNO, BDR or PEF variability but still suspected on clinical grounds, refer for consideration of a bronchial challenge test. Diagnose asthma if bronchial hyper-responsiveness is present. [BTS/NICE/SIGN 2024]

Children aged 5 to 16

See also algorithm B for a summary of objective tests for diagnosing asthma in children aged 5 to 16 with a history suggesting asthma.

Measure the FeNO level in children with a history suggestive of asthma. Diagnose asthma if the FeNO level is 35 ppb or more. [BTS/NICE/SIGN 2024]

If the FeNO level is not raised, or if FeNO testing is not available, measure BDR with spirometry. Diagnose asthma if the FEV₁ increase is 12% or more from baseline (or if the FEV₁ increase is 10% or more of the predicted normal FEV₁). [BTS/NICE/SIGN 2024]

If spirometry is not available or it is delayed, measure PEF twice daily for 2 weeks. Diagnose asthma if PEF variability (expressed as amplitude percentage mean) is 20% or more. [BTS/NICE/SIGN 2024]

If asthma is not confirmed by FeNO, BDR or PEF variability but still suspected on clinical grounds, either perform skin prick testing to house dust mite or measure total IgE level and blood eosinophil count.

→ Exclude asthma if there is no evidence of sensitisation to house dust mite on skin prick testing or if the total serum IgE is not raised.

→ Diagnose asthma if there is evidence of sensitisation or a raised total IgE level and the eosinophil count is more than 0.5×10^9 per litre. [BTS/NICE/SIGN 2024]

If there is still doubt about the diagnosis, refer to a paediatric specialist for a second opinion, including consideration of a bronchial challenge test. [BTS/NICE/SIGN 2024]

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on objective tests for diagnosing asthma in adults, young people and children aged 5 to 16 with a history suggestive of asthma.

Full details of the evidence and the committee's discussion are in:

- evidence review A: diagnostic test accuracy of spirometry in people suspected of asthma
- evidence review B: diagnostic test accuracy for bronchodilator reversibility in people suspected of asthma
- evidence review C: diagnostic test accuracy of peak expiratory flow variability for the diagnosis of asthma
- evidence review D: accuracy of skin prick test in children for the diagnosis of asthma
- evidence review E: diagnostic test accuracy of IgE in children
- evidence review F: diagnostic accuracy of fractional exhaled nitric oxide (FeNO) measures
- evidence review G: diagnostic accuracy of eosinophil blood count measures in the diagnosis of asthma
- evidence review H: bronchial challenge with histamine and methacholine for the diagnosis of asthma
- evidence review I: bronchial challenge test with mannitol
- evidence review J: bronchial challenge testing in response to exercise for the diagnosis of asthma
- evidence review K: diagnostic accuracy of combination of tests.

Diagnosing asthma in children under 5

Diagnosis is hard in this age group because it is difficult to do the tests and there are no good reference standards.

For children under five with suspected asthma, treat with inhaled corticosteroids in line with the recommendations on medicines for initial management in children under 5, and review the child on a regular basis. If they still have symptoms when they reach 5 years, attempt objective tests (see the section on objective tests for diagnosing asthma in adults, young people and children aged 5 to 16). [NICE 2017]

If a child is unable to perform objective tests when they are aged 5:

→ try doing the tests again every 6 to 12 months until satisfactory results are obtained

→ refer for specialist assessment if the child's asthma is not responding to treatment. [NICE 2017, BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

Refer to a specialist respiratory paediatrician any preschool child with an admission to hospital, or two or more admissions to an emergency department, with wheeze in a 12 month period. [BTS/NICE/SIGN 2024]

Diagnosing occupational asthma

See the BTS clinical statement on occupational asthma.

In people with adult-onset asthma, poorly controlled established asthma, or reappearance of childhood asthma, check for a possible occupational component by asking:

→ Are symptoms the same, better or worse on days away from work?

→ Are symptoms the same, better or worse when on holiday (time away from work, longer than usual breaks, at weekends or between shifts)? Make sure all answers are recorded for later review. [NICE 2017, BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

Refer people with suspected occupational asthma to an occupational asthma specialist. [NICE 2017]

Monitoring asthma control

Monitor asthma control at every review. In addition to asking about symptoms, check:

→ time off work or school due to asthma

→ amount of reliever inhaler used, including a check of the prescription record

→ number of courses of oral corticosteroids

→ any admissions to hospital or attendance at an emergency department due to asthma. If control is suboptimal, see the section on principles of pharmacological treatment. [BTS/NICE/SIGN 2024]

Consider using a validated symptom questionnaire (for example, the Asthma Control Questionnaire, the Asthma Control Test or the Childhood Asthma Control Test) at any asthma review. [BTS/NICE/SIGN 2024]

Do not use regular peak expiratory flow (PEF) monitoring to assess asthma control unless there are person-specific reasons for doing so (for example, when PEF measurement is part of the personalised asthma action plan). [BTS/NICE/SIGN 2024]

Consider fractional exhaled nitric oxide (FeNO) monitoring for adults with asthma:

→ at their regular review, and

→ before and after changing their asthma therapy. [BTS/NICE/SIGN 2024]

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on monitoring asthma control.

Full details of the evidence and the committee's discussion are in:

- evidence review L: symptom diary for monitoring asthma
- evidence review M: pulmonary function monitoring in asthma
- evidence review N: FeNO measures to monitor asthma.

Principles of pharmacological treatment

Licensed indications for asthma inhalers vary between different medicines, different doses and different devices. Not all asthma inhalers are licensed for use in line with the recommendations in this gui-

deline. See NICE's information on prescribing medicines or SIGN's information on prescribing licensed medicines out with their marketing authorisation and refer to the summary of product characteristics for individual products.

Take into account and try to address the possible reasons for uncontrolled asthma before starting or adjusting medicines for asthma in adults, young people and children. These may include:

- alternative diagnoses or comorbidities
- suboptimal adherence (see the recommendation on adherence)
- suboptimal inhaler technique
- smoking (active or passive), including vaping using e-cigarettes
- occupational exposures (see the recommendation on checking for possible occupational asthma).
- psychosocial factors (for example, anxiety and depression, relationships and social networks)
- seasonal factors
- environmental factors (for example, air pollution, indoor mould exposure). [NICE 2017, BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

If possible, check the fractional exhaled nitric oxide (FeNO) level when asthma is uncontrolled. If it is raised this may indicate poor adherence to treatment or the need for an increased dose of inhaled corticosteroid (ICS). [BTS/NICE/SIGN 2024]

Do not prescribe short-acting beta2 agonists to people of any age with asthma without a concomitant prescription of an ICS. [BTS/NICE/SIGN 2024]

After starting or adjusting medicines for asthma, review the response to treatment in 8 to 12 weeks (see the recommendations on monitoring asthma control). [NICE 2017, amended BTS/NICE/SIGN 2024]

For a short explanation of why the committee made these 2024 recommendations and how they might affect practice, see the rationale and impact section on principles of pharmacological treatment.

Full details of the evidence and the committee's discussion are in evidence review P: drug classes for initial asthma management.

Inhalers

Base the choice of inhaler(s) for asthma on:

- an assessment of correct technique
- the preference of the person receiving the treatment
- the lowest environmental impact among suitable devices
- the presence of an integral dose counter. A spacer should usually be prescribed for use with a metered dose inhaler, particularly in children. See the patient decision aid on asthma inhalers and climate change. [BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

Give people with asthma information on their inhaler treatments. This should include the medicines they contain, how they work, when they should be taken and the correct technique to use for each device. [BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

Observe the person using their inhaler device (and spacer if used) to check they can use it properly:

- at every asthma review, either routine or unscheduled
- at every asthma-related consultation
- when there is deterioration in asthma control
- when the inhaler device is changed
- when the person asks for it to be checked or changed. If the person is assessed as being unable to use a device properly, find an alternative. [NICE 2017, BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

If possible, prescribe the same type of device to deliver preventer and reliever treatments where more than one inhaler is needed. Consider providing an additional metered dose short-acting beta2 agonist (SABA) inhaler plus spacer for emergency use for children under 12 years who may be unable to activate a dry powder inhaler during an acute asthma attack. [BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

Encourage people to take their used or expired inhalers to their pharmacy for disposal. [BTS/SIGN 2019]

Digital Inhalers

Digital inhalers are not recommended for routine use in people with asthma. [BTS/NICE/SIGN 2024]

For a short explanation of why the committee made this 2024 recommendation and how it might affect practice, see the rationale and impact section on digital inhalers.

Full details of the evidence and the committee's discussion are in evidence review R: smart inhalers.

Pharmacological management in people aged 12 and over

See also algorithm C for a summary of the pharmacological management of asthma in people aged 12 years and over.

Initial management of newly diagnosed asthma in people aged 12 and over

Offer a low-dose inhaled corticosteroid (ICS)/formoterol combination inhaler to be taken as needed for symptom relief (as-needed AIR therapy) to people aged 12 and over with newly diagnosed asthma. [BTS/NICE/SIGN 2024]

In November 2024, only certain budesonide/formoterol inhalers were licensed for as-needed AIR therapy in mild asthma. The use of any other ICS/formoterol inhalers would therefore be off-label. The current evidence supporting the use of budesonide/formoterol is based on the use of a dry powder inhaler. See NICE's information on prescribing medicines or SIGN's information on prescribing licensed medicines out with their marketing authorisation.

If the person needing asthma treatment presents highly symptomatic (for example, regular nocturnal waking) or with a severe exacerbation, start treatment with low-dose MART (maintenance and reliever therapy) in addition to treating the acute symptoms as indicated (that is, a course of oral corticosteroids may be needed). Consider stepping down to as-needed AIR therapy using a low-dose ICS/formoterol inhaler at a later date if their asthma is controlled. [BTS/NICE/SIGN 2024]

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on medicines for the initial management of newly diagnosed asthma in people aged 12 and over.

Full details of the evidence and the committee's discussion are in evidence review P: drug classes for initial asthma management.

For guidance on dose ranges of inhaled corticosteroids see inhaled corticosteroid doses for the BTS, NICE and SIGN asthma guideline.

Offer low-dose MART to people aged 12 and over with asthma that is not controlled on a low-dose ICS/formoterol combination inhaler used only as needed. [BTS/NICE/SIGN 2024]

Offer moderate-dose MART to people aged 12 and over with asthma that is not controlled on low-dose MART. [BTS/NICE/SIGN 2024]

For people aged 12 and over with asthma that is not controlled on moderate-dose MART despite good adherence:

- Check the fractional exhaled nitric oxide (FeNO) level if available, and the blood eosinophil count. If either of these is raised, refer to a specialist in asthma care.
- If neither FeNO or eosinophil count is raised, consider a trial of either a leukotriene receptor antagonist (LTRA) or a long-acting muscarinic receptor antagonist (LAMA) used in addition to moderate-dose MART. Give the medicine for a trial period of 8 to 12 weeks unless there are side effects. At the end of the trial:
 - if asthma is controlled, continue the treatment
 - if control has improved but is still inadequate, continue the treatment and start a trial of the other medicine (LTRA or LAMA)
 - if control has not improved, stop the LTRA or LAMA and start a trial of the complementary medicine (LTRA or LAMA). [BTS/NICE/SIGN 2024] November 2024: Follow the MHRA safety advice on the risk of neuropsychiatric reactions in people taking montelukast.

Refer people to a specialist in asthma care when asthma is not controlled despite treatment with moderate-dose MART, and trials of an LTRA and a LAMA. (See the Accelerated Access Collaborative consensus pathway on the management of uncontrolled asthma in adults.) [BTS/NICE/SIGN 2024]

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on medicine combination and sequencing in people aged 12 and over.

Full details of the evidence and the committee's discussion are in evidence review Q: drug combinations and sequencing for asthma management.

Transferring people aged 12 and over from other treatment pathways

These recommendations are for people with uncontrolled asthma who are on the treatment pathway recommended by previous NICE and BTS/SIGN guidelines.

Change treatment for people with confirmed asthma who are currently using a short-acting beta2 agonist (SABA) only to a low-dose ICS/formoterol combination inhaler used as needed (as-needed AIR therapy). [BTS/NICE/SIGN 2024]

Consider changing treatment to low-dose MART for people with asthma that is not controlled on:

- regular low-dose ICS plus SABA as needed
- regular low-dose ICS/LABA (long-acting beta2 agonist) combination inhaler plus SABA as needed
- regular low-dose ICS and supplementary therapy (LTRA) plus SABA as needed.
- regular low-dose ICS/LABA combination inhaler and supplementary therapy (LTRA) plus SABA as needed. [BTS/NICE/SIGN 2024]

Consider changing treatment to moderate-dose MART for people with asthma that is not controlled on:

- regular moderate-dose ICS plus SABA as needed
- regular moderate-dose ICS/LABA combination inhaler plus SABA as needed
- regular moderate-dose ICS and supplementary therapy (LTRA or LAMA, or both) plus SABA as needed
- regular moderate-dose ICS/LABA combination inhaler and supplementary therapy (LTRA or LAMA, or both) plus SABA as needed. [BTS/NICE/SIGN 2024]

When changing from low- or moderate-dose ICS (or ICS/LABA combination inhaler) plus supplementary therapy to MART, consider whether to stop or continue the supplementary therapy based on the degree of benefit achieved when first introduced. [BTS/NICE/SIGN 2024]

Refer people with asthma that is not controlled on treatment containing a high dose of ICS to a specialist in asthma care. [BTS/NICE/SIGN 2024]

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on transferring people aged 12 and over from other treatment pathways.

Full details of the evidence and the committee's discussion are in evidence review P: drug classes for initial asthma management and evidence review Q: drug combinations and sequencing for asthma management.

Pharmacological management in children aged 5 to 11

For guidance on doses on inhaled corticosteroids see inhaled corticosteroid doses for the BTS, NICE and SIGN asthma guideline.

See also algorithm D for a summary of the pharmacological management of asthma in children aged 5 to 11 years.

Initial management in children aged 5 to 11

Offer a twice-daily paediatric low-dose inhaled corticosteroid (ICS), with a short-acting beta2 agonist (SABA) as needed, as initial treatment for children aged 5 to 11 years with newly diagnosed asthma. [BTS/NICE/SIGN 2024]

For a short explanation of why the committee made this recommendation and how it might affect practice, see the rationale and impact section on medicines for initial management in children aged 5 to 11.

Full details of the evidence and the committee's discussion are in evidence review P: drug classes for initial asthma management.

Medicine combination and sequencing in children aged 5 to 11

MART pathway

Consider paediatric low-dose MART (maintenance and reliever therapy) for children with asthma that is not controlled on paediatric low-dose ICS plus SABA as needed, as long as they are assessed to have the ability to manage a MART regimen. [BTS/NICE/SIGN 2024] In November 2024, no asthma inhalers were licensed for MART in children under 12, so this use would be off-label. The current evidence supporting the use of MART in children aged 5 to 11 is based on the use of a dry powder inhaler. See NICE's information on prescribing medicines or SIGN's information on prescribing licensed medicines outwith their marketing authorisation.

Consider increasing to paediatric moderate-dose MART if asthma is not controlled on paediatric low-dose MART. [BTS/NICE/SIGN 2024]

Conventional pathway

Consider adding a leukotriene receptor antagonist (LTRA) to twice daily paediatric low-dose ICS plus SABA as needed when a child has uncontrolled asthma and is assessed as unable to manage the MART regimen. Give the LTRA for a trial period of 8 to 12 weeks (unless there are side effects), then stop it if it is ineffective. [BTS/NICE/SIGN 2024] November 2024: Follow the MHRA safety advice on the risk of neuropsychiatric reactions in people taking montelukast.

Offer a twice daily paediatric low-dose ICS/LABA (long-acting beta2 agonist) combination inhaler plus SABA as needed to children assessed as unable to manage the MART regimen if their asthma is not controlled on paediatric low-dose ICS plus SABA as needed (with or without an LTRA depending on previous response). [BTS/NICE/SIGN 2024]

Offer a twice daily paediatric moderate-dose ICS/LABA inhaler plus SABA as needed to children with asthma that is not controlled on paediatric low-dose ICS/LABA plus SABA as needed (with or without an LTRA depending on previous response). [BTS/NICE/SIGN 2024]

All children aged 5 to 11

Refer children to a specialist in asthma care if their asthma is not controlled on paediatric moderate-dose MART or paediatric moderate-dose ICS/LABA maintenance treatment (with or without an LTRA, depending on previous response). [BTS/NICE/SIGN 2024]

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on medicine combination and sequencing in children aged 5 to 11.

Full details of the evidence and the committee's discussion are in evidence review Q: drug combinations and sequencing for asthma management.

Pharmacological management in children under 5

These recommendations are for children under five with newly suspected or confirmed asthma, or with asthma symptoms that are uncontrolled on their current treatment.

See also algorithm E for a summary of the pharmacological management of asthma in children under 5.

Consider an eight to 12 week trial of twice-daily paediatric low-dose inhaled corticosteroid (ICS) as maintenance therapy (with a short-acting beta2 agonist (SABA) for reliever therapy) in children under five with suspected asthma and:

- symptoms at presentation that indicate the need for maintenance therapy (for example, interval symptoms in children with another atopic disorder), or
- severe acute episodes of difficulty breathing and wheeze (for example, requiring hospital admission, or needing two or more courses of oral corticosteroids). [BTS/NICE/SIGN 2024]

If symptoms do not resolve during the trial period, take the following sequential steps:

- check inhaler technique and adherence
- check whether there is an environmental source of their symptoms (for example mould in the home, cold housing, smokers or indoor air pollution)

→ review whether an alternative diagnosis is likely. If none of these explain the failure to respond to treatment, refer the child to a specialist in asthma care. [BTS/NICE/SIGN 2024]

Consider stopping ICS and SABA treatment after 8 to 12 weeks if symptoms are resolved. Review the symptoms after a further 3 months. [BTS/NICE/SIGN 2024]

If symptoms resolve during the trial period, but then:

→ symptoms recur by the 3 month review, or

→ the child has an acute episode requiring systemic corticosteroids or hospitalisation, restart regular ICS (begin at a paediatric low dose and titrate up to a paediatric moderate dose if needed) with SABA as needed and consider a further trial without treatment after reviewing the child within 12 months. [BTS/NICE/SIGN 2024]

If suspected asthma is uncontrolled in children under five on a paediatric moderate dose of ICS as maintenance therapy (with SABA as needed), consider a leukotriene receptor antagonist (LTRA) in addition to the ICS. Give the LTRA for a trial period of 8 to 12 weeks (unless there are side effects), then stop it if it is ineffective. [BTS/NICE/SIGN 2024] November 2024: Follow the MHRA safety advice on the risk of neuropsychiatric reactions in people taking montelukast.

If suspected asthma is uncontrolled in children under five on a paediatric moderate dose of ICS as maintenance therapy and a trial of an LTRA has been unsuccessful or not tolerated, stop the LTRA and refer the child to a specialist in asthma care for further investigation and management. [BTS/NICE/SIGN 2024]

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on pharmacological management in children under 5.

Full details of the evidence and the committee's discussion are in evidence review P: drug classes for initial asthma management.

Decreasing maintenance therapy

At annual review discuss with the person with asthma (or their family or carer, if appropriate) the potential risks and benefits of decreasing their maintenance therapy when their asthma has been well controlled on their current maintenance therapy. [NICE 2017, BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

When decreasing maintenance therapy:

→ Stop or reduce dose of medicines in an order that takes into account the clinical effectiveness when introduced, side effects and the person's preference.

→ Allow at least 8 to 12 weeks before considering a further treatment reduction.

→ If considering step-down treatment for people aged 12 and over who are using low-dose maintenance inhaled corticosteroid (ICS) plus a short-acting beta2 agonist (SABA) as needed or low-dose MART (maintenance and reliever therapy), step down to low-dose ICS/formoterol combination inhaler as needed (as-needed AIR therapy). [NICE 2017, BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

Agree with the person (or their family or carer if appropriate) how the effects of decreasing maintenance therapy will be monitored and reviewed, including self-monitoring and follow-up with a healthcare professional. [NICE 2017] Review and update the person's asthma action plan when decreasing maintenance therapy. [NICE 2017]

Adherence

Check adherence, using prescription records, and inhaler technique at every asthma-related healthcare review. Use the principles outlined in the NICE guidelines on shared decision making (endorsed by SIGN for use in Scotland) and medicines adherence. [NICE 2017, BTS/SIGN 2019]

Asthma in pregnancy and breastfeeding

For recommendations on intrapartum care, see the NICE guideline on intrapartum care for women with existing medical conditions or obstetric complications and their babies.

Pregnancy

People with asthma should have an asthma review during early pregnancy and in the postpartum period. Emphasise the importance and safety of maintaining good control of asthma during pregnancy and of continuing asthma medicines to avoid problems for themselves and their baby. [BTS/SIGN 2019]

Advise anyone who is pregnant and who smokes about the dangers for themselves and their babies and give appropriate support to stop smoking. See the NICE guideline on tobacco for more information. [BTS/SIGN 2019]

Advise using the following medicines as normal during pregnancy:

→ short-acting and long-acting beta2 agonists

→ inhaled corticosteroids

→ oral theophyllines. [BTS/SIGN 2019]

Offer oral corticosteroids during pregnancy if needed to treat exacerbations of asthma. Advise that the benefits of treatment with oral corticosteroids outweigh the risks. [BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

If leukotriene receptor antagonists or long-acting muscarinic receptor antagonists are needed to achieve asthma control, they should not be stopped during pregnancy. [BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

Breastfeeding

Use medicines as normal when breastfeeding in line with recommendations in the BNF. [BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

Asthma in adolescents

For guidance on transitioning to adult services, see the NICE guideline on transition from children's to adults' services for young people using health or social care services and the Scottish Parliament Information Centre briefing on transitions of young people with service and care needs between child and adult services in Scotland.

Discuss future career choices with adolescents with asthma and highlight occupations that might increase susceptibility to work-related asthma symptoms. [BTS/SIGN 2019]

Ask adolescents with asthma if they vape or smoke and encourage them to stop. If they smoke, give them advice and signpost them to local NHS stop smoking services. [BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

Ask about factors that may affect a person's use of their inhaler device in real life settings, such as school and social situations. [BTS/SIGN 2019]

Self-management

For adults, young people and children aged five and over with a diagnosis of asthma (and their families or carers, if appropriate):

→ Offer an asthma self-management programme, comprising a documented personalised action plan and education. In adults, they may be based on symptoms or peak expiratory flow (or both); symptom-based plans are usually preferred for children.

→ Explain that there are things that can trigger asthma symptoms and exacerbations, including indoor and outdoor pollution. Include in the personalised action plan approaches for minimising exposure to air pollution and any other personal triggers. For more guidance on how to minimise exposure and the effect of air pollution on health, see the recommendations on:

– vulnerable groups in the NICE guideline on air pollution: outdoor air quality and health

– people with asthma, other respiratory conditions or cardiovascular conditions in the NICE guideline on indoor air quality at home, and

→ smoking in the NICE guideline on tobacco. [NICE 2017, amended 2021; BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

Review the content of the personalised action plan, and check that the person understands it, at the following:

→ hospital admission, including in virtual wards

- acute consultations in primary care or emergency department
- annual reviews. [BTS/SIGN 2019, amended BTS/NICE/ SIGN 2024]

Consider an asthma self-management programme, comprising a written personalised action plan (including approaches to minimising exposure to indoor and outdoor air pollution) and education, for the families or carers of children under five with suspected or confirmed asthma. [NICE 2017, amended NICE 2021]

For adults (aged 17 and over) who are using an inhaled corticosteroid (ICS) in a single inhaler, offer an increased dose of ICS for 7 days, within a self-management programme, when asthma control deteriorates. Clearly outline in the person's asthma action plan how and when to do this, and what to do if symptoms do not improve. When increasing ICS treatment:

- consider quadrupling the regular ICS dose
- do not exceed the maximum licensed daily dose. [NICE 2017]

Include advice in self-management programmes on contacting a healthcare professional for a review if asthma control deteriorates (see the recommendations on monitoring asthma control). [NICE 2020, amended BTS/NICE/SIGN 2024]

When implementing self-management interventions in primary care, take into account strategies to aid this, which could include:

- the use of proactive alerts to ensure routine reviews
- structured protocols for asthma reviews
- support from primary care and community pharmacists
- mailing or emailing of educational resources
- telephone calls to provide ongoing support and advice
- IT-based education and monitoring
- involvement of community workers to support clinical teams in deprived and/or ethnic minority communities. [BTS/SIGN 2019]

Schools and health services should work together to provide in-school asthma self-management education programmes provided by appropriately trained personnel. [BTS/SIGN 2019]

Provide self-management education in line with the recommendations on education programmes in the section on enabling patients to actively participate in their care in the NICE guideline on patient experience in adult NHS services. [BTS/SIGN 2019, amended BTS/NICE/SIGN 2024]

For a short explanation of why the committee made the 2020 recommendation on self-management and how it might affect practice, see the rationale and impact section on self-management.

Full details of the evidence and the committee's discussion are in the evidence review from NG80: increasing ICS treatment within supported self-management for children and young people.

Risk-stratified care

Consider actively identifying people with asthma who are at risk of poor outcomes and tailor care to their needs. Risk factors should include:

- non-adherence to medicines
- over-use of short-acting beta2 agonist (SABA) inhalers (more than two inhalers per year)
- needing two or more courses of oral corticosteroids per year
- two or more visits to an emergency department or any hospital admission for asthma. [BTS/NICE/SIGN 2024]

For a short explanation of why the committee made this recommendation and how it might affect practice, see the rationale and impact section on risk-stratified care.

Full details of the evidence and the committee's discussion are in evidence review O: risk stratified care for people with asthma.

Organisation and delivery of care

In primary care, people with asthma should be reviewed at least annually and after any exacerbation by a healthcare professional with appropriate training in asthma management. The review should incorporate a written personalised action plan. [BTS/ SIGN 2019, amended BTS/NICE/SIGN 2024]

Consider telehealthcare as an option for supporting self-management. [BTS/SIGN 2019]

Consider computerised decision support systems for patient use to support self-management. [BTS/SIGN 2019]

TERMS USED IN THIS GUIDELINE

This section defines terms that have been used in a particular way for this guideline. For other definitions see the NICE glossary and the Think Local, Act Personal Care and Support Jargon Buster.

Air therapy

Anti-inflammatory reliever (AIR) therapy is treatment with a reliever inhaler that contains a combination of an inhaled corticosteroid and formoterol. When this is used in response to symptoms without regular maintenance therapy it is called as-needed AIR therapy. In November 2024 the only product licensed for as-needed AIR therapy contained budesonide/formoterol.

Asthma control

Complete control of asthma is defined as no daytime symptoms, no night-time awakening due to asthma, no asthma attacks, no need for rescue medication, no limitations on activity including exercise, normal lung function (in practical terms forced expiratory volume in 1 s [FEV₁] and/or peak expiratory flow (PEF) more than 80% predicted or best), and minimal side effects from treatment.

Bronchial challenge test

A test to measure airway responsiveness (bronchial responsiveness). It is performed by giving small increments of a bronchoconstrictor (most commonly methacholine) and measuring the FEV₁ after each dose until it falls by a predetermined amount (usually 20% from baseline).

Bronchial hyperresponsiveness

A measure of how easily bronchospasm can be induced in the airways. It is measured using a bronchial challenge test.

Bronchodilator reversibility

A measure of the ability to reverse obstruction in the airways using medicines that widen the airways (bronchodilators).

Eosinophil count

The number of eosinophils (a type of white blood cell) measured in a blood sample. Their levels are raised in asthma and other allergic diseases, and less commonly with malignant diseases, parasite infections, reactions to some medicines, and a small number of rare diseases.

FeNO test

A test that measures the amount of nitric oxide (NO) present on exhalation, usually expressed in parts per billion.

FEV₁

The amount of air that can be forcibly exhaled from the lungs in one second (forced expiratory volume in one second).

Leukotriene receptor antagonist

A type of oral medicine that blocks cysteinyl leukotrienes, used in the treatment of asthma and seasonal allergies. Also known as leukotriene modifiers.

Long-acting muscarinic receptor antagonist

A long-acting medicine that acts on muscarinic receptors in the airway to relax airway smooth muscle and relieve symptoms of asthma.

Maintenance and reliever therapy (MART)

A form of combined ICS plus formoterol treatment in which a single inhaler containing ICS and formoterol is used for daily maintenance therapy and the relief of symptoms as needed. The terms low-dose MART and moderate-dose MART refer to the dosage of the maintenance component of MART. People using MART do not normally need a SABA.

Peak expiratory flow (PEF) variability

PEF is a measure of the maximum speed of expiration, generally expressed in litres per minute. PEF variability is a measure of the extent to which this varies over time and can be expressed numerically as amplitude percentage mean. This is calculated by subtracting the lowest value measured each day from the highest value on the same day, and averaging this over the number of days on which PEF is measured

Skin prick testing

A test that measures the allergic response of an individual to certain specific allergens when a very small amount of the specific allergen is introduced into the skin (usually the inner forearm).

Specialist in asthma care

A healthcare professional with higher training in respiratory medicine and proficiency in the management of asthma. In the context of this guideline, this requires both the relevant expertise and access to the resources that enable delivery of the diagnostic and management pathways described in the recommendations.

Uncontrolled asthma

A term used when asthma is having an impact on a person's lifestyle, or is restricting their normal activities, because of symptoms such as coughing, wheezing, shortness of breath and chest tightness. Uncontrolled asthma can include one or both of: any asthma exacerbation needing treatment with oral corticosteroids frequent regular symptoms such as: needing a reliever inhaler three or more days per week, or having one or more nights per week when asthma causes night-time waking.

These can be quantified by questionnaires such as the Asthma Control Questionnaire or Asthma Control test.

RECOMMENDATIONS FOR RESEARCH

The guideline committee has made the following recommendations for research.

Medicines for initial management

What is the clinical and cost-effectiveness of regular 'fixed-dose' inhaled corticosteroid (ICS) regimens (using SABA [short-acting beta2 agonist] as a reliever) compared with 'as-needed' strategies (for example ICS/formoterol) as the initial standard treatment for asthma in children aged 5 to 11 years? [2024]

For a short explanation of why the committee made this recommendation for research, see the rationale and impact section on medicines for initial management in children aged 5 to 11.

Full details of the evidence and the committee's discussion are in evidence review P: pharmacological management of asthma in people who are treatment-naïve or receiving SABA-only.

Medicine combination and sequencing

What is the best step-up treatment for people whose asthma is not controlled on a combination inhaler of ICS plus formoterol used as needed? [2024]

For a short explanation of why the committee made this recommendation for research, see the rationale and impact section on medicine combination and sequencing in people aged 12 and over.

Full details of the evidence and the committee's discussion are in evidence review Q: drug combinations and sequencing for asthma management. title.

Diagnostic pathways

What is the cost-effectiveness and feasibility of the proposed BTS/NICE/SIGN diagnostic pathways for asthma in children and young people aged five and over and in adults aged 17 and over? [2024]

For a short explanation of why the committee made this recommendation for research, see the rationale and impact section on objective tests for diagnosing asthma in adults, young people and children aged 5 to 16 with a history suggestive of asthma.

Full details of the evidence and the committee's discussion are in: evidence review A: accuracy and clinical and cost-effectiveness of spirometry for diagnosis of asthma

evidence review B: accuracy and clinical and cost-effectiveness of bronchodilator response in the diagnosis of asthma

evidence review C: accuracy and clinical and cost-effectiveness of peak expiratory flow in the diagnosis of asthma

evidence review D: accuracy and clinical and cost-effectiveness of skin prick test in children for diagnosis of asthma

evidence review E: accuracy and clinical and cost-effectiveness of serum IgE measures in diagnosing asthma in children

evidence review F: accuracy and clinical and cost-effectiveness of FeNO in the diagnosis of asthma

evidence review G: accuracy and clinical and cost-effectiveness of eosinophil blood count measures in the diagnosis of asthma

evidence review H: accuracy and clinical and cost-effectiveness of histamine and methacholine in the diagnosis of asthma

evidence review I: accuracy and clinical and cost-effectiveness of bronchial challenge testing (indirect) with mannitol in diagnosing asthma

evidence review J: accuracy and clinical and cost-effectiveness of bronchial challenge testing in response to exercise in diagnosis of asthma

evidence review K: accuracy and clinical and cost-effectiveness of combination tests for diagnosis in people with suspected asthma.

Inhalers

Can digital inhaler monitors cost-effectively improve adherence to preventer inhalers for people with asthma? Does this improve asthma control and who would benefit most from this intervention? [2024]

For a short explanation of why the committee made this recommendation for research, see the rationale and impact section on digital inhalers.

Full details of the evidence and the committee's discussion are in evidence review R: smart preventer/maintenance inhalers for the management of asthma.

Monitoring inhaler technique

What is the current frequency and the current method being used to check the inhaler technique of people with asthma? What is the optimal frequency and the best method of checking inhaler technique to improve clinical outcomes for people with asthma? [NICE 2017]

Monitoring asthma control using telehealthcare

What is the long-term (more than 12 months) clinical and cost-effectiveness of using telehealthcare as a means to monitor asthma control in adults, young people and children? Methods of telehealthcare can include telephone interview (with healthcare professional involvement) and internet or smartphone-based monitoring support (no healthcare professional involvement). [NICE 2017]

Decreasing pharmacological treatment

In adults, young people and children with well-controlled asthma, what are the objective measurements and prognostic factors that indicate that a decrease in regular maintenance treatment is appropriate? [NICE 2017]

Improving adherence to asthma medication

What are the most clinically and cost-effective strategies to improve medicines adherence in adults, young people and children with asthma who are non-adherent to prescribed medicines? [NICE 2017]

Other recommendations for research

Increasing the dose of ICS within a personalised self-management programme for children and young people

For children and young people with asthma that is managed in primary care, is there an advantage to increasing the ICS dose when asthma control has deteriorated compared with using the usual dose in a self-management programme? [NICE 2020]

For a short explanation of why the committee made this recommendation for research, see the rationale and impact section on self-management.

Full details of the evidence and the committee's discussion are in evidence review A: increasing ICS treatment within supported self-management for children and young people.

TOOLS AND RESOURCES: ALGORITHMS

Algorithm A: Objective tests for diagnosing asthma in adults and young people (aged over 16 years) with a history suggesting asthma – [click here to access](#)

Algorithm B: Objective tests for diagnosing asthma in children aged 5 to 16 with a history suggesting asthma – [click here to access](#)

Algorithm C: Pharmacological management of asthma in people aged 12 years and over – [click here to access](#)

Algorithm D: Pharmacological management of asthma in children aged 5 to 11 years – [click here to access](#)

Algorithm E: Pharmacological management of asthma in children under 5 – [click here to access](#)

Contributors Not applicable.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; internally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ARTIGO ORIGINAL

Incidência e prevalência de asma, doença pulmonar obstrutiva crônica (DPOC) e doença pulmonar intersticial (DPI) entre 2004 e 2023: análises harmonizadas de coortes longitudinais na Inglaterra, País de Gales, Sudeste da Escócia e Irlanda do Norte

Hannah Whittaker,¹ Adriana Kramer Fiala Machado,² Sara Hatam,³ Sarah Cook,⁴ Sean Scully,⁵ Hywel Turner T Evans,⁶ Thomas Bolton,^{7,8} Constantinos Kallis,⁹ John Busby,¹⁰ Liam G Heaney,¹¹ Aziz Sheikh,¹² Jennifer K Quint,¹³ on behalf of the CVD-COVID-UK/ COVID-IMPACT

► Additional supplemental material is published online only. To view, please visit the journal (<https://doi.org/10.1136/thorax-2024-222699>).

For numbered affiliations see end of article.

Correspondence to

Dr Hannah Whittaker; h.whittaker@imperial.ac.uk

AKFM, SH, SC, SS and HTTE contributed equally.

Received 4 November 2024

Accepted 16 January 2025

Published Online First 8 April 2025



© Author(s) (or their employer(s)) 2025. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Whittaker H, Kramer Fiala Machado A, Hatam S, et al. Thorax 2025;80:466–477.

RESUMO

Contexto Descrevemos a epidemiologia da asma, DPOC e DPI entre 2004 e 2023 na Inglaterra, País de Gales, Escócia e Irlanda do Norte (IN) utilizando uma abordagem harmonizada.

Métodos Foram utilizados dados do Serviço Nacional de Saúde da Inglaterra (NHSE), do banco de dados *Clinical Practice Research Datalink Aurum* na Inglaterra, do *Secure Anonymised Information Linkage Databank* no País de Gales, do *DataLoch* no sudeste da Escócia e do *Honest Broker Service* na Irlanda do Norte. Foi realizada uma abordagem harmonizada para definição de casos de DPOC, asma e DPI, desenho dos estudos e populações estudadas nas quatro nações. As taxas de incidência padronizadas por idade e sexo e a prevalência pontual foram calculadas entre 2004 e 2023, dependendo da disponibilidade dos dados. Regressões logísticas e binomiais negativas foram utilizadas para comparar as taxas de incidência e prevalência entre o início e o fim de cada período de estudo. A extrapolação linear projetou as taxas de incidência entre 2020 e 2023 para ilustrar como as taxas observadas e projetadas diferiram.

Resultados As taxas de incidência foram menores em 2019 em comparação com 2005 para asma (Inglaterra: razão de taxa de incidência 0,89, IC 95%: 0,88 a 0,90; País de Gales: 0,66, 0,65 a 0,68; Escócia: 0,67, 0,64 a 0,71; IN: 0,84, 0,81 a 0,86), DPOC (Inglaterra: 0,83, 0,82 a 0,85; País de Gales: 0,67, 0,65 a 0,69) e maiores para DPI (Inglaterra: 3,27, 3,05 a 3,50; País de Gales: 1,39, 1,27 a 1,53; Escócia: 1,63, 1,36 a 1,95; IN: 3,03, 2,47 a 3,72).

No NHSE, a incidência de asma foi semelhante em junho de 2023 em relação a novembro de 2019, mas menor para DPOC e maior para DPI. A prevalência de asma em 2019 na Inglaterra, País de Gales, Escócia e IN foi de 9,7%, 15,9%, 13,2% e 7,0%, respectivamente; para DPOC foi de 4,5%, 5,1%, 4,4% e 3,0%; e para DPI foi de 0,4%, 0,5%, 0,6% e 0,3%. As taxas de incidência projetadas foram 2,8, 3,4 e 1,8 vezes menores para asma, DPOC e DPI, respectivamente, em comparação com as taxas observadas no auge da pandemia.

Interpretação Asma, DPOC e DPI afetam mais de 10 milhões de pessoas nas quatro nações, e um número substancial de diagnósticos foi perdido durante a pandemia.

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► The burden of asthma, chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) has been explored in standalone countries with varying study designs and methods, thus limiting the comparability and representativeness of study results.

WHAT THIS STUDY ADDS

► This is the first study to describe the burden of asthma, COPD and ILD across England, Wales, Scotland and Northern Ireland over a 20-year period using harmonised electronic health records and paves the way for federated data analyses across the UK.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► This study demonstrates the value of using a harmonised methodological approach to using national electronic healthcare records across the UK to allow for large-scale comparable, replicable and updatable data that can be used for future policy and public health planning.

INTRODUCTION

Asthma, chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) are the three most common chronic respiratory diseases worldwide and in the UK and are associated with substantial morbidity and mortality.^{1,2} While previous studies have investigated changes in incidence and prevalence of asthma over time, these have been limited to specific populations, such as paediatric asthma populations, or are now outdated with data up until 2016.^{3–5} In addition, many studies have used data from England only, and no studies have investigated trends across England, Wales and Scotland combined. Similarly, the prevalence of COPD over time has been investigated in England

only up until 2019 and studies investigating trends in incidence and prevalence of COPD and ILD across the UK are lacking and outdated.^{6–8}

Cross-national studies of the burden of asthma, COPD and ILD in the UK are assessed through the metric of health service use. This metric is important for public health planning and identifying areas for future research and development to improve patient care. It is also important to understand in which groups of people incidence of asthma, COPD and ILD are higher to target these groups with more efficient interventions to reduce the burden of these three conditions. Likewise, given the emphasis on health inequalities in research and policy, it is important to understand where and in whom incidence or prevalence is perhaps lower than expected to target disease awareness and management campaigns. No previous studies have described the burden of these diseases across the UK in a harmonised way whereby results are more comparable. Similarly, no studies have estimated the burden of these diseases across the pandemic period where healthcare utilisation dramatically changed. Our aim was to describe the changing epidemiology of asthma, COPD and ILD between 2004 and 2023 in England, Wales, Scotland and Northern Ireland (NI) using electronic healthcare records (EHR) through standardised methodologies to improve the understanding of the evolving impacts of these diseases on individuals and provide robust methodology which can be repeated going forward to monitor trends.

METHODS

Databases

For England, primary care EHRs from the Clinical Practice Research Datalink (CPRD) Aurum (February 2022 build), for data between 2004 and 2019 and the General Practice Extraction Service for Pandemic Planning and Research (GDPPR) through the National Health Service England Secure Data Environment, via the

British Heart Foundation Data Science Centre's CVD-COVID-19 UK/COVID-19 IMPACT consortium, for data between 2019 and June 2023, were used (online supplemental file 1).⁹ For Wales, primary care data from the Welsh Longitudinal General Practice data set (WLGP) through the Secure Anonymised Information Linkage (SAIL) Databank was used to provide data between 2004 and 2019. For Scotland, the DataLoch service was used to provide data between 2004 and March 2023, which included primary care data from ~80% of general practices (GPs) in Lothian (South-East Scotland) and linked secondary care data. For NI, primary care data from the Honest Broker Service (HBS) was used to provide data between 2004 and 2022. Harmonisation of key variables between CPRD, SAIL and DataLoch has been described previously, and online supplemental table S1 summarises the harmonisation methods taken to standardise these variables across all five data sources. Our previous work contains detailed information on how key variables were harmonised.¹⁰

Chronic respiratory disease definitions (defining the numerator)

People with diagnosed and recorded asthma, COPD and ILD were defined using a harmonised approach to data curation across the databases to ensure cohort definitions were the same. Details of the methodology used have been described previously.¹⁰ For each disease, to be included as a case, individuals had to have at least one valid code within their primary care record, and the date of diagnosis was defined as a minimum of the earliest event date in primary or secondary care, using International Classification of Disease 10th revision codes in the primary position for hospitalisations. For NI, only primary care data were available and thus only a primary care diagnosis date was used. For COPD and ILD events, people were required to be at least 40 years old. In CPRD Aurum, DataLoch and SAIL, for all three diseases, people had to have at least 1 year of follow-up from GP registration prior to their

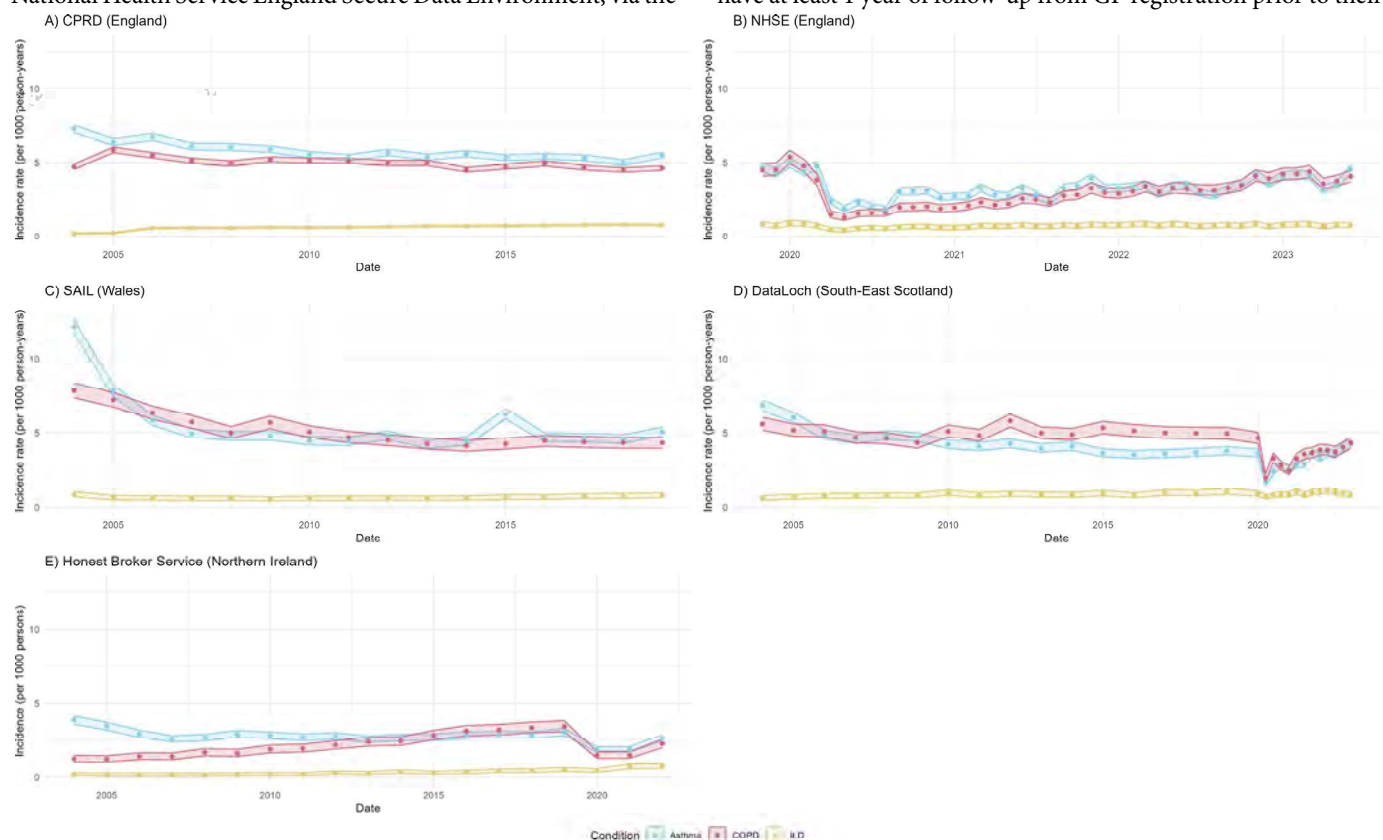


Figure 1 Age and sex adjusted incidence rate of asthma, COPD and ILD. Estimates illustrate incidence rates of asthma, COPD and ILD per 1000 person-years and 95% CIs calculated separately at each time point for England, Wales and Scotland. Yearly incidence rates were calculated for the years 2004 up until the end of 2020 for CPRD, SAIL and DataLoch, monthly incidence rates were calculated from November 2019 up until June 2023 for NHSE and 3-monthly incidence rates were calculated from January 2020 up until March 2023. Yearly incidence was calculated for Northern Ireland. COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; ILD, interstitial lung disease; NHSE, National Health Service England; SAIL, Secure Anonymised Information Linkage.

incidence code to be included in the numerator. Code lists for the asthma, COPD and ILD definitions are available on GitHub (<https://github.com/NHLI-Respiratory-Epi/Curation-Harmonisation>).

Defining the denominator

The number of patients and patient follow-up time in the total CPRD population were obtained from patient denominator files provided by CPRD per data release for all 'acceptable' (ie, research-ready) patients and was limited to those with linkage eligibility.¹⁰ For National Health Service England (NHSE), the denominator was derived from GPPR and therefore included patients with active, current GP registrations at participating practices in England (98% of GP practices in England), who were alive on 1 November 2019. Additional inclusion and exclusion criteria were applied for quality assurance purposes (online supplemental file 1). For SAIL Databank, the total number of patients was the population who had an active GP registration in the WLGP data set in Wales and who had 1 year of follow-up following GP registration. For DataLoch, people were included in the denominator if they were alive, registered and research-ready (ie, had a valid unique Community Health Index (CHI) and date of birth and sex matching CHI) with a DataLoch-registered GP and had 1 year of follow-up following GP registration. For HBS, the denominator was the mid-year estimate of the NI population (<https://data.nisra.gov.uk/>). For incidence rates, the denominator was the person-time for each time period in which individuals were still alive and registered with their GP and had not been diagnosed with the condition of interest. In NI, the denominator was incidence, which was defined as the number of people in each time period who were still alive and had not been diagnosed with the condition of interest. For prevalence, the denominator was the number of people who were still alive and or remained registered at their GP for each time period.

The same age restrictions for the numerator were applied to the denominator; for COPD and ILD, namely people aged 40 years or older were included, and there were no age restrictions for asthma.

Statistical analysis

Data were analysed separately for each data source. In England, yearly incidence rates were calculated from 2004 to 2019 in CPRD, and monthly incidence rates were calculated between November 2019 and June 2023 in NHSE. In Wales, yearly incidence rates were calculated between 2004 and 2019 in SAIL. In NI, yearly incidence was calculated from 2004 to 2022. In South-East Scotland, yearly incidence rates were calculated from 2004 to 2019 and 3-monthly incidence rates were calculated between January 2020 and March 2023 in DataLoch due to data availability. Monthly or 3-monthly rates were calculated to better understand the changing epidemiology during and after the COVID-19 pandemic in more granular detail; however, yearly incidence was calculated for NI due to data availability. Incidence rates were based on the number of incident cases in a specific year or month divided by the person-time at risk for each person in each time period presented as per 1000 person-years. In NI, incidence was based on the number of incident cases in a specific year divided by mid-year population and presented as per 1000 persons. Incidence or incidence rates for each disease were stratified by age and sex in all nations and were additionally stratified by region for CPRD and NHSE, Index of Multiple Deprivation (IMD) and ethnicity in NHSE and IMD in HBS (online supplemental file 1). In addition, to facilitate comparisons between the four nations, incidence rates were directly standardised to the European 2013 standard population.¹¹

Annual point prevalence of diagnosed and recorded disease was calculated using point prevalence for each disease for each year on 1 July from 2004 to 2019 for CPRD, SAIL and from 2004 to 2022 for DataLoch. For HBS, prevalence was calculated from 2011 to 2022 as the data sets used to identify study exit (ie, medications, secondary care utilisation and outpatient use) were available from 2010.

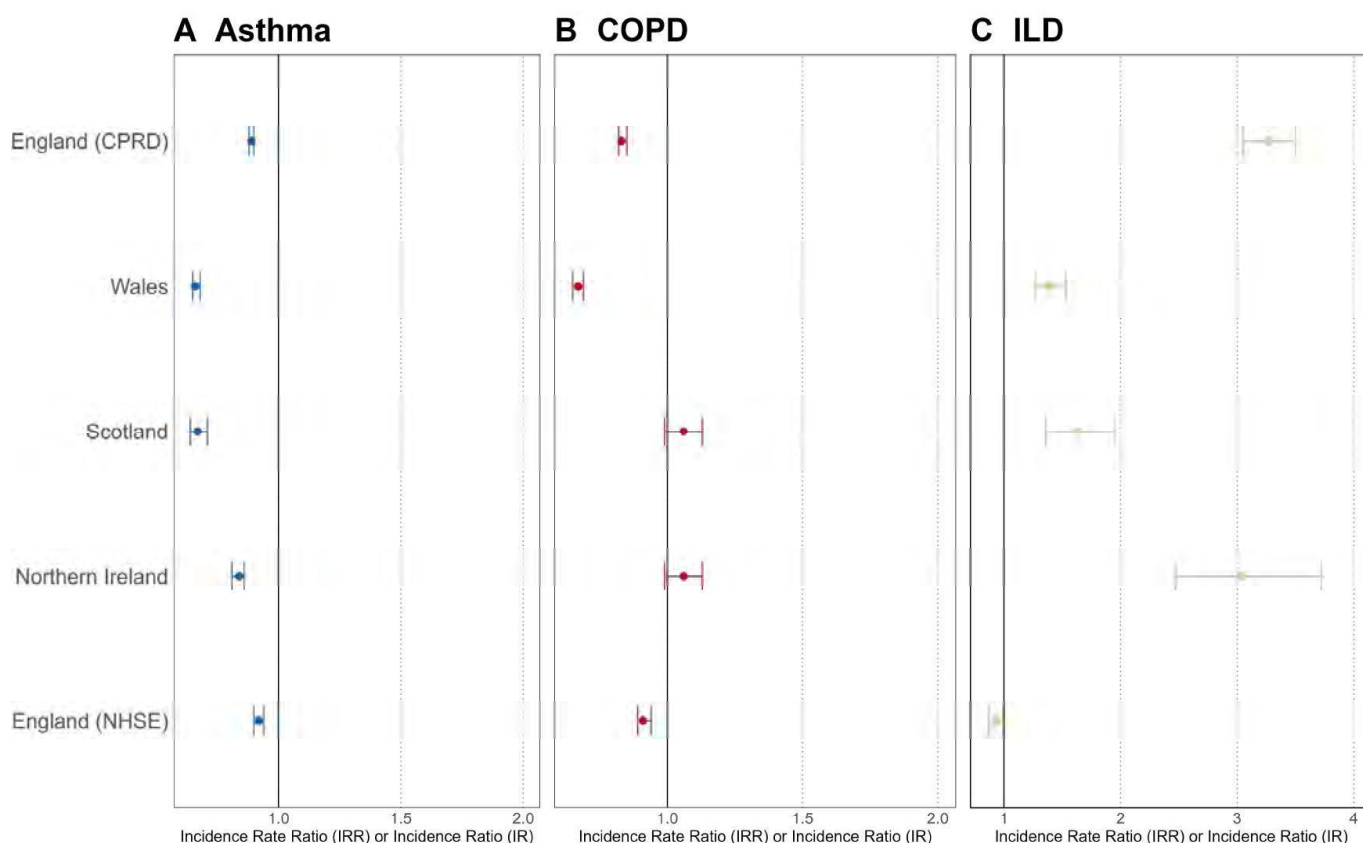


Figure 2 Crude incidence rate ratios (IRR) or incidence ratio (IR) of (A) asthma, (B) COPD and (C) ILD in 2019 versus 2005 for England, Wales, South-East Scotland and Northern Ireland and in June 2023 versus November 2019 for NHSE. Estimates illustrate IRR and 95% CIs for England, Wales and Scotland and IR for Northern Ireland. COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; ILD, interstitial lung disease; IR, incidence ratio; IRR, incidence rate ratio; NHSE, National Health Service England.

Crude incidence rate ratios (IRR) were calculated to compare the incidence of asthma, COPD and ILD in 2019 compared with 2005 in CPRD, SAIL and DataLoch. For HBS, the incidence risk ratio was calculated for each disease for 2019 compared with 2005. 2005 rather than 2004 was used for this analysis due to the introduction of the quality and outcomes framework in 2004 which could have led to more biased estimates in 2004 compared with those in 2005. For NHSE, IRRs were calculated to compare the incidence rates of asthma, COPD and ILD in June 2023 with November 2019 to determine whether incidence pre-COVID-19 pandemic differed from the most up-to-date estimates. Crude ORs were calculated to compare the prevalence of asthma, COPD and ILD in 2019 with 2005 in CPRD, SAIL and DataLoch, and in 2019 with 2011 in HBS.

Exploratory analyses

To illustrate how incidence rates of asthma, COPD and ILD would have differed if the pandemic had not occurred, we projected incidence rates for England and South-East Scotland from January 2020 to June or March 2023, respectively. In addition, linear extrapolation was used to understand whether more recent incidence rates were similar to what would have been expected if the pandemic had not occurred. This method used estimated incidence rates based on the last two data points and was based on incidence rates in 2018 and 2019 for each country separately (online supplemental file 1).

RESULTS

Online supplemental figure S1 reports the number of people in each nation with at least one chronic respiratory condition or a combination of diseases.

Trends in incidence

Asthma

Yearly adjusted incidence rates of asthma declined between 2004 and 2019 in all four nations (figure 1, online supplemental file 2).

Across England, Wales and Scotland, incidence rates of asthma declined more rapidly between 2004 and 2010 (standardised incidence rates for England, Wales and Scotland from 2004 to 2010: 7.30 (95% CI 7.05 to 7.57) to 5.55 (95% CI 5.33 to 5.77), 12.16 (95% CI 11.69 to 12.65) to 4.47 (95% CI 4.18 to 4.77) and 6.85 (95% CI 6.49 to 7.22) to 4.22 (95% CI 3.94 to 4.51) per 1000 person-years (PY), respectively; online supplemental file 2). In NI, a substantial decline in asthma incidence was observed between 2004 and 2007: 3.86 (95% CI 3.59 to 4.14) to 2.60 (95% CI 2.38 to 2.83) per 1000 persons. From 2011 to 2019 the incidence of asthma remained more stable in all four nations (standardised incidence rates for England, Wales and Scotland in 2019: 5.52 (95% CI 5.32 to 5.72), 5.08 (95% CI 4.77 to 5.40) and 3.79 (CI 3.53 to 4.07) per 1000 PY, respectively. Incidence in NI in 2019: 2.66 (95% CI 2.44 to 2.90); online supplemental file 2). During the early COVID-19 pandemic years, the incidence of asthma declined rapidly (2020–2022), before increasing to 4.57 (95% CI 4.27 to 4.87) per 1000 person-years in June 2023 in England and to 4.25 (95% CI 3.97 to 4.55) per 1000 person-years between January and March 2023 in Scotland. Incidence rates of asthma were lower in 2019 compared with 2005 in England (0.89, 95% CI 0.88 to 0.90), Wales (0.66, 95% CI 0.65 to 0.68), South-East Scotland (0.67, 95% CI 0.64 to 0.71) and incidence in NI (0.84, 95% CI 0.81 to 0.86) (figure 2, online supplemental table S2).

Overall, differences were seen across all nations by sex whereby female adults had higher rates of asthma compared with males and males less than 18 had higher rates of asthma than females less than 18. In terms of age, younger individuals had the highest rates of asthma, although the rates have decreased since 2004 in these age groups. Rates were similar over time across regions for asthma. When incidence rates were stratified by IMD and ethnicity in NHSE, the incidence of asthma was higher in those in the more deprived IMD deciles and differed by ethnicity (online supplemental figures S2–S4 and S9–S11).

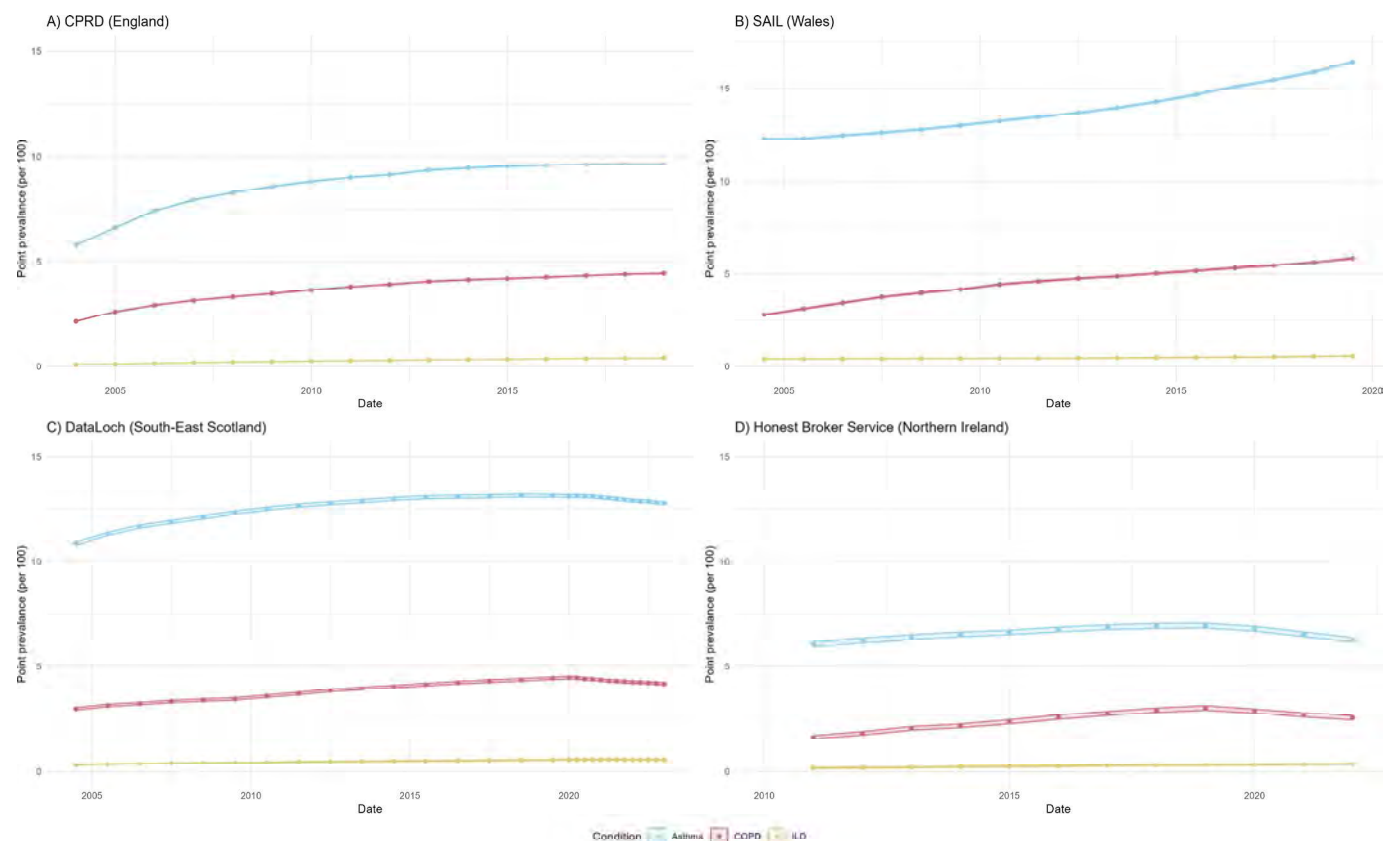


Figure 3 Point prevalence of asthma, COPD and ILD. Estimates illustrate point prevalence per 100 individuals and 95% CIs calculated separately at each time point. Point prevalence was calculated on the first of July of each year between 2004 and 2019 for England and Wales and between 2004 and 2022 for Lothian, Scotland and Northern Ireland. COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; ILD, interstitial lung disease; SAIL, Secure Anonymised Information Linkage.

Chronic obstructive pulmonary disease

Incidence rates of COPD remained stable between 2004 and 2019 in England (standardised incidence rates in 2004 and 2019: 4.74 (95% CI 4.57 to 4.91) and 4.66 (95% CI 4.50 to 4.82); online supplemental file 2, figure 1). In Scotland, incidence rates of COPD declined between 2004 and 2009 (standardised incidence rates in 2004 and 2009: 5.60 (95% CI 5.19 to 6.04) and 4.33 (95% CI 3.97 to 4.71)) but remained stable between 2010 and 2019 (standardised incidence rates in 2010 and 2019: 5.11 (95% CI 4.72 to 5.53) and 4.96 (95% CI 4.58 to 5.37)). However, the incidence of COPD declined in Wales between 2004 and 2015 (standardised incidence rates in 2004 and 2015: 7.86 (95% CI 7.36 to 8.37) and 4.26 (95% CI 3.91 to 4.64)) and remained stable between 2016 and 2019 (standardised incidence rates in 2016 and 2019: 4.45 (95% CI 4.09 to 4.84) and 4.32 (95% CI 3.96 to 4.70)). In NI, COPD incidence increased substantially during the period, with largely consistent year-on-year increases observed between 2004 and 2019 (1.23, 95% CI 1.02 to 1.46) and 3.44 (95% CI 3.10 to 3.82) per 1000 persons, respectively. During the pandemic years, the incidence of COPD declined rapidly before increasing back to similar pre-pandemic rates in June 2023 in England and March 2023 in Scotland (standardised incidence rates: 4.09 (95% CI 3.72 to 4.50) and 4.33 (95% CI 3.97 to 4.71), respectively). Crude incidence rates of COPD were also lower in 2019 compared with 2005 in England (0.83, 95% CI 0.82 to 0.85) and Wales (0.67, 95% CI 0.65 to 0.69) but were similar in South-East Scotland (1.06, 95% CI 0.99 to 1.13), and incidence was higher in NI (2.82, 95% CI 2.62 to 3.03).

Males had higher incidence rates than females. In terms of age, older individuals had the highest incidence rates. A slight difference in rates was seen for COPD in more recent years whereby northern regions had higher incidence rates of COPD. When incidence rates were stratified by IMD and ethnicity in NHSE, incidence of asthma was higher in those in the more deprived IMD deciles and differed by ethnicity (online supplemental figures S5 and S6 and S9–S11).

Interstitial lung disease

Incidence rates of ILD increased in England, Scotland and NI between 2004 and 2019, but this trend was not seen for Wales (figure 1, online supplemental file 2). In England, the incidence of ILD increased between 2004 and 2006 (standardised incidence rates in 2004 and 2006: 0.20 (95% CI 0.17 to 0.24) and 0.57 (95% CI 0.51 to 0.63)) but remained similar between 2007 and 2010 (standardised

incidence rates in 2007 and 2010: 0.59 (95% CI 0.53 to 0.65) and 0.60 (95% CI 0.55 to 0.66)) and increased between 2011 and 2019 (standardised incidence rates in 2011 and 2019: 0.62 (95% CI 0.56 to 0.68) and 0.76 (95% CI 0.71 to 0.82)). In Scotland, incidence rates increased between 2004 and 2010 (standardised incidence rates in 2004 and 2010: 0.61 (95% CI 0.47 to 0.77) and 0.95 (95% CI 0.78 to 1.15)), remained similar between 2011 and 2016 (standardised incidence rates in 2011 and 2016: 0.76 (95% CI 0.62 to 0.96) and 0.77 (95% CI 0.62 to 0.95)) and increased up until 2019 (standardised incidence rates 2019: 1.03 (95% CI 0.85 to 1.24)). In NI, incidence increased substantially between 2004 and 2019 (standardised incidence in 2004 and 2019: 0.18 (95% CI 0.13 to 0.28) and 0.49 (95% CI 0.37 to 0.64), respectively). In Wales, the incidence of ILD decreased between 2004 and 2009 (standardised incidence rates in 2004 and 2009: 0.83 (95% CI 0.67 to 1.01) and 0.52 (95% CI 0.40 to 0.68)), remained similar between 2010 and 2014 (standardised incidence rates for 2010 and 2014: 0.57 (95% CI 0.44 to 0.73) and 0.59 (95% CI 0.46 to 0.75)) and increased between 2015 and 2019 (standardised incidence rates in 2015 and 2019: 0.65 (95% CI 0.51 to 0.82) and 0.78 (95% CI 0.62 to 0.96)). During the pandemic years, the incidence of ILD declined before increasing back to similar pre-pandemic rates in June 2023 in England, but lower rates were seen in March 2023 in Scotland compared with pre-pandemic rates (standardised incidence rates: 0.75 (95% CI 0.59 to 0.93) and 0.78 (95% CI 0.62 to 0.96), respectively). Crude incidence rates of ILD were higher in 2019 compared with 2005 in England (3.27, 95% CI 3.05 to 3.50), Wales (1.39, 95% CI 1.27 to 1.53), South-East Scotland (1.63, 95% CI 1.36 to 1.95) and incidence was higher in NI (3.03, 95% CI 2.47 to 3.72). Crude incidence rates of asthma, COPD and ILD in England were lower in June 2023 compared with November 2019 (0.92, 95% CI 0.90 to 0.94, 0.91, 95% CI 0.89 to 0.94 and 0.93, 95% CI 0.87 to 0.99, respectively).

Males had higher incidence rates than females. In terms of age, older individuals had the highest incidence rates. Rates were similar over time across regions. When incidence rates were stratified by IMD and ethnicity in NHSE, the incidence of asthma was higher in those in the more deprived IMD deciles and differed by ethnicity (online supplemental figures S7–S11).

Trends in prevalence

Asthma

In England, Wales and Scotland, the prevalence of asthma increased between 2004 and 2019 and between 2011 and 2019 in NI

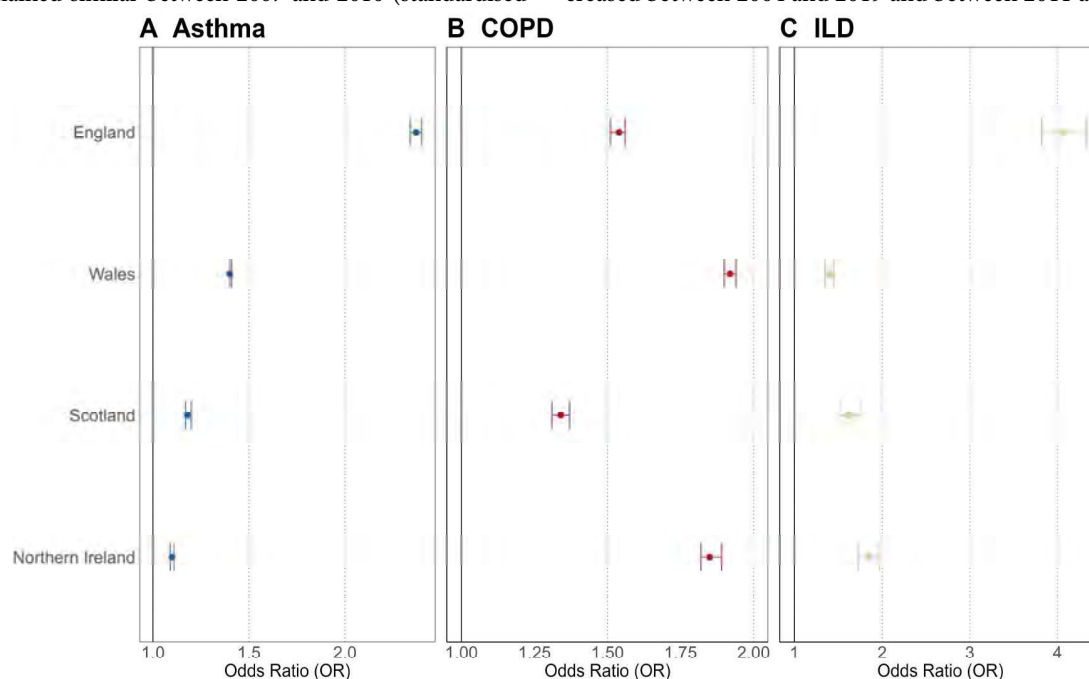


Figure 4 Crude odds ratios (OR) for the odds of (A) asthma, (B) COPD and (C) ILD in 2019 versus 2005 in England, Wales and South-East Scotland and 2019 versus 2011 in Northern Ireland. Estimates illustrate OR and 95% CIs. COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

(figure 3, online supplemental table S3, online supplemental file 3). In England and Scotland, the prevalence of asthma increased between 2004 and 2015 (prevalence of asthma in 2004 and 2015: 5.79 (95% CI 5.78 to 5.81) and 9.53 (95% CI 9.52 to 9.55) in England and 10.87 (95% CI 10.79 to 10.94) and 13.07 (95% CI 13.0 to 13.14) in Scotland). The prevalence of asthma in England and Scotland was similar between 2016 and 2019. However, in Wales, the difference in prevalence between 2004 and 2010 was smaller, and prevalence of asthma increased between 2011 and 2019 to a larger extent (prevalence of asthma in 2004, 2010 and 2019 in Wales: 12.28 (95% CI 12.23 to 12.32), 13.25 (95% CI 13.21 to 13.29) and 16.43 (95% CI 16.38 to 16.47)). Crude odds of asthma were higher in 2019 compared with 2005 in England (2.37, 95% CI 2.34 to 2.40), Wales (1.35, 95% CI 1.34 to 1.35) and Lothian Scotland (1.18, 95% CI 1.17 to 1.20) (figure 4). In NI, crude OR of asthma was higher in 2019 compared with 2011 (1.10, 95% CI 1.09 to 1.11).

Chronic obstructive pulmonary disease

In England and Scotland, the prevalence of COPD increased between 2004 and 2015 (prevalence of COPD in 2004 and 2015: 2004 and 2015 in England and Scotland: 2.15 (95% CI 2.14 to 2.16) and 4.20 (95% CI 4.18 to 2.22) in England and 3.00 (95% CI 2.94 to 3.05) and 4.14 (95% CI 4.08 to 4.20) in Scotland). The prevalence of COPD in England and Scotland was similar between 2016 and 2019. However, in Wales, the difference in prevalence between 2004 and 2010 was smaller. Crude odds of COPD were also higher in 2019 compared with 2005 in England (1.54, 95% CI 1.51 to 1.56), Wales (1.89, 95% CI 1.87 to 1.91) and South-East Scotland (1.34, 95% CI 1.31 to 1.37). In NI, crude OR of COPD was higher in 2019 compared with 2011 (1.85, 95% CI 1.82 to 1.89).

Interstitial lung disease

Prevalence of ILD increased steadily between 2004 and 2019 in England and Scotland (prevalence of ILD in 2004 and 2019 in England: 0.08 (95% CI 0.08 to 0.09) and 0.40 (95% CI 0.40 to 0.41), respectively, and in Scotland: 0.33 (95% CI 0.31 to 0.35) and 0.57 (95% CI 0.55 to 0.60), respectively; figure 4 and online supplemental file 3). In NI, prevalence increased between 2011 and 2019 (0.17 (95% CI 0.15 to 0.2) and 0.36 (95% CI 0.32 to 0.40), respectively; figure 4 and online supplemental file 3). In Wales, prevalence increased steadily between 2004 and 2014 (0.40 (95% CI 0.39 to 0.41) and 0.47 (95% CI 0.46 to 0.48), respectively; figure 4 and online supplemental file 3), before increasing more rapidly up to 2019 (0.56 (95% CI 0.55 to 0.58); figure 4 and online supplemental file 3). Crude odds of ILD were higher in 2019 compared with 2005 in England (4.07, 95% CI 3.82 to 4.33). Crude odds of ILD were also higher in 2019 compared with 2005 in Wales and South-East Scotland, but at a smaller magnitude (Wales 1.34, 95% CI 1.30 to 1.39 and Scotland 1.63, 95% CI 1.42 to 1.75). In NI, crude OR of ILD was higher in 2019 compared with 2011 (1.85 95% CI 1.73 to 1.97).

Observed versus projected incidence rates during the COVID-19 pandemic

The lowest incidence rate of asthma, COPD and ILD over the COVID-19 period in England was 1.86, 1.28 and 0.42 per 1000 person-years in May 2020, respectively. These were 2.8, 3.4 and 1.8 times lower than projected rates of asthma, COPD and ILD, respectively. The lowest incidence rate of asthma, COPD and ILD over the COVID-19 period in South-East Scotland was 1.65, 1.96 and 0.67 per 1000 person-years in April 2020, respectively. These were 2.4, 2.3 and 1.8 times lower than projected rates of asthma, COPD and ILD, respectively (online supplemental figure S12).

DISCUSSION

This is the first study to describe incidence and prevalence trends in asthma, COPD and ILD in England, Wales, Scotland and NI using harmonised methodologies and to describe the trends pre and post COVID-19. We found a decrease in the incidence of asthma in all four nations between 2004 and 2019, and a decrease in the incidence of COPD in Wales and England. The incidence

of asthma, ILD and COPD declined during the COVID-19 pandemic period, but since then has gradually increased close to pre-pandemic rates. The prevalence of asthma has increased in four nations; however, a plateau was seen in South-East Scotland and England between 2015 and 2020, with a decrease during the pandemic. The prevalence of COPD also increased across all nations and decreased during the pandemic; however, the prevalence of ILD has increased over the study period and the decrease during the pandemic was much smaller relative to the other diseases.

Asthma

Previous studies have found that the prevalence of asthma has increased over time in adults but has declined in children.^{3–5 12 13} While we did not stratify our prevalence rates by age group, we did find that incidence rates differed by age group and children aged less than 10 years had the steepest decline in asthma incidence between 2004 and 2019 compared with other age groups. The more pronounced decline seen in this population could be due to healthcare providers not giving children with suspected asthma a confirmed diagnosis of asthma, instead using a diagnosis of preschool wheeze when asthma is suspected.¹⁴ In addition, there has been a shift in attitudes to diagnosing asthma, as previously it tended to be overdiagnosed and in more recent years it is possible that physicians are more cautious when making a diagnosis of asthma, particularly in children.¹⁵ The incidence of asthma also varied by men and women in different age groups. It is well known that asthma is more common in males during childhood as compared with females, but in an adult population, asthma is more common in females than males.¹⁶ This is thought to be hormone-related, whereby after puberty the rise in oestrogen has an inflammatory effect which can lead to the development of inflammatory diseases including asthma.¹⁷

We also found that the incidence of asthma varied by IMD with higher rates of diagnoses made in more deprived individuals. This is consistent with the literature and persisted over the COVID-19 pandemic period too.^{18 19} Higher incidence rates in those who are more deprived may be due to factors including housing conditions, occupational exposures and air pollution.²⁰ Similarly, there was some variation by ethnicity whereby people with Asian and mixed ethnicity had higher rates than those with other or unknown ethnicity. While the trends are less clear, other studies have found that people with black and Asian ethnicity also have poorer asthma outcomes, including asthma exacerbations and hospitalisations.²¹ Further research into understanding reasons for these disparities is crucial to determining where efforts are needed to reduce the incidence of asthma in these populations.

Chronic obstructive pulmonary disease

Previous studies, including global estimates from the Global Burden of Disease study, have found that the incidence of COPD has decreased since 2004 and prevalence has increased, which is in line with our findings.^{7 22 23} While some studies have found that there are still disparities in people being diagnosed with COPD across the UK, others have found that the proportion of people dying of COPD and who had received a diagnosis of COPD has increased with time.²⁴ One explanation for the decline in COPD incidence could be reduced levels of smoking over time, notably since the introduction of smoke-free legislation in 2006/2007.²⁵ Interestingly, we did not find a decline in the incidence of COPD in Scotland or NI. In Scotland, this could be due to a higher prevalence of cigarette smoking compared with England and Wales, found notably in men in 2006.²⁶ In NI, smoking cessation trends have been less pronounced than in other UK nations and air quality in Belfast remains among the worst in the UK.^{27 28} Across all UK nations, COPD prevalence increased, likely due to better diagnosis, improved treatments and ageing population.^{6 10}

In addition, one systematic review found that the prevalence of COPD has historically been higher in males compared with females, but that the prevalence is similar between the two sexes in more recent years.²⁹ While we did not stratify prevalence by sex,

we did find that the incidence of COPD was consistently higher in males compared with females and varied by region, with the highest incidence in Northeast England in keeping with other work.⁸⁻²⁹ The incidence of COPD was also higher in people with white ethnicity; however, it is possible that healthcare access in this group is more accessible and therefore individuals are more likely to get a diagnosis of COPD compared with other ethnic groups who have worse access to healthcare.³⁰⁻³¹ On the other hand, in England, the incidence of COPD was higher in the most deprived populations, which could be due to higher smoking rates and more exposure to pollution.³²

In England, the incidence of COPD was higher in people who were more socioeconomically deprived and who had white ethnicity. As with asthma, factors such as occupation and housing may play a role as well as cigarette smoking.³³ Unlike asthma, people with white ethnicity had the highest rates of COPD diagnoses. Studies report that white ethnicity was more likely to be breathless, which could suggest that people with white ethnicity were more likely to seek healthcare when symptomatic.³⁰

Interstitial lung disease

There is a smaller body of research for ILD; however, evidence suggests that the incidence and prevalence of ILD have been increasing over time in all nations which were in our study, but also across Europe.³⁴ One reason for the increased incidence and prevalence over time could be increased awareness of ILD and improved diagnosis and management of people with this disease.³⁵ However, similarly to COPD, it could also be due to an ageing population, given that older age is a risk factor for ILD.³⁶ Studies have also found that the prevalence of ILD is higher in males compared with females and a higher mortality rate for more deprived people with ILD.³⁷⁻³⁸ While we did not look at disparities in prevalence or mortality, we did find that the incidence of ILD was higher in males compared with females, and there was evidence to suggest that incidence was higher in people who were most deprived compared with those who were least deprived; however, the difference was relatively small.

While incidence rates of ILD in England were less clear by socioeconomic deprivation, people with Asian and white ethnicity had higher rates over time. It is unclear as to why these differences exist, and they could be largely due to residual confounding, particularly with socioeconomic status. Further understanding into why disparities in chronic respiratory diseases exist is crucial to improving population health.

COVID-19

The incidence of clinically recorded COPD, asthma and ILD declined during the pandemic and gradually increased close to pre-pandemic levels by June 2023. The reduction in clinically recorded diagnoses reflects access to care during the pandemic and changes in health-seeking behaviours.³⁹⁻⁴⁰ Specifically, there were fewer face-to-face GP and outpatient appointments during the early months of the pandemic, leading to fewer diagnoses.⁴¹ The incidence rates of asthma, COPD and ILD in June 2023 remained slightly lower than the incidence rate in November 2019. This lag in diagnosing people with chronic respiratory disease could be due to the need for spirometry, which would have been limited during the pandemic.⁴² In addition, based on projected rates for if the pandemic had not occurred, up to 2.8 times fewer people were diagnosed with asthma, 3.4 times fewer people were diagnosed with COPD and 1.8 times fewer people were diagnosed with ILD at the height of the pandemic. Given the changes in diagnostic practices during the pandemic, the observed decline in incidence rates suggests that there were missed diagnoses, which could have a great impact on the future health of people with chronic respiratory diseases but who may not be diagnosed with the condition due to changes in care during the pandemic. Not only does this affect individuals who may be living with an undiagnosed respiratory disease, but it would affect individuals who are diagnosed with a respiratory di-

sease later on in their disease trajectory. This is particularly important for people with ILD as diagnosis is less straightforward and is already diagnosed at a late stage whereby patients have a short life expectancy. Further studies are needed to quantify the long-term burden of undiagnosed and late-diagnosed individuals.

Implications for policy, practice and research

Given the Office for National Statistics (ONS) population estimates in 2023 and assuming no dramatic increase in prevalence over the pandemic years, our prevalence estimates suggest that approximately 5.5 million (9.6%) people are living with asthma in England, 590 000 (16.4%) in Wales, 720 000 (13.2%) in Scotland and 146 000 (7.6%) in NI. For COPD our prevalence estimates in 2019 reflect approximately 2.5 million (4.5%) people in England, 185 000 (5.9%) in Wales, 241 000 (4.4%) in Scotland and 58 000 (3.0%) in NI. For ILD our prevalence estimates in 2019 reflect approximately 230 000 (0.4%) in England, 18 000 (0.6%) in Wales, 31 000 (0.6%) in Scotland and 6000 (0.3%) in NI. Overall, these three diseases affect over 10 million people across the UK, highlighting the importance of continued research into these diseases to improve management of people with asthma, COPD and ILD, to reduce morbidity and mortality. These estimates suggest that the UK still has some of the worst respiratory outcomes worldwide, as mean global age-standardised prevalence estimates for 2019 for asthma and COPD were lower than those seen in our study however, the declining trends seen in our study have also been reported globally.²³

Our study is one of the first studies to use cross-national data in a harmonised approach to describe trends in the three most prevalent chronic respiratory diseases of asthma, COPD and ILD over a 20-year period. Our harmonised methodology not only allows more comparable findings across the four UK nations, but also allows more replicable and updatable cohorts of people with asthma, COPD and ILD in the UK.

Limitations

Despite our study's strengths, limitations exist. First, EHR data were used, which may have limitations in terms of coding of diagnoses; however, we used codes that have been validated in CPRD for COPD, asthma and ILD diagnoses to minimise any biases from this.⁴³⁻⁴⁵ Second, the GPPR primary care data set in NHSE includes all individuals in England who are alive with active registration on 1 November 2019 and therefore we were unable to estimate monthly prevalence rates. Third, we were unable to stratify by region, IMD and ethnicity in CPRD due to the lack of denominator data for these specific variables. Fourth, this paper investigated trends in diagnosed disease and cannot separate out changes related to diagnosis and coding practices from true changes in incidence and prevalence. Fifth, denominators over the pandemic period varied by England and Scotland (monthly vs 3-monthly) which could have led to less variation in rates in Scotland over this period. In addition, the rates over the pandemic period could have been affected by seasonality and should be interpreted with this in mind. Furthermore, there is possible overlap between people included in CPRD and NHSE; however, this would have only occurred for the months of November and December in NHSE, and rates were similar. In addition, extrapolation assumed linearity; however, data from 2004 to 2019 was relatively linear for CPRD and Data-Loch. Moreover, for NI data the definition of study exit was pragmatic and may have led to the inappropriate exclusion of some prevalent cases who still resided in NI, especially those with less severe diseases who may not be in regular contact with the healthcare system. Furthermore, data were analysed separately for each data source and aggregate data were combined. Therefore, incidence rates were age and sex standardised to the European Union (EU) standard population to allow for comparable rates across the data sources and no other covariates were adjusted for. Lastly, case definitions were based on diagnoses made in primary and secondary care alone as spirometry measurements were not used.

A previous systematic review found that between 50% and 75% of COPD populations in the literature had airflow obstruction as defined using post-bronchodilator spirometry. On the other hand, spirometry-confirmed COPD without a clinically recorded diagnosis was common.⁴⁶ Similarly for asthma, misdiagnosis is possible, notably in those who did not have testing for airflow limitation.⁴⁷ Therefore, it is possible that the incidence and prevalence of COPD, asthma and ILD could have been over or under-estimated; however, we used algorithms for disease diagnosis that have been validated in UK EHRs to reduce the risk of misdiagnosis.^{43–45}

CONCLUSION

This is the first study using harmonised EHR data from the four nations in the UK to describe the trend in epidemiology of three chronic respiratory diseases over a combined 20-year period. In the four nations, the incidence of asthma has decreased, the incidence of ILD has increased; however, the incidence of COPD has decreased in England and Wales only. Changes in incidence rates were likely due to changes in behaviours and disease awareness. Disparities in incidence rates exist by sex, age, region, IMD and ethnicity, and missed diagnoses from the COVID-19 pandemic could have a great impact on the future health of people with chronic respiratory diseases. Overall, these data form a strong baseline for future policy work and public health planning.

Author affiliations

¹School of Public Health, Imperial College London, London, UK

²Queen's University Belfast, Belfast, UK

³The University of Edinburgh Usher Institute of Population Health Sciences and Informatics, Edinburgh, UK

⁴Imperial College London School of Public Health, London, UK

⁵Swansea University, Swansea, UK

⁶Population Data Science, Swansea University, Swansea, UK

⁷British Heart Foundation Data Science Centre, London, UK

⁸Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK

⁹National Heart and Lung Institute, Imperial College London, London, UK

¹⁰Centre for Experimental Medicine, Queen's University Belfast School of Medicine Dentistry and Biomedical Sciences, Belfast, UK

¹¹Centre of Infection and Immunity, Queens University Belfast, Belfast, UK

¹²Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK

¹³NHLI, Imperial College London, London, UK

X Aziz Sheikh @DrAzizSheikh

Acknowledgements This work was carried out with the support of the BHF Data Science Centre led by HDR UK (BHF Grant no. SP/19/3/34678). This study makes use of de-identified data held in NHS England's Secure Data Environment service for England and made available via the BHF Data Science Centre's CVD-COVID-UK/COVID-IMPACT consortium. This work used data provided by patients and collected by the NHS as part of their care and support. We would also like to acknowledge all data providers who make health-relevant data available for research.

Collaborators CVD-COVID-UK/COVID-IMPACT Consortium: Barts Health NHS Trust: Alastair Proudfoot; Barts Health NHS Trust: Andrew Constantine; Barts Health NHS Trust: Dan Jones; Barts Health NHS Trust: Krishnaraj Rathod; Barts Health NHS Trust: Nida Ahmed; Barts Health NHS Trust: Richard Fitzgerald; British Heart Foundation: Dan O'Connell; British Heart Foundation: Rony Arafin; British Heart Foundation: Sonya Babu-Narayan; British Heart Foundation: Zainab Karim; Cancer Research UK: Jon Shelton; Cancer Research UK: Martina Slapkova; Cancer Research UK: Rosie Hindcliffe; Cancer Research UK: Shane Johnson; Cardiff Metropolitan University: Renin Toms; Cardiff University: Julia Townsend; European Bioinformatics Institute: Ewan Birney; European Bioinformatics Institute: Moritz Gerstung; European Bioinformatics Institute: Tomas Fitzgerald; Great Ormond Street Hospital: Katherine Brown; Guy's and St Thomas' NHS Foundation Trust: Benjamin Zuckerman; Guy's and St Thomas' NHS Foundation Trust: Ernest Wong; Guy's and St Thomas' NHS Foundation Trust: Lily Benton; Guy's and St Thomas' NHS Foundation Trust: Tasneem Braithwaite; Health Data Research UK: Alexis Webb; Health Data Research UK/BHF Data Science Centre: Anna Stevenson; Health Data Research UK/BHF Data Science Centre: Annette Jackson; Health Data Research UK/BHF Data Science Centre: Cathie Sudlow; Health Data Research UK/BHF Data Science Centre: Fionna Chalmers; Health Data Research UK/BHF Data Science Centre: Jadene Lewis; Health Data Research UK/BHF Data Science Centre: James Farrell; Health Data Research UK/BHF Data Science Centre: Jemma Austin; Health Data Research UK/BHF Data Science Centre: John Nolan; Health Data Research UK/BHF Data Science Centre: Lars Murdoch; Health Data Research UK/BHF Data Science Centre: Lynn Morrice; Health Data Research UK/BHF Data Science Centre: Mehrdad Mizani; Health Data Research UK/BHF Data Science Centre: Melissa Webb; Health Data Research UK/BHF Data Science Centre: Ross Forsyth; Health Data Research UK/BHF Data Science Centre: Rouven Priedon; Health Data Research UK/BHF Data Science Centre: Samaira Khan; Health Data Research UK/BHF Data Science Centre: Steffen Petersen; Health Data Research UK/BHF Data Science Centre: Thomas Bolton; Health Data Research UK/BHF Data Science Centre: Zach Welshman; Healthcare Quality Improvement Partnership: Caroline Rogers; Hull York Medical School: Donna Wakefield; Imperial College London: Alun Davies; Imperial College London: Arunashis Sau; Imperial College London: Costas Kallis; Imperial College London: Fu Siong Ng; Imperial College London: Hannah Whittaker; Imperial College London: Ioanna Tzoulaki; Imperial College London: Jennifer Quint; Imperial College London: Juliette Unwin; Imperial College London: Libor Pastika; Imperial College London: Petter Brodin; Imperial College London: Philip Stone; Imperial College London: Safa Salim; Imperial College London: Sarah Cook; Imperial College London: Sarah Onida; Imperial College London (LCP): Alistair Marsland; Imperial College London (LCP): Andrew Thompson; Imperial College London (LCP): Sara Holloway; Imperial College London (LCP): Thomas Porter; INSIGHT: Alastair Denniston; Keele University: Mamas Mamas; King's College London: Abdel Douiri; King's College London: Adejoke Oluysa; King's College London: Ajay Shah; King's College London: Alexandru Dregan; King's College London: Amy Ronaldson; King's College London: Anna Bone; King's College London: Antonio Cannata; King's College London: Ben Bray; King's College London: Charles Wolfe; King's College London: Daniel Bromage; King's College London: Dominic Oliver; King's College London: Elena Nikiphorou; King's College London: Emeka Chukwusa; King's College London: Gareth Williams; King's College London: Gayan Perera; King's College London: Harry Kwaka; King's College London: Ian Marshall; King's College London: Irene Higginson; King's College London: Javiera Leniz Martelli; King's College London: Jayati Das-Munshi; King's College London: Joanna Davies; King's College London: Johnny Downs; King's College London: Katherine Sleeman; King's College London: Laia Becares; King's College London: Linglong Qian; King's College London: Matthew O'Connell; King's College London: Mevhibe Hocaoglu; King's College London: Natasha Chilman; King's College London: Rachel Cripps; King's College London: Richard Killick; King's College London: Theresa McDonagh; King's College London: Vasa Curcin; King's College London: Zeljko Kraljevic; Leeds Teaching Hospitals NHS Trust: Carin van Doorn; London School of Economics & Political Science: Rocco Friebe; London School of Hygiene & Tropical Medicine: Antonio Gasparini; London School of Hygiene & Tropical Medicine: Arturo de la Cruz; London School of Hygiene & Tropical Medicine: Dorothea Nitsch; London School of Hygiene & Tropical Medicine: Julian Matthewsman; London School of Hygiene & Tropical Medicine: Neil Pearce; London School of Hygiene & Tropical Medicine: Patrick

Bidulka; London School of Hygiene & Tropical Medicine: Qiuju Li; London School of Hygiene & Tropical Medicine: Sinead Langan; London School of Hygiene & Tropical Medicine: Thiago Silva; London School of Hygiene & Tropical Medicine: Zhenqian Zhu; Manchester University NHS Foundation Trust: Martin Rutter; Newcastle-upon-Tyne Hospitals NHS Foundation Trust: Alex Grundmann; NHS England: Adam Hollings; NHS England: Angeliki Antonarou; NHS England: Daniel Schofield; NHS England: Deborah Lowe; NHS England: Elizabeth Kelly; NHS England: Richardson; NHS England: Humaira Hussein; NHS England: Jake Kasan; NHS England: Nickie Wareing; NHS England: Russell Healey; NHS England: Shoab Ali Ajaib; NHS Lanarkshire: Mark Barber; NHS Scotland: Carole Morris; NICE: Felix Greaves; NICE: Jennifer Beveridge; NICE: Seamus Kent; NICE: Thomas Lawrence; NICE: Vandana Ayyar-Gupta; Office for National Statistics: Myer Glickman; Office for National Statistics: Vahé Nafilyan; Queen Mary University of London: Deepthi Gurdasani; Queen's University Belfast: Frank Kee; Royal Brompton and Harefield Hospitals: Paz Tayaj; Royal College of Surgeons of England: David Cromwell; Royal Free London NHS Foundation Trust: Amar Shah; Royal Free London NHS Foundation Trust: Swapna Mandal; Royal Papworth Hospital NHS Foundation Trust: Florian Falter; Royal Papworth Hospital NHS Foundation Trust: Joseph Newman; Royal United Hospitals Bath NHS Foundation Trust: Jennifer Rossdale; St George's University of London: Baboucar Njie; St George's University of London: Elijah Behr; St George's University of London: Nuria Sanchez; St George's University of London: Xinkai Wang; Swansea Bay University Health Board: Daniel Harris; Swansea University: Amanda Marchant; Swansea University: Ashley Akbari; Swansea University: Daniel King; Swansea University: David Powell; Swansea University: Elizabeth A Ellins; Swansea University: Fatemeh Torabi; Swansea University: Gareth Davies; Swansea University: Hoda Abbasizanjani; Swansea University: Huw Trafford; Swansea University: Jane Lyons; Swansea University: Julian Halcox; Swansea University: Laura North; Swansea University: Marcos del Pozo Banos; Swansea University: Owen Pickrell; Swansea University: Ronan Lyons; Swansea University - DATAMIND: Ann John; University College: Robert Aldridge; University College London: Abraham Olvera-Barrios; University College London: Adnan Tufail; University College London: Alasdair Warwick; University College London: Alex Handy; University College London: Alexei Yavinsky; University College London: Alvina Lai; University College London: Ami Banerjee; University College London: Ana Torralba; University College London: Ana-Catarina Pinho-Gomes; University College London: Andrej Ivanovic; University College London: Andrew Lambarth; University College London: Anthony Khawaja; University College London: Ashkan Dashtban; University College London: Ashley Dickson; University College London: Becky White; University College London: Christina Pagel; University College London: Christopher Tomlinson; University College London: Chu Siyu; University College London: David Selby; University College London: Eloise Withnell; University College London: Emma Whitfield; University College London: Eva Keller; University College London: Evaleen Malgapo; University College London: Ferran Espuny-Pujol; University College London: Flavien Hardy; University College London: Florian Schmidt; University College London: Freya Allery; University College London: Harry Hemingway; University College London: Honghan Wu; University College London: Jinge Wu; University College London: Johan Thygesen; University College London: Johannes Heyl; University College London: Julia Iwe; University College London: Kate Cheema; University College London: Katie Harron; University College London: Ken Li; University College London: Kerrie Stevenson; University College London: Laura Pasea; University College London: Louise Choo; University College London: Luca Grieco; University College London: Manuel Gomes; University College London: Matt Sydes; University College London: Mehrdad Mizani; University College London: Michalis Katsoulis; University College London: Mohamed Mohamed; University College London: Naomi Launders; University College London: Nushrat Khan; University College London: Paula Lorgelly; University College London: Pedro Machado; University College London: Pia Haredeli; University College London: Qi Huang; University College London: Riyaz Patel; University College London: Roy Schwartz; University College London: Rui Providencia; University College London: Ruth Gilbert; University College London: Samuel Kim; University College London: Simon Ellershaw; University College London: Sonya Crowe; University College London: Spiros Denaxas; University College London: Tuankasfee Hama; University College London: Waty Lilaontikul; University College London: Yi Mu; University College London: Yohel Hamada; University College London: Yoryos Lyratzopoulos; University College London / DATAMIND: David Osborn; University Hospital of North Midlands: Arun Pherwani; University of Aberdeen: Mary Joan Madeod; University of Birmingham: Sarah Wang; University of Birmingham and Queen Elizabeth Hospital Birmingham: Mark Thomas; University of Bristol: Arun Karthikeyan Suseeladevi; University of Bristol: Ben Gibbison; University of Bristol: Dann Mitchell; University of Bristol: Deborah Lawler; University of Bristol: Eleanor Walsh; University of Bristol: Elsie Horne; University of Bristol: Ewan Walker; University of Bristol: Gianni Angelini; University of Bristol: Jeremy Chan; University of Bristol: John Macleod; University of Bristol: Jonathan Sterne; University of Bristol: Katharine Looker; University of Bristol: Kurt Taylor; University of Bristol: Livia Pierotti; University of Bristol: Luisa Zuccolo; University of Bristol: Martha Elwenspeck; University of Bristol: Marwa Al Arab; University of Bristol: Massimo Caputo; University of Bristol: Mira Hidayat; University of Bristol: Neil Davies; University of Bristol: Paul Madley-Dowd; University of Bristol: Rachel Denholm; University of Bristol: Rochelle Knight; University of Bristol: Shubhra Sinha; University of Bristol: Tim Dong; University of Bristol: Tom Palmer; University of Bristol: Venexia Walker; University of Bristol: Yueying Li; University of Bristol: Yvonne Natter; University of Cambridge: Alexia Sampi; University of Cambridge: Angela Wood; University of Cambridge: Carmen Pettigrew; University of Cambridge: Chimiweta Chiala; University of Cambridge: Chriselda Oliver; University of Cambridge: David Brind; University of Cambridge: Elena Raffetti; University of Cambridge: Elias Allara; University of Cambridge: Emanuele Di Angelantonio; University of Cambridge: Eoin McKinney; University of Cambridge: Eric Harshfield; University of Cambridge: Fabian Falck; University of Cambridge: Genevieve Cezard; University of Cambridge: Hannah Harrison; University of Cambridge: Haoting Zhang; University of Cambridge: Holly Pavey; University of Cambridge: Isabel Walter; University of Cambridge: Jessica Barrett; University of Cambridge: John Danesh; University of Cambridge: John Ford; University of Cambridge: Katie Saunders; University of Cambridge: Lisa Pennells; University of Cambridge: Lois Kim; University of Cambridge: Mayank Dalakoti; University of Cambridge: Megan Ritson; University of Cambridge: Mike Inouye; University of Cambridge: Millie Zhou; University of Cambridge: Robert Fletcher; University of Cambridge: Rutendo Mapeta; University of Cambridge: Samantha Ip; University of Cambridge: Spencer Keene; University of Cambridge: Stelios Boultsakis Logothetis; University of Cambridge: Stephen Kaptoke; University of Cambridge: Tianxiao Wang; University of Cambridge: Tom Pape; University of Cambridge: Wen Shi; University of Cambridge: Xilin Jiang; University of Cambridge: Xiyun Jiang; University of Cambridge: Yanfan Li; University of Dundee: Daniel Morales; University of Dundee: Huan Wang; University of Dundee: Ify Mordi; University of Dundee: Samira Bell; University of Edinburgh: Alan Carson; University of Edinburgh: Alice Hosking; University of Edinburgh: Annemarie Docherty; University of Edinburgh: Athina Spiliopoulou; University of Edinburgh: Baljean Dhillon; University of Edinburgh: Carlos Sanchez Soriano; University of Edinburgh: Caroline Jackson; University of Edinburgh: Christian Schner; University of Edinburgh: Claire Tocheil; University of Edinburgh: Gwennetta Curry; University of Edinburgh: Helen Colhoun; University of Edinburgh: Gue Mellor; University of Edinburgh: Kelly Fleetwood; University of Edinburgh: Laura Sherlock; University of Edinburgh: Luke Blackburn; University of Edinburgh: Michelle Williams; University of Edinburgh: Miguel Bernabeu Linares; University of Edinburgh: Niamh McLennan; University of Edinburgh: Rebecca Reynolds; University of Edinburgh: Richard Chin; University of Edinburgh: Steven Kerr; University of Edinburgh: Tim Wilkinson; University of Edinburgh: Veronica Cabreira; University of Edinburgh: William Berthon; University of Edinburgh: William Whiteley; University of Exeter: John Dennis; University of Exeter: Kerry Pearn; University of Exeter: Michael Allen; University of Glasgow: Angela Henderson; University of Glasgow: Clea du Toit; University of Glasgow: Colin Berry; University of Glasgow: Craig Melville; University of Glasgow: Deborah Kinneir; University of Glasgow: Dennis Tran; University of Glasgow: Filip Sosenko; University of Glasgow: Frederick Ho; University of Glasgow: Jill Pell; University of Glasgow: Jocelyn Friday; University of Glasgow: John Cleland; University of Glasgow: Naveed Sattar; University of Glasgow: Ninian Lang; University of Glasgow: Salil Deo; University of Glasgow: Sandosh Padmanabhan; University of Glasgow: Terry Quinn; University of Leeds: Jianhua Wu; University of Leeds: Ramesh Nadarajah; University of Leicester: Anna Hansell; University of Leicester: Anvesha Singh; University of Leicester: Cameron Razieh; University of Leicester: Claire Lawson; University of Leicester: Clare Gillies; University of Leicester: Francesco Zaccardi; University of Leicester: Iain Squire; University of Leicester: Kamlesh Khunti; University of Leicester: Matthew Bown; University of Leicester: Muhammad Rashid; University of Leicester: Sharmin Shabnam; University of Leicester: Shirley Sze; University of Leicester: Tom Yates; University of Leicester: Yogini Chudasama; University of Liverpool: Andrew Mason; University of Liverpool: Benedict Michael; University of Liverpool: Caroline Dale; University of Liverpool: David Hughes; University of Liverpool: Francesca Zaccagnino; University of Liverpool: Maria Sudell; University of Liverpool: Mark Green; University of Liverpool: Munir Pirmohamed; University of Liverpool: Parris Biglarbegi; University of Liverpool: Reecha Sofat; University of Liverpool: Rohan Takhar; University of Liverpool: Ruwanthi Kolamunnage-Dona; University of Liverpool: Stephen McKeever; University of Manchester: Bernard Keavney; University of Manchester: Catriona Harrison; University of Manchester: Craig Smith; University of Manchester: David Jenkins; University of Manchester: Eva Henning; University of Manchester: Evan Kontopantelis; University of Manchester: George Tilston; University of Manchester: Glen Martin; University of Manchester: Hector Chinoy; University of Manchester: Joseph Firth; University of Manchester: Lana Bojani; University of Manchester: Matthew Sperrin; University of Manchester: Max Lyon; University of Manchester: Maya Buch; University of Manchester: Richard Williams; University of Manchester: Ruth Norris; University of Manchester: Ruth Watkinson; University of Manchester: Sarah Steeg; University of

Manchester: Simon Frain; University of Manchester: Simon Williams; University of Manchester: Steven Zhao; University of Manchester: Zenas Yiu; University of Newcastle: Camille Carroll; University of Newcastle: Charlotte Parbery-Clark; University of Newcastle: Dexter Canoy; University of Newcastle: Precious Onyeachu; University of Nottingham: Fiona Pearce; University of Nottingham: Laila Tata; University of Nottingham: Ralph Akyea; University of Nottingham: Stephanie Lax; University of Oxford: Aashna Uppal; University of Oxford: Akshay Shah; University of Oxford: Antonella Delmestri; University of Oxford: Antony Palmer; University of Oxford: Ben Goldacre; University of Oxford: Ben Lacey; University of Oxford: Dani Prieto-Alhambra; University of Oxford: Eva Morris; University of Oxford: George Nicholson; University of Oxford: Hayley Evans; University of Oxford: James Sheppard; University of Oxford: Joseph Kamtchum Tatuene; University of Oxford: Julia Hippisley-Cox; University of Oxford: Kazem Rahimi; University of Oxford: Linxin Li; University of Oxford: Lucy Wright; University of Oxford: Marta Pineda Moncusí; University of Oxford: Mohammad Mamouei; University of Oxford: Nick Hall; University of Oxford: Parag Gajendragadkar; University of Oxford: Paula Dhiman; University of Oxford: Qingze Gu; University of Oxford: Raph Goldacre; University of Oxford: Salma Chaudhry; University of Oxford: Sara Khalid; University of Oxford: Seb Bacon; University of Oxford: Seyed Alireza Hasheminasab; University of Oxford: Shishir Rao; University of Oxford: Xiaomin Zhong; University of Oxford: Zeinab Bidel Talehmekaeli; University of Oxford/KU Leuven: Nathalie Conrad; University of Plymouth: Marie-Louise Zeissler; University of Sheffield: Jen-Yu Amy Chang; University of Sheffield: Norman Briffa; University of Sheffield: Peter Bath; University of Sheffield: Simone Croft; University of Sheffield: Suzanne Mason; University of Sheffield: Tim Chico; University of Southampton: Nazrul Islam; University of Strathclyde: Amanj Kurdi; University of Strathclyde: Kim Kavanagh; University of Strathclyde: Marion Bennie; University of Strathclyde: Tanja Mueller; University of Warwick: Harry Wilde; University of Warwick: Majel McGranahan; University of York: Christina van der Feltz-Cornelis; University of York: Han-I Wang; University of York: Lorna Fraser; Wellcome Sanger Institute: Tapiwa Tungamirai. Contributors HW analysed the NHSE and aggregate data and wrote the original manuscript. AKFM analysed the Northern Ireland data. SH analysed the DataLoch data, SC analysed the CPRD data, SS and HTTE analysed the SAIL data. TB curated the NHSE data. All authors (HW, AKFM, SH, SC, SS, HTTE, TB, CK, LGH, JB, AS, JKQ) reviewed the results and approved the final version of the manuscript. JKQ is the guarantor. Funding This work was partly funded by BREATHE-The Health Data Research Hub for Respiratory Health (MC_PC_19004) and the Health Data Research (HDR) UK Inflammation and Immunity programmes (DRUK2023.0027). In addition, an NIHR BRC grant funded access to the British Heart Foundation Data Science Centre for use of the NHSE SDE data (BRC RS PII P50767). The British Heart Foundation Data Science Centre (grant No SP/19/3/34678, awarded to Health Data Research (HDR) UK) funded co-development (with NHS England) of the Secure Data Environment service for England, provision of linked data sources, data access, user software licences, computational usage and data management and wrangling support, with additional contributions from the HDR UK Data and Connectivity component of the UK Government Chief Scientific Adviser's National Core Studies programme to coordinate national COVID-19 priority research. Consortium partner organisations funded the time of contributing data analysts, biostatisticians, epidemiologists and clinicians. This research is part of the Data and Connectivity National Core Study, led by Health Data Research UK in partnership with the Office for National Statistics and funded by UK Research and Innovation (grant ref: MC_PC_20058).

Competing interests HW reports a grants from NIHR BRC for work conducted in the NHSE SDE. SH reports employment from DataLoch for the submitted work. SS reports grants from Industrial Strategy Challenge Fund, MRC and HDR UK for the submitted work. AS reports grants from HDR UK and ISCF for the submitted work and from asthma and lung UK outside the submitted work. JKQ reports grants from Industrial Strategy Challenge Fund, MRC and HDR UK for the submitted work and from GSK, Evidera, Chiesi and AZ outside the submitted work. SC, HTTE, TB, AKFM, LGH, JB and CK have no conflicts of interest.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. The data used in this study are available in NHS England's Secure Data Environment (SDE) service for England, but as restrictions apply, they are not publicly available (<https://digital.nhs.uk/coronavirus/coronavirus-data-services-updates/trusted-research-environment-service-for-england>; <https://digital.nhs.uk/services/secure-data-environment-service>). The CVD-COVID-UK/COVID-IMPACT programme led by the BHF Data Science Centre (<https://bhfdatasciencecentre.org/>; <https://www.hdr.uk.ac.uk/helping-with-healthdata/bhf-data-science-centre/>) received approval to access data in NHS England's SDE service for England from the Independent Group Advising on the Release of Data (IGARD) (<https://digital.nhs.uk/about-nhs-digital/corporate-information-and-documents/independent-group-advising-on-the-release-of-data>) via an application made in the Data Access Request Service (DARS) Online system (ref. DARS-NIC-381078-Y9C5K) (<https://digital.nhs.uk/services/data-access-request-service-dars/dars-products-and-services>). The CVD-COVID-UK COVID-IMPACT Approvals & Oversight Board (<https://bhfdatasciencecentre.org/areas/cvd-covid-uk-covid-impact/>; <https://www.hdr.uk.ac.uk/projects/cardiavasculard-covid-uk-project/>) subsequently granted approval to this project to access the data within NHS England's SDE service for England. The de-identified data used in this study were made available to accredited researchers only. Those wishing to gain access to the data should contact bhfdsc@hdr.uk.ac.uk in the first instance. The Northeast - Newcastle and North Tyneside 2 research ethics committee provided ethical approval for the CVD-COVID-UK/COVID-IMPACT research programme (REC No 20/N06/0161) to access, within secure SDE trusted research environments, unconsented, whole-population, de-identified data from EHR data collected as part of patients' routine healthcare. Our analysis was performed according to a prespecified analysis plan published on GitHub, along with the phenotyping and analysis code (https://github.com/BHFDSC/CCU052_01). To ensure anonymity and compliance with the NHSE SDE-COVID-UK consortium rules of statistical disclosure, all reported numbers were rounded to the nearest 5. Counts less than 10 were expressed as '<10'. CPRD has NHS Health Research Authority (HRA) Research Ethics Committee (REC) approval to allow the collection and release of anonymised primary care data for observational research (NHS HRA REC reference number: 05/MRE04/87). Each year CPRD obtains Section 251 regulatory support through the HRA Confidentiality Advisory Group (CAG), to enable patient identifiers, without accompanying clinical data, to flow from CPRD contributing GP practices in England to NHSE, for the purposes of data linkage (CAG reference number: 21/CAG/0008). The protocol for this research was approved by CPRD's Research Data Governance (RDG) Process (protocol number: 22_001769) and the approved protocol is available upon request. Linked pseudonymised data was provided for this study by CPRD. Data is linked by NHSE, the statutory trusted third party for linking data, using identifiable data held only by NHSE. Select general practices consent to this process at a practice level with individual patients having the right to opt-out. All work conducted in SAIL Databank was completed under the permission and approval of the SAIL independent Information Governance Review Panel (IGRP) under project number 1387. Researchers can apply for the data and scripts within the SAIL trusted research environment, subject to the standard SAIL project application process (saildatabank.com/contact). The DataLoch work was reviewed and approved under the project number DL_2022_054. The underlying DataLoch data are available as part of the DataLoch Respiratory Registry—a de-identified registry of linked respiratory data from the South-East Scotland region—which can be accessed by application to the DataLoch service (dataloch.org/connect-with-us). Accredited researchers could only access the de-identified HBS data used in this study by signing a Disclosure Policy Agreement and Research Data Access Agreement. The data was accessible from a secure location, the UK Secure e-Research Platform (UK SeRP). Ethical approval was not required for this study as it was facilitated via HBS. Consent was not required for this study as data was provided in anonymised format, the rights of individuals are respected with adequate privacy protection.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed.

Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise. Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: <https://creativecommons.org/licenses/by/4.0/>.

ORCID iDs

Hannah Whittaker <http://orcid.org/0000-0002-7705-0300>
 Adriana Kramer Fiala Machado <http://orcid.org/0000-0002-6800-1064>
 Hywel Turner T Evans <http://orcid.org/0000-0001-6745-4187>
 Constantinos Kallis <http://orcid.org/0000-0003-0866-5421>
 John Busby <http://orcid.org/0000-0003-4831-7464>
 Jennifer K Quint <http://orcid.org/0000-0003-0149-4869>

REFERENCES

- Mukherjee M, Stoddart A, Gupta RP, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Med* 2016;14:113.
- GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 2017;5:(2213–2619) (Electronic).
- Kallis C, Maslova E, Morgan AD, et al. Recent trends in asthma diagnosis, preschool wheeze diagnosis and asthma exacerbations in English children and adolescents: a SABINA Jr study. *Thorax* 2023;78:1175–80.
- Bloom CI, Saglani S, Feary J, et al. Changing prevalence of current asthma and inhaled corticosteroid treatment in the UK: population-based cohort 2006–2016. *Eur Respir J* 2019;53:(1399–3003) (Electronic).
- Simpson CR, Sheikh A. Trends in the epidemiology of asthma in England: a national study of 333,294 patients. *J R Soc Med* 2010;103:98–106.
- Stone PW, Osen M, Ellis A, et al. Prevalence of Chronic Obstructive Pulmonary Disease in England from 2000 to 2019. *Int J Chron Obstruct Pulmon Dis* 2023;18:1565–74.
- Simpson CR, Hippisley-Cox J, Sheikh A. Trends in the epidemiology of chronic obstructive pulmonary disease in England: a national study of 51 804 patients. *Br J Gen Pract* 2010;60:e277–84.
- Nacul L, Soljak M, Samarasinghe E, et al. COPD in England: a comparison of expected, model-based prevalence and observed prevalence from general practice data. *J Public Health (Oxf)* 2011;33:108–16.
- NHS. General practice extraction service (GPES) data for pandemic planning and research: a guide for analysts and users of the data. 2024. Available: <https://digital.nhs.uk/coronavirus/gpes-data-for-pandemic-planning-and-research/guide-for-analysts-and-users-of-the-data> [Accessed 19 Mar 2024].
- Hatam S, Scully ST, Cook S, et al. A Harmonised Approach to Curating Research-Ready Datasets for Asthma, Chronic Obstructive Pulmonary Disease (COPD) and Interstitial Lung Disease (ILD) in England, Wales and Scotland Using Clinical Practice Research Datalink (CPRD), Secure Anonymised Information Linkage (SAIL) Databank and DataLoch. *Clin Epidemiol* 2024;16:235–47.
- Eurostat. Revision of the European standard population, EE Commission, editor. 2013.
- Anandan C, Nurmatov U, Van Schayck OCP, et al. Is the prevalence of asthma declining? Systematic review of epidemiological studies. *Allergy* 2010;65:(1398–9995) (Electronic).
- NICE. What is the prevalence of asthma?, N.I.F.H.a.C. excellence, Editor. 2023.
- Loonjans-van den Akker I, van Luijk K, Verheij T. Overdiagnosis of asthma in children in primary care: a retrospective analysis. *Br J Gen Pract* 2016;66:e152–7.
- Kavanagh J, Jackson DJ, Kent BD. Over- and under-diagnosis in asthma. *Breathe (Sheff)* 2019;15:(1810–6838) (Print).
- Dharmage SC, Perret JL, Custovic A. Epidemiology of Asthma in Children and Adults. *Front Pediatr* 2019;7:246.
- Radzikowska U, Golebski K. Sex hormones and asthma: The role of estrogen in asthma development and severity. *Allergy* 2023;78:620–2.
- Ellison-Loschmann L, Sunyer J, Plana E, et al. Socioeconomic status, asthma and chronic bronchitis in a large community-based study. *Eur Respir J* 2007;29:897–905.
- Schyllert C, Lindberg A, Hedman L, et al. Low socioeconomic status relates to asthma and wheeze, especially in women. *ERJ Open Res* 2020;6:00258–2019.
- On the edge: how inequality affects people with asthma, a UK, editor. 2018.
- Hayanga B, Stafford M, Bécarea L-O. Ethnic Inequalities in Healthcare Use and Care Quality among People with Multiple Long-Term Health Conditions Living in the United Kingdom: A Systematic Review and Narrative Synthesis. *Int J Environ Res Public Health* 2021;18:12599.
- Snell N, Strachan D, Hubbard R, et al. S32 Epidemiology of chronic obstructive pulmonary disease (COPD) in the uk: findings from the british lung foundations' respiratory health of the nation' project. *Thorax* 2016;71:A20.
- Montazmanesh S. Global burden of chronic respiratory diseases and risk factors, 1990–2019: an update from the Global Burden of Disease Study 2019. *EclinicalMedicine* 2023;59:101936.
- Gayle A, Lenoir A, Minelli C, et al. Are we missing lifetime COPD diagnosis among people with COPD recorded death? A population-based retrospective cohort study. *BJGP Open* 2022;6:BJGP0.2022.0060.
- Dai X, Gakidou E, Lopez AD. Evolution of the global smoking epidemic over the past half century: strengthening the evidence base for policy action. *Tob Control* 2022;31:129–37.
- S Government. Scottish health survey: topic report UK comparisons, Ed. 2010.
- Swinney K.E.V.Q.P. Cities outlook 2020 holding our breath, centreforcities, editor. 2020.
- ONS. Adult smoking habits in the UK: 2022. 2023. Available: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2022>
- Stolz D, Kostikas K, Loeffroth E, et al. Differences in COPD Exacerbation Risk Between Women and Men: Analysis From the UK Clinical Practice Research Datalink Data. *Chest* 2019;156:(1931–3543) (Electronic).
- Martin A, Badrick E, Mathur R, et al. Effect of ethnicity on the prevalence, severity, and management of COPD in general practice. *Br J Gen Pract* 2012;62:e76–81.
- Ajayi Sotubo O. A perspective on health inequalities in BAME communities and how to improve access to primary care. *Future Healthc J* 2021;8:36–9.
- Levin KA, Anderson DR, Crighton EM. Prevalence of COPD by age, sex, socioeconomic position and smoking status: a cross-sectional study. *HE 2020*;120:275–88.
- Hitchman SC, Fong GT, Zanna MP, et al. Socioeconomic status and smokers' number of smoking friends: Findings from the International Tobacco Control (ITC) Four Country Survey. *Drug Alcohol Depend* 2014;143:158–66.
- Saliccioli JD, Marshall DC, Goodall R, et al. Interstitial lung disease incidence and mortality in the UK and the European Union: an observational study, 2001–2017. *ERJ Open Res* 2022;8:00058–2022.
- Silva M, Fernandes A, Pereira AR, et al. Awareness towards the main ILD among primary care physicians. *Multidiscip Respir Med* 2022;17:(1828–695X) (Print).
- Choi W-I, Dauti S, Kim HJ, et al. Risk factors for interstitial lung disease: a 9-year Nationwide population-based study. *BMC Pulm Med* 2018;18:(1471–2466) (Electronic).
- Kawano-Dourado L, Glassberg MK, Assayag D, et al. Sex and gender in interstitial lung diseases. *Eur Respir Rev* 2021;30:210105.
- Goobie GC, Ryerson CJ, Johannson KA, et al. Neighborhood-Level Disadvantage Impacts on Patients with Fibrotic Interstitial Lung Disease. *Am J Respir Crit Care Med* 2022;205:(1535–4970) (Electronic).
- Van den Bulck S, Crèvecoeur J, Aertgeerts B, et al. The impact of the Covid-19 pandemic on the incidence of diseases and the provision of primary care: A registry-based study. *PLoS ONE* 2022;17:(1932–6203) (Electronic).
- Mansfield KE, Mathur R, Tazare J, et al. Indirect acute effects of the COVID-19 pandemic on physical and mental health in the UK: a population-based study. *Lancet Digit Health* 2021;3:e217–30.
- Bottle A, Neale FK, Foley KA, et al. Impact of COVID-19 on outpatient appointments in children and young people in England: an observational study. *BMJ Open* 2022;12:e060961.
- Qi C, Osborne T, Bailey R, et al. Impact of COVID-19 pandemic on incidence of long-term conditions in Wales: a population data linkage study using primary and secondary care health records. *Br J Gen Pract* 2023;73:e332–9.
- Quint JK, Milleroval R, DiSantostefano RL, et al. Validation of chronic obstructive pulmonary disease recording in the Clinical Practice Research Datalink (CPRD-GOLD). *BMJ Open* 2014;4:e005540.
- Nissen F, Morales DR, Mullerova H, et al. Validation of asthma recording in the Clinical Practice Research Datalink (CPRD). *BMJ Open* 2017;7:e017474.
- Morgan A, Gupta RS, George PM, et al. Validation of the recording of idiopathic pulmonary fibrosis in routinely collected electronic healthcare records in England. *BMC Pulm Med* 2023;23:256.
- Perret J, Yip SWS, Idroes NS, et al. Undiagnosed and 'overdiagnosed' COPD using postbronchodilator spirometry in primary healthcare settings: a systematic review and meta-analysis. *BMJ Open Respir Res* 2023;10:e001478.
- Aaron SD, Vandenheden KL, FitzGerald JM, et al. Reevaluation of Diagnosis in Adults With Physician-Diagnosed Asthma. *JAMA* 2017;317:269.



ALLERGY & RESPIRATORY SUMMIT 2026

Centro de Congressos - Hotel Sheraton Porto
5, 6 E 7 DE FEVEREIRO 2026



COORDENADORES



Dr. Mário Morais de Almeida



Dr. Rui Costa

Inscreva-se em allergyrespiratory.com

O impacto do horário de administração de corticosteroides inalatórios na asma: um ensaio randomizado cruzado com três vias

Ran Wang,^{1,2} Robert Maidstone,² Dave Singh,^{1,2,3} David Ray,^{4,5} Andrew S Loudon,² Angela Simpson,^{1,2} Hannah Jane Durrington^{1,2}

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/thorax-2024-222073>).

¹NIHR Manchester Biomedical Research Centre, Manchester, UK

²School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

³Medicines Evaluation Unit, Wythenshawe, UK

⁴NIHR Oxford Biomedical Research Centre, Oxford, UK

⁵Oxford Centre for Diabetes Endocrinology and Metabolism, Oxford, UK

Correspondence to

Dr Hannah Jane Durrington; hannah.durrington@manchester.ac.uk

Received 12 June 2024

Accepted 27 December 2024

Published Online First 15 April 2025



► <https://doi.org/10.1136/thorax-2025-223094>



© Author(s) (or their employer(s)) 2025. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Wang R, Maidstone R, Singh D, et al. Thorax 2025;80:504–511.

RESUMO

Contexto A asma apresenta um ritmo diário bem definido, com obstrução das vias aéreas e inflamação pulmonar atingindo o pico durante a noite. Alinhar o horário da administração do medicamento com os ritmos da doença (cronoterapia) pode melhorar a eficácia terapêutica. O objetivo deste estudo foi avaliar o impacto do horário de administração de corticosteroides inalatórios na asma.

Métodos Este é um ensaio randomizado cruzado com três vias. Participantes com asma atópica leve a moderada foram randomizados para receber dipropionato de beclometasona nas seguintes formas: (1) 400 µg uma vez ao dia entre 08:00 e 09:00 (ODAM); (2) 400 µg uma vez ao dia entre 15:00 e 16:00 (ODPM); (3) 200 µg duas vezes ao dia entre 08:00 e 09:00 e entre 20:00 e 21:00 (BD), durante 28 dias, com um período de *washout* de 2 semanas entre os regimes. Espirometria a cada seis horas e biomarcadores foram medidos ao longo de 24 horas após o período de adaptação e ao final de cada período de tratamento.

Resultados Dos 25 participantes, 21 completaram todos os regimes. O regime OD_{PM} foi superior na melhora do FEV₁ às 22:00 (mediana [IQR]: +160 [+70, +270] ml) em comparação com OD_{AM} (–20 [–80, +230] ml) e BD (+80 [–20, +200] ml). OD_{PM} também resultou em melhor supressão noturna (às 22:00 e 04:00) da contagem de eosinófilos no sangue em comparação com BD e OD_{AM}. Todos os regimes melhoraram o controle da asma e reduziram os níveis de óxido nítrico exalado fracionado e cortisol sérico, sem diferenças significativas entre os horários de dosagem.

Conclusão O regime OD_{PM} suprime melhor a queda noturna da função pulmonar e o pico de eosinófilos no sangue em comparação com BD e OD_{AM}, sem aumento de eventos adversos. Ensaios futuros são necessários para validar esses achados em cenários reais e determinar quais populações podem se beneficiar mais da cronoterapia.

INTRODUCTION

Asthma demonstrates a robust rhythm in both symptoms and pathophysiology¹: up to three quarters of patients experience worsening symptoms and up to 80% of fatal asthma attacks occur overnight.^{2,3} Coincident with nocturnal symptoms, there is an overnight peak in airflow obstruction, airway inflammation and bronchial hyperresponsiveness.^{4–5} The excessive diurnal variation and nocturnal dip in lung function is also a marker for disease severity, poor control and mortality.^{3,4,6} Notably, glucocorticoid receptor functionality fluctuates over 24 hours in individuals exhibiting nocturnal symptoms and airflow obstruction, with impaired steroid responsiveness at night compared

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► To date, results from clinical trials of inhaled corticosteroid (ICS) chronotherapy in asthma have been inconclusive, focusing on daytime measurements of lung function. Our study is the first to show the effect of chronotherapy on the daily fluctuations in both physiological and immunological domains over 24 hours, using a commonly prescribed ICS.

WHAT THIS STUDY ADDS

► Mid-afternoon (once a day) dosing of inhaled corticosteroid (beclomethasone) improved nocturnal lung function and reduced blood eosinophil counts compared with alternative dosage timings (including the usual, twice daily dosing regimen) without additional adrenal suppression.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► Mid-afternoon dosing of inhaled beclomethasone may lead to better clinical outcomes without increasing steroid-related morbidity or costs. Our findings warrant further validation in a larger clinical trial to establish clinical feasibility in a real-life setting and to evaluate the health-economics impact.

with mid-afternoon.^{7–8} We recently demonstrated enhanced steroid sensitivity in immune cells at 16:00 compared with 04:00,⁹ further supporting the notion that the optimal timing for corticosteroids administration may be at this time.

Aligning dosage timing to biological rhythms of disease (chronotherapy) is a strategy to improve drug efficacy and/or reduce associated side effects. To date, results from clinical trials of inhaled corticosteroid (ICS) chronotherapy in asthma have been inconclusive. Pincus et al demonstrated once-daily mid-afternoon dosing of inhaled triamcinolone acetonide (an uncommonly used ICS in asthma) was better for improving morning peak flow compared with once-daily morning dosing and non-inferior to the standard four-times-a-day dosing regimen.^{10–11} Gagnon showed no difference between once-daily (at 17:00 or 22:00) or twice-daily

dosing of high-dose beclomethasone dipropionate (BDP, 1000 µg) in moderate asthma.¹² However, these studies focused on daytime measurements of lung function and did not investigate the effects of dosage timing on the nocturnal dip in lung function and associated changes in T2 inflammatory biomarkers.

The objective of this randomised controlled trial was to test the hypothesis that administering inhaled BDP mid-afternoon will result in superior suppression of the nocturnal peak in asthma pathophysiology (lung function and airway inflammation) compared with morning dosing and standard twice-daily dosing regimens.^{13,14}

METHODS

We conducted a randomised, open-label, three-way crossover trial of BDP (Clenil Modulite, delivered via pressurised metered dose inhaler) 400 µg daily dose (200 µg per inhalation) in the morning (between 08:00 and 09:00 (ODAM)) versus mid-afternoon (between 15:00 and 16:00 (ODPM)), versus 200 µg twice a day (between 08:00 and 09:00, and between 20:00 and 21:00 (BD)), in participants with mild to moderate atopic asthma. Briefly, adults aged 18–65 years with a history of physician-diagnosed asthma and with symptoms consistent with asthma for at least 1 year prior to screening were recruited.

All participants were treated with low to medium doses of ICS with or without long-acting β agonists at screening and had documented allergy to at least one common inhaled allergen (ie, cat dander, house dust mite or grass pollen) as confirmed on skin prick tests; a positive skin prick test was defined as a weal size of ≥3 mm in diameter, over the negative control. All participants had evidence of at least one of the following prior to consent: (1) bronchial hyperresponsiveness to methacholine (defined as a ≥20% fall in forced expiratory volume within 1 s (FEV₁) of ≤1 mg in dose or ≤16 mg/mL in concentration)¹⁵; or (2) ≥12% or ≥200 mL improvement in FEV₁ in bronchodilator reversibility test within 2 years prior to the study. The main exclusion criteria were smoking within the past 12 months or those with a smoking history of more than five pack years; uncontrolled asthma (6-item Asthma Control Questionnaire (ACQ-6) score of 1.5 points or more); asthma exacerbations or chest infection requiring oral corticosteroids or antibiotics within 3 months prior to screening and randomisation; any clinically significant uncontrolled diseases other than asthma. Detailed inclusion and exclusion criteria are outlined in the online supplemental figure section E1.

Non-permitted concomitant medications included systemic corticosteroids within 3 months, ICS other than study medications, nebulised β² agonist/anticholinergics, inhaled long-acting β² agonists, inhaled short-acting β² agonists other than study supply, inhaled short and long-acting muscarinic antagonist within 7 days and leukotriene modifiers within 72 hours prior to screening visit and during the study period. This study was approved by the Research Ethics Committee (North West Greater Manchester South, 20/NW/0011) and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (registered clinical trial <https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-004309-28>, <https://www.clinicaltrialsregister.eu/ctr-search/trial/2019-004309-28/GB>). All participants provided informed written consent.

Study design

Baseline assessment

Demographic data and medical history were recorded during screening. All eligible participants stopped asthma maintenance therapies during the run-in period for 14–21 days prior to the baseline assessment. At baseline visit (day –4 and day –3), participants stayed overnight, during which six hourly (04:00, 10:00, 16:00, 22:00) spirometry, fractional exhaled nitric oxide (FeNO), blood eosinophils and serum cortisol levels were measured, and ACQ-6 and Munich Chronotype Questionnaire administered.⁶ Sputum induction was carried out at 04:00 (day –3) and 16:00 (day –1), >48 hours apart to ensure the second sputum sample was not affected by the first. Randomisation numbers were assigned, which confirmed treatment sequences (figure 1).

Treatment periods

The baseline visit was followed by three 28-day treatment periods in random order with a washout period between each treatment period of 14–21 days. The ACQ-6, 6 hourly spirometry, FeNO and blood samples were taken on day 25 and day 26 into each treatment period. Morning and afternoon sputum induction were carried out 48 hours apart, on day 26 at 04:00 and day 28 at 16:00.

Peak flow metres and diary cards, which recorded morning and evening peak expiratory flow (PEF), salbutamol use, adverse events (AEs) and ICS adherence, were provided during each washout and treatment period. Full verbal and written instructions were given on inhaler technique. All participants were contacted weekly by telephone during the study period during which AEs, changes to concomitant medications and drug adherence were checked.

Study procedures are detailed in the online supplemental section E1.

End points

Prespecified primary end points included the treatment differences for FEV₁, PEF and FeNO changes from baseline. The key secondary end points were the treatment differences in the changes in blood eosinophil counts, serum cortisol levels and ACQ-6, reliever medication use and AEs. The daily rhythms in lung function parameters, FeNO, blood eosinophil counts and serum cortisol levels were examined.

Statistical analysis

The sample size calculation was based on our previously published data.⁵ With an estimated dropout rate of 20%, we anticipated that to reach a total of 20 completed and evaluable subjects, we would need to randomise a total of 25 subjects. With n=20 completing all dosing regimens, with a type I error rate of 5% and a within group SD of 9.3% in percent predicted FEV₁, there was an estimated 80% power of detecting a difference of 10% between groups in the mean group changes from baseline.^{5,11}

The within-day variability among all time points was tested using the Friedman test in the intention-to-treat population; pairwise comparisons between time points were subsequently carried out if the overall test had a p-value < 0.05. Treatment effects were described as the differences between the end of each treatment period and baseline (defined as post run-in period) values. Comparisons of treatment effects among the three treatment regimens were performed using the Friedman test in patients who had completed all treatment periods. Pairwise comparisons (Wilcoxon signed-rank test) were performed if the overall test had p < 0.05. The p-values of all pairwise comparisons were also adjusted using the Benjamini-Hochberg false discovery rate correction method (FDR, < 0.1 defined as significant) (rstatix R package); both raw p-values and FDR adjusted values were presented.

A mixed-effects (adjusted for repeated measures) exploratory cosinor model (cosinor mixed-effects R package¹⁶) was used to examine the changes in the daily rhythmicity in lung function, FeNO, blood eosinophil counts and serum cortisol levels following treatments from baseline and among treatment regimens in individuals who completed all treatment regimens; data that were not normally distributed were log transformed; 95% CI of the Midline Statistic Of Rhythm (MESOR, a rhythm-adjusted mean), amplitude (a measure of half the extent of predictable variation within a cycle) and acrophase (the timing of peak within a circadian cycle)¹⁷ (figure 2) were estimated using 1000 iterations of bootstrapping. Any potential carry over effects were examined by adjusting treatment sequence using multivariate mixed-effects cosinor modelling. Frequency of reliever use and AEs were reported using descriptive statistics where the number of participants and events were summarised. The peak flow diurnal variability during the last week of the run-in period and 1 week prior to the end of each treatment period were calculated as: (difference between maximum of 03:00 and maximum of 15:00)/mean per day and averaged over the number of days; tests performed outside the predefined time windows were excluded. Missing data were excluded from the analysis. All statistical analyses were performed using R version 4.2.2 (Rstudio 2022.12.0).

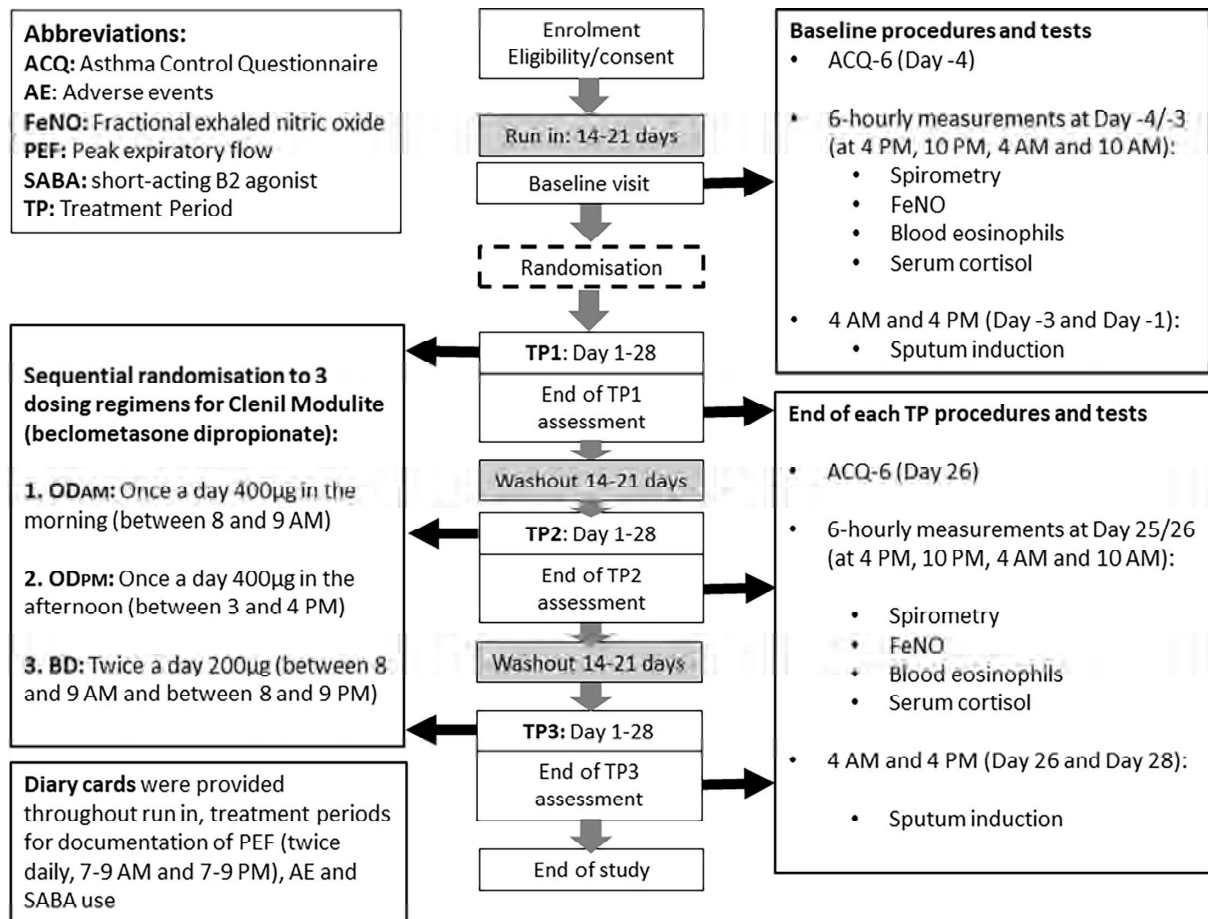


Figure 1 Study flow chart.

RESULTS

Baseline characteristics

Of 25 participants who consented to participate in the study (between 18 June 2021 and 5 May 2022), 22 completed OD_{AM}, 21 OD_{PM} and 23 BD dosing regimens (online supplemental figure E1). Approximately equal numbers were allocated to each sequence of treatment (online supplemental figure E2). Twenty-one participants (84%) completed all treatment regimens (table 1) and had similar chronotypes (timing for sleep/wake cycle) (online supplemental figure E3). Adherence rates (BD 98.4% adherence (97.8% within instructed time window); OD_{AM} 99.9% (96.3%) and OD_{PM} 99.9% (98.1%)) for each of the treatment regimens were excellent.

At baseline, lung function demonstrated significant variation throughout 24 hours, with increased airflow obstruction overnight compared with during the daytime. This coincided with blood eosinophil levels peaking overnight. In contrast, FeNO and serum cortisol levels peaked at 10:00 and with a nadir overnight (online supplemental table E1, online supplemental figures 4; 5).

Effect of chronotherapy

Lung function

All treatment regimens improved lung function compared with baseline, but the timing of lung function improvement was different depending on dosing regimens (online supplemental figures 6–10). There was a larger improvement in FEV₁ following OD_{PM} than OD_{AM} (by median (IQR) of +170 (+30, +220) mL, $p<0.01$) and BD dosing (by +60 (–10, +240) mL, $p=0.02$; 10/21 participants had $>+100$ mL difference) at 22:00. A similar but smaller effect was also observed in the differences of improvement in FEV₁ % predicted (OD_{PM}–OD_{AM}: by +4% (+1%, +9%), $p<0.01$; OD_{PM}–BD: by +2% (–1%, +9%), $p=0.02$) and FEV₁/FVC ratio (OD_{PM}–OD_{AM}: $p=0.02$; OD_{PM}–BD: $p=0.03$) at 22:00 (table 2, online supplemental figure 11). A modest improvement in FVC % predicted was also found following OD_{PM} compared with OD_{AM} dosing ($p=0.01$, table 2, online supplemental figure 11). There was no difference in PEF among treatment regimens (online supplemental table E2, online supplemental figure 12).

Using cosinor modelling, the mean (95% CI) MESOR for FEV₁ was 2.65 (2.29 to 3.02) L at baseline; a higher MESOR for FEV₁ was found following the OD_{PM} dosing regimen (2.80 (2.43 to 3.16) L) compared with OD_{AM} (2.72 (2.35 to 3.08) L, $p=0.01$) and BD (2.73 (2.36 to 3.10) L, $p=0.04$) (figure 3). Similarly, with the FVC MESOR of 4.07 (3.59 to 4.56) L at baseline, a higher FVC MESOR was observed following OD_{PM} (4.18 (3.70 to 4.66) L) compared with OD_{AM} (4.09 (3.61 to 4.57) L, $p<0.01$) (figure 3).

Biomarkers for airway inflammation

All dosing regimens suppressed FeNO levels with no significant differences among dosing regimens (table 3, figure 3, online supplemental figure 13).

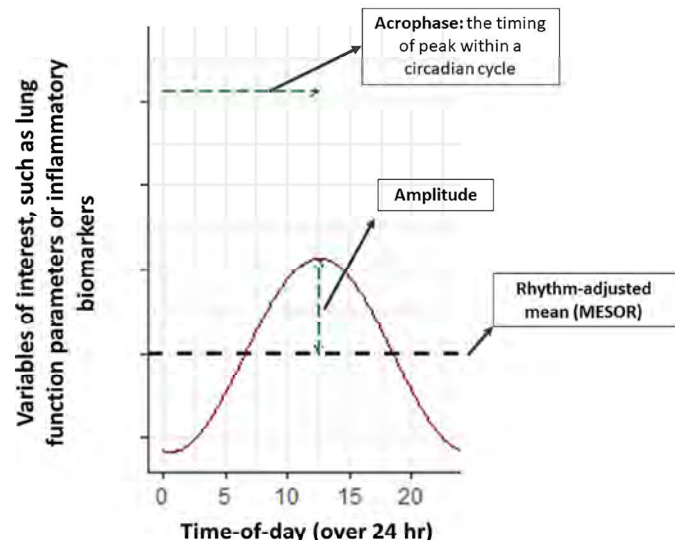


Figure 2 Parameters assessed in mixed-effect cosinor modelling.

Table 1 Baseline characteristics.

Baseline characteristics	n=25
Age (years)*	42 (34–52)
Sex (male), n (%)	16 (64.0)
Ethnicity (white), n (%)	19 (76.0)
Height (cm)*	172 (166–180)
Weight (kg)*	73.8 (69.9–83.6)
BMI (kg/m ²)*	26.1 (24.5–28.6)
ACQ-6 (points)*	1.0 (0.3–1.3)
FEV ₁ (L)*	2.8 (2.4–3.5)
FEV ₁ % predicted (%)*	86 (71–89)
FEV ₁ /FVC (%)*	70.6 (63.4–76.8)
FeNO (ppb)*	50 (26–97)
Blood eosinophil counts (x10 ⁹ cells/L)*	0.23 (0.18–0.35)

*Median (IQR).
ACQ-6, 6-item Asthma Control Questionnaire; BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

All regimens reduced blood eosinophil counts compared with baseline at all time points (online supplemental figure 14). The reduction in blood eosinophil counts overnight following OD_{PM} dosing was significantly larger than those following BD dosing (by median (IQR) of -0.07 (-0.13 , -0.05) $\times 10^9$ cells/L at 22:00, $p<0.01$; -0.04 (-0.08 , -0.02) $\times 10^9$ cells/L at 04:00, $p=0.03$); this was also observed compared with OD_{AM} dosing, but to a smaller effect (by -0.05 (-0.08 , -0.01) $\times 10^9$ cells/L at 22:00, $p=0.03$; -0.04 (-0.08 ,

$+0.01$) $\times 10^9$ cells/L at 04:00, $p=0.04$) (table 3, online supplemental figure 15).

With a baseline mean (95% CI) MESOR in blood eosinophil counts of 0.31 (0.25 to 0.39) $\times 10^9$ cells/L, both OD_{PM} (0.17 (0.14 to 0.22) $\times 10^9$ cells/L) and OD_{AM} (0.18 (0.14 to 0.22) $\times 10^9$ cells/L) resulted in lower MESOR following the treatment period compared with the standard BD dosing regimen (0.23 (0.18 to 0.29) $\times 10^9$ cells/L, $p<0.01$) (figure 3).

The number of participants who were able to produce sufficient sputum were limited for statistical analysis (online supplemental figure 16, online supplemental section E4).

Serum cortisol levels

All treatment regimens suppressed serum cortisol levels compared with baseline, but the degree of suppression differed among treatment regimens at different time points; there was no difference in the 10:00 cortisol suppression among treatment regimens (online supplemental table E3, online supplemental figures 17; 18). While all dosing regimens reduced MESOR for serum cortisol levels compared with baseline (median (IQR) of 149 (127 , 174) nmol/L), there were no differences among three dosing regimens (figure 3).

The same results were obtained following adjustment of treatment sequence within the model, suggesting there was no carry over effect (online supplemental figure 19).

Asthma control, reliever medication use and adverse events

All dosing regimens improved ACQ-6 scores with no difference seen among dosing regimens (online supplemental figure 20). There was no difference in reliever medication use and AE profiles among dosing regimens (online supplemental table E4, online supplemental figure 21).

Table 2 Changes in lung function parameters at end of each treatment period compared with baseline

Time of measurements	OD _{AM}	BD	OD _{PM}	p-value [†]
Improvement in FEV₁ (mL), median (IQR)				
04:00 (n=21)	60 (10, 200)	110 (0, 240)	120 (40, 210)	0.33
10:00 (n=21)	40 (−10, 100)	30 (−20, 190)	110 (−20, 200)	0.33
16:00 (n=21)	110 (−30, 200)	100 (50, 260)	80 (−40, 210)	0.72
22:00 (n=21)	−20 (−80, 230)	80 (−20, 200)	160 (70, 270)	<0.01
Improvement in FEV₁ % predicted, median (IQR)				
04:00 (n=21)	2 (0, 5)	4 (0, 6)	4 (1, 8)	0.22
10:00 (n=21)	1 (0, 3)	1 (−1, 7)	3 (−1, 5)	0.44
16:00 (n=21)	3 (−1, 8)	2 (2, 7)	3 (−1, 6)	0.85
22:00 (n=21)	0 (−3, 6)	4 (0, 5)	5 (2, 8)	<0.01
Improvement in FVC (mL), median (IQR)				
04:00 (n=21)	50 (20, 150)	50 (−50, 270)	100 (0, 230)	0.44
10:00 (n=21)	40 (0, 130)	80 (−20, 190)	150 (−30, 190)	0.50
16:00 (n=21)	20 (−180, 180)	90 (−190, 220)	20 (−70, 130)	0.83
22:00 (n=20)	−35 (−208, 62)	10 (−165, 130)	55 (−80, 198)	0.08
Improvement in FVC % predicted, median (IQR)				
04:00 (n=21)	1 (0, 3)	1 (−1, 5)	3 (0, 5)	0.49
10:00 (n=21)	2 (0, 3)	2 (0, 4)	3 (0, 5)	0.33
16:00 (n=21)	1 (−5, 4)	2 (−4, 5)	1 (−1, 3)	0.85
22:00 (n=20)	−1.5 (−5, 2)	0 (−4, 3)	2 (−2, 5)	0.03
Changes in FEV₁/FVC ratio (%), median (IQR)				
04:00 (n=21)	0.8 (−0.5, 2.4)	1.5 (−1.4, 5.6)	1.9 (0.8, 2.9)	0.07
10:00 (n=21)	0.1 (−1.1, 1.8)	−0.8 (−2.2, 1.7)	0.1 (−1.3, 3.6)	0.47
16:00 (n=21)	2.1 (0.4, 4.9)	2.0 (0.2, 4.4)	1.2 (−0.2, 3.2)	0.54
22:00 (n=20)	1.4 (−0.7, 4.2)	1.3 (−0.7, 3.9)	3.1 (1.2, 5.1)	<0.05

Bold indicates statistical significance and subsequent pairwise comparison carried out and demonstrated in online supplemental figure 11.

BD, twice a day; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; OD_{AM}, once a day in the morning; OD_{PM}, once a day in the afternoon.

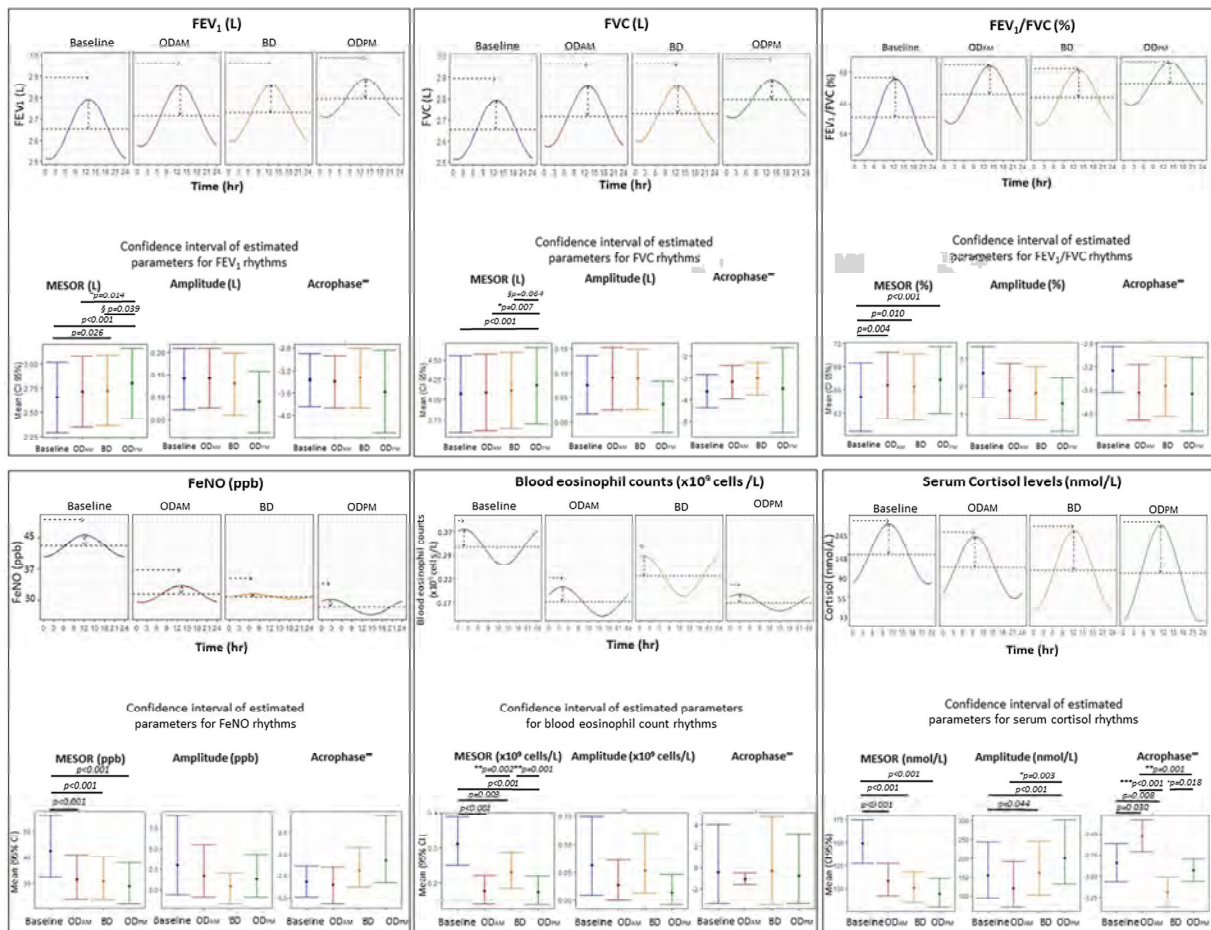


Figure 3 Dynamic circadian changes in lung function, FeNO, blood eosinophil counts and serum cortisol levels at baseline and following each dosing regimen using cosinor modelling. Top panel shows cosinor analysis over time (x-axis); the dotted line indicates MESOR, vertical dotted arrows indicate amplitude and the horizontal dotted arrows indicate acrophase (as demonstrated in figure 2); bottom panels demonstrate the overall mean (95% CI) of MESOR, amplitude and acrophase, estimated using 1000 iterations of bootstrapping. For pairwise comparison among three dosing regimens, p-value and FDR are presented: §FDR<0.1, *FDR<0.05, **FDR<0.01, ***FDR<0.001. Based on 24 hour period; acrophase is a measure of the timing of overall high values occurring in the cycle, expressed in negative radians. BD, twice a day; FDR, false discovery rate; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; MESOR, Midline Statistic Of Rhythm; OD_{AM}, once a day in the morning; OD_{PM}, once a day in the afternoon.

DISCUSSION

We have shown that once-daily mid-afternoon dosing of BDP resulted in greater improvement in FEV₁ and reduction in blood eosinophil counts compared with once-daily morning and standard twice-daily dosing regimens. Mid-afternoon dosing demonstrated the greatest effect on improving nocturnal airflow obstruction, reaching significance compared with other dosing regimes at 22:00, and blood eosinophilia which reached significance compared with other dosing regimes at 10:00 and 04:00. Mid-afternoon dosing did not demonstrate additional overall cortisol suppression (measured in MESOR) or AEs compared with the alternative dosage timings. Our findings further support the hypothesis that the optimal timing of ICS administration is at 16:00, coincident with enhanced glucocorticoid sensitivity at that time. The notion that the onset of the inflammatory cascade begins mid-afternoon may also explain the findings we observed, and the attenuation of the predictable rhythmic recruitment of airway inflammatory cells at this time point may abolish the subsequent excessive nocturnal dip in lung function in asthma.^{18 19}

We used cosinor modelling to evaluate the effect of ICS chronotherapy on the dynamic fluctuation in asthma. This analytical method uses multiple measurements to model the continuous diurnal variation observed in asthma, including the rhythmic peak and trough changes which may be easily missed (resulting in an underestimation of amplitude) unless continuous or sufficiently frequent measurements occur over a 24-hour period. Not only would this be impractical, but the frequent test procedures would profoundly disrupt sleep and circadian rhythm of study participants.

We have confirmed that maximal airflow obstruction and inflammation occur overnight in asthma; FeNO peaks late morning, with a nadir overnight.^{1 5 20 21} The magnitude of within-day variations in lung function and inflammatory biomarkers were large, highlighting the importance of timing of tests when results are interpreted.¹

Previously, Beam and colleagues found that a single dose of oral prednisolone at 15:00 resulted in a significant improvement in the nocturnal dip in lung function, blood eosinophil counts and a pan-cellular reduction in bronchoalveolar lavage cytology at 04:00 in uncontrolled asthma, but these were not observed in participants dosed at 08:00 or 20:00.¹⁸ Frezza et al also demonstrated that a single dose of inhaled BDP or fluticasone propionate given at 16:00 was sufficient to reduce the nocturnal dip in FEV₁ at 04:00 in patients with steroid-naïve asthma compared with placebo, but no comparison was made with other times of dosing.¹⁹ Similarly, Postma et al found that evening (between 16:00 and 20:00) administration of inhaled ciclesonide resulted in more pronounced improvement in the morning peak expiratory flow compared with a once-daily morning dosing regimen.²² Although several randomised controlled trials have previously investigated mid-afternoon dosing of ICS in asthma,^{10–12} our study is the first to show the effect of chronotherapy on the daily fluctuations in both physiological and immunological domains over 24 hours and compared these with widely used dosing regimens.

The current study is limited by small sample size, short therapeutic and follow-up duration. Nevertheless, the three-way cross-over design allows repeated measurements to be performed within

Table 3 Changes in biomarkers at the end of each treatment period compared with baseline.

Time of measurements	OD _{AM}	BD	OD _{PM}	p-value
Changes in FeNO (ppb), median (IQR)				
04:00 (n=21)	−8.5 (−12.0, −1.0)	−4.5 (−14.0, 4.5)	−2.0 (−23.0, 2.0)	0.85
10:00 (n=21)	−10.0 (−23.0, −5.5)	−10.5 (−29.5, −1.0)	−9.5 (−33.0, −4.0)	0.87
16:00 (n=21)	−6.5 (−20.5, −2.0)	−7.5 (−21.0, 0.5)	−12.5 (−27.0, −0.5)	0.69
10:00 (n=21)	−8.0 (−18.5, −2.0)	−8.5 (−23.5, −2.0)	−9.5 (−28.5, 1.0)	0.74
Changes in blood eosinophil counts (×10⁹ cells/L), median (IQR)				
04:00 (n=19)	−0.10 (−0.22, −0.03)	−0.08 (−0.20, −0.03)	−0.12 (−0.24, −0.10)	0.04
10:00 (n=16)	−0.04 (−0.19, −0.01)	−0.04 (−0.12, 0)	−0.09 (−0.20, −0.03)	0.65
16:00 (n=21)	−0.13 (−0.25, −0.03)	−0.10 (−0.17, −0.01)	−0.12 (−0.19, −0.05)	0.07
22:00 (n=19)	−0.13 (−0.15, 0)	−0.06 (−0.16, −0.02)	−0.18 (−0.21, −0.07)	<0.01

Bold indicates statistical significance and subsequent pairwise comparison carried out and demonstrated in online supplemental figure 15.

BD, twice a day; FeNO, fractional exhaled nitric oxide; OD_{AM}, once a day in the morning; OD_{PM}, once a day in the afternoon.

the same individual, increasing study power for parameters of interest. While the small effect size may increase the risk of type II error (false negative results), we have demonstrated statistical significance in the prespecified key end points in MESOR and 22:00 time point; the negative results may be due to the limited power. Nevertheless, the data presented in our study form the basis for the design of future larger trials to establish the efficacy of ICS chronotherapy.

Opinions regarding what constitutes the minimum clinically important difference (MCID) in FEV₁ varies considerably (100–200 mL).^{23–24} While we have found a 170 mL difference in the improvement of FEV₁ at 22:00 following mid-afternoon compared with the morning dosing regimen, the benefit over the standard twice-daily regimen was smaller (median +60 mL). However, it is also important to note that almost half of participants had >100 mL of FEV₁ improvement at 22:00 following OD_{PM} than BD dosing. We did not demonstrate any difference in ACQ-6 among dosing regimens, likely due to mild symptoms at baseline and short treatment duration. Although the MCID in the reduction of blood eosinophil counts is unclear, a level of >0.2×10⁹ cells/L has been associated with increased asthma exacerbations.²⁵ We observed that mid-afternoon dosing improved the MESOR of blood eosinophil counts from over 0.2×10⁹ cells/L following a twice-daily dosing regimen to under this threshold, suggesting mid-afternoon dosing may result in a reduction in asthma exacerbation risk compared with twice-daily dosing.^{26,27} However, this could not be confirmed due to the limited follow-up period. An efficacy trial with an extended dosing duration is needed to validate our findings, and to establish the longer-term impact of chronotherapy in asthma control, exacerbation rates, adherence and side effects. Our study population included individuals with mild-to-moderate allergic asthma and therefore the results cannot be extrapolated to other phenotypes.

While mid-afternoon dosing may be complicated by the challenges around non-adherence in some patients,²⁸ the advantages of taking ICS at the optimal timing may overcome some of the identified barriers (eg, achieving efficacy with lower cost).^{29–30} Our findings also provide key opportunities for novel chronopharmacological and chronotherapeutics development,^{31–32} leading to the possibilities of tailored therapy based on individuals' preference in timing of drug administration and their biological rhythm in disease.

CONCLUSIONS

Mid-afternoon dosing of inhaled BDP better improved nocturnal lung function and inflammatory biomarkers compared with the alternative dosage timings without additional adrenal suppression, hence may lead to better clinical outcomes without increasing

steroid-related morbidity or costs. A future large, real-world chronotherapy study framed within the new asthma guidelines,³³ using formoterol/ICS will determine if afternoon dosing leads to a reduction in exacerbations, better overall symptom control, health-economic benefits, and crucially, determine patient preference for afternoon dosing.

X Robert Maidstone @robertmaidstone and Hannah Jane Durrington @h_durrington

Acknowledgements We would like to thank the study participants for their time and commitment to the study and the Medicines Evaluation Unit (MEU) study team for help with the completion of the study. RW, AS, DS and HJD are supported by the Manchester 'NIHR Biomedical Research Centre' (BRC). DWR NIHR Oxford Health Biomedical Research Centre grant reference number: NIHR203316. MRC MR/W019000/1 and MR/V034049/1. This study is funded/supported by the National Institute for Health and Care Research (NIHR) Oxford Health Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. NIHR Oxford Health Biomedical Research Centre grant reference number: NIHR203316.

Contributors RW contributed to the data acquisition, statistical analysis and writing of the submitted article. HJD, DR, ASL and DS contributed to the conception of the study, planning, set up and reviewing of the submitted article. RM contributed to statistical analysis. HJD is responsible for the overall content as guarantor. The guarantor accepts full responsibility for the finished work and the conduct of the study.

Funding This work was supported by the JP Moulton Charitable Foundation. The funder has no role in the study design, data collection, analysis, and design of the manuscript. HJD is funded by MRC-CSF-MR/V029460/1 and received support from Asthma and Lung UK AUK-WAPG22/100005. RM is funded by Asthma and Lung UK WAPG22/100005.

Competing interests RW, RM, DR, AL, AS and HD have no conflict of interest; DS received consulting fees from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, EpiEndo, Genentech, GlaxoSmithKline, Glenmark, Gossamer Bio, Kinaset Therapeutics, Menarini, Novartis, Orion, Pulmatrix, Sanofi, Synairgen, Teva, Theravance Biopharma and Verona Pharma.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by North West Greater Manchester South, 20/NW/0011. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The study protocol is available on trial registration website. Individual participant data that underlie the results reported in this article after deidentification will be shared 3 years following article publication with investigators whose proposed use of data has been approved by the study sponsor. Proposal will be directed to pmoore@crossolutions.co.uk. To gain access, data requestors will need to sign a data access agreement.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed.

Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial.

See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Robert Maidstone <http://orcid.org/0000-0002-3482-3246>

Angela Simpson <http://orcid.org/0000-0003-2733-6666>

Hannah Jane Durrington <http://orcid.org/0000-0002-9990-9446>

REFERENCES

- Wang R, Murray CS, Fowler SJ, et al. Asthma diagnosis: into the fourth dimension. *Thorax* 2021;76:624–31.
- Turner-Warwick M. Nocturnal asthma: a study in general practice. *J R Coll Gen Pract* 1989;39:239–43.
- Hetzel MR, Clark TJ, Branthwaite MA. Asthma: analysis of sudden deaths and ventilatory arrests in hospital. *Br Med J* 1977;1:808–11.
- Martin RJ, Cicuttio LC, Ballard RD. Factors related to the nocturnal worsening of asthma. *Am Rev Respir Dis* 1990;141:33–8.

5. Durrington HJ, Gioan-Tavernier GO, Maidstone RJ, et al. Time of Day Affects Eosinophil Biomarkers in Asthma: Implications for Diagnosis and Treatment. *Am J Respir Crit Care Med* 2018;198:1578–81.
6. Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902–7.
7. Kraft M, Vianna EO, Martin RJM, et al. Nocturnal asthma is associated with reduced glucocorticoid receptor binding affinity and decreased steroid responsiveness at night. *J Allergy Clin Immunol* 1999;103:66–71.
8. Kraft M, Hamid Q, Chrousos GP, et al. Decreased Steroid Responsiveness at Night in Nocturnal Asthma. *Am J Respir Crit Care Med* 2001;163:1219–25.
9. Krakowiak K, Maidstone RJ, Chakraborty A, et al. Identification of diurnal rhythmic blood markers in bronchial asthma. *ERJ Open Res* 2023;9:00161-2023.
10. Pincus DJ, Humeston TR, Martin RJ. Further studies on the chronotherapy of asthma with inhaled steroids: the effect of dosage timing on drug efficacy. *J Allergy Clin Immunol* 1997;100:771–4.
11. Pincus DJ, Szeffler SJ, Ackerson LM, et al. Chronotherapy of asthma with inhaled steroids: the effect of dosage timing on drug efficacy. *J Allergy Clin Immunol* 1995;95:1172–8.
12. Gagnon M, Côté J, Milot J, et al. Comparative safety and efficacy of single or twice daily administration of inhaled beclomethasone in moderate asthma. *Chest* 1994;105:1732–7.
13. British National Formulary. Available: <https://bnf.nice.org.uk> [Accessed 31 Jan 2024].
14. Global Initiative for Asthma (GINA) Main Report, 2023. Available: <https://ginasthma.org/gina-reports>
15. Schulze J, Rosewich M, Riemer C, et al. Methacholine challenge--comparison of an ATS protocol to a new rapid single concentration technique. *Respir Med* 2009;103:1898–903.
16. Hou R, Tomalin LE, Suárez-Fariñas M. cosinoRmixedeffects: an R package for mixed-effects cosinor models. *BMC Bioinformatics* 2021;22:553.
17. Cornelissen G. Cosinor-based rhythmometry. *Theor Biol Med Model* 2014;11:16.
18. Beam WR, Weiner DE, Martin RJ. Timing of prednisone and alterations of airways inflammation in nocturnal asthma. *Am Rev Respir Dis* 1992;146:1524–30.
19. Frezza G, Terra-Filho J, Martinez JAB, et al. Rapid effect of inhaled steroids on nocturnal worsening of asthma. *Thorax* 2003;58:632–3.
20. Scheer FAJL, Hilton MF, Evoniuk HL, et al. The endogenous circadian system worsens asthma at night independent of sleep and other daily behavioral or environmental cycles. *Proc Natl Acad Sci U S A* 2021;118:e2018486118.
21. Wilkinson M, Maidstone R, Loudon A, et al. Circadian rhythm of exhaled biomarkers in health and asthma. *Eur Respir J* 2019;54:1901068.
22. Postma DS, Sevette C, Martinat Y, et al. Treatment of asthma by the inhaled corticosteroid ciclesonide given either in the morning or evening. *Eur Respir J* 2001;17:1083–8.
23. Bonini M, Di Paolo M, Bagnasco D, et al. Minimal clinically important difference for asthma endpoints: an expert consensus report. *Eur Respir Rev* 2020;29:190137.
24. Tepper RS, Wise RS, Covar R, et al. Asthma outcomes: pulmonary physiology. *J Allergy Clin Immunol* 2012;129:S65–87.
25. Mallah N, Rodriguez-Segade S, Gonzalez-Barcala FJ, et al. Blood eosinophil count as predictor of asthma exacerbation. A meta-analysis. *Pediatr Allergy Immunol* 2021;32:465–78.
26. Price DB, Rigazio A, Campbell JD, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med* 2015;3:849–58.
27. Kerkhof M, Tran TN, van den Berge M, et al. Association between blood eosinophil count and risk of readmission for patients with asthma: Historical cohort study. *PLoS One* 2018;13:e0201143.
28. Rand CS, Wise RA. Measuring adherence to asthma medication regimens. *Am J Respir Crit Care Med* 1994;149:S69–76.
29. Bender BG, Bender SE. Patient-identified barriers to asthma treatment adherence: responses to interviews, focus groups, and questionnaires. *Immunol Allergy Clin North Am* 2005;25:107–30.
30. McQuaid EL. Barriers to medication adherence in asthma: The importance of culture and context. *Ann Allergy Asthma Immunol* 2018;121:37–42.
31. Ohdo S, Koyanagi S, Matsunaga N. Chronopharmacology of immune-related diseases. *Allergol Int* 2022;71:437–47.
32. Buttgereit F, Spies CM, Bijlsma JWJ. Novel glucocorticoids: where are we now and where do we want to go? *Clin Exp Rheumatol* 2015;33:S29–33.
33. Asthma: diagnosis, monitoring and chronic asthma management (BTS, NICE, SIGN). n.d. Available: <https://www.nice.org.uk/guidance/NG245>

ARTIGO ORIGINAL

Diferenças entre os sexos na DPOC em relação à exposição ao tabagismo: um estudo de coorte baseado na população

Yunus Çolak,^{1,2} Børge G Nordestgaard,^{2,3} Peter Lange,^{1,2,4} Shoaib Afzal^{2,3}

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/thorax-2024-222682>).

¹Department of Respiratory Medicine and the Copenhagen General Population Study, Copenhagen University Hospital, Copenhagen, Denmark

²Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

³Department of Clinical Biochemistry and the Copenhagen General Population Study, Copenhagen University Hospital, Copenhagen, Denmark

⁴Department of Public Health, Section of Epidemiology, University of Copenhagen, Copenhagen, Denmark

Correspondence to
Dr Shoaib Afzal; shoib.afzal@regionh.dk

Received 1 November 2024
Accepted 14 March 2025
Published Online First 4 April 2025



© Author(s) (or their employer(s)) 2025. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Çolak Y, Nordestgaard BG, Lange P, et al. Thorax 2025;80:512–519.

RESUMO

Contexto As discrepâncias entre os sexos na associação entre tabagismo e o desenvolvimento e prognóstico da doença pulmonar obstrutiva crônica (DPOC) são controversas. Testamos a hipótese de que mulheres, em comparação com homens, são mais suscetíveis aos efeitos prejudiciais do tabagismo em relação à DPOC.

Métodos Identificamos 47.231 homens e 57.806 mulheres a partir do Estudo da População Geral de Copenhaga. A quantidade de tabagismo foi avaliada com interação por sexo em relação aos desfechos associados à DPOC, incluindo associação transversal com obstrução das vias aéreas, bronquite crônica e dispneia, analisadas por regressão logística, e associação longitudinal com exacerbações e mortalidade, analisadas por regressão de riscos proporcionais de Cox ajustada para potenciais fatores de confusão.

Resultados O aumento do risco de obstrução das vias aéreas (N=7367), bronquite crônica (N=9206) e dispneia (N=8541) com maior carga tabágica foi maior em mulheres do que em homens. Durante 15 anos de acompanhamento (mediana de 9,3 anos), o aumento do risco de exacerbações (eventos=2756), mortalidade respiratória (eventos=711) e mortalidade por todas as causas (eventos=10.658) com maior tabagismo também foi maior para mulheres em comparação com homens. Em comparação com não fumantes, os riscos relativos ajustados (HRs) para exacerbações aumentaram de 4,64 (IC 95%: 2,83 a 7,61) em mulheres com 10 anos-maço para 41,6 (IC 95%: 28,8 a 60,2) em mulheres com ≥50 anos-maço; e de 2,21 (IC 95%: 0,92 a 5,32) em homens com 10 anos-maço para 23,7 (IC 95%: 12,9 a 43,5) em homens com ≥50 anos-maço. Os aumentos correspondentes nos HRs para mortalidade respiratória foram de 2,04 (IC 95%: 1,27 a 3,26) a 11,1 (IC 95%: 7,39 a 16,8) em mulheres, e de 1,09 (IC 95%: 0,62 a 1,92) a 5,66 (IC 95%: 3,96 a 8,11) em homens. Para mortalidade por todas as causas, os HRs aumentaram de 1,50 (IC 95%: 1,34 a 1,67) a 3,53 (IC 95%: 3,11 a 4,00) em mulheres, e de 1,62 (IC 95%: 1,45 a 1,81) a 2,94 (IC 95%: 2,69 a 3,21) em homens.

Conclusões As mulheres parecem ser mais suscetíveis aos efeitos prejudiciais do tabagismo no desenvolvimento e prognóstico da DPOC em comparação com os homens.

INTRODUCTION

Tobacco smoking stands as the single most important risk factor for the development of chronic obstructive pulmonary disease (COPD) in large parts of the world.¹ Despite widespread awareness of this, the prevalence of daily smokers remains notably high, with rates reported at 18% in the EU and 13% in the UK and the USA.^{2–4} Recently, it was shown that even low levels of smoking exposure, below the critical threshold of 10 pack-years, can significantly increase the risk of severe COPD within 5 years and lead to a poor long-term prognosis comparable to heavy smokers.⁵

Over the last two decades in the EU, the prevalence of COPD continues to decrease in males, but

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- While it has long been hypothesised that males and females differ in their susceptibility to the harmful effects of smoking, sex-based differences in the association between smoking and the development and prognosis of chronic obstructive pulmonary disease (COPD) remain controversial.
- We the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) document calls for further research in this area.

WHAT THIS STUDY ADDS

- By identifying 105 037 randomly selected individuals from the general population, we found that females compared with males have much more severe disease with comparable smoking exposures, manifesting as lower lung function and a higher risk of airway obstruction, chronic bronchitis, dyspnoea and a higher risk of COPD exacerbation and early death.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Our findings suggest that females may be more susceptible to smoking-related harm in both the development and prognosis of COPD than males.
- This indicates that even lower levels of smoking exposure should be assessed with greater caution in females than in males, potentially warranting earlier intervention or tailored risk assessment.

the prevalence in females appears to be increasing, and in some countries, the prevalence in females now exceeds that in males.⁶ Furthermore, the risk of death from cigarette smoking continues to increase among females, and the increased risks are now nearly identical for males and females.⁷ This trend necessitates a reassessment of how smoking impacts COPD risk and prognosis across sexes. While it has long been hypothesised that males and females differ in their susceptibility to the harmful effects of smoking, sex-based differences in the association between smoking and the development and prognosis of COPD are controversial.^{8–15} In the recent version of the Global Initiative for Chronic

Obstructive Lung Disease (GOLD) document, it is suggested that more research is needed in this area.¹⁶ Understanding sex differences in COPD is crucial for developing targeted prevention and treatment strategies. In the present study, we tested the hypothesis that females compared with males are more susceptible to the detrimental effects of smoking in relation to COPD. For this purpose, we investigated males and females from the general population to determine the association between smoking amount and COPD-related outcomes.

METHODS

Study design and population

Individuals were selected from the Copenhagen General Population Study, an ongoing Danish population-based cohort initiated in 2003.^{17–19} All individuals in Denmark are assigned a unique identification number (Central Person Registration number) at birth or immigration and recorded in the national Danish Civil Registration System.²⁰ We therefore randomly invited individuals living in the Capital Region of Denmark from the national Danish Civil Registration System to reflect the adult Danish general population (response rate ~45%). All participants completed a questionnaire, underwent a physical examination and gave blood for biochemical analyses. All participants provided written informed consent.

Smoking amount

Smoking amount was calculated in pack-years at study entry for both former and current smokers based on self-reported information on duration and amount of consumed tobacco, including number of daily consumed cigarettes, cheroots and cigars, and grams of weekly consumed pipe tobacco (1 cheroot ~3 g of tobacco, 1 cigar ~5 g of tobacco, and 1 cigarette ~1 g of tobacco); a pack-year was defined as 20 cigarettes or equivalent smoked daily for a year.²¹ Never-smokers were defined as individuals with no history of smoking in any form.

COPD-related outcomes

COPD-related outcomes included measures of disease severity and prognosis. For disease severity, we assessed lung function, airway obstruction, chronic bronchitis and dyspnoea, with data collected at study entry. For prognosis, we included hospitalisations due to COPD exacerbation and pneumonia, as well as respiratory and all-cause mortality, with information collected longitudinally during follow-up. Patients with COPD are often hospitalised due to pneumonia, which is relevant to the disease course and prognosis. Furthermore, pneumonias are sometimes reported as exacerbations, making it important to investigate whether sex differences apply similarly or separately to both exacerbations and pneumonias.

Lung function was measured using pre-bronchodilator forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC).²² Airway obstruction was defined as FEV₁/FVC <0.70 and FEV₁ <80% predicted. We chose to additionally include FEV₁ <80% of predicted in airway obstruction, as we intended to focus on clinically relevant impaired lung function. Predicted values were calculated using internally derived reference values based on a subsample of over 11 000 healthy, asymptomatic, never-smoking individuals without any chronic disease, with age and height as covariates, separately for males and females.²²

Chronic bronchitis was defined as an affirmative response to the question: 'Do you cough up phlegm from the lungs in the morning and/or during the day as long as three consecutive months each year?' Dyspnoea was defined as an affirmative response to at least one of the following three questions: 'Do you get breathless when walking on level ground with people of the same age?', 'Do you stop for a breath when walking on level ground in your own tempo?', and/or 'Do you get breathless when taking a bath or getting dressed?', corresponding to a value of the modified Medical Research Council dyspnoea scale (mMRC) ≥2.

Hospitalisations due to COPD exacerbation (International Classification of Diseases (ICD)-10: J41–J44) and pneumonia (ICD-10:

J12–J18) were defined as emergency department visits/hospital admissions with the mentioned primary diagnosis. Information was obtained from the national Danish Patient Registry, which records all public and private hospital contacts in Denmark, recorded from baseline examination until 7 December 2018.²³ Information on vital status was obtained from the national Danish Civil Registration System, which contains date of death for all individuals resident in Denmark, recorded from baseline examination until 13 December 2018. Information on the cause of death was obtained from the national Danish Causes of Death Registry, which contains date of causes of death for all individuals resident in Denmark, recorded until 31 December 2016. Death due to respiratory disease (ICD-10: J00–J99) was based on the underlying cause of death. Since the national Danish Causes of Death Registry lags the national Danish Civil Registration System by approximately 2 years, not all deaths could be classified by cause. All diagnoses recorded in the registries are strictly made by a medical doctor according to national Danish laws using the WHO ICD codes. Since follow-up was done using the above-mentioned register linkage based on the unique Central Person Registration number provided to everyone at birth or immigration, no person was lost to follow-up, and individuals who emigrated were censored at the date of emigration.²⁰

Statistical analyses

Wilcoxon's rank-sum and Pearson's χ^2 tests were used for group comparisons. Smoking amount was measured in pack-years for both former and current smokers, while never-smokers were assigned 0 pack-years in the analyses. Linear regression was used to investigate the cross-sectional association between age and smoking amount with FEV₁ % predicted and FEV₁/FVC. Logistic regression was used to determine the cross-sectional association between smoking amount with risk of airway obstruction, chronic bronchitis and dyspnoea by using restricted cubic splines with never-smokers without smoking amount as the reference, and three knots chosen and placed according to Harrell's recommendation at the 10th, 50th and 90th percentiles. The number of knots was chosen with the use of Akaike's and Bayesian information criteria. Cox proportional hazard regression with age as underlying timescale (=age adjustment) and left truncation (=delayed entry) was used to determine the longitudinal association between smoking amount with risk of hospitalisations due to COPD exacerbation and pneumonia, and respiratory and all-cause mortality. Multiple failure-time analysis was carried out for COPD exacerbation and pneumonia using Andersen-Gill, meaning that individuals were at risk of recurrent events. Analyses were conducted separately in males and females according to smoking amount for all COPD-related outcomes. The interaction between sex and smoking amount was assessed by comparing two models: the unrestricted model, which included the interaction term between sex and smoking amount, and the restricted model, which did not include the interaction term. To evaluate whether the interaction significantly improved the model, we used the likelihood ratio test to compare the fit of the two models. All cross-sectional and longitudinal analyses were multivariable adjusted for potential confounders believed to have importance for disease severity and prognosis in patients with COPD, which was collected at baseline examination and included age, smoking status (never-smokers, former smoker and current smoker), body mass index (BMI), asthma, occupational exposure to dust/fumes and socioeconomic status. BMI was calculated as measured weight (kg) divided by measured height in squared (m²). Asthma was defined as an affirmative response to the question: 'Do you have asthma?' Occupational exposure to dust/fumes was defined as an affirmative response to the question: 'Have you for longer periods of your working life been exposed to dust or fumes?' Sociodemographic status was determined based on the longest level of education attained after compulsory schooling and annual household income. In a sensitivity analysis, we adjusted for cardiovascular disease with regard to risk of dyspnoea, and cardiovascular disease and cancer with regard to all-cause mortality. Cardiovascular disease included ischaemic heart

disease (ICD-8: 410–414 and ICD-10: I20–I25), atrial fibrillation (ICD-8: 427.93–427.94 and ICD-10: I48), heart failure (ICD-8: 427.09–427.11 and ICD-10: I50) and stroke (ICD-8: 432–435 and ICD-10: I60, I61, I63, I64 and G45), identified from the national Danish Patient Registry. Cancer included all cancer forms except for non-melanoma skin cancers (ICD-7: 140–205 and ICD-10: C00–D09), identified from the national Danish Cancer Registry, which records all cancers diagnosed in Denmark since 1943. In another sensitivity analysis, BMI was treated as a time-varying covariate; however, since estimates only varied on second to third decimal places, we opted to keep the simpler model using BMI as a time-invariant variable. Analyses were performed using STATA/SE V.15.1 for Windows (StataCorp, College Station, Texas, USA), and a two-sided p value <0.05 was considered significant.

RESULTS

In total, 105 037 individuals were included from the Copenhagen General Population Study, of whom 47 231 (45%) were males and 57 806 (55%) were females, examined in the period from November 2003 until April 2015. Characteristics are presented in table 1. Males were slightly older (median age 58.9 vs 57.5 years), had higher height and weight (179 vs 166 cm and 84.2 vs 68.0 kg), more often active smokers (18% vs 16%), and had higher smoking amount (20.0 vs 12.3 pack-years) compared with females. In contrast, females had slightly higher lung function and more often asthma (7% vs 5%) compared with males.

Characteristics according to the presence of airway obstruction are provided in online supplemental table S1. Among those with airway obstruction, males were slightly older (median age 67.8 vs 65.7 years), had higher smoking amount (37.5 vs 27.9 pack-years), but no difference in active smoking (36% vs 36%) compared with females. In contrast, females had slightly higher lung function and more often asthma (21% vs 18%) and dyspnoea (28% vs 25%) but had less chronic bronchitis (22% vs 28%) compared with males.

Sex differences in smoking amount and COPD disease severity

Interestingly, higher age was associated with lower FEV₁ % predicted in males but higher FEV₁ % predicted in females after multivariable adjustment (figure 1, upper panel). As expected, higher age was associated with lower FEV₁/FVC in both males and females (figure 1, lower panel). Compared with females, FEV₁ % predicted was lower and FEV₁/FVC higher with higher age in males (P for interaction <0.0001).

Higher smoking amount was associated with lower FEV₁ % predicted and FEV₁/FVC in both males and females after multivariable adjustment (figure 2). An interaction analysis showed lower lung function in females versus males with the same smoking amount (P for interaction <0.0001). FEV₁ % predicted decreased by 2.00% (95% CI 1.90% to 2.10%) on average per 10 pack-years higher smoking amount in all individuals, with an additional decrease in females compared with males of 0.82% (95% CI 0.68% to 0.96%). Consequently, FEV₁/FVC, on average, decreased from 0.77 (95% CI 0.77 to 0.77) in females with 10 pack-years of smoking to 0.72 (95% CI 0.72 to 0.73) in females with 50 pack-years of smoking, and from 0.77 (95% CI 0.77 to 0.77) in males with 10 pack-years of smoking to 0.74 (95% CI 0.74 to 0.74) in males with 50 pack-years of smoking.

A total of 7367 (7%) individuals had airway obstruction, 9206 (9%) had chronic bronchitis and 8541 (8%) had dyspnoea. After multivariable adjustment, a higher smoking amount was associated with an increased risk of airway obstruction, chronic bronchitis and dyspnoea in both males and females (figure 3). However, interaction analyses indicated an even higher risk in females versus males with the same smoking amount (P for interaction <0.0001 for airway obstruction and chronic bronchitis and P for interaction=0.03 for dyspnoea). Nonetheless, the specific patterns were different for the outcomes with gradually increasing differences in estimates between females and males with higher smoking amounts for airway obstruction (≥10 pack-years) and dyspnoea

Table 1 Baseline characteristics of 105 037 randomly selected males and females from the Copenhagen General Population Study*

	All individuals (N=105 037)	Males (N=47 231)	Females (N=57 806)
Age, years	58.0 (48.1–67.3)	58.6 (48.6–67.9)	57.5 (47.7–66.8)†
Height, cm	171 (165–178)	179 (174–183)	166 (161–170)†
Weight, kg	75.7 (65.8–86.5)	84.2 (76.6–93.0)	68.0 (61.2–76.7)†
BMI, kg/m ²	25.6 (23.2–28.4)	26.4 (24.3–28.8)	24.7 (22.4–27.9)†
Lung function			
FEV ₁ , L	2.93 (2.38–3.57)	3.55 (2.97–4.11)	2.58 (2.15–3.00)†
FEV ₁ % predicted	97 (87–106)	96 (86–106)	97 (87–107)†
FVC, L	3.81 (3.15–4.60)	4.61 (3.94–5.27)	3.34 (2.84–3.84)†
FVC % predicted	99 (90–109)	99 (90–109)	99 (90–109)
FEV ₁ /FVC	0.77 (0.73–0.82)	0.77 (0.72–0.82)	0.78 (0.73–0.82)†
FEV ₁ /FVC<0.70, n (%)	16 061 (15)	7702 (16)	8359 (14)†
FEV ₁ ≥80% predicted, n (%)	89 755 (85)	39 817 (84)	49 938 (86)†
FEV ₁ 50–79% predicted, n (%)	14 029 (13)	6747 (14)	7282 (13)†
FEV ₁ 30–49% predicted, n (%)	1111 (1)	591 (1)	520 (1)†
FEV ₁ <30% predicted, n (%)	142 (<1)	76 (<1)	66 (<1)†
Smoking history			
Never-smokers, n (%)	45 093 (43)	18 475 (39)	26 618 (46)†
Former smokers, n (%)	42 115 (40)	20 234 (43)	21 881 (38)†
Current smokers, n (%)	17 829 (17)	8522 (18)	9307 (16)†
Smoking amount, pack-years‡	15.4 (6.0–30.0)	20.0 (9.0–36.0)	12.3 (4.5–25.0)†
Asthma, n (%)	6333 (6)	2502 (5)	3831 (7)†
Occupational exposure to dust/fumes, n (%)	10 461 (10)	8100 (17)	2361 (4)†
Poor socioeconomic status, n (%)	18 455 (18)	7015 (15)	11 440 (20)†

Numbers may not add up to 100% due to rounding.
*Data presented as median and 25th and 75th percentiles, or number (percent).
†P<0.05 for comparison between males and females.
‡Only reported for former and current smokers.
BMI, body mass index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

(≥30 pack-years), whereas the estimates for chronic bronchitis showed a more complex pattern. Results for dyspnoea were similar when adjusting for cardiovascular disease (online supplemental figure S1).

Sex differences in smoking amount and COPD prognosis

During 15 years of follow-up (median 9.3 years), we recorded 2756 COPD exacerbations, 7878 pneumonias and 10 658 deaths, of which 711 had respiratory disease as underlying cause. Follow-up times were similar between males and females, with no difference in total follow-up duration (15 years) and a small difference in median follow-up times (9.1 vs 9.5 years). A higher smoking amount was associated with an increased risk of COPD exacerbation, pneumonia and respiratory, and all-cause mortality, and there was an interaction with sex for all outcomes except for pneumonia (figure 4). Compared with never-smokers, multivariable adjusted HRs for COPD exacerbation increased from 4.64 (95% CI 2.83 to 7.61) in females with 10 pack-years of smoking to 41.6 (95% CI 28.8 to 60.2) in females with ≥50 pack-years of smoking, and from 2.21 (95% CI 0.92 to 5.32) in males with 10 pack-years of smoking to 23.7 (95% CI 12.9 to 43.5) in males with ≥50 pack-years of

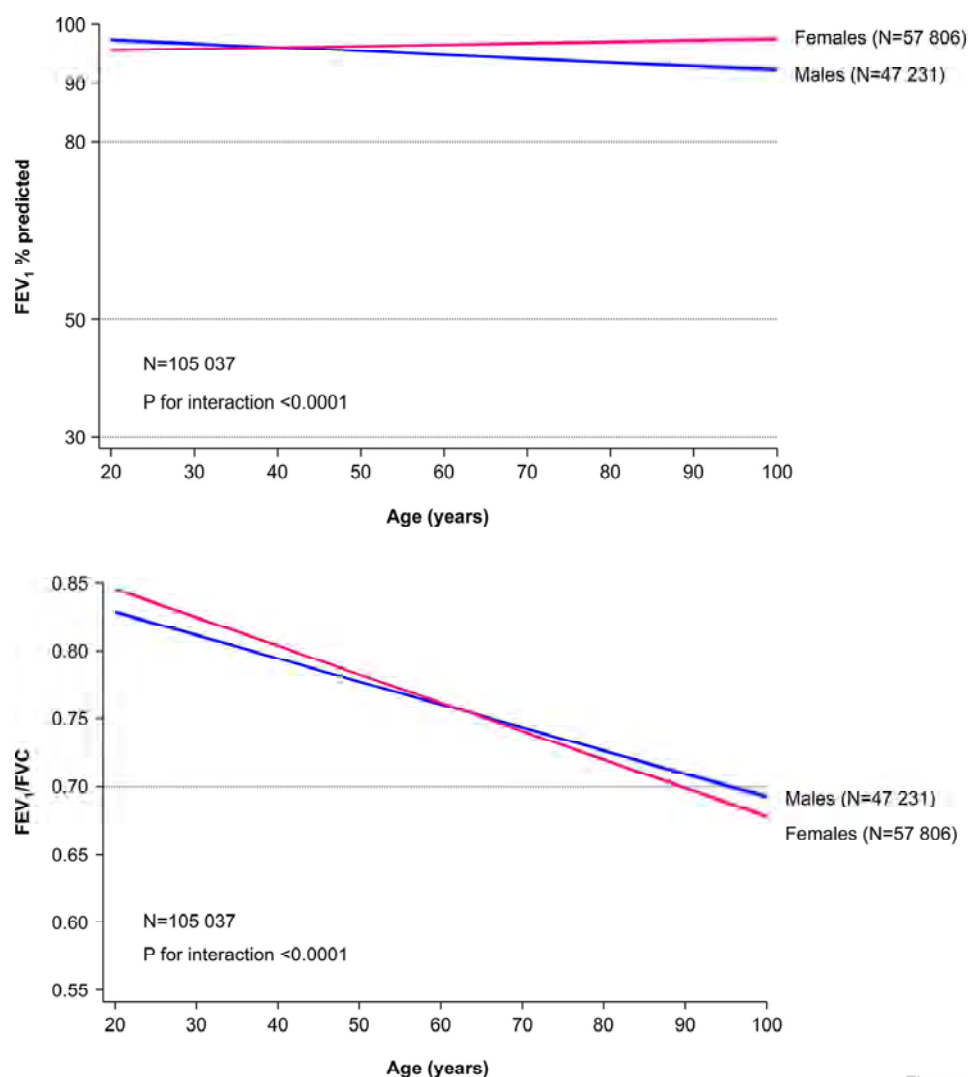


Figure 1

Figure 1 Association between age and lung function in males and females. Smoking amount was measured in pack-years for both former and current smokers, while never-smokers were assigned 0 pack-years in the analyses. Linear regression was used to assess the association between age with forced expiratory volume in 1 second (FEV₁) % predicted and FEV₁/forced vital capacity (FVC) at baseline examination. The interaction between age and sex was assessed using the likelihood ratio test. Analyses were multivariable adjusted for smoking status, smoking amount (pack-years), body mass index, asthma, occupational exposure to dust/fumes and socioeconomic status.

smoking. Corresponding HR increases with increasing smoking amount for pneumonia were 1.54 (95% CI 1.32 to 1.79) to 3.59 (95% CI 3.01 to 4.27) in females and 1.36 (95% CI 1.14 to 1.61) to 2.96 (95% CI 2.57 to 3.40) in males, for respiratory mortality were 2.04 (95% CI 1.27 to 3.26) to 11.1 (95% CI 7.39 to 16.8) in females and 1.09 (95% CI 0.62 to 1.92) to 5.66 (95% CI 3.96 to 8.11) in males, and for all-cause mortality were 1.50 (95% CI 1.34 to 1.67) to 3.53 (95% CI 3.11 to 4.00) in females and 1.62 (95% CI 1.45 to 1.81) to 2.94 (95% CI 2.69 to 3.21) in males, respectively. Results for all-cause mortality were similar when adjusting for cardiovascular disease and cancer (online supplemental figure S2).

DISCUSSION

In a population-based cohort of 105 037 individuals, we tested the hypothesis that females compared with males are more susceptible to the detrimental effects of smoking in relation to COPD. Our findings indicate that females compared with males have much more severe disease with comparable smoking exposure, manifesting as lower lung function and a higher risk of airway obstruction, chronic bronchitis and dyspnoea. Furthermore, females compared with males exhibit a poorer prognosis with higher smoking exposure, including a higher risk of COPD exacerbation and early death. These results indicate that females seem more susceptible to the detrimental effects of smoking in development and prognosis of COPD compared with males.

Potential mechanisms explaining increased susceptibility to smoking effects in females may be related to the anatomy of the respiratory system. Airway lumen sizes are smaller in females than in males even after accounting for height and lung sizes, suggesting that this lower airway lumen may enhance toxic effects of smoking and hence lead to the increased risk of developing COPD and the following poor prognosis.^{24 25} This hypothesis is further supported by the fact that even with chronic smoking exposure over several decades, the lumen size remains lower in females.²⁴ Furthermore, sex differences in breathing mechanics while smoking, and the way cigarette smoke is inhaled and distributed throughout the lungs, may also contribute to the increased susceptibility in females. Females tend to preferentially engage the rib cage with less contribution from the abdomen when smoking, whereas males predominantly engage the abdominal compartment.²⁶ As a result, females exhibit greater inspiratory rib cage muscle involvement and volume expansion during resting breathing compared with males, likely reflecting an improved mechanical advantage provided by the greater inclination of the ribs. This difference may lead to higher exposure to the harmful effects of smoking in females compared with males.

Another potential mechanism for the observed sex differences in COPD susceptibility may be related to hormonally mediated differences. In a mouse model of COPD, smoking exposure led

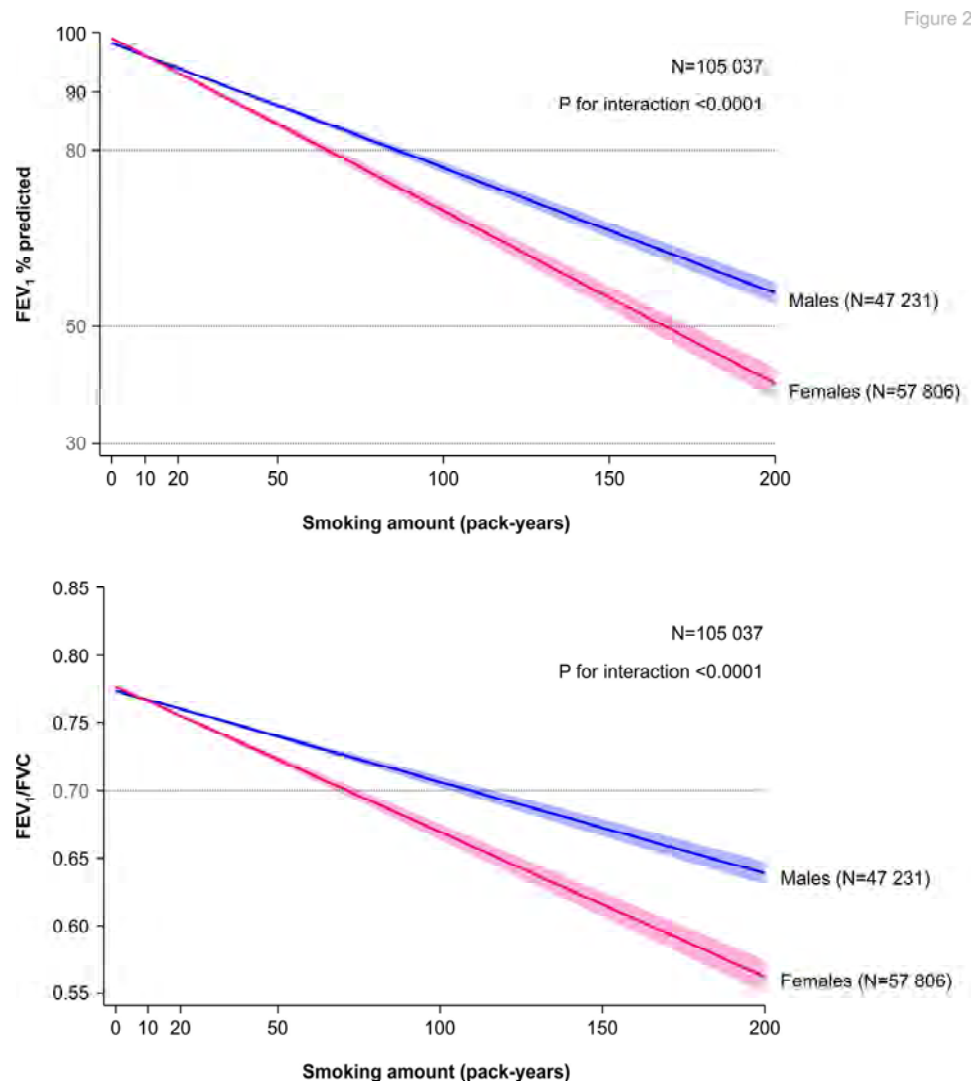


Figure 2 Association between smoking amount and lung function in males and females. Smoking amount was measured in pack-years for both former and current smokers, while never-smokers were assigned 0 pack-years in the analyses. Linear regression was used to assess the association between smoking amount (pack-years) with forced expiratory volume in 1 second (FEV₁) % predicted and FEV₁/forced vital capacity (FVC) at baseline examination. The interaction between smoking amount and sex was assessed using the likelihood ratio test. Analyses were multivariable adjusted for age, smoking status, body mass index, asthma, occupational exposure to dust/fumes and socioeconomic status.

to increased small airway remodelling and peripheral airway obstruction in female mice compared with male mice, while male mice had predominantly more emphysema, and these sex differences diminished following ovariectomy, indicating that female sex hormones in relation to smoking exposure may influence the development and progression of COPD.²⁷

Previous studies on sex-based differences in the association between smoking and COPD have been controversial.^{8–15} In a Danish longitudinal population study with 13 897 individuals, females compared with males displayed lower lung function and higher risk of hospitalisation due to COPD with similar smoking amount, but there was no sex interaction.¹² In the Vlagtwedde-Vlaardingen Study with 4554 individuals, higher smoking amount was associated with higher lung function decline in females compared with males, which also showed significant sex interaction with a higher decline in females.¹⁵ In the UK Biobank with 249 327 individuals, females compared with males had a higher risk of airway obstruction with similar smoking amounts.²⁸ We now demonstrate that females compared with males have a lower lung function and higher risk of airway obstruction, chronic bronchitis and dyspnoea with higher smoking exposure. Furthermore, females compared with males have a higher risk of COPD exacerbation and early death with higher smoking exposure. Females not only appear to be more susceptible to the detrimental effects of smoking in

terms of COPD development, but they also seem to experience a worse COPD prognosis compared with males.

Interestingly, in the COPD Cohorts Collaborative International Assessment (3CIA) initiative, which included approximately 17 000 individuals with COPD from 22 cohorts from various countries, including Denmark, females were reported to experience more dyspnoea and frequent exacerbations but had better survival compared with males, which may seem paradoxical when compared with our present findings.²⁹ A potential contributing factor may be that males reported a higher smoking amount than females (mean 47.8 vs 33.3 pack-years), and survival analyses were only adjusted for smoking status but not for amount. Hypothetically, if both males and females with COPD had similar smoking amounts, our findings suggest that females might be more affected than males.

Strengths of the present study include a sample size of 105 037 randomly selected individuals, with comprehensive information to assess both the severity and prognosis of COPD.

A potential limitation is that post-bronchodilator spirometry was not available, thereby making it difficult to assess the type of airway obstruction, whether it is persistent or reversible. Some individuals may have a reversible form of airway obstruction suggesting undiagnosed/uncontrolled asthma. However, pre-bronchodilator airway obstruction has been shown to identify high-risk individuals with COPD before, as demonstrated in

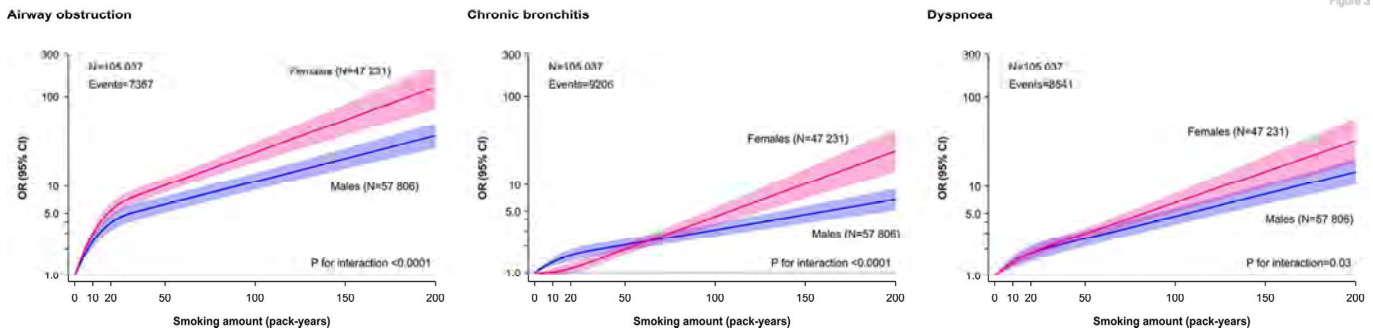


Figure 3 Smoking amount and risk of airway obstruction, chronic bronchitis and dyspnoea in males and females. Smoking amount was measured in pack-years for both former and current smokers, while never-smokers were assigned 0 pack-years in the analyses. Logistic regression was used to assess the association between smoking amount (pack-years) and airway obstruction, chronic bronchitis and dyspnoea at baseline examination using restricted cubic splines with never-smokers without smoking amount as the reference, and three knots chosen and placed according to the 10th, 50th and 90th percentiles. The interaction between smoking amount and sex was assessed using the likelihood ratio test. Airway obstruction was defined as forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) <0.70 and $FEV_1 <80\%$ predicted. Chronic bronchitis was defined as cough and phlegm from the lungs in the morning and/or during the day for at least three consecutive months each year. Dyspnoea corresponded to a value of the modified Medical Research Council dyspnoea scale (mMRC) ≥ 2 . Analyses were multivariable adjusted for age, smoking status, body mass index, asthma, occupational exposure to dust/fumes and socioeconomic status.

the Copenhagen General Population Study,³⁰ and similar findings have recently been reported in the SPIROMICS cohort.³¹ In addition, airway obstruction was defined using $FEV_1 <80\%$ predicted, which included only cases with moderate to severe disease, and we primarily focused on higher smoking exposure well beyond 10 pack-years, consistent with inclusion criteria used in randomised controlled trials for COPD. Nonetheless, results remained consistent when considering other COPD-related disease measures such as chronic bronchitis, dyspnoea with mMRC ≥ 2 , severe exacerbations and mortality. Thus, we believe we have effectively addressed various clinical aspects of COPD. A severe COPD exacerbation diagnosis has previously been shown to have a high positive predictive value of 92% for the diagnosis of COPD.³² Another potential limitation is that we did not have information on indoor or outdoor air pollution.

The clinical implications of our findings are that we need to be more aware of the importance of recognising and addressing

sex differences in the prevention, diagnosis and management of COPD. Our study suggests that females compared with males appear more susceptible to the detrimental effects of smoking in both the development and prognosis of COPD. Our findings also highlight the need for further research to elucidate the underlying mechanisms driving the observed sex inequalities in smoking exposure and COPD susceptibility. By better understanding these mechanisms, we can develop more effective strategies for early detection, personalised treatment and improved outcomes for all patients with COPD.

In conclusion, our study suggests that females seem more susceptible to the detrimental effects of smoking in development and prognosis of COPD compared with males.

Contributors YÇ and SA had full access to all the data in the study and had final responsibility for the decision to submit for publication, serving as the guarantors. YÇ and SA contributed to the study concept and design. YÇ, BGN, PL and SA collected, analysed and interpreted the data. YÇ wrote the draft manuscript and did the statistical

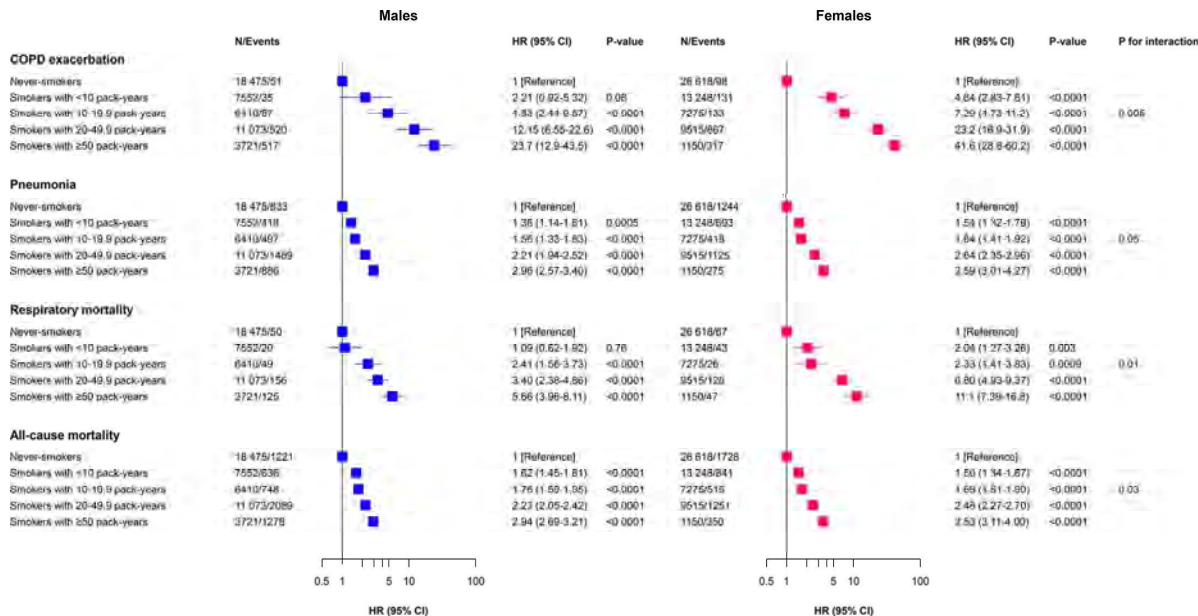


Figure 4 Smoking amount and risk of chronic obstructive pulmonary disease (COPD) exacerbation, pneumonia and mortality in males and females. Smoking amount was measured in pack-years for both former and current smokers. Cox proportional hazard regression with age as underlying timescale was used to determine the risk of hospitalisations due to COPD exacerbation and pneumonia, and respiratory and all-cause mortality during follow-up. Multiple failure-time analysis was carried out for COPD exacerbation and pneumonia. The interaction between smoking amount and sex was assessed using the likelihood ratio test. Analyses were multivariable adjusted for age (=as timescale), smoking status, body mass index, asthma, occupational exposure to dust/fumes and socioeconomic status.

analyses. YÇ, BGN, PL and SA revised the manuscript for important intellectual content. BGN provided administrative, technical or material support.

Funding The Copenhagen University Hospital – Herlev and Gentofte. The funder had no role in the design and conduct of the study; collection, management, analysis or interpretation of the data; preparation, review or approval of the manuscript; or decision to submit the manuscript for publication.

Competing interests YÇ reports personal fees from AstraZeneca, Boehringer Ingelheim, and GlaxoSmithKline, and grants and personal fees from Sanofi outside the submitted work. PL reports grants and personal fees from AstraZeneca and Sanofi and personal fees from Boehringer Ingelheim and GlaxoSmithKline outside the submitted work. BGN and SA have nothing to disclose. The views expressed are those of the authors.

Patient consent for publication Not applicable.

Ethics approval The study was conducted according to the Declaration of Helsinki and was approved by Copenhagen University Hospital – Herlev and Gentofte and the regional ethics committee (approval number: H-KF-01-144/01). Written informed consent was provided from all participants. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available on reasonable request. Data access for further analyses is possible through direct collaborative agreement or through locally managed access arranged through the study's principal investigators.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed.

Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs

Yunus Çolak <http://orcid.org/0000-0003-2045-829X>

Peter Lange <http://orcid.org/0000-0003-0401-0081>

Shoaib Afzal <http://orcid.org/0000-0002-1442-4694>

REFERENCES

- Agustí A, Hogg JC. Update on the Pathogenesis of Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2019;381:1248–56.
- Office for National Statistics. Adult smoking habits in the UK: 2022. 2023. Available: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2022/pdf> [Accessed 14 Jun 2024].
- Centers for Disease Control and Prevention. Current cigarette smoking among adults in the United States. 2023. Available: https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm [Accessed 14 Jun 2024].
- Eurostat. Tobacco consumption statistics - statistics explained. 2023. Available: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Tobacco_consumption_statistics [Accessed 14 Jun 2024].
- Çolak Y, Løkke A, Marott JL, et al. Low smoking exposure and development and prognosis of COPD over four decades: a population-based cohort study. *Eur Respir J* 2024;64:2400314.
- Marshall DC, Al Omari O, Goodall R, et al. Trends in prevalence, mortality, and disability-adjusted life-years relating to chronic obstructive pulmonary disease in Europe: an observational study of the global burden of disease database, 2001–2019. *BMC Pulm Med* 2022;22:289.
- Thun MJ, Carter BD, Feskanich D, et al. 50-year trends in smoking-related mortality in the United States. *N Engl J Med* 2013;368:351–64.
- Chen Y, Horne SL, Dosman JA. Increased susceptibility to lung dysfunction in female smokers. *Am Rev Respir Dis* 1991;143:1224–30.
- Criner GJ, Martinez FJ, Aaron S, et al. Current Controversies in Chronic Obstructive Pulmonary Disease. A Report from the Global Initiative for Chronic Obstructive Lung Disease Scientific Committee. *Ann Am Thorac Soc* 2019;16:29–39.
- Gan WQ, Man SFP, Postma DS, et al. Female smokers beyond the perimenopausal period are at increased risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Respir Res* 2006;7:52.
- Langhammer A, Johnsen R, Gulsvik A, et al. Sex differences in lung vulnerability to tobacco smoking. *Eur Respir J* 2003;21:1017–23.
- Prescott E, Bjerg AM, Andersen PK, et al. Gender difference in smoking effects on lung function and risk of hospitalization for COPD: results from a Danish longitudinal population study. *Eur Respir J* 1997;10:822–7.
- Sørheim IC, Johannessen A, Gulsvik A, et al. Gender differences in COPD: are women more susceptible to smoking effects than men? *Thorax* 2010;65:480–5.
- Xu X, Li B, Wang L. Gender difference in smoking effects on adult pulmonary function. *Eur Respir J* 1994;7:477–83.
- Xu X, Weiss ST, Rijcken B, et al. Smoking, changes in smoking habits, and rate of decline in FEV1: new insight into gender differences. *Eur Respir J* 1994;7:1056–61.
- Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2024 report. Available: <https://goldcopd.org/> [Accessed 20 Aug 2024].
- Çolak Y, Afzal S, Nordestgaard BG, et al. Importance of Early COPD in Young Adults for Development of Clinical COPD: Findings from the Copenhagen General Population Study. *Am J Respir Crit Care Med* 2021;203:1245–56.
- Çolak Y, Afzal S, Nordestgaard BG, et al. Prevalence, Characteristics, and Prognosis of Early COPD: The Copenhagen General Population Study. *Am J Respir Crit Care Med* 2019.
- Çolak Y, Nordestgaard BG, Lange P, et al. Prognosis of Patients with Chronic Obstructive Pulmonary Disease Not Eligible for Major Clinical Trials. *Am J Respir Crit Care Med* 2022;206:271–80.
- Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019;11:563–91.
- Lange P, Nyboe J, Appleyard M, et al. Relationship of the type of tobacco and inhalation pattern to pulmonary and total mortality. *Eur Respir J* 1992;5:1111–7.
- Løkke A, Marott JL, Mortensen J, et al. New Danish reference values for spirometry. *Clin Respir J* 2013;7:153–67.
- Schmidt M, Schmidt SAJ, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449–90.
- Bhatt SP, Bodduluri S, Nakhmani A, et al. Sex Differences in Airways at Chest CT: Results from the COPD Gene Cohort. *Radiology* 2022;305:699–708.
- Kim Y-I, Schroeder J, Lynch D, et al. Gender differences of airway dimensions in anatomically matched sites on CT in smokers. *COPD* 2011;8:285–92.
- Polverino M, Capuozzo A, Cicchitto G, et al. Smoking Pattern in Men and Women: A Possible Contributor to Sex Differences in Smoke-related Lung Diseases. *Am J Respir Crit Care Med* 2020;202:1048–51.
- Tam A, Churg A, Wright JL, et al. Sex Differences in Airway Remodeling in a Mouse Model of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2016;193:825–34.
- Amaral AFS, Strachan DP, Burney PGJ, et al. Female Smokers Are at Greater Risk of Airflow Obstruction Than Male Smokers. *UK Biobank. Am J Respir Crit Care Med* 2017;195:1226–35.
- Perez TA, Castillo EG, Ancochea J, et al. Sex differences between women and men with COPD: A new analysis of the 3CIA study. *Respir Med* 2020;171:106105.
- Çolak Y, Nordestgaard BG, Vestbo J, et al. Comparison of five major airflow limitation criteria to identify high-risk individuals with COPD: a contemporary population-based cohort. *Thorax* 2020;75:944–54.
- Buhr RG, Barjaktarevic IZ, Quirbrera PM, et al. Reversible Airflow Obstruction Predicts Future Chronic Obstructive Pulmonary Disease Development in the SPIROMICS Cohort: An Observational Cohort Study. *Am J Respir Crit Care Med* 2022;206:554–62.
- Thomsen RW, Lange P, Hellquist B, et al. Validity and underrecording of diagnosis of COPD in the Danish National Patient Registry. *Respir Med* 2011;105:1063–8.

Variabilidade na sensibilidade à inflamação nos músculos e pulmões de doentes com DPOC pode estar relacionada à suscetibilidade à perda da função pulmonar

Paul R Kemp,¹ Mark Griffiths,^{1,2} Michael I Polkey,^{1,3} Amanda Sathyapala^{1,4}

► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/thorax-2024-221901>).

¹National Heart and Lung Institute, Imperial College London, London, UK

²Barts Heart Centre, St Bartholomew's Hospital, London, UK

³NIHR Respiratory BRU, Guy's and St Thomas' Hospitals NHS Trust, London, UK

⁴Guy's and St Thomas' NHS Foundation Trust, London, UK

Correspondence to

Dr Paul R Kemp; p.kemp@imperial.ac.uk

Received 9 May 2024

Accepted 3 April 2025

Published Online First 16 April 2025



© Author(s) (or their employer(s)) 2025. Re-use permitted under CC BY. Published by BMJ.

RESUMO

Contexto A perda de massa muscular e a fraqueza (sarcopenia) são comumente associadas à Doença Pulmonar Obstrutiva Crônica (DPOC), causando fragilidade e redução da qualidade de vida. A contribuição da inflamação para a perda muscular e a suscetibilidade à rápida queda da função pulmonar ainda é debatida. A nossa hipótese foi que a comparação entre o transcriptoma muscular e os perfis de citocinas inflamatórias circulantes em doentes poderia identificar qualquer contribuição da inflamação sistêmica para a atrofia muscular.

Métodos A expressão gênica diferencial no músculo quadríceps foi determinada entre doentes com DPOC leve (n=28) e DPOC grave (n=51) usando o conjunto de dados GSE100281. Esses dados de microarranjo foram comparados por correlação biweight mid com a função pulmonar e os níveis plasmáticos de citocinas dos mesmos doentes.

Resultados Doentes com DPOC grave apresentaram menor índice de massa livre de gordura (medida da massa muscular) em comparação com doentes com DPOC leve, apesar de níveis semelhantes de atividade física e citocinas inflamatórias. Conjuntos de genes associados à inflamação e à transição epitelial-mesenquimal (EMT) estavam elevados na DPOC grave, sugerindo que a inflamação pode contribuir para a perda de massa muscular. Em doentes com DPOC grave, os conjuntos de genes de EMT e inflamação estavam fortemente associados a citocinas pró-inflamatórias e anti-inflamatórias circulantes. No entanto, em doentes com DPOC leve, as citocinas anti-inflamatórias mostraram associações negativas com esses conjuntos de genes, e as associações com citocinas pró-inflamatórias foram fracas. Em dados de amostras de pulmão e sangue, doentes com DPOC grave apresentaram expressão gênica inflamatória e de EMT elevada em comparação com doentes com DPOC leve, sugerindo que esse fenômeno não é específico do músculo.

Conclusões Em doentes no extremo grave do espectro da DPOC, predomina a resposta pró-inflamatória no músculo, enquanto em doentes no extremo leve, predomina a resposta anti-inflamatória. Essa hipótese precisa ser confirmada em uma coorte longitudinal.

INTRODUCTION

Muscle loss limits the functional capacity of patients with Chronic Obstructive Pulmonary disease (COPD) and other chronic diseases, reducing their ability to perform the tasks of daily living, their quality of life and lifespan.¹

Chronic inflammation is common to diseases that lead to muscle wasting,² including COPD. Inflammation increases protein turnover, increasing blood urea nitrogen, leading to a negative nitrogen balance,³ and inflammatory cytokines promote protein breakdown in both in vitro and in vivo studies.⁴⁻⁶ While inflammation is likely to play a key role in COPD-associated muscle loss, some studies show associations of circulating inflammatory cytokines with muscle loss, whereas others do not.^{7,8} There are

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Inflammation plays a key role in the pathogenesis of COPD and sarcopenia associated with various diseases. However, the role that individual susceptibility to inflammation plays in COPD disease progression and associated sarcopenia is poorly understood.

WHAT THIS STUDY ADDS

► Correlation of the transcriptomes of muscle and lung in patients with mild and severe COPD with markers of bloodborne inflammation suggests that patients with mild COPD may be relatively protected by an anti-inflammatory profile and patients with severe COPD are relatively susceptible to circulating proinflammatory mediators.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► This study suggests that it may be possible to select susceptible patients for early anti-inflammatory intervention to prevent muscle atrophy and progressive COPD. Longitudinal studies and further investigation of individual pathways are required to validate our findings.

several potential reasons for this variability. First, inflammation is not the only proposed mechanism of muscle loss, with inactivity, oxidative stress and malnutrition all proposed as important regulators.⁹ Second, there is significant interplay between these mechanisms, with inflammatory cytokines reducing appetite and activity, altering mood and motivation, and increasing oxidative stress.¹⁰ Each of these responses adds variability to the data, with different individuals having different changes in activity, for example, for a given inflammatory load. Third, there are multiple potential inflammatory mediators which can contribute to the loss of muscle mass, making it difficult to identify the effects of individual cytokines. Fourthly, each factor (inflammation, inactivity, etc) may have greater relative importance at different stages of the disease. Lastly, some cytokine components of the inflammatory response have anti-inflammatory activity,¹¹ so the relative levels of proinflammatory and antiinflammatory cytokines determine the responses of target tissues.

To cite: Kemp PR, Griffiths M, Polkey MI, et al. *Thorax* 2025;80:520–529.

Furthermore, individuals are likely to have different intrinsic sensitivities to inflammatory stimulus in the muscle and other tissues.^{12,13} Mechanisms that could affect sensitivity include different levels of expression of receptors or signalling intermediates that affect the signal provided by a given amount of cytokine. Such variation is likely to be both genetically and environmentally determined. Consistent with such a suggestion, analyses of individual polymorphisms and a meta-analysis of Genome Wide Association Study (GWAS) data have implicated toll-like receptors^{14–16} as well as interleukins and their receptors^{17–19} as susceptibility loci for lung function and rate of lung function decline. A meta-analysis of GWAS data also implicated transcription factors including NF-Kb1, signal transducer and activator of transcription (STAT) 1, 2 and 6, KLF4, 12 and 16 that are involved in inflammatory responses.¹²

The changes in protein turnover and gene expression that cause muscle loss are likely to reflect a co-ordinated programme of responses to the circulating milieu. We hypothesised that the altered programme may be elucidated by comparing levels of circulating cytokines with the skeletal muscle transcriptome, thereby getting a more detailed picture of the changes in gene expression that any individual cytokine is responsible for. We have previously measured a panel of inflammatory cytokines in the plasma of well-phenotyped patients with COPD²⁰ and separately quantified the skeletal muscle transcriptome by microarray in the same patients.²¹ However, we have not previously combined these data sets. We, therefore, compared plasma cytokine levels with the quadriceps transcriptome to determine the relative importance of each cytokine to skeletal muscle phenotype. Subsequently, we obtained published transcriptome data from studies of lung and blood in patients with COPD, where relative disease severity or lung function data were also available, and compared gene expression profiles within these data sets for validation.^{22–23}

METHODS

Patients

The subjects in this study are subsets from a previously reported cohort of patients with COPD.²⁴ The inclusion and exclusion criteria and descriptions of the physiological analysis have been described previously.²⁴ Biopsies of the vastus lateralis were taken by Bergstrom needle and plasma prepared from whole blood at the same visit. The methodology for the assessment of all clinical and lung function parameters (forced expiratory volume in 1 s and capacity of the lung for the transfer of carbon monoxide (FEV₁ and TL_{CO})), exercise capacity (6 min walk distance) as well as physical activity (time spent moving) is described in the previous publications.^{24–26} The demographics of the whole cohort and for the microarray cohort are given in online supplemental tables S1 and S2, respectively.

Inflammatory cytokines and CRP were quantified in plasma samples as previously described.²⁰ The methodology and initial analysis of muscle fibre type has been described,²⁴ as has the generation and overall analysis of the RNA isolated from the same patients.²¹

Statistical analysis

Patients were divided into two groups based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria: GOLD 1 or 2 as mild and GOLD 3 or 4 as severe COPD.

Normality of variables within each group was determined by the Shapiro-Wilk test. Differences in phenotypic variables across the three groups (control, mild and severe) were determined by analysis of variance in Aabel 3.0 for normally distributed variables using the Dunn-Bonferroni correction for multiple testing. For phenotypic variables that did not show a normal distribution, these groups were compared using the Kruskal-Wallis test in SPSS V.24 with a Dunn-Bonferroni correction.

Bioinformatic analysis

The muscle microarray data were generated using Affymetrix Human Gene 1.1 ST microarray (covering 20 926 different genes). The data have been published²¹ and are available as GSE100281.

Data for all 79 patients with COPD were used in this study (28 mild COPD and 51 severe COPD). Differences in gene expression between groups were determined using the R package LIMMA (Linear Models for Microarray Data) and the output loaded into GSEA (Gene Set Enrichment Analysis) using fold difference as the ranking metric. Significance of gene set enrichment is presented as false discovery rate calculated within the GSEA programme to account for gene set size as described.²⁷

To identify differentially enriched gene sets, the rank order was compared with the Hallmark gene sets. To identify gene associations with circulating cytokines and TL_{CO} % predicted, gene expression data for the relevant patients was compared with cytokine levels using biweight mid correlation in the R package Weighted Genome Co-expression Network Analysis. The correlation coefficient was then used as the ranking metric in GSEA again using comparison with the Hallmark gene sets (see online supplemental methods).

Lung biopsy and whole blood RNA data were downloaded from previously published datasets (GSE69818²² and GSE71220²³, respectively). GSE69818 is a microarray study of lung tissue from patients requiring transplantation or cancer resection, and for our study, it was analysed by including all samples (n=70, 51 mild and 19 severe) and by selecting only those with emphysema to remove potential bias (n=38, 22 mild and 16 severe). The array was run using the Affymetrix GeneChip Human Genome U219 of 19 943 genes. GSE71220 is a study of whole blood from patients with COPD comparing the effect of statins on gene expression profile. Gene expression was profiled using the Affymetrix Human Gene 1.1 ST microarray covering 20 926 different genes. Only those not taking statins were selected (n=451) to remove any effect of the drug from the result. Each data set was divided into mild and severe COPD based on GOLD grade and analysed using LIMMA and GSEA as described above.

RESULTS

Comparisons of muscle gene expression between patients with COPD and controls may be complicated by differences in physical activity. Comparison of activity between healthy controls, mild COPD and severe COPD groups showed that both patient groups had reduced locomotion time and movement intensity, but there was no difference in these measures of activity between the two patient groups (figure 1A,B). Comparison of body composition of these three groups showed that patients with mild COPD had similar fat-free mass index (FFMI) to controls, but a higher FFMI than patients with severe COPD. They also had a higher fat mass index (FMI) than patients with severe COPD (figure 1C,D). Consequently, comparing gene expression profiles between mild and severe COPD will identify differences in muscle gene expression associated with FFMI in the absence of the effects of activity.

Differential gene expression analysis in muscle biopsies followed by GSEA showed increased expression of gene sets associated with the epithelial mesenchymal transition (EMT) and inflammation (tumour necrosis factor alpha (TNF-α) signalling) in severe COPD compared with mild COPD (table 1), an observation supported by GSEA following correlation of the transcriptome with TLCO%pred (online supplemental table S3). The enrichment for inflammatory gene sets occurred without a difference in circulating inflammatory cytokine levels between mild and severe patients (online supplemental table S4A, B). Consequently, the circulating inflammatory milieu did not account for increased inflammatory signalling in the muscle of patients with severe COPD.

To identify mechanisms contributing to the differences in muscle inflammatory response between patients with mild and severe COPD, we correlated cytokine levels with gene expression measured by array. In patients with severe COPD, for both proinflammatory and anti-inflammatory cytokines (table 2 and online supplemental tables S5–S11), genes ranked by correlation coefficient with the cytokine showed positive enrichment for the EMT and inflammatory gene sets (TNF-α signalling, interferon signalling and IL6 signalling). Conversely, in patients with mild COPD, the proinflammatory cytokines showed no or a weak positive enrichment

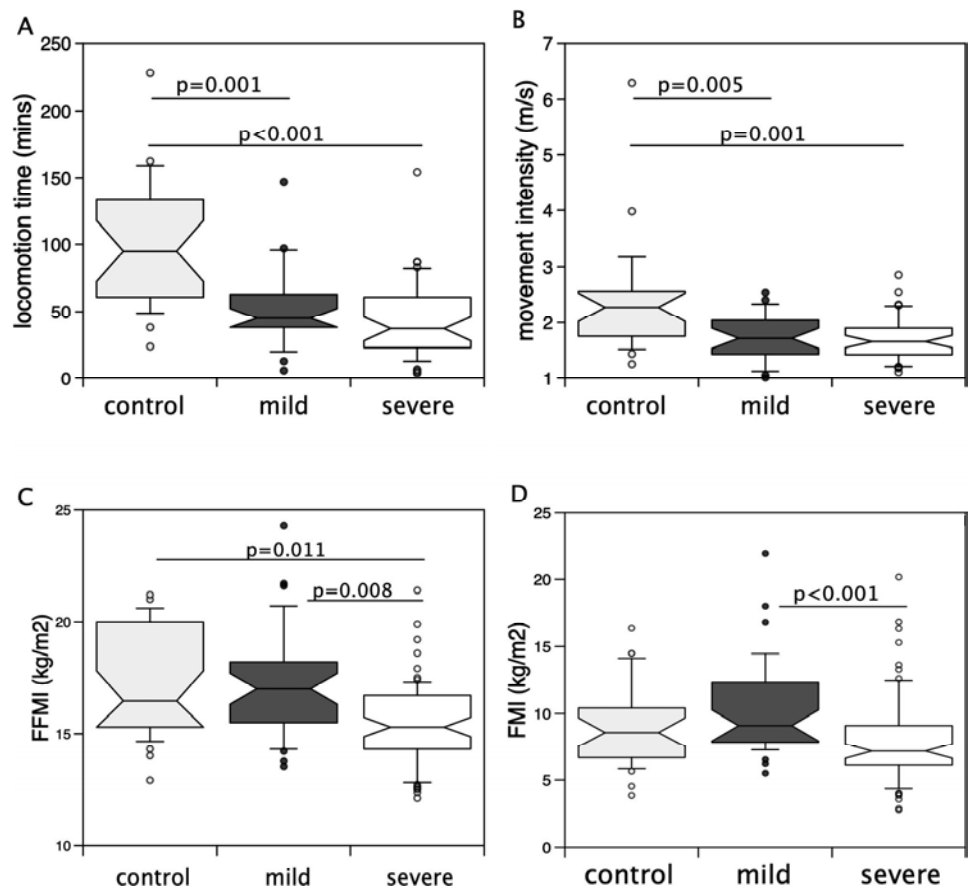


Figure 1 Comparison of activity and fat-free mass index (FFMI) and fat mass index (FMI) with severity of Chronic Obstructive Pulmonary disease (COPD). Locomotion time (A) and the intensity of movement (B) determined by triaxial accelerometry were lower in both patient groups compared with controls but did not differ between patients with mild and severe COPD. Conversely, FFMI (C) was different between the severe patients compared with the other two groups but not between mild patients and controls. FMI (D) was lower in severe patients than the mild patients but there was no difference between either patient group and controls.

for inflammatory gene sets with a reduced net enrichment score (NES) and at lower statistical significance compared with that in patients with severe COPD (table 2 and online supplemental tables S5–S11), whereas the anti-inflammatory cytokines showed negative enrichment for inflammatory gene sets (table 2). Although gender distribution did not differ between the groups, to ensure that there were no effects of differences between males and females, the analysis was repeated within males alone (as this group was large enough). This showed similar results (online supplemental results and online supplemental figure S1 and online supplemental tables S12–S16) with one addition where mild patients had higher fat mass than severe patients and controls, perhaps suggesting that in these individuals, the relative inactivity promoted fat accumulation. These data suggest that in patients with mild COPD, the anti-inflammatory response is sufficient to suppress muscle inflammatory signalling, whereas in severe COPD, the proinflammatory signal predominates.

The lack of difference in circulating cytokines between patients with mild and severe COPD suggests that severe patients have a greater response to circulating proinflammatory cytokines than patients with mild COPD or a weaker response to anti-inflammatory cytokines. Analysis of the inflammatory gene set with the greatest positive enrichment with $\text{TLCO}_{\% \text{pred}}$ (IL6/JAK/STAT3 signalling) showed that the strongest associations of individual genes with $\text{TLCO}_{\% \text{pred}}$ included inflammatory cytokine receptors (TNFRSF21, IL1R2, oncostatin M receptor (OSMR), TNSFR12A) and signal transducer/adaptor proteins (IRF1, signal transducing adaptor molecule 2 (STAM2), STAT1 and STAT2) (online supplemental figure S2 and table S17). Further analysis showed that the IL31 receptor (IL31RA), a coreceptor with OSMR, also associated with $\text{TLCO}_{\% \text{pred}}$ but was not annotated in the IL6/JAK/STAT gene set (figure 2). Consistent with a role for inflammatory signalling in muscle wasting, IL31RA expression and STAM (a protein

involved in cytokine receptor signalling) were inversely proportional to FFMI (online supplemental figure S2).

It is possible that increasing disease severity promotes the expression of inflammatory gene sets or that differences in gene expression cause individuals to progress through disease at different rates. As patients with severe disease must have had mild disease at some point, those with severe disease should be older than those with mild disease for a given level of smoking. However, despite similar smoking histories, patients with mild disease were older than those with severe disease, suggesting that the mild disease

Table 1 Gene set enrichment for differentially expressed genes in the quadriceps of patients with severe and those with mild COPD

Hallmark gene set	NES	FDR q-val
Positive enrichment		
EMT	2.28	<0.001
TNFA signalling via NFkB	1.81	0.007
Heme metabolism	1.78	0.007
UV response down	1.72	0.008
Apical junction	1.64	0.016
Angiogenesis	1.61	0.021
Negative enrichment		
Fatty acid metabolism	−2.40	<0.001
Oxidative phosphorylation	−2.08	0.002
Peroxisome	−1.72	0.035

Differential gene expression was determined using LIMMA (severe–mild) and used to rank genes. The ranked genes were then analysed by GSEA using the Hallmark gene sets. COPD, Chronic Obstructive Pulmonary disease; EMT, epithelial mesenchymal transition; FDR, false discovery rate; GSEA, Gene Set Enrichment Analysis; LIMMA, Linear Models for Microarray Data; NES, Normalised Enrichment Score; UV, Ultra-Violet.

Table 2 Gene set enrichment for genes expressed in the quadriceps correlating with circulating IL1B and IL10 in COPD

Mild COPD			Severe COPD		
Hallmark gene set	NES	FDR	Hallmark gene set	NES	FDR
Positive enrichment with IL1B					
EMT	1.72	0.029	EMT	3.14	<0.001
Interferon alpha response	1.68	0.026	Allograft rejection	3.06	<0.001
			Interferon gamma response	2.84	<0.001
			IL6 JAK STAT3 Signalling	2.70	<0.001
			TNFA signalling via NFkB	2.67	<0.001
			Inflammatory response	2.57	<0.001
			KRAS signalling up	2.50	<0.001
			Complement	2.47	<0.001
			Apoptosis	2.38	<0.001
			Interferon alpha response	2.37	<0.001
Negative enrichment with IL1b					
MTORC1 signalling	−1.94	0.004	Nothing		
Myc targets v1	−1.90	0.002			
Oxidative phosphorylation	−1.90	0.001			
Protein secretion	−1.76	0.005			
E2F targets	−1.75	0.005			
Unfolded protein response	−1.58	0.020			
Mitotic spindle	−1.51	0.033			
Myc targets v2	−1.50	0.032			
Positive enrichment with IL10					
Nothing			EMT	2.34	<0.001
			TNFA signalling via NFkB	2.30	<0.001
			IL6 JAK STAT3 signalling	2.20	<0.001
			Interferon gamma response	2.07	<0.001
			MTORC1 signalling	2.06	<0.001
			Myc targets v1	1.99	0.001
			Apoptosis	1.89	0.001
			Interferon alpha response	1.87	0.001
			Protein secretion	1.86	0.002
			Myc targets v2	1.85	0.001
Negative enrichment with IL10					
E2F targets	−2.22	<0.001	Oxidative phosphorylation	−2.51	<0.001
EMT	−2.20	<0.001	Fatty acid metabolism	−2.35	<0.001
Unfolded protein response	−2.09	<0.001	Bile acid metabolism	−1.98	0.000
TNFA signalling via NFkB	−2.08	<0.001	Wnt beta catenin signalling	−1.76	0.003
Interferon alpha response	−2.08	<0.001	Adipogenesis	−1.72	0.003
Mitotic spindle	−2.06	<0.001	Peroxisome	−1.46	0.037
Interferon gamma response	−2.05	<0.001			
Apoptosis	−2.04	<0.001			
G2M checkpoint	−1.92	<0.001			
Protein secretion	−1.91	<0.001			

Gene expression was correlated with IL1B or IL10 levels in circulation by robust biweight mid correlation and the genes ranked as described in online supplemental methods. The ranks were then analysed in GSEA.

COPD, Chronic Obstructive Pulmonary disease; EMT, epithelial mesenchymal transition; FDR, false discovery rate; GSEA, Gene Set Enrichment Analysis; NES, Normalised Enrichment Score.

group was enriched for patients more resistant to the initiation or progression of the disease (online supplemental tables S1 and S2).

As the transcription factor MYC promotes EMT²⁸ and MYC targets were also positively enriched in association with TL_{CO%pred}, we compared MYC expression with the rest of the transcriptome. Positively enriched gene sets included the EMT, MYC targets and the inflammatory gene sets for TNF-α signalling, IL2 and IL6 sig-

nalling as well as interferon signalling (online supplemental table S18). MYC expression was directly associated with IL31RA, OSMR expression as well as with MCP-1 and IL6 expression (online supplemental figure S3). We next examined published data sets for lung and blood from patients with COPD, where we could separate the patients into mild and severe disease. Differential gene expression analysis of lung biopsies (GSE69818) again showed enrich-

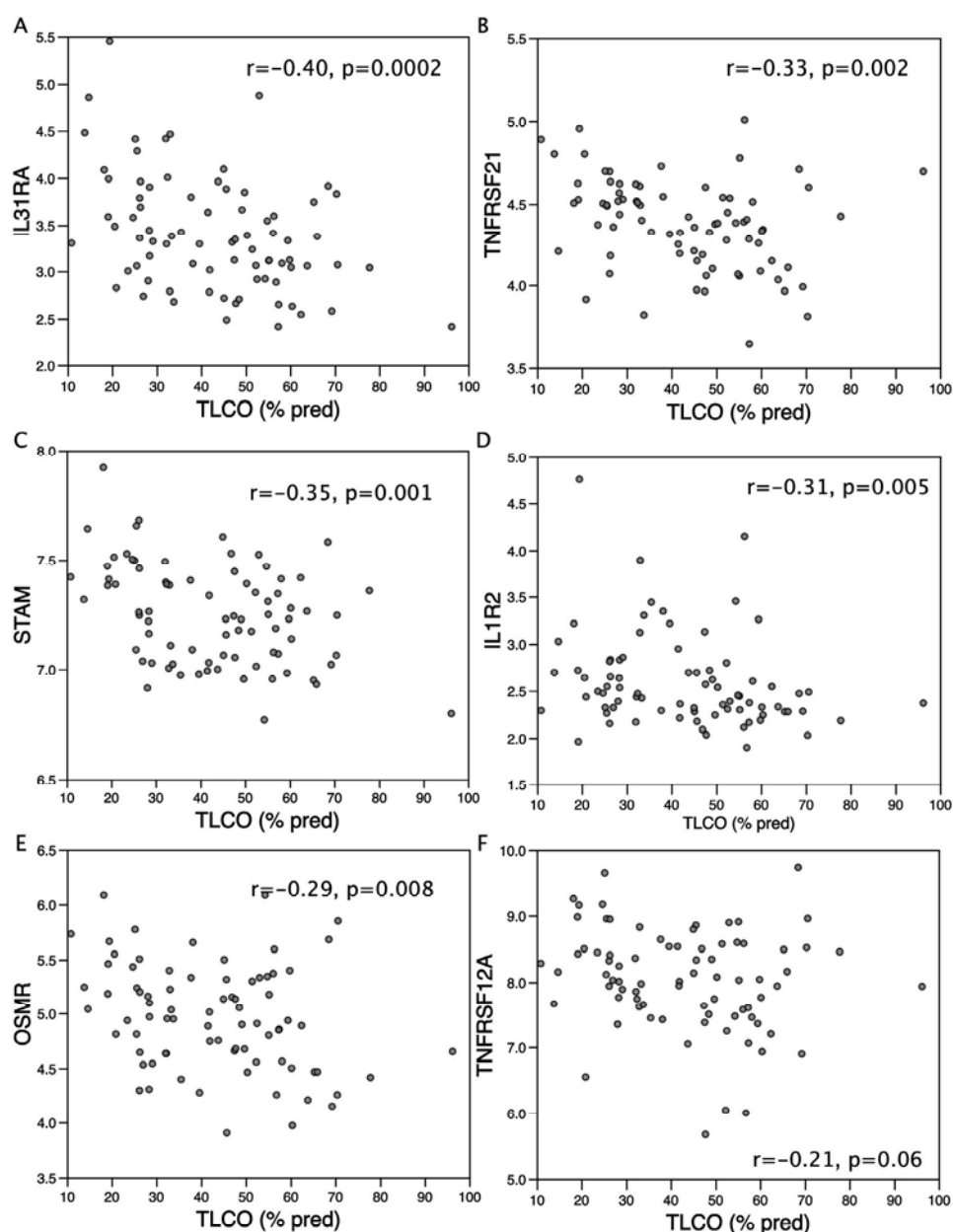


Figure 2 Expression of inflammatory receptors and signalling proteins in the muscle of patients with Chronic Obstructive Pulmonary disease (COPD). Expression (determined by microarray) of components of the inflammatory system identified as part of the IL6/JAK/STAT hallmark set and of IL31RA was compared with lung function (TLCO % predicted) in the patients. The expression of the IL31 receptor, IL31RA (A) TNF receptor superfamily member 21 TNFRSF21 (B), signal transducer adaptor molecule, STAM (C), IL1 receptor 2, IL1R2 (D), Oncostatin M receptor, OSMR (E), TNF receptor superfamily member 12A, TNFRSF12A (F).

ment for inflammatory gene expression gene sets, the EMT and MYC (table 3). This analysis was repeated using data only from those with emphysema, and the same results were obtained (online supplemental table S19). A similar differential gene expression analysis of RNA isolated from the blood of patients not receiving statins taken from GSE71220 also showed enrichment for inflammatory gene sets with the EMT also among the gene sets with an $FDR < 0.05$ (table 4). As these data sets did not include values for plasma cytokines, we were not able to reproduce that analysis in these additional sets. Consequently, gene expression profiles from three tissues (muscle, lung and blood) in severe COPD show relatively greater inflammatory responses and increased EMT compared with mild COPD.

DISCUSSION

In this study, we analysed differences in gene expression profiles in patients with moderate and severe COPD to elucidate the associated loss of muscle mass in these patients. We initially showed that patients with more severe disease had a lower FFMI and FMI than patients with mild disease despite similar levels of physical activity.

The lower FFMI and FMI in more severe disease is consistent with ECLIPSE, where patients with GOLD 4 COPD had a lower FFMI and BMI than those with GOLD 2 COPD.²⁹

Gene expression profiles from quadriceps muscle biopsies in mild and severe COPD showed positive enrichment for inflammatory gene subsets (including TNF- α and IL6-STAT signalling), EMT and negative enrichment for gene sets associated with mitochondrial functions (fatty acid metabolism and oxidative phosphorylation). While the quadriceps of severe patients had a greater inflammatory load than those of mild patients, there were no differences in circulating levels of inflammatory cytokines between the two groups. The lack of difference in cytokines is not consistent with some studies which have reported an association of inflammatory cytokines with FEV₁ % predicted,^{30,31} in particular IL6. However, in the ECLIPSE study of over 1700 patients with COPD, there was no association with IL6 or TNF- α with baseline FEV₁ and a positive association with IL8.³² Consistent with the variable findings from these data sets, the effect of actual levels of cytokines is likely to be small. Bradford et al estimate that IL-6 accounts for 4%–5% of the variability in FEV₁ % predicted; consequently, our

Table 3 Gene set enrichment for genes differentially expressed in the lung of patients with severe COPD compared with patients with mild COPD

Hallmark gene set	NES	FDR q-val
Positive enrichment		
Allograft rejection	2.43	<0.001
E2F targets	2.39	<0.001
MYC targets v2	2.27	0.001
IL6 JAK STA3 signalling	2.13	<0.001
Interferon gamma response	2.06	<0.001
G2M checkpoint	2.03	<0.001
Inflammatory response	2.01	<0.001
MTORC1 signalling	1.88	0.001
Complement	1.73	0.003
KRAS signalling up	1.70	0.005
Oxidative phosphorylation	1.69	0.005
Unfolded protein response	1.66	0.006
Glycolysis	1.64	0.008
Xenobiotic metabolism	1.59	0.011
EMT	1.59	0.012
Interferon alpha response	1.57	0.012
Coagulation	1.54	0.013
Reactive oxygen species pathway	1.47	0.025
Oestrogen response late	1.44	0.025
Spermatogenesis	1.41	0.029
IL2 STAT5 signalling	1.41	0.034
PI3K AKT mTOR signalling	1.39	0.034
MYC targets v1	1.34	0.045
Negative enrichment		
UV response down	-2.18	<0.001
TGF beta signalling	-2.05	<0.001
Myogenesis	-1.85	0.001
Hedgehog signalling	-1.78	0.003
Apical junction	-1.77	0.003
Wnt beta catenin signalling	-1.75	0.003
TNFA signalling via NFkB	-1.55	0.019
Oestrogen response early	-1.53	0.020
Apoptosis	-1.50	0.024
Protein secretion	-1.47	0.028
Notch signalling	-1.46	0.031

Differential gene expression was determined using LIMMA (severe–mild) and used to rank genes. The ranked genes were then analysed by GSEA using the Hallmark gene sets.
COPD, Chronic Obstructive Pulmonary disease; EMT, epithelial mesenchymal transition; FDR, false discovery rate; GSEA, Gene Set Enrichment Analysis; LIMMA, Linear Models for Microarray Data; NES, Normalised Enrichment Score.

study is underpowered to find such differences. However, our data add to the role of cytokines like IL-6 and IL-1b in COPD pathogenesis by suggesting that some individuals have a larger response to the same level of cytokine than others. This variability in response will reduce the observed association of any individual cytokine with disease progression. In our data set, the inclusion of controls produced negative associations of cytokines with FEV₁ % predicted indicative of systemic inflammation (online supplemental table S3), but these were not present when the controls were excluded.

In severe patients, both proinflammatory and anti-inflammatory cytokines were positively associated with inflammatory response gene sets, whereas in mild patients, anti-inflammatory cytokines

Table 4 Gene set enrichment for genes differentially expressed in the blood of severe patients with COPD compared with patients with mild COPD

Hallmark gene set	NES	FDR q-val
Positive enrichment		
TNFA signalling via NFkB	2.16	<0.001
Inflammatory response	2.02	<0.001
IL6 JAK STAT3 signalling	1.92	0.001
Hypoxia	1.84	0.003
Cholesterol homeostasis	1.76	0.007
P53 pathway	1.74	0.007
Interferon alpha response	1.61	0.017
Wnt beta catenin signalling	1.61	0.016
Angiogenesis	1.60	0.016
Complement	1.59	0.016
Apical junction	1.58	0.017
Myogenesis	1.56	0.020
Coagulation	1.55	0.021
Oestrogen response early	1.53	0.022
EMT	1.53	0.021
Reactive oxygen species pathway	1.47	0.032
Notch signalling	1.46	0.033
Glycolysis	1.45	0.032
Xenobiotic metabolism	1.44	0.033
KRAS signalling up	1.43	0.035
Hedgehog signalling	1.41	0.040
Negative enrichment		
MYC targets v1	-2.89	<0.001
E2F targets	-2.38	<0.001
G2M checkpoint	-2.04	<0.001
MYC targets v2	-1.98	<0.001
Unfolded protein response	-1.81	<0.001
MTORC1 signalling	-1.51	0.015

Differential gene expression was determined using LIMMA (severe–mild) and used to rank genes. The ranked genes were then analysed by GSEA using the Hallmark gene sets.
COPD, Chronic Obstructive Pulmonary disease; EMT, epithelial mesenchymal transition; FDR, false discovery rate; GSEA, Gene Set Enrichment Analysis; LIMMA, Linear Models for Microarray Data; NES, Normalised Enrichment Score.

were negatively associated with the same gene sets. These data imply either that patients with severe COPD are more sensitive to proinflammatory cytokines than those with mild COPD or that they are less sensitive to anti-inflammatory cytokines. Comparison of gene expression profiles in blood and lung samples implied that this difference in inflammatory sensitivity was not limited to skeletal muscle. This greater responsiveness of patients with severe COPD to inflammatory stimuli appears to lead to more rapid loss of muscle.

Consistent with greater sensitivity to proinflammatory signals, patients with more severe disease had higher expression of inflammatory cytokine receptors and signal transducers, and expression of IL31RA and STAM not only contributed to inflammatory gene sets associated with lung function, but also associated negatively with FFMI.

In muscle and lung tissue, in addition to the inflammatory gene and EMT gene sets, gene sets associated with the transcription factor MYC were also enriched in those with more severe disease. MYC promotes both the EMT and inflammation, and in muscle, we found that MYC expression was proportional to MCP-1, IL6, IL31RA and OSMR expression. In the blood, the associations with MYC gene sets were in the opposite direction with higher expres-

sion in those with mild COPD. Our analysis showing increased inflammatory gene expression from IL6/STAT/JAK and TNF- α signalling pathways and reduced expression of MYC gene sets in the blood of patients with severe COPD is consistent with a study developing a blood transcriptional risk score for decline in lung function and susceptibility to COPD.³³ The mechanisms causing differences in enrichment for the MYC gene sets in blood and muscle/lung are unclear, but it seems likely that they reflect differences in the role of MYC in the tissues in response to disease.

The increased expression of EMT genes is likely to reflect a fibrotic response that is part of an overall 'repair' response of the tissue to injury. Our previous study showed that patients with COPD have a significant increase in genes associated with the extracellular matrix and repair, including periostin (POSTN), a gene that contributes to the EMT gene set we identify here.²¹ The coagulation gene set was also enriched. This data set may also reflect a role in repair/fibrosis, as has been suggested in fibrosis in chronic inflammatory conditions.^{34,35}

We cannot determine whether patients become more sensitive to inflammation as disease progresses or whether those that are intrinsically more sensitive progress through the disease more rapidly. However, several lines of evidence point towards the latter. First, patients with severe COPD must have had mild disease at some point, suggesting that they should be older than those with mild COPD. In our cohort, the reverse was true despite similar levels of smoking. Furthermore, the rate of change in FEV₁ in patients with COPD has been shown to be very variable.³² In the cohort analysed for lung cell gene expression, neither age nor smoking status was reported, and in the cohort analysed for blood cell gene expression, age did not differ between those with mild and those with severe COPD, but there were no data relating to smoking history. In the ECLIPSE study, there was no difference in the ages of individuals with more severe COPD than those with mild COPD.²⁹ Second, the observation is consistent across three tissue types, suggesting that this feature is not unique to muscle. Finally, polymorphisms in inflammatory genes have been associated with the development of COPD. Indeed, ingenuity pathway analysis of data from the GWAS meta-analysis identified not only inflammatory gene sets (eg, STAT3 signalling, IL8 signalling, IL15 production) but also those associated with EMT, wound healing and MYC mediated apoptosis signalling.¹²

Our data have most relevance to muscle loss and suggest that inflammation is a key component of muscle loss in COPD. It is interesting that despite markedly lower activity levels, patients with mild COPD had similar FFMI to controls. Indeed, the tendency of these patients to have a higher FMI suggests that inactivity contributes to adiposity. In patients with severe COPD, both FFMI and FMI are reduced compared with patients with mild COPD despite similar levels of activity, indicating that these patients are sarcopenic.

The greatest association with inflammatory response gene sets in the muscle was shown by IL1 β , suggesting that it is a major driver of the inflammatory response in severe COPD. However, the increase in IL1 β compared with controls is small, making it possible that IL1 β is just correlating with other more important cytokines. Alternatively, it is possible that the response observed in people with severe disease is the combined response to all the proinflammatory cytokines present. Consistent with this observation, several studies have also linked individual cytokines or combinations with muscle mass in studies of patients with chronic disease, whereas other studies have failed to find such an association.^{36–39}

The strongest association of disease severity with receptor expression was with IL31RA and its coreceptor OSMR, raising the possibility that IL31 and/or oncostatin M (OSM) are important regulators of muscle wasting. Unfortunately, we were unable to quantify IL31 or OSM in the blood of these patients as we no longer have the appropriate samples. IL31RA is expressed in a restricted range of tissues including peripheral blood lymphocytes and skeletal muscle (<https://www.proteinatlas.org/ENSG00000164509-IL31RA/tissue>). It is, therefore, possible that IL31 promotes muscle

atrophy either directly or through the recruitment of lymphocytes that subsequently promote atrophy through other pathways. However, to our knowledge, the contribution of IL31 to muscle wasting has yet to be tested. By contrast, OSM promoted muscle atrophy in vitro and in murine models⁴⁰ and may contribute to muscle wasting in cancer.⁴¹ Furthermore, increased OSM was detected in patients with COPD and in a recent study of inflammatory markers in patients with COPD, OSM-associated pathways were implicated in the pathology of COPD, although OSM itself was not quantified.⁴² The role of these proteins in COPD-associated muscle wasting, therefore, remains to be determined.

As indicated above, the patients with more severe disease had lower expression of genes associated with mitochondrial function (oxidative phosphorylation and fatty acid metabolism). Furthermore, a negative association of these mitochondrial genes with several of the cytokines was present within the severe disease group (eg, with IL2, IL8, interferon- γ gamma and TNF- α , online supplemental tables S5 and S9–S11). Mitochondrial dysfunction is associated with muscle loss in a range of conditions including COPD.^{43,44} The associated reduction in energy provision may well contribute to wasting and will also contribute to the reduced exercise capacity of the patients. Our previous studies have shown that quadriceps expression of miRNAs that promote mitochondrial ribosome stress leading to mitochondrial dysfunction is inversely proportional to lung function in these patients providing a possible mechanism.^{45,46} Whether these miRNAs are regulated by inflammatory cytokines remains to be established, but the data provided in this paper suggest that identifying individual associations of any individual cytokine would be complicated by the sensitivity of individuals to the stimulus.

Several anti-inflammatory agents have been trialled in COPD with limited success.^{47,48} Targets included IL-1 β , which we show here is the agent with the strongest association with muscle inflammatory gene signalling. Negative results of these studies may indicate the limited importance of inflammation in the progression of COPD, contrary to our suggestion. However, there are several other potential reasons for the apparent failure of this approach. The first is kinetics: the trials may simply not have been long enough to reach their primary end points. The second is whether inhibiting inflammation can reverse damage already done, as improvement in lung function is one end point that has been tested. Stabilising function may be the best that can be achieved with this approach. Third, in terms of muscle mass, the studies done to date have focused on lung function rather than muscle mass, making it possible that antagonism of IL-1 signalling may improve muscle mass but not affect lung function. Finally, the data from this paper raise the possibility that only a subset of patients would respond significantly to anti-IL1 therapy so that preselection of responsive patients might show beneficial effects of such therapy.

Limitations of the study

This study is cross-sectional so does not demonstrate causative effects of the changes in gene expression and the association with FFMI. To further understand this process, analysis of the muscle inflammatory profile in younger individuals with early-stage COPD followed by a longitudinal assessment of their disease progression and muscle atrophy would provide the next step. It would then be possible to determine the effect of inhibiting inflammation in those with the greatest sensitivity to inflammation. Furthermore, FFMI is a surrogate for muscle mass, and so the data should be interpreted with caution. However, for a study of muscle gene expression in disease, the cohorts that we have examined are comparatively large. We have focused on gene expression in patients alone, comparing mild and severe COPD, to reduce the effects of activity that occur if controls are used as the comparator. This analysis, therefore, limits the generalisability of our findings. We did not examine the associations of gene expression with physical performance in this study. Our analysis of the data from lung and blood samples is also limited by the availability of data from those studies. We cannot determine whether there were differences in cytokine levels between mild and

severe patients in these groups, nor compare cytokine levels with gene expression profiles, as we were able to do in the skeletal muscle study. However, the overall expression profiles concur with our general findings of greater sensitivity of patients with severe disease to inflammatory signalling. This interpretation is further supported by the observation that TNF- α production by blood cells in response to bacterial lipopolysaccharide was greater in patients with severe compared with mild COPD.⁴⁹

Our demonstration of associations of circulating cytokines with the levels of target transcription pathways in the muscle of patients with severe disease is suggestive of a direct effect of these cytokines on muscle phenotype. That we see similar transcription profiles in other tissues is consistent with this suggestion, as are studies of the effects of exogenous cytokines on muscle loss in animals. These data also support the idea that there is communication between the diseased lung and the muscle to promote the use of muscle as a resource for repair and the immune response,⁵⁰ or that there is inflammation spill-over from the lung to muscle contributing to muscle loss, though our studies suggest that this is modified by factors that control the sensitivity of individuals to such stimuli. However, we did not measure tissue cytokines which are also likely to contribute to the overall loss of muscle.

The advantage of studies based on transcriptomics is the breadth of analytes that can be measured so that an overall picture can be generated and the consequent identification of potential targets and pathways. However, a significant limitation is that RNA levels do not always reflect the levels of proteins in the tissue. The relative contribution of tissue-derived inflammatory cytokines is, therefore, difficult to determine. Unfortunately, we no longer have the samples available to identify differences in protein levels from these patients so further studies will be required to determine whether the levels of key proteins in the identified pathways differ.

CONCLUSIONS

Our study shows that patients with COPD with more advanced disease have greater inflammatory gene expression in their quadriceps muscles despite similar levels of circulating inflammatory cytokines. This appears to be due to lower sensitivity to anti-inflammatory cytokines and/or higher sensitivity to proinflammatory cytokines in patients with more severe disease. Our data suggest that this occurs because of higher expression of receptors and signalling components of the proinflammatory pathways. These differences may be intrinsic to the individual rather than having developed during the disease process because the severe COPD cohort was not older than the mild group. This further suggests that targeting inflammation in selected patients may be an appropriate strategy to prevent muscle atrophy and progressive COPD. Confirmation of this observation will require analysis in a longitudinal cohort of patients.

Contributors PRK conceived the concept, carried out the data analysis and wrote the first draft of the paper. AS collected the samples and carried out the original experiments on the muscle samples under the supervision of MIP. MIP, AS and MG critically reviewed and appraised the manuscript. PRK is the guarantor of the publication.

Funding The original sample collection was funded by a Wellcome Trust Clinical Research Training Fellowship (WT 079686/Z/06/Z).

Disclaimer The views expressed in this publication are those of the authors and not necessarily those of the funding organisation.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Patients provided written informed consent, and the studies were approved by the relevant Research Ethics Committee (06/Q0404/35 and 06/Q0410/54).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The array data sets containing the expression data are freely available on the NCBI gene expression omnibus (<https://www.ncbi.nlm.nih.gov/geo/>). Data relating to physiology and circulating cytokine levels are available on reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed.

Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: <https://creativecommons.org/licenses/by/4.0/>.

ORCID iDs

Paul R Kemp <http://orcid.org/0000-0001-8975-7293>

Mark Griffiths <http://orcid.org/0000-0002-1615-1896>

Michael I Polkey <http://orcid.org/0000-0003-1243-8571>

Amanda Sathyapala <http://orcid.org/0000-0001-7887-4494>

REFERENCES

- Wilkinson DJ, Piasecki M, Atherton PJ. The age-related loss of skeletal muscle mass and function: Measurement and physiology of muscle fibre atrophy and muscle fibre loss in humans. *Ageing Res Rev* 2018;47:123–32.
- Tuttle CSL, Thang LAN, Maier AB. Markers of inflammation and their association with muscle strength and mass: A systematic review and meta-analysis. *Ageing Res Rev* 2020;64:101185.
- Friman G, Wesslén L. Special feature for the Olympics: effects of exercise on the immune system: infections and exercise in high-performance athletes. *Immunol Cell Biol* 2000;78:510–22.
- Li J, Yi X, Yao Z, et al. TNF Receptor-Associated Factor 6 Mediates TNF α -Induced Skeletal Muscle Atrophy in Mice During Aging. *J Bone Miner Res* 2020;35:1535–48.
- Ma JF, Sanchez BJ, Hall DT, et al. STAT3 promotes IFN γ /TNF α -induced muscle wasting in an NF- κ B-dependent and IL-6-independent manner. *EMBO Mol Med* 2017;9:622–37.
- Bonaldo P, Sandri M. Cellular and molecular mechanisms of muscle atrophy. *Dis Model Mech* 2013;6:25–39.
- Barreiro E, Schols AMWJ, Polkey MI, et al. Cytokine profile in quadriceps muscles of patients with severe COPD. *Thorax* 2008;63:100–7.
- Montes de Oca M, Torres SH, De Sanctis J, et al. Skeletal muscle inflammation and nitric oxide in patients with COPD. *Eur Respir J* 2005;26:390–7.
- Man WD-C, Kemp P, Moxham J, et al. Skeletal muscle dysfunction in COPD: clinical and laboratory observations. *Clin Sci (Lond)* 2009;117:251–64.
- Dantzer R. Cytokine-induced sickness behavior: mechanisms and implications. *Ann N Y Acad Sci* 2001;933:222–34.
- Sharanya A, Ciano M, Withana S, et al. Sex differences in COPD-related quadriceps muscle dysfunction and fibre abnormalities. *Chron Respir Dis* 2019;16:1479973119843650.
- Shrine N, Izquierdo AG, Chen J, et al. Multi-ancestry genome-wide association analyses improve resolution of genes and pathways influencing lung function and chronic obstructive pulmonary disease risk. *Nat Genet* 2023;55:410–22.
- Jones G, Trajanoska K, Santanasto AJ, et al. Genome-wide meta-analysis of muscle weakness identifies 15 susceptibility loci in older men and women. *Nat Commun* 2021;12:654.
- Sun S, Shen Y, Feng J. Association of toll-like receptors polymorphisms with COPD risk in Chinese population. *Front Genet* 2022;13:955810.
- Budulac SE, Boezen HM, Hiemstra PS, et al. Toll-like receptor (TLR2 and TLR4) polymorphisms and chronic obstructive pulmonary disease. *PLoS One* 2012;7:e43124.
- Ding X, Lin Q, Zhao J, et al. Synonymous mutations in TLR2 and TLR9 genes decrease COPD susceptibility in the Chinese Han population. *Pulmonology* 2024;30:230–8.
- He J-Q, Foreman MG, Shumansky K, et al. Associations of IL6 polymorphisms with lung function decline and COPD. *Thorax* 2009;64:698–704.
- Ahmadi A, Ghaedi H, Salimian J, et al. Association between chronic obstructive pulmonary disease and interleukins gene variants: A systematic review and meta-analysis. *Cytokine* 2019;117:65–71.
- Stemmler S, Arinir U, Klein W, et al. Association of interleukin-8 receptor alpha polymorphisms with chronic obstructive pulmonary disease and asthma. *Genes Immun* 2005;6:225–30.
- Donaldson A, Natanek SA, Lewis A, et al. Increased skeletal muscle-specific microRNA in the blood of patients with COPD. *Thorax* 2013;68:1140–9.
- Willis-Owen SAG, Thompson A, Kemp PR, et al. COPD is accompanied by co-ordinated transcriptional perturbation in the quadriceps affecting the mitochondria and extracellular matrix. *Sci Rep* 2018;8:12165.
- Faner R, Cruz T, Casserras T, et al. Network Analysis of Lung Transcriptomics Reveals a Distinct B-Cell Signature in Emphysema. *Am J Respir Crit Care Med* 2016;193:1242–53.
- Obeidat M, Fishbane N, Nie Y, et al. The Effect of Statins on Blood Gene Expression in COPD. *PLoS One* 2015;10:e0140022.
- Natanek SA, Gosker HR, Slot IGM, et al. Heterogeneity of quadriceps muscle phenotype in chronic obstructive pulmonary disease (COPD): implications for stratified medicine? *Muscle Nerve* 2013;48:488–97.
- Natanek SA, Gosker HR, Slot IGM, et al. Pathways associated with reduced quadriceps oxidative fibres and endurance in COPD. *Eur Respir J* 2013;41:1275–83.
- Natanek SA, Riddoch-Contreras J, Marsh GS, et al. MuRF-1 and atrogin-1 protein expression and quadriceps fiber size and muscle mass in stable patients with COPD. *COPD* 2013;10:618–24.
- Subramanian A, Tamayo P, Mootha VK, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci U S A* 2005;102:15545–50.
- Cho KB, Cho MK, Lee WY, et al. Overexpression of c-myc induces epithelial mesenchymal transition in mammary epithelial cells. *Cancer Lett* 2010;293:230–9.
- Agusti A, Calverley PMA, Celli B, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010;11:122.
- Bradford E, Jacobson S, Varasteh J, et al. The value of blood cytokines and chemokines in assessing COPD. *Respir Res* 2017;18:180.
- Huang H, Huang X, Zeng K, et al. Interleukin-6 is a Strong Predictor of the Frequency of COPD Exacerbation Within 1 Year. *Int J Chron Obstruct Pulmon Dis* 2021;16:2945–51.
- Vestbo J, Edwards LD, Scanlon PD, et al. Changes in forced expiratory volume in 1 second over time in COPD. *N Engl J Med* 2011;365:1184–92.
- Moll M, Boueiz A, Ghosh AJ, et al. Development of a Blood-based Transcriptional Risk Score for Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2022;205:161–70.
- Pant A, Kopec AK, Luyendyk JP. Role of the blood coagulation cascade in hepatic fibrosis. *Am J Physiol Gastrointest Liver Physiol* 2018;315:G171–6.
- Chambers RC, Scotton CJ. Coagulation cascade proteinases in lung injury and fibrosis. *Proc Am Thorac Soc* 2012;9:96–101.
- Eid AA, Ionescu AA, Nixon LS, et al. Inflammatory response and body composition in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:1414–8.
- Karadag F, Karul AB, Cildag O, et al. Determinants of BMI in patients with COPD. *Respirology* 2004;9:70–5.
- Liu SF, Chin CH, Wang CC, et al. Correlation between serum biomarkers and BODE index in patients with stable COPD. *Respirology* 2009;14:999–1004.
- Webster JM, Kempen LJAP, Hardy RS, et al. Inflammation and Skeletal Muscle Wasting During Cachexia. *Front Physiol* 2020;11:597675.
- Jengelly DHA, Wang M, Narasimhan A, et al. Exogenous Oncostatin M induces Cardiac Dysfunction, Musculoskeletal Atrophy, and Fibrosis. *Cytokine* 2022;159.
- Bilgic SN, Domaniuk A, Toledo B, et al. EDA2R-NIK signalling promotes muscle atrophy linked to cancer cachexia. *Nature New Biol* 2023;617:827–34.
- Vanfleteren LEGW, Weidner J, Franssen FME, et al. Biomarker-based clustering of patients with chronic obstructive pulmonary disease. *ERJ Open Res* 2023;9:00301-2022.
- Ji LL, Yeo D. Mitochondrial dysregulation and muscle disuse atrophy. *F1000Res* 2019;8:F1000 Faculty Rev-1621.
- Henrot P, Dupin I, Schilfarth P, et al. Main Pathogenic Mechanisms and Recent Advances in COPD Peripheral Skeletal Muscle Wasting. *Int J Mol Sci* 2023;24:6454.
- Garros RF, Paul R, Connolly M, et al. MicroRNA-542 Promotes Mitochondrial Dysfunction and SMAD Activity and Is Elevated in Intensive Care Unit-acquired Weakness. *Am J Respir Crit Care Med* 2017;196:1422–33.
- Farre-Garros R, Lee JY, Natanek SA, et al. Quadriceps miR-542-3p and -5p are elevated in COPD and reduce function by inhibiting ribosomal and protein synthesis. *J Appl Physiol (1985)* 2019;126:1514–24.
- Osei ET, Brandsma CA, Timens W, et al. Current perspectives on the role of interleukin-1 signalling in the pathogenesis of asthma and COPD. *Eur Respir J* 2020;55:190563.
- Cazzola M, Hanania NA, Page CP, et al. Novel Anti-Inflammatory Approaches to COPD. *Int J Chron Obstruct Pulmon Dis* 2023;18:1333–52.
- von Haehling S, Hopkinson NS, Polkey MI, et al. Elevated TNF α production in whole blood in patients with severe COPD: the potential link to disease severity. *Wien Klin Wochenschr* 2009;121:303–8.
- Kemp PR, Griffiths M, Polkey MI. Muscle wasting in the presence of disease, why is it so variable? *Biol Rev Camb Philos Soc* 2019;94:1038–55.

Pneumonia grave adquirida na comunidade (sCAP): avanços no tratamento e direções futuras

Ignacio Martin-Loeches,¹ Luis Felipe Reyes,² Alejandro Rodriguez³

¹University of Dublin Trinity College, Dublin, Ireland

²Universidad de La Sabana, Chia, Colombia

³Joan XXIII University Hospital, Tarragona, Spain

Correspondence to

Professor Ignacio Martin-Loeches;
drmartinloeches@gmail.com

Received 22 November 2024

Accepted 3 April 2025

Published Online First 13 May 2025

RESUMO

A pneumonia grave adquirida na comunidade (sCAP) é um grande desafio global de saúde, com alta morbidade e mortalidade, especialmente entre doentes que necessitam de cuidados intensivos. Apesar dos avanços nas terapias antimicrobianas e nos cuidados de suporte, a sCAP continua sendo uma ameaça significativa, particularmente para aqueles que precisam de ventilação mecânica invasiva ou suporte com vasopressores.

Progressos recentes em diagnóstico, terapêutica e estratégias de gestão oferecem esperança para melhores desfechos. O tratamento específico para o patógeno tornou-se central no cuidado da sCAP, com diagnósticos moleculares aprimorando a precisão na detecção de agentes infecciosos e permitindo terapias antimicrobianas personalizadas. Essas ferramentas ajudam a combater a resistência antimicrobiana ao reduzir o uso desnecessário de antibióticos de amplo espectro.

As respostas imunológicas do hospedeiro na sCAP variam amplamente e impactam significativamente os resultados. Alguns doentes enfrentam uma carga patogênica avassaladora, enquanto outros apresentam respostas imunes excessivas, como a síndrome do desconforto respiratório agudo. Essa distinção é essencial para orientar terapias imunomoduladoras, já que a imunossupressão pode beneficiar estados hiper-inflamatórios, mas prejudicar aqueles dominados pela infecção. Os corticosteroides, embora controversos, mostram benefícios potenciais em populações específicas, mas trazem riscos como infecções secundárias e hiperglicemia, exigindo uma abordagem cuidadosa.

Estratégias de suporte respiratório não invasivo, como o oxigênio nasal de alto fluxo, transformaram o cuidado ao melhorar a oxigenação e reduzir a necessidade de ventilação invasiva. No entanto, a sua eficácia depende do momento da aplicação, da tolerância do doente e da gravidade da doença, exigindo monitoramento rigoroso. As disparidades globais na gestão da sCAP, especialmente em países de baixa e média renda, destacam a necessidade de guidelines específicas para cada região e soluções escaláveis. O acesso limitado a diagnósticos avançados e recursos de cuidados intensivos agrava os resultados ruins, ressaltando a importância de investimentos em diagnósticos acessíveis, controle de infecções e treinamento multidisciplinar.

Tecnologias emergentes, como inteligência artificial e imagem avançada, prometem revolucionar a gestão da sCAP ao permitir medicina de precisão e insights em tempo real sobre a gravidade da doença. Uma abordagem holística e multidisciplinar que integre esses avanços é essencial para melhorar os resultados e promover cuidados personalizados para essa condição potencialmente fatal.

INTRODUCTION

Severe community-acquired pneumonia (sCAP) is a global healthcare challenge, characterised by its high mortality risk and complex management. The American Thoracic Society and Infectious Diseases Society Association (ATS/IDSA) criteria for sCAP highlight key markers of disease severity, including the need for invasive mechanical ventilation (iMV) and vasopressor support in septic

shock.¹ Patients meeting these criteria face mortality rates exceeding 40%, underscoring the critical nature of the condition and the urgency for effective interventions.² Despite advancements in supportive care, new antibiotics and pharmacological therapies, mortality rates for sCAP have remained persistently high, particularly in those requiring iMV and vasopressors.³ This reflects the need for novel strategies to address this pressing healthcare challenge. In addition to major criteria, the ATS/IDSA outlines other minor criteria that capture the severity of CAP and highlight the potential need for Intensive Care Unit (ICU) admission.¹ Radiological findings, including bilateral infiltrates or multilobar opacities resembling acute respiratory distress syndrome (ARDS), are critical indicators of progressive and fatal severe lung injury.⁴ These findings reflect profound inflammatory responses and systemic complications, which often lead to severe hypoxaemia and multiorgan dysfunction, complicating the clinical course of this disease.⁵ Differential diagnosis is paramount for adequate recognition and management (box 1).

Differentiating sCAP from non-severe forms is essential for tailoring treatment approaches. Non-severe CAP is often managed in outpatient or general ward settings, while sCAP may require specialised ICU care due to its potentially life-threatening clinical features. However, ICU admission decisions should also consider site-specific factors, such as available resources, local care capacities and individual patient circumstances.⁶ Box 2 proposes essential items integrating sCAP and sepsis guidelines to identify patients that need to be managed in ICU settings. However, defining sCAP based solely on ICU admission introduces limitations, as resource availability varies globally.⁷ Some sCAP cases are handled outside ICUs with appropriate monitoring in resource-rich environments, but such cases are anecdotal.⁸ Thus, ICU settings remain the primary and ideal context for managing most sCAP cases.⁹

This manuscript examines the multifaceted nature of sCAP, focusing on pathogen-specific treatments, diagnostic advancements and updated clinical guidelines. It aims to optimise care strategies, particularly for high-risk groups while addressing global disparities in sCAP management in low-income and middle-income countries (LMICs).

METHODS

This review synthesises the latest evidence on sCAP to comprehensively understand its management, including updated guidelines, diagnostic innovations and therapeutic strategies. The literature review was conducted using an extensive search of PubMed, Embase and Web of Science databases, employing Medical Subject Headings (MeSH) terms and free-text search terms such as “severe CAP,” “community-acquired pneumonia,” “critically ill patients,” “biomarkers,” “molecular diagnostics,” “antimicrobial resistance” and “artificial intelligence in pneumonia.”



© Author(s) (or their employer(s)) 2025. Re-use permitted under CC BY. Published by BMJ.

To cite: Martin-Loeches I, Reyes LF, Rodriguez A. Thorax 2025;80:565–575.

Box 1 Differential diagnosis of lung consolidation in severe community-acquired pneumonia

- ⇒ Pneumonia
 - ⇒ Bacteria Pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Legionella* species.
 - ⇒ Viral pathogens: Influenza, SARS-CoV-2, respiratory syncytial virus.
 - ⇒ Fungal Pathogens: *Aspergillus*, *Histoplasma*, *Coccidioides* (more common in immunocompromised patients).
- ⇒ Pulmonary embolism
 - ⇒ Presentation: Sudden-onset chest pain, dyspnoea and haemoptysis; imaging may show wedge-shaped consolidation.
- ⇒ Congestive heart failure
 - ⇒ Presentation: Bilateral lung involvement, peripheral oedema and jugular venous distention.
- ⇒ Malignancy (primary lung cancer or metastasis)
 - ⇒ Presentation: Persistent cough, haemoptysis, weight loss; may present with unilateral or nodular opacities on imaging.
- ⇒ Interstitial lung disease (ILD)
 - ⇒ Types: Idiopathic pulmonary fibrosis, sarcoidosis, connective tissue disease-associated ILD.
 - ⇒ Presentation: Progressive dyspnoea, dry cough, imaging shows diffuse ground-glass or honeycomb patterns.
- ⇒ Aspiration pneumonitis
 - ⇒ Cause: Chemical injury from inhaled gastric contents.
 - ⇒ Presentation: Localised consolidation typically in dependent lung zones (eg, right lower lobe).
- ⇒ Organising pneumonia
 - ⇒ Cause: Non-infectious inflammatory condition, often idiopathic but may be secondary to infection, connective tissue disease or drug toxicity.
 - ⇒ Presentation: Subacute cough, fever, malaise; imaging shows patchy, migratory consolidation.
- ⇒ Pulmonary haemorrhage
 - ⇒ Cause: Bleeding into the alveoli due to vasculitis, connective tissue disease or trauma.
 - ⇒ Presentation: Haemoptysis, anaemia, dyspnoea; imaging shows diffuse, bilateral consolidations that may change with repeated imaging.
- ⇒ Eosinophilic pneumonia
 - ⇒ Cause: Eosinophil accumulation in the lung, often related to drug reaction, parasitic infection or allergic response.
 - ⇒ Presentation: Fever, night sweats, cough, dyspnoea; imaging shows peripheral lung consolidations, often migratory.
- ⇒ Pulmonary alveolar proteinosis
 - ⇒ Cause: Accumulation of surfactant in alveoli due to impaired macrophage clearance.
 - ⇒ Presentation: Progressive dyspnoea and cough; imaging shows 'crazy paving' pattern with ground-glass opacities and septal thickening.
- ⇒ Radiation pneumonitis
 - ⇒ Cause: Lung tissue damage following radiation therapy, typically in patients treated for thoracic malignancies.
 - ⇒ Presentation: Cough, dyspnoea, fever; imaging shows consolidation in the radiation field area.
- ⇒ Drug-induced lung disease
 - ⇒ Cause: Certain drugs (eg, amiodarone, methotrexate, chemotherapy) can lead to lung inflammation and consolidation.
 - ⇒ Presentation: Cough, dyspnoea, potentially with fever; imaging shows patterns varying by drug type, often bilateral.

Filters were applied to focus on studies involving adult populations with sCAP requiring ICU-level care. Articles were limited to those published in English to ensure accessibility and relevance.

The date range for the literature search spanned from 2000 to 2024, ensuring the inclusion of the most up-to-date research and clinical guidelines.

In addition to database searches, reference lists of critical articles and relevant textbooks were reviewed to ensure comprehensive topic coverage. Studies were included if they provided data on sCAP management, including pathogen profiles, treatment innovations, immune response mechanisms or diagnostic advancements. Exclusion criteria encompassed studies on paediatric populations or those patients in non-ICU care settings and immunosuppressed.

This review was collaboratively authored by specialists in critical care, pulmonology and infectious diseases. Each contributor provided expertise to specific sections, ensuring a comprehensive and multidisciplinary synthesis of the available evidence. Although the manuscript does not follow a formal Delphi process or expert panel consensus, it is a robust aggregation of insights to advance understanding and guide future research in managing patients with sCAP.

PATHOGEN PROFILES AND RESISTANCE TRENDS

The management of sCAP is closely linked to the pathogen profile, which varies across geographical and demographic settings.^{10–12} In recent years, shifts have been seen in pathogen prevalence, with a significant rise in antibiotic-resistant strains complicating treatment and increasing mortality risk.¹³ *Streptococcus pneumoniae* remains the leading bacterial cause of sCAP,¹⁴ particularly among high-risk groups such as older adults or vulnerable populations, accounting for up to 50% of identified pathogens.^{15 16 17}

Methicillin-resistant *S. aureus* has been an emerging concern in healthcare-associated sCAP in some world regions, often requiring potent antibiotics like vancomycin or linezolid.¹⁸ These agents, however, carry risks such as toxicity, higher costs and the potential for further resistance. The rise in multidrug resistance (MDR) underscores the need for timely and precise diagnostic strategies to optimise treatment outcomes and reduce mortality rates.¹⁹

Gram-negative organisms, such as *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, are increasingly implicated in sCAP, particularly those with recurrent episodes or multiorgan failure presentation.²⁰ The prevalence of these MDR organisms (MDROs) highlights the urgent need for early identification and tailored therapeutic strategies to improve outcomes.²¹

Seasonal influenza significantly contributes to sCAP severity, often predisposing patients to coinfection or secondary bacterial infections, particularly *S. pneumoniae* and *S. aureus*.^{22–24} In ICU settings, influenza-associated pneumonia has also been linked to an increased risk of invasive fungal infections, such as invasive pulmonary *aspergillosis*, which complicates the clinical course and worsens outcomes. The role of *Aspergillus* in sCAP remains a subject of ongoing debate, and we acknowledge that the current literature does not firmly establish its significance as a common aetiological agent. While detection of *Aspergillus* by PCR or other molecular methods has shown promise in improving diagnostic sensitivity, distinguishing between colonisation, contamination or true infection remains challenging. Furthermore, large aetiological studies on SCAP have not identified *Aspergillus* as a frequent pathogen. Future research should focus on clarifying the diagnostic and therapeutic implications of *Aspergillus* detection in SCAP to guide evidence-based recommendations.^{25 26}

Overusing corticosteroids, often employed to manage inflammatory complications in sCAP, can exacerbate the risk of fungal infections, especially in influenza-associated cases.²⁷ While corticosteroids have shown benefits in specific scenarios, such as refractory septic shock, their indiscriminate use can suppress immune responses and increase susceptibility to opportunistic infections. A careful, evidence-based approach to corticosteroid use is essential to mitigate these risks.²⁸

Box 2 Severity criteria for the need of Intensive Care Unit (ICU) admission (severe community-acquired

- ⇒ Invasive mechanical ventilation.
- ⇒ Vasopressor support for septic shock.
- ⇒ Arterial oxygen tension/fractional inspired oxygen (FiO₂) ratio <250.
- ⇒ Respiratory rate ≥30 breaths/min.
- ⇒ Oxygen saturation ≤88%.
- ⇒ FiO₂ requirement ≥0.5 by either mask or high-flow nasal oxygen.
- ⇒ Arterial carbon dioxide tension (from Arterial Blood Gas (ABG)) ≥50 mm Hg (if not chronic obstructive pulmonary disease).
- ⇒ pH (ABG) <7.3 and/or Lactate >2 mmol/L despite adequate fluid resuscitation.
- ⇒ ROX Index <22.
- ⇒ Hypotension (Systolic Blood Pressure (SBP) <90 mm Hg or MAP <60 mm Hg) despite adequate fluid resuscitation.
- ⇒ Heart rate (Tachycardia >125 bpm) or new-onset arrhythmia.
- ⇒ Confusion-Glasgow Coma Scale (GCS) Score ≤14.
- ⇒ Multiorgan failure indicators (high Sequential Organ Failure Assessment (SOFA) score) when not considering cardiovascular or respiratory.

Maintaining the integrity of the microbiome through targeted interventions remains a key consideration in reducing the incidence of secondary infections, particularly in high-risk patients. However, this approach must be balanced against evidence from strategies such as selective digestive decontamination (SDD) and nebulised antibiotics, which, while potentially reducing infection rates in specific settings, may also alter the microbiome in unintended ways. The use of SDD and nebulised antibiotics remains controversial, with conflicting recommendations and varying impacts on microbiome preservation, antimicrobial resistance and clinical outcomes.²⁹ Further research is needed to clarify their role and to better align microbiome-targeted interventions with optimal patient care strategies.

HOST IMMUNE RESPONSE IN SEVERE CAP

The host immune response in sCAP is a dynamic and intricate interplay between innate, adaptive and a new approach called trained immunity.³⁰ Together, these systems determine whether the host can effectively clear pathogens or if immune dysregulation exacerbates disease progression. Different pathogens elicit distinct immune mechanisms that profoundly influence clinical outcomes. Innate immunity is the first line of defence, rapidly detecting pathogens through pattern recognition receptors and activating inflammasomes and neutrophils to clear infections.³¹ While this response is critical for pathogen control, excessive activation can lead to tissue damage, such as necroptosis and pyroptosis, exacerbating respiratory failure.^{32–34} This ‘cytokine storm’ has been debated during the recent COVID-19 pandemic.^{35–37} Moreover, the interplay between innate and adaptive immunity becomes often dysregulated in the most severe clinical presentations.³⁸ While adaptive immunity provides specificity and durability through T and B cell activation, an overwhelming innate response can delay adaptive activation, resulting in immune dysfunction.³⁹ This is especially pronounced in the most severe forms of SCAP with Multiple Organ Failure (MOF), where T-cell exhaustion and impaired antigen presentation hinder pathogen clearance.

Trained immunity—a form of innate immune memory—bridges these systems and enhances rapid and robust responses to subsequent infections through epigenetic and metabolic reprogramming of cells like macrophages and monocytes.⁴⁰ However, in sCAP, overactivation of trained immunity can exacerbate cytokine

storms, causing severe lung damage and systemic complications.⁴¹ Targeting immunometabolic pathways to modulate trained immunity offers a promising therapeutic avenue to balance protective immune responses while mitigating excessive inflammation.⁴² To comprehensively understand the interplay between innate, adaptive and trained immunity in sCAP, a figure (figure 1) is included to summarise cell integration and interactions. These immune components work together, shaping the host's ability to control infection or contributing to disease progression. Together, this intricate immune network highlights the complexity of sCAP and informs strategies for therapeutic interventions aimed at optimising immune balance and improving clinical outcomes.

A critical aspect of host immunity in SCAP that warrants further discussion is the dichotomy in disease progression and outcomes. Some patients succumb to overwhelming pathogen burden, as seen in severe cases of COVID-19 during the first week, where high pathogen loads drive mortality. In contrast, others die due to an exaggerated immune response, characterised by the ARDS/Diffuse Alveolar Damage phenotype, often in the absence of detectable pathogens. Understanding this distinction is crucial, as therapeutic approaches diverge significantly between these groups: immunosuppression may worsen outcomes in patients overwhelmed by infection, while it may benefit those with hyper-inflammatory responses. This highlights the need for precision diagnostics and tailored treatment strategies to improve outcomes.

UPDATED GUIDELINES IN SEVERE CAP MANAGEMENT

The management of sCAP has undergone significant advancements. Updated clinical guidelines reflect the latest diagnostics, therapeutic strategies and multidisciplinary care developments. These updates address the complexities of managing critically ill patients by emphasising precision medicine and evidence-based interventions.^{43–49} Recent guidelines advocate for a pathogen-specific approach to sCAP management.⁴⁵ This strategy prioritises rapid identification of causative pathogens and individualised therapies tailored to local antimicrobial resistance patterns. Empirical treatments that rely heavily on extended-spectrum antibiotics are increasingly being replaced by more targeted interventions, reducing unnecessary antibiotic exposure and mitigating the development of resistance. Different guidelines highlight the critical importance of a multidisciplinary approach to managing sCAP, involving pulmonologists, infectious disease specialists, intensivists and clinical pharmacists.⁴⁸ Intensivists are particularly emphasised for managing complications like septic shock and multiorgan dysfunction, ensuring that patients receive optimal haemodynamic and ventilatory support. In the recently published clinical guidelines for sCAP, Martin-Loeches et al highlighted that supportive measures—ranging from lung-protective ventilation strategies to fluid resuscitation and vasopressor therapy—are as critical as pharmacological interventions in achieving better outcomes.⁵⁰ This collaborative model ensures comprehensive patient care, addressing pharmacological and supportive interventions.

High-flow nasal oxygen (HFNO) has revolutionised respiratory care over the last 10 years by offering enhanced oxygenation and ventilation in patients with moderate respiratory failure.^{51, 52} Considerable evidence suggests that NIV use is associated with higher mortality than HFNO in acute respiratory failure, and it has been suggested that ventilator-associated lung injury is the cause. The use of NIV is not recommended in patients with severe respiratory failure unless they have chronic obstructive pulmonary disease.⁴⁵ Its ability to deliver precise oxygen concentrations and humidified air at high flow rates improves gas exchange while providing significant comfort compared with traditional non-invasive ventilation methods.⁵³ This patient-centred comfort can enhance adherence to therapy, particularly in prolonged use.⁵⁴ Studies have shown that HFNO can significantly reduce the need for iMV in specific patient populations, highlighting its potential to prevent invasive procedures and associated complications. However, its success depends heavily on appropriate patient selection.⁵⁵ There is a risk of underestimating disease severity when relying solely on HFNO, particularly in patients progressing to severe respiratory failure or

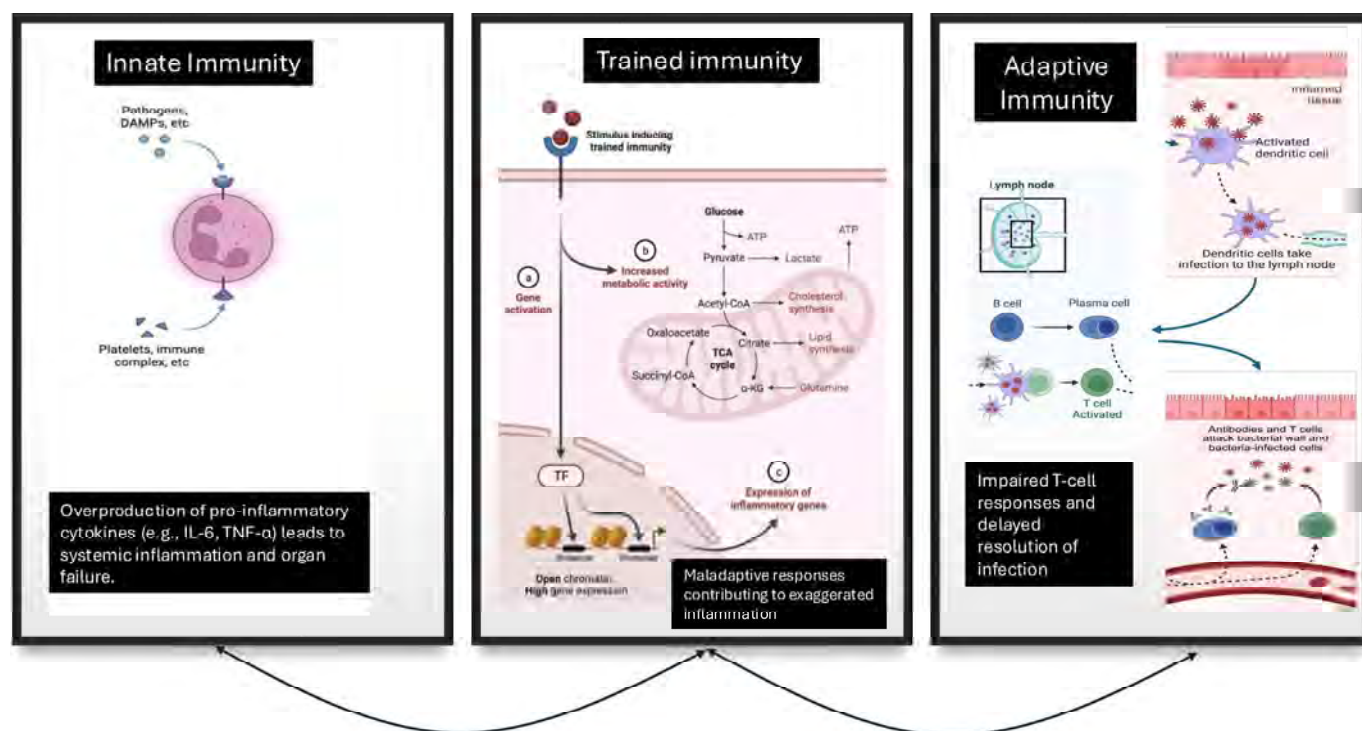


Figure 1 Immune system dynamics in community-acquired pneumonia: the role of innate, trained and adaptive immunity. This figure illustrates the three interconnected components of the immune system—innate immunity, trained immunity and adaptive immunity—and their critical roles in defending against community-acquired pneumonia (CAP). It also highlights key pathways contributing to disease severity and potential targets for immunomodulatory therapies. Innate immunity is the first line of defence, providing rapid and non-specific responses to pathogens commonly implicated in CAP, such as *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*. This system uses physical barriers, phagocytic cells and inflammatory mediators to contain infections. However, excessive activation of proinflammatory cytokines like Interleukin-6 (IL-6) and Tumour Necrosis Factor alpha (TNF- α) and dysregulated neutrophil activity can result in lung injury and worsen disease severity. Targeting these pathways with immunomodulators, such as IL-6 inhibitors or therapies that reduce neutrophil extracellular traps (NETs), offers a promising strategy to mitigate inflammation-driven tissue damage. Trained immunity, a relatively novel concept within the innate immune system, involves monocytes and macrophages acquiring memory-like properties through epigenetic and metabolic changes. This adaptation enhances the host's ability to respond to repeated infections more robustly. However, maladaptive or excessively trained immunity can trigger hyperinflammation and prolonged immune activation, exacerbating CAP severity. Strategies to modulate these responses, including statins or histone deacetylase inhibitors, could help fine-tune immune activity and improve outcomes. Adaptive immunity provides a more precise and long-lasting defence mediated by T and B lymphocytes. These cells are essential for producing antibodies and cytotoxic T cells tailored to specific CAP pathogens, ensuring adequate pathogen clearance and recovery. Yet, severe CAP can disrupt the balance between proinflammatory Th1 responses and regulatory T cells (Tregs), leading to uncontrolled inflammation. Therapies to restore Treg function or curb excessive Th17 activity, such as IL-17 inhibitors, represent potential interventions to counteract this dysregulation. CoA, coenzyme A; DAMPs, Damage-associated Molecular Patterns; TCA, Tricyclic Antidepressant.

ARDS.⁵⁶ This underscores the importance of vigilant monitoring and timely escalation to iMV when HFNO fails to stabilise the patient. When used judiciously, HFNO represents a pivotal advancement in non-invasive respiratory support, blending efficacy, comfort and the potential to improve outcomes in carefully selected patients.⁵⁷ The use of non-invasive respiratory support has gained increasing attention in managing severe respiratory failure, and the awake prone position (APP) has emerged as a potential adjunctive strategy. APP, which involves positioning awake, non-intubated patients in the prone position, has been associated with improved oxygenation and recruitment of dependent lung regions in hypoxaemic respiratory failure, including COVID-19-associated ARDS. While early studies suggest a potential benefit in reducing the need for intubation in select patients, its efficacy appears to depend on patient tolerance, timing and disease severity.⁵⁸ Moreover, robust evidence from large randomised controlled trials is still needed to establish its role in routine practice and identify the subgroups of patients most likely to benefit.

MOLECULAR TESTING (PATHOGEN DETECTION AND BIOMARKERS) IN SCAP (INCLUDING INTEGRATION)

Updated guidelines recognise the variability in pathogen prevalence and resistance patterns and stress the importance of tailoring therapeutic strategies to regional epidemiology.¹ Up to 50% of CAP cases historically lacked an identifiable pathogen, often necessitating empirical broad-spectrum antibiotic use.⁵⁹ A recent study in-

cluding almost 5000 patients found that the lack of definitive identification was even higher in immunosuppressed patients.⁶⁰ These findings highlight the need to improve diagnostic tools, as their development and implementation have been inadequate for many years. Evolving advancements in molecular diagnostics enable faster and more accurate identification of pathogens, significantly enhancing the diagnosis and management of infections (table 1).⁶¹ This enhances the precision of treatment and potentially reduces unnecessary antimicrobial exposure.⁶²

Despite these advancements, integrating molecular diagnostics into routine ICU workflows presents significant challenges.⁷ The complexity of interpreting diagnostic data, combined with the resource-intensive nature of these technologies, demands specialised training and active engagement from clinicians.⁶³ Additionally, the need for standardisation in protocols and diagnostic platforms across institutions can impede widespread implementation. Addressing these barriers requires focused efforts on clinician education, investment in user-friendly diagnostic tools, and the development of streamlined workflows to ensure that molecular diagnostics can be effectively used to improve patient outcomes and implemented in daily clinical practice.⁶⁴

Molecular diagnostics have redefined the management of sCAP by enabling rapid and precise pathogen identification, particularly in critically ill patients. Traditional culture-based techniques, with their low sensitivity and prolonged turnaround times, often need to be revised to guide timely therapy.⁶⁵ The US Food and Drug

Table 1 Available molecular testing platforms for diagnosing community-acquired pneumonia^{65 101–103}

Platform	Technology	Time to results	Unique features
BioFire FilmArray Pneumonia Panel	Multiplex PCR	~1 hour	Detects 33 respiratory pathogens, including resistance markers
Verigene Gram-Positive Test	Microarray-based nucleic acid test	~2.5 hours	Direct testing from blood cultures
Cepheid Xpert Xpress SARS-CoV-2	Real-time RT-PCR	30–45 min	Rapid simultaneous viral detection
Roche cobas Liat System	Real-time RT-PCR	~20 min	Fast, portable system for quick respiratory virus diagnosis
GenMark eSensor Panel	Multiplex PCR	~2 hours	Comprehensive bacterial and viral pathogen detection for respiratory infections

Administration (FDA) has approved several PCR-based diagnostic platforms for respiratory infections, providing rapid and targeted pathogen identification. For instance, multiplex PCR panels, such as the BioFire FilmArray Respiratory Panel, can identify up to 20 bacterial and viral pathogens in under an hour, significantly reducing the time to diagnosis. These systems are advantageous in detecting common sCAP pathogens like *S. pneumoniae* and *Haemophilus influenzae* and viral agents such as influenza and respiratory syncytial virus (RSV). Similarly, the Cepheid Xpert Xpress Flu/RSV panel delivers accurate results in as little as 30 min, enabling prompt antiviral therapy in appropriate cases.⁶⁵ The interpretation of pathogen testing from upper respiratory tract specimens requires meticulous attention. For instance, a positive PCR result from a nasal swab may not accurately reflect the active presence of the pathogen in the lung. Still, it could instead indicate residual viral shedding from a resolved primary infection, such as RSV. This distinction is critical, as relying on upper respiratory samples could lead to misdiagnosis or inappropriate treatment. Additionally, much of the literature referenced in sCAP studies is derived from upper respiratory sampling rather than bronchoalveolar lavage (BAL), which more accurately represents lower respiratory tract infections.⁶⁶ Addressing this limitation is essential to improving pathogen identification accuracy and ensuring treatments are effectively targeted. Future research should emphasise BAL sampling or comparable methods for better insights into lower respiratory tract pathogens.

PCR-based methods are highly sensitive and specific, but their targeted approach limits the range of pathogens detected to those included in the assay. Other molecular testing, including metagenomic next-generation sequencing (mNGS), has revolutionised pathogen detection by enabling broad-spectrum identification of microorganisms, including bacteria, viruses and fungi, directly from clinical samples. However, these techniques are not without limitations. One significant challenge, particularly with mNGS, is adjudicating potential pathogens as causal agents. Distinguishing between true pathogens, colonisers and contaminants can be difficult, especially in polymicrobial environments or where low

microbial loads are detected. We must also consider that molecular testing might not reveal antimicrobial susceptibility, necessitating additional diagnostic methods. More research is essential to enhance these techniques and develop standardised protocols for incorporating molecular testing into everyday clinical practices, all while minimising potential complications and misinterpretation. For example, mNGS has been instrumental in identifying novel pathogens like SARS-CoV-2 during the COVID-19 pandemic. Wu et al demonstrated that mNGS identified pathogens in 90.3% of sCAP cases compared with 39.5% with conventional methods.⁶⁷ Additionally, NGS excels in detecting mixed infections, which are present in nearly 57% of sCAP cases, and in identifying pathogens that traditional diagnostics may miss. This comprehensive approach is invaluable, particularly in immunocompromised patients, where the spectrum of pathogens is broader and more complex.

Molecular testing might significantly enhance clinical decision-making by guiding personalised antimicrobial therapy.⁶⁸ For instance, PCR panels can rapidly confirm or rule out common pathogens, enabling early de-escalation of broad-spectrum antibiotics when bacterial infections are unlikely. In cases where PCR results are inconclusive or mixed infections are suspected, mNGS can provide additional insights, identifying rare pathogens or coinfections like *Pneumocystis jirovecii* that have been reported on a current rise.⁶⁹ NGS findings can also lead to a de-escalation of antibiotics in 52.9% of cases, reducing unnecessary drug use and associated toxicity risks while enabling escalation in 26.1% of cases to target specific pathogens.⁶⁷ Equally, there is a need to consider the health-economic implications of expensive new testing platforms, as none have yet demonstrated significant improvements in patient clinical outcomes.

While these technologies may offer potential benefits, such as promoting antibiotic de-escalation, reducing treatment durations and minimising antibiotic-related toxicity, they also present challenges. For example, with NGS, the issue of overcalling a positive detection as an infection is significant, as thresholds for most pathogens have not been firmly established. This limitation raises

Table 2 Recent antibiotics launched for sCAP

Drug	Formulation	Activity	Unique features	Approval year
Ceftaroline	IV	MRSA, resistant pneumococci, Gram-negative pathogens	Only beta-lactam with activity against MRSA; also effective against resistant pneumococci	2010
Ceftobiprole	IV	MRSA, multidrug-resistant Gram-positive and Gram-negative bacteria	Broadest cephalosporin spectrum; includes MRSA and <i>Pseudomonas aeruginosa</i>	2024
Lefamulin	IV/PO	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , atypical pathogens	Novel pleuromutilin class, effective against respiratory atypicals, including Legionella	2019
Delafloxacin	IV/PO	MRSA, <i>S. pneumoniae</i> and Gram-negative bacteria	Improved safety compared with older fluoroquinolones; potent against MRSA	2017
Eravacycline	IV/PO	Resistant Gram-negative bacteria, Enterobacteriaceae and MRSA	First tetracycline derivative effective against carbapenem-resistant bacteria	2018
Oritavancin	IV	MRSA, vancomycin-resistant Enterococcus (VRE) and Gram-positive pathogens	Single-dose treatment with long half-life, effective against MRSA and VRE	2014
Dalbavancin	IV	MRSA, VRE and Gram-positive pathogens	Single or infrequent dosing suitable for outpatient IV therapy	2014
Tedizolid	IV/PO	MRSA, VRE and Gram-positive pathogens	Oxazolidinone more potent than linezolid with reduced myelosuppression risks	2014
Omadacycline	IV/PO	MRSA, <i>S. pneumoniae</i> and atypical pathogens	Novel tetracycline with activity against resistant Gram-positive and atypical pathogens; suitable for oral and IV use	2018

IV, intravenous (administered through a vein); PO, per os (Latin for "by mouth"; oral administration); sCAP, severe community-acquired pneumonia.

Table 3 Case-specific considerations for corticosteroid use in severe CAP^{21 44 45 104–106}

Scenario	Potential benefits	Potential harms
Refractory septic shock	Improved haemodynamic stability	Increased risk of secondary infections
Severe inflammatory response (eg, ARDS)	Reduction in cytokine storm and inflammation	Delayed clearance of primary infection
Adjunctive therapy in adrenal insufficiency	Restoration of appropriate stress response	Risk of adrenal suppression with prolonged use
Severe CAP with high inflammatory markers	Possible reduction in mortality when paired with antibiotics in select high-risk patients	Hyperglycaemia and increased insulin requirements
Use in viral pneumonias (eg, COVID-19)	Reduced mortality in hypoxaemic patients when used appropriately	Potential worsening of viral replication in the absence of hypoxaemia or bacterial superinfection risk
Routine use in mild-to-moderate CAP	None documented	Unnecessary exposure leading to side effects such as osteoporosis, muscle weakness or mood disorders
Patients with pre-existing immunosuppression	Possible stabilisation of baseline condition	Exacerbation of underlying immunosuppressive state and increased susceptibility to opportunistic infections

ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia.

concerns about the potential for misinterpretation and overtreatment, emphasising the importance of refining diagnostic criteria and focusing on targeted applications to maximise their clinical and economic value.

While understanding the pathogen is critical, adopting a holistic approach that considers the patient's response to the infection is equally essential. Host-specific biomarkers, such as procalcitonin (PCT) and C reactive protein (CRP), are critical for managing sCAP, providing insights into the host's inflammatory and infectious status.⁷⁰ Despite its limited sensitivity in early or atypical CAP presentations, PCT is recommended by the European Respiratory Society, European Society of Intensive Care Medicine, Latin American Thoracic Association and European Society of Clinical Microbiology and Infectious Diseases guidelines for its role in reducing antibiotic use.^{45 46} Studies show that tracking PCT trends enables safe antibiotic de-escalation, supporting antimicrobial stewardship and reducing risks associated with broad-spectrum antibiotic overuse, particularly in ICUs.^{71 72} CRP and PCT were initially developed as tools to aid in detecting bacterial infections, but their utility in this regard has limitations. While they may assist in guiding antibiotic de-escalation, notably when clinicians are hesitant to stop treatment, the evidence does not support the assertion that they are 'critical.' Studies showing reduced antibiotic use with these biomarkers often involve control groups with therapy durations far exceeding guideline recommendations. Furthermore, none of these studies have included control arms utilising validated clinical stability tools, as strongly advised in the latest ATS/IDSA guidelines. Although elevated CRP and PCT levels can strongly suggest bacterial coinfection in the context of a known viral infection, normal levels frequently fail to exclude significant bacterial infections.^{45 46 73} However, biomarkers should complement clinical judgement and management, not replace them.⁷⁴ Used alongside thorough clinical assessment, these tools enable precise, effective management of sCAP and improve outcomes in critically ill patients.⁷⁵

The integration of molecular diagnostics with biomarkers further enhances precision in sCAP management. For example, combining PCR results with PCT levels allows targeted decision-making.⁷⁶ A low PCT level with a PCR-confirmed viral pathogen could indicate that antibiotics are unnecessary, while mNGS data can identify bacterial coinfections requiring treatment. Similarly, PCT trends paired with mNGS findings can guide dynamic adjustments to therapy, such as identifying new pathogens like *Aspergillus* in ventilator-associated pneumonia (VAP). The appearance of *Aspergillus* in this context often occurs later and may represent a superinfection rather than an initial cause of severe CAP. Rapid detection of *Aspergillus* or other pathogens in VAP can support timely adjustments to therapy. Still, it is essential to emphasise that this does not justify stopping antibiotics entirely, as such decisions require careful consideration of the clinical scenario.⁷⁷

Integrating biomarkers and vital signs with advanced diagnostics and artificial intelligence (AI) has transformed the management of sCAP.⁷⁸ Vital signs, including heart rate, respiratory rate and blood pressure, offer real-time data on a patient's physiological

state, which is essential for assessing disease severity and monitoring response to treatment.⁷⁹ Combining these clinical parameters with molecular diagnostics and AI-enhanced imaging facilitates a comprehensive, individualised approach to sCAP care.⁸⁰ In addition, advancing patient monitoring by integrating multimodal clinical data. Wearable devices and AI-powered non-invasive monitors can analyse parameters like heart rate variability and respiratory patterns to detect early signs of clinical deterioration.^{81 82} These systems outperform traditional risk scores, such as qSOFA, by providing continuous, real-time assessments. Moreover, AI-driven models can combine imaging, biomarkers and clinical data to stratify patients into phenotypes, guiding personalised treatment and improving predictive accuracy.⁸³

This integration enables precise diagnosis, optimises antimicrobial use and reduces healthcare costs by minimising unnecessary interventions. Ongoing research and education are critical to overcoming implementation barriers and ensuring these technologies reach their full potential in improving patient outcomes.

ADVANCES IN IMAGING SCAP MANAGEMENT

Imaging and AI have advanced the management of sCAP, improving diagnosis, monitoring and treatment.⁸² Chest X-rays (CXR) and CT remain the mainstays of imaging. CXR offers rapid assessment, and CT provides more detailed evaluations of subtle findings like ground-glass opacities and abscesses. CT also aids in guiding invasive procedures and detecting complications such as empyema and ARDS.⁸⁴

Point-of-care ultrasound has become a valuable bedside tool, particularly in ICUs and resource-limited settings, due to its ability to visualise pulmonary consolidations, pleural effusions and dynamic lung changes without radiation. While these capabilities offer real-time monitoring that can assist clinicians in diagnosing complications such as empyema and provide reassurance in specific scenarios, there is currently no robust evidence to support its routine use for adjusting care in severe CAP. Further high-quality studies are needed to determine its role in clinical decision-making and assess whether it should be considered a standard of care.⁸⁵

Imaging is probably the field where AI has developed more over the last few years. AI and machine learning are transforming imaging interpretation in clinical imaging, improving the precision of CXR and CT analyses, and differentiating sCAP from other conditions like malignancy or heart failure by semiautomated algorithms analysis. AI applications, demonstrated in COVID-19 research, have shown their potential to identify severity markers and enhance clinical decision-making.⁴ These tools support personalised and effective sCAP management while addressing diagnostic limitations.⁸⁶

NEW ANTIBIOTICS AND NOVEL THERAPIES FOR SEVERE CAP

Antibiotic treatment remains the cornerstone of sCAP management, yet immunomodulatory agents and tailored therapeutic combinations are emerging as novel strategies to improve outcomes.⁸⁷ While the impact of increasing macrolide and beta-lactam resistance on outcomes in sCAP remains controversial,

there is limited evidence to suggest that resistance in *S. pneumoniae* has led to widespread adverse outcomes across the USA, Europe or Asia. Current guidelines recommend beta-lactam/macrolide combination therapy in SCAP patients without risk factors for *P. aeruginosa*. Nevertheless, a rapid and precise diagnostic workup is paramount, particularly in ventilated patients, to identify unusual pathogens or resistance patterns that may necessitate deviations from standard dual therapy regimens. Advanced diagnostic techniques, such as multiplex PCR and NGS, could enhance pathogen identification and guide tailored antimicrobial therapy, potentially improving outcomes in these complex cases.⁸⁸ New agents have demonstrated efficacy in achieving rapid clinical stability, a key goal in managing severe CAP, particularly in the most severe presentations.⁴⁸ New agents (table 2) have been developed to improve efficacy in achieving rapid clinical stability, a key goal in managing sCAP, particularly in the most severe presentations.²⁰

One significant limitation in evaluating new antibiotics is the under-representation of patients with sCAP in many randomised controlled trials (RCTs). This omission is critical, as sCAP patients often exhibit altered pharmacokinetics and pharmacodynamics due to disease severity, organ dysfunction and systemic inflammation, which may influence drug absorption, distribution, metabolism and excretion. The exclusion of these patients limits the generalisability of trial results and may lead to suboptimal dosing or efficacy in real-world clinical scenarios.⁸⁰ Including sCAP patients in future RCTs is essential to optimise antibiotic design and prescription for this high-risk population, improving therapeutic outcomes and antimicrobial stewardship efforts.

The dysregulated inflammatory response in severe CAP often exacerbates disease progression, making immunomodulatory therapies an area of growing interest. Among these, corticosteroids have been the most extensively studied for their potential to mitigate excessive inflammation, but their role remains nuanced and controversial.⁸⁹

Two recently published trials have revolutionised current recommendations because they have analysed more patients than any other trials until now. The CAPE COD trial provided compelling evidence that hydrocortisone significantly reduced 28-day mortality in ICU patients with severe CAP, including administration within 24 hours, suggesting that corticosteroids may be particularly beneficial in carefully selected, critically ill populations.⁹⁰ Conversely, the ESCAPE trial highlighted the complexities of corticosteroid use, finding no significant mortality benefit with prolonged low-dose methylprednisolone in a more elderly population analysed (US veterans).⁹¹ This variability underscores the importance of corticosteroid type, dosing regimens and patient selection in determining outcomes.

Corticosteroids have been widely studied in severe CAP, with evidence suggesting potential benefits in specific contexts, such as reducing inflammation and improving outcomes in patients with refractory septic shock or severe inflammatory responses. However, their overuse is associated with significant risks, including secondary infections, hyperglycaemia and delayed recovery from underlying infections. Balancing these considerations requires careful patient selection and further high-quality studies to refine indications. The accompanying table (table 3) highlights scenarios where corticosteroids may offer benefits versus where their use could lead to harm, aiding clinicians in making informed decisions. Despite these mixed findings, corticosteroids remain a cornerstone of adjunctive therapy in select cases of severe CAP. Their ability to address the inflammatory cascade can be lifesaving for some patients, yet their application requires precision and a balance between benefit and potential harm. Further research is necessary to refine their use, focusing on identifying optimal dosing, duration and the profiles of patients most likely to benefit.

These insights into immunomodulation, coupled with advances in personalised medicine, underscore the importance of tailoring treatment strategies to the infectious agent and individual patients' unique inflammatory and immune responses. By addressing both pathogen clearance and host response, these approaches can pave the way for improved outcomes in severe CAP.

CHALLENGES AND SOLUTIONS FOR SCAP MANAGEMENT IN RESOURCE-LIMITED SETTINGS

sCAP poses a significant global health challenge, especially in LMICs, where systemic inequalities, economic barriers and limited healthcare infrastructure amplify its burden. These regions face delays in diagnosis and treatment due to inadequate access to primary and preventive healthcare. Many patients present at advanced stages of the disease, requiring intensive care, yet ICU capacity, ventilators and trained personnel are often insufficient. Seasonal pneumonia surges and pandemics like COVID-19 further strain already limited resources, emphasising the need for scalable and resilient healthcare systems.⁹²

Infection control challenges in LMICs worsen sCAP outcomes. Overcrowded healthcare facilities, poor sanitation and limited access to clean water contribute to healthcare-associated infections, including those caused by MDROs.^{79 93 94} These infections complicate treatment and diminish the effectiveness of antibiotics. Addressing these risks requires investments in basic infection control measures, such as improved hospital hygiene, access to antimicrobials and enhanced sanitation infrastructure.⁹⁵

Global guidelines for sCAP management often need to catch up in LMICs. They are typically developed in high-income settings with access to advanced diagnostics and robust critical care. This disconnect underscores the urgent need for region-specific protocols that align with local epidemiology, resource availability and cost-effectiveness. Tailored guidelines can ensure clinical relevance and improve patient outcomes.⁹⁶

RESEARCH PRIORITIES AND INNOVATIONS

Advancing sCAP management requires targeted research and innovative solutions. Priorities include developing affordable, rapid diagnostic tools for low-resource settings to enhance early detection and timely intervention. Exploring targeted immunomodulatory therapies offers promise in mitigating excessive immune activation in severe cases. Integrating AI and wearable technologies into routine workflows could transform patient monitoring and enable real-time decision-making.

Long-term studies are also essential to evaluate novel antibiotics and combination therapies, addressing the growing challenge of antimicrobial resistance.⁹⁷

Guidelines must be adapted to reflect regional variations in sCAP epidemiology and healthcare infrastructure. This includes conducting specific clinical trials for high-risk populations, such as the immunocompromised, to refine personalised treatment strategies.⁹⁸

THE ROLE OF GLOBAL INITIATIVES

Global funding initiatives, including support from the Bill & Melinda Gates Foundation, Wellcome Trust and the European Union, have been instrumental in addressing healthcare disparities.⁹⁹ These organisations have invested in vaccine distribution, antimicrobial resistance research and healthcare infrastructure development. For example, the Gates Foundation's pneumococcal vaccine programmes have reduced pneumonia incidence, while the Wellcome Trust's antimicrobial stewardship efforts combat MDROs. Collaborative efforts like these are crucial for adapting sCAP management to the realities of LMICs.¹⁰⁰

CONCLUSIONS

sCAP remains a critical global health challenge, with disproportionately high mortality rates and management difficulties, particularly in LMICs. While advancements in diagnostics, imaging technologies and personalised medicine offer promising avenues for improving outcomes, significant barriers persist in resource-limited settings, exacerbating global health inequities. Addressing these disparities requires targeted investments, innovative research and multidisciplinary collaboration to ensure that novel interventions are accessible and effective across diverse healthcare systems.

Despite progress, several unanswered questions continue to shape the sCAP landscape. For instance, the role of molecular diagnostic platforms in reliably distinguishing between colonisation,

contamination and true infection remains unclear. Standardised thresholds for pathogen detection, particularly with advanced techniques such as multiplex PCR and metagenomic sequencing, are yet to be established. Similarly, understanding the dichotomy in host immune responses—distinguishing those overwhelmed by pathogen burden from those with excessive inflammatory responses—is essential for tailoring therapeutic strategies. Biomarkers that accurately stratify patients based on these immune phenotypes and guide real-time clinical decisions remain an area of active investigation.

In addition, therapeutic optimisation remains a key challenge. While corticosteroids and other immunomodulatory therapies have shown promise in select patient populations, their use must be carefully contextualised to balance potential benefits against the risks of secondary infections. Similarly, using non-invasive respiratory support strategies, such as HFNO and awake-prone positioning, requires further evidence to define best practices and identify optimal timing for interventions.

Global disparities in sCAP management underscore the need for region-specific solutions. In LMICs, limited access to advanced diagnostics, critical care infrastructure and trained personnel often translates into poorer outcomes. Addressing these challenges involves scaling up access to cutting-edge technologies and developing cost-effective, scalable approaches tailored to resource-constrained settings.

By integrating advances in precision medicine, innovative diagnostics and multidisciplinary approaches, the healthcare community has the potential to bridge existing gaps and improve outcomes in sCAP. Tackling these unanswered questions through collaborative research and targeted investments will enhance our understanding of sCAP and significantly reduce the global burden of this life-threatening condition, paving the way for a more equitable future in healthcare.

X Ignacio Martin-Loeches@imloeches

Contributors IM-L served as the guarantor for this manuscript, accepting full responsibility for the overall content, study conduct, data access and the decision to publish. IM-L contributed significantly to the conceptualisation and design of the study, drafted and revised the manuscript and ensured the integrity and accuracy of the work. LFR provided critical insights during the drafting process and revised the manuscript for important intellectual content. AR contributed to developing the study framework, reviewed and provided valuable revisions to enhance the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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.

Provenance and peer review Commissioned; externally peer reviewed.

ORCID iDs

Ignacio Martin-Loeches

<https://orcid.org/0000-0002-5834-4063>

Luis Felipe Reyes <https://orcid.org/0000-0003-1172-6539>

REFERENCES

- Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019;200:e45–67.
- Reyes LF, Garcia-Gallo E, Pinedo J, et al. Scores to Predict Long-term Mortality in Patients With Severe Pneumonia Still Lacking. *Clin Infect Dis* 2021;72:e442–3.
- Aliberti S, Dela Cruz CS, Amati F, et al. Community-acquired pneumonia. *Lancet* 2021;398:906–19.
- Munera N, Garcia-Gallo E, Gonzalez A, et al. A novel model to predict severe COVID-19 and mortality using an artificial intelligence algorithm to interpret chest radiographs and clinical variables. *ERJ Open Res* 2022;8.
- Li H-Y, Guo Q, Song W-D, et al. Modified IDSA/ATS Minor Criteria for Severe Community-Acquired Pneumonia Best Predicted Mortality. *Medicine (Baltimore)* 2015;94:e1474.
- Brown SM, Dean NC. Defining and predicting severe community-acquired pneumonia. *Curr Opin Infect Dis* 2010;23:158–64.
- Salluh JIF, Póvoa P, Beane A, et al. Challenges for a broad international implementation of the current severe community-acquired pneumonia guidelines. *Intensive Care Med* 2024;50:526–38.
- Reyes LF, Murthy S, Garcia-Gallo E, et al. Clinical characteristics, risk factors and outcomes in patients with severe COVID-19 registered in the International Severe Acute Respiratory and Emerging Infection Consortium WHO clinical characterisation protocol: a prospective, multinational, multicentre, observational study. *ERJ Open Res* 2022;8.
- Torres A, Martin-Loeches I, Menéndez R. Research in community-acquired pneumonia: the next steps. *Intensive Care Med* 2017;43:1395–7.
- Villafuerte D, Aliberti S, Soni NJ, et al. Prevalence and risk factors for Enterobacteriaceae in patients hospitalized with community-acquired pneumonia. *Respirology* 2020;25:543–51.
- Radovanovic D, Sotgiu G, Jankovic M, et al. An international perspective on hospitalized patients with radicalovirus pneumonia. *Eur J Intern Med* 2019;60:54–70.
- Carugati M, Aliberti S, Reyes LF, et al. Microbiological testing of adults hospitalised with community-acquired pneumonia: an international study. *ERJ Open Res* 2018;4.
- Gramegna A, Sotgiu G, Di Pasquale M, et al. Atypical pathogens in hospitalized patients with community-acquired pneumonia: a worldwide perspective. *BMC Infect Dis* 2018;18:677.
- Aliberti S, Cook GS, Babu BL, et al. International prevalence and risk factors evaluation for drug-resistant *Streptococcus pneumoniae* pneumonia. *J Infect* 2019;79:300–11.
- Nair GB, Niederman MS. Updates on community acquired pneumonia management in the ICU. *Pharmacol Ther* 2021;217:107663.
- Di Pasquale M, Sotgiu G, Gramegna A, et al. Prevalence and Etiology of Community-acquired Pneumonia in Immunocompromised Patients. *Clin Infect Dis* 2019;68:1482–93.
- Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. *Lancet* 2015;386:1097–108.
- Aliberti S, Reyes LF, Faverio P, et al. Global initiative for metacillin-resistant *Staphylococcus aureus* pneumonia (GLIMP): an international, observational cohort study. *Lancet Infect Dis* 2016;16:1364–76.
- Martin-Loeches I, Reyes LF, Nseir S, et al. European Network for ICU-Related Respiratory Infections (ENIRRI): a multinational, prospective, cohort study of nosocomial LRTI. *Intensive Care Med* 2023;49:1212–22.
- Restrepo MI, Babu BL, Reyes LF, et al. Burden and risk factors for *Pseudomonas aeruginosa* community-acquired pneumonia: a multinational point prevalence study of hospitalised patients. *Eur Respir J* 2018;52:1701190.
- Torres A, Chalmers JD, Dela Cruz CS, et al. Challenges in severe community-acquired pneumonia: a point-of-view review. *Intensive Care Med* 2019;45:159–71.
- Metzger DW, Sun K. Immune dysfunction and bacterial coinfections following influenza. *J Immunol* 2013;191:2047–52.
- Martin-Loeches I, van Someren Gréve F, Schultz MJ. Bacterial pneumonia as an influenza complication. *Curr Opin Infect Dis* 2017;30:201–7.
- Proañón NJ, Reyes LF, Bastidas A, et al. Prior influenza vaccine is not a risk factor for bacterial coinfection in patients admitted to the ICU due to severe influenza. *Medicina Intensiva (English Edition)* 2022;46:436–45.
- Claverias L, Daniel X, Martin-Loeches I, et al. Impact of *Aspergillus* spp. isolation in the first 24 hours of admission in critically ill patients with severe influenza virus pneumonia. *Med Intensiva (Engl Ed)* 2022;46:426–35.
- Rouzé A, Lemaître E, Martin-Loeches I, et al. Invasive pulmonary aspergillosis among intubated patients with SARS-CoV-2 or influenza pneumonia: a European multicenter comparative cohort study. *Crit Care* 2022;26:11.
- Moreno G, Rodríguez A, Reyes LF, et al. Corticosteroid treatment in critically ill patients with severe influenza pneumonia: a propensity score matching study. *Intensive Care Med* 2018;44:1470–82.
- Li Z, Denning DW. The Impact of Corticosteroids on the Outcome of Fungal Disease: A Systematic Review and Meta-analysis. *Curr Fungal Infect Rep* 2023;17:54–70.
- Kean IRL, Clark JA, Zhang Z, et al. Short-duration selective decontamination of the digestive tract infection control does not contribute to increased antimicrobial resistance burden in a pilot cluster randomised trial (the ARCTIC Study). *Gut* 2024;73:910–21.
- Bhargavi G, Subbian S. The causes and consequences of trained immunity in myeloid cells. *Front Immunol* 2024;15:1365127.
- Karazum H, Datta SK. Adaptive Immunity Against *Staphylococcus aureus*. *Curr Top Microbiol Immunol* 2017;409:419–39.
- Thakur A, Mikkelsen H, Jungersen G. Intracellular Pathogens: Host Immunity and Microbial Persistence Strategies. *J Immunol Res* 2019;2019:1356540.
- Gonzalez-Juarbe N, Bradley KM, Riegler AN, et al. Bacterial Pore-Forming Toxins Promote the Activation of Caspases in Parallel to Necroptosis to Enhance Alarmin Release and Inflammation During Pneumonia. *Sci Rep* 2018;8:5846.
- Gilley RP, González-Juarbe N, Shenoy AT, et al. Infiltrated Macrophages Die of Pneumolysin-Mediated Necroptosis following *Pneumococcal* Myocardial Invasion. *Infect Immun* 2016;84:1457–69.
- Garduno A, Cusack R, Leone M, et al. Multi-Omics Endotypes in ICU Sepsis-Induced Immunosuppression. *Microorganisms* 2023;11:1119.
- Garduno A, Martínez GS, Ostadgavahi AT, et al. Parallel Dysregulated Immune Response in Severe Forms of COVID-19 and Bacterial Sepsis via Single-Cell Transcriptome Sequencing. *Biomedicines* 2023;11:778.
- Martínez GS, Ostadgavahi AT, Al-Rafat AM, et al. Model-interpreted outcomes of artificial neural networks classifying immune biomarkers associated with severe infections in ICU. *Front Immunol* 2023;14:1137850.
- Martin-Loeches I, Sganzerla Martínez G, Garduno A, et al. Transcriptomics reveals shared immunosuppressive landscapes in ventilator-associated lower respiratory tract infections (VA-LRTI) patients. *Expert Rev Anti Infect Ther* 2023;21:1135–41.
- Ibáñez-Prada ED, Guerrero JL, Bustos JG, et al. The unique metabolic and lipid profiles of patients with severe COVID-19 compared to severe community-acquired pneumonia: a potential prognostic and therapeutic target. *Expert Rev Respir Med* 2024;18:815–29.
- Reyes LF, Restrepo MI, Hinojosa CA, et al. Severe *Pneumococcal* Pneumonia Causes Acute Cardiac Toxicity and Subsequent Cardiac Remodeling. *Am J Respir Crit Care Med* 2017;196:609–20.
- Ibáñez-Prada ED, Fish M, Fuentes YV, et al. Comparison of systemic inflammatory profiles in COVID-19 and community-acquired pneumonia patients: a prospective cohort study. *Respir Res* 2023;24:60.
- Netea MG, Domínguez-Andrés J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol* 2020;20:375–88.
- Martin-Loeches I, Nagavci B, Torres A. Guidelines for the management of severe community-acquired pneumonia: one confusing recommendation. Author's reply. *Intensive Care Med* 2023;49:1261–2.
- Martin-Loeches I, Nagavci B, Torres A. Final approval for corticosteroids in severe CAP? For sure, in septic shock. *Crit Care* 2023;27:342.
- Martin-Loeches I, Torres A, Nagavci B, et al. ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. *Intensive Care Med* 2023;49:615–32.
- Martin-Loeches I, Torres A, Nagavci B, et al. ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. *Eur Respir J* 2023;61:2200735.
- Martin-Loeches I, Torres A, Nagavci B, et al. Correction: ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. *Intensive Care Med* 2023;49:1040–1.
- Martin-Loeches I, Garduno A, Póvoa P, et al. Choosing antibiotic therapy for severe community-acquired pneumonia. *Curr Opin Infect Dis* 2022;35:133–9.
- Martin-Loeches I, Torres A. New guidelines for severe community-acquired pneumonia. *Curr Opin Pulm Med* 2021;27:210–5.
- Martin-Loeches I, de Haro C, Dellinger RP, et al. Effectiveness of an inspiratory pressure-limited approach to mechanical ventilation in septic patients. *Eur Respir J* 2013;41:157–64.
- Ospina-Tascón GA, Calderón-Tapia LE, García AF, et al. Effect of High-Flow Oxygen Therapy vs Conventional Oxygen Therapy on Invasive Mechanical Ventilation and Clinical Recovery in Patients With Severe COVID-19: A Randomized Clinical Trial. *JAMA* 2021;326:2161–71.
- Frat J-P, Thille AW, Mercat A, et al. High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure. *N Engl J Med* 2015;372:2185–96.
- Wyatt KD, Goel NN, Whittle JS. Recent advances in the use of high flow nasal oxygen therapies. *Front Med (Lausanne)* 2022;9:1017965.
- Frat J-P, Coudroy R, Marjanovic N, et al. High-flow nasal oxygen therapy and noninvasive ventilation in the management of acute hypoxemic respiratory failure. *Ann Transl Med* 2017;5:297.
- Oczkowski S, Ergon B, Bos L, et al. ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. *Eur Respir J* 2022;59:2101574.
- Ware LB. Go with the Flow: Expanding the Definition of Acute Respiratory Distress Syndrome to Include High-Flow Nasal Oxygen. *Am J Respir Crit Care Med* 2022;205:380–2.
- Renda T, Corrado A, Iskandar G, et al. High-flow nasal oxygen therapy in intensive care and anaesthesia. *Br J Anaesth* 2018;120:18–27.
- Perez Y, Luo J, Ibarra-Estrada M, et al. Awake prone positioning for patients with COVID-19: induced acute hypoxemic respiratory failure. *J Intensive Care Med* 2022;2:233–40.
- Sharma R, Sandrock CE, Meehan J, et al. Community-Acquired Bacterial Pneumonia-Changing Epidemiology, Resistance Patterns, and Newer Antibiotics: Spotlight on Delafloxacin. *Clin Drug Investig* 2020;40:947–60.
- Viñan Garcés AE, Sanabria-Herrera N, Duque S, et al. Severe community-acquired pneumonia in immunosuppressed patients admitted to the ICU. *Respir Med* 2025;240:108014.
- Murdoch DR. How recent advances in molecular tests could impact the diagnosis of pneumonia. *Expert Rev Mol Diagn* 2016;16:533–40.
- Carbonell R, Moreno G, Martín-Loeches I, et al. The Role of Biomarkers in Influenza and COVID-19 Community-Acquired Pneumonia in Adults. *Antibiotics (Basel)* 2023;12:161.
- Liesenfeld O, Lehman L, Hunfeld K-P, et al. Molecular diagnosis of sepsis: New aspects and recent developments. *Eur J Microbiol Immunol (Bp)* 2014;4:1–25.

64. Macklin PS, Pillay N, Lee JL, et al. CM-Path Molecular Diagnostics Forum-consensus statement on the development and implementation of molecular diagnostic tests in the United Kingdom. *Br J Cancer* 2019;121:738–43.
65. Martin-Loeches I, Pereira JG, Teoh TK, et al. Molecular antimicrobial susceptibility testing in sepsis. *Future Microbiol* 2024;19:61–72.
66. Wang L, Lu S, Guo Y, et al. Comparative study of diagnostic efficacy of sputum and bronchoalveolar lavage fluid specimens in community-acquired pneumonia children treated with fiberoptic bronchoscopy. *BMC Infect Dis* 2023;23:565.
67. Wu X, Li Y, Zhang M, et al. Etiology of Severe Community-Acquired Pneumonia in Adults Based on Metagenomic Next-Generation Sequencing: A Prospective Multicenter Study. *Infect Dis Ther* 2020;9:1003–15.
68. Kan C-M, Tsang HF, Pei XM, et al. Enhancing Clinical Utility: Utilization of International Standards and Guidelines for Metagenomic Sequencing in Infectious Disease Diagnosis. *Int J Mol Sci* 2024;25:3333.
69. Xue T, Kong X, Ma L. Trends in the Epidemiology of Pneumocystis Pneumonia in Immunocompromised Patients without HIV Infection. *J Fungi (Basel)* 2023;9:812.
70. Nora D, Salluh J, Martin-Loeches I, et al. Biomarker-guided antibiotic therapy-strengths and limitations. *Ann Transl Med* 2017;5:208.
71. Zilahi G, McMahon MA, Povoa P, et al. Duration of antibiotic therapy in the intensive care unit. *J Thorac Dis* 2016;8:3774–80.
72. Bréchet N, Hékimian G, Chastre J, et al. Procalcitonin to guide antibiotic therapy in the ICU. *Int J Antimicrob Agents* 2015;46 Suppl 1:S19–24.
73. de Noijer AH, Pickers P, Netea MG, et al. Inflammatory biomarkers to predict the prognosis of acute bacterial and viral infections. *J Crit Care* 2023;78:154360.
74. Rodríguez A, Gómez J, Martín-Loeches I, et al. A Machine Learning Approach to Determine Risk Factors for Respiratory Bacterial/Fungal Coinfection in Critically Ill Patients with Influenza and SARS-CoV-2 Infection: A Spanish Perspective. *Antibiotics (Basel)* 2024;13:968.
75. Khan F, Owens MB, Restrepo M, et al. Tools for outcome prediction in patients with community acquired pneumonia. *Expert Rev Clin Pharmacol* 2017;10:201–11.
76. Walker AM, Timbrook TT, Hommel B, et al. Breaking Boundaries in Pneumonia Diagnostics: Transitioning from Tradition to Molecular Frontiers with Multiplex PCR. *Diagnostics (Basel)* 2024;14:752.
77. Massey B, Stromberg S, McFann K, et al. Procalcitonin levels and antibiotic use associations with COVID-19 disease severity in hospitalized adults and the potential for an increase in antibiotic resistance: a cross-sectional clinical and public health analysis. *J Public Health Emerg* 2023;7:11.
78. Shaddock EJ. How and when to use common biomarkers in community-acquired pneumonia. *Pneumonia (Nathan)* 2016;8:17.
79. Póvoa P, Coelho L, Cidade JP, et al. Biomarkers in pulmonary infections: a clinical approach. *Ann Intensive Care* 2024;14:113.
80. Martin-Loeches I, Metersky M, Kalil A, et al. Strategies for implementation of a multidisciplinary approach to the treatment of nosocomial infections in critically ill patients. *Expert Rev Anti Infect Ther* 2021;19:759–67.
81. Kayser SA, Williamson R, Siefert G, et al. Respiratory rate monitoring and early detection of deterioration practices. *Br J Nurs* 2023;32:620–7.
82. Mizera L, Boehm K, Duckheim M, et al. Autonomic Nervous System Activity for Risk Stratification of Emergency Patients With Pneumonia. *J Emerg Med* 2018;55:472–80.
83. Cascarano A, Mur-Petit J, Hernández-González J, et al. Machine and deep learning for longitudinal biomedical data: a review of methods and applications. *Artif Intell Rev* 2023;56:1711–71.
84. Cysneiros A, Galvão T, Domingues N, et al. ARDS Mortality Prediction Model Using Evolving Clinical Data and Chest Radiograph Analysis. *Biomedicine* 2024;12:439.
85. Lau YH, See KC. Point-of-care ultrasound for critically-ill patients: A mini-review of key diagnostic features and protocols. *World J Crit Care Med* 2022;11:70–84.
86. Chassagnon G, Vakalopoulou M, Battistella E, et al. AI-driven quantification, staging and outcome prediction of COVID-19 pneumonia. *Med Image Anal* 2021;67:101860.
87. Pletz MW, Jensen AV, Bahrs C, et al. Unmet needs in pneumonia research: a comprehensive approach by the CAPNETZ study group. *Respir Res* 2022;23:239.
88. van Duin D, Paterson DL. Multidrug-Resistant Bacteria in the Community: An Update. *Infect Dis Clin North Am* 2020;34:709–22.
89. Bode C, Weis S, Sauer A, et al. Targeting the host response in sepsis: current approaches and future evidence. *Crit Care* 2023;27:478.
90. Friedrich JO, Gouvêa Bogossian E. Hydrocortisone in Severe Community-Acquired Pneumonia. *N Engl J Med* 2023;389:670–1.
91. Meduri GU, Shih M-C, Bridges L, et al. Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia. *Intensive Care Med* 2022;48:1009–23.
92. Ong M. A comprehensive framework identifying barriers to global health R&D innovation and access. *BMJ Glob Health* 2023;8:e013076.
93. Garnacho-Montero J, Barrero-García I, Gómez-Prieto M de G, et al. Severe community-acquired pneumonia: current management and future therapeutic alternatives. *Expert Rev Anti Infect Ther* 2018;16:667–77.
94. Liapikou A, Rosales-Mayor E, Torres A. The management of severe community acquired pneumonia in the intensive care unit. *Expert Rev Respir Med* 2014;8:293–303.
95. Bertagnolio S, Dobrev Z, Centner CM, et al. WHO global research priorities for antimicrobial resistance in human health. *Lancet Microbe* 2024;5:100902.
96. Turner HC, Hao NV, Yacoub S, et al. Achieving affordable critical care in low-income and middle-income countries. *BMJ Glob Health* 2019;4:e001675.
97. Caliendo AM, Gilbert DN, Ginocchio CC, et al. Better tests, better care: improved diagnostics for infectious diseases. *Clin Infect Dis* 2013;57 Suppl 3:S139–70.
98. Beauchemin M, Cohn E, Shelton RC. Implementation of Clinical Practice Guidelines in the Health Care Setting: A Concept Analysis. *ANS Adv Nurs Sci* 2019;42:307–24.
99. Chikwari CD, Tadesse AW, Shanaube K, et al. Achieving equitable leadership in Global Health partnerships: barriers experienced and strategies to improve grant funding for early- and mid-career researchers. *BMC Glob Public Health* 2024;2:17.
100. Ginsburg AS, Duncan K, Klugman KP, et al. Access to antibiotics for pneumonia and sepsis in LMICs. *Lancet Glob Health* 2024;12:e1928–9.
101. Poole S, Clark TW. Rapid syndromic molecular testing in pneumonia: The current landscape and future potential. *J Infect* 2020;80:1–7.
102. Monard C, Pehlivan J, Auger G, et al. Multicenter evaluation of a syndromic rapid multiplex PCR test for early adaptation of antimicrobial therapy in adult patients with pneumonia. *Crit Care* 2020;24:434.
103. Babady NE. The FilmArray respiratory panel: an automated, broadly multiplexed molecular test for the rapid and accurate detection of respiratory pathogens. *Expert Rev Mol Diagn* 2013;13:779–88.
104. Cusack R, Little E, Martin-Loeches I. Practical Lessons on Antimicrobial Therapy for Critically Ill Patients. *Antibiotics (Basel)* 2024;13:162.
105. Martin-Loeches I, Torres A. Corticosteroids for CAP, influenza and COVID-19: when, how and benefits or harm? *Eur Respir Rev* 2021;30:200346.
106. Bos LD, Martin-Loeches I, Schultz MJ. ARDS: challenges in patient care and frontiers in research. *Eur Respir Rev* 2018;27:170107.



A sua editora de publicações médicas

Se ainda não recebe gratuitamente a *Thorax* com artigos do *Archives Disease in Childhood*, envie os seus dados para geral@medjournal.pt

Cuidados respiratórios sustentáveis: o que realmente importa

Gary Connett,¹ Mary Slingo,² Ian Sinha,^{3,4} Dame Julia Slingo⁵

O BTS/SIGN/NICE publicou recentemente *guidelines* atualizadas para o tratamento da asma.¹ A orientação recomenda que a escolha do inalador seja baseada no menor impacto ambiental entre os dispositivos adequados e fornece um *link* para uma ferramenta de decisão que informa os doentes sobre a pegada de carbono relativa entre inaladores de pó seco e inaladores em aerossol dosimetrado. Essa recomendação está alinhada com grande parte da literatura publicada que sugere medidas pelas quais os sistemas de saúde podem reduzir o seu impacto nas mudanças climáticas e ajudar a cumprir a estratégia de carbono zero do Serviço Nacional de Saúde (NHS) do Reino Unido.²⁻⁴

Os supostos benefícios ambientais da substituição por inaladores de pó seco coincidem convenientemente com a necessidade de abordar o uso excessivo de beta-agonistas de curta duração em aerossol no Reino Unido e os benefícios da transição para o tratamento combinado de manutenção e alívio (MART), geralmente em formulação de pó seco.⁵⁻⁷

Embora essa nova *guideline* seja louvável e consistente com as melhores evidências atuais para o tratamento da asma, a ciência do clima sugere que, infelizmente, os benefícios ambientais alegados são insignificantes. Situação semelhante ocorreu na anestesia. *Guidelines* nacionais que alteraram a prática para reduzir o uso de gases anestésicos foram baseadas em uma simplificação excessiva da ciência climática, resultando em respostas equivocadas que podem aumentar as emissões de CO₂ e comprometer o cuidado ao doente.⁸

Esses problemas surgiram porque o setor médico, com boas intenções, está a utilizar uma métrica idealizada de emissão de gases de efeito estufa, conhecida como Potencial de Aquecimento Global (GWP) e a sua equivalência em CO₂ (CO₂e), para inferir impactos climáticos e pegadas de carbono. O CO₂e é calculado como o produto do GWP e da emissão de um determinado gás. O CO₂e calculado é frequentemente expresso em termos de quilômetros percorridos por um carro movido a combustíveis fósseis. Consequentemente, o impacto dos hidrofluoroalcanos (HFAs) na literatura

médica é geralmente representada como a distância percorrida por um veículo.

Representar os efeitos dos gases de efeito estufa dessa forma é facilmente compreendida por profissionais de saúde e doentes, e tem sido amplamente adotada. Infelizmente, há falhas importantes nessa abordagem que tornam inválidos os impactos climáticos alegados, as pegadas de carbono e os quilômetros de carro equivalentes. Apesar do nome, o GWP não indica o potencial real de aquecimento global de uma emissão de gás. Foi criado em 1990 como uma ferramenta simples para auxiliar negociações internacionais e informar políticas climáticas multigás, como o Protocolo de Kyoto.⁹

O GWP não leva em conta a complexidade do sistema climático e sua resposta a emissões específicas.⁸ Para a prática médica, há um vasto corpo de evidências na literatura climática mostrando que o GWP é inválido para gases de vida curta com tempo de permanência inferior a 20 anos, como os agentes anestésicos voláteis e os propelentes dos inaladores dosimetrados (MDIs).^{10,11} A resposta do sistema climático a esses gases é fundamentalmente diferente da resposta aos gases de vida longa, como o CO₂ e o óxido nitroso, que permanecem na atmosfera por mais de 100 anos. O GWP nunca foi projetado para gerir emissões mínimas de gases de vida curta e superestima grosseiramente seu impacto climático potencial.⁹ Da mesma forma, a conversão para emissões de CO₂e, baseada no GWP, exagera suas pegadas de carbono e os supostos quilômetros de carro.

Reconhecendo as limitações de avaliar impactos climáticos com base em métricas de emissão, cientistas climáticos defendem o uso do forçamento radiativo — a diferença entre a energia que entra no planeta e a que sai — como medida fundamental dos efeitos de temperatura da atividade humana.¹² Essa métrica representa com precisão os efeitos reais de temperatura. O forçamento radiativo fornece uma comparação fisicamente robusta da contribuição real de cada gás para o aquecimento global e, ao contrário do GWP, leva em conta o comportamento diferente dos gases de vida curta *versus* os de vida longa.

A ciência climática é clara ao afirmar que o forçamento radiativo e o aquecimento causados pelo CO₂ continuarão a aumentar à medida que as emissões se acumulam década após década. No entanto, para os HFAs de vida curta, o forçamento radiativo não aumenta indefinidamente, pois as emissões não podem se acumular na atmosfera além da vida útil do gás.¹¹ Expressar as emissões de HFAs em termos de CO₂e distorce o seu impacto de curto

prazo na temperatura global e exagera o seu impacto climático de longo prazo.¹⁰ Cada quilograma de CO₂ emitido se acumula na atmosfera ao longo da vida e altera irreversivelmente o clima por gerações, enquanto o efeito de cada quilograma de HFA desaparece em cerca de uma década. É importante observar que o que importa é a taxa de emissão dos HFAs. Se o uso de MDIs continuar no ritmo atual, por exemplo, não ocorrerá aquecimento adicional — que já é mínimo. Em contraste, não existe um nível seguro de emissões de CO₂.

Os dois principais gases usados como propelentes em MDIs são o HFC-134a e o HFC-227ea.¹³ Nenhum deles é substância destruidora da camada de ozônio, mas ambos são gases de efeito estufa ativos. O HFC-134a é o HFA mais abundante e o mais utilizado em MDIs. Tem um GWP alto de cerca de 1470, mas sua vida útil na atmosfera é de aproximadamente 14 anos. O HFC-227ea também é usado em MDIs, com vida útil de 36 anos e GWP de 3580.

As emissões e a abundância atmosférica do HFC-134a estão a aumentar. A sua fração molar média anual global atingiu 113 ppt em 2020, acima dos 89 ppt em 2016.¹⁴ A abundância do HFC-227ea é muito menor, em 1,7 ppt. Assim, em 2020, o HFC-134a de todas as fontes de emissão contribuiu com um forçamento radiativo global de 19,5 mW/m², e o HFC-227ea contribuiu com 0,46 mW/m². Para contextualizar, o forçamento radiativo do CO₂ é estimado em 2160 mW/m².

Os HFAs usados em MDIs representam apenas uma pequena parte de todas as fontes de emissão. O HFC-134a é amplamente utilizado como refrigerante em refrigeradores móveis e domésticos, como componente de mistura para ar-condicionado estacionário e refrigeração comercial, como agente expander de espuma e como propelente para aerossóis industriais. O HFC-227ea é amplamente utilizado como agente extintor de incêndio.

As estimativas das emissões globais anuais provenientes de MDIs são difíceis de encontrar. O Comité Técnico Europeu de Fluorocarbonos relatou que, em 2018, a fabricação global de 800 milhões de MDIs utilizou cerca de 11.500 toneladas (11,5 Gg) de HFAs, dos quais 92% eram HFC-134a.¹⁵ As estimativas globais de emissão de HFC-134a de todas as fontes giram em torno de 160 Gg/ano. Se todos esses MDIs fossem utilizados, contribuiriam com no máximo 6% das emissões anuais totais de HFC-134a. Da mesma forma, os inaladores contendo HFC-227ea contribuiriam com no máximo 15% das emissões totais anuais de 6,3 Gg/ano.

Assumindo que a composição atmosférica seja proporcional à taxa de emissão dos inaladores, e que todos os inaladores fabricados tenham sido usados no mesmo ano, uma estimativa aproximada e de pior cenário da contribuição dos inaladores para o forçamento radiativo total do HFC-134a de 19,5 mW/m² seria de ~1,2 mW/m². Usando a mesma lógica para o HFC-227ea,

¹Paediatric Respiratory Medicine, University of Southampton, Southampton, UK

²Anaesthetics, University Hospital Southampton NHS

Foundation Trust, Southampton, UK

³University of Liverpool, Liverpool, UK

⁴Alder Hey Children's Hospital, Liverpool

⁵Department of Meteorology, University of Reading, Reading, UK

Correspondence to Dr Gary Connett; garyconnett@mac.com

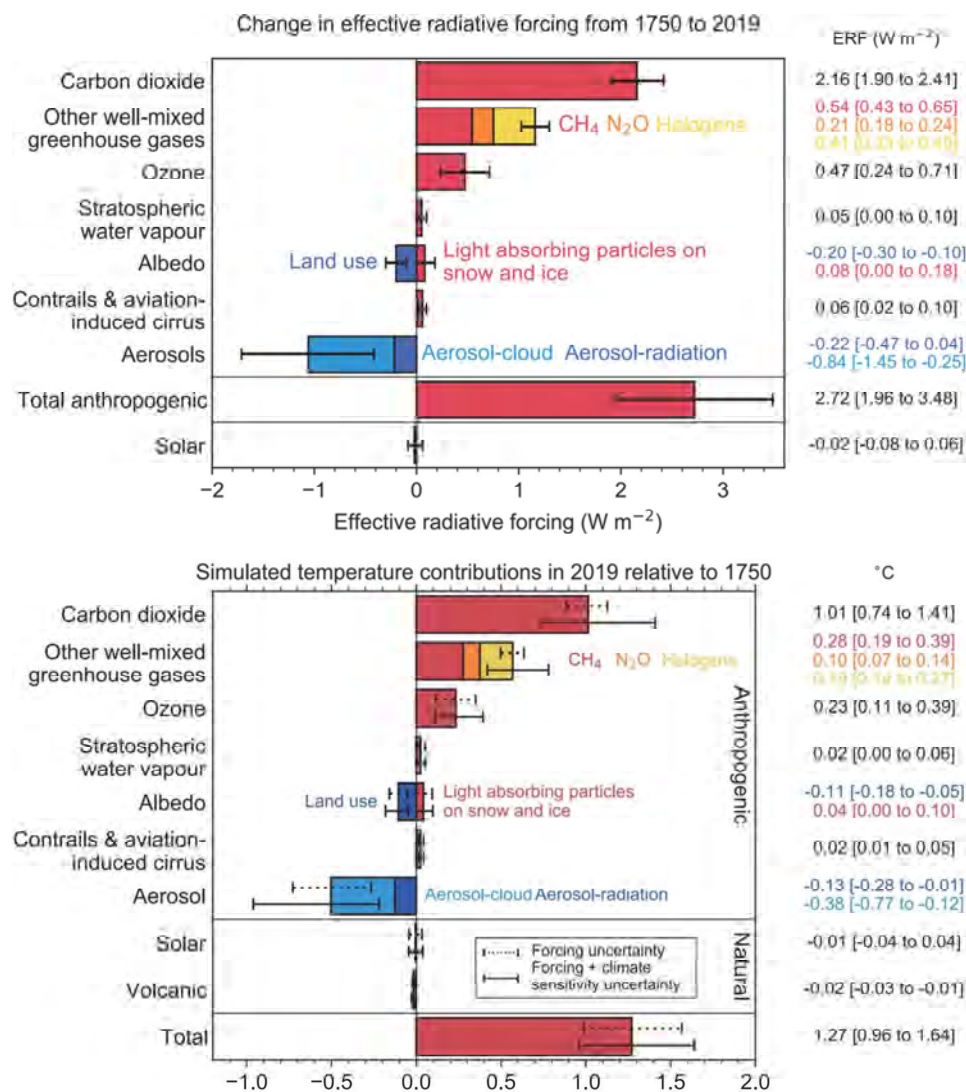


Figure 1 Change in effective radiative forcing (ERF) and surface temperature change from 1750 to 2019 by contributing forcing agents. Note the scale of the uncertainty in the radiative forcing and surface temperature change. CH₄, Methane; N₂O, Nitrous Oxide. Reproduced from figures 7.6 and 7.7 in chapter 7: The physical science basis. Contribution of working group I to the sixth assessment report of the intergovernmental panel on climate change, doi: 10.1017/9781009157896.008.

a estimativa de pior cenário seria de 0,07 mW/m². Isso significa que a estimativa de pior cenário do forçamento radiativo dos MDIs em todo o mundo é de ~1,27 mW/m². Quando comparado ao forçamento radiativo estimado do CO₂ de 2160±250 mW/m², qualquer contribuição dos propelentes dos MDIs é insignificante.⁸ Assim como os gases anestésicos, os efeitos climáticos dos MDIs médicos são extremamente pequenos e irrelevantes. Remover os MDIs da prática médica não terá impacto no sistema climático nem na trajetória do aquecimento global.

Métricas simples de emissão tornaram-se populares por serem fáceis de usar, mas claramente apresentam limitações. Todas as métricas de emissão são simplificações grosseiras da resposta climática aos gases de efeito estufa, mas o Potencial de Aquecimento Global por Temperatura (GTP) possui várias vantagens em relação ao GWP. O GTP tenta considerar aspectos fundamentais da resposta climática ao forçamento radiativo, incluindo a sensibilidade climática e a inércia térmica dos oceanos.¹⁰ No entanto, trata-se de uma métrica de ponto final baseada na mudança de temperatura ao final de um período específico (por exemplo, 100 anos), e por isso envolve suposições sobre trajetórias futuras de emissão. Assim como o GWP, o GTP pode ser convertido em equivalência de CO₂ (CO₂e). Ambas as métricas são relatadas na Avaliação Científica da Depleção da Camada de Ozônio da OMM/PNUMA.¹⁴

Uma comparação entre GWP e GTP (tabela 1) destaca o quanto o uso do GWP para derivar CO₂e superestima substancialmente o impacto climático e a pegada de carbono de gases de vida curta, como o metano e os propelentes de inaladores dosimetrados (MDIs). Se o GTP fosse usado em vez do GWP, as estimativas de CO₂e citadas pelo NICE seriam reduzidas em até 80%. O uso dessa métrica mais apropriada impacta significativamente a estimativa de quanto a pegada de carbono poderia ser reduzida ao remover MDIs da prática clínica — embora ainda seja uma simplificação considerável da complexidade do sistema climático.

Contrariando a sugestão de que poderíamos obter “vitórias rápidas” ao trocar para inaladores “de baixo carbono”, o forçamento radiativo minúsculo e a curta vida útil dos HFAs em aerossóis médicos os tornam irrelevantes para a trajetória das mudanças climáticas. Da mesma forma, a substituição

Table 1 Comparison of GWP and GTP for major greenhouse gases and the propellants used in MDIs

Greenhouse gas	Atmospheric lifetime (years)	GWP ₁₀₀	GTP ₁₀₀
Carbon dioxide (CO ₂)	100+	1	1
Methane (CH ₄)	11.8	27	4.7
Nitrous oxide (N ₂ O)	109	273	233
HFC-134a	14	1470	292
HFC-227ea	39	5820	1470

Data from Ref.¹⁴
GTP, Global Temperature Potential; GWP, Global Warming Potential.

por propelentes mais “amigos do clima” provavelmente não resultará em benefícios climáticos significativos.¹⁶ Em vez disso, o custo ambiental das emissões diretas de CO₂ provenientes da interrupção da produção atual de MDIs, da pesquisa essencial para o desenvolvimento de novos medicamentos e da introdução de novos processos de produção levará décadas para ser compensado. Avaliações de segurança demoradas, atraso na disponibilidade no mercado e novas patentes provavelmente resultarão em aumento de custos para o sistema de saúde e afetarão desproporcionalmente as crianças.¹⁷

Embora tenha sido sugerido que a substituição de aerossóis por equivalentes em pó seco possa gerar economia financeira para o NHS do Reino Unido, essa análise não considerou a mudança para regimes MART, como atualmente recomendado.¹⁸ Seguir as diretrizes do NICE/BTS/SIGN provavelmente resultará em economia de custos, mas isso se deve à redução da necessidade de tratamento hospitalar, e não ao uso de inaladores mais ecológicos.¹⁹

Se não houver efeitos prejudiciais ao cuidado do doente nem custos desnecessários, há bons argumentos clínicos para a substituição por inaladores de pó seco sempre que possível — embora isso não seja uma opção para crianças em idade pré-escolar. Os argumentos relacionados à pegada de carbono e aos impactos climáticos dos MDIs devem ser corrigidos para garantir que representem com precisão a ciência climática subjacente. Supervalorizar os atributos ecológicos das boas práticas pode desviar a atenção de muitas outras formas mais significativas pelas quais os profissionais de saúde podem reduzir os seus impactos ambientais. Como já destacado nesta publicação, fazer com que os doentes se sintam obrigados a trocar seus inaladores pode também estigmatizar ou desestabilizar indivíduos já altamente vulneráveis.²⁰

Uma melhor compreensão da ciência que fundamenta a importância relativa dos dife-

rentes gases de efeito estufa para o aquecimento global tem implicações importantes para a forma como os profissionais de saúde podem abordar a escolha do dispositivo inalador, as recomendações dos formuladores de políticas sobre as melhores práticas e o desenvolvimento de novos dispositivos de administração de medicamentos pela indústria farmacêutica.²¹ Profissionais de saúde que desejam reduzir significativamente as suas emissões de gases de efeito estufa — especialmente CO₂ — podem, de forma útil, oferecer consultas por telefone quando for seguro fazê-lo, separar rigorosamente resíduos médicos de resíduos domésticos para evitar a incineração desnecessária, minimizar o uso de nebulizadores, evitar acompanhamentos desnecessários, investigações duplicadas e ineficiências administrativas, desligar o ar condicionado, evitar viagens aéreas, caminhar ou pedalar sempre que possível e compartilhar viagens de carro com colegas. Mudar práticas para reduzir a queima de combustíveis fósseis é a estratégia mais eficaz que os profissionais de saúde podem adotar para minimizar a sua contribuição para o aquecimento global.

X Gary Connett @garyconnett

Contributors GC conceptualised the article and drafted the initial manuscript. IS contributed to the development of arguments relating to clinical practice, MS and JS provided critical content and revisions related to climate science. All authors helped refine the manuscript. All authors approved the final version and take responsibility for its content. GC 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 Not applicable.

Provenance and peer review Not commissioned; externally peer-reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed.

Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.



OPEN ACCESS

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial.

See: <http://creativecommons.org/licenses/by-nc/4.0/>.

© Author(s) (or their employer(s)) 2025. Re-use permitted under CC BY-NC. No commercial re-use.

See rights and permissions. Published by BMJ Group.

►Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/thorax-2025-223195>).



Check for updates

To cite Connett G, Slingo M, Sinha I, et al. Thorax

2025;80:500–503.

Published Online First 11 May 2025

Thorax 2025;80:500–503.

doi:10.1136/thorax-2025-223195

REFERENCES

1. Asthma pathway (BTS, NICE, SIGN). NICE guideline [NG244]. Available: <https://www.nice.org.uk/guidance/ng244> [Accessed 10 Feb 2025].
2. Braithwaite J, Smith CL, Leask E, et al. Strategies and tactics to reduce the impact of healthcare on climate change: systematic review. *BMJ* 2024;387:e081284.
3. Janson C, Henderson R, Löfdahl M, et al. Carbon footprint impact of the choice of inhalers for asthma and COPD. *Thorax* 2020;75:82–4.
4. Delivering a 'net zero' national health service. 2025. Available: <https://www.england.nhs.uk/greenmhs/wp-content/uploads/sites/51/2022/07/B1728-delivering-a-net-zero-nhs-july-2022.pdf> [accessed 10 Feb 2025].
5. Wilkinson A, Menzies-Gow A, Sawyer M, et al. S26 An assessment of short-acting β₂-agonist (SABA) use and subsequent greenhouse gas (GHG) emissions in five European countries and the consequence of their potential overuse for asthma in the UK. *Thorax* 2021;76:A19–A.
6. Bloom CL, Cabrera C, Arnetorp S, et al. Asthma-Related Health Outcomes Associated with Short-Acting β₂-Agonist Inhaler Use: An Observational UK Study as Part of the SABINA Global Program. *Adv Ther* 2020;37:4190–208.
7. Beasley R, Harrison T, Peterson S, et al. Evaluation of Budesonide-Formoterol for Maintenance and Reliever Therapy Among Patients With Poorly Controlled Asthma: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2022;5:e220615.
8. Slingo JM, Slingo ME. The science of climate change and the effect of anaesthetic gas emissions. *Anaesthesia* 2024;79:252–60.
9. Shine KP. The global warming potential—the need for an interdisciplinary retrieval. *Clim Change* 2009;96:467–72.
10. Shine KP, Fuglestad J, Hailemariam K, et al. Alternatives to the Global Warming Potential for Comparing Climate Impacts of Emissions of Greenhouse Gases. *Clim Change* 2005;68:281–302.
11. Pierrehumbert RT. Short-Lived Climate Pollution. *Annu Rev Earth Planet Sci* 2014;42:341–79.
12. Fuglestad J. Metrics of climate change: assessing radiative forcing and emission indices. *Clim Change* 2003;58:267–331.
13. Wilkinson AJK, Braggins R, Steinbach I, et al. Costs of switching to low global warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England. *BMJ Open* 2019;9:e028763.
14. World Meteorological Organization/United Nations Environment Programme. Ozone assessment report 2022. Annex: summary of abundances, lifetimes, ODPs, REs, GWPs, and GTPs. 2025. Available: https://csf.noaa.gov/assessments/ozone/2022/downloads/Annex_2022OzoneAssessment.pdf [accessed 12 Feb 2025].
15. European Fluorocarbons Technical Committee. Metered dose inhalers. Available: <https://www.fluorocarbons.org/applications/metered-dose-inhalers/2022> [Accessed 10 Feb 2025].
16. van Hove M, Leng G. A more sustainable NHS. *BMJ* 2019;366:l4930.
17. Brennan SK, Coates AC, Laube B, et al. Climate Policy and Pediatric Asthma: How Transition to Nonhydrofluorocarbon Propellants Will Disproportionately Impact Children. *Ann Am Thorac Soc* 2024;21:1242–4.
18. Wilkinson A, Woodcock A. The environmental impact of inhalers for asthma: A green challenge and a golden opportunity. *Br J Clin Pharmacol* 2022;88:3016–22.
19. Report BSNEa. Cost-utility analysis. Step up therapy for management of uncontrolled asthma. 2024. Available: <https://www.nice.org.uk/guidance/ng245/documents/economic-report-2> [accessed 10 Feb 2025].
20. Partridge MR. Green respiratory healthcare: need for proportionality. *Thorax* 2020;75:369.
21. Feldman WB, Furie G. The Moral Injury of Inhaler Prescribing. *N Engl J Med* 2025;392:836–9.

Atenção à lacuna (dos prematuros): a desigualdade na atual abordagem de imunização contra o VSR no Reino Unido deixará muitos bebês prematuros desprotegidos contra o vírus neste inverno

James E G Charlesworth^{1,2}

INTRODUÇÃO

A Agência de Segurança da Saúde do Reino Unido (UKHSA) anunciou recentemente programas de vacinação contra o vírus sincicial respiratório (VSR) para proteger bebês por meio da vacinação de gestantes com 28 semanas de gestação e adultos com 75 anos ou mais.¹ Essa decisão, que oferece proteção aos bebês contra o VSR por pelo menos seis meses, é extremamente bem-vinda, apoiada pela recomendação do Comitê Conjunto de Vacinação e Imunização (JCVI) em junho de 2023 (atualizada em setembro de 2023)² e por uma carta aberta do Colégio Real de Pediatria e Saúde Infantil (RCPCH) em março de 2024, solicitando a implementação da política.

A recomendação do JCVI analisou dois produtos: primeiro, a imunização infantil por meio de uma única dose de anticorpo monoclonal de meia-vida estendida contra a proteína F (nirsevimabe, desenvolvido pela Sanofi e AstraZeneca, comercializado como Beyfortus); e segundo, a vacinação materna com uma vacina bivalente da proteína F pré-fusão (comercializada como Abrysvo, fabricada pela Pfizer). Ambos os produtos demonstraram oferecer profilaxia eficaz contra o VSR, levando o Departamento de Saúde e Assistência Social a licitar o programa de profilaxia infantil contra o VSR, com base em critérios de viabilidade e custo-benefício definidos pelo Tesouro.

A Pfizer foi selecionada para fornecer a vacinação materna, iniciada em agosto de 2024 na Escócia e em setembro de 2024 nas demais nações do Reino Unido. A vacinação materna pode ter se mostrado mais econômica quando oferecida durante todo o ano (como recomendado pelo JCVI) e fornecida juntamente com a mesma vacina para adultos mais velhos, que representam uma coorte muito maior. Além disso, essa estratégia pode ter maior adesão, com a UKHSA demonstrando que a vacinação materna tem maior aceitação (89,5%) do que a imunização infantil com anticorpos monoclonais (81,4%), segundo pesquisa com 1061 gestantes ou mães recentes (*webinar* da UKHSA, 12 de julho de 2024).

Ambas as estratégias de imunização protegem contra hospitalizações por bronquiolite associada ao VSR

Os ensaios clínicos de referência para ambas as abordagens mostraram alta eficácia. A hospitalização associada ao VSR foi reduzida com eficácia de 83,2% (IC 95%: 67,8% a 92,0%) no estudo HARMONIE com nirsevimabe,³ e de 56,8% (IC 95%: 10,1% a 80,7%) no estudo MATISSE com vacinação materna.⁴ A maior eficácia observada no HARMONIE pode refletir a inclusão de mais bebês prematuros (14% vs 5,6% no MATISSE), que têm maior risco de complicações por VSR, com imunização monoclonal oferecida a bebês nascidos com 29 semanas de gestação ou mais.

A eficácia na redução de infecções graves do trato respiratório inferior associadas ao VSR foi semelhante entre os estudos, aos seis meses após a imunização no HARMONIE (75,7%, IC 95%: 32,8% a 92,9%) e desde o nascimento no MATISSE (69,4%, IC 95%: 44,3% a 84,1%). No entanto, como observa o JCVI,² as definições de doença grave e hospitalização diferiram entre os estudos.

A eficácia e viabilidade do nirsevimabe são apoiadas por um estudo observacional pragmático com 23.127 bebês imunizados na Catalunha no inverno de 2023–2024.⁵ Para os imunizados *versus* os não imunizados, houve alta eficácia contra hospitalização relacionada ao VSR (87,6%, IC 95%: 82,1% a 91,4%) e admissão em unidade de terapia intensiva pediátrica (90,1%, IC 95%: 76,3% a 95,9%). Esse programa atingiu 87,2% de cobertura entre os bebês elegíveis, mas não relatou eficácia ou cobertura entre prematuros. Importante destacar que todos os estudos mencionados demonstram possibilidade de infecção entre bebês imunizados, o que é desejável para a geração de imunidade do hospedeiro, já que a imunidade passiva derivada de anticorpos monoclonais ou maternos diminui com o tempo. No entanto, como resultado, é provável que não haja redução significativa na transmissão viral com nenhuma das estratégias, ao contrário de programas que visam imunidade coletiva.

Bebês prematuros têm maior risco de hospitalização por bronquiolite

Bebês prematuros apresentam risco significativamente maior de hospitalização e complicações por bronquiolite associada ao VSR do que bebês nascidos a termo. Um grande estudo observacional (BronchStart), realizado na Inglaterra, Escócia e Irlanda durante duas temporadas pós-pandemia de

VSR, demonstrou que bebês nascidos com menos de 28 semanas de gestação têm risco aumentado de internação por bronquiolite (OR 3,28; IC 95%: 2,48 a 4,36),⁶ em comparação com os nascidos a termo. Esse risco permanece elevado entre os nascidos entre 32 e 36 semanas (OR 1,91; IC 95%: 1,71 a 2,14). Além disso, a admissão em unidades de terapia intensiva pediátrica (UTIP) foi mais de cinco vezes maior entre todos os bebês prematuros (RR 5,69; IC 95%: 4,05 a 7,96). Esses dados não foram desagregados entre bebês com e sem outras condições de alto risco que os tornariam elegíveis para imunização passiva com anticorpos monoclonais no programa atual de alto risco (informações suplementares *online*).

A abordagem do Reino Unido para imunização contra o VSR gera desigualdade no cuidado de bebês prematuros

Os programas infantis de imunização contra o VSR no Reino Unido incluem vacinação materna a partir da 28ª semana de gestação, juntamente com o programa existente de anticorpos monoclonais para bebês a termo e prematuros com alto risco. O programa de alto risco agora recomenda o uso de nirsevimabe (anteriormente palivizumabe), quando disponível. O nirsevimabe é um anticorpo monoclonal de longa duração administrado em dose única no início da temporada de VSR. Como o fornecimento de nirsevimabe será limitado devido à demanda internacional, o palivizumabe pode ser usado como alternativa, mas requer injeções mensais durante toda a temporada.

Os bebês elegíveis apresentam características de alto risco, como comorbidades respiratórias, cardíacas ou imunológicas, ou prematuridade associada a comorbidades respiratórias ou cardíacas (resumidas nas informações suplementares *online*). Embora o “Green Book” sugira que o julgamento clínico pode ser usado para oferecer imunização com anticorpos monoclonais a doentes “com risco particular de complicações por VSR”, o JCVI observou que “não há um sistema fácil para obter vacinação contra o VSR com base no julgamento clínico no NHS”.²

Bebês nascidos antes das 28 semanas não beneficiarão da imunização materna. Aqueles nascidos entre 28 e 30 semanas terão benefício limitado ou nenhum, e após as 30 semanas podem ter algum benefício (não definido) com a transferência de anticorpos maternos. No entanto, está bem estabelecido que os bebês prematuros têm níveis mais baixos de anticorpos maternos, que atingem o pico no termo, e os títulos de anticorpos protetores nesses bebês diminuem mais rapidamente.⁷ Dado que poucos bebês nasceram prematuros no estudo MATISSE (n=371),⁴ é improvável que estejam disponíveis dados estatisticamente significativos sobre a eficácia por idade gestacional. Pode ser possível determinar um limite inferior de gestação para o qual foi demonstrada uma eficácia protetora aceitável (ou seja, o tempo entre a vacinação materna e o parto). Esta desigualdade na proteção foi considerada na decisão do JCVI, que observou

¹Department of Paediatrics, Medical Sciences Division, University of Oxford, Oxford, UK

²Paediatrics, Milton Keynes University Hospital NHS Foundation Trust, Milton Keynes, UK

Correspondence to Dr James E G Charlesworth; james.charlesworth@paediatrics.ox.ac.uk

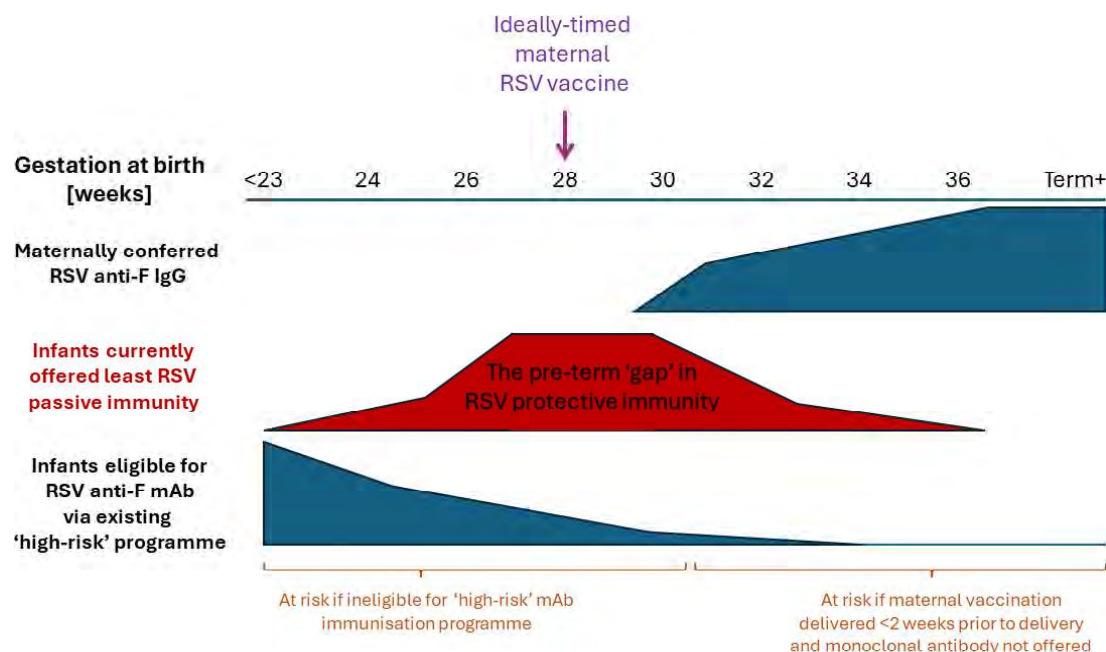


Figure 1 Representation of respiratory syncytial virus (RSV) immunity by gestation, following maternal vaccination at 28 weeks combined with the existing 'high-risk' monoclonal antibody programme. Shown is a representative schematic of likely RSV-conferred immunity following maternal vaccination (upper right curve) and among infants eligible for monoclonal antibody immunisation (nirsevimab, or if supply is lacking then palivizumab) through the existing 'high-risk' programme (lower left curve). No data have been published on vaccine efficacy following maternal vaccination versus time since vaccine to delivery; however, putative data are referenced within the 'green book' (Public Health England, chapter 27a, page 9),¹⁰ suggesting protective antibody transfer to the baby demonstrated by 2 weeks following maternal vaccination. If maternal vaccination is ideally timed, this suggests protection from 30 weeks' gestation, which would expect to increase until term, where >100% of maternal antibodies are typically reported. IgG, immunoglobulin G; mAb, monoclonal antibody.

que "o nascimento prematuro comprometeria a quantidade de anticorpos maternos disponíveis para o bebê, sendo assim provável que fosse necessário o uso suplementar de MAB [anticorpo monoclonal] para os bebês mais prematuros."²

Mesmo que a imunização seja oferecida a todas as mães e bebês elegíveis, e com adesão total, um número significativo de bebês prematuros terá imunidade protetora limitada ou inexistente (representado na figura 1). Com base nos dados do Escritório Nacional de Estatísticas de 2022, bebês nascidos com menos de 32 semanas representam 1,23% dos nascimentos vivos (n=7447 em 2022).⁸ Apenas 0,23% de todos os nascimentos prematuros são elegíveis para imunização monoclonal dentro do programa de alto risco, com base em dados de saúde de 2010–2016.⁹ Esse estudo também demonstrou que apenas um terço dos bebês elegíveis recebeu ao menos uma dose de palivizumabe, possivelmente devido à complexidade dos critérios de elegibilidade por idade gestacional e cronológica. Combinando esses dados, estima-se que cerca de 1% de todos os nascimentos vivos (n=6154 bebês em 2022) com menos de 32 semanas de gestação atualmente não seriam elegíveis para imunização monoclonal e não teriam imunidade suficiente da vacinação materna, mesmo com adesão total.

Após o anúncio do programa de vacinação materna, não houve medidas para garantir proteção igualitária para bebês prematuros, considerando a cobertura universal oferecida aos bebês a termo. É lamentável que a provisão para bebês prematuros não tenha sido simultaneamente incluída na licitação para profilaxia universal contra o VSR. Há uma

complexidade significativa na implementação de uma solução temporária neste inverno e na reconfiguração da oferta de anticorpos monoclonais posteriormente, com limitações na aquisição econômica e no fornecimento do produto. O subcomitê do JCVI sobre o VSR se reuniu em junho de 2024, e aguardamos o resultado da reunião completa do comitê em outubro de 2024. No entanto, novas recomendações neste estágio correm o risco de deixar pouco tempo para a contratação, fornecimento e distribuição do nirsevimabe para bebês prematuros desprotegidos.

CONCLUSÃO

O programa de imunização materna contra o VSR é extremamente bem-vindo, mas deixa uma parcela de bebês prematuros sem a proteção conferida aos bebês a termo. A maioria dos prematuros não é elegível para imunização monoclonal dentro do programa de "alto risco", embora tenha maior risco de hospitalização por VSR do que os bebês a termo. Será necessário expandir a oferta de anticorpos monoclonais para incluir todos os bebês prematuros que não se beneficiam da vacinação materna, a fim de garantir equidade no cuidado nesta e nas futuras temporadas de VSR. Uma adaptação rápida da política atual é necessária para esta temporada.

Correction notice This paper has been amended since it was first published. The wrong competing interests statement was inadvertently added during the production stage.

X James E G Charlesworth @jeg_cworth

Contributors JEGC is the sole author.

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 JEGC is a sub-investigator on the Merck Sharp & Dohme (MSD, a subsidiary of Merck) sponsored MK-1654-004 and MK-1654-007 studies of clesrovimab, an investigational extended half-life monoclonal antibody towards RSV fusion protein. He has not nor has ever been employed or funded by Merck.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed. **Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed.

Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise. © Author(s) (or their employer(s)) 2025. No commercial re-use. See rights and permissions. Published by BMJ Group.



Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/archdischild-2024-327741>).

To cite Charlesworth JEG. Arch Dis Child 2025;110:662–664.

Received 25 July 2024

Accepted 27 September 2024

Published Online First 8 October 2024



→ <http://dx.doi.org/10.1136/archdischild-2024-327844>

Arch Dis Child 2025;110:662–664.

doi:10.1136/archdischild-2024-327741

ORCID iD

James E G Charlesworth <http://orcid.org/0000-0001-9859-7383>

REFERENCES

1. UK Health Security Agency. Introduction of new nhs vaccination programmes against respiratory syncytial virus (RSV). 2024.
2. Joint Committee on Vaccination and Immunisation (JCVI). Respiratory syncytial virus (rsv) immunisation programme for infants and older adults: JCVI full statement. 2023.
3. Drysdale SB, Cathie K, Flamein F, et al. Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants. *N Engl J Med* 2023;389:2425–35.
4. Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. *N Engl J Med* 2023;388:1451–64.
5. Coma E, Martinez-Marcos M, Hermosilla E, et al. Effectiveness of nirsevimab immunoprophylaxis against respiratory syncytial virus-related outcomes in hospital and primary care settings: a retrospective cohort study in infants in Catalonia (Spain). *Arch Dis Child* 2024;109:736–41.
6. Williams TC, Marlow R, Hardelid P, et al. Clinical Impact of Serious Respiratory Disease in Children Under the Age of 2 Years During the 2021–2022 Bronchiolitis Season in England, Scotland, and Ireland. *J Infect Dis* 2024;230:e111–20.
7. Fouda GG, Martinez DR, Swamy GK, et al. The Impact of IgG transplacental transfer on early life immunity. *Immunohorizons* 2018;2:14–25.
8. Office for National Statistics, UK. Birth characteristics in England and Wales: 2022. 2024. Available: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/livebirths/bulletins/birthcharacteristicsinenglandandwales/2022>
9. Zylberstein A, Almossawi O, Gudka N, et al. Access to palivizumab among children at high risk of respiratory syncytial virus complications in English hospitals. *Brit J Clinical Pharma* 2022;88:1246–57.
10. UK Health Security Agency. Respiratory Syncytial Virus: The Green Book, Chapter 27a, Page 9. Available: https://assets.publishing.service.gov.uk/media/5a80e88ac5274a2e87dbcf7f/Green_Book_Chapter_27a_v2_0W.PDF [accessed 7 Oct 2024].

Novo programa para prevenir bronquiolite em bebês

Andrew J Pollard,¹ Mary Elizabeth Ramsay,² Conall Watson³

Na sua carta ao *Archives of Disease in Childhood* (ADC)¹, Charlesworth chama corretamente a atenção para uma importante iniciativa de prevenção contra o vírus sincicial respiratório (VSR), recomendada pelo Comité Conjunto de Vacinação e Imunização (JCVI) e com início previsto para este ano. Espera-se que essa medida tenha um grande impacto na prática pediátrica, ao conter o número excessivo de bebês com bronquiolite e reduzir a pressão sobre as enfermarias pediátricas do Serviço Nacional de Saúde (NHS) durante o inverno, se for plenamente implementada.

Este é um marco significativo na medicina preventiva, resultado de uma década em que o JCVI vem destacando a importância da prevenção do VSR para melhorar a saúde infantil, além de vários anos de análise e discussão dos novos produtos profiláticos contra o VSR à medida que se aproximavam da aprovação.

Ao final das deliberações do JCVI, foram feitas recomendações ao Departamento de Saúde e Assistência Social (DHSC) em setembro de 2023² para um programa de prevenção contra o VSR, considerando dois produtos disponíveis: uma vacina contra o VSR a ser administrada durante a gravidez (proporcionando proteção ao bebê por meio da transferência placentária de anticorpos maternos) ou um anticorpo monoclonal administrado diretamente ao recém-nascido. As evidências dos ensaios clínicos existentes indicavam que ambos os produtos teriam impacto substancial na redução de hospitalizações e admissões em unidades de terapia intensiva por VSR. Apesar das diferenças nos desenhos dos estudos e nos critérios de avaliação, ambos os produtos eram considerados aceitáveis e provavelmente trariam benefícios significativos na prevenção da doença por VSR na infância. O NHS considerou que qualquer um dos produtos poderia ser facilmente implementado no programa.

Desde a recomendação do JCVI, o uso precoce do nirsevimabe na Espanha³ e em Luxemburgo⁴ durante a temporada 2023/2024 confirmou os resultados dos ensaios clínicos, mostrando grandes reduções nas hospitalizações por VSR em

uso real. Dados de impacto em uso real para a vacina administrada na gravidez ainda não estão disponíveis, e as primeiras análises dos EUA (temporada 2023/2024) e da Argentina (inverno de 2024 no Hemisfério Sul) são aguardadas com expectativa.

Após a recomendação do JCVI, a Agência de Segurança da Saúde do Reino Unido (UKHSA) abriu licitação para um produto profilático contra o VSR, visando o melhor uso dos recursos públicos com base nas análises de custo-benefício do JCVI. A vacina (produzida pela Pfizer) venceu a licitação, e o programa de vacinação durante a gravidez deve começar neste mês de setembro, com oferta da vacina a partir da 28ª semana de gestação.

O uso da vacina materna significa que a maioria dos bebês pode ser protegida contra formas graves de VSR, desde que a mãe receba a dose antes do parto. No entanto, como Charlesworth aponta corretamente, os bebês nascidos com menos de 30–32 semanas de gestação podem não se beneficiar, seja porque a mãe ainda não foi vacinada, seja porque o bebê nasce antes que ocorra uma transferência placentária significativa dos anticorpos induzidos pela vacina.

Embora a maioria das hospitalizações por VSR envolva bebês nascidos a termo, o risco individual de hospitalização é muito maior entre os prematuros, o que cria uma situação insatisfatória em que uma minoria importante de bebês não pode se beneficiar dessa proteção.

Antes das recomendações universais de setembro de 2023, o JCVI havia aconselhado que o programa para bebês de alto risco (atualmente baseado em múltiplas doses do anticorpo monoclonal palivizumabe, administradas ao longo da temporada de VSR) fosse substituído por uma única dose do recém-licenciado anticorpo monoclonal de meia-vida estendida, o nirsevimabe, para a temporada 2023/2024. Não foi possível adquirir esse produto para o NHS, e o uso do palivizumabe continuou na última temporada como anteriormente. Espera-se que o programa com palivizumabe seja mantido novamente no Reino Unido em 2024/2025.

O JCVI observou que um programa mais amplo com anticorpos monoclonais para bebês prematuros teria que ser considerado, caso a vacinação materna contra o VSR (em vez do monoclonal) fosse usada como estratégia universal — como agora sabemos que é o caso. O JCVI continua a revisar ativamente essa questão.

Enquanto houver essa lacuna na oferta de proteção universal por meio da vacina,

há vantagens potenciais — embora ainda não comprovadas — como a proteção da mãe contra o VSR, o que pode reduzir o risco de transmissão ao bebê, e a indução de uma resposta imunológica mais ampla, que poderia diminuir o risco de mutações no vírus que levem à evasão vacinal.

Além do uso no NHS, talvez o aspecto mais importante seja que as vacinas podem ser produzidas com maior rendimento do que os anticorpos monoclonais, aumentando o potencial de preços acessíveis que poderiam viabilizar o acesso global. Cerca de 97% das 100.000 mortes anuais por VSR ocorrem em países de baixa e média renda, onde o impacto da prevenção será muito mais profundo do que em países de alta renda.⁵

A UKHSA continuará monitorizando a epidemiologia do VSR e o impacto do programa para apoiar o JCVI, que fornecerá aconselhamento contínuo ao DHSC sobre o acesso equitativo à prevenção do VSR para todos os bebês, incluindo a análise de novos produtos que aumentarão a oferta e as opções no futuro.

Como Charlesworth afirma corretamente, o início da prevenção contra o VSR no Reino Unido é “extremamente bem-vindo”. Nós iríamos além em nosso entusiasmo pelas bases do programa do NHS contra o VSR deste ano, pois esperamos olhar para 2024 como o início de uma nova era na pediatria.

X Andrew J Pollard @ajpollard1

Contributors The authors contributed equally. AJP 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 AJP is chair of JCVI. MER and CW are employees of UKHSA; UKHSA has provided vaccine manufacturers with postmarketing surveillance reports on meningococcal, Haemophilus influenzae and pneumococcal infections, which the companies are required to submit to the UK Licensing Authority in compliance with their risk management strategy. A cost recovery charge is made for these reports.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; internally peer reviewed.

© Author(s) (or their employer(s)) 2025. No commercial re-use.

See rights and permissions. Published by BMJ Group.



To cite Pollard AJ, Ramsay ME, Watson C.

Arch Dis Child 2025;110:573–574.

Received 15 August 2024

Accepted 27 September 2024

Published Online First 8 October 2024



→ <http://dx.doi.org/10.1136/archdischild-2024-327741>

Arch Dis Child 2025;110:573–574.

doi:10.1136/archdischild-2024-327844

ORCID iD

Andrew J Pollard <http://orcid.org/0000-0001-7361-719X>

REFERENCES

- Charlesworth J. Mind the (preterm) gap – Inequality in the UK's current RSV immunisation approach will leave many preterm babies unprotected against RSV this winter. Arch Dis Child 2024. 10.1136/archdischild-2024-327741. [Epub ahead of print: 8 Oct 2024].
- Immunisation JCoVa. Respiratory syncytial virus (rsv) immunisation programme for infants and older adults:jcv full statement, 11 september 2023.gov.uk. 2023. Available: <https://www.gov.uk/government/publications/rsv-immunisation-programme-jcvi-advice-7-june-2023>
- Ares-Gómez S, Mallah N, Santiago-Pérez M-I, et al. Effectiveness and impact of universal prophylaxis with nirsevimab in infants against hospitalisation for respiratory syncytial virus in Galicia, Spain: initial results of a population-based longitudinal study. Lancet Infect Dis 2024;24:817–28.
- Ernst C, Bejko D, Gaasch L, et al. Impact of nirsevimab prophylaxis on paediatric respiratory syncytial virus (RSV)-related hospitalisations during the initial 2023/24 season in Luxembourg. Euro Surveill 2024;29:2400033.
- Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet 2022;399:2047–64.

¹Paediatrics, University of Oxford, Oxford, UK

²Immunisation, Hepatitis and Blood Safety, UK Health

Security Agency, London, UK

³UKHSA, London, UK

Correspondence to Professor Andrew J Pollard; andrew.pollard@paediatrics.ox.ac.uk



ALLERGY & RESPIRATORY SUMMIT 2026

Centro de Congressos - Hotel Sheraton Porto
5, 6 E 7 DE FEVEREIRO 2026



JÁ CONHECE?

ALLERGY & RESPIRATORY EDUCATION

No website allergyrespiratory.com pode inscrever-se e aceder a conteúdos exclusivos, incluindo *webinars* dedicados à saúde respiratória e às doenças alérgicas.