

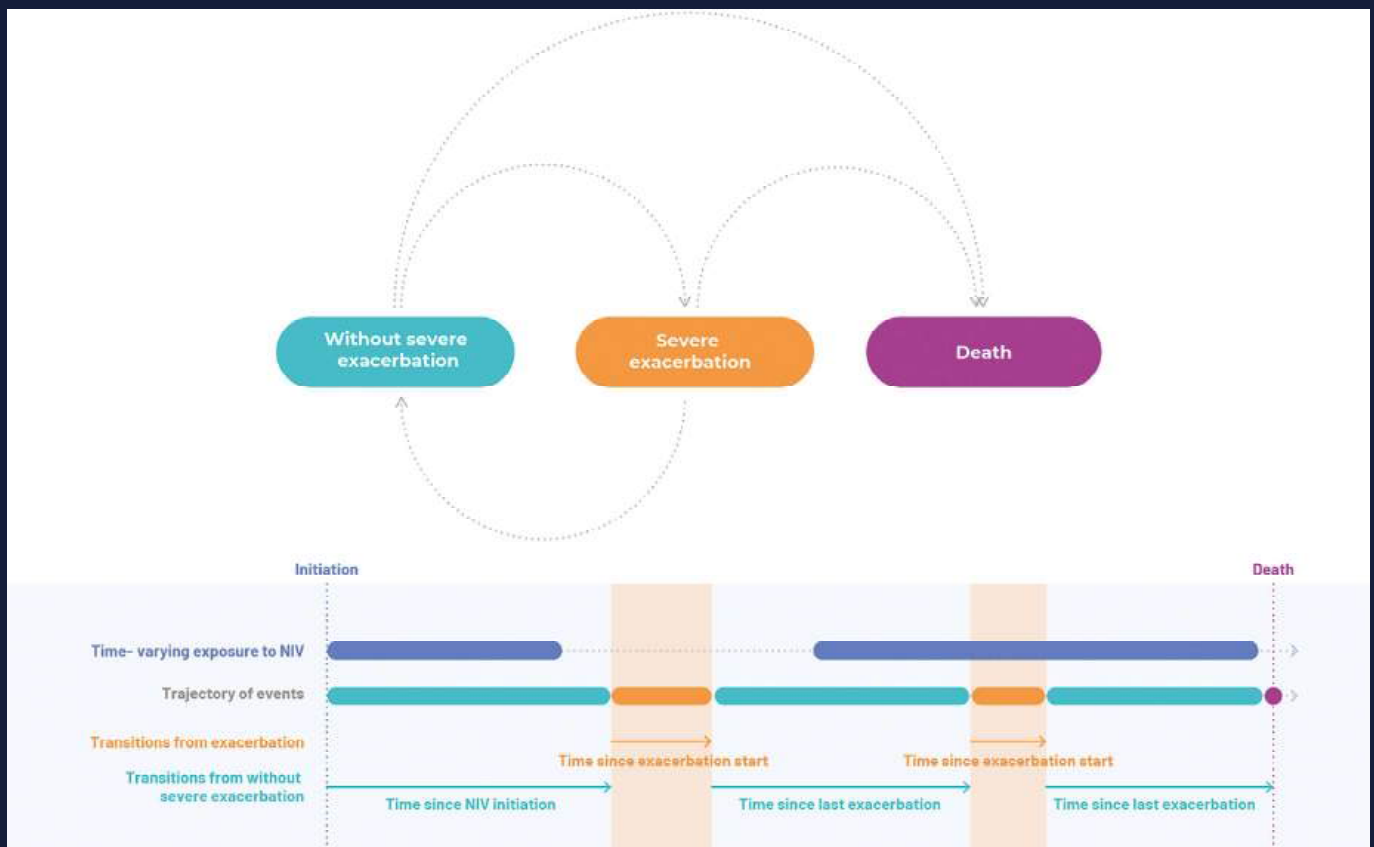
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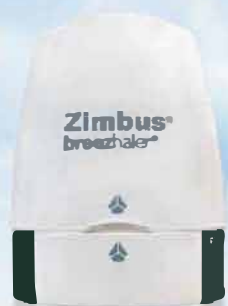
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**1ª associação
LABA/LAMA/ICS**
indicada na ASMA⁴
Dose fixa diária¹

1 vez dia¹

**Zimbus[®]
breezhaler[®]**

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



**NOVA
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/ICS¹**

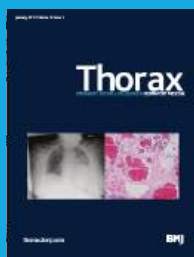
Dá ritmo à vida^{2,3}

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 continuação 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 Medinfar - Produtos Farmacêuticos, S.A. - Rua Henrique de Paiva Couceiro, N.º 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
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Twitter: [@ThoraxBMJ](https://twitter.com/ThoraxBMJ)
ISSN: 0040-6376 (print)
ISSN: 1468-3296 (online)
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novembro / dezembro 2025

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Thorax

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

Edição bimestral em língua portuguesa
Editada por:

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Tiragem: 2000 exemplares

Tradução
Tradução de inglês para português,



Sea of Words - Traduções Técnicas, Lda
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1250-067 Lisboa

Paginação e impressão
Ligação Visual
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Periodicidade: 6 números anuais



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ISSN: 0003-9888 (print)

ISSN: 1468-2044 (online)

Impact factor: 3.2

Journal of the Royal College of
Paediatrics and Child Health

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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

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

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Editorial

Ao chegar ao fim de mais um ano de boa produção científica, estamos de novo convosco para vos sugerir uma seleção de artigos das revistas Thorax e Archives of Disease in Childhood.

O primeiro artigo cuja leitura sugerimos é um editorial sobre ventilação não invasiva domiciliária (NIV) na com doença pulmonar obstrutiva crónica (DPOC). Tem havido algum debate sobre os potenciais benefícios da NIV domiciliária em doentes com DPOC. Dois estudos fundamentais vieram demonstrar melhorias significativas na sobrevivência global e na sobrevivência sem internamentos em doentes com insuficiência respiratória crónica hipercápnica moderadamente grave, quando a NIV é ajustada para controlar a hipoventilação. Estes dados ajudam os clínicos ao reforçar a evidência sobre a capacidade da NIV domiciliária para melhorar a sobrevivência em doentes com DPOC grave, numa situação em que poucas outras terapias conseguem modificar este desfecho.

A segunda sugestão vai, de novo, para um editorial sobre terapia farmacológica dirigida aos endótipos da apneia obstrutiva do sono (OSA). Nos últimos anos, tem-se defendido uma abordagem mais personalizada ao tratamento da OSA, embora a pressão positiva contínua nas vias aéreas (CPAP) continue a ser a terapia de primeira linha. Para os doentes que toleram o CPAP, este é quase universalmente eficaz na redução do índice de apneia-hipopneia (AHI) e na melhoria de vários desfechos clínicos, o que lhe confere uma vantagem sobre outros tipos de tratamento. Mas, o principal obstáculo do CPAP continua a ser a adesão variável por parte dos doentes. O artigo original de Aishah e colaboradores demonstra que a combinação de viloxazina com trazodona proporciona uma redução clinicamente significativa do AHI em doentes com OSA moderada a grave. A farmacoterapia não virá, por si só curar a OSA, mas poderá potenciar a eficácia dos tratamentos já estabelecidos, enquanto se espera que o sonho de uma terapêutica farmacológica para a OSA se torne realidade.

O próximo artigo, “Corticosteroides sistémicos orais em crianças com exacerbações agudas de asma” é uma revisão sistemática que procura avaliar as diferenças de eficácia entre esquemas de corticosteroides segundo o tipo, a dosagem e a duração. A conclusão principal é que a dexametasona oral de curta duração pode ser uma alternativa aceitável à prednisolona em esquemas mais prolongados.

Por fim, no meio de vários artigos com interesse, sugerimos ainda a leitura do estudo prospetivo, observacional e multicêntrico “Utilização domiciliária de agonistas β_2 de ação curta por crianças com asma”, cujo objetivo foi investigar a utilização real de salbutamol por crianças com asma em contexto domiciliário e compará-la com as instruções dos respetivos planos de ação escritos para a asma utilizando uma aplicação para smartphone. As conclusões foram que as famílias tendem a administrar entre 2 a 4 inalações de salbutamol nas primeiras 2 horas após o início dos sintomas de asma, pelo que sugere que ajustar os planos de ação escritos para iniciar com 2 a 4 inalações de salbutamol, repetindo se necessário, parece estar mais alinhado com a prática real das famílias e seria eficaz na maioria das situações.

Aproximando-se a época festiva queremos que todos usufruam deste período para confraternização e reencontro com familiares e amigos, desejando-vos um excelente ano de 2026.

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£625

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

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Informações essenciais compatíveis com o Resumo das Características do Medicamento

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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 tirotoxicose 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).**

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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, que 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 protease 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 procarbazina, 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:

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PT-M0331 aprovado em 12/2023, revalidado anualmente



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Ventilação não invasiva domiciliária (NIV) na DPOC: os dados e os detalhes importam

Patrick Brian Murphy,^{1,2} Swapna Mandal^{3,4}

Os dados que sustentam os benefícios da ventilação não invasiva domiciliária (NIV) em doentes com doença pulmonar obstrutiva crónica (DPOC) grave têm vindo a acumular-se ao longo da última década. Historicamente, existia debate sobre os potenciais benefícios da NIV domiciliária nesta população, com estudos iniciais de pequena escala realizados em centros especializados a demonstrarem alterações fisiológicas;¹⁻³ no entanto, esses resultados não se traduziram em benefícios clínicos nos primeiros ensaios clínicos randomizados de grande escala.^{4,5} Dois estudos fundamentais vieram demonstrar melhorias significativas na sobrevivência global e na sobrevivência sem internamentos em doentes com insuficiência respiratória crónica hipercápnica moderadamente grave, quando a NIV é ajustada para controlar a hipoventilação.^{6,7} A análise dos dados destacou a importância da seleção da população e da entrega otimizada e temporização da intervenção. Está claro que a NIV domiciliária só é eficaz em doentes selecionados com DPOC, e que a intervenção deve ser orientada para o controlo da insuficiência respiratória hipercápnica. Análises adicionais dos dados clínicos atuais demonstraram diferenças clinicamente relevantes em desfechos importantes para os doentes, incluindo número de exacerbações e mortalidade,⁸ bem como benefícios sistémicos como a redução de custos em saúde.^{9,10}

A forma ideal de implementar a NIV domiciliária continua a ser controversa: alguns defendem uma monitorização fisiológica detalhada para minimizar a assincronia entre doente e ventilador, enquanto outros preferem uma abordagem mais simplificada.¹¹⁻¹³ Estudos recentes demonstraram que as alterações nos níveis de pCO₂ diurno estão associadas a vários desfechos importantes e são mais preditivas da sobrevivência a longo prazo do que o controlo da hipoventilação durante o sono.¹⁴ Assim, é essencial que a NIV domiciliária seja administrada em centros especializados, pois a simples disponibilização de um dispositivo, sem capacidade para otimizar a intervenção (incluindo a adesão ao tratamento), dificilmente resultará em melhorias clínicas.

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Tal como na gestão geral da DPOC, há uma crescente valorização dos fenótipos e, em particular, dos traços tratáveis.¹⁵ Dados recentes sugerem que terapias biológicas podem melhorar os desfechos após exacerbações agudas da DPOC,¹⁶ e a fenotipagem tem sido explorada também em doentes tratados com NIV domiciliária.

Janssens e colaboradores identificaram dois fenótipos distintos: respiratório e sistémico — numa coorte de doentes tratados com NIV domiciliária, com características clínicas e desfechos diferentes, permitindo a sua classificação através de um algoritmo simples. Pepin *et al.* também exploraram fenótipos em doentes com DPOC iniciados em NIV domiciliária,¹⁷ através de análise de clusters numa base de dados nacional com mais de 54.000 doentes.¹⁸ Foram identificados quatro grupos com diferentes características e trajetórias clínicas: 1. Início em ambulatório ou após uma única exacerbação. 2. Após duas ou mais exacerbações graves nos últimos 6 meses. 3. Após múltiplas exacerbações graves no último ano. 4. Após exacerbações prolongadas e de recuperação lenta. Embora não abordado diretamente nos estudos de fenotipagem, a presença de apneia obstrutiva do sono (AOS) em doentes com DPOC e insuficiência respiratória parece ter um efeito paradoxal, com melhor sobrevivência comparativamente aos doentes com DPOC isolada.¹⁹ Este fenómeno poderá estar relacionado com o desenvolvimento mais precoce de hipercapnia em doentes com espirometria mais preservada e AOS associada.

Nesta edição da Thorax, Pepin *et al.* apresentam mais dados sobre os benefícios da ventilação não invasiva domiciliária (NIV) em doentes com DPOC grave e o seu impacto nos diferentes agrupamentos fenotípicos.²⁰ O estudo utiliza a mesma base de dados nacional do estudo anterior,¹⁸ que tem cobertura quase completa em França, para examinar o impacto da NIV domiciliária em desfechos relevantes na DPOC (exacerbação grave e morte), recorrendo a um modelo multiestadístico (sem exacerbação, exacerbação grave e morte). A principal força deste trabalho reside na metodologia estatística robusta e no grande conjunto de dados (49 503 doentes que iniciaram NIV domiciliária entre 2015 e 2019, com dados de desfecho até dezembro de 2020), com dados ausentes mínimos, permitindo o ajustamento para múltiplos fatores de confusão. Importa referir que os autores excluíram qualquer doente que tenha realizado menos de 3 meses de terapia com NIV domiciliária, considerando esse período insuficiente para influenciar desfechos a longo prazo.

As principais limitações do estudo são a falta de detalhe em algumas características

importantes dos doentes e do tratamento, nomeadamente os parâmetros do ventilador, a adesão à terapêutica e a avaliação da insuficiência respiratória, que são fundamentais para compreender a aplicação da NIV domiciliária como tratamento. No entanto, mesmo com estas limitações, o estudo transmite várias mensagens relevantes.

Os dados confirmam novamente o potencial da NIV domiciliária para melhorar a sobrevivência em doentes com DPOC grave, com reduções significativas na transição para morte tanto a partir do estado sem exacerbação (HR 0,88; IC 95%: 0,83–0,93) como a partir do estado de exacerbação grave (HR 0,84; IC 95%: 0,79–0,91). Embora não tenha havido impacto na transição de “sem exacerbação” para “exacerbação grave” (HR 0,98; IC 95%: 0,95–1,00) na coorte não selecionada, observou-se impacto no maior subgrupo, o agrupamento fenotípico 1 (HR 0,88; IC 95%: 0,85–0,92), confirmando a importância da seleção dos doentes.

Estes dados ajudam os clínicos ao reforçar a evidência sobre a capacidade da NIV domiciliária para melhorar a sobrevivência em doentes com DPOC grave, numa situação em que poucas outras terapias conseguem modificar este desfecho. Além disso, permitem avaliar o benefício individual da terapêutica, possibilitando que doentes e clínicos discutam se o peso associado à NIV domiciliária justifica a sua iniciação e continuidade. Estes dados reforçam ainda a confiança dos clínicos na utilização da NIV domiciliária em doentes com DPOC grave para melhorar desfechos relevantes para o doente, incluindo a mortalidade, com trabalho contínuo no sentido de permitir decisões terapêuticas individualizadas e garantir uma seleção otimizada dos doentes.

Contributors PBM and SM wrote and revised the editorial. PBM 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 see forms.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

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To cite Murphy PB, Mandal S. Thorax 2025;80:585–586.

Accepted 1 May 2025

Published Online First 19 May 2025



→ <https://doi.org/10.1136/thorax-2024-2-22392>

Thorax 2025;80:585–586.

doi:10.1136/thorax-2025-223321

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Terapia farmacológica dirigida aos endótipos da apneia obstrutiva do sono (OSA): sonho ou realidade?

Peter A Cistulli,^{1,2} Anna Mohammadieh^{1,2}

A apneia obstrutiva do sono (OSA) é cada vez mais reconhecida como uma doença altamente heterogênea.¹ Os fatores que contribuem para o seu desenvolvimento incluem características anatómicas — como o estreitamento das vias aéreas superiores devido à interação entre a estrutura craniofacial e a obesidade — e traços fisiológicos, como: Limiar de despertar baixo (nível mínimo de estímulo respiratório necessário para acordar), Ganho de controlo elevado (sistema respiratório hipersensível). Baixa responsividade muscular das vias aéreas superiores (capacidade reduzida de evitar o colapso da via aérea.²

Nos últimos anos, tem-se defendido uma abordagem mais personalizada ao tratamento da OSA,¹ embora a pressão positiva contínua nas vias aéreas (CPAP) continue a ser a terapia de primeira linha.

Para os doentes que toleram o CPAP, este é quase universalmente eficaz na redução do índice de apneia-hipopneia (AHI) e na melhoria de vários desfechos clínicos, independentemente do endótipo ou fenótipo subjacente. Esta eficácia generalizada confere-lhe uma vantagem sobre terapias alternativas, como dispositivos orais, terapias posicionais e abordagens cirúrgicas, que são geralmente mais direcionadas e eficazes apenas em subgrupos específicos.^{3,4} No entanto, o principal obstáculo do CPAP continua a ser a adesão variável por parte dos doentes.

A terapia ideal para a OSA seria altamente eficaz e associada a elevada adesão — um objetivo ainda por concretizar. Nesse contexto, o “Santo Graal” da área seria um fármaco capaz de substituir o CPAP. Ao longo dos últimos 50 anos,⁵ foram realizados vários estudos com medicamentos, mas só recentemente a FDA aprovou o primeiro fármaco para tratar a OSA: a tirzepatida, um agonista dos recetores GIP e GLP-1 utilizado na perda de peso, com base num ensaio clínico randomizado positivo.⁶ No entanto, dado que a OSA é uma doença heterogênea, é improvável que um fármaco que atua apenas sobre a obesidade seja eficaz para todos os doentes. Por isso, são aguardados com expectativa novos estudos que explorem medicamentos dirigidos a outros endótipos da OSA.

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Na revista *Thorax*, Aishah e colaboradores⁷ demonstram que a combinação de viloxazina com trazodona proporciona uma redução clinicamente significativa do AHI em doentes com OSA moderada a grave. Este trabalho baseia-se no conhecimento dos endótipos não anatómicos da OSA, que têm permitido identificar novos alvos terapêuticos farmacológicos.^{8,9} A estratégia de reaproveitamento de fármacos existentes para aumentar o limiar de despertar, melhorar a responsividade muscular das vias aéreas superiores e/ou reduzir o ganho de controlo tem gerado estudos com resultados encorajadores.^{10,14} Em particular, a combinação de agentes noradrenérgicos com hipnóticos tem mostrado potencial. Um ensaio clínico de fase 2 com o fármaco AD109 (aroxibutinina + atomoxetina) demonstrou melhorias significativas na OSA ao fim de 4 semanas em adultos com OSA ligeira a grave.¹⁵

No estudo atual, os investigadores combinaram viloxazina (inibidor da recaptação de serotonina e noradrenalina, com potencial para melhorar a responsividade muscular das vias aéreas superiores) com trazodona (antagonista da serotonina com propriedades sedativas, usada para compensar o efeito estimulante da viloxazina). O estudo foi desenhado de forma robusta: duplamente cego, controlado por placebo e com três braços — viloxazina isolada, combinação viloxazina/trazodona e placebo. Ambos os grupos de tratamento ativo apresentaram uma redução semelhante do AHI (~50%). A combinação pareceu atenuar alguns efeitos adversos da viloxazina isolada, como a redução do tempo total de sono. Curiosamente, embora a combinação tenha sido desenhada para atuar sobre doentes com baixa responsividade muscular e/ou limiar de despertar baixo, os participantes não foram recrutados com base em características endotípicas, mas sim com base no AHI (10–45/hora) e sintomas clínicos. De forma contraintuitiva, a análise por subgrupos mostrou que os doentes com maior responsividade muscular beneficiaram mais da combinação, enquanto o oposto foi observado com viloxazina isolada. Não houve diferenças significativas entre doentes com limiar de despertar alto *versus* baixo. Os autores referem que este fenómeno paradoxal já foi observado com outras terapias dirigidas a endótipos, e que são necessários estudos mais detalhados para compreender a eficácia real destas abordagens dentro e fora dos perfis teóricos de doente.

Um ponto crítico é o perfil de efeitos adversos dos fármacos. Viloxazina é utilizada no tratamento do défice de atenção/hiperatividade, associada a sonolência, perda de

apetite, fadiga, náuseas, vômitos, insónia, irritabilidade e risco aumentado de ideação suicida.¹⁶ Trazodona: usada na depressão, pode reduzir despertares noturnos em doentes com insónia,¹⁷ mas não é recomendada como monoterapia. Os seus efeitos adversos incluem risco de quedas, sonolência, visão turva, obstipação e tonturas.¹⁸

Foram aplicados critérios de exclusão rigorosos, incluindo retenção urinária, hipertensão não controlada, hiperplasia benigna da próstata, refluxo gastroesofágico, glaucoma de ângulo fechado não tratado, insuficiência hepática ou renal significativa, ideação suicida e gravidez. Os efeitos adversos mais comuns foram insónia, obstipação e xerostomia. Cinco dos 25 participantes abandonaram o estudo devido a efeitos adversos ligeiros, como visão turva, cefaleia e aumento da pressão arterial. Importa também referir que os resultados dos questionários centrados no doente pioraram nos grupos de tratamento ativo. Assim, a combinação viloxazina/trazodona poderá ter utilidade clínica apenas num perfil restrito de doentes.

A área da terapêutica farmacológica para a OSA continua a procurar o “Santo Graal”. Existem ferramentas, alvos e fármacos disponíveis, mas persistem desafios significativos. O caminho passa por desenvolver uma abordagem estratégica para os ensaios clínicos, e é encorajador observar o crescimento de estudos promovidos por investigadores e pela indústria. No entanto, dada a heterogeneidade da OSA, é necessário manter expectativas realistas quanto à possibilidade de encontrar uma solução universal.

Mais provável será o desenvolvimento de terapias farmacológicas dirigidas (monoterapia ou combinação) para endótipos específicos, servindo segmentos clínicos bem definidos da população com OSA. No caso da reaplicação de fármacos, o desafio reside em encontrar a combinação certa, com eficácia aceitável e perfil de segurança adequado, para o doente certo — uma tarefa comparável a encontrar uma agulha num palheiro.

Ainda que a farmacoterapia não venha a curar a OSA por si só, poderá potenciar a eficácia dos tratamentos já estabelecidos.¹⁹ Resta esperar que o sonho da terapêutica farmacológica para a OSA se torne realidade.

Contributors Both authors contributed to the conception and original drafting of this editorial. PC 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 PAC has an appointment to an endowed academic Chair at the University of Sydney that was created from ResMed funding. He receives no personal fees and this relationship is managed by an Oversight Committee of the University. He has received research support from ResMed, SomnoMed and SleepImage. He is a consultant/adviser to ResMed, SomnoMed, Signifier Medical Technologies, Sunrise Medical and Eli Lilly. AM has received in-kind research support from ResMed for investigator-initiated studies, and honoraria from SomnoMed for speaking at educational meetings.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

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To cite Cistulli PA, Mohammadi A. Thorax 2025;80:589–590.

Accepted 20 June 2025

Published Online First 27 June 2025



→ <https://doi.org/10.1136/tthorax-2024-222513>

Thorax 2025;80:589–590.

doi:10.1136/tthorax-2025-223409

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ARTIGO ORIGINAL

Corticosteroides sistêmicos orais em crianças com exacerbações agudas de asma: uma revisão sistemática e meta-análise em rede

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/archdischild-2024-327523>).

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Received 10 June 2024

Accepted 25 May 2025

Published Online First 8 June 2025

RESUMO

Objetivo Para avaliar as diferenças de eficácia entre esquemas de corticosteroides segundo o tipo, a dosagem e a duração, realizamos uma revisão sistemática e uma meta-análise em rede de ensaios clínicos randomizados (ECR).

Métodos Pesquisamos quatro bases de dados desde a sua criação até março de 2024 e incluímos ECR que avaliaram corticosteroides orais em exacerbações de asma em jovens com menos de 21 anos. Comparamos seis esquemas: Dexametasona (DEXA) 0,3 mg/kg/dia durante 1 dia, DEXA 0,6 mg/kg/dia durante 1 dia, DEXA 0,6 mg/kg/dia durante 2 dias, Prednisolona (PSL) 1,0 mg/kg/dia durante 3 dias, PSL 1,0–1,5 mg/kg/dia durante 5 dias, PSL 2,0 mg/kg/dia durante 5 dias. O desfecho primário foi a recaída dentro de 14 dias, definida como visita não programada ao serviço de urgência ou ao médico de cuidados primários.

Resultados Onze estudos envolvendo 2353 doentes foram incluídos na síntese quantitativa. Não foram observadas diferenças significativas nas taxas de recaída entre as 15 comparações dos seis esquemas. A estimativa da rede mostrou que: DEXA (0,3 mg/kg/dia × 1 dia) comparada com PSL (1,0 mg/kg/dia × 3 dias) teve um rácio de risco (RR) de 0,99 (IC 95%: 0,56 a 1,74), DEXA (0,6 mg/kg/dia × 2 dias) comparada com PSL (1,0–1,5 mg/kg/dia × 5 dias) teve um RR de 1,29 (IC 95%: 0,84 a 1,98). A certeza da evidência para as comparações incluídas foi considerada baixa a muito baixa.

Conclusão Nesta meta-análise em rede, não foram encontradas diferenças significativas na eficácia dos esquemas de corticosteroides mais utilizados para exacerbações agudas de asma na infância. A dexametasona oral de curta duração pode ser uma alternativa aceitável à prednisolona em esquemas mais prolongados.

Número de registro PROSPERO: CRD42023449189.

INTRODUCTION

Children with asthma may experience exacerbations triggered by infection or other factors, often necessitating emergency medical care in a substantial subset.^{1–3} Treatment begins with bronchodilators for immediate relief, followed by systemic corticosteroids, which are critical for reducing inflammation and airway hyperreactivity.⁴ Current guidelines recommend prompt corticosteroid use for moderate-to-severe episodes and mild cases unresponsive to beta-agonists.⁵ Nevertheless, symptom recurrence requiring further intervention or hospitalisation occurs in approximately 5–25% of cases.⁶

The outpatient management of paediatric asthma exacerbations frequently involves oral corticosteroid therapy, with prescribed regimens ranging from prednisolone (1–2 mg/kg daily for 3–5 days) to dexamethasone (0.3–0.6 mg/kg daily for 1–2 days).^{7–11} Comparative studies, including trials and meta-analyses, have shown similar efficacy between short-term and extended prednisolone courses.^{7–11} However, these meta-analyses com-

Key messages

What is known about this topic

► Short-term dexamethasone and long-term prednisolone are not significantly different in acute asthma exacerbations in children.

What this study adds

► A network meta-analysis approach compared the type, dosage and duration of treatment with oral corticosteroids and found no significant differences in the incidence of relapse among currently used regimens.

How this study might affect research practice or policy

► Short-term oral dexamethasone may be an acceptable alternative to a longer course of prednisolone.

pared prednisolone regardless of dose, duration or route of administration (oral, intramuscular), and few detailed comparative studies have addressed differences in the type, dosage and duration of treatment with oral corticosteroids.

To address this gap, we conducted a systematic review and network meta-analysis (NMA) of randomised controlled trials (RCTs) involving patients treated with oral corticosteroids, aiming to evaluate the efficacy differentials among oral corticosteroid regimens in terms of type, dosage and duration.

MATERIALS AND METHODS

Protocols and registration

This systematic review was designed based on the Preferred Reporting Items for Systematic Reviews and the Meta-analyses (PRISMA) extension statement for reporting systematic reviews incorporating NMAs.¹² The review protocol was registered in PROSPERO on 7 August 2023 (CRD 42023449189).

Studies, participants, interventions/comparators and outcomes

This review included RCTs. When the number of trials incorporating specific interventions and outcomes was limited, making NMA infeasible, they were assessed qualitatively. Conference abstracts were generally excluded from synthesis and instead evaluated qualitatively. This ensured inclusion of potentially valuable data and reduced information bias. This meta-analysis included paediatric patients aged 1–20 years with acute asthma exacerbations who were treated in an outpatient or emergency department setting, not in an inpatient setting. The NMA was used to compare multiple



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To cite: Amagasa S, Utsumi S, Okajima K, et al. Arch Dis Child 2025;110:824–831.

corticosteroid protocols for managing acute asthma exacerbations encompassing the following: 0.3 mg/kg/day for a single day, 0.6 mg/kg/day for a single day, dexamethasone 0.6 mg/kg/day for 2 days, prednisolone 1.0 mg/kg/day for 3 days, prednisolone 1.0–1.5 mg/kg/day for 5 days and prednisolone 2.0 mg/kg/day for 5 days.

The primary outcome was relapse within 14 days, defined as an unplanned visit to an emergency department or primary care physician. Secondary outcomes were hospital re-admission within 14 days and vomiting at the hospital or at home. Although quantitative integration was not possible due to insufficient numbers of studies and heterogeneity issues, we conducted a qualitative assessment of missed school days, missed parental workdays and improved scores, such as the Pediatric Respiratory Assessment Measure (PRAM).

Data sources and search details

We searched the Cochrane Central Register of Controlled Trials and MEDLINE via Ovid for eligible published clinical trials. The WHO's International Clinical Trials Platform search portal and the ClinicalTrials.gov trials registry were also searched for ongoing trials. The final searches were conducted on 24 March 2024. Details of the search strategy and searches performed are provided in the online supplemental appendix.

Study selection, data collection process and data elements

Rayyan software was used for systematic review.¹³ Two authors (SA and SU) individually screened titles and abstracts retrieved via the search and additional sources to determine eligibility based on the selection criteria. Full texts of potentially eligible studies were independently assessed by the same authors, with disagreements resolved through discussion with the third reviewer (KO). A standardised pre-pilot form was used to extract data on study quality and synthesis. Data included baseline characteristics, intervention and control details, methods, outcomes, time points and risk of bias. Two authors (SA and SU) extracted data independently; discrepancies were discussed with KO. Variables, such as age, severity and outcomes, were extracted. Age was recorded as a continuous variable, severity categorised by scores or qualitatively, and outcomes extracted as binary, including the number analysed and outcome occurrences per intervention.

Assessment of risk of bias within trials

The methods for assessment of risk of bias within trials are provided in the Supplementary Methods of the online supplemental file.

Statistical analysis

This study used NMA to compare the effects of multiple interventions simultaneously.^{14 15} Network plots were constructed to identify the number of studies and patients included in the meta-analysis. The R package 'netmeta 2.5-0' (V.4.1.2) and Confidence

in Network Meta-Analysis (CINeMA), a web application that uses R, were used to perform NMA. A frequentist approach with multivariate meta-analysis was used, using a random-effects model to account for variability between studies. Effect sizes were expressed as relative risks with 95% CIs. The network meta-analysis in this study used individual arm data. Indirect and direct estimates were calculated using a node-split model. Analyses were performed using the number of patients analysed (not the number of patients randomised) for each trial. The certainty of network estimates was assessed using the CINeMA framework,¹⁶ based on six domains from the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework: bias within studies, bias across studies, indirectness, imprecision, heterogeneity and inconsistency.¹⁷

The transitivity assumption was assessed by comparing the distribution of clinical and methodological variables that may act as effect modifiers across treatment comparisons. Risk of bias between studies was assessed by considering pairwise meta-analyses. Conditions associated with 'suspected' and 'unrecognised' bias across studies were determined by the presence of publication bias as indicated by direct comparison. Each study within the network was assessed for indirectness in relation to the study topic, taking into account the study population, intervention, outcome and study setting. Indirectness was then categorised as low, moderate or high. A contribution matrix was then created using the study level judgements. Methods to address imprecision included contrasting the range of treatment effects covered by the 95% CI with the corresponding range. The heterogeneity of treatment effects relative to clinically important risk ratios (<0.75 or >1.33) in the CI was assessed. We compared the estimated heterogeneity variance with its predicted distribution derived from the model.¹⁸ The importance of heterogeneity with and without heterogeneity capture was assessed using CI-based assessments and agreement between predicted intervals. A prediction interval is calculated from the variance of the distribution of treatment effects (τ^2). Heterogeneity of treatment effect was assessed when the clinically significant risk ratio was between 0.75 and 1.33 within the prediction interval. Inconsistency was evaluated using node-splitting analysis. Per-design interaction tests were used to statistically assess consistency, and network model discrepancies were estimated from discrepancy factors and their uncertainty.¹⁹ In our analysis using CINeMA, we assessed inconsistency within the network by comparing direct and indirect evidence.^{16 17} This involved assessing the agreement between effect estimates from different sources. Although statistical tests, such as treatment interaction tests, were used to identify potential discrepancies, the primary focus was on a qualitative assessment of the coherence of the evidence. Rather than relying solely on p values, CINeMA considers the context and potential clinical relevance of observed differences. This holistic approach includes consideration of whether differences between direct and indirect evidence are meaningful and significant in the context of the overall evidence base.

The assessment of publication bias and the ranking analysis are described in the Supplementary Methods in the online supplemental file.

Sensitivity analysis

To assess the robustness of the results, an NMA/MA with different assumptions about drug/dosage/duration was performed as a sensitivity analysis, with relapse, hospital re-admission and vomiting as outcomes. The first approach pools all dosages and durations of the same drug, assuming that neither dosage nor duration alters the treatment effect. The type of drug (dexamethasone vs prednisolone) is compared in this manner. The second approach pools different dosages of the same drug into a single treatment group, while differentiating between treatment nodes based on the duration of the drug's use, focusing on the potential impact of treatment duration. The third approach takes the opposite stance, combining treatment nodes based on the duration of the drug's use, but distinguishing between different dosages, thus focusing on the potential impact of varying dosages.

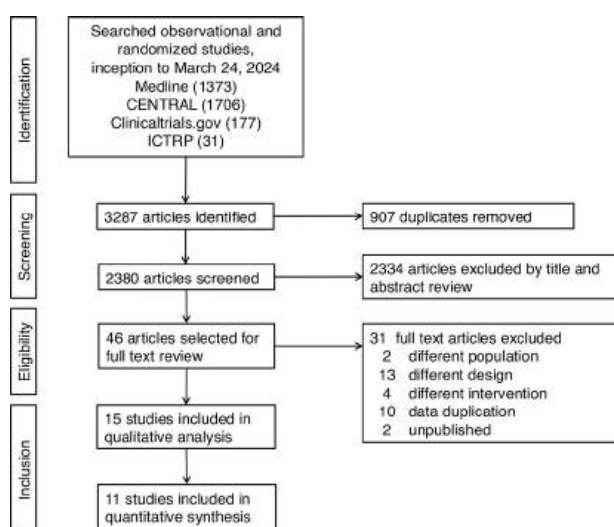


Figure 1 Flowchart of the included studies.

Table 1 Study characteristics II

Study	Years of recruitment	Country of recruitment	Age	Intervention	Comparator	Asthma severity		Number of patients	
						Intervention	Comparator	Intervention	Comparator
Studies included in quantitative synthesis									
Qureshi <i>et al</i> 2001 ⁶	1998–1999	USA	2–18 years	DEXA (0.6 mg/kg/day×2 days)	PSL (1.0 mg/kg/day×5 days)	Mild 21.7%, moderate 56.5%, severe 22.1%*	Mild 23.0%, moderate 55.9%, severe 21.1%*	272	261
Kayani <i>et al</i> 2002 ²¹	NA	USA	2–16 years	PSL (1.0 mg/kg/day×5 days)	PSL (2.0 mg/kg/day×5 days)	NA		43	43
Altamimi <i>et al</i> 2006 ²²	2001–2003	Canada	2–16 years	DEXA (0.6 mg/kg/day×1 day)	PSL (1.0 mg/kg/day×5 days)	Mild to moderate†		56	54
Greenberg <i>et al</i> 2008 ²³	2004–2005	USA	2–18 years	DEXA (0.6 mg/kg/day×2 days)	PSL (1.0 mg/kg/day×5 days)	PAS 8 (range 5–14)	PAS 6 (range 5–12)	51	38
Chang <i>et al</i> 2008 ²⁴	2004–2007	Australia	2–15 years	PSL (1.0 mg/kg/day×3 days)	PSL (1.0 mg/kg/day×5 days)	ASS 4.6 (SD 1.8)	ASS 4.5 (SD 1.8)	101	100
Cronin <i>et al</i> 2016 ²⁵	2011–2012	Ireland	2–16 years	DEXA (0.3 mg/kg/day×1 day)	PSL (1.0 mg/kg/day×3 days)	PRAM 4.38 (SD 2.53)	PRAM 4.51 (SD 2.35)	123	122
Paniagua <i>et al</i> 2017 ²⁰	2014–2015	Spain	1–14 years	DEXA (0.6 mg/kg/day×2 days)	PSL (1.5 mg/kg/day×1 day, followed by 1 mg/kg/day×4 days)	NA		281	276
Jara-Almonte <i>et al</i> 2018 ²⁶	NA	USA	18 months–20 years	DEXA (0.6 mg/kg/day×1 day)	DEXA (0.6 mg/kg/day×2 days)	PIS 4 (SD 2)	PIS 5 (SD 2.85)	37	39
Ullah <i>et al</i> 2019 ²⁷	2015–2016	Pakistan	2–12 years	DEXA (0.6 mg/kg/day×1 day)	PSL (2.0 mg/kg/day×5 days)	Severe or life-threatening asthma were excluded†		80	80
Elkharwili <i>et al</i> 2020 ²⁸	2016–2017	Egypt	2–11 years	DEXA (0.6 mg/kg/day×2 days)	DEXA (0.3 mg/kg/day×1 day)/ PSL (1.5 mg/kg/day×5 days)	NA		20	20/20
Martin <i>et al</i> 2022 ²⁹	2015–2018	USA	2–20 years	DEXA (0.6 mg/kg/day×1 day)	DEXA (0.6 mg/kg/day×2 days)	PAS 7.2 (SD 1.8)	PAS 6.9 (SD 1.5)	116	116
Studies not being included in quantitative synthesis but included in qualitative analysis									
Ghafouri <i>et al</i> 2010 ³⁰	NA	USA	2–17 years	DEXA (0.6 mg/kg/day×1 day)	DEXA (0.6 mg/kg/day×2 days)	Mild to moderate†		52	48
Prasannavenkatesh 2018	2015–2016	India	2–12 years	DEXA (0.3 mg/kg/day×1 day)	PSL (1.0 mg/kg/day×3 days)	PRAM 5.83 (SD 0.83)	PRAM 6.13 (SD 0.82)	30	30
Banoth <i>et al</i> 2022 ³²	NA	India	2–14 years	DEXA (0.3 mg/kg/day×2 days)	PSL (2.0 mg/kg/day×5 days)	PRAM 5.4 (SD 1.06)	PRAM 5.28 (SD 1.13)	88	87
Tayyab <i>et al</i> 2022 ³³	2018–2019	Pakistan	2–12 years	DEXA (0.3 mg/kg/day×1 day)	PSL (1.0 mg/kg/day×3 days)	PRAM <6 140.7%, PRAM ≥6 850.3%	PRAM <6 120.8%, PRAM ≥6 870.2%	156	156
*Patients were classified as ‘mild’ if their PEFR was greater than 70% of predicted or their asthma score was 5–7, ‘moderate’ if their PEFR was 50% to 70% of predicted or their asthma score was 8–11, and ‘severe’ if their PEFR was less than 50% of predicted or their asthma score was 12–15.									
†Inclusion or exclusion criteria include asthma severity, but no actual number is given.									
ASS, Asthma Severity Scale; DEXA, dexamethasone; PAS, Pediatric Asthma Score; PIS, Pulmonary Index Score; PRAM, Pediatric Respiratory Assessment Measure; PSL, prednisolone.									

*Patients were classified as 'mild' if their PEFR was greater than 70% of predicted or their asthma score was 5–7, 'moderate' if their PEFR was 50% to 70% of predicted or their asthma score was 8–11, and 'severe' if their PEFR was less than 50% of predicted or their asthma score was 12–15.

†Inclusion or exclusion criteria include asthma severity, but no actual number is given.

ASS, Asthma Severity Scale; DEXA, dexamethasone; PAS, Pediatric Asthma Score; PIS, Pulmonary Index Score; PRAM, Pediatric Respiratory Assessment Measure; PSL, prednisolone.

RESULTS

Study selection and study characteristics

A literature search yielded 3287 articles (figure 1). After removing duplicates, 2380 publications were screened, and 46 underwent full-text review. The quantitative (network meta-analysis) analyses included 11 studies.^{6 20–29} One trial was included despite being a conference abstract, as detailed data were available on ClinicalTri-

als.gov.²⁶ Four studies, excluded from the quantitative analysis due to differing outcomes or other factors, were assessed qualitatively.^{30–33} Inclusion and exclusion criteria, outcomes and follow-up periods for each study are shown in online supplemental table 1.

This network meta-analysis incorporated data from 2353 patients. The relevant studies, published between 2001 and 2022, recruited patients from 1999 to 2018, as indicated in table 1. The

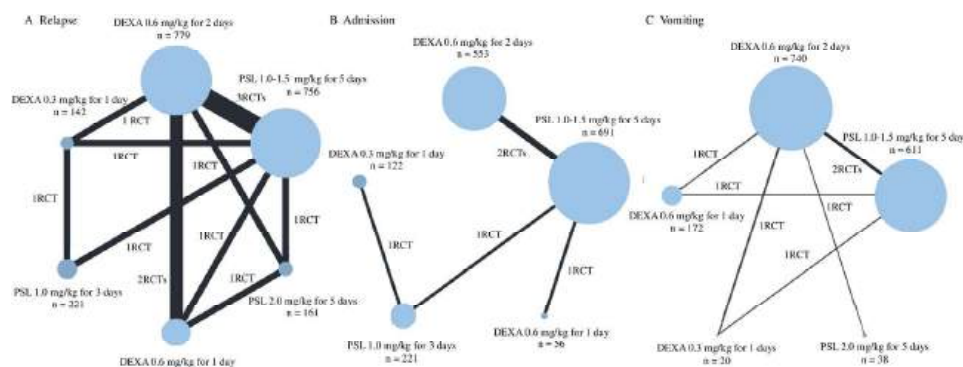


Figure 2 Network plots for relapse, admission and vomiting. The network plot is a visual representation of direct and indirect comparisons between different treatments and interventions. The nodes represent specific interventions, with the size of each node proportional to the number of patients who received that intervention. The edges between nodes indicate direct comparisons made in trials, with the thickness of the edges reflecting the number of trials that compared the linked interventions. DEXA, dexamethasone; PSL, prednisolone; RCT, randomised controlled trial.

Table 2 (A) Direct estimates, indirect estimates and network estimates for relapse; (B) direct estimates, indirect estimates and network estimates for admission; (C) direct estimates, indirect estimates and network estimates for vomiting

Comparison	Direct estimate RR (95% CI)	Indirect estimate RR (95% CI)	P-value for inconsistency measures*	Network estimate RR (95% CI)	Certainty of evidence
(A)					
DEXA (0.3 mg/kg/day×1 day) vs DEXA (0.6 mg/kg/day×2 days)	1.17 (0.48 to 2.86)	1.34 (0.41 to 4.37)	0.87	1.23 (0.60 to 2.51)	Very low
DEXA (0.3 mg/kg/day×1 day) vs PSL (1.0 mg/kg/day×3 days)	0.98 (0.53 to 1.83)	1.00 (0.25 to 3.97)	0.98	0.99 (0.56 to 1.74)	Low
DEXA (0.3 mg/kg/day×1 day) vs PSL (1.0–1.5 mg/kg/day×5 days)	1.75 (0.61 to 5.06)	1.46 (0.57 to 3.71)	0.8	1.58 (0.78 to 3.18)	Very low
DEXA (0.6 mg/kg/day×1 day) vs DEXA (0.6 mg/kg/day×2 days)	1.34 (0.71 to 2.53)	0.56 (0.18 to 1.75)	0.19	1.09 (0.63 to 1.90)	Very low
DEXA (0.6 mg/kg/day×1 day) vs PSL (1.0–1.5 mg/kg/day×5 days)	3.67 (0.42 to 31.87)	1.26 (0.62 to 2.58)	0.36	1.40 (0.71 to 2.77)	Very low
DEXA (0.6 mg/kg/day×1 day) vs PSL (2.0 mg/kg/day×5 days)	1.34 (0.71 to 2.53)	0.56 (0.18 to 1.75)	0.04	1.09 (0.63 to 1.90)	Very low
DEXA (0.6 mg/kg/day×2 days) vs PSL (1.0–1.5 mg/kg/day×5 days)	1.23 (0.78 to 1.93)	2.13 (0.49 to 9.22)	0.48	1.29 (0.84 to 1.98)	Very low
DEXA (0.6 mg/kg/day×2 days) vs PSL (2.0 mg/kg/day×5 days)	1.99 (0.56 to 7.00)	0.36 (0.15 to 0.82)	0.03	0.60 (0.30 to 1.22)	Very low
PSL (1.0 mg/kg/day×3 days) vs PSL (1.0–1.5 mg/kg/day×5 days)	1.58 (0.54 to 4.68)	1.62 (0.57 to 4.62)	0.98	1.60 (0.75 to 3.40)	Very low
PSL (1.0–1.5 mg/kg/day×5 days) vs PSL (2.0 mg/kg/day×5 days)	0.33 (0.01 to 7.96)	0.48 (0.21 to 1.10)	0.83	0.47 (0.21 to 1.04)	Very low
DEXA (0.3 mg/kg/day×1 day) vs DEXA (0.6 mg/kg/day×1 day)	NA	1.13 (0.46 to 2.75)	NA	1.13 (0.46 to 2.75)	Very low
DEXA (0.3 mg/kg/day×1 day) vs PSL (2.0 mg/kg/day×5 days)	NA	0.74 (0.28 to 1.99)	NA	0.74 (0.28 to 1.99)	Very low
DEXA (0.6 mg/kg/day×1 d) vs PSL (1.0 mg/kg/day×3 days)	NA	0.88 (0.34 to 2.28)	NA	0.88 (0.34 to 2.28)	Very low
DEXA (0.6 mg/kg/day×2 days) vs PSL (1.0 mg/kg/day×3 days)	NA	0.80 (0.36 to 1.78)	NA	0.80 (0.36 to 1.78)	Very low
PSL (1.0 mg/kg/day×3 days) vs PSL (2.0 mg/kg/day×5 days)	NA	0.75 (0.26 to 2.14)	NA	0.75 (0.26 to 2.14)	Very low
(B)					
DEXA (0.3 mg/kg/day×1 day) vs PSL (1.0 mg/kg/day×3 days)	2.95 (0.31 to 27.97)	NA	NA	2.95 (0.31 to 27.97)	Very low
DEXA (0.6 mg/kg/day×1 day) vs PSL (1.0–1.5 mg/kg/day×5 days)	2.89 (0.31 to 26.96)	NA	NA	2.89 (0.31 to 26.96)	Very low
DEXA (0.6 mg/kg/day×2 days) vs PSL (1.0–1.5 mg/kg/day×5 days)	0.98 (0.27–3.47)	NA	NA	0.98 (0.27–3.47)	Very low
PSL (1.0 mg/kg/day×3 days) vs PSL (1.0–1.5 mg/kg/day×5 days)	2.97 (0.12 to 72.05)	NA	NA	2.97 (0.12 to 72.05)	Very low
DEXA (0.3 mg/kg/day×1 day) vs DEXA (0.6 mg/kg/day×1 day)	NA	3.03 (0.03 to 271.48)	NA	3.03 (0.03 to 271.48)	Very low
DEXA (0.3 mg/kg/day×1 day) vs DEXA (0.6 mg/kg/day×2 days)	NA	8.94 (0.15 to 540.50)	NA	8.94 (0.15 to 540.50)	Very low
DEXA (0.3 mg/kg/day×1 day) vs PSL (1.0–1.5 mg/kg/day×5 days)	NA	8.77 (0.18 to 433.94)	NA	8.77 (0.18 to 433.94)	Very low
DEXA (0.6 mg/kg/day×1 day) vs DEXA (0.6 mg/kg/day×2 days)	NA	2.95 (0.23 to 38.37)	NA	2.95 (0.23 to 38.37)	Very low
DEXA (0.6 mg/kg/day×1 day) vs PSL (1.0 mg/kg/day×3 days)	NA	0.97 (0.02 to 47.74)	NA	0.97 (0.02 to 47.74)	Very low
DEXA (0.6 mg/kg/day×2 days) vs PSL (1.0 mg/kg/day×3 days)	NA	0.33 (0.01 to 10.19)	NA	0.33 (0.01 to 10.19)	Very low
(C)					
DEXA (0.3 mg/kg/day×1 day) vs DEXA (0.6 mg/kg/day×2 days)	0.75 (0.19 to 2.93)	1.14 (0.08 to 17.27)	0.79	0.82 (0.24 to 2.76)	Very low
DEXA (0.3 mg/kg/day×1 day) vs PSL (1.0–1.5 mg/kg/day×5 days)	0.43 (0.13 to 1.43)	0.21 (0.001 to 29.72)	0.79	0.41 (0.13 to 1.33)	Very low
DEXA (0.6 mg/kg/day×1 day) vs DEXA (0.6 mg/kg/day×2 days)	2.50 (0.81 to 7.74)	0.61 (0.02 to 15.49)	0.42	2.14 (0.74 to 6.23)	Very low
DEXA (0.6 mg/kg/day×1 day) vs PSL (1.0–1.5 mg/kg/day×5 days)	0.32 (0.01 to 7.72)	1.31 (0.37 to 4.67)	0.42	1.08 (0.33 to 3.51)	Very low
DEXA (0.6 mg/kg/day×2 days) vs PSL (1.0–1.5 mg/kg/day×5 days)	0.53 (0.30 to 0.94)	0.13 (0.004 to 3.76)	0.42	0.50 (0.29 to 0.89)	Very low
DEXA (0.6 mg/kg/day×2 days) vs PSL (2.0 mg/kg/day×5 days)	0.53 (0.18 to 1.55)	NA	NA	0.53 (0.18 to 1.55)	Very low
DEXA (0.3 mg/kg/day×1 day) vs DEXA (0.6 mg/kg/day×1 day)	NA	0.38 (0.08 to 1.89)	NA	0.38 (0.08 to 1.89)	Very low
DEXA (0.3 mg/kg/day×1 day) vs PSL (2.0 mg/kg/day×5 days)	NA	0.43 (0.09 to 2.20)	NA	0.43 (0.09 to 2.20)	Very low
DEXA (0.6 mg/kg/day×1 day) vs PSL (2.0 mg/kg/day×5 days)	NA	1.14 (0.25 to 5.17)	NA	1.14 (0.25 to 5.17)	Very low
PSL (1.0–1.5 mg/kg/day×5 days) vs PSL (2.0 mg/kg/day×5 days)	NA	1.06 (0.32 to 3.54)	NA	1.06 (0.32 to 3.54)	Very low

The RR represents the risk of outcome occurrence in the group on the left side of the comparison relative to the group on the right side. RR >1 indicates a higher risk in the left-side group, while RR <1 indicates a higher risk in the right-side group (eg, in the top comparison, the network estimate shows that DEXA (0.3 mg/kg/day×1 day) is associated with a 1.23 times higher risk of relapse compared to DEXA (0.6 mg/kg/day×2 days)).

RR >1 indicates a higher risk in the group on the left side of the comparison relative to the group on the right side (eg, in the top comparison, the network estimate shows that DEXA (0.3 mg/kg/day×1 day) is associated with a 2.95 times higher risk of admission compared to PSL (1.0 mg/kg/day×3 days)).

RR >1 indicates a higher risk in the group on the left side of the comparison relative to the group on the right side (eg, in the top comparison, the network estimate shows that DEXA (0.3 mg/kg/day×1 day) is associated with a 20% lower risk of vomiting compared to DEXA (0.6 mg/kg/day×2 days)).

*Inconsistency measures are the difference between direct and indirect estimates

DEXA, dexamethasone; PSL, prednisolone; RR, risk ratio.

analysis evaluated six variants of oral corticosteroid therapy, differentiated by type, dosage and duration, in relation to the primary outcome. These variants comprised dexamethasone 0.3 mg/kg/day administered for 1 day (n=142, 6.0%), dexamethasone 0.6 mg/kg/day for 1 day (n=294, 12.5%), dexamethasone 0.6 mg/kg/day for 2 days (n=779, 33.1%), prednisolone 1.0 mg/kg/day for 3 days (n=221, 9.4%), prednisolone 1.0–1.5 mg/kg/day for 5 days (n=736, 31.3%) and prednisolone 2.0 mg/kg/day for 5 days (n=161, 6.8%).

The number of patients and occurrence of outcomes for each study included in the quantitative synthesis are shown in online supplemental table 2. The pharmaceutical formulations of each study included in the quantitative synthesis are shown in online supplemental table 3.

Risk of bias within individual studies

The results for assessment of risk of bias within trials are provided in the Supplementary Results and online supplemental tables 4–6 of the online supplemental file.

Relapse

The primary outcome of relapse was reported in 11 studies involving 2353 patients.^{6 20–29} The network plot for relapse is shown in figure 2A, and network estimates are in table 2A and figure 3A. Forest plots of direct, indirect and network estimates for relapse are in online supplemental figure 1. There was no evidence that any specific type, dosage or duration of corticosteroid reduced the rate of relapse. There was no significant publication bias (online supplemental figure 2). A summary of confidence in network estimates for the primary outcome is in online supplemental table 7, with certainty of evidence rated low to very low. The P-scores for relapse are in online supplemental table 8.

Hospital re-admission

The secondary outcome of admission was reported in five studies involving 1643 patients.^{6 20 22 24 25} The network plot for admission is shown in figure 2B, and network estimates are in table 2B and figure 3B. There was no evidence that any specific type, dosage or duration of corticosteroid reduced the rate of admission. A sum-

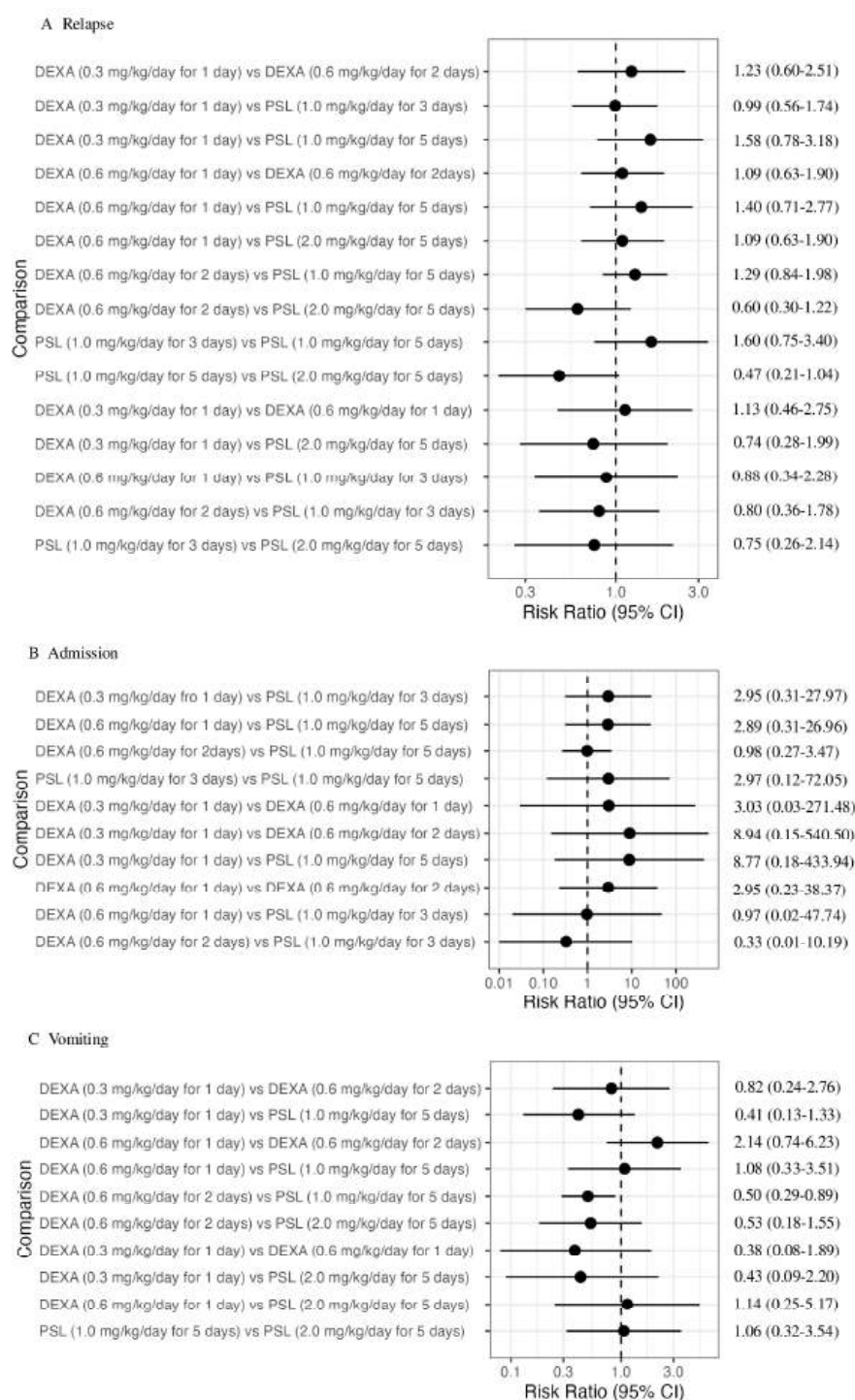


Figure 3 Forest plots of network estimates for (A) relapse, (B) admission and (C) vomiting. DEXA, dexamethasone; PSL, prednisolone.

mary of confidence in network estimates for admission is in online supplemental table 9, with all values rated very low. The P-scores for admission are in online supplemental table 8.

Vomiting

The secondary outcome of vomiting was reported in five studies involving 1581 patients.^{6 20 22 23 28 29} The network plot for vomiting is shown in figure 2C, and network estimates are in table 2C and figure 3C. Dexamethasone (0.6 mg/kg/day×2 days) was associated with less vomiting compared with prednisolone (1.0 mg/kg/day×5 days) (risk ratio 0.50 (95% CI 0.29–0.89)). There was no evidence that another specific type, dosage or duration of corticosteroid decreased the rate of vomiting. A summary of confidence in network estimates for vomiting is shown in online supplemental table 10, with all values rated very low. The P-scores for vomiting are in online supplemental table 8.

Results of qualitative evaluation

The results of the qualitative evaluation are shown in the Supplementary Results and online supplemental tables 11, 12 of the online supplemental file.

Sensitivity analysis

Pairwise analyses for relapse, hospital re-admission and vomiting comparing all dosage and duration combinations of dexamethasone and prednisolone are shown in online supplemental figures 3–5. Network plots and the results of the NMA for recurrence, re-admission and vomiting, pooling different dosages of the same drug type into one treatment group and distinguishing nodes by duration, are presented in online supplemental tables 13–15 and figures 6–8. Similarly, network plots and NMA results pooling different durations and distinguishing nodes by dosage are shown in online supplemental tables 16–18 and figures 6–8. No significant

differences were found among drug type, dosage or duration in any of the sensitivity analyses, as relapse and hospital re-admission. In a sensitivity analysis with vomiting as the outcome, dexamethasone was associated with significantly less vomiting in a pairwise analysis of dexamethasone and prednisolone, and in a NMA of dexamethasone (any dose×1 day) versus prednisolone (any dose×5 days) and dexamethasone (0.6 mg/kg/day) versus prednisolone (1.0 mg/kg/day).

DISCUSSION

The current study assessed six commonly used corticosteroid protocols for managing acute asthma exacerbations in paediatric populations, ranging from dexamethasone (0.3–0.6 mg/kg daily for 1–2 days) to prednisolone (1–2 mg/kg daily for 3–5 days). The NMA suggested that there were no significant differences in important clinical outcomes, such as relapse rates, hospital admissions or instances of vomiting, among the varied corticosteroid types, dosages and treatment durations.

Previous meta-analyses found no significant difference between short-term dexamethasone and 3–5 days of prednisolone in paediatric asthma management.^{7–11} However, these studies grouped dexamethasone and prednisolone regardless of dosage or duration^{7 8 10 11} and did not distinguish administration routes, such as intramuscular versus oral.^{7 10 11} One NMA compared placebo with short-term prednisolone, dexamethasone and intramuscular corticosteroids but lacked detailed examinations of treatment types, amounts and durations.⁹ The current NMA addressed these gaps by employing a methodology that meticulously examined the differences in type, dosage and duration of oral corticosteroid regimens. Our analysis found no significant differences in relapse rates across regimens. Qualitative evaluations also found no substantial differences in PRAM score changes or consumer-focused outcomes, such as missed school or parental workdays. Therefore, these findings suggest that short-term oral dexamethasone offers advantages in patient compliance and familial convenience.

In some analyses, vomiting risk differed between prednisolone and dexamethasone, possibly due to formulation and taste.³⁴ Cronin et al, for instance, used the superior but more expensive prednisolone sodium phosphate and observed little difference in vomiting rates between the two. However, as some studies lacked detailed formulation and taste data, further research is needed to clarify their impact.

Although no significant differences were observed and the certainty of the evidence is low to very low, some relapse comparisons with relatively narrow confidence intervals are noteworthy. For example, the network estimate for dexamethasone (0.3 mg/kg/day for 1 day) versus prednisolone (1.0 mg/kg/day for 3 days) showed a risk ratio of 0.99 (95% CI 0.56 to 1.74), indicating comparable efficacy. Moreover, absolute numbers in online supplemental table 2 suggest that relapse rates are similarly equivalent in the actual study population. For prednisolone (1.0–1.5 mg/kg/day for 5 days) versus prednisolone (2.0 mg/kg/day for 5 days), the network estimate showed a risk ratio of 0.47 (95% CI 0.21 to 1.04), suggesting the risk is less than half, with the upper CI close to 1. Online supplemental table 2 also does not indicate any clear advantage of higher doses of prednisolone.

The anti-inflammatory potency of corticosteroids indicates that 1 mg of prednisolone is equivalent to 0.15 mg of dexamethasone,³⁵ implying greater daily dose potency for dexamethasone in many studies. However, our sensitivity analysis did not reveal a notable difference between doses, suggesting that the impact of this potency difference is limited.

There is ongoing debate about the diagnosis and management of asthma and viral-induced wheezing, particularly in children aged 5 years and younger. This controversy centres on the challenges of distinguishing asthma from transient viral-induced wheezing, leading to different management approaches. According to the Global Initiative for Asthma (GINA) guidelines, age-specific considerations are critical for accurate diagnosis and treatment, underscoring the need for careful clinical assessment in this population.

However, no studies have compared the type and dosage of oral corticosteroids specifically for children under five, and the impact of age on corticosteroids efficacy remains unclear. Age may be an effect modifier; however, evidence for age-related differences is limited. Moreover, analysing infants, children and adolescents as a single group may have masked true effects. Further clinical trials focusing on specific age groups, particularly on children under five, are needed to provide clearer guidance on optimal treatment strategies.

In this study, the certainty of evidence was very low for most comparisons, primarily due to ‘serious concerns’ about imprecision.^{16 17} This stemmed from the small number of cases and events in each RCT, resulting in wide confidence intervals for effect sizes. This was also a consequence of the large number of groups compared with studying each treatment in detail. The risk of bias in each trial also reduced the certainty of the evidence. Large, high-quality RCTs are needed to provide further evidence and enable detailed comparisons of regimen effectiveness.

Strengths and limitations

In this study, we used NMA to examine the effects of oral corticosteroids on acute asthma exacerbations, focusing on type, dosage and duration of administration. This method enables simultaneous comparisons of multiple regimens using direct and indirect evidence, while reducing treatment heterogeneity compared with previous meta-analyses. We also performed three sensitivity analyses to confirm the robustness of our results under different hypotheses for drug type/dosage/duration.

However, this study has limitations. First, due to the detailed comparisons for each treatment regimen and several smaller trials, there may be a small group of cases, which may have caused problems with the precision and power of the comparisons. Second, several RCTs had concerns or a high risk of bias due to problems with the randomisation process, deviations from the intended interventions, and missing outcome data. Third, although the detailed subdivision of regimens reduced heterogeneity in treatment interventions, heterogeneity in inclusion criteria, follow-up protocols, and so forth was observed, as in previous meta-analyses.

CONCLUSIONS

In this network meta-analysis, there were no significant differences in the efficacy of commonly used corticosteroid regimens for acute exacerbations in childhood asthma. Short-term oral dexamethasone may be an acceptable alternative to a longer course of prednisolone.

Contributors SA and S Uematsu contributed to the conception and design of the study. SA, S Utsumi and KO contributed to data acquisition, analysis and interpretation of data. SA contributed to analysis and data interpretation. SA drafted the article. S Utsumi, KO and S Uematsu critically revised the article for important intellectual content. All authors have read and approved the final version of the article. SA takes responsibility for the paper as a whole. SA is responsible for the overall content as 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.

Data availability statement Data are available upon reasonable request.

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ARTIGO ORIGINAL

Associação entre pneumonia infantil hospitalizada e radiografias torácicas de seguimento em populações de alto risco: análise secundária de um ensaio clínico multicêntrico randomizado

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/archdischild-2024-327888>).

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Received 27 August 2024
Accepted 20 February 2025
Published Online First 6 March 2025



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To cite: Kok HC, Yerkovich ST, McCallum GB, et al. Arch Dis Child 2025;110:786–792.

RESUMO

Objetivo Como as crianças hospitalizadas com pneumonia adquirida na comunidade (PAC) estão em risco de apresentar anomalias persistentes na radiografia torácica (CXR) e sequelas respiratórias, investigámos os fatores associados à resolução incompleta da CXR às 4 semanas e aos 12 meses após a alta hospitalar em crianças de populações com elevado risco de doença pulmonar crônica. Desenho Análise secundária de um ensaio clínico multicêntrico, randomizado e controlado por placebo.

Contexto e participantes Foram incluídas 324 crianças com idades entre 3 meses e ≤5 anos, hospitalizadas com PAC confirmada por radiografia, recrutadas em sete hospitais na Austrália, Nova Zelândia e Malásia. Após 1–3 dias de antibióticos intravenosos, seguidos de 3 dias de amoxicilina-clavulanato oral, foram randomizadas para esquemas prolongados (13–14 dias) ou padrão (5–6 dias) de antibióticos.

Intervenção Foram realizadas radiografias torácicas na admissão, às 4 semanas e aos 12 meses após a alta, avaliadas de forma cega.

Principais desfechos Alterações radiográficas de pneumonia às 4 semanas e aos 12 meses após a alta, comparadas com as radiografias da admissão.

Resultados Entre as crianças com radiografias interpretáveis, a resolução incompleta foi observada em 42 de 253 (17%) às 4 semanas e em 29 de 212 (14%) aos 12 meses. As características na admissão associadas à resolução incompleta da CXR às 4 semanas foram: hospitalização prévia por pneumonia (odds ratio ajustado [ORadj] = 6,46; intervalo de confiança [IC] 95%: 2,21 a 18,85) e idade mais avançada (ORadj = 0,60 por ano; IC 95%: 0,38 a 0,94). A presença de sintomas ou sinais respiratórios persistentes às 4 semanas após a alta também esteve associada à resolução incompleta (OR = 5,63; IC 95%: 2,38 a 13,32). Aos 12 meses, a hospitalização prévia por pneumonia manteve-se associada à resolução incompleta da CXR (OR = 4,03; IC 95%: 1,25 a 13,02).

Conclusão Em contextos de alto risco, idade mais jovem, antecedentes de hospitalização por pneumonia e sintomas ou sinais respiratórios persistentes às 4 semanas após a alta hospitalar por PAC podem estar associados à resolução incompleta da radiografia torácica. Assim, pode justificar-se a realização de exames de seguimento e monitorização nestas crianças.

INTRODUCTION

Community-acquired pneumonia (CAP) is the leading cause of global mortality in children aged 1–59 months.¹ It is also associated with long-term respiratory sequelae,^{2–3} including impaired lung function in children and adults,^{4–6} premature adult respiratory-related death (hazard ratio [HR]=1.93,

Key messages

What is known about this topic

► The necessity of performing a chest radiograph (CXR) post-hospitalisation for community-acquired pneumonia (CAP) in children, particularly those at high risk of chronic lung disease, remains unclear, while factors associated with persistent CXR changes are unknown.

What this study adds

► CXR follow-up of children from high-risk settings hospitalised for radiographic-confirmed pneumonia found that prior pneumonia hospitalisation and younger age were associated with persistent CXR abnormalities at 4 weeks. Furthermore, prior pneumonia hospitalisation was also significantly associated with CXR abnormalities at 12 months.

How this study might affect research practice or policy

► Our findings help inform targeted follow-up strategies for chronic lung disease in children hospitalised with CAP from high-risk settings. This primarily involves post-discharge CXR and closer monitoring of children with identified risk factors and the potential of long-term respiratory sequelae.

95% confidence interval [CI] 1.10 to 3.37)⁷ and bronchiectasis.^{8–9} A case-control study found Australian Indigenous children hospitalised previously for pneumonia were significantly more likely to develop bronchiectasis than other Indigenous children hospitalised for non-respiratory illnesses (odds ratio [OR]=15.2, 95% CI 4.4 to 52.7).⁸

Children in low- and middle-income countries (LMICs),¹⁰ and Indigenous children living in socially-disadvantaged communities in high-income countries (HICs), have the greatest burden of CAP^{1,11} and its sequelae.^{12–13} In a prospective study involving indigenous Australian children hospitalised with chest radiograph (CXR) evidence of airspace consolidation, those with ‘minimal’ (0–20%) resolution of consolidation on their pre-discharge CXR,

compared with those with ‘near-complete’ (80–100%) resolution, had increased risk (relative risk [RR]=6.93, 95% CI 1.78 to 26.60) of chronic suppurative lung disease (CSLD) or bronchiectasis.¹⁴

Follow-up CXRs for children hospitalised with CAP are considered important for those at high risk of chronic lung disorders.¹⁴ However, performing follow-up CXRs for uncomplicated pneumonia is controversial.¹⁵ The British Thoracic Society guidelines state routine follow-up CXRs are not required in previously healthy children but should be considered in those with round pneumonia, atelectasis, or persisting symptoms.¹⁶ Several studies have examined the necessity of follow-up CXRs after childhood pneumonia in both inpatient and outpatient settings.^{17–21} However, these focused on short-term (3–7 weeks post-discharge) outcomes. Nevertheless, CXRs beyond these time periods are crucial, as children with incomplete CXR resolution at 6 and 12 months after acute lower respiratory infections (ALRIs) or pneumonia may have persistent lung abnormalities, suggesting underlying chronic respiratory disorders.^{22,23}

Furthermore, previous studies^{17–21} did not explore associations of specific characteristics of children hospitalised with CAP, such as age, illness severity, or clinical features and follow-up CXRs. Understanding these associations could help identify factors influencing persistent CXR abnormalities, allowing for more timely interventions. Finally, prior studies were conducted in HICs and were single-centre investigations (except one involved two centres within the same region of the United States),¹⁷ potentially limiting generalisability. Data on long-term respiratory outcomes, the value of follow-up CXRs, and risk factors for persistent CXR abnormalities to inform future clinical practice for following children hospitalised with CAP are clearly needed.

We aimed to determine factors associated with incomplete CXR resolution at 4 weeks and 12 months post-discharge in children in high-risk settings who were hospitalised with uncomplicated CAP. We also assessed the association between incomplete CXR resolution at 4 weeks and the time to the next hospitalised ALRI episode. We used data from our multicentre, randomised controlled trial (RCT), conducted between 1 March 2016 and 30 June 2022, which compared an extended 13–14 day versus a standard 5–6 day antibiotic course for children hospitalised with CAP from communities at high risk of chronic lung diseases.^{24,25} As the extended-course did not improve respiratory outcomes at 4 weeks or 24 months, data from both treatment arms were combined for this analysis.^{24,25}

METHODS (DETAILED FURTHER IN ESM ONLINE SUPPLEMENTAL METHODS)

Study design

Children were enrolled at seven hospitals; one in Australia (Darwin), two in New Zealand (Auckland) and four in Malaysia (Kota Kinabalu, Kuching, Klang, Kuala Lumpur). Informed consent was obtained for all children (ESM online supplemental methods).

Participants and procedures

Children aged 3 months to ≤5 years were eligible for enrolment if they were Aboriginal/Torres Strait Islander (Australia), Māori/Pacific Islander (New Zealand) or any child (Malaysia) with clinical and radiographic signs of pneumonia. After receiving intravenous antibiotics for 1–3 days, eligible children were switched to oral amoxicillin–clavulanate for the next 3 days and randomised to then receive either extended-course (8 days oral amoxicillin–clavulanate) or standard-course (8 days oral placebo). Children were reviewed at 4 weeks, 12 and 24 months post-discharge. Children were considered ‘clinically cured’ if all respiratory symptoms/signs had resolved at the 4-week review.²⁴

CXRs were obtained at admission and repeated during the 4-week and 12-month reviews (when feasible). The CXRs at 4 weeks and 12 months were compared with admission CXRs. An independent senior respiratory paediatrician (IBM), masked to patient information, interpreted the CXRs. The CXRs were assessed for quality, categorised as acceptable, suboptimal, or uninterpretable.²⁶ Acceptable and suboptimal CXRs were interpreted based on six lung zones: (1) right [upper, middle, lower] and (2) left [up-

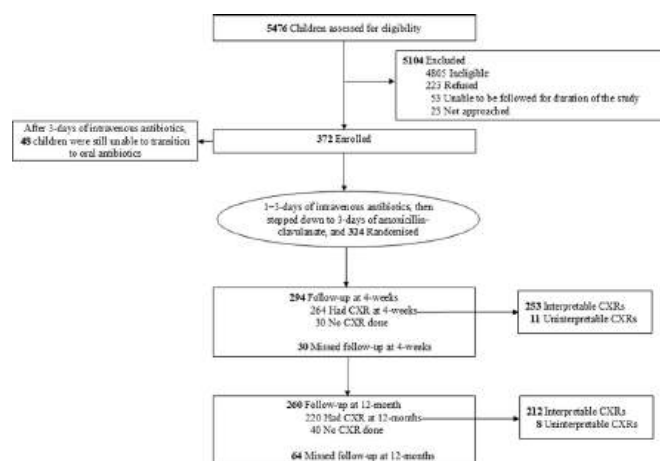


Figure 1 Participant flow diagram. CXR, chest radiograph.

per, middle, lower]. Each lung zone was scored according to the presence/absence of: (1) airspace changes; (2) interstitial changes; or (3) pleural effusion/thickening, cavities, or nodules/mass.

Each affected lung zone on follow-up CXRs was scored as: (1) complete resolution; (2) 75% to <100% resolution; (3) 50% to <75% resolution; (4) 25% to <50% resolution; or (5) <25% resolution. If more than one lung zone was affected, the most severe category was used as the overall score. For 4-week CXRs, near-complete/complete resolution was grouped as ‘≥75% resolution’ (groups 1–2) and ‘<75% resolution’ for incomplete resolution (groups 3–5). For 12-month CXRs, incomplete resolutions were assessed for those in groups 2–5. Incomplete resolution was defined as persistent abnormality in the same lung zone on follow-up CXR. Complete resolution was defined as the resolution of the abnormality in the same lung zone on follow-up CXR.

Statistical analysis

Descriptive statistics are presented as median (interquartile range [IQR]) for continuous data and frequency (percentage) for categorical data. Continuous data were analysed using the Mann-Whitney U test and categorical data were analysed using Fisher’s exact test. All tests were two-tailed and $p < 0.05$ considered significant.

We undertook logistic regression analyses based on backward elimination with a p -value criterion of 0.157 and limited the number of variables in our analyses.²⁷ We selected variables based on risk factors identified by the World Health Organization (WHO),²⁸ systematic review evidence,²⁹ and findings from well-established literature.^{8,30} In the regression analysis considering radiographic changes at 4 weeks, the five variables included in the initial model were tachypnoea and/or chest wall recession, poor feeding/unable to drink, age, hypoxaemia, and previous pneumonia hospitalisation. In the regression analysis considering radiographic changes at 12 months, the variables were tachypnoea and/or chest wall recession, age, hypoxaemia and previous pneumonia hospitalisation. A Kaplan-Meier plot was used to display time to the next hospitalised ALRI episode and Cox proportional hazard modelling to calculate HRs. All were censored at 730 days (24 months). Missing data were not imputed. We used Stata V.17 (StataCorp) to analyse data.

Table 1 Radiographic findings at 4 weeks and 12 months

	CXR at 4 weeks n=253*	CXR at 12 months n=212*
Complete resolution	135 (53)	183 (86)†
75% to <100% resolution	76 (30)	19 (9)
50% to <75% resolution	7 (3)	3 (1)
25% to <50% resolution	9 (4)	3 (1)
<25% resolution	26 (10)	4 (2)

*Data are expressed as number (%).

†Percentages do not add up to 100 due to rounding.

CXR, chest radiograph.

RESULTS
Patient characteristics

We enrolled 372 children, whereby 324 (52% male) were randomised. The median age was 1.3 years (IQR=0.9–1.9). Overall, 264 (81%) and 220 (68%) CXRs were performed at 4 weeks and 12 months, respectively (figure 1). Of these, 253/264 (96%) were interpretable at 4 weeks, and 212/220 (96%) were interpretable at 12 months. Thirty (10%) and 64 (25%) children were lost to follow-up at 4 weeks and 12 months, respectively. Baseline characteristics of those without CXRs at 4 weeks and 12 months were broadly similar to those with follow-up CXRs (ESM online supplemental table 1). However, children without follow-up CXRs had higher preterm birth rates, exposure to maternal and household cigarette smoke and C-reactive protein (CRP) levels than those with at least one follow-up CXR, but these factors did not influence our outcomes presented below (ESM online supplemental table 2). Table 1 details

the radiographic findings at 4 weeks and 12 months. Overall, 83% of children with CXRs at 4 weeks had complete (53%) or near-complete (30%) radiographic resolution, while 86% had complete radiographic resolution at 12 months.

Baseline characteristics of children with interpretable CXRs included in our study are displayed in table 2. In the multivariable regression model, the two most important factors associated with incomplete CXR resolution at 4 weeks were previous pneumonia hospitalisation (adjusted OR [O_{Radj}]=6.46, 95% CI 2.21 to 18.85) and age (O_{Radj} =0.60 per-year, 95% CI 0.38 to 0.94). The only significant factor associated with incomplete CXR resolution at 12 months was previous pneumonia hospitalisation (OR=4.03, 95% CI 1.25 to 13.02) (table 3).

Among children with interpretable 4-week CXRs, 34/253 (13%) had ≥ 1 subsequent hospitalised ALRI between 4 weeks and 24 months post-discharge (figure 2). There was no difference

Table 2 Baseline characteristics

Characteristics*	CXR at 4 weeks			CXR at 12 months		
	Near-complete/complete resolution† n=211	Incomplete resolution† n=42	P value	Complete resolution‡ n=183	Incomplete resolution‡ n=29	P value
Sociodemographic						
Age (years)	1.36 (0.95–2.00)	1.10 (0.82–1.81)	0.05	1.28 (0.92–1.90)	1.24 (0.89–1.81)	0.49
Male	108/211 (52)	19/42 (45)	0.50	21/183 (50)	15/29 (52)	1.00
Household demographic						
Exposure to household tobacco smoke	124/208 (60)	21/42 (50)	0.30	101/181 (56)	17/29 (59)	0.84
Overcrowding	99/211 (47)	19/42 (45)	0.87	83/183 (45)	12/29 (42)	0.84
Medical history						
Preterm birth (<37 weeks)	14/211 (7)	3/42 (7)	1.00	12/183 (7)	1/29 (3)	1.00
Breastfed for at least 6 months	144/209 (69)	24/42 (57)	0.15	122/182 (67)	18/29 (62)	0.67
Mother smoked tobacco during pregnancy	12/205 (6)	1/41 (2)	0.70	8/176 (5)	0/29 (0)	0.60
Previous pneumonia hospitalisation	8/211 (4)	8/42 (19)	0.001	9/183 (5)	5/29 (17)	0.03
Fever	205/211 (97)	42/42 (100)	0.60	178/183 (97)	29/29 (100)	1.00
Cough	208/211 (99)	41/42 (98)	0.52	179/183 (98)	28/29 (98)	0.52
Poor feeding/unable to drink	88/193 (46)	22/39 (56)	0.23	79/169 (47)	15/27 (56)	0.42
Persistent vomiting	44/189 (23)	11/39 (28)	0.54	40/163 (25)	7/27 (26)	1.00
Lethargy	87/185 (47)	19/37 (51)	0.72	77/162 (48)	14/27 (52)	0.68
Clinical features on admission						
Fever (temperature $\geq 38.0^{\circ}\text{C}$)	104/211 (49)	19/42 (45)	0.74	91/183 (50)	14/29 (48)	1.00
Tachypnoea§	121/210 (58)	26/40 (65)	0.48	101/182 (55)	16/28 (57)	1.00
Chest wall recession	63/98 (64)	18/22 (82)	0.14	54/85 (64)	9/14 (64)	1.00
Crackles on auscultation	188/211 (89)	40/42 (95)	0.39	166/183 (91)	26/29 (90)	0.74
Hypoxaemia (oxygen saturation $\leq 92\%$)	19/211 (9)	4/42 (10)	1.00	17/183 (9)	2/29 (7)	1.00
Blood indices						
White blood cell count ($\times 10^9/\text{L}$)	13.5 (8.9–20.1)	14.0 (9.8–18.8)	0.93	14.4 (10.2–21.0)	11.4 (9.0–15.8)	0.10
Neutrophil count ($\times 10^9/\text{L}$)	8.6 (5.2–17.8)	7.7 (4.6–11.7)	0.24	8.9 (5.4–17.9)	6.7 (3.7–9.1)	0.02
C-reactive protein (mg/L)	13.8 (1.6–58.7)	16.5 (4.0–32.0)	0.84	12.3 (0.6–52.6)	19.6 (6.0–31.1)	0.50
Management						
Oxygen supplementation	146/211 (69)	23/42 (55)	0.07	125/183 (68)	16/29 (55)	0.20
Intravenous or nasogastric tube fluid supplementation	76/202 (38)	14/39 (36)	1.00	59/172 (34)	10/29 (35)	1.00
Length of stay (days)	3 (2–4)	3 (2–3)	0.84	3 (2–4)	3 (2–4)	0.27
Extended course (13–14-days) antibiotics	109/211 (52)	19/42 (45)	0.50	93/183 (51)	14/29 (48)	0.84
4-week clinic review						
Chronic cough (>4 weeks)	NA	NA	NA	7/183 (4)	1/28 (4)	1.00
Crackles on auscultation	NA	NA	NA	13/183 (7)	5/29 (17)	0.08
Wheeze on auscultation	NA	NA	NA	9/183 (5)	5/29 (17)	0.03
Medical chart review (from 4 weeks to 12 months post-discharge)						
≥ 1 subsequent hospitalised ALRI episode(s)	NA	NA	NA	23/188 (12)	6/24 (25)	0.11

*Data are expressed as number (%) or median (IQR).

†At the 4-week CXR review, near-complete/complete resolution = 75–100% resolution and incomplete resolution = <75% resolution.

‡At the 12-month CXR review, complete resolution = 100% resolution and incomplete resolution = <100% resolution.

§World Health Organization criteria: children aged 2–11 months: respiratory rate ≥ 50 breaths/minute; children aged 1–5 years: respiratory rate ≥ 40 breaths/minute.

ALRI, acute lower respiratory infection; CXR, chest radiograph; NA, not applicable.

Table 3 Multivariable logistic regression analyses		
Baseline characteristics	Incomplete CXR resolution at 4 weeks*	
	Multivariable analysis	
	OR _{adj} (95% CI)	P value
Age (years)	0.60 (0.38 to 0.94)	0.03
Previous pneumonia hospitalisation	6.46 (2.21 to 18.85)	0.001
Baseline characteristics	Incomplete CXR resolution at 12 months†	
	Multivariable analysis	
	OR _{adj} (95% CI)	P value
Previous pneumonia hospitalisation	4.03 (1.25 to 13.02)	0.02

*At the 4-week CXR review, incomplete resolution = <75% resolution.
†At the 12-month CXR review, incomplete resolution = <100% resolution.
CI, confidence interval; CXR, chest radiograph; OR_{adj}, adjusted odds ratio.

in the 4-week CXR outcomes and the time to the next hospitalised ALRI.

An outcome of our RCT was clinical cure (all respiratory symptoms/signs resolved at 4 weeks).²⁴ Children without clinical cure at 4 weeks were more likely to have incomplete CXR resolution at 4 weeks than those with clinical cure (OR=5.63, 95% CI 2.38 to 13.32).

At medical chart review, 5/324 (2%) children had chest computed-tomography (cCT) scans ordered by their paediatrician revealing bronchiectasis within 2 years of their hospitalisation. Of these, two had incomplete CXR resolution at both 4 weeks and 12 months, one had complete resolution at 4 weeks and 12 months, another had no follow-up CXRs, and one had uninterpretable CXRs. At the 12 months review, 29/212 (14%) children had persistent CXR abnormalities. Of these, 14/29 (48%) did not have chronic cough or observed wet/productive cough in the clinic.

DISCUSSION

In children aged ≤5 years hospitalised for CAP in settings with a high risk of chronic lung disease among community members, we found at 4 weeks post-discharge, previous pneumonia hospitalisation and age were associated with incomplete CXR resolution. Children without a clinical cure at 4 weeks also had increased odds of incomplete CXR resolution at this time point. Furthermore, previous pneumonia hospitalisation was also positively associated with persistent CXR abnormalities at 12 months. However, the

time to the next respiratory-related hospitalisation was not significantly different between those with incomplete versus those with near-complete/complete CXR resolution at 4 weeks.

Our findings are novel for several reasons. First, they suggest that recurrent pneumonia hospitalisation may be associated with abnormal follow-up CXRs, possibly indicating an underlying chronic pulmonary disorder. These findings align with a previous study of Australian Indigenous children where recurrent (>1) hospitalised pneumonia and severe pneumonia episodes increased the risk of developing bronchiectasis ($P_{\text{trend}} < 0.01$ for both).⁸ A South African birth cohort study also revealed infants with >1 ALRI episode had impaired lung function with a lower tidal volume (−1.7 mL, 95% CI −3.27 to −0.21) and a higher lung clearance index (LCI) indicating less efficient lung function (0.13 turnovers, 95% CI 0.00 to 0.26) at 1 year of age, compared with infants without ALRI.³¹ The impact on LCI was greatest in infants hospitalised for ALRI (0.36 turnovers, 95% CI 0.09 to 0.63).

Second, as postnatal lung development is a continuous process that is most critical in early childhood,³² an infectious insult to the developing alveoli and growing airways may result in long-term consequences.^{3 5 6} Similarly, we observed a possible association between younger age and incomplete CXR resolution at 4 weeks. Furthermore, a national Great Britain birth cohort study demonstrated ALRI before age 1 year was associated with an increased risk of premature adult respiratory mortality (HR=2.12, 95% CI 1.16 to 3.88), especially if recurrent (≥3 episodes, HR=2.87, 95% CI 1.18 to 7.02) or needing hospitalisation (HR=4.35, 95% CI 1.31 to 14.5) compared with those without ALRI.⁷

Third, children with persistent respiratory symptoms/signs at 4 weeks post-discharge were more likely to have continuing CXR abnormalities, which may herald an underlying chronic pulmonary disorder. While under such circumstances major international guidelines advocate clinical review and follow-up CXRs,^{16 33} we provide supporting evidence for this recommendation.

Fourth, nearly half the children with persistent CXR abnormalities at 12 months have no chronic respiratory symptoms/signs, although these may be under-reported or not apparent clinically. Nevertheless, some may be asymptomatic during a stable phase of the disease despite ongoing pathology. Without follow-up imaging, these children risk delayed diagnosis, highlighting the importance of post-hospitalisation CXR in detecting long-term respiratory complications.

Our findings suggest that omitting routine follow-up CXRs in children hospitalised with uncomplicated CAP may warrant re-evaluation.^{17–21} In a prospective Finnish study, of the 196 children hospitalised with pneumonia with follow-up CXRs performed 3–7 weeks post-discharge, 30% showed abnormalities.²⁰ Medical records and parental questionnaires were collected 8–10 years later. Twenty-six patients had recurrent pneumonia, and 6 had underlying diseases. The study concluded that no new illnesses during the 8–10 years were linked to the previous pneumonia.²⁰ However, the findings may be influenced by recall bias affecting the accuracy of the reported outcomes, given the very long delay of 8–10 years. Moreover, including children with comorbidities in that study²⁰ could have confounded the results, which might not be generalisable to the broader population.

A Norwegian retrospective study found that of 245 children hospitalised for CAP, 133 had follow-up CXRs, with 27 (20%) showing abnormalities.²¹ Among those with follow-up CXRs, 1 had chronic lung disease, and another had recurrent pneumonia, whereas of 112 children without follow-up CXRs, 3 were later suspected of chronic lung disease. The authors concluded a follow-up CXR could benefit just 5/245 (2%) cases.

Our study differs from previous studies in two key aspects. First, it was conducted in populations with high rates of chronic lung disease in children, including CSLD and bronchiectasis,^{34–36} where early detection of these conditions is crucial for managing and halting disease progression.³⁷ Second, we prospectively performed follow-up CXRs at 4 weeks and 12 months, correlating clinical with radiographic findings. This contrasts with other studies,^{17 18,20} where all but one²³ conducted follow-up CXRs 3–7 weeks post-

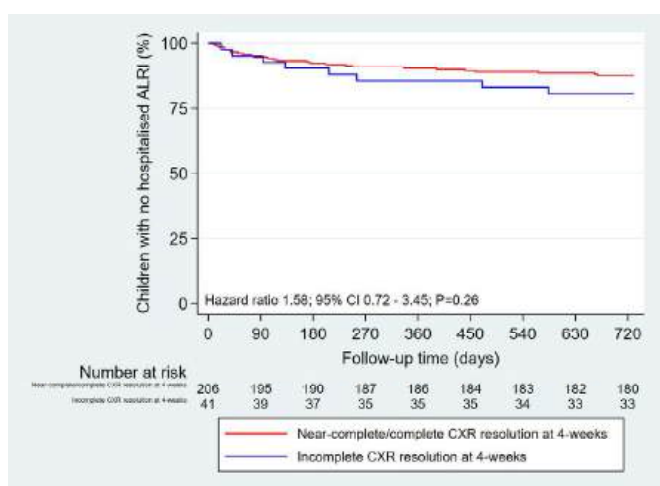


Figure 2 Kaplan-Meier curves showing the proportion of children without hospitalised ALRI during the 24-month follow-up period. *The total number of children with an interpretable CXR at 4 weeks was 247 (instead of n=253), as 6 had another hospitalised ALRI episode before 4 weeks post-discharge and were excluded from the analysis. ALRI, acute lower respiratory infection; CXR, chest radiograph.

index pneumonia. Therefore, our study contributes valuable data on the long-term outcomes of follow-up imaging in children hospitalised with CAP.

Our results corroborate findings of a retrospective case-control study that evaluated 95 Alaska Native children aged <3 years hospitalised with respiratory syncytial viral infection.²² The researchers found the risk of bronchiectasis was increased in children aged <2 years with CXRs showing lung parenchymal densities (RR=3.92, $p=0.013$), densities persisting >6 months (RR=3.0, $p=0.024$) and densities occurring in >1 episode ($P_{\text{trend}}=0.003$). Pneumonia in children aged <2 years was also significantly associated with developing bronchiectasis (RR=9.83, $p=0.007$).

The main strength of our study is that enrolment was based on a pre-established set of strict inclusion and exclusion criteria for CAP. The international and multicentre design increased the generalisability of our findings to LMICs and disadvantaged Indigenous communities in HICs. Moreover, the 24-month follow-up of children ensured all hospitalised ALRI episodes were captured in our study, and CXRs were assessed by a single, masked expert.

The foundation study cited in this report used the following categories: 80–100% as ‘near-complete’ resolution, 20–80% as ‘moderate’ resolution and 0–20% as ‘minimal’ resolution.¹⁴ However, we adopted a different threshold system to allow a more even distribution of percentage categories. Dividing the broad 20–80% range into smaller intervals increased the granularity of the CXR data, providing a more detailed assessment of resolution.

Nevertheless, important limitations exist. First, 19% and 32% of participants had no follow-up CXRs performed at 4 weeks and 12 months, respectively. This occurred mainly in children from remote communities facing travel difficulties when transport or accompanying parents/guardians were unavailable to take the child for a CXR. Furthermore, travel limitations were aggravated by the ‘wet season’ and enforced isolation during the coronavirus disease 2019 pandemic. Although differences were observed between children with or without follow-up CXRs (ie, household tobacco smoke exposure, maternal smoking during pregnancy, preterm birth and CRP levels), these factors were unlikely to have significantly affected the overall findings, as shown in the ESM online supplemental file 1. It is also possible that children lost to follow-up had better clinical outcomes, including complete CXR resolution, than those who returned for follow-up CXRs. While this may have overestimated the prevalence of persistent radiographic abnormalities, it is unlikely as children without follow-up CXRs were more likely to be preterm-born and have tobacco-smoke exposure, both risk factors for chronic lung disease. Nevertheless, given the limited number of outcome events and the exploratory nature of this secondary analysis, we did not impute missing data, as it could introduce additional uncertainty.

Second, routine cCT scans to exclude bronchiectasis were not included in our RCT.^{30 37} Consequently, there are no cCT data for children with incomplete CXR resolution at 12 months. However, given their young age (median age=2.3 years), cCT scans would have required general anaesthesia, making this impractical for study participants.

Third, although previous pneumonia hospitalisation was independently associated with incomplete CXR resolution at 4 weeks and 12 months, the number of pneumonia episodes was not collected. These dose-response data would help assess the risk of complications, such as CSLD or bronchiectasis, which are more likely in children with recurrent pneumonia.^{8 22}

Fourth, we acknowledge the gold standard for CXR interpretation is a paediatric radiologist. However, in our study setting, most CXRs are typically interpreted by clinicians, as dedicated paediatric radiology expertise is not routinely available. This reflects real-world practice in similar healthcare settings. To reduce variability, all CXRs were reviewed by a single respiratory paediatrician in a blinded manner. Despite these limitations, our study provides valuable insights, as it represents the largest cohort, specifically evaluating radiographic follow-up of pneumonia in children.^{17–21}

Fifth, our sample size may limit our ability to identify all prognostic variables. When determining prognostic factors, we did not

use a univariable prefiltering method as this can lead to unstable results, since it relies on p values that may vary randomly due to chance. Important predictors may also be excluded simply because they do not show statistical significance in univariable analysis, despite being relevant in a multivariable context due to confounding or interaction effects. Consequently, we used backward elimination and limited the number of variables chosen for the initial full multivariable model, and used a selection criterion of 0.157 as recommended.²⁷ This arguably provides a more robust approach. Our chosen variables were selected carefully based on prior clinical plausibility. In the WHO case management guidelines, tachypnoea and chest wall recession are key clinical signs of pneumonia, while inability to drink is a danger sign of severe pneumonia.²⁸ Younger age and hypoxaemia are strong predictors of severe pneumonia and mortality,^{29 38} while recurrent pneumonia is a known risk factor for bronchiectasis.^{8 30} Nevertheless, the limited overall number of events may mean some important factors were not identified due to issues with statistical power. Consequently, it is important that future work confirms the relevance of the factors we identified, including conducting sensitivity analyses to assess the robustness of our findings in similar patient populations and in other settings.

In conclusion, in children aged ≤5 years from populations at high risk of chronic lung disease, we identified factors that may be associated with incomplete CXR resolution 4 weeks and 12 months post-hospitalisation for severe CAP. In this setting, children with previous pneumonia hospitalisation, younger age and persistent respiratory symptoms/signs 4 weeks post-discharge may benefit from follow-up CXRs. Children with persistently abnormal CXRs should be monitored closely for long-term respiratory complications, including CSLD and bronchiectasis. These considerations are important as early diagnosis of childhood bronchiectasis, along with optimal treatment, may lead to its reversal.^{30 39 40}

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Acknowledgements The study was funded by an NHMRC project grant (number 1098443) and supported by an NHMRC Centre for Research Excellence in Lung Health of Aboriginal and Torres Strait Islander Children (grant number 1040830). The New Zealand site was supported by a 2-year grant from CureKids, New Zealand (grant 3571). The Kuala Lumpur site was partially funded by a University of Malaya Research Grant (RP026-14HTM). HCK is supported by a Charles Darwin International PhD Scholars (CDIPS) Scholarship. ABC is supported by an NHMRC L3 Investigator Grant (2025379) and a Senior Practitioner Fellowship (1154302). We thank the children and their families for participating in the study. We also thank the research staff (Francisca Tenorio, Sarah Sim, Erin Plumb, Charmaine Mobberley, Shirley Lawrence, Blueren Elogius, Ila Zulaika, Quaisiah Adam, Rahimah Jubkar, Lesley Versteegh and Cate Wilson) for participant recruitment and follow-up, and Anita Champion for assistance in obtaining the trial medications. We are also grateful to members of the Australian First Nations Reference Group of the Child and Maternal Health Division at the Menzies School of Health Research for their support and for overseeing the cultural aspects of this study and the Mori Research Review Committee in Auckland, who reviewed and approved the study prior to submitting the New Zealand grant application. We also thank Professors Alan Isles, Kok Meng John Chan, Lucy Lum, Helen Wihongi (Ngati Porou, Ngāpuhi, Te Whānau ā Apanui, Ngāti Hine), Paul Bauert and Carolyn MacLennan, who generously provided their time as members of the independent data monitoring committee.

Contributors ABC, KG, PSM, JWU, SMF, TWY, MHO, AMN, JAdB, RSW and PJT contributed to the conception and design of the study. HCK, GBM, STY, SMF, AMN, CAB, NN, NS, KPE and MHO contributed to data extraction and collection. IBM independently assessed all chest radiographs as part of the data collection process. HCK and STY contributed to data analysis and had access to all data. HCK wrote the first draft of the manuscript. ABC, KG, STY, NF, SMF, GBM and RSW provided insights on data analysis and oversaw the writing of the paper. All authors commented on previous versions of the manuscript, read and approved the final manuscript. ABC accepts full responsibility for the finished work and the conduct of the study, had access to the data and controlled the decision to publish as the guarantor.

Funding The study was funded by an NHMRC project grant (number 1098443) and supported by an NHMRC Centre for Research Excellence in Lung Health of Aboriginal and Torres Strait Islander Children (grant number 1040830). The New Zealand site was supported by a 2-year grant from CureKids, New Zealand (grant 3571). The Kuala Lumpur site was partially funded by a University of Malaya Research Grant (RP026-14HTM). AC is supported by an NHMRC L3 Investigator Grant (2025379) and a Senior Practitioner Fellowship (1154302).

Competing interests ABC, KG, STY, RSW, GBM, NF, PSM, JWU and PJT report grants from the Australian National Health and Medical Research Council (NHMRC) and NHMRC-managed grants (Medical Research Futures Fund), during the conduct of the study. AC is also an independent data management committee member for clinical trials

for Moderna (COVID-19 and EBV vaccines) and of an unlicensed vaccine (GlaxoSmithKline) and monoclonal antibody (AstraZeneca), received fees to the institution for consulting on the study designs for Zambon and Boehringer Ingelheim, airfares for travel from the European Respiratory Society and Boehringer Ingelheim and personal fees for being an author of two UpToDate chapters that are outside the submitted work. HCK, SMF, AMN, CAB, NN, NS, TWY, VMO, IBM, JAdB, KPE, BL and MHO have no conflicts of interest to disclose.

Patient consent for publication Not applicable.

Ethics approval The Human Research Ethics Committee at each participating institution approved the study: Australia (Human Research Ethics Committee of the Northern Territory Department of Health and Families and the Menzies School of Health Research, ID: HREC-16-2539), Malaysia (University of Malaya Research Ethics Committee, ID: 21789; Medical Research and Ethics Committee, ID: NMRR-16-216-29143 (IIR)) and New Zealand (Health and Disability Ethics Committees, ID: 17/CEN/87).

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.

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ARTIGO ORIGINAL

Asma quase fatal em crianças e jovens adultos: um estudo internacional eDelphi

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/archdischild-2024-327888>).

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Received 27 August 2024

Accepted 20 February 2025

Published Online First 6 March 2025



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To cite: McMurray A, Fleming L, Cunningham S. Arch Dis Child 2025;110:693–700.

RESUMO

Contexto As diretrizes e a evidência disponível indicam que crianças e jovens que morrem devido a asma frequentemente apresentam um episódio grave prévio. Atualmente, não existe uma designação nem uma definição de caso consensual para a forma mais grave de crise asmática. Este estudo teve como objetivo resolver essa lacuna através de uma revisão estruturada da literatura, de diretrizes e de relatos multimídia, que serviu de base para um processo Delphi eletrônico internacional (eDelphi).

Métodos Foi realizada uma revisão exploratória da literatura, de diretrizes internacionais e de evidência anecdótica (relatos multimídia), a partir da qual se identificaram itens e potenciais denominações para a primeira de três rondas do processo eDelphi. A pontuação foi feita numa escala de Likert de 1 a 5, sendo considerado consenso um total combinado de $\geq 70\%$ nas pontuações 4 e 5. Os participantes puderam ainda sugerir novos itens e nomes em campo de texto livre. Participaram médicos especialistas no tratamento agudo da asma em contexto pediátrico e de adultos, nas áreas de pneumologia, medicina de urgência e cuidados intensivos, provenientes de 25 países. Na ronda final, foi apresentada uma definição-base com duas opções adicionais de complementação.

Resultados Foram identificados 52 estudos na revisão exploratória (de um total de 586), e 27 diretrizes internacionais forneceram 41 itens e 4 nomes potenciais para a primeira ronda. Um total de 104 participantes completou as três rondas, tendo sido propostos mais 10 itens e 3 nomes adicionais na segunda ronda. O termo “asma quase fatal” (Near-Fatal Asthma – NFA) foi o nome preferido na terceira ronda (66,7%). Os 22 itens que atingiram consenso na segunda ronda foram integrados no texto-base, resultando numa definição consensual aprovada por 83 dos 104 participantes (79,8%).

Conclusões Este estudo fornece uma designação preferencial e uma definição consensual de asma quase fatal (NFA) em crianças e jovens. Estes resultados poderão permitir uma melhor caracterização clínica e uma resposta assistencial mais eficaz para esta população vulnerável.

INTRODUCTION

Children and young people (CYP) with severe asthma have a higher risk of an asthma-related death when compared with adults¹. This increased risk is partly due to a higher proportion of modifiable risk factors in CYP.² Asthma deaths in CYP in the UK, Australia, New Zealand and the USA are more frequent than comparable countries for inadequately explained reasons.³ As with older people, CYP who die from asthma frequently experience a notably severe exacerbation in the period before death.⁴ CYP are a particularly vulnerable group as this age traverses parental dependence to independence and psychological risk maturation, with 24 years of age now considered the upper boundary of adolescence.⁵

Guidelines categorise the severity of asthma attacks into mild, moderate and severe.^{6,7} Many clinicians also recognise another category. Status asthmaticus (SA) is used within Medical Subject Headings and the International Classification of

Key messages

What is known about this topic

- A near-fatal asthma (NFA) attack is often a precursor to death from asthma, which remains intractably high in some countries including the UK.
- Children and young people (CYP) are a particularly vulnerable population given the transition from parent-delivered to individual-delivered care and perceptions of risk over this age range.
- There is no standard definition of an NFA attack.

What this study adds

- This study provides the first case definition of NFA attacks in CYP, agreed by an international Delphi consensus supported by a guideline and scoping review.

How this study might affect research practice or policy

- Delphi-defined identification of NFA attacks could be used to better understand and reduce the risk of subsequent attacks or death in this population through guideline alignment, international meta-analysis and common care pathways.

Diseases (medical coding). However, SA does not have a consistent definition, and a range of synonymous terms are in common usage across studies and guidelines, including near-fatal asthma (NFA), life-threatening asthma, severe life-threatening asthma with progressive respiratory failure and critical asthma syndrome (CAS). This variance in terminology and lack of an appropriate case definition limits both the capability to understand the frequency of these events and also the consistency of follow-up care to reduce future risk.⁸

To support consistent terminology and derive a case definition, the aim of this study was: (1) To use a scoping and guideline review to provide terms and descriptors for an electronic Delphi (eDelphi) first round, and (2) To perform an international three-stage eDelphi process to provide clinical consensus to an agreed name and case definition.

METHODS

The study used the term ‘critical asthma attack’ to describe a penultimate event which, if not recognised by the individual, parent or carer and then skilfully treated by a clinical team, would result in death. This term is used within this manuscript to describe this attack, until determination of the name by the modified eDelphi process. We performed an international eDelphi survey to

determine a consensus name for a critical asthma attack and to provide the defining features of such an attack. To populate the initial round of the eDelphi survey, we performed (1) A systematic scoping review of current literature, (2) A review of global asthma guidelines and (3) Incorporated anecdotal evidence, patient stories in press reports and social media. An overview of the methodology is provided in online supplemental appendix figure 1.

Systematic scoping review

The objectives were to identify features of a critical asthma attack including (1) Names and definitions, (2) Clinical features, (3) Objective physiological measurements, (4) Experience of the event in a child (over 5 years) by patient/parent/carers, and adolescents/young adults themselves (up to age 24 years). Four databases were searched initially on 01 February 2017 to inform the Delphi consensus and repeated on 01 June 2024 to ensure continued validity of the output at the time of publication. PubMed, Web of Science, Embase and CINAHL plus were searched for human studies in full texts published in English using the terms Child* OR pediatri* OR Adolocen* OR young adult AND 'near fatal asthma' OR 'status asthmaticus' OR 'life threatening asthma' OR 'acute asphyxia asthma'. Following removal of duplicates, studies were screened (title and abstract) for eligibility by a single reviewer (AM). Eligible studies had full text review by AM, SC and LF. Full text studies had screening of references and removal of manuscripts that were not adherent to inclusion/exclusion criteria (see online supplemental appendix page 5). Studies selected for review were agreed by consensus (AM, SC, LF).

Global asthma guideline review

To identify global asthma guidelines, we searched using (1) Two international repositories for asthma guidelines (www.theipcr.org, date accessed 01 August 2017 (now removed)) and www.globalasthmanetwork.org (date accessed 23 October 2017), (2) The University of Edinburgh Library search tool and (3) Google Scho-

lar by country using the terms 'asthma guideline' and the name of the country (conducted 01 August 2017). Guidelines which did not include acute wheeze management were excluded. All eligible guidelines were included at their most recent update published in the previous 10 years (2007–2017 inclusive) (table 1), with source reference data (see online supplemental appendix table 1). To provide continued validity at the time of publication, the Global Asthma Network repository was searched again (01 July 24) with the same exclusion criteria applied.

Unless otherwise stated, text refers to the initial data searches. Data from the scoping and guideline reviews were extracted to charting tables. Text descriptions (ie, 'speaking few words' and 'phrases') were coalesced, where appropriate, by discussion and agreement between two researchers (AM and SC). Definitions of severe asthma were compared across sources, including clinical features, objective measurements and activities of daily living. Where appropriate, the mode and ranges for each were determined.

Anecdotal evidence, patient stories and multimedia

As experienced clinicians, AM, SC and LF added features which they had learnt from colleagues and families who had experienced these events (eg, going outside for fresh air). Asthma and Lung UK social media pages and other asthma-related social media were scrutinised for news stories/comments in post threads.

From these sources, key clinical, physiological and behavioural parameters informed the first round of a Delphi process (table 2).

Modified eDelphi

A modified eDelphi process was performed in three rounds between 07 March 2018 and 14 August 2018. Participants were adult and paediatric specialists within respiratory, emergency and critical care medicine. The three rounds were to enable participants to: (1) Suggest names and identify key clinical and physiological features, with free text contributions possible, (2) Refine round 1 options and (3) Agree on a name, choose a definition and agree on physiological parameters.

Table 1 Asthma guideline according to year, country, targeted age range, source

Year	Country	Adult	Paediatric	Source of guideline
2017	GINA (worldwide)	Combined for children aged 5 years and above and adults		Library
	Japan	✓	✓	Global Asthma Network
	New Zealand		✓	International Primary Care Respiratory Group
2016	New Zealand	✓		International Primary Care Respiratory Group
	Saudi Arabia*	✓	✓	Global Asthma Network
	The United Kingdom*	✓	✓	Library
2015	France (adults and adolescents)	✓		Global Asthma Network
	India	✓		Google Scholar
	Ireland	✓		Google Scholar
2014	Australia	✓		International Primary Care Respiratory Group
	Malaysia		✓	Global Asthma Network
2013	Argentina	✓		Google Scholar
	Chile	✓		International Primary Care Respiratory Group
	China	✓		Global Asthma Network
	Colombia	✓		Global Asthma Network
	Ireland		✓	Google Scholar
	The United Arab Emirates		✓	Google Scholar
	South Africa		✓	Global Asthma Network
2012	Finland	✓		Global Asthma Network
2011	Chile		✓	International Primary Care Respiratory Group
	Uruguay		✓	Global Asthma Network
	Kenya	✓		Global Asthma Network
2009	Philippines	✓		Google Scholar
	Spain	✓		Global Asthma Network

*(1 guideline with separate flow charts)

Table 2 The characteristics of asthma at different severities provided by guidelines (age-specific values not included in this table as these values vary with age: objective measurements, mode (range) (n)/clinical features, mode (other term) (n)/activities of daily living, mode (other term) (n)

Objective measurements	Mild (n=15)	Moderate (n=24)	Acute severe (n=26)	Life-threatening (n=26)
SpO ₂	>95% (>92% to >96%) (n=12)	90%–95% (<90% to >95%) (n=17)	≤90% (90%–95%) (n=22)	<90% (<90% to <92%) (n=16)
Peak expiratory flow rate	≥80% (>70% to ≥80%) (n=13)	≥50% (40%–80%) (n=19)	≤50% (30%–70%) (n=21)	<30% (unmeasurable to <25% to <50%) (n=16)
Heart rate	<100/min (normal to <100/min) (n=9)	100–120/min (normal to ≤125/min) (n=15)	≥120/min (increased, bradycardia or 100/min to >125/min) (n=18)	Bradycardia (bradycardia, arrhythmia to >120/min to >140/min) (n=17)
Respiratory rate	Increased (increased to <40/min) (n=14)	Increased (increased to >40/min) (n=17)	>30/min (increased or >20/min to >40/min) (n=18)	Poor effort (undetermined, poor effort, panting >30/min, increased) (n=7)
Pulsus paradoxus	Absent or <10 mm Hg (absent or <10 mm Hg) (n=6)	10–20 mm Hg (10–25 mm Hg) (n=5)	>25 mm Hg—child, 20–40 mm Hg—adult (>10–40 mm Hg) (n=9)	Absent suggests fatigue (absent or >40 mm Hg) (n=5)
PaO ₂	Normal (normal) (n=5)	≥60 mm Hg/8 kPa (≥60 mm Hg/8 kPa) (n=4)	≤60 mm Hg/8 kPa (≤60 mm Hg/8 kPa to 80 mm Hg/10.6 kPa) (n=7)	<60 mm Hg/8 kPa (<60 mm Hg/8 kPa) (n=8)
PaCO ₂	<42 mm Hg/5.6 kPa (<35–45 mm Hg/4.66–6 kPa) (n=8)	<42 mm Hg (<40–45 mm Hg/<5.55–6 kPa) (n=8)	≥42 mm Hg/5.6 kPa (<40 mm Hg to ≥45 mm Hg) (n=8)	≥45 mm Hg (normal or hypercapnia or 35–60 mm Hg/4.6–8 kPa) (n=12)
Scoring tools	PRAM, pulmonary score (n=2) PRAM Score 1–3	PRAM (PRAM) (n=1) PRAM Score 4–7	PRAM (PRAM) (n=1) PRAM Score 8–12	PRAM (PRAM) (n=1) PRAM Score 8–12 (despite treatment)
Clinical features				
Accessory muscle use	No (no, usually not, mild) (n=11)	Mild (no, mild or moderate) (n=14)	Accessory muscle use (accessory muscle use) (n=18)	Paradoxical thoracoabdominal movement 2 (n=18)*
Chest sounds	Mild wheeze (wheeze present, mild or moderate) (n=13)	Moderate wheeze (moderate wheeze) (n=13)	Moderate wheeze (moderate wheeze, decreased air entry, silent chest) (n=15)	Silent chest (silent chest) (n=24)
Colour	N/A	N/A	Cyanosis (cyanosis) (n=2)	Cyanosis (cyanosis) (n=2)
Behaviour	May be agitated (may be agitated or normal) (n=9)	Agitated (agitated or normal) (n=14)	Agitated (agitated or normal) (n=14)	Drowsy or confused (n=26)†
Activities of daily living				
Talking	In sentences (in sentences) (n=12)	In phrases (in sentences or in phrases) (n=21)	In words (in words, unable to speak) (n=25)	Unable to talk (unable to talk, words) (n=11)
Eating/drinking	Normal (normal) (n=1)	Difficult (difficult) (n=5)	Difficult (difficult) (n=5)	Unable (unable) (n=3)
Walking	Breathless (slightly breathless or breathless) (n=10)	Difficult (can walk or difficult) (n=3)	Difficult (difficult) (n=2)	Cannot walk (cannot walk) (n=2)
Sleeping	Can sleep (can sleep) (n=1)	Occasionally wakes (occasionally wakes) (n=1)	Disturbed (disturbed) (n=1)	Unable to sleep (disturbed, unable to sleep) (n=2)
Posture	Can lie down (can lie down) (n=8)	Prefers sitting (prefers sitting) (n=8)	Hunched forward (hunched forward) (n=7)	Orthopnoea (orthopnoea) (n=2)

*Includes poor effort, permanent contraction of the sternocleidomastoid, marked depression of the suprasternal, significant subcostal and subglottic retraction

†Includes confusion, impaired consciousness, drowsiness, altered mental status, exhaustion

PaCO₂, partial pressure of carbon dioxide; PaO₂, partial pressure of oxygen; PRAM, Paediatric Respiratory Assessment Measure; SpO₂, oxygen saturation.

We used an electronic online survey (www.onlinesurveys.ac.uk) accessed via an invitation email that included a Participant Information Sheet and consent form. Participants were recruited via (1) Targeted email using contacts within the three fields of practice or (2) Via a global email sent by societies worldwide providing free distribution to relevant respiratory, emergency and critical care medicine specialties (see online supplemental appendix table 2). Screening questions confirmed participants were medically qualified at an appropriate Board Certification level (consultant), with age-appropriate practice (5–24 years of age) which included experience of managing severe asthma attacks. The following headings were used for each section: about the critical attack; clinical signs; objective measurements; other features and future self-management. Failure to complete a round was considered a withdrawal, and subsequent participation was not invited.

Participants were asked to consider throughout, ‘what makes this event different from a severe asthma attack?’. Likert scale ranking was used: 1—Irrelevant, 2—Unimportant, 3—Of equivocal importance, 4—Important and 5—Very important. Consensus was agreed a priori as ≥70% of combined score 4 or 5 responses, consistent with thresholds used for other clinical conditions.⁹ Free text responses were analysed thematically (clinical features) or numerically (physiological measurements).

Following rounds 1 and 2, participants were provided with individualised feedback and summary report as per standard Delphi methodology. Round 1 free text suggestions were included in round 2. Consensus responses populated round 3. For the third and final round, participants were provided with a choice between the two most popular names for the event, a definition stem with four options to consider and variables for three objective measurements (oxygen saturation (SpO₂), partial pressure of carbon dioxide (PaCO₂), pH).

RESULTS

The scoping review identified 586 studies and included 52 studies (online supplemental appendix figure 2 and online supplemental appendix table 3). Four names were observed to describe a critical asthma attack: SA (n=28/52); severe/acute life-threatening asthma with progressive respiratory failure (n=5/52); NFA (n=15/52); and CAS (n=1/52). Definitions of this attack or criteria used to recruit to cohort studies were offered by 36 authors (n=36/52), with failure to respond to treatment (n=18/36), rising PaCO₂ (n=12/36) and/or mechanical ventilation (n=9/36) most commonly given. Objective measurements and clinical features were included within 47 and 45 (out of 52) studies, respectively, which included cohort studies (18 and 18, respectively), case reports (19 and 19, respectively) and expert opinion (10 and 8, respectively). Only two case

Table 3 Combined Delphi rounds 1 and 2

Item	Round 1		Round 2	
	Response, n (total 159)	Combined importance (4 and 5) % (n)	Response, n (total 116)	Combined importance (4 and 5) % (n)
Cardiac arrest	154	55.2 (85)	115	56.5 (65)
Imminent cardiac arrest			116	76.8 (89)
Respiratory arrest	157	79 (124)	114	80.7 (92)
Imminent respiratory arrest			116	94.9 (110)
Non-invasive ventilation	156	65.4 (102)	115	59.1 (68)
Invasive ventilation	156	87.8 (137)	116	87.9 (102)
Hypoxic seizure	153	49.7 (76)	112	50.9 (57)
Silent chest	158	77.6 (121)	116	81.9 (95)
Apnoeic episode	154	64.3 (99)	116	67.3 (78)
Sternocleidomastoid muscle use	154	59.1 (91)	116	59.5 (69)
Paradoxical thoracoabdominal movement	155	59.1 (91)	116	56.9 (66)
Central cyanosis	155	75.5 (117)	116	83.6 (97)
Unable to speak	157	87.3 (137)	116	90.6 (105)
Unable to sleep	153	42.4 (65)	116	45.7 (53)
Need to sit upright	155	58.1 (90)	116	59.5 (69)
Unable to maintain posture	152	52.6 (80)	116	52.6 (61)
Exhausted	154	84.4 (130)	116	87.1 (101)
Severely agitated	153	72.5 (111)	116	76.8 (89)
Confused	156	68 (106)	116	67.2 (78)
Severe dyspnoea	155	85.1 (132)	116	88.8 (103)
Immeasurable PEFR	152	34.9 (53)	116	37.9 (44)
Tachycardia	153	44.5 (68)	116	49.1 (57)
Bradycardia	151	67.6 (102)	116	65.6 (76)
SpO ₂ <90%	155	79.3 (123)	116	85.4 (99)
Increased RR	152	54.6 (83)	116	56 (65)
Decreased RR	152	67.1 (102)	116	59.5 (69)
Cap refill >2 s	155	45.8 (71)	116	59.5 (69)
The AVPU Scale will be P or U	153	72.5 (111)	116	75.9 (88)
Pulsus paradoxus	153	49.1 (75)	116	45.7 (53)
Hypotensive	152	51.4 (78)	116	46.5 (54)
The pH value will fall	153	78.4 (120)	116	82.8 (96)
PaO ₂ will fall	155	82.6 (128)	116	83.6 (97)
PaCO ₂ will rise	157	90.4 (142)	116	95.7 (111)
Lactate levels rise	152	57.9 (88)	116	63.8 (74)
Chest X-ray	154	51.3 (79)	116	46.6 (54)
Air hunger	154	53.3 (82)	116	58.6 (68)
Go outside/open window	151	15.3 (23)	116	13.8 (16)
Steam	151	4.6 (7)	116	3.4 (4)
Attack at night	152	28.3 (43)	116	18.1 (21)
Attack in the morning	148	21 (31)	116	9.5 (11)
Excessive short-acting β_2 agonist use			116	57.7 (67)
Seasonal	150	23.3 (35)	116	15.5 (18)
Uncooperative			116	50.9 (59)
Gut feeling	155	70.3 (109)	116	75 (87)
Extremely anxious			116	72.4 (84)
Asthma 'out of control'			116	60.4 (70)
Not responding to the emergency Acute Asthma Plan			116	72.4 (84)
Epinephrine autoinjector (had NFA)			116	58.6 (68)
Epinephrine autoinjector (at risk of NFA)			112	39.3 (44)
Epinephrine autoinjector (at risk of NFA)	159	47.2 (75)		

The colours used in the table represent the degree of consensus.

consensus $\geq 70\%$.

consensus 50%–60%.

consensus $\leq 49\%$.

AVPU, alert, verbal, pain, unresponsive; NFA, near-fatal asthma; PaCO₂, partial pressure of carbon dioxide; PaO₂, partial pressure of oxygen; SpO₂, oxygen saturation.

reports could be identified providing parent/patient perspectives (2/45), both written from a clinician's perspective; one reported a sense of awareness of the attack severity, the other was indicative of air hunger by going outdoors. Two additional features were also

extracted and considered potentially relevant: (1) The enhanced risk of being a poor perceiver of asthma symptoms after a critical asthma attack^{10 11} and (2) The provision of an epinephrine autoinjector for use in subsequent critical asthma attacks.¹² The

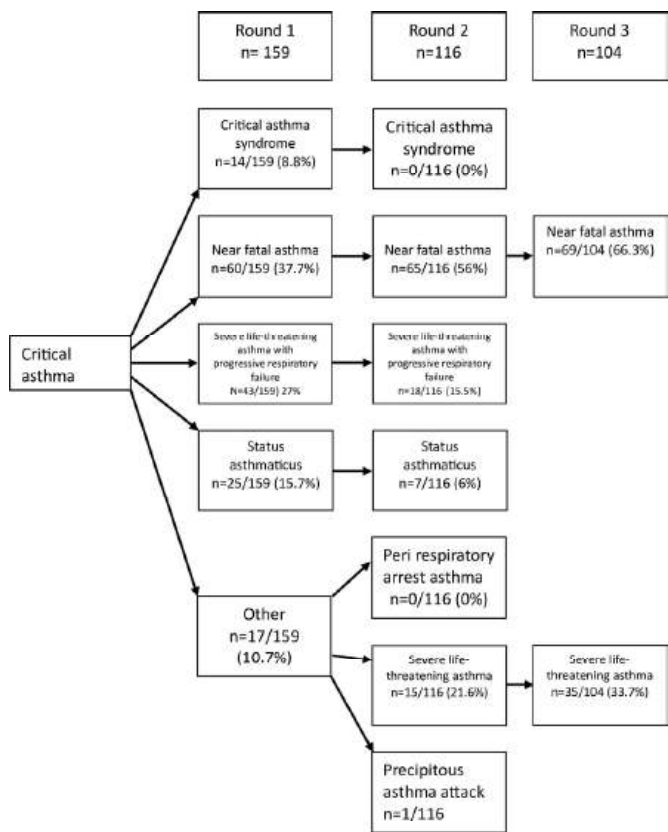


Figure 1 Determining the attack name by electronic Delphi (eDelphi).

updated scoping review in 2024 identified no new features. We identified a single publication, by members of this study team, which used the definition of NFA derived from this study and referenced from an European Respiratory Society abstract submission.^{13 14}

Twenty-five guidelines, with 27 flow charts were identified from international repositories: 1/27 (4%) was a combined adult and child guideline which contained a single flow chart, 16/27 (59%) were adult and 10/27 (37%) were child-specific guidelines (table 1). No further guidelines were identified in a search of 195 countries using University of Edinburgh Library resources and Google Scholar (August 2017). The identified guidelines represented all five continents: Africa (n=2), Asia (n=7), Europe (n=5), South America (n=4) and Oceania (n=2) and were published between 2009–2014 (n=15/27) or 2015–2017 (n=9/27). Guideline asthma characteristics at different severities are pro-

vided in table 2. Guidelines identified severe 25/27 (92%) and life-threatening 26/27 (96%) asthma attacks (one French guideline combined attacks) with NFA described in 12/27 (44%) of guidelines. Guidelines did not identify any new terms to name a critical asthma attack but did contribute features additional to those from the scoping review: fatal asthma and intensive care treatment if apnoeic or in a coma. Anecdotal evidence derived from cohort studies, case reports and expert reviews are provided in online supplemental appendix table 4. The combined factors derived from all sources were used to populate the eDelphi round 1 (table 3). For round 2, participants were provided with an additional three features contributed by round 1 participants (see online supplemental appendix table 7). The updated 2024 guideline review (see online supplemental appendix table 5) identified an additional 10 countries using seven guidelines that incorporated acute asthma management; however, no new novel features were identified.

The first round eDelphi link was emailed to approximately 7134 potential participants with crossover expected between targeted emails and distribution lists (see online supplemental appendix table 2). 159 participants took part in round 1, 116 (72%) in round 2 and 104 (65%) all three rounds. Participants were from 25 countries (final round) with the highest country representation from the UK (37/104 (35.6%)) and continental Europe (67/104 (64.4%)) (see online supplemental appendix figure 3). Of the 104 participants completing all three rounds, the specialty disciplines were in paediatrics (n=72): respiratory (54), ICU (11), ED (7); and in adult medicine (n=32): respiratory (20), ICU (12), ED (0). Participants were highly or quite specialised in asthma management (92/104 (88.2%)) and management of a critical asthma attack (71/104 (68.3%)).

Round 1

There was no consensus for a preferred term of four options provided for a critical asthma attack, with six further free text options provided and taken to round 2 (figure 1). Of 41 variables, 14 achieved consensus, 15 fell just below the level of consensus and 12 had no consensus (table 3 and online supplemental appendix table 6). Objective measurements did not reach consensus with a wide range of responses (see online supplemental appendix figure 3a–k). Additional features provided as free text responses were taken to round 2 (table 3).

Round 2

The preferred term did not reach overall consensus, though NFA remained the preference for 65/116 (56%). A further 4 variables to round 1 achieved consensus, with 18 just below consensus and 12 no consensus (table 3 and online supplemental appendix table 7).

Table 4 Definition of near-fatal asthma stem

Definition(s) option	Definition(s)	Response n/N (missing data)	Combined most preferred (3 and 4) % (N)
A	A 'critical asthma attack' occurs in a person who is exhausted, with severe dyspnoea, unable to speak with a silent chest. Respiratory arrest is considered imminent and invasive ventilation will likely be required. They will be responding poorly to emergency asthma therapies.	104/104	46.1% (48)
A and B	A 'critical asthma attack' occurs in a person who is exhausted, with severe dyspnoea, unable to speak with a silent chest. Respiratory arrest is considered imminent and invasive ventilation will likely be required. They will be responding poorly to emergency asthma therapies. A 'critical asthma attack' is associated with hypoxaemia (value if consensus), with hypercarbia (value if consensus) and a falling pH (value if consensus)	104/104	79.8% (83)
A and C	A 'critical asthma attack' occurs in a person who is exhausted, with severe dyspnoea, unable to speak with a silent chest. Respiratory arrest is considered imminent and invasive ventilation will likely be required. They will be responding poorly to emergency asthma therapies. A person experiencing a 'critical asthma attack' will have a 'gut feeling' of the severity of their situation, be severely agitated and extremely anxious.	104/104	19.2% (20)
A, B and C	A 'critical asthma attack' occurs in a person who is exhausted, with severe dyspnoea, unable to speak with a silent chest. Respiratory arrest is considered imminent and invasive ventilation will likely be required. They will be responding poorly to emergency asthma therapies. A 'critical asthma attack' is associated with hypoxaemia (value if consensus), with hypercarbia (value if consensus) and a falling pH (value if consensus). A person experiencing a 'critical asthma attack' will have a 'gut feeling' of the severity of their situation, be severely agitated and extremely anxious.	104/104	54.8% (57)

Absolute values for objective measurements did not achieve consensus despite fewer options; however, there was consensus for $\text{SpO}_2 < 90\%$ (99/116, 85.4%), falling partial pressure of oxygen (97/116, 83.6%), rising arterial PaCO_2 (111/116, 95.7%), falling pH value (96/116, 82.8%), and AVPU (alert, verbal, pain, unresponsive—a scale of consciousness) P or U (88/116, 75.9%).

Round 3

In the final round, 104 participants were provided with the two most popular name options, with NFA 70/104 (66.7%) more than twice as popular as severe life-threatening asthma, 34/104 (32.3%) as the preferred name for the attack.

Items that achieved consensus in round 2 had near duplicates removed, and through iterative discussion within the research team, placed the consensus items into three categories and within each category into definition statements that could be linked (table 4). Participants were provided with a stem definition which could act as a stand-alone definition but could be enriched with optional add-ons. There was clear consensus achieved with options A and B, 83/104 (79.8%).

Participants were unable to achieve consensus on two values for the objective measurements which were perceived to be of importance; however, there was a preference for the following values: SpO_2 in room air $< 85\%$, (55.8%) and $\text{PaCO}_2 > 60$ mm Hg/8 kPa, (57.7%) (online supplemental appendix figure 4). Consensus was achieved on the pH value < 7.2 , (71.2%). The definition of an NFA attack was therefore: 'A near-fatal asthma attack occurs in a person who is exhausted, with severe dyspnoea, unable to speak with a silent chest. Respiratory arrest is considered imminent and invasive ventilation will likely be required. They will be responding poorly to emergency asthma therapies. A near fatal asthma attack is associated with hypoxaemia, with hypercarbia and a falling pH.'

DISCUSSION

This study used a systematic approach to describe wide variability in the names and descriptions of 'critical' asthma attacks and subsequently agree on a name and develop a clinical case definition for NFA in CYP by eDelphi.

Neither death from asthma nor admissions to critical care with asthma are reducing in frequency in CYP. NFA is recognised as a critical indicator of loss of asthma control with a high proportion of subsequent returns to intensive care and deaths from asthma. 11%–41% of CYP admitted to critical care will be admitted on a second or more occasion,^{16–18} with 1 in 20 of those CYP dying from asthma within 10 years.¹⁷ Despite this disproportionate risk in those who experience NFA, there is a lack of focus at a research level in identifying mechanistic targets and at a clinical level in devising and testing methods of care to reduce future risk. Recent mechanistic data suggest profiling may be helpful. Cytokine profiles in CYP admitted to critical care with asthma cluster to two profiles, one with a higher risk of early re-admission with acute asthma.¹⁹ In adults admitted with life-threatening asthma, higher blood eosinophils are associated with more frequent ED or hospital attendance.²⁰ Different definitions of NFA within such studies place limits on how efficiently research outputs can be synthesised. It is hoped that future alignment with the eDelphi-derived case definition described here could enable research impacts to deliver faster improvements in care to CYP who experience such events. The eDelphi case definition of NFA has been used as an inclusion criterion for a qualitative study evaluating the lived experience of CYP and their parents who have experienced NFA (and fatal asthma). The eDelphi output is also being used as a surveillance case definition for NFA in CYP in the UK and Ireland, which will result in a care bundle to suppress variance in care (<https://www.rcpch.ac.uk/work-we-do/bpsu/bpsu-study-near-fatal-asthma>).²¹

There were limitations to the study. We informed the eDelphi from global guidelines to support global generalisability. We used four search methods to identify global guidelines where definitions and terms were explored to inform round 1 of the Delphi

process. Use of a wider search (ie, google rather than Google Scholar) may have identified other national guidelines; however, as no new definitions or terms were identified in the eight new national guidelines found in the 2024 updated search, it is probable that we had reached saturation at the point of starting the Delphi process. Limited funding made the eDelphi survey available in English language only and via clinical societies that enabled free distribution of surveys to members. The eDelphi participants had relevant specialist experience in managing NFA in CYP. The geographical and specialist representation contributing to the Delphi process was limited by the cost and access limitations of relevant societies in relation to survey distribution requests (see online supplemental appendix table 2). Surveys for multispecialist diseases like asthma can achieve limited specialist representation, which may impact generalisability.²² We only included experienced physicians in the survey and acknowledge that other healthcare professionals providing care for CYP with an NFA attack may have provided different perspectives. There was a delay in publication, due among other reasons to the COVID-19 pandemic. To ensure continued validity, we have presented updated searches, which we consider do not identify any key changes that would impact the results or conclusions. The ideal number of participants within a Delphi study is debated, with healthcare panel sizes ranging from 4 to 300.²³ Recent panels considering respiratory-related topics had fewer final round participants (27–47) than we engaged (104), and represented fewer countries (6–21, vs our 27), though our dropout rate between the first to final rounds was at the higher end of that range (0%–38% versus our 35%) (see online supplemental appendix table 8).^{9 24–26} NFA was the preferred term in round 3 (66.3%), scoring almost double the other option (33.7%). While this did not reach the consensus (70%), this was consistently the most preferred term across all three rounds and so was adopted.

Despite an extensive search, we were unable to find any academic literature on either parent or patient perspective of an NFA or fatal asthma attack. While some patient behaviours (extremely anxious, severely agitated) were prioritised by clinicians, others, that is air hunger, steam, go outside/open window had a lower importance placed on them (table 3). These latter behaviours are within press reports of fatal asthma in CYP. Public and patient engagement contributes positively to asthma research, particularly where lived experience can be provided, and future work should provide patient perspectives to this case definition.

To our knowledge, this is the first international consensus definition of NFA, a condition which is discussed within death reviews and guidelines internationally but acknowledged as poorly defined.²⁷ Differentiating and defining this type of attack from a severe attack could help with the evaluation of interventions both acutely (ie, anaesthetic gases²⁸ or extracorporeal membrane oxygenation²⁹) and also to reduce future risk based on care interactions and models.³⁰ This Delphi definition of NFA in CYP could be used to support international guideline alignment and future meta-analyses of these infrequent, but devastating asthma attacks.

Acknowledgements The authors thank all clinicians who contributed to the eDelphi survey. The names of all those who contributed to all three rounds of the survey are listed in the appendix pages 2 and 3. The authors also thank Marshall Dozier, college lead for library academic support, University of Edinburgh, for her guidance and support with the scoping review.

Contributors SC, LF and AM designed, analysed and interpreted the study data. AM acquired the study data. SC, LF and AM drafted, reviewed and approved the final version of the manuscript published. SC, LF and AM agree to be accountable for all aspects of the work. SC is the guarantor.

Funding This work was funded by Asthma and Lung UK as part of the Asthma UK Centre for Applied Research [AUK-AC-2012-01 and AUK-AC-2018-01]. The funder had no role in the design, collection, analysis or interpretation of the data, nor the writing of the report or submission to submit the paper for publication.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics This study involves human participants and was approved by the Usher Research Ethics Group, University of Edinburgh, UK (Ethics application number 1746). 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.

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ARTIGO ORIGINAL

Utilização domiciliar de agonistas β_2 de ação curta por crianças com asma: um estudo prospectivo multicêntrico digital

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/archdischild-2024-327447>).

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Received 27 May 2024

Accepted 17 March 2025

Published Online First 31 March 2025



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To cite: Gonsard A, Giovannini-Chami L, Cros P, et al. Arch Dis Child 2025;110:701–705.

RESUMO

Objetivo Investigar a utilização real de salbutamol por crianças com asma em contexto domiciliário e compará-la com as instruções dos respectivos planos de ação escritos para a asma (WAAPs).

Desenho do estudo Estudo prospectivo, observacional e multicêntrico.

Local Cinco hospitais de cuidados terciários em França. Participantes 120 crianças com asma, com idades entre os 3 e os 11 anos.

Intervenções Os pais utilizaram uma aplicação para smartphone ligada por Bluetooth a um inalador inteligente para registar a utilização de salbutamol e responder a questionários sobre os sintomas de asma da criança, durante um período de 6 meses.

Principais medidas de resultado O desfecho primário foi o número mediano de inalações de salbutamol administradas nas primeiras 2 horas após o início de sintomas de asma, de acordo com o tipo de sintoma. Os desfechos secundários incluíram a forma como as famílias aplicaram as instruções dos WAAPs e a proporção de famílias que administraram mais ou menos salbutamol do que o prescrito.

Resultados 43 famílias utilizaram o inalador inteligente para episódios de sintomas de asma, registando 124 episódios de utilização de salbutamol. O número mediano de inalações nas primeiras 2 horas foi de 3 (intervalo interquartil 2–4; intervalo total 1–26), variando entre 2 e 4 consoante o tipo de sintoma inicial. O número de inalações não diferiu significativamente entre episódios com e sem resolução dos sintomas. 18 famílias (42%) utilizaram um número de inalações semelhante ao indicado no WAAP, 21 (49%) usaram menos, apenas 4 (9%) usaram mais do que o prescrito. **Conclusões** As famílias tendem a administrar entre 2 a 4 inalações de salbutamol nas primeiras 2 horas após o início dos sintomas de asma. Ajustar os WAAPs para iniciar com 2 a 4 inalações de salbutamol, repetindo se necessário, estaria mais alinhado com a prática real das famílias e seria eficaz na maioria das situações.

Número de registo do ensaio clínico: NCT04810169.

INTRODUCTION

National and international guidelines recommend that patients with asthma should be provided with a written asthma action plan (WAAP).^{1–3} Combined with self-management education and regular review of asthma control, treatment and skills by a healthcare provider, WAAPs improve asthma control and reduce the need for unscheduled healthcare.⁴

The main instruction on children's WAAPs is to increase the reliever treatment, that is, the use of a short-acting beta agonist (SABA) in case of asthma

Key messages

What is known about this topic

- Recommendations for salbutamol dosing in children's written asthma action plans (WAAPs) vary widely.
- There is limited real-world data on how families actually use salbutamol at home during asthma symptoms.

What this study adds

- This prospective study using smart inhalers found that families typically use 2–4 puffs of salbutamol in the first two hours of an asthma symptom.
- WAAPs starting with 2–4 puffs of salbutamol have better adherence than those recommending higher doses.

How this study might affect research practice or policy

- The results of this study suggest that WAAPs starting with 2–4 puffs of salbutamol are more in line with family practice, and effective in most situations.

symptoms. In children, the SABA most frequently used is salbutamol. However, the recommended doses of salbutamol vary widely across different guidelines. The international experts from the Global Initiative for Asthma (GINA) recommend parents of preschool children with asthma to initiate two puffs of salbutamol (corresponding to 200 µg), given one puff at a time via a spacer, and to repeat this twice more at 20-min interval if needed before consulting a physician if there is no improvement. This dose is increased to 4–10 puffs every 20 min in children aged 6 years and older.² For the British Thoracic Society, children who start an asthma attack at home should receive one puff at a time and depending on the response, another puff every 60s up to a maximum of 10 puffs.³ The French Paediatrician's Society of Pulmonology and Allergology recommends one puff per 2 kg of body weight, with a minimum of 4 puffs and a maximum of 10–15 puffs, to be repeated every 20 min twice at home before giving oral steroids and seeking medical help in the absence of improvement.¹ This heterogeneity in recommendations shows the lack of clinical data on the appropriate numbers of salbutamol puffs that children and their families should use at home.

Receiving varying advice on the number of salbutamol puffs to administer can cause stress and confusion for parents. As one parent remarked: 'I need to get one final plan, not different ones by different people'.⁵ Several studies showed that excessive prescribing and dispensing of salbutamol were associated with increased morbidity (higher risk of exacerbations) and mortality in children.^{6–8} It is essential to standardise home administration guidelines for salbutamol dosing in WAAPs.

To inform future recommendations on the number of puffs of salbutamol to be administered as part of the WAAP, we felt it was important to gather data on how families actually use salbutamol to treat asthma symptoms. Children and their families often develop their own experiences over the years on how to use salbutamol, and thus how they operationalise the WAAP provided by their doctors could serve as an additional indicator of whether the prescribed doses of salbutamol are appropriate. Therefore, this study aimed to explore how families managed asthma symptoms at home using salbutamol and the extent to which they followed their WAAPs.

METHODS

Study design and settings

We conducted a multicentre, prospective, open, observational cohort study in the departments of paediatric pulmonology and/or general paediatrics of five hospitals in France between December 2021 and July 2023 (online supplemental table S1). The study was registered with ClinicalTrials.gov (identification number: NCT04810169). In accordance with the Jardé law in France, because this study was not interventional, children and their legally authorised representatives provided oral consent which was recorded in their health records.

Study population

Parents were eligible if they owned a smartphone compatible with the smart inhaler, had a child aged 3 years to 11 years and 11 months with physician-diagnosed asthma, and if their child was prescribed a pressurised metered dose inhaler of salbutamol with a spacer as their reliever treatment. Parents' inability to write and speak French was the only exclusion criterion.

Study procedure

On inclusion, the physician filled out a questionnaire on the child's characteristics, including the child's age, their asthma severity and asthma symptom control according to GINA guidelines,² and the WAAP provided (online supplemental table S1). During the same visit, a clinical research assistant helped parents download the research mobile application (Kap Code, Paris, France) on their smartphone and guided them through connecting the provided smart inhaler via

Bluetooth. The research assistant then demonstrated how to use the smart inhaler correctly and verified with the parents that they could successfully perform a test inhalation that was properly recorded in the application. When parents experienced poor cellular network coverage at the hospital, or when they wished to connect the inhaler to a different smartphone (eg, the other parent's device), the research assistant provided telephone support to complete the setup process at a later time. When first connecting to this application, the parents registered, connected the smart inhaler provided and filled out a questionnaire on their characteristics, and the parent self-efficacy scale.¹⁰

During their 6-month participation, each time the smart inhaler-linked salbutamol was used, parents received a notification on the research application asking them to complete a questionnaire on the reason for using salbutamol. 24 hours later, another questionnaire was sent to assess the efficacy of the salbutamol administered the previous day.

Outcomes

The primary outcome was the number of salbutamol puffs administered within the first 2 hours of management in episodes where symptom resolution was observed, depending on symptom type (dry cough, wheezing, shortness of breath and respiratory distress).

Symptom resolution was defined as cessation of salbutamol use for any asthma-related symptom within 24 hours of symptom onset, characterised by:

- No salbutamol use detected by the smart inhaler from 2 hours to 24 hours following initial salbutamol administration.
- Salbutamol use detected by the smart inhaler within this period, but for a reason unrelated to asthma symptoms (eg, SABA was used pre-emptively before sports).

Secondary outcomes included:

- The number of salbutamol puffs administered within the first 2 hours of management in episodes where parents reported an improvement (ie, reported that symptoms improved or disappeared in the questionnaire sent after 24 hours), depending on symptom type.
- A custom-made score of alignment with the WAAP instructions taking into account the full sequence of actions recommended in the WAAP, including oral steroid use and seeking emergency medical help when necessary (WAAP alignment score, online supplemental table S2). It was calculated as follows: (number of actions recorded on the research application/number of actions expected based on the child's WAAP)×100.
- The percentage of families using more or less salbutamol than prescribed in their WAAP, defined as families for whom the total number of puffs recorded/puffs expected by the WAAP×100 was >150% and <50%, respectively.

Sample size estimation

We calculated that with 100 patients, we would be able to show a difference of at least 4 puffs between salbutamol administrations for 'cough' and 'respiratory distress', assuming a common SD of 7 noted in the Patel et al study that analysed salbutamol use in 303 adults with asthma at risk of severe exacerbation, and considering an alpha risk of 5% and a power of 80%.¹¹ Because we anticipated that 20% of parents may not be able to correctly connect their smart inhalers to their smartphone, we planned to recruit 120 parents.

Statistical analysis

We reported categorical variables as proportions and percentages, and continuous variables as medians, IQRs and full ranges. We compared the median number of puffs used for each symptom type by a Kruskal–Wallis test, with a Bonferroni post-hoc test if statistically significant to compare pairs of scores. Analyses were performed with R (V.4.1.2).

RESULTS

Population and episodes of salbutamol use

Of the 120 parent–child dyads included in the study, 28 (23%) never connected the smart inhaler and 36 (30%) connected it but never used it (figure 1). Among the 56 remaining dyads, 43 used the smart inhaler linked to salbutamol for asthma symptoms, for a total of 124

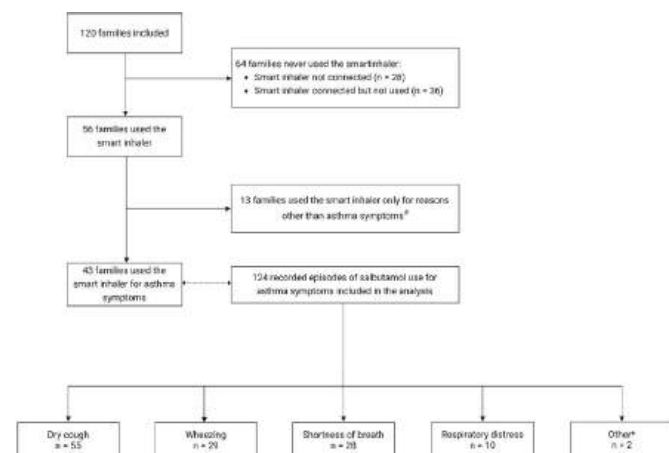


Figure 1 Flowchart of the study population and recorded episodes of salbutamol use. *The reasons other than asthma symptoms included parents administering salbutamol to their child as a precaution when they had a cold, in the absence of asthma symptoms; systematic use following an asthma attack; preventive use before sports activities; and accidental actuations of the smart inhaler. *Two parents ticked 'other asthma symptom' but did not provide details of the symptom.

Table 1 Characteristics of children whose parents used the smart inhaler for asthma symptoms

	n=43
Age—median (IQR) (min–max)	6.00 (4.50–9.00) (3–11)
Weight—median (IQR) (min–max)	21 (19–35) (14–57)
Asthma duration—n (%)	
0–1 year	3 (7)
1–3 years	10 (23)
> 3 years	30 (70)
Asthma symptom control (according to GINA) – n (%)	
Controlled	15 (35)
Partly controlled	21 (49)
Uncontrolled	7 (16)
Asthma severity (GINA medication step)—n (%)	
1	2 (4.7)
2	9 (21)
3	17 (40)
4	14 (33)
5	1 (2)
Severe asthma attack in the last 12 months—n (%)	
Oral corticosteroids	34 (79)
Emergency room visit	11 (26)
Hospital admission	5 (12)
ICU admission	1 (2)
Own an asthma action plan—n (%)	43 (100)
GINA, Global INitiative for Asthma; ICU, intensive care unit.	

episodes of salbutamol use. The characteristics of the 43 children included are presented in table 1. They did not differ from those of the 77 other children (online supplemental table S3).

The triggers of asthma symptoms reported by the parents were a cold in 47 (38%) of cases, a physical activity in 42 (34%), an allergy in 5 (4%), a psychological event in 2 (1.6%), the heat in 1 (0.8%) and other or unknown reasons in 27 (22%). An oral steroid was used for 10 (8%) of these episodes in nine patients, an additional visit to the doctor was required in 5 (4%) episodes in five patients and no emergency department visit or hospital admission was reported. The median number of puffs taken in the first 2 hours was higher when an oral corticosteroid was added (5 (2–7) vs 2 (1–4) when salbutamol was used alone, $p=0.06$).

Of the 124 episodes, resolution of symptoms was observed in 92 (74%) episodes, including 4 episodes where oral steroids were used within the first 2 hours. Parents, who assessed 95 episodes (29 missing values), reported improvement in 91 (96%) episodes. The median number of puffs administered within the first 2 hours was 3 (IQR 2–4, range 1–26) overall (figure 2) but varied from 2 to 4 depending on initial symptom type: usage was higher for respiratory distress compared with other symptoms, and for dry cough relative to wheezing ($p<0.05$) (table 2). When limiting the analysis to episodes resulting in symptom resolution or noted improvement as assessed by parents, the previously observed differences were no longer statistically significant (table 2). Furthermore, when comparing the median number of puffs administered in the first 2 hours between episodes with and without symptom resolution, no statistically significant differences were detected (online supplemental table S4).

Operationalisation of the written asthma action plan by families

The median alignment percentage to the WAAP was 25% (IQR 0–61, range 0–100). We observed no significant difference in the characteristics of families who followed the WAAP closely (alignment $\geq 80\%$) or those who did not ($<80\%$) (online supplemental table S5). Of the 43 families using salbutamol for asthma symptoms, 21 (49%) used less and 4 (9%) used more than the amount prescribed in their WAAP during the first 2 hours (online supplemental table S6). Finally, the number of puffs given during the first administration of salbutamol corresponded to the exact number written on the WAAP in 25 (20%) of the 124 episodes (figure 3). The percentage of families who administered

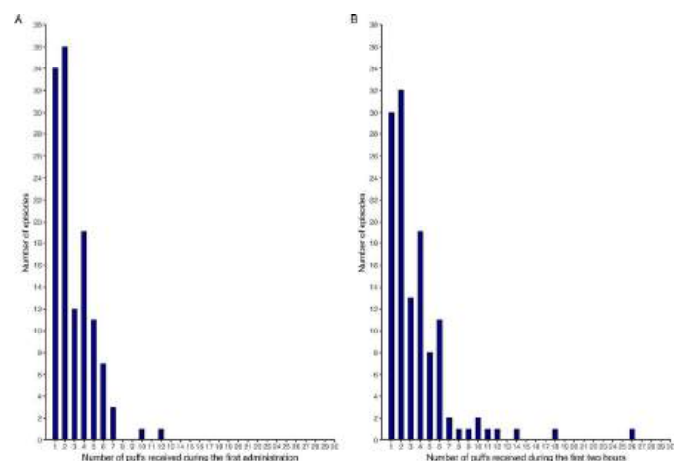


Figure 2 Distribution of the number of salbutamol puffs administered for asthma symptoms during the first administration (A) or the first 2 hours (B).

nistered salbutamol according to their WAAP prescriptions (rather than giving more or less than prescribed) was significantly higher when the WAAP began with either 2 or 4 puffs of salbutamol, compared with 5–10 puffs (online supplemental table S7). The proportion of episodes of asthma symptoms that were resolved after the first 2 hours did not differ among families with a WAAP starting with 2, 4 or more puffs of salbutamol (online supplemental table S7).

DISCUSSION

The main findings of this study are as follows: (1) The use of smart inhaler technology was problematic with the majority of patients included failing to submit data; (2) in families who used the smart inhaler, most administered between 2 and 4 puffs of salbutamol within the first 2 hours of an asthma symptom, with only a small proportion administering more than prescribed; (3) families often did not follow their WAAP's written instructions exactly.

To our knowledge, this study is the first to have collected objective data on the use of salbutamol at home by families. Two studies have questioned families about their home use of salbutamol, but in the first, parents were asked about a hypothetical asthma attack scenario,¹² and in the second, parents were questioned during their visit to the emergency department, thus retrospectively with a risk of recall bias.¹³ The strength of our study is to have empirical data, collected objectively and prospectively via smart inhalers, about the families' salbutamol use in relation to developing asthma symptoms.

The use of smart inhaler technology in our study proved to be quite problematic, however. Nearly a quarter of families never managed to

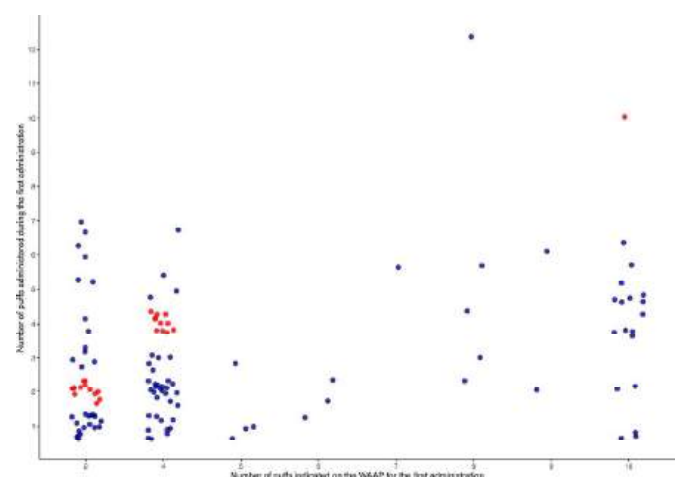


Figure 3 Comparison of the number of salbutamol puffs administered during the first administration with the number of puffs indicated on the written asthma action plan (WAAP) for each episode of salbutamol use for asthma symptoms. Red points indicate that the number of puffs

Table 2 Median number of puffs administered within the first 2 hours of an episode according to the initial asthma symptom

	Overall	Dry cough	Wheezing	Shortness of breath	Respiratory distress	P value*
	n=122	n=55	n=29	n=28	n=10	
All episodes	3.00 (2.00–4.00); (1.00–26.00)	3.00† (2.00–5.00); (1.00–18.00)	2.00 (1.00–3.00); (1.00–6.00)	2.00 (1.00–5.00); (1.00–10.00)	4.00‡ (2.25–6.75); (1.00–26.00)	0.021
	n=90	n=39	n=25	n=19	n=7	
Episodes with symptom resolution	3.00 (2.00–4.00); (1.00–26.00)	3.00 (2.00–5.00); (1.00–18.00)	2.00 (1.00–3.00); (1.00–6.00)	4.00 (2.00–4.50); (1.00–10.00)	4.00 (2.00–9.00); (1.00–26.00)	0.11

Results are presented as median (IQR); (min–max).

*Kruskal-Wallis rank sum test.

†p<0.05 for comparison between dry cough and wheezing.

‡p<0.05 for comparison between respiratory distress and each of the other symptoms.

connect the smart inhaler to the mobile application due to technical problems despite careful support to avoid such difficulties. In addition, almost one- third of families managed to connect the smart inhaler but never used it. Given that 79% of children required oral corticosteroids in the 12 months preceding inclusion, technical difficulties rather than absence of symptoms requiring salbutamol may explain some of this non- use, though we did not collect information from families about reasons for non- use. Such implementation challenges are not unique to our study, as demonstrated in the Improving Technology- Assisted Recording of Asthma Control in Children (iTRACC) trial where the number of participants with actively transmitting sensors decreased from 102 at baseline to 56 at the 12-month follow-up.¹⁴

We observed that most families limited salbutamol administration to 2–4 puffs during the first 2 hours following an asthma symptom, and thus used less salbutamol than recommended by their WAAP. Strikingly, the proportion of parents who used more than that recommended in their WAAP was low, 9% in our study. Even in episodes where more salbutamol was used than recommended in the WAAP, the number of puffs exceeded 10 puffs in the first 2 hours in only 5 out of 124 (4%) episodes, with the maximum being 26 puffs (2.6 mg) in the first 2 hours. This is much less than the 10 puffs every 20 min that many emergency departments would administer in the first hour using a metered dose inhaler and spacer. Similar findings were observed among parents questioned in the emergency department about their home use of salbutamol, with most parents administering less salbutamol than prescribed and only 5% administering more than prescribed.¹³ These results are reassuring, given that excessive use of salbutamol can lead to increased bronchial inflammation and airway reactivity, as well as tachyphylaxis and, consequently, a reduction in treatment efficacy¹⁵ and that recent studies have linked increased SABA prescription and dispensation with higher morbidity and mortality in children.^{6–8}

Our results finally show that families often did not follow their WAAP's written instructions exactly. A first explanation could be that families had their own experience of using salbutamol and its effectiveness, and that the salbutamol doses listed on their WAAP were simply not appropriate for their child. Indeed, although half of the families used doses of salbutamol lower than those prescribed on their WAAP, there was no further use of salbutamol after the first 2 hours in 74% of episodes, and the parents reported an improvement in asthma symptoms in 96% of episodes. A second explanation could be that families did not have their WAAP with them when asthma symptoms started. However, studies using digital WAAPs accessible from smartphones did not find better results.^{16,17} A third explanation concerns the family's understanding of the WAAP, either because it was not adapted to the family's level of health knowledge, or because it was not sufficiently explained during the consultation. Alternative formats for the WAAP, eg with pictograms might help address this last issue.^{18 19}

Our study has several limitations. First, our results are based on a small number of families, as only 43 out of the 120 recruited families were able to provide data with their smart inhalers during the study. Second, most children experienced mild symptoms, and we were unable to assess the number of puffs during severe asthma attacks as no episodes led to hospitalisation. This could explain why the doses of salbutamol used during most episodes were low, typically in the

range of 2–4 puffs. Finally, this is an observational study, and only a randomised controlled trial would make it possible to determine the most appropriate salbutamol dose.

In conclusion, the results of this study indicate that an action plan starting with 2–4 puffs of salbutamol, to be repeated if necessary, would be in line with families' actual use of salbutamol.

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Acknowledgements The authors thank URC-CIC Paris Centre for the implementation of the study.

Contributors DD conceptualised and designed the study, collected data, carried out the analyses, drafted the initial manuscript and revised the manuscript. CD participated in the conceptualisation of the study design. AG participated in the revision of the manuscript. AG, LG-C, PC, AM, CMe, CMo, CC, JP, CR, CP, RAT, AH, AP and CD collected data and critically revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. DD is the guarantor of the study.

Funding This study was funded by the IdEx Université de Paris, grant ANR-18-IDEX-0001 and by the Université de Paris-Cité (grant « Sauver la Vie »). The sponsor was Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et à l'Innovation).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was approved by the Institutional Review Board 'CPP SUD-EST IV' (2020-A02722-37).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available upon reasonable request to the corresponding author.

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ARTIGO ORIGINAL

Genes do desenvolvimento pulmonar, função pulmonar na idade adulta e comorbilidades cardiovasculares

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► Additional supplemental material is published online only. To view, please visit the journal (<https://doi.org/10.1136/thorax-2024-222474>).

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Received 17 September 2024

Accepted 12 May 2025

Published Online First 30 May 2025



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To cite: Portas L, Talaei M, Dean C, et al. Thorax 2025;80:738–747.

RESUMO

Contexto A associação entre função pulmonar reduzida na idade adulta e aumento da comorbilidade cardiovascular ainda não foi adequadamente explicada. Investigamos se vias de sinalização compartilhadas, fundamentais para o desenvolvimento e reparação pulmonar, poderiam contribuir para essa relação.

Métodos Utilizamos dados do UK Biobank (UKB) para realizar uma análise de colocação emparelhada de variantes genéticas em 55 genes relacionados com o desenvolvimento pulmonar, associados à capacidade vital forçada (FVC) ou ao volume expiratório forçado no primeiro segundo (FEV₁/FVC) na idade adulta. Avaliámos se essas variantes estavam também associadas a doença coronária (CHD), pressão arterial (sistólica, diastólica, hipertensão), pressão de pulso, índice de rigidez arterial e espessura íntima-média carotídea. Para a doença coronária, realizámos uma meta-análise combinando dados do UKB e do consórcio CARDIOGRAM.

Resultados Identificámos que 12 dos 55 genes partilhavam a mesma variante genética entre uma (ou mais) característica da função pulmonar e uma (ou mais) característica cardiovascular (colocalização H4). A direção dos efeitos foi sempre consistente com a nossa hipótese (função pulmonar mais baixa – maior risco cardiovascular) no caso da FVC, mas nem sempre para FEV₁/FVC. Os sete sinais genéticos associados à hipertensão e à doença coronária replicaram-se nominalmente no estudo FinnGen, mas apresentaram fraca replicação no estudo China Kadoorie Biobank (CKB). Além disso, encontramos mais 10 genes em que as associações genéticas com a função pulmonar e os traços cardiovasculares ocorriam dentro do mesmo gene, mas envolviam variantes diferentes (colocalização H3). Curiosamente, seis dos 22 genes identificados (H4 e H3) eram novos no contexto das características cardiovasculares; quatro replicaram-se no FinnGen e três no CKB.

Conclusão A função pulmonar e os traços cardiovasculares partilham vias de desenvolvimento comuns, o que pode ajudar a explicar, pelo menos em parte, porque é que uma função pulmonar mais baixa — especialmente a FVC — está associada a um risco cardiovascular aumentado.

INTRODUCTION

Lower adult lung function, especially a restrictive spirometry pattern characterised by a lower forced vital capacity (FVC), is strongly associated with higher cardiovascular (CV) mortality.^{1,2} This association is not explained by smoking; in UK Biobank (UKB), among never-smokers, those in the lowest quartile of FVC had more than double the risk of death from a circulatory disease compared with those in the highest quartile.³ Even in young adults, lower lung function has been associated with premature CV mortality.⁴ Lower lung function is also associated with incident coronary

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Lower adult lung function, particularly a restrictive pattern, has been strongly linked to higher cardiovascular mortality and morbidity even after adjusting for shared risk factors, but this association has not been fully explained.

WHAT THIS STUDY ADDS

► We show that lung development pathways influencing adult lung function may also influence adult cardiovascular outcomes, thus partly explaining the link between lower adult lung function and higher cardiovascular risk.

► The same variant in 12 genes was associated with a lung function trait and one or more cardiovascular traits; importantly, variants in nine of these genes showed direction of effects supporting our hypothesis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► Our findings could inform future research on druggable targets aimed at optimising lung and cardiovascular development and repair.

heart disease (CHD),⁵ hypertension (HTN),⁶ increased carotid intima-media thickness (CIMT)⁷ and central arterial stiffness.⁸ Compared with other lifetime spirometric trajectories, a restrictive-only pattern is associated with the highest prevalence of CV comorbidities.⁹ These associations persist after adjustment for other adult risk factors, including inflammatory markers,¹⁰ and have not been adequately explained.

Lower lung function in late adult life is a measure of poorer lung health and may arise through sub-optimal lung development and a failure to attain maximal capacity as a young adult.^{11–13} This developmental paradigm for lung ageing complements the alternative model of accelerated lung function decline in later life. It has been mooted that the environmental and genetic factors that influence lung development might also affect the development of other organ systems.¹⁴ For example, low birth weight, a marker of impaired fetal growth,

has been implicated in the aetiology of both restrictive lung function impairment and increased CV risk and mortality.^{15,16} A limitation of observational studies implicating the early environment is the possibility of spurious findings caused by environmental and lifestyle confounding, a problem which does not affect genetic studies. Investigating genetic factors influencing organ development can therefore strengthen causal inference regarding pathogenetic mechanisms related to early life, as well as provide insight into the role of specific developmental signalling pathways.

In a previous study, we provided further evidence that lung development plays a crucial role in adult lung health.¹⁷ We identified (and externally replicated) 55 lung development genes associated with adult lung function in UKB, influencing both restrictive and obstructive patterns, 36 of which had not been previously identified in genome-wide association studies (GWAS). The fundamental function of the majority of the 55 genes is to regulate organ size and cell integrity. We therefore propose that signalling pathways, which are critical to lung development and repair, are also important for the development and repair of the CV system and that perturbation of these shared developmental pathways may partly explain the association between lower adult lung function, especially FVC, and CV comorbidities.

We investigate this hypothesis by looking for shared genetic signals between adult lung function and CV traits in the 55 genes, using colocalisation analysis¹⁸ applied to UKB data, complemented by CHD data from the international CARDIoGRAM consortium.¹⁹ We sought replication of our main CV findings in the Finnish FinnGen study²⁰ and in the China Kadoorie Biobank (CKB).²¹

METHODS

DATA

UK Biobank

UKB is a study of about 500 000 volunteers aged 40–69 years from the UK, with information on risk factors for chronic disease and related traits, and genetic data.²² Here, we included participants of self-reported white ethnicity with good quality lung function data. Details on UKB data and variables used are reported in online supplemental methods and table S1.

We analysed:

- FVC and forced expiratory volume in 1 s (FEV₁) to FVC ratio (FEV₁/FVC; n=3 06 476).
- Blood pressure (n=369 905): systolic and diastolic blood pressure (SBP, DBP); HTN (n=380 689; 217 771 cases, SBP ≥140 or DBP ≥90 mm Hg or antihypertensive treatment)
- Pulse pressure (PP) (n=369 905), calculated as the difference between SBP and DBP
- Arterial Stiffness Index (ASI) (n=55 041), measured using finger photo-plethysmography.
- CIMT (n=38 469), a measure of subclinical atherosclerosis, measured using ultrasound.
- CHD (n=405 570; 19 294 cases), defined as self-reported myocardial infarction or angina; coronary artery bypass or coronary angioplasty.

CARDIoGRAM

To increase statistical power for CHD analyses, we combined UKB data with data from CARDIoGRAMplusC4D (www.cardiogram-plusc4d.org/data-downloads), resulting in a total of 80 095 CHD cases and 509 780 controls. CARDIoGRAMplusC4D is a GWAS meta-analysis including 60 801 CHD cases and 123 504 controls, mostly of European ancestry, with CHD defined as myocardial infarction, acute coronary syndrome, chronic stable angina or coronary stenosis >50%.¹⁹

Statistical analysis

The analyses are summarised in figure 1. We investigated whether any of the 55 lung development genes we previously identified as associated with adult lung function¹⁷ share an effect on CV traits, through a colocalisation analysis of variants (single nucleotide

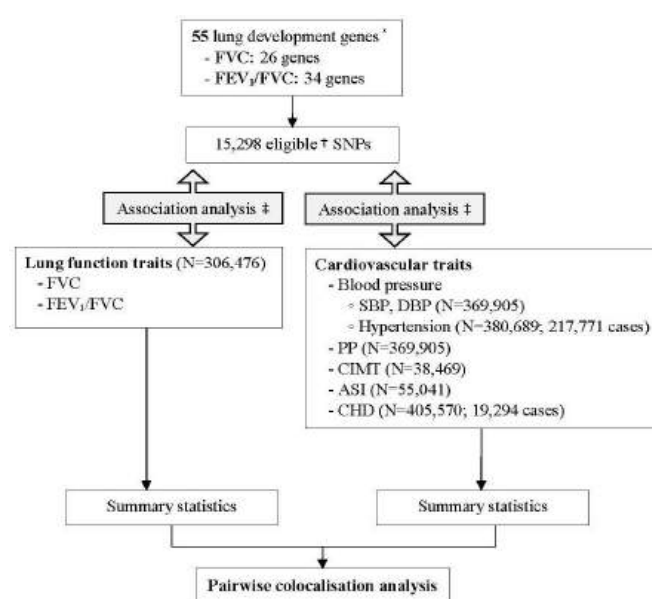


Figure 1 Analysis flow chart. *Previously identified in: Portas *et al.*¹⁷ †Minor allele frequency ≥1% and imputation quality ≥0.5 (online supplemental table S6). ‡Linear/Logistic regression analysis, adjusted for age, sex, genotyping array, centre and 10 ancestry principal components. Analysis of FVC additionally adjusted for height. ASI, Arterial Stiffness Index; CHD, coronary heart disease; CIMT, carotid intima-media thickness; DBP, diastolic blood pressure; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; PP, pulse pressure; SBP, systolic blood pressure; SNP, single nucleotide polymorphism.

polymorphisms (SNPs)) in the 55 genes, based on summary data. In our previous work, the 55 genes were identified from a list of 391 genes related to lung development prepared by two experts (CD and MDH). Briefly, they independently compiled initial lists based on knowledge from human and experimental data, then merged them into a single list, and extended it to include further genes identified from KEGG (Kyoto encyclopedia of genes and genomes) pathways and HuGE Navigator literature.¹⁷

We obtained summary statistics (beta and SE) for the association of all SNPs within the 55 lung development genes with lung function measures and with CV traits using Regenie,²³ assuming an additive genetic model and adjusting for age, sex, genotyping array, centre and first 10 ancestry principal components. Analysis of FVC was additionally adjusted for height to ensure effects were independent of body size, and analysis of ASI for the device used. For CHD, a fixed-effect meta-analysis was used to combine UKB and CARDIoGRAM summary statistics.

We applied colocalisation analysis to all SNPs within the boundaries of the 55 genes with minor allele frequency ≥1% and imputation quality ≥0.5 (online supplemental table S2). Pairwise colocalisation analysis (each lung function measure vs each CV trait) was conducted using *coloc.abf* in the R package *coloc*.¹⁸ Colocalisation analysis in *coloc* is performed using a Bayesian framework; while there is no need to correct for multiple testing, prior beliefs about SNP-specific associations under each scenario must be specified and the choice of priors justified (see online supplemental methods). The Bayesian approach provides an estimate of the posterior probability that a genetic variant is shared between the traits studied, based on probabilistic models that incorporate the prior beliefs and the observed data.¹⁸ In particular, results are expressed as posterior probability of association under each of five possible scenarios: H0=no association with either trait; H1=association with trait 1 (lung function trait), but not trait 2 (CV trait); H2=association with trait 2, but not trait 1; H3=association with both traits, but separate variants; H4=association with both traits, same variant. The term ‘colocalisation’ has been used, strictly speaking, to refer to a shared association with the same

variant (H4), but colocalisation analysis also allows the identification of associations with different variants within the same gene (H3). Although our main interest is in H4, we broadly refer to colocalisation to indicate either scenario. This is because the focus of our study is on genes rather than individual variants, and H3 complements H4 in supporting our hypothesis of shared genetic effects of lung development genes on adult lung function and CV comorbidities.

Colocalisation was defined as a posterior probability ≥ 0.70 of either one common associated variant (H4) or two distinct associated variants (H3, 'regional' posterior probability). For H4 findings, we investigated the direction of the two genetic effects by looking at the summary results for the lung function and CV traits used in the colocalisation analysis. We included in the H4 findings the case where colocalisation was at two variants in high linkage disequilibrium (LD), which we refer to as 'H4 equivalent'. 'H4-equivalent' cases were identified using fine mapping analysis (finemap. abf in coloc) to pinpoint the two variants with the highest posterior probability for each trait, and checking whether they were in high LD ($r^2 > 0.8$).

Sensitivity analysis

Only prebronchodilator lung function data are available in UKB, so we could not rule out that a lower FEV₁/FVC might be due to reversible airflow obstruction, caused by asthma. As asthma and HTN have previously shown genetic overlap,²⁴ we repeated the FEV₁/FVC analyses after excluding participants with self-reported doctor-diagnosed asthma ($\approx 12\%$ of the sample).

Replication

We sought replication of the CV associations for the shared variants identified by our H4 findings using the publicly available FinnGen dataset ($n=377\,277$),²⁰ where GWAS results are available for two of our CV traits, HTN ($n=111\,581$ cases) and CHD ($n=43\,518$ cases). We also sought replication in CKB (sample sizes ranging from 22 543 for CIMT to 100 453 for blood pressure), 21 where all our CV traits are available. We defined replication as an effect size in the same direction as in UKB, and for this reason, we used a one-sided p value. We applied Bonferroni correction to account for multiple testing, but we also report replication at only nominal level (one-sided $p < 0.05$ but not surviving Bonferroni cor-

Table 1 Colocalisation results for lung function (FVC and FEV₁/FVC) and CV traits

Gene	Lung function trait	CV traits	Posterior probability*	Previously reported association of the gene with any CV trait (PubMed ID)†
<i>ACTN4</i>	FVC	PP, DBP	1, 1	PP (34594039), HR (23583979)
<i>AGER</i>	FVC	DBP, PP	1, 1	SBP (27618447), CHD (29212778)
	FEV ₁ /FVC	DBP, PP	1, 1	
<i>CLDN20</i>	FVC	PP	0.8	None
<i>CSNK2B</i> ‡	FVC	CHD, HTN, SBP, DBP	1, 1, 1, 1	None§
	FEV ₁ /FVC	HTN, SBP, DBP, PP	1, 1, 1, 1	
<i>CTNND1</i>	FEV ₁ /FVC	HTN, SBP, PP	0.8, 1, 1	SBP (30595370), PP (34594039, 30578418)
<i>DSP</i>	FEV ₁ /FVC	PP	0.8	SBP and DBP (34989438)
<i>ELN</i>	FEV ₁ /FVC	PP	0.7	PP (33230300, 34594039, 30224653), SBP and DBP (34989438)
<i>FARP2</i>	FEV ₁ /FVC	HTN, PP, SBP	0.9, 0.9, 0.9	SBP (30224653)
<i>GFI1</i> ¶	FEV ₁ /FVC	HTN	0.9	None
<i>IGF1</i>	FVC	HTN	0.8	SBP (30224653)
<i>ITGB5</i>	FVC	CHD	*	PP (27841878), SBP (27841878, 30578418, 30595370, 34594039), DBP (27841878, 34594039), MAP (34594039), CHD (28714975)
<i>KAT8</i>	FVC	HTN	0.7	None
<i>MAPRE1</i>	FEV ₁ /FVC	PP	0.9	None
<i>MMP24</i>	FVC	PP, CIMT, CHD	1, 0.9, 1	CIMT (34852643)
<i>PPARD</i>	FEV ₁ /FVC	HTN, DBP, SBP	0.7, 0.9, 0.8	SBP (30595370, 34594039), MAP (34594039)
<i>RUNX3</i>	FEV ₁ /FVC	DBP	0.8	MAP (34594039)
<i>SERPING1</i>	FEV ₁ /FVC	PP, SBP	0.7, 0.7	None
<i>TCF7L1</i>	FEV ₁ /FVC	PP, SBP	1, 0.9	PP (27841878, 28135244, 27841878, 30578418, 30487518, 34594039)
<i>TGFB2</i>	FEV ₁ /FVC	HTN, DBP	1, 1	SBP (30578418), DBP (30224653)
<i>TNS1</i>	FVC	HTN, SBP, DBP, CHD	1, 1, 1, 0.9	SBP (27841878, 30578418, 30595370, 34594039), DBP (27841878, 28135244, 34594039), MAP (34594039), CHD (29212778, 33020668), MI (33532862)
	FEV ₁ /FVC	SBP, DBP, CHD	1, 1, 1	
<i>WNT2B</i>	FVC	HTN, PP, DBP, SBP	1, 1, 1, 1	HTN (30487518), SBP (27618452, 30578418, 29403010, 30487518, 30595370, 34594039, 29455858), DBP (27618452, 29403010, 30487518, 34594039, 29455858), MAP (29403010, 30487518, 34594039), PP (30487518, 34594039), CHD (30595370)
<i>WNT9A</i>	FVC	HTN, PP, DBP, SBP	1, 1, 1, 1	SBP (27841878, 34594039), DBP (27841878)

H4 results are highlighted in bold—colocalisation pairs for 12 genes where the variants for the two traits were either the same (H4), or, for the *GFI1* gene, distinct but in high LD (H4 equivalent).

*Highest posterior probability for H4 (in bold) or H3.

†Previous GWAS associations ($p < 5 \times 10^{-8}$) with any CV trait in GWAS catalogue (www.ebi.ac.uk/gwas), accessed on 8 May 2024.

‡Two different SNPs for FVC and FEV₁/FVC (table 3).

§SBP (27618447, 21909115; $p=2.14 \times 10^{-6}$ and $p=2.2 \times 10^{-6}$), PP (27618447; $p=2.3 \times 10^{-6}$) and CHD (29212778; $p=1.2 \times 10^{-6}$).

¶Two different SNPs for HTN and FEV₁/FVC, but in high LD, $r^2=0.85$ (H4 equivalent).

CHD, coronary heart disease; CIMT, carotid intima-media thickness; CV, cardiovascular; FEV₁/FVC, forced expiratory volume in 1 s to forced vital capacity ratio; GWAS, genome-wide association studies; HR, heart rate; HTN, hypertension; LD, linkage disequilibrium; MAP, mean arterial pressure; MI, myocardial infarction; PP, pulse pressure; SBP/DBP, systolic/diastolic blood pressure; SNP, single nucleotide polymorphism.

rection). The definition of CV traits in UKB, CKB and FinnGen, as well as the baseline characteristics of UKB and CKB, are reported in online supplemental tables S3 and S4, respectively.

RESULTS

All colocalisation findings

Of the 55 genes, we found colocalisation (H4 or H3) with at least one CV trait for 22 genes, of which eight genes with FVC, 11 with FEV1/FVC, and three with both. The highest posterior probability for all other genes supported H1—association with the lung function trait only—reflecting the selection of the 55 genes.

Table 1 reports all identified colocalisation pairs, with colocalisation posterior probabilities. Table 2 summarises the function of the 22 genes and the biological category they belong to, defined as in our previous work17; 17 of the 22 are either transcriptional modifiers (six genes) or genes affecting cell:cell integrity, that is, cell-to-cell adhesion, cytoskeleton or extracellular matrix (ECM) genes (11 genes). Colocalisation was found predominantly with blood pressure traits for both lung function measures. For FVC, we also found colocalisation with CHD (CSNK2B, ITGB5, MMP24 and TNS1) and CIMT (MMP24), while for FEV1/FVC we only found colocalisation with CHD in one gene (TNS1). We found no colocalisation with ASI for either lung function measure.

For the 22 genes with colocalisation, we investigated gene expression in both human lung and CV tissues, in particular, heart (heart left/right ventricle, left/right cardiac atrium, heart muscle) and vasculature (artery), using the ‘Expression Atlas’ database (www.ebi.ac.uk/gxa/home). All 22 genes are expressed in both human lung and heart, with 11 being also expressed in the vasculature (table 2).

H4 colocalisation findings

Of main interest for our study are the 13 signals in 12 genes, where the same SNP is shared between the lung function and CV traits, for which we could investigate the direction of the two genetic effects (regression analysis), and for which we sought replication. Of these, 11 shared the same variant (H4) and one colocalised at two variants in high LD (H4 equivalent; see table 1). For FVC, all colocalisation pairs (seven genes) showed directions consistent with the hypothesis that a variant which reduces lung function also has a detrimental effect on the CV trait (higher risk of disease or higher continuous measure) (table 3). For FEV1/FVC, among the colocalisation pairs (seven genes), the direction of the effect was consistent with our hypothesis in four genes (table 3).

The sensitivity analysis for FEV1/FVC excluding participants with asthma confirmed the findings of the main analysis (data not shown).

Table 2 Gene function and evidence of gene expression for the genes identified in the colocalisation analysis

Gene	Full name and function (biological category)	Evidence on tissue expression*		
Lung	Heart	Vasculature		
ACTN4	Actinin α 4: actin-binding protein, part of the cytoskeleton (<i>cell-to-cell adhesion and cytoskeleton</i>)	++	++	++
AGER	Advanced glycosylation end-product (AGE) specific receptor: multiligand receptor, also called RAGE; role in chronic vascular injury (<i>oxidative stress and endothelial dysfunction</i>)	+++	+	—
CLDN20	Claudin 20: encodes a tight junction protein; important for cell polarity and regulating movement of molecules via the paracellular route (<i>cell-to-cell adhesion and cytoskeleton</i>)	+	+	—
CSNK2B	Casein kinase 2 β : ubiquitous protein kinase that regulates metabolic pathways, signal transduction, transcription, translation and replication (<i>transcriptional regulators</i>)	++	++	++
CTNND1	Catenin delta 1: armadillo protein family, which function in adhesion between cells and signal transduction (<i>cell-to-cell adhesion and cytoskeleton</i>)	+++	+++	++
DSP	Desmoplakin: encodes a protein component of functional desmosomes (<i>cell-to-cell adhesion and cytoskeleton</i>)	+++	+++	—
ELN	Elastin: encodes a protein that is one of the two components of elastic fibres (<i>extracellular matrix</i>)	+++	+++	—
FARP2	FERM, ARH/RhoGEF and pleckstrin domain protein 2: ρ guanidine exchange factor (<i>cell-to-cell adhesion and cytoskeleton</i>)	+++	+++	+
GFI1	Growth factor independent 1 transcriptional repressor: encodes a nuclear zinc-finger protein that functions as a transcriptional repressor (<i>transcriptional regulators</i>)	++	++	—
IGF1	Insulin-like growth factor 1: encodes an insulin-like protein involved in mediating growth and development (<i>growth factors</i>)	++	++	—
ITGB5	Integrin subunit β 5: encodes the integrin β subunit 5 protein (<i>extracellular matrix</i>)	+++	+++	+
KAT8	Lysine acetyltransferase 8: encodes a member of the MYST histone acetylase protein family; the encoded protein regulates gene transcription by influencing chromatin conformation (<i>transcriptional regulators</i>)	+++	+++	++
MAPRE1	Microtubule-associated protein RP/EB family member 1: encodes a protein that localises to microtubules, a dynamic network of filaments that form part of the cytoskeleton (<i>cell-to-cell adhesion and cytoskeleton</i>)	+++	+++	—
MMP24	Matrix metalloproteinase 24: encodes a member of the peptidase M10 family of MMPs (<i>extracellular matrix</i>)	++	+	—
PPARD	Peroxisome proliferator-activated receptor delta: encodes a member of the PPAR family that is believed to function as an integrator of transcriptional repression and nuclear receptor signalling (<i>transcriptional regulators</i>)	+++	++	+
RUNX3	Runt-related transcription factor 3: encodes for a member of the runt family of transcription factors that regulate haematopoiesis and skeletal development (<i>transcriptional regulators</i>)	+++	+++	—
SERPING1	Serpin family G member 1: encodes a highly glycosylated plasma protein involved in the regulation of the complement cascade. Mutations in <i>SERPING1</i> cause hereditary angioedema (<i>extracellular matrix</i>)	+++	+++	+
TCF7L1	Transcription factor 7-like 1: encodes a member of the T-cell factor/lymphoid enhancer factor family of transcription factors (<i>transcriptional regulators</i>)	++	++	+
TGFB2	Transforming growth factor β 2: encodes a secreted ligand of the TGF- β superfamily of proteins (<i>growth factors</i>)	+++	+++	—
TNS1	Tensin 1: encodes for a protein that localises to focal adhesions and crosslinks actin filaments (<i>cell-to-cell adhesion and cytoskeleton; extracellular matrix</i>)	+++	+++	+
WNT2B	Wnt family member 2: member of the WNT gene family (<i>growth factors</i>)	+++	+++	+
WNT9A	Wnt family member 9A: member of the WNT gene family (<i>growth factors</i>)	+++	+++	—

*Evidence of gene expression (high: +++, medium: ++, low: +) from Expression Atlas (www.ebi.ac.uk/gxa/home) for lung and for cardiovascular tissues, in particular heart (heart left/right ventricle, left/right cardiac atrium, heart muscle) and vasculature (artery).



In FinnGen, all seven colocalisation signals for FVC or FEV₁/FVC with either HTN or CHD (available phenotypes) showed replication of the CV association at nominal level ($p < 0.05$), with five of them surviving Bonferroni correction for multiple testing; three SNPs also showed associations with myocardial infarction (table 4a).

In CKB, data were available for 11 of the 13 SNPs. Only three replicated at nominal significance, none surviving Bonferroni correction; for another signal, replication was observed for SBP and DBP, although not for the original HTN. Replication power was limited in this Chinese population by low minor allele frequency of six of the 11 SNPs (table 4b).

Novelty of our colocalisation findings for CV traits

To assess whether any of the 22 genes identified by our overall colocalisation analysis were novel for CV traits, we searched for previous GWAS findings using the GWAS catalogue (www.ebi.ac.uk/gwas) (table 1). Six of the 22 genes (CLDN20, CSNK2B, GFI1, KAT8, MAPRE1 and SERPING1) have not been associated with any CV trait in previous GWAS, although for CSNK2B there was some evidence of association with CHD and blood pressure failing to reach genome-wide significance. For all six novel genes, we found evidence supporting a genuine association from animal studies, cell/in vitro studies or previous candidate-gene studies (online supplemental table S5).

In FinnGen, we observed associations with CV traits for four of the six genes: CSNK2B (HTN, CHD, myocardial infarction), KAT8 (HTN) and GFI1 (HTN) (table 4a); and CLDN20 (HTN) (online supplemental table S6). In CKB, there was some evidence of association only for CLDN20 (PP), SERPING1 (PP) and KAT8 (SBP, DBP) (table 4b).

DISCUSSION

The findings of this study support the hypothesis that signalling pathways critical to lung development and repair, and hence lung

ageing, are also important for the development and/or repair of the CV system. We found colocalisation predominantly with blood pressure traits, and we speculate that this may reflect pathways required to drive vascular development in the lungs, heart and blood vessels. In the lungs, reciprocal interactions between the airways and blood vessels are essential to drive the development of both the airways and the alveoli.^{25 26} Our findings for blood pressure traits may reflect impaired vascular development, resulting in either fewer vessels/capillaries or reduced integrity of them, and impaired capacity for vascular growth may underlie essential HTN.²⁷ Particularly for FVC, we also found colocalisation with CHD (CSNK2B, ITGB5, MMP24 and TNS1) and CIMT (MMP24). A lack of colocalisation with ASI may reflect limited statistical power, as this phenotype was measured in a smaller subsample of UKB participants. In fact, while we were able to detect a signal for CIMT in an even smaller subsample, the power of the ASI analysis is likely to be further reduced by the measurement error and variability associated with finger photo-plethysmography measurements, compared with measurements of aortic stiffness from tonometry/Doppler techniques (pulse wave velocity) or CV MRIs.²⁸

Importantly, when focusing on colocalisation defined in the strictest form, that is, sharing of the same signal within a gene (H4), all results for FVC showed directions of the genetic effects consistent with our hypothesis that a variant that decreases lung function will have a detrimental effect on the CV trait. In contrast, this was not always the case for FEV₁/FVC. However, this is perhaps not surprising, given that the epidemiological evidence for a link between lower lung function and increased CV risk is stronger for a restrictive defect (as indicated by a lower FVC) than for an obstructive defect (as measured by lower FEV₁/FVC).^{1 2 6 9} Associations with CV traits identified by our H4 colocalisation findings were replicated in FinnGen, although not all survived correction for multiple testing. On the contrary, replication was

Table 3 Direction of the genetic effect on both lung function and CV trait for the 12 genes with H4 colocalisation (same signal)

FVC								
Gene	SNP (EA)*	FVC (mL)	PP (mm Hg)	SBP (mm Hg)	DBP (mm Hg)	HTN	CIMT (mm)	CHD
		Beta (p value)	Beta (p value)	Beta (p value)	Beta (p value)	OR (p value)	Beta (p value)	OR (p value)
CLDN20	rs1969863 (T)	−9.09 (2.2×10^{-9})	0.17 (6.6×10^{-9})	—	—	—	—	—
CSNK2B	rs3117578 (G)	−17.75 (8.2×10^{-18})	—	0.32 (5.5×10^{-9})	—	1.05 (1.0×10^{-15})	—	1.04 (3.1×10^{-5})
IGF1	rs10745941 (T)	−9.58 (4.2×10^{-8})	—	—	—	1.03 (3.7×10^{-6})	—	—
ITGB5	rs17282078 (A)	−9.32 (2.1×10^{-5})	—	—	—	—	—	1.06 (6.2×10^{-10})
KAT8	rs1978487 (T)	−9.30 (1.4×10^{-9})	—	—	—	1.02 (5.4×10^{-5})	—	—
MMP24	rs6120880 (G)	−11.35 (4.8×10^{-14})	0.16 (1.3×10^{-8})	—	—	—	0.01 (5.0×10^{-8})	—
TNS1†	rs2571445 (A)	−11.46 (3.3×10^{-14})	—	0.21 (1.6×10^{-7})	0.13 (5.4×10^{-9})	1.02 (1.5×10^{-5})	—	1.04 (2.9×10^{-7})
FEV ₁ /FVC								
Gene	SNP (EA)*	FEV ₁ /FVC (%)	PP (mm Hg)	SBP (mm Hg)	DBP (mm Hg)	HTN	CHD	
		Beta (p value)	Beta (p value)	Beta (p value)	Beta (p value)	OR (p value)	OR (p value)	
CSNK2B	rs9267531 (G)	−0.30 (5.6×10^{-38})	0.23 (2.1×10^{-8})	—	−0.28 (1.5×10^{-17})	—	—	
FARP2	rs139354822 (T)	−0.18 (2.7×10^{-4})	0.47 (1.0×10^{-7})	0.68 (2.3×10^{-8})	—	1.10 (2.8×10^{-9})	—	
GFI1	rs6676846‡ (A)	−0.13 (8.1×10^{-12})	—	—	—	0.97 (2.7×10^{-6})	—	
PPARD	rs2395623 (T)	−0.12 (1.9×10^{-10})	—	—	0.14 (1.0×10^{-7})	—	—	
RUNX3	rs111283598 (G)	−0.21 (6.6×10^{-8})	—	—	−0.26 (1.3×10^{-6})	—	—	
SERPING1	rs10896631 (C)	−0.13 (1.4×10^{-13})	−0.22 (2.4×10^{-12})	−0.25 (9.3×10^{-10})	—	—	—	
TNS1†	rs2571445 (A)	−0.11 (2.8×10^{-12})	—	0.21 (1.6×10^{-7})	0.13 (5.4×10^{-9})	1.02 (1.5×10^{-5})	1.04 (2.9×10^{-7})	

Results from linear/logistic regression analysis adjusted for age, sex, genotyping array, centre and 10 principal components, in addition to height for FVC. As the EA considered is the allele detrimental for lung function, the results for CV traits consistent with our hypothesis of lower lung function associated with higher CV risk are those with OR >1 (HTN and CHD) or beta >0 (continuous traits); these results are in bold.

*To simplify interpretation, results are presented by considering the EA as the allele, which is detrimental for lung function.

†Please note that for the TNS1 gene, the SNP is the same for FVC and FEV₁/FVC, which explains why the results for SBP, DBP, HTN and CHD are identical in the final rows of the two tables.

‡The best variants for HTN and FEV₁/FVC are not the same but are in high LD, $r^2 = 0.85$ (H4 equivalent): FEV₁/FVC_rs6676141 and HTN_rs6676846; betas and p values refer to the HTN SNP, rs6676846, identified with fine mapping in coloc.

CHD, coronary heart disease; CIMT, carotid intima-media thickness; CV, cardiovascular; EA, effect allele; FEV₁/FVC, forced expiratory volume in 1 s to forced vital capacity ratio; HR, heart rate; HTN, hypertension; LD, linkage disequilibrium; PP, pulse pressure; SBP/DBP, systolic/diastolic blood pressure; SNP, single nucleotide polymorphism.

Table 4 Replication of H4 localisation signals for CV traits

(a) FinnGen (only data on HTN and CHD were available)									
Gene	SNP	LF trait	CV trait	EA	EAF UKB/FinnGen	UKB	FinnGen		
						OR (p value)	OR (p value; one-sided p value)*	Association with other CV traits	
CSNK2B	rs3117578	FVC	HTN	G	0.85/0.86	1.05 (1.0×10 ⁻¹⁵)	1.04 (9.7×10 ⁻⁶ ; 4.8×10 ⁻⁶)*	MI (1.05; p=6.6×10 ⁻⁴)	
			CHD		1.04 (3.1×10 ⁻⁵)	1.06 (2.9×10 ⁻⁶ ; 1.4×10 ⁻⁵)*			
FARP2	rs139354822	FEV ₁ /FVC	HTN	T	0.97/0.95	1.10 (2.8×10 ⁻⁶)	1.06 (5.3×10 ⁻⁵ ; 2.6×10 ⁻⁵)*		
GFI1	rs6676846	FEV ₁ /FVC	HTN	A	0.79/0.78	0.97 (2.7×10 ⁻⁶)	0.98 (1.7×10 ⁻³ ; 8.3×10 ⁻⁴)*		
IGF1†	rs10745941	FVC	HTN	T	0.76/0.77	1.03 (3.7×10 ⁻⁶)	1.02 (0.02; 9.3×10 ⁻³)		
ITGB5	rs17282078	FVC	CHD	A	0.13/0.10	1.06 (6.2×10 ⁻¹⁶)	1.03 (0.04; 0.02)	MI (1.04; p=0.03)	
KAT8	rs1978487	FVC	HTN	T	0.64/0.62	1.02 (5.4×10 ⁻⁵)	1.01 (0.06; 0.03)		
TMS1	rs2571445	FVC, FEV ₁ /FVC	HTN	A	0.39/0.44	1.02 (1.5×10 ⁻⁵)	1.01 (0.02; 8.4×10 ⁻³)	MI (1.04; p=1.3×10 ⁻⁴)	
			CHD		1.04 (2.9×10 ⁻⁷)	1.04 (3.7×10 ⁻⁷ ; 1.9×10 ⁻⁷)*			
(b) CKB (data on all phenotypes were available)									
Gene	SNP	LF trait	CV trait	EA	EAF UKB/CKB	UKB	CKB		
						Beta/OR (p value)	Beta/OR (p value; one-sided p value)*	Association with other CV traits	
CLDN20	rs1969863	FVC	PP	T	0.62/0.98	0.17 (6.6×10 ⁻⁵)	0.37 (0.11; 0.05)		
CSNK2B	rs3117578	FVC	SBP	G	0.85/0.98	0.32 (5.5×10 ⁻⁶)	-0.47 (p=0.17)		
			HTN		1.05 (1.0×10 ⁻¹⁵)	1.01 (0.78; 0.39)			
			CHD			1.04 (3.1×10 ⁻⁵)	1.01 (0.87; 0.44)		
GFI1	rs6676846	FEV ₁ /FVC	HTN	A	0.79/0.96	0.97 (2.7×10 ⁻⁶)	0.99 (0.70; 0.35)		
IGF1	rs10745941	FVC	HTN	T	0.76/0.84	1.03 (3.7×10 ⁻⁶)	1.01 (0.75; 0.37)		
ITGB5	rs17282078	FVC	CHD	A	0.13/0.08	1.06 (6.2×10 ⁻¹⁶)	1.01 (0.72; 0.36)		
KAT8	rs1978487	FVC	HTN	T	0.64/0.09	1.02 (5.4×10 ⁻⁵)	1.02 (0.25; 0.13)	SBP (0.50; p=3.3 ⁻³) DBP (0.32; p=7.9 ⁻⁴)	
MMP24	rs6120880	FVC	PP	G	0.42/0.35	0.16 (1.3×10 ⁻⁸)	0.10 (0.14; 0.07)		
			CIMT		0.01 (5.0×10 ⁻⁶)	0.01 (0.19; 0.09)			
PPARD	rs2395623	FEV ₁ /FVC	DBP	T	0.23/0.29	0.14 (1.0×10 ⁻⁷)	-0.12 (p=0.04)		
RUNX3	rs111283598	FEV ₁ /FVC	DBP	G	0.96/0.91	-0.26 (1.3×10 ⁻⁶)	-0.09 (0.38; 0.19)		
SERPINC1	rs10896631	FEV ₁ /FVC	PP	C	0.27/0.14	-0.22 (2.4×10 ⁻¹²)	-0.16 (0.08; 0.04)		
			SBP		-0.25 (9.3×10 ⁻⁶)	-0.16 (0.24; 0.12)	0.24 (0.12)		
TMS1	rs2571445	FVC, FEV ₁ /FVC	SBP	A	0.39/0.40	0.21	0.21 (0.03; 0.02)	0.03 (0.02)	
			DBP		0.13	0.12 (0.03; 0.01)	0.03 (0.01)		
		HTN			1.02	0.99 (p=0.32)	0.32		
		CHD			1.04	1.02 (0.25; 0.12)	0.25 (0.12)		
In bold are results replicated at least at nominal level (same effect direction and one-sided p<0.05), with an asterisk indicating replication at Bonferroni correction (FinnGen: p<5.6×10 ⁻³ , 0.05/8 tests), Statistically significant association with other CV traits are also reported with OR (binary variables) or beta (continuous variables) and p values (two-sided).									
EA: allele associated with decreased lung function, as shown in table 3.									
*One-sided p values calculated only for effects in same direction as in UKB.									
†A proxy was used, rs742694 (r ² =0.91), as rs10745941 was not available in FinnGen.									
CHD, coronary heart disease; CKB, China Kadoorie Biobank; CV, cardiovascular; EA, effect allele; EAF, effect allele frequency; FEV ₁ , forced expiratory volume in 1 s; FVC, forced vital capacity; HTN, hypertension; LB, lung function; SBP/DBP, systolic/diastolic blood pressure; UKB, UK Biobank.									

poor in CKB. Limited statistical power is a possible explanation for this: the sample size in CKB was smaller than in FinnGen and much smaller than in UKB, and the minor allele frequency for many SNPs was lower in this Chinese population. Reduced replication ability in CKB might also be due to ethnic differences in LD patterns; a marker SNP identified in Europeans as in LD with the underlying causal variant may not be in LD with the causal variant in a Chinese population.²⁹

Our findings show that the magnitude of the effects of the individual genetic variants is small, as is typically the case in genetic association studies, and therefore these shared genetic signals are likely to explain only a modest part of the observational relationship between low lung function and CV disease. The importance of our findings rather rests on the demonstration of shared developmental pathways, with the identification of specific genes and variants that are worth further investigation.

Biological interpretation

One of our strongest colocalisation signals was in CSNK2B. This gene encodes for the beta subunit of casein kinase II, a protein known to mediate diverse cellular pathways (online supplemental table S5); one of these is Wnt signalling, which plays a key role in lung and CV development (online supplemental table S5). Notably, three other genes with colocalisation are also involved in Wnt signalling: WNT2B, WNT9A and TCF7L1. The proteins encoded by MMP24 and TNS1, two of our strongest colocalisation findings, affect the ECM, and ECM remodelling is a cause of both vascular and respiratory diseases.³⁰ Regulation of ECM is tightly controlled by balancing maintenance of its components, such as collagen and elastin (coded by ELN, also showing colocalisation), with their degradation by matrix metalloproteases (MMPs). MMPs influence vascular ECM remodelling, and MMP24 (with other MMP genes) has been recently linked to intracranial aneurysms (online supplemental table S5). Our colocalisation finding for the ELN gene (FEV₁/FVC and PP) is of interest because elastin is essential for elastic recoil, both in the lung and in the walls of the aorta and large arteries. As elastin is only produced early in life and is difficult to repair later in life,³¹ optimal deposition of elastin in these tissues during development is crucial. Impaired elastin synthesis in early life could increase the risk of an emphysematous form of airflow obstruction,³² and also reduced compliance (ie, increased stiffness) of the aorta and large arteries, with widening of PP.³³

Another gene showing colocalisation was CLDN20, which encodes the tight junction protein CLDN20 (claudin 20). Tight junctions regulate paracellular permeability, and their dysfunction disrupts the tissue barrier leading to oedema. While other claudins are known to influence the regulation of blood pressure (online supplemental table S5), the specific role of CLDN20 has barely been investigated despite its expression in the heart, lungs and vasculature; however, CLDN20 has been recently shown to be significantly decreased after ischaemia in a multi-omics mouse study of ischaemic stroke (online supplemental table S5). Among the other genes identified, DSP encodes desmoplakin, which is involved in cell:cell interactions and, like claudins, is important for tissue integrity. In a zebrafish model, the knockout of DSP has been shown to result in loss of cardiac Wnt signalling.³⁴ We also found colocalisation for MAPRE1, which encodes a microtubule-associated protein. Microtubules are part of the cytoskeletal network that maintains cell tension and integrity. In particular, MAPRE1 has been shown to play a role in cardiomyocyte integrity and adaptation to pressure overload, and in cardiac conduction and arrhythmias (online supplemental table S5).

Finally, we looked for evidence of the association of the proteins coded by the identified genes with both lung function and CV traits. We did so by interrogating the publicly available Proteome PheWAS Browser (www.epigraphdb.org/pqtl/), which leverages protein quantitative trait loci data from published proteomic studies and Mendelian Randomisation analysis to investigate the causal effects of multiple circulating proteins on multiple pheno-

types. For the IGF1 gene, the colocalisation for FVC with HTN is supported by the association of the IGF1 protein with DBP and SBP, in addition to association with lung function and disease traits. Similarly for SERPING1, one of the six genes with no previous GWAS association with CV traits, our colocalisation findings for FEV₁/FVC with SBP and PP are supported by association of the SERPING1 protein with SBP, in addition to association with lung function. With the continuously accumulating genome-wide proteomic studies, similar evidence for further genes identified in our colocalisation analysis is likely to become available in the near future.

Strengths and limitations

Our study has a number of strengths. First, the large sample size provided by UKB, complemented by publicly available data from CARDIoGRAM, meant we had considerable statistical power to analyse blood pressure and CHD phenotypes. Second, our findings provide stronger evidence for the importance of the shared developmental origins of adult lung function and CV disease than could be achieved in observational studies, which are prone to confounding. Third, six of the 22 genes found in our colocalisation analysis (CLDN20, CSNK2B, GFI1, KAT8, MAPRE1, SERPING1) have not been associated with any CV trait in previous GWASs, and yet, for all of them, we found evidence from laboratory studies and candidate-gene studies supporting a genuine association. This gives added value to our study and illustrates the potential of hypothesis-driven investigations to complement a GWAS approach for the identification of novel candidate genes.

Our study also has some limitations. Some of the genes that we investigated have a role in lung development, and later in life, in adult lung homeostasis and repair through alveolar maintenance and regeneration after injury. In fact, we expect the majority of the 22 colocalised genes identified in this study will play a role in repair in addition to their developmental role. There is already published evidence of such a role for some of the genes, including RUNX3,³⁵ IGF1³⁶ and SERPING1.³⁷ For others, such as FARP2 and CLDN20, there is not yet published evidence for a role in lung repair, but this is probably just because these specific studies have not been done yet. FARP2 regulates the actin cytoskeleton, and this fundamental cellular process is critical for repair. Likewise, CLDN20 is a tight junction protein that helps cells stick together, so it will also be important for repair. Our results highlight the importance of investigating the role of these genes in repair in the near future.

Yet, given the age at which lung function and CV phenotypes were measured cross-sectionally in UKB participants, we cannot say whether our findings predominantly reflect effects on development or repair. While distinguishing between the two aspects is important, data from longitudinal cohorts covering the life course are needed to address this. It would be interesting to investigate the effects of lung development genes on lung function and CV phenotypes in younger cohorts, before lung function decline has occurred; a stronger genetic signal in children and young adults would suggest that the effect seen in older adults in UKB predominantly reflects an effect on lung and CV development, rather than repair in later life. On the contrary, a stronger effect in older adults following lung function decline would point to an important role in maintenance and regeneration. Indeed, indirect evidence that later repair might be relevant to our FVC-HTN findings comes from the CARDIA (coronary artery risk development in young adults) study, in which faster decline in FVC in young adults was associated with incident HTN, after controlling for smoking and other confounders.³⁸ Another limitation is that UKB only measured prebronchodilator lung function, thus a low prebronchodilator FEV₁/FVC cannot exclude reversible obstruction, the hallmark of asthma; however, a sensitivity analysis for FEV₁/FVC excluding individuals with a diagnosis of asthma showed similar findings.

Finally, the UKB study population is not fully representative of the general UK population. Participants tend to be healthier, of higher socioeconomic status and predominantly of white European ancestry compared with the UK population as a whole.³⁹

Due to the voluntary recruitment and low response rate in UKB, there is also a risk of healthy volunteer bias, which can lead to systematic differences between the study population and the overall UK population.³⁹ However, while this has been shown to distort genetic associations with behaviour, lifestyles and social outcomes, a limited impact has been observed for genetic associations with physical traits.⁴⁰ A more general limitation of genetic association studies related to the characteristics of a given study population is the potential bias and limited generalisability of findings due to gene-environment interactions, if the interacting environmental factors vary across populations and population subgroups. Future studies in different populations and ethnic groups will be important to establish the generalisability of our findings.

CONCLUSION

In conclusion, our results provide evidence that adult lung function and CV comorbidities have shared developmental signalling pathways. This may partly explain why lower lung function, especially FVC, is associated with increased CV risk. Our findings may inform future research on druggable targets aimed at optimising lung and CV development and/or repair, and preventing premature morbidity and mortality. Of note, our work has also identified potentially novel CV genes.

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Acknowledgements We thank the UK Biobank participants and the UK Biobank team for making this study possible and for providing access to this valuable resource. UK Biobank data used in this study were obtained under approved access (application number 19136; <https://www.ukbiobank.ac.uk>). We also acknowledge the participants and investigators of the FinnGen study. The China Kadoorie Biobank (CKB) acknowledges the participants and the members of the survey teams in each of the 10 regional centres, as well as the project development and management teams based in Beijing, Oxford and the 10 regional centres.

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Contributors SOS conceived the hypothesis. CM and LP planned and undertook the colocalisation analyses. AP and RW provided summary statistics from CKB for SNP replication. MT clarified previous evidence on associations between gene variants and cardiovascular traits. CD and MDH advised on the lung development genes. NA and SP advised on the analysis of cardiovascular outcomes. CM, LP, SOS, MT, CD and PGJB interpreted the findings. CM, LP, SOS, CD and MT drafted the manuscript. LP is the guarantor of this work and accepts full responsibility for the conduct of the study, had access to the data and controlled the decision to publish.

Funding This research was conducted using the UK Biobank Resource under application number 19136. It used the computing resources of the UK Medical Bioinformatics partnership-aggregation, integration, visualisation and analysis of large, complex data (UK MED-BIO), supported by the Medical Research Council (grant number MR/L01632X/1). LP was funded through a donation to MH from the Thompson Family Charitable Trust. MT was supported by a grant from Barts Charity (MGU0570). SP acknowledges support from the National Institute for Health Research (NIHR) Biomedical Research Centre at Barts.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the National Health Service National Research Ethics Service (reference 11/NW/0382). All participants provided informed consent prior to taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data supporting the findings of this study are included in the manuscript and supplementary materials. Additional datasets and results can be shared on reasonable request to the corresponding author, subject to relevant ethical and data protection regulations.

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Efeito da viloxazina e da trazodona na apneia obstrutiva do sono: estudo cruzado, randomizado e controlado por placebo

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/thorax-2024-222513>).

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Received 27 September 2024

Accepted 3 April 2025

Published Online First 13 May 2025



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To cite: Aishah A, Kim M, Gell L, et al. *Thorax* 2025;80:641–649.

RESUMO

Introdução A combinação da atomoxetina (noradrenérgica) com aroxibutinina (antimuscarínica) ou trazodona demonstrou reduzir a gravidade da apneia obstrutiva do sono (OSA). No entanto, a atomoxetina pode contribuir para ciclos de apneia e menor tolerabilidade, devido ao seu efeito estimulante, especialmente em subgrupos com metabolismo lento da enzima citocromo 2D6, o que leva a concentrações plasmáticas mais elevadas do fármaco. Investigamos o efeito de uma alternativa noradrenérgica potencialmente mais bem tolerada — a viloxazina — isoladamente e em combinação com trazodona, na gravidade da OSA.

Métodos Este estudo cruzado, randomizado, duplamente cego e controlado por placebo incluiu 24 doentes com OSA (idades entre 18 e 75 anos). Os participantes foram aleatorizados para um dos seguintes regimes: 500 mg de viloxazina, 500/75 mg de viloxazina-trazodona (vilo-trazo) e placebo. Os medicamentos foram administrados ao deitar durante 2 semanas, com um período de washout de 1 semana entre os tratamentos. No final de cada fase, foi realizada polissonografia em laboratório. A análise estatística por modelos mistos comparou o efeito de vilo-trazo versus placebo no índice de apneia-hipopneia com dessaturações de 4% (AHI4, desfecho primário) e na carga hipóxica (desfecho secundário). Foram também avaliados o tempo total de sono (TST) e o tempo de vigília após início do sono (WASO), bem como parâmetros de segurança (questionários autorreportados, frequência cardíaca e eventos adversos).

Resultados A combinação vilo-trazo reduziu significativamente o AHI4 (diferença média [IC 95%]: 10,5 [6,6–13,6] eventos/hora; $p < 0,001$) e a carga hipóxica (16,7 [9,6–21,8] %min/h; $p < 0,001$) em comparação com o placebo. Comparativamente à viloxazina isolada, o TST foi tendencialmente superior com vilo-trazo (22,3 [–1,4–46,0] minutos; $p < 0,065$), enquanto o WASO não apresentou alterações. Tanto o TST como o WASO foram significativamente melhores com vilo-trazo do que com placebo. Ambas as intervenções pioraram os resultados autorreportados pelos doentes, embora em menor grau com vilo-trazo, e aumentaram a frequência cardíaca em relação ao placebo. Os efeitos adversos mais comuns foram insônia, obstipação, cefaleia e xerostomia.

Conclusão A combinação viloxazina-trazodona reduziu a gravidade da OSA. Os potenciais efeitos negativos da viloxazina na qualidade do sono pareceram ser parcialmente atenuados pela trazodona.

Número de registo do ensaio clínico: NCT05793684

INTRODUCTION

In recent years, pharmacotherapy has risen as a potential innovation in the treatment of obstructive sleep apnoea (OSA). Current available therapeutics have presented several challenges including poor adherence, variable response rates or limited accessibility among patients.¹ Therefore,

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Pharmacotherapy is emerging as a potential treatment for obstructive sleep apnoea (OSA), as existing options face challenges with adherence and varying efficacy. Atomoxetine-oxybutynin can reduce OSA severity, but atomoxetine's wake-promoting effects and CYP2D6 metabolism can be limiting its suitability in some patients. Oxybutynin has sedative properties, but alternative hypnotics may offer broader applicability.

WHAT THIS STUDY ADDS

► This study demonstrates that viloxazine, a similar drug class agent to atomoxetine, reduces OSA severity, with trazodone mitigating some of its adverse effects. The viloxazine-trazodone combination significantly lowered OSA severity, suggesting its potential as an alternative therapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► These findings support combining noradrenergic agents with hypnotics as a promising OSA treatment strategy. Future studies should explore optimal dosing to maximise efficacy while minimising side effects, potentially improving accessibility and adherence to pharmacological OSA treatments.

there is an unmet need for alternative treatments that offer effectiveness and access, to ultimately improve cardiovascular and functional outcomes in OSA.² Recent trials demonstrate the efficacy of atomoxetine and oxybutynin (particularly, aroxibutinina) on OSA severity.^{3–6} Atomoxetine, a selective noradrenergic reuptake inhibitor, exerts its effect on OSA by improving upper-airway muscle responsiveness,^{5,6} while the antimuscarinic oxybutynin is suggested to partly contribute to upper airway muscle activation and offset atomoxetine's wake-promoting properties via a modest sedative hypnotic effect.⁷ Other studies testing similar drug combinations have corroborated the potential of this treatment approach.^{8,9}

A key aspect that could hinder the acceptance or long-term use of these drug combinations is

the potential associated side effects. Atomoxetine may cause sympathomimetic and gastrointestinal reactions,¹⁰ especially in ~7% of Caucasians who have little activity of the cytochrome P450 (CYP) isoenzyme 2D6 which metabolises the drug (ie, poor metabolisers).^{11–12} Likewise, oxybutynin reduces bladder sensitivity and may be less suitable in patients with urinary retention concerns. Therefore, combination agents with similar effects on OSA severity, but lower risks of side effects are of interest.

Viloxazine, an alternative norepinephrine reuptake inhibitor to atomoxetine, can be metabolised by other CYPs,¹² thus circumventing the poor metaboliser issue. Specifically, viloxazine's peak blood concentration will not be as elevated as atomoxetine's in poor metabolisers for CYP2D6,¹² lowering the likelihood for viloxazine's blood levels to rise beyond expectations. Trazodone, as an alternative to oxybutynin, has established hypnotic properties¹³ and has been shown to reduce symptoms of insomnia.¹⁴ It is postulated that the main physiological mechanism of oxybutynin is to raise the arousal threshold and consolidate sleep. Trazodone is likely to provide a stronger hypnotic effect which could be more suitable for a broader range of patients including those with greater arousability.

Therefore, we investigated the effect of viloxazine, with and without trazodone, on OSA severity in this double-blinded, placebo-controlled, cross-over study. The main endpoint was reduction in OSA severity for viloxazine and trazodone (vilo-trazo) as per the apnoea hypopnoea index (AHI4, with hypopnoeas scored when flow reduction is associated with 4% oxygen desaturation, HB4) versus placebo. Secondary endpoints were the effect of vilo-trazo on hypoxic burden with HB4 versus placebo, and the effect of vilo-trazo on total sleep time and wake after sleep onset (WASO) versus viloxazine alone. Additional exploratory endpoints were the across-arm differences in other OSA severity parameters, sleep stage distribution, arousals and questionnaires to measure sleepiness and sleep impairment (ie, Epworth Sleepiness Scale (ESS) and patient-reported outcomes measurement information systems (PROMIS)). In exploratory analyses, predictors of treatment response and treatment efficacy were also assessed, as well as dose-dependent efficacy using at-home wearable, non-invasive monitoring (ie, to evaluate the minimal efficacious dose).

METHODS

Participants

25 participants with OSA were recruited across three sites: Clayton, St. Louis, Missouri, USA (N=14), and Santa Monica Clinical Trials, Los Angeles, California, USA (N=10), Brigham and Women's Hospital, Boston, Massachusetts, USA (N=1). Participants were included if they had an AHI4 of 10–45 events/hour inclusive, a score above 11 at the PROMIS-Fatigue Short Form 8a, PROMIS-sleep-related impairment Short Form 8a or PROMIS-sleep disturbance Short Form 8b, if they were treatment naïve or not currently on treatment for their OSA, and if they had a body mass index (BMI) between 18.5 and 40 kg/m². Exclusion criteria were uncontrolled hypertension, any underlying major organ disease, any sleep disorder besides OSA, clinically significant urinary or gastrointestinal retention, benign prostatic hypertrophy, severe or frequent gastrointestinal reflux, pregnancy, untreated narrow angle glaucoma, attempted suicide within 1 year prior to screening or current suicidal ideation. People were also excluded if, at the baseline assessment, they exhibited a prolonged QTc interval (>450 ms in men or >470 ms in women), hypokalaemia or hypomagnesaemia, high hepatic transaminases or high total bilirubin and estimated glomerular filtration rate <50 mL/min. The study protocol was preregistered online at ClinicalTrials.gov (NCT05793684).

Protocol

This was a randomised, placebo-controlled, multiple-dose, three-period cross-over study (figure 1). Details are outlined in the online supplemental document. Briefly, eligible participants were randomised to three arms: 500 mg viloxazine, 500/75 mg vilo-trazo or placebo. Each arm consisted of 2 weeks of treatment, followed by a 1-week wash-out. The medications were taken nightly approximately 30 min prior to bed, with a first week of run-in of 200 mg viloxazine and 50 mg trazodone (if on the vilo-trazo arm). At-home oximetry monitoring was performed on two nights during the run-in dose and two nights during the full dose period of each treatment. Another in-lab polysomnography (PSG) was performed after 2 weeks, at the end of each cross-over period. At each in-laboratory PSG visit, vital signals and questionnaires (PROMIS-Fatigue, PROMIS-sleep impairment, PROMIS-sleep disturbance, ESS) were completed in the evening. Next morning

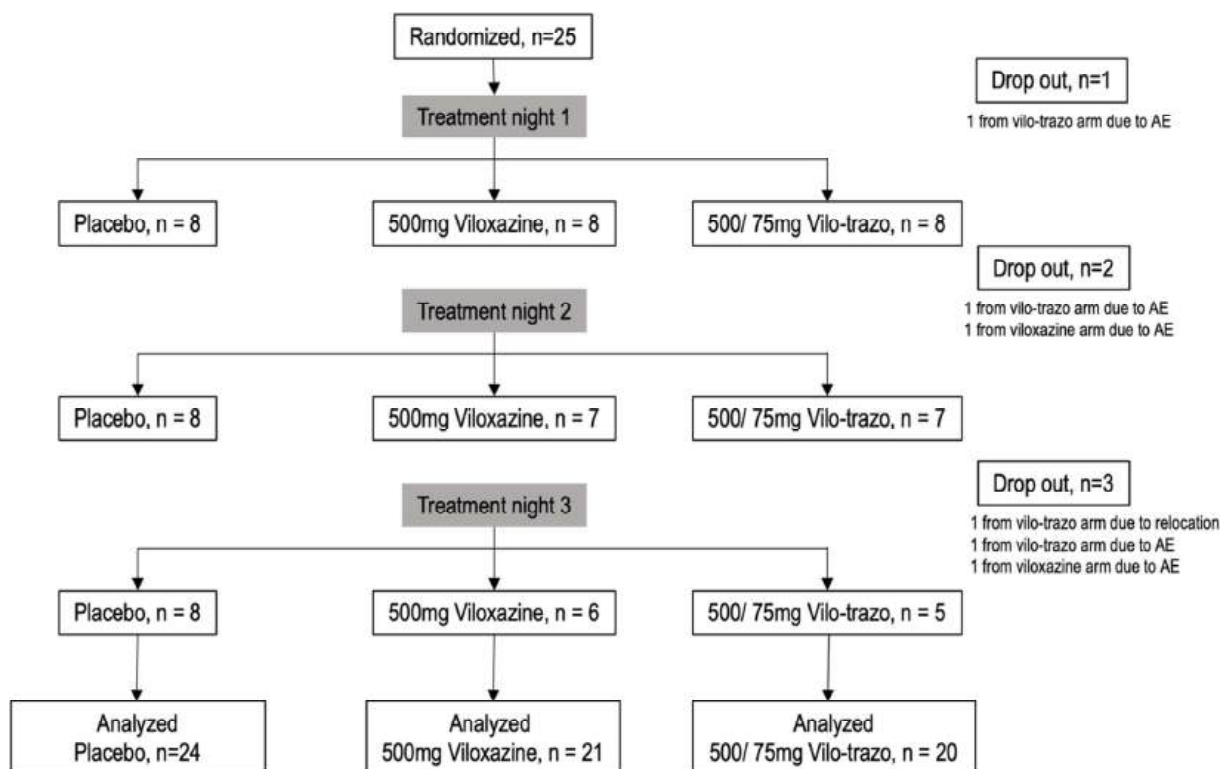


Figure 1 CONSORT diagram. AE, adverse event; CONSORT, Consolidated Standards of Reporting Trials; Vilo-trazo: viloxazine-trazodone.

Table 1 Baseline participant characteristics	
Age, years	55±8
Sex, M:F	13:11
BMI, kg/m ²	32±5
Race, black:white:other	3:17:4
Ethnicity, Hispanic:non-Hispanic	3:21
Baseline AHI ₄ , events/hour	24±12
Baseline HB ₄ , %/min/hour	58±32
Data are presented as mean±SD. N=24. AHI ₄ , apnoea-hypopnoea index with 4% oxygen desaturation; BMI, body mass index; HB ₄ , hypoxic burden with 4% oxygen desaturation.	

procedures included recording of vital signs, Karolinska Sleepiness Scale questionnaire and symbol digit modalities test, 1-hour postawakening. Adverse events and concomitant medication were monitored regularly during treatment, wash-out periods and after each in-laboratory PSG.

Data analysis

PSGs were scored by a centralised PSG centre (Sleep Strategies, Ottawa, ON), blinded to treatment assignment, following AASM scoring criteria.¹⁵ Previously validated algorithms¹⁶ were used to estimate baseline VCOMP (estimate of pharyngeal muscle responsiveness). Further details outlined in online supplemental file. The study was powered at 80% to detect a difference in the primary endpoint (AHI4 on Vilo-trazo vs placebo) of 11±11 events/hour at α=0.05. Data are expressed as mean±SD or median (IQR) where appropriate (Shapiro-Wilk normality test) and were analysed using linear mixed effect analyses with the treatment arm as fixed effect and the subject as random effect. All models were adjusted by period, sequence and body position during sleep. More details are outlined in the online supplemental file.

RESULTS

25 participants were randomised, including six dropouts, one due to relocation and five due to adverse events (figure 1). Baseline characteristics of all 24 participants who contributed to the final analysis (ie, completed at least one treatment arm) are outlined in table 1.

Effects of the combination on OSA severity and sleep

The primary endpoint of the study was met, as vilo-trazo reduced the AHI4 by 10.5 (6.6, 13.6) events/hour (mean difference (95% CI)) versus placebo, corresponding to a 54% reduction in OSA severity (p<0.001; figure 2A, table 2, online supplemental figure S1). HB4 was also reduced by 16.7 (9.6, 21.8) %·min/hour on vilo-trazo versus placebo (p<0.001; secondary outcome; figure 2B, table 2). Additionally, vilo-trazo reduced non-REM and REM AHI4, as well as the AHI3a, HB3 and OD14 (table 2). However, vilo-trazo also reduced total sleep duration by 37.7 (14.5, 60.9) min, (p=0.002) and increased WASO by 26.6 (4.7, 48.6) min (p=0.018) compared with placebo.

Effects of viloxazine alone on OSA severity and sleep

Viloxazine had similar effects to vilo-trazo on OSA severity versus placebo, including reductions in the AHI4 (15.6 (9.4, 20.5) events/hour, p<0.001; figure 2A, table 2) and the HB4 (16.5 (9.4, 21.6) %·min/hour, p<0.001; figure 2B, table 2). These reductions were also observed for non-REM and REM AHI4, as well as AHI3a, HB3 and OD14. Additionally, viloxazine decreased total sleep time and raised WASO.

Comparison between active treatments

The reduction of total sleep time on viloxazine was of a greater magnitude than on the combination versus placebo. There were no differences in WASO on vilo-trazo versus viloxazine (13.0 (−9.5, 35.5) min, p=0.254; secondary outcome).

Sleep architecture changes were observed across different treatment arms. Overall, viloxazine alone and vilo-trazo increased N2 sleep while reducing REM sleep. Vilo-trazo also increased N3 sleep compared with viloxazine alone (table 2).

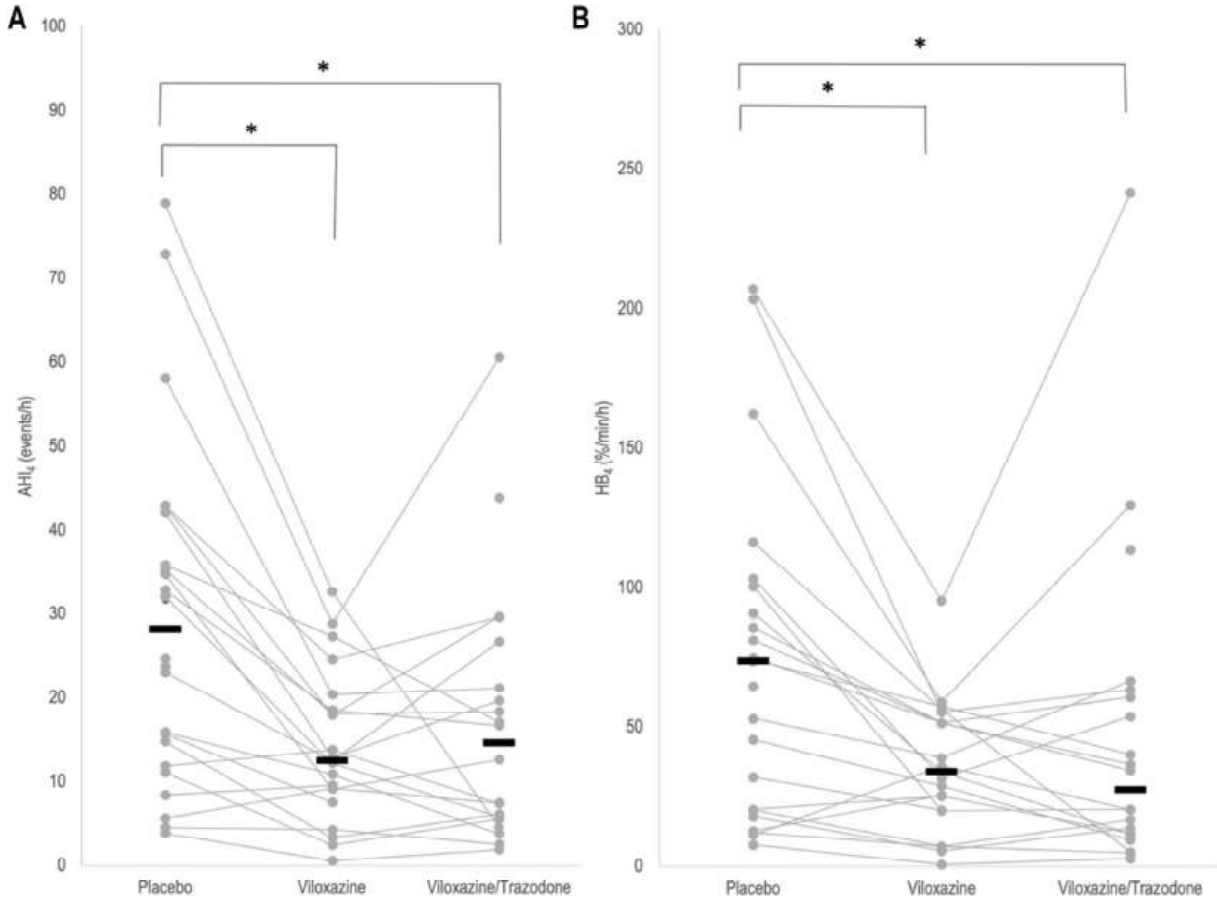


Figure 2 Effect of viloxazine and viloxazine-trazodone (Vilo-trazo) on (A) apnoea-hypopnoea index with 4% oxygen desaturation (AHI₄) and (B) hypoxic burden with 4% oxygen desaturation (HB₄) compared with placebo. Bars are medians. *p<0.05.

Effects of active treatments on participant-reported outcomes and safety metrics

Both vilo-trazo and viloxazine alone increased PROMIS-sleep disturbance compared with placebo (6.5 (2.7, 10.3), $p=0.001$; 6.1 (2.4, 9.8), $p=0.002$, respectively; higher values reflect greater disturbance), while PROMIS-sleep impairment (5.2 (1.0, 9.4), $p=0.016$) and PROMIS-fatigue (6.7 (2.3, 11.0), $p=0.003$) were only reduced on viloxazine versus placebo (table 3). ESS was higher (greater sleepiness) on vilo-trazo (2.1 (0.6, 3.7), $p=0.008$), but not on viloxazine alone (1.3 (−0.2, 2.8), $p=0.084$) compared with placebo (table 3).

Both vilo-trazo (5.6 (3.6, 7.6) beats/min) and viloxazine alone (3.5 (1.5, 5.5) beats/min) increased heart rate during sleep compared with placebo. Vilo-trazo—but not viloxazine alone—increased diastolic blood pressure in the evening before the PSG by 4.0 (0.5, 7.4) mm Hg versus placebo; all other blood pressure measurements were unchanged across treatment arms (table 3).

Unlike viloxazine alone, vilo-trazo reduced single-digit modality test written score by 3.7 (0.8, 6.6) points ($p=0.012$) vs placebo (lower values reflect greater alertness impairment; table 3).

Side effects and adverse events

42%, 67% and 72% of people on placebo, viloxazine, vilo-trazo experienced at least one side effect, respectively. Commonly reported adverse events on viloxazine, vilo-trazo and placebo were headache, insomnia, constipation, and xerostomia of mild-to-moderate severity (online supplemental table S1). For both viloxazine and vilo-trazo, an estimated OR above 2.0 was observed for insomnia, constipation and xerostomia, but not for headache (figure 3).

Five participants discontinued the study due to AEs: one participant experienced mild blurry vision with moderate fatigue after 14 days on the vilo-trazo arm and was withdrawn from the study before completing any study night. Similarly, another participant dropped out of the study while on vilo-trazo after experiencing moderate fatigue and mild blurry vision after 14 days of drug administration. Another participant dropped out due to reported moderate headache after 10 days on vilo-trazo. A participant had elevated blood pressures after 10 days of viloxazine and experienced left upper chest pain starting after 14 days of viloxazine, leading to study withdrawal. Another participant withdrew from the study due to moderate headache and mild symptoms of flushing, loss of appetite,

Table 2 Polysomnography parameters

	Placebo N=24	Viloxazine vs placebo		Vilo-trazo vs placebo		Vilo-trazo vs viloxazine	
	Estimate (95% CI)	Adjusted mean difference (95% CI) P value		Adjusted mean difference (95% CI) P value		Adjusted mean difference (95% CI) P value	
AHI ₄ , events/hour	19.3 (10.9, 30.1)	−11.4 (−14.4, −7.8) <0.001		−10.5 (−13.6, −6.6) <0.001		1.0 (−2.3, 5.0) 0.588	
NonREM AHI ₄ , events/hour	18.1 (9.3, 30.0)	−10.6 (−13.7, −6.7) <0.001		−9.1 (−12.6, −4.9) <0.001		1.5 (−2.1, 5.9) 0.449	
REM AHI ₄ , events/hour	22.2 (9.8, 39.4)	−14.3 (−19.4, −6.7) 0.001		−16.9 (−20.9, −10.1) <0.001		−2.3 (−6.8, 5.3) 0.461	
AHI ₄ supine, events/hour	28.5 (16.5, 43.7)	−15.6 (−20.5, −9.4) <0.001		−13.3 (−18.8, −6.6) <0.001		2.2 (−3.4, 9.2) 0.464	
AHI _{3a} , events/hour	35.6 (23.9, 49.6)	−13.1 (−17.9, −7.8) <0.001		−14.5 (−19.2, −9.3) <0.001		−1.5 (−6.3, 3.8) 0.553	
HB ₄ , %.min/hour	33.2 (16.7, 65.0)	−16.5 (−21.6, −9.4) <0.001		−16.7 (−21.8, −9.6) <0.001		−0.2 (−5.4, 7.2) 0.950	
HB ₃ , %.min/hour	53.0 (31.0, 90.2)	−20.4 (−28.3, −10.1) 0.001		−22.3 (−29.8, −12.4) <0.001		−1.9 (−9.6, 8.4) 0.684	
ODI ₄ , events/hour	23.7 (15.0, 34.3)	−10.3 (−13.7, −6.3) <0.001		−10.0 (−13.5, −6.0) <0.001		0.3 (−3.3, 4.5) 0.883	
ODI ₃ , events/hour	32.2 (22.2, 44.1)	−12.1 (−16.1, −7.7) <0.001		−12.1 (−16.1, −7.6) <0.001		−0.01 (−4.2, 4.6) 0.998	
T90, %	7.7 (−0.4, 15.8)	−3.9 (−9.6, 1.8) 0.173		1.5 (−4.3, 7.3) 0.618		5.4 (−0.6, 11.3) 0.075	
TST, min	422.7 (379.4, 466.0)	−60.0 (−82.7, −37.2) <0.001		−37.7 (−60.9, −14.5) 0.002		22.3 (−1.4, 46.0) 0.065	
N1, %TST	14.4 (8.7, 20.1)	4.7 (1.3, 8.1) 0.007		1.04 (−2.4, 4.5) 0.552		−3.7 (−7.2, −0.1) 0.042	
N2, %TST	63.9 (58.7, 69.1)	6.4 (2.4, 10.4) 0.002		6.8 (2.7, 10.9) 0.001		0.4 (−3.7, 4.6) 0.835	
N3, %TST	7.9 (2.6, 13.3)	−1.1 (−0.6, 5.9) 0.507		2.7 (−0.58, 5.9) 0.106		3.7 (0.4, 7.0) 0.028	
REM, %TST	13.9 (10.1, 17.6)	−10.3 (−12.8, −7.7) <0.001		−10.8 (−13.4, −8.2) <0.001		−0.5 (−3.2, 2.1) 0.685	
SOL, min	7.1 (1.7, 12.4)	2.4 (−1.5, 6.2) 0.221		1.8 (−2.1, 5.7) 0.372		−0.6 (−4.6, 3.4) 0.759	
WASO, min	53.1 (17.9, 88.3)	39.6 (18.1, 61.2) <0.001		26.6 (4.7, 48.6) 0.018		−13.0 (−35.5, 9.5) 0.254	
Arousal index, events/hour	33.4 (23.0, 43.8)	0.35 (−5.0, 5.7) 0.896		−4.3 (−9.8, 1.1) 0.119		−4.7 (−10.3, 0.9) 0.099	

Analyses were conducted with mixed models. Viloxazine, N=21; Vilo-trazo, N=20.

AHI₄, apnoea-hypopnoea index with 4% oxygen desaturation; AHI_{3a}, apnoea-hypopnoea index with 3% oxygen desaturation and arousals; HB₃, hypoxic burden with 3% oxygen desaturation; HB₄, hypoxic burden with 4% oxygen desaturation; ODI₃, oxygen desaturation index with 3% oxygen desaturation; ODI₄, oxygen desaturation index with 4% oxygen desaturation; REM, rapid eye movement; SOL, sleep-onset latency; T90, sleep time under 90% oxygen desaturation; TST, total sleep time; Vilo-trazo, viloxazine-trazodone; WASO, wake after sleep onset.

Table 3 Participant reported outcomes and safety metrics

	Placebo N=24	Viloxazine vs placebo	Vilo-trazo vs placebo	Vilo-trazo vs viloxazine
	Estimate (95% CI)	Adjusted mean difference (95% CI) P value	Adjusted mean difference (95% CI) P value	Adjusted mean difference (95% CI) P value
Evening measurements				
PROMIS sleep impairment	53.3 (46.1, 60.5)	5.2 (1.0, 9.4) 0.016	3.8 (−0.5, 8.1) 0.080	−1.4 (−5.8, 3.0) 0.532
PROMIS sleep disturbance	51.4 (44.3, 58.4)	6.1 (2.4, 9.8) 0.002	6.5 (2.7, 10.3) 0.001	0.4 (−3.4, 4.3) 0.827
PROMIS fatigue	53.3 (47.5, 59.0)	6.7 (2.3, 11.0) 0.003	4.5 (0.0, 8.9) 0.050	−2.2 (−6.8, 2.4) 0.345
ESS	8.9 (4.8, 13.0)	1.3 (−0.2, 2.8) 0.084	2.1 (0.6, 3.7) 0.008	0.8 (−0.8, 2.4) 0.323
Evening SBP, mm Hg	121.3 (114.7, 128.0)	−0.8 (−4.3, 2.7) 0.666	2.6 (−1.0, 6.1) 0.151	3.4 (−0.3, 7.0) 0.071
Evening DBP, mm Hg	77.6 (71.9, 83.2)	1.5 (−1.9, 4.9) 0.378	4.0 (0.5, 7.4) 0.025	2.5 (−1.1, 6.0) 0.169
HR during sleep, beats/min	66.6 (59.7, 73.5)	3.5 (1.5, 5.5) 0.001	5.6 (3.6, 7.6) <0.001	2.1 (0.4, 4.2) 0.045
Next-morning measurements				
KSS	4.4 (2.8, 6.1)	0.8 (−0.06, 1.7) 0.069	0.7 (−0.2, 1.6) 0.121	−0.11 (−1.0, 0.8) 0.813
Morning SBP, mm Hg	119.5 (113.4, 125.6)	2.9 (−0.6, 6.4) 0.105	0.5 (−3.1, 4.1) 0.766	−2.4 (−6.0, 1.3) 0.204
Morning DBP, mm Hg	78.5 (72.0, 85.0)	2.9 (−0.2, 6.0) 0.069	1.5 (−1.6, 4.7) 0.339	−1.4 (−4.6, 1.9) 0.409
SDMT oral score	46.4 (36.6, 56.1)	0.60 (−2.3, 3.5) 0.693	−19 (−4.9, 1.1) 0.206	−2.5 (−5.6, 0.6) 0.107
SDMT written score	43.9 (35.5, 52.3)	−1.0 (−3.8, 1.8) 0.489	−3.7 (−6.6, −0.8) 0.012	−2.7 (−5.7, 0.2) 0.069

Analyses were conducted with mixed models. Viloxazine, N=21, Vilo-trazo, N=20.
DBP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; HR, average heart rate; KSS, Karolinska Sleepiness Scale; PROMIS, patient-reported outcomes measurement information system; SBP, systolic blood pressure; SDMT, Symbol Digit Modalities Test; Vilo-trazo, viloxazine-trazadone.

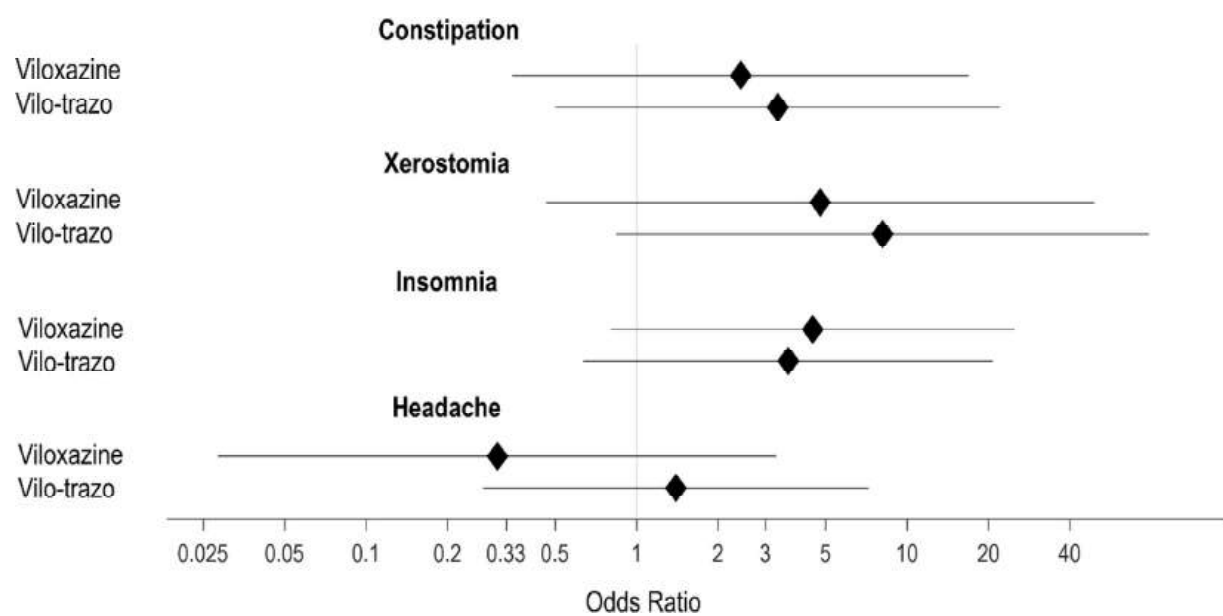


Figure 3 OR for common side effects complained by participants on viloxazine and viloxazine-trazodone (vilo-trazo) compared with placebo.

Table 4 Effect of the interventions on AHI₄ divided by subgroups

	Placebo	Viloxazine vs placebo	Vilo-trazo vs placebo	Vilo-trazo vs viloxazine
	Estimate	Estimate (95% CI) P value	Estimate (95% CI) P value	Estimate (95% CI) P value
High AHI ₄ (N=8) AHI ₄ >31 events/hour	54.6	−31.4 (−40.2, −20.5) <0.001	−32.8 (−40.0, 24.3) <0.001	−1.4 (−9.3, 8.2) 0.741
Low AHI ₄ (N=7) AHI ₄ <17 events/hour	10.5	−2.9 (−7.1, 2.9) 0.270	−1.3 (−6.0, 5.0) 0.636	1.7 (−4.0, 9.9) 0.605
High V _{COMP} (N=7) V _{COMP} >7.8% _{eupnoea}	39.7	−13.9 (−24.4, −0.7) 0.041	−21.3 (−29.6, −10.6) 0.001	−7.5 (−16.4, 4.5) 0.189
Low V _{COMP} (N=8) V _{COMP} ≤4.3% _{eupnoea}	29.1	−16.7 (−23.1, −8.1) 0.002	−7.3 (−15.1, 2.2) 0.116	9.4 (0.9, 20.0) 0.030
High BMI (N=8) BMI>34 kg/m ²	29.8	−23.0 (−32.5, −11.7) <0.001	−31.8 (−38.2, −24.2) <0.001	−8.8 (−16.3, 0.4) 0.060
Low BMI (N=8) BMI<28 kg/m ²	26.4	−14.0 (−20.8, −4.4) 0.009	−5.9 (−14.3, 4.7) 0.235	8.0 (−0.9, 19.5) 0.080
High ESS (N=8) ESS>11	36.1	−16.2 (−24.4, −5.9) 0.005	−17.8 (−26.0, −7.2) 0.004	−1.8 (−6.5, 5.2) 0.520
Low ESS (N=6) ESS≤8	10.7	−1.5 (−5.2, 3.3) 0.475	−3.3 (−7.4, 2.5) 0.204	−1.6 (−10.1, 9.6) 0.742

All parameters explored represent baseline values and were based on top and bottom tertiles to explore differences in outcomes. All values represent a change in (AHI₄, events/hour).

AHI₄, apnoea hypopnoea index with 4% desaturation; BMI, body mass index; ESS, Epworth Sleepiness Scale.

nausea, light-headedness and chills after 2–3 days of viloxazine. All these adverse events were deemed probably associated with the drug administration in the analysis of relatedness.

Predictors of treatment response

In the subgroup of patients with higher baseline AHI₄ (>31 events/hour, top tertile), vilo-trazo and viloxazine decreased AHI₄ by 60% and 57%, respectively; interventions had no observable effect in the subgroup with lower baseline AHI₄ (<17 events/hour, bottom tertile; table 4). In individuals with high baseline V_{COMP} (>7.8%_{eupnoea}), AHI₄ fell by ~54% on vilo-trazo and by ~35% on viloxazine alone versus placebo; effects of vilo-trazo in low V_{COMP} (−4.3% of V_{COMP}_{EUPNOEA}) were minimal. Efficacy also appeared greater in patients with higher BMI (>34 kg/m²), in whom AHI₄ was lowered by ~60% vs placebo but was reduced within lower BMI (<28 kg/m²). Similarly, vilo-trazo and viloxazine alone reduced AHI₄ by ~50% and 45%, respectively, only in people with a high baseline ESS (≥11). Other baseline endotypic traits (loop gain, V_{PASSIVE}, arousal threshold) were explored, but no meaningful differential effects on AHI₄ between subgroups were observed.

Effects of treatment dose on efficacy using at-home oximetry

At the lower run-in dose, ODI4 from at-home oximetry was reduced on both viloxazine (−4.8 (−7.4, −1.9) events/hour, p=0.002) and vilo-trazo (−5.3 (−7.8, −2.4) events/hour, p=0.001) compared with placebo (13.3 events/hour). There was no significant effect of high dose versus low dose on efficacy (per treatment×dose interaction) in either viloxazine (1.65 (−3.2, 7.4) events/hour, p=0.528) or vilo-trazo (0.9 (−3.7, 6.5) events/hour, p=0.719).

DISCUSSION

The main finding of this study is that the combination of viloxazine and trazodone reduces OSA severity compared with placebo by roughly 54%. Despite the recognised REM suppression associated with noradrenergic drugs, this reduction in severity persisted even in non-REM sleep, with AHI4 drops of ~50% and ~58% on vilo-trazo and viloxazine versus placebo, respectively. Vilo-trazo improved total sleep time and deep sleep compared with viloxazine alone. In contrast to viloxazine alone, it did not exacerbate subjective symptoms such as fatigue and sleep impairment, suggesting that trazodone could somewhat mitigate the noradrenergic effects of viloxazine. Despite meeting the study outcomes, vilo-trazo increased self-reported sleepiness (ESS) and was associated with several

side effects. Nevertheless, this study underscores that noradrenergic reuptake inhibitors in combination with a hypnotic are a viable strategy for OSA management and require further investigation.

Aspects of pharmacodynamics

For the first time, the current study demonstrated that the noradrenergic reuptake inhibitor viloxazine provides a substantial reduction in OSA severity. Given that OSA severity was reduced similarly when viloxazine was administered with or without trazodone, and that trazodone alone is not expected to have a potent effect on OSA,¹³ our study suggests that the main effect on OSA severity is driven by viloxazine. This further builds on previous work on noradrenergic agents combined with antimuscarinic or hypnotics in improving OSA severity.^{6 8 9 17–20} Notably, vilo-trazo systematically reduced all indexes of OSA severity, compared with the effect of atomoxetine and trazodone, which reduced only AHI₄, but not in AHI3A.²⁰ Overall, the efficacy of viloxazine was similar to selective noradrenergic reuptake inhibitors, atomoxetine and reboxetine,^{3 21} which in contrast to less specific noradrenergic agents, milnacipram or duloxetine, that appeared less efficacious.²² In combination, data suggest that noradrenergic reuptake inhibitors with fewer dual or off-target effects on the noradrenalin transporter are preferred for reducing OSA severity and should be prioritised for future investigation.

Addition of trazodone appeared to mitigate some of the wake-promoting noradrenergic effects of viloxazine that are disruptive of sleep continuity. PROMIS questionnaires, total sleep time and N3 sleep duration shifted favourably with the combination compared with viloxazine alone. However, the differences in total sleep time and WASO between treatment arms were minor and not statistically significant. These findings should, therefore, be interpreted cautiously and considered exploratory. The effect of trazodone was similar to that of antimuscarinics when combined with the noradrenergic component, consistent with the notion that a key function of antimuscarinics when paired with a noradrenergic may lie with their hypnotic effects. In the current study, unlike others, we observed that the addition of trazodone increased N3 sleep duration. While total sleep time and additional sleep quality measures remained inferior to placebo on vilo-trazo, a fine-tuning of dosage of viloxazine or trazodone or a combination with different hypnotics (ie, oxybutynin plus zolpidem), may minimise this concern.²³ Indeed, reductions in ODI4 from at-home oximetry measurement were similar on run-in and full dose of vilo-trazo, supporting the notion that efficacy could be maintained at a lower dose. Nevertheless, further investigation is warranted.

Safety considerations

Similarly, to previous trials involving noradrenergic drugs,^{3,17} vilotrazo was associated with instances of xerostomia and insomnia. However, a higher incidence of constipation was observed compared with other studies (figure 3). One in five patients dropped out on the low dose of therapy, suggesting a lower dosage of viloxazine could potentially lead to more favourable outcomes.

Mild increases in heart rate were anticipated and observed in previous studies due to the sympathomimetic effect of viloxazine.^{3,6} The mild increase in evening diastolic blood pressure on vilotrazo was not supported by increases in morning values or systolic levels or with viloxazine alone. Diastolic blood pressure changes have been absent in most,^{6,17} but not all trials³ of noradrenergic combination interventions.

The increase in ESS observed with vilotrazo is comparable to the effect seen after CPAP withdrawal²⁴ and has not been reported in previous trials of other noradrenergic combinations. The significance of this increase is further validated by the single-digit modality test performance on vilotrazo, which decreased by ~4 points vs placebo—a drop accepted as clinically significant.²⁵ Trazodone is not typically considered to induce a ‘hangover effect’¹⁴ and has been used safely at higher doses to raise the arousal threshold in individuals with OSA.¹³ There may be instances in which trazodone’s half-life can increase.^{26,27} Moreover, side effects are dose-dependent,¹⁴ such that the dosage of trazodone used in this study might have been too high (previous studies on insomnia have shown that 50 mg of trazodone is sufficient for sleep maintenance). Of note, reducing the dosage of viloxazine would potentially decrease the ‘need’ to offset its noradrenergic effects. In addition, increased morning sleepiness might be of lesser concern if investigated in a targeted subgroup of patients with comorbid OSA and insomnia.

Physiological considerations

Participants with good muscle compensation (high V_{COMP}) showed better responses to vilotrazo compared with those with low V_{COMP} . This contradicts previous assumptions suggesting that interventions targeting a specific endotype are more likely to be effective in individuals with an abnormal endotype. Recent studies, however, started to indicate that treatment responders are often those with the least severely altered endotype, since more readily ‘fixable’. For example, oral appliances work best in patients with milder collapsibility,²⁸ and acetazolamide in those with lower loop gain,¹⁸ despite these characteristics not being the theoretical targets of the intervention (ie, oral appliances and acetazolamide reduce collapsibility and loop gain, respectively). Similarly, individuals with good muscle responsiveness exhibit better response to interventions targeting pharyngeal muscles, including hypoglossal nerve stimulation, acetazolamide and atomoxetine-oxybutynin,^{5,18,29} as a functional increase in muscle force and airway patency may be more readily achieved with muscle stimulation, while people with less muscle compensation may have difficulty translating neural activation into airway patency. Of note, vilotrazo led to a further ~30% AHI₄ drop versus viloxazine alone in people with high V_{COMP} (table 4), which implies a potential synergistic effect of trazodone on the stimulation of the upper airway muscles in this group,³⁰ an expected effect of raising the arousal threshold. Preliminary data demonstrated that reduced V_{COMP} is associated with complete lateral pharyngeal wall collapse,³¹ a site of collapse that may be particularly challenging to improve with muscle activation. Therefore, more than one intervention may be required to manage these OSA patients. Additionally, while the reduction in REM sleep observed in this study may contribute to improvements in OSA severity, our results indicate that the magnitude of overall AHI and non-REM AHI reduction with treatment was similar, suggesting that it is unlikely that the reduction in REM duration could contribute to the whole-night efficacy observed. Notably, longer-term studies using similar noradrenergic and antimuscarinic combinations have shown that REM sleep often returns over time without corresponding decline in improvements to breathing disturbances¹⁷; longer-term studies of the current combination are needed to confirm this notion.

In this study, patients with higher BMI responded better to both active treatments, and in particular to vilotrazo (a further 30% drop), which is somewhat in contrast with previous preliminary findings where low BMI was a predictor for response to atomoxetine-oxybutynin.³² One possible explanation for this discrepancy is that non-obese OSA patients often have a more heterogeneous OSA pathogenesis characterised by other abnormal traits, such as a low arousal threshold.³³ Regardless, obese OSA patients typically have more respiratory events than their non-obese counterparts, and thus are more susceptible to symptoms and cardiovascular risk, making treatment more compelling. To further support this notion, patients with more severe OSA or sleepiness at baseline greatly responded to the active treatments compared with milder/non-sleepy patients. These findings may help guide those most likely to benefit from such a therapy, and thus potential targets for future clinical studies.

Methodological considerations

This study has several limitations: its small sample size did not allow for a conclusive assessment on patients reported outcomes (especially in consideration of the 20% drop-out rate). However, there was a clear signal for objective reduction in OSA severity and objective and subjective sleep disruption, especially when viloxazine was administered alone. This relatively short duration of 1 week of full dose intervention was sufficient to detect an efficacy signal and characterise the early safety profile of the agents studied, and ultimately indicate that dosing could be further optimised.

Lack of an arm with trazodone alone is a limitation; however, based on previous trials,¹³ we expected minimal efficacy (AHI) of this hypnotic in patients with OSA.

The endotypes used to explore treatment response were assessed non-invasively without gold-standard procedures. However, we note that all the most important recent studies investigating the effects of pharmacotherapies on OSA severity have followed a similar approach to avoid concerns relating to effects of invasive instrumentation on sleep.

CONCLUSIONS

The combination of viloxazine and trazodone demonstrated significant reductions in AHI and hypoxic burden. Viloxazine, in the combination, is the third noradrenergic reuptake inhibitor found to be efficacious in OSA. It was found to be the primary driver of AHI reduction, while trazodone partially mitigated some of the noradrenergic side effects of viloxazine. People with high V_{COMP} and high BMI at baseline had the strongest responses to vilotrazo. The current study supports the notion that pairing a noradrenergic agent with a hypnotic—which does not necessarily need to be an antimuscarinic—is a promising strategy for OSA treatment. However, since vilotrazo reduced total sleep time and increased ESS compared with placebo, future studies are warranted to determine whether a reduced dose of viloxazine (and potentially trazodone) could improve sleep-related measures and minimise side effects while maintaining therapeutic efficacy.

Acknowledgements We would like to thank all the technical and research staff at the Brigham and Women’s Hospital, Santa Monica Clinical Trial, and Clayton Sleep Institute for their support in coordinating and managing the day-to-day study operations.

Contributors AAi is the guarantor of this work and accepts full responsibility for its overall content, the conduct of the study, access to the data and the decision to publish. Study design: LT-M and LM; Data collection: MK, DN and JO; Data analysis: AAi, LG and LM; Manuscript drafting: AAi and LM; Interpretation of results: all authors; Review of the manuscript for important intellectual content: all authors.

Funding This study was funded by Apnimed.

Competing interests AAi (corresponding author) has served as a consultant for Apnimed Inc in the past. HP, LG and LT-M are employees at Apnimed. DV serves as a consultant for Inspire Medical Systems. AAi reports grant support from Somnifix and serves as a consultant for Somnifix, Respicardia, Eli Lilly, Inspire, Cerebra and Apnimed. AAZ and AW serves as a consultant for Apnimed, Nox, Inspire, Mosanna and Takeda. He has received grants from Prosummus. He also has a financial interest in Apnimed Corp., a company developing pharmacological therapies and wearable oximetry devices for sleep apnoea. AW interests were reviewed and are managed by Brigham and Women’s Hospital and Partners HealthCare in accordance with their conflict-of-interest policies. SS received grants from Apnimed, Prosummus and Dynaflex, and personal fees from Apnimed, Merck, Nox Medical, LinguaFlex, Lilly, Respicardia and Foreport. LM received Apnimed grant funding for this study.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants. The study protocol was approved by WIRB-Copernicus Group Institutional Review Board. 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 on reasonable request. 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.

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ARTIGO ORIGINAL

Impacto da ventilação não invasiva de longa duração nas exacerbações graves e na sobrevivência na DPOC: estudo de coorte nacional francês com modelos multiestado

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/thorax-2024-222392>).

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Received 27 August 2024
Accepted 18 February 2025
Published Online First 19 May 2025



► <https://doi.org/10.1136/thorax-2025-222321>



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To cite: Pépin JL, Herquelot E, Denis H, et al. Thorax 2025;80:616–623.

RESUMO

Justificação A doença pulmonar obstrutiva crônica (DPOC) é a indicação mais comum para a ventilação não invasiva domiciliária (NIV), mas os dados sobre os resultados a longo prazo são limitados.

Objetivo Esta análise baseada em modelos multiestado estimou o impacto da continuação versus cessação da terapia com NIV nas transições entre três estados clínicos distintos da doença.

Métodos Os dados do modelo foram obtidos a partir da base de dados do sistema nacional francês de reembolso de seguros de saúde, incluindo indivíduos com ≥40 anos, diagnóstico de DPOC e pelo menos um registro de reembolso de NIV entre 2015 e 2019.

Avaliação e principais resultados Foram incluídos dados de 49 503 doentes iniciados em NIV (idade mediana: 70 anos; 51,2% homens; mediana de 1 exacerbação no ano anterior). Durante o período de estudo, registraram-se 80 361 exacerbações graves e 18 125 óbitos (dos quais 7 805 ocorreram durante exacerbações graves). Nos modelos multiestado, a continuação da NIV esteve associada a uma redução significativa na transição para morte: A partir de exacerbação grave: HR 0,84 (IC 95%: 0,79–0,91), sem exacerbação prévia: HR 0,88 (IC 95%: 0,83–0,93) A continuação da NIV, em comparação com a sua cessação, não teve efeito significativo na transição de estado sem exacerbação para exacerbação grave (HR 0,98; IC 95%: 0,95–1,00), mas esteve significativamente associada a uma transição mais lenta de exacerbação grave para estado sem exacerbação (HR 0,87; IC 95%: 0,84–0,89).

Conclusão Esta análise com modelos multiestado demonstrou que o uso prolongado de NIV domiciliária está associado a um menor risco de transição para morte em doentes com DPOC, embora não esteja associado a uma recuperação mais rápida após exacerbações graves. Estes dados reforçam os potenciais benefícios da NIV de longa duração na redução da mortalidade e podem servir como evidência adicional para apoiar recomendações clínicas baseadas na evidência.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common and debilitating lower respiratory tract illness. There were 202.3 million prevalent cases of COPD and 3.3 million deaths related to COPD in 2019, and in the same year, COPD caused the loss of 74.4 million disability-adjusted life-years.¹ It has recently been estimated that there will be nearly 600 million cases of COPD worldwide by 2050, a 23% increase compared with 2020.² For several reasons, including a systemic failure to limit the availability and use of tobacco products, ongoing exposure to air pollution, non-specific diagnostic approaches and a lack of disease-modifying treatment options, COPD is recognised as a global health crisis.³ COPD

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Chronic obstructive pulmonary disease (COPD) is a highly prevalent chronic condition and a major cause of disability and death. Chronic hypercapnic COPD is the most common indication for long-term domiciliary noninvasive ventilation (NIV). However, existing evidence for the mid- to long-term impact of domiciliary NIV on hard clinical outcomes remains limited and inconsistent.

WHAT THIS STUDY ADDS

► This study provides real-world evidence from a large unselected cohort, showing that continuation of long-term domiciliary NIV therapy is associated with a lower risk of all-cause death in patients with chronic hypercapnic COPD. It also suggests that early initiation of domiciliary NIV may reduce the rate of severe exacerbations and mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► These findings support earlier and sustained use of domiciliary NIV in selected patients with hypercapnic COPD, potentially informing clinical decision-making and guidelines. They also highlight the value of multistate models for analysing the complex trajectories of chronic respiratory diseases, paving the way for future research on personalized treatment strategies.

is also associated with significant cost burden, with total COPD-related direct costs in Europe estimated to be €38.6 billion.⁴ Furthermore, COPD has a negative impact on health status and quality of life. Hypercapnic COPD is one of the main indications for long-term domiciliary non-invasive ventilation (NIV).^{5–8} However, the current level of evidence for the mid- to long-term impact of NIV on hard outcomes in chronic hypercapnic COPD is limited. The majority of studies included in a 2021 Cochrane review had an unblinded design and were

therefore potentially biased.⁵ In addition, the combined number of participants in all randomised trials to date is <500. Based on data available at the time, the Cochrane review concluded that chronic NIV therapy improved admission-free survival, but did not appear to have a positive impact on all-cause mortality.⁵ Therefore, there is clearly a need for additional evidence regarding the long-term benefit of domiciliary NIV in COPD.

Multistate models are a reference methodology for determining the impact of an intervention on specific but inter-related outcomes, allowing consideration of individuals' progression to multiple events of interest, and transitions to intermediate events (eg, exacerbations in the case of COPD).^{9–12} In COPD, multistate modelling was applied to data from the Efficacy and Safety of Triple Therapy in Obstructive Lung Disease study to assess the transitions between exacerbations and mortality, and showed that the occurrence of severe exacerbations had an acute and chronic effect on mortality risk.¹³ Furthermore, a multistate model with transitions between COPD diagnosis, readmission and all-cause mortality was used to evaluate the impact of offspring and their educational level on the risk of readmission or death in older adults with COPD.¹⁴

The French national health insurance reimbursement system database ('Système national des données de santé'; SNDS) covers 99% of individuals in the French health system.^{15–18} This analysis of the MONTANA (HoMe NOn INvasive VenTilAtion iN FrAnce) cohort study estimated the impact of NIV therapy continuation versus cessation on transition intensities between three states (without severe exacerbation, severe exacerbation and death) using SNDS data from individuals with COPD who were started on domiciliary NIV to inform a multistate Markovian model.

METHODS

Study design and data source

Data were extracted from the SNDS, which covers 99% of the French population and collects individual pseudoanonymised data on health spending reimbursements for participants in nearly all French health insurance schemes.¹⁸ Based on the availability of comprehensive mortality information, data for this analysis was restricted to individuals in the general scheme (for private sector employees), which covers about 76% of the French population (approximately 40 million adults). Retirees, unemployed individuals and welfare beneficiaries are covered by the scheme that corresponds to their previous occupation and were included in the analysis.

The information included in the SNDS includes socio-demographic data (age, sex, area), all healthcare expenses (including outpatient visits, reimbursed medication, medical procedures, hospital admission diagnoses and procedures) and date of death. It also contains a list of 30 long-term chronic diseases coded using the International Classification of Diseases 10th revision (ICD-10) for which full reimbursement of disease-related healthcare expenses is granted; details of laboratory test results or other examinations are not included.

Study population

Individuals aged ≥40 years who had at least one reimbursement for domiciliary NIV between 1 January 2015 and 31 December 2019 were identified based on ICD-10 codes, treatment with COPD medications and the occurrence of COPD-related hospitalisations (see online supplemental methods for full details). Those who had not received NIV treatment in the previous 5 years were included (ie, incident cases). The date of first delivery of domiciliary NIV during the study inclusion period was defined as the index date. Data collection for included individuals continued until December 2020. Claims data from the 5 years preceding domiciliary NIV initiation (ICD-10 codes and medications) were used to identify comorbidities and relevant medical history, and to confirm incident status. Cessation of long-term NIV was deemed to have occurred when there were no longer any reimbursement codes for this therapy. Individuals with, or hospitalisation for, neuromuscular diseases or cystic fibrosis were excluded. Those who had early

interruption of domiciliary NIV (≤3 months after therapy initiation) were also excluded because the exposure to interventions was considered too short to accurately reflect the long-term impact of NIV on the hard clinical outcomes that were included in our model. Acute therapy with NIV was represented by hospitalisation codes and was not included in this analysis.

Outcomes and definitions

Severe COPD exacerbations that required hospitalisation were identified based on the algorithm published by the French public health institute (INV)¹⁹ (codes are detailed in the online supplemental file 1). Absence of severe COPD exacerbation was defined as the absence of any of the codes used to define a severe exacerbation of COPD. Transition from 'without severe exacerbation' to 'severe exacerbation' was defined as occurring on the date of hospitalisation for a severe exacerbation of COPD. Transition from 'severe exacerbation' to 'without severe exacerbation' was defined as occurring on the date of hospital discharge for severe COPD exacerbation. Transition from 'severe exacerbation' to 'death' was defined as occurring on the date of death recorded in the SNDS.

Statistical analysis

Details of the study population are presented using descriptive statistics (median and IQR for quantitative variables, frequency and percentage for qualitative variables).

Kaplan-Meier estimates for the occurrence of NIV discontinuation (death or end of NIV) were used to determine the duration of NIV therapy. The cumulative incidence of end of treatment considering death before end of treatment as a competing event was estimated using the Aalen-Johansen method. If the time between the end of the NIV coverage period and the next delivery was <30 days, an individual was considered to be treated continuously for the entire period. If hospitalisation occurred within 30 days after the end of the NIV coverage period, an individual was considered to have been treated with NIV during hospitalisation, and therefore time in hospital contributed to the overall NIV treatment duration. Finally, if the end of the follow-up took place within 30 days of the end of NIV, an individual was considered to be on NIV at the end of follow-up.

The occurrence of severe exacerbation and/or all-cause death was studied using a multistate model (with Markovian hypothesis) that included three states: 'without severe exacerbation', 'with severe exacerbation' and 'death'.^{9,20} All possible transitions between these three states were studied by considering the occurrence and time of occurrence for each transition (figure 1). Any one individual could have multiple different transitions during follow-up. The multistate model based on a stratified Cox model with clock reset approach allowed estimation of the hazard of each transition,⁹ adjusted for socio-demographic patient characteristics at inclusion and NIV usage status.

Based on our recent identification of four different health trajectories before initiation of domiciliary NIV for COPD,¹⁷ we also tested the interaction between health trajectory cluster and time-varying NIV utilisation (continuation vs cessation). The association between each hazard of transition and NIV usage status was presented for each of the four clusters of health trajectories before NIV. Cluster 1 included patients started on domiciliary NIV in an ambulatory setting or after ≤1 hospitalisation for a severe event/exacerbation (ie, early NIV initiation), Cluster 2 had domiciliary NIV initiation after ≥2 hospitalisations for severe COPD exacerbations in the previous 6 months, Cluster 3 started domiciliary NIV after frequent hospitalisations for severe COPD exacerbations in the previous year and Cluster 4 had initiation of domiciliary NIV after many long-lasting COPD-related hospitalisations (ie, late NIV initiation).¹⁷

Statistical analyses were performed using SAS 9.4 software.

RESULTS

Study population

A total of 49 503 incident patients initiated on long-term NIV were included in the analysis (online supplemental figure S1). The study population was elderly and had multiple comorbidities (most often

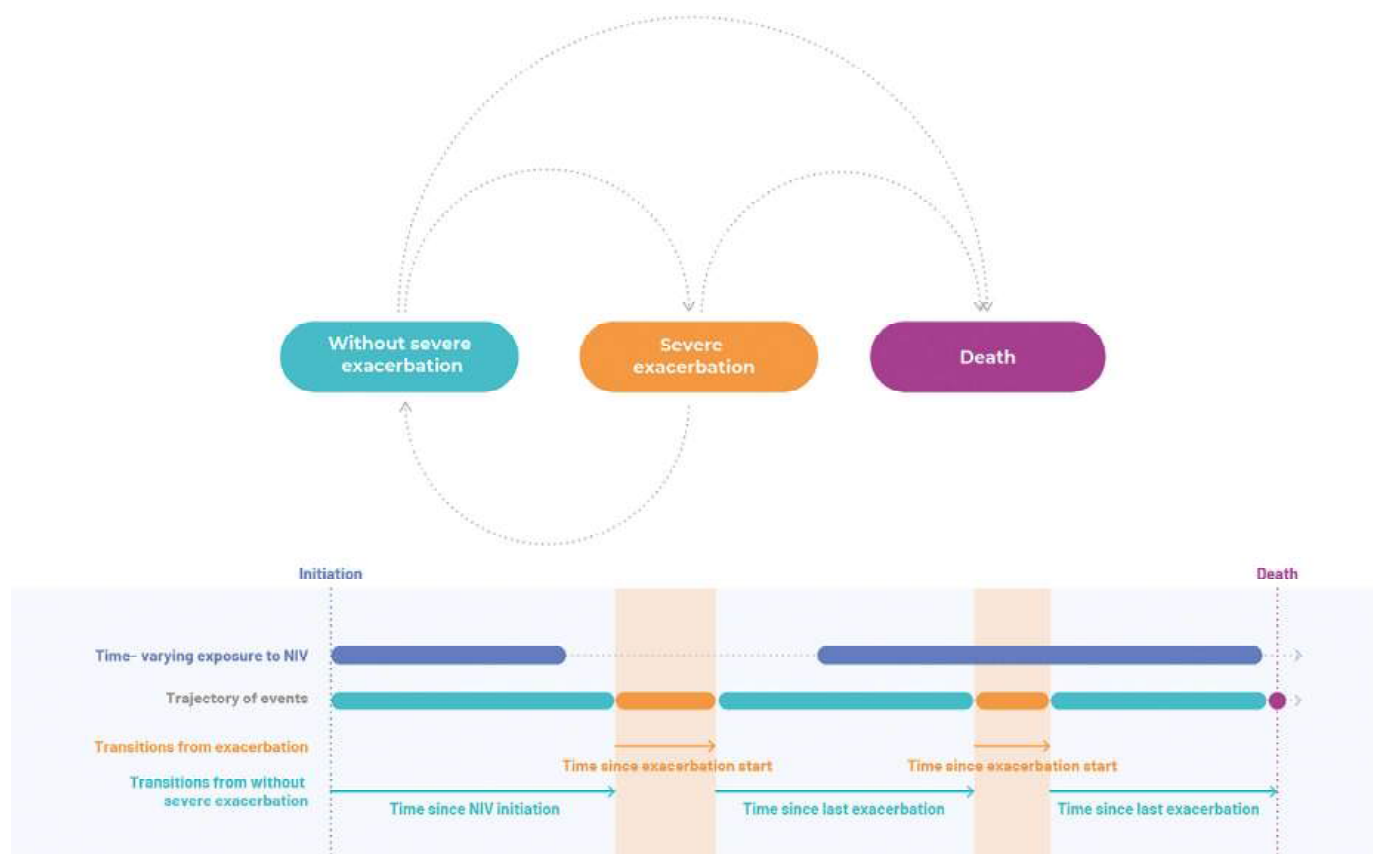


Figure 1 Multistate model components, including transitions between states and the time of occurrence of each transmission. NIV, non-invasive ventilation.

hypertension and cardiovascular disease) (table 1). During follow-up, there were a total of 80 361 severe exacerbations and 18 125 deaths (of which 7805 were deaths during a severe exacerbation)

(figure 2). The crude rate of exacerbation for the observation was 0.72 per patient-year during NIV cessation and 0.93 per patient-year during NIV continuation.

Table 1 Baseline demographics and characteristics of the study population	
	Participants (n=49 503)
Age, years	70 (62, 79)
Male sex, n (%)	25 337 (51.2)
Number of exacerbations requiring hospitalisation in the year before NIV initiation	1 (0–2)
Received bronchodilator, corticosteroids, LABA and/or LAMA*, n (%):	
In the 6 months either side of the index date	39 164 (79)
Any time in the pre-index or follow-up periods	48 572 (89)
Medical history within the previous 5 years*, n (%)	
Undernutrition	13 821 (28)
Morbid obesity	23 280 (47)
Obstructive sleep apnoea	17 209 (35)
Hypertension or cardiovascular disease	37 576 (76)
Diabetes	14 854 (30)
Psychiatric diseases, anxiety or depression	18 640 (38)
Charlson comorbidity index, n (%)	
0	3464 (7)
1–2	38 698 (78)
3–4	6884 (14)
≥5	457 (1)
Values are median (IQR) or number of patients (%).	
*Based on drug/disease coding, as detailed in the online supplemental file 1.	
LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; NIV, non-invasive ventilation.	

NIV therapy
NIV was initiated in the ambulatory setting in 20% of participants and NIV was added to long-term oxygen therapy in 51%. For health trajectories before NIV initiation,¹⁷ 32 357 individuals (65.4%) were in Cluster 1, 6003 (12.1%) were in Cluster 2, 10 527 (21.3%) were in Cluster 3 and 616 (1.2%) were in Cluster 4. Mean duration of NIV therapy was 2.86±0.01 years (median 2.20 years (IQR 2.15–2.24)). The probability of discontinuing NIV therapy

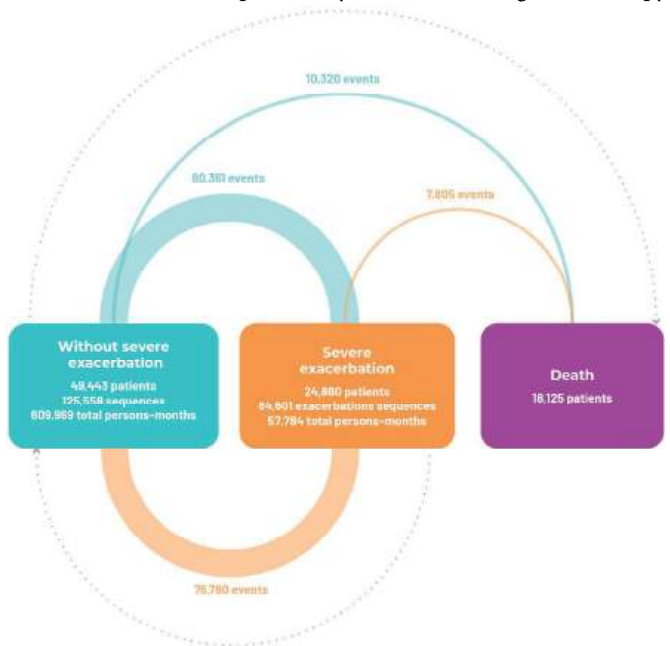


Figure 2 Number of events and transitions.

was 31% at 1 year (including 17% due to death) and 48% at 2 years (including 26% due to death).

Multistate models

Transition from 'without exacerbation' to 'severe exacerbation'

The adjusted risk of transitioning from a state without severe exacerbation to a severe exacerbation was not significantly different between individuals who continued versus ceased NIV therapy (HR 0.98, 95% CI 0.95 to 1.00; $p=0.09$) (figure 3A).

The adjusted risk of transition from without exacerbation to severe exacerbation significantly increased with age, was higher in males versus females, in those with a higher comorbidity burden, in individuals with vs without undernutrition or anxiety/depression/psychiatric disease, in those receiving long-term oxygen therapy at the time of NIV initiation and in those in Cluster 2, 3 or 4 versus Cluster 1. Conversely, the adjusted risk of transition from without exacerbation to severe exacerbation was significantly lower in people with vs without diabetes or obesity (figure 3A).

Transition from 'without exacerbation' to 'death'

The adjusted risk of transition from without severe exacerbation to death was significantly lower in individuals who continued ver-

sus ceased NIV therapy (HR 0.88, 95% CI 0.83 to 0.93; $p<0.01$) (figure 3B). Other significant risk factors for this transition were older age (>65 years vs 40–44 years), male versus female sex, comorbidity burden, having hypertension/cardiovascular disease, undernutrition or depression/anxiety/psychiatric disease and for individuals in Cluster 2 or 3 versus Cluster 1; in contrast, this transition risk was lower in individuals with versus without obesity and in those receiving long-term oxygen therapy at the time of NIV initiation (figure 3B).

Transition from 'severe exacerbation' to 'death'

The adjusted risk of death during a severe exacerbation (transition from exacerbation to death) was significantly lower in individuals who continued versus ceased NIV therapy (HR 0.84, 95% CI 0.79 to 0.91; $p<0.01$) (figure 3C). The adjusted risk of death during a severe exacerbation was also significantly increased in individuals aged >65 versus 40–44 years, males versus females, when comorbidity burden was higher and in individuals with versus without hypertension/cardiovascular disease or undernutrition, and was significantly lower in individuals in Cluster 2, 3 or 4 versus Cluster 1, and those with versus without depression/anxiety/psychiatric illness or obesity (figure 3C).

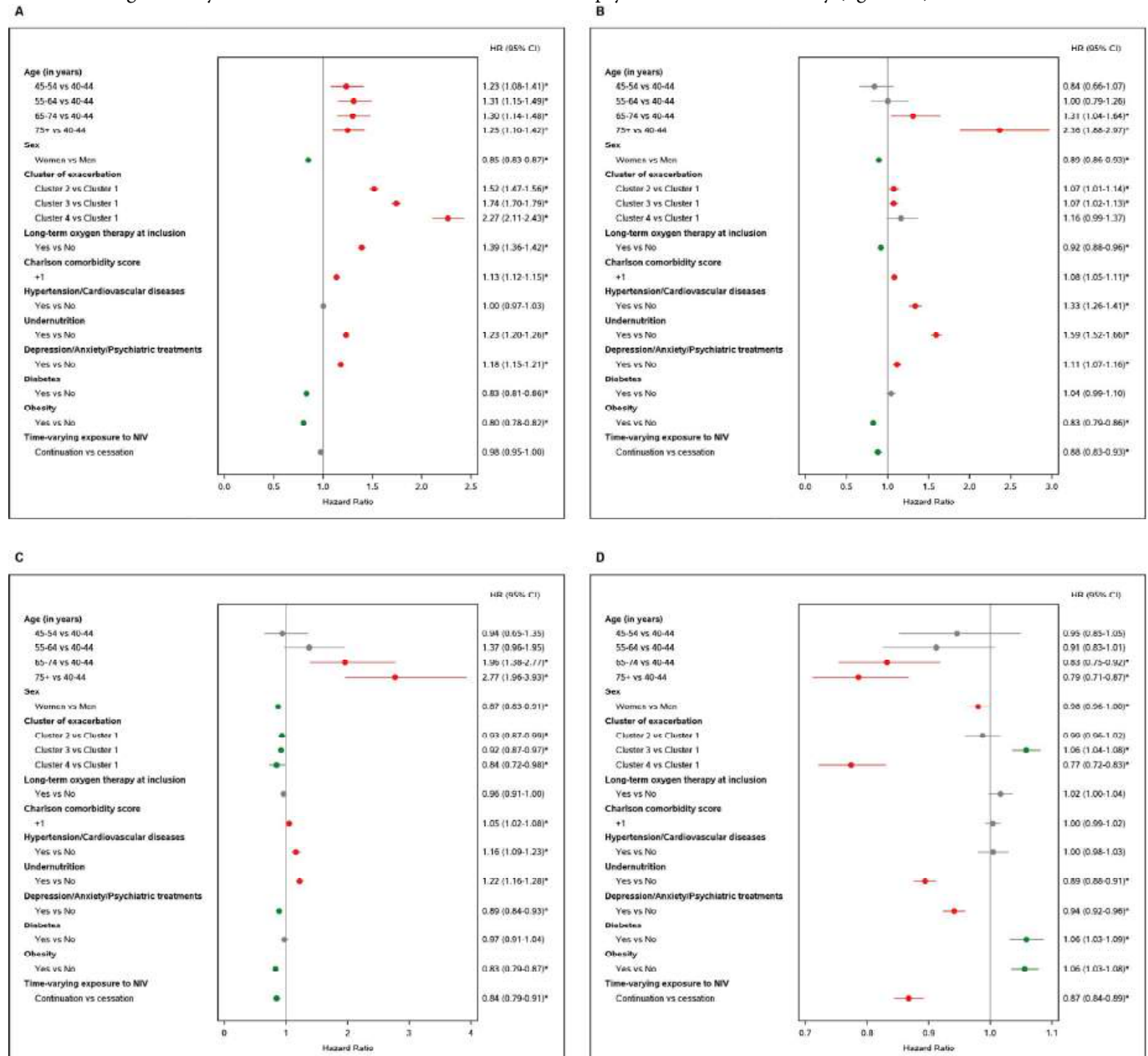


Figure 3 Overall population multistate models for the adjusted risk of transition from: (A) without severe exacerbation to severe exacerbation; (B) without severe exacerbation to death; (C) severe exacerbation to death; and (D) severe exacerbation to without severe exacerbation (recovery). Values are HR and 95% CI. * $p<0.05$. NIV, non-invasive ventilation.

Transition from 'severe exacerbation' to 'without exacerbation'

The adjusted risk for transitioning from severe exacerbation to without exacerbation (recovery) was significantly lower in individuals who continued versus ceased NIV (HR 0.87, 95% CI 0.84 to 0.89) (figure 3D). Other significant risk factors for slower recovery from severe exacerbation were aged ≥ 65 versus 40–44 years, undernutrition, having depression/anxiety/psychiatric treatments and being in Cluster 4 versus Cluster 1. In contrast, the transition from severe exacerbation to recovery was significantly faster in individuals with diabetes or obesity, and in those who were in Cluster 3 versus Cluster 1 (figure 3D).

Analysis by health trajectory before NIV initiation cluster

The risk of transitioning from without exacerbation to severe exacerbation (HR 0.88, 95% CI 0.85 to 0.92) (figure 4A) and from without exacerbation to death (HR 0.81, 95% CI 0.75 to 0.87) (figure 4B) was significantly lower for individuals in Cluster 1 who continued NIV versus ceased NIV. The risk of transitioning from a severe exacerbation to death was significantly lower for individuals in both Cluster 1 and Cluster 3 who continued versus ceased NIV (HR 0.82, 95% CI 0.74 to 0.90 and HR 0.76, 95% CI 0.64 to 0.91, respectively) (figure 4C). There was no interaction by cluster for the transition from exacerbation to without exacerbation (figure 4D).

DISCUSSION

This study of a large population of individuals with COPD started on long-term domiciliary NIV used multistate models to analyse transition intensities between three clinically relevant states: 'without exacerbation', 'severe exacerbation' and 'all-cause death'. In adjusted models for the overall population, we found that continuing domiciliary NIV therapy was associated with reduced risk of transitions to death, from both severe exacerbation and exacerbation-free states, compared with NIV cessation. In contrast, continuation versus cessation of long-term domiciliary NIV had no significant influence on transitions to severe exacerbation and did not accelerate recovery from severe exacerbation. However, long-term domiciliary NIV therapy did prevent transitions to severe exacerbation in individuals who had less severe COPD and early NIV initiation (Cluster 1). Overall, several other significant predictors of transitions to severe exacerbation and/or death were also identified.

The multistate Cox model used to study associations between each transition and time-varying exposure to NIV (ie, continuation or cessation) was adjusted for patient characteristics at the time of NIV initiation. The multistate model approach allowed us to determine how long-term domiciliary NIV affects the onset and duration of adverse health conditions until death. This approach differs from classical time-to-event Cox models because it considers a person's progression to multiple events of interest and allows the inclusion of transitions to intermediate events, such as COPD exacerbations.^{9–11} Our data suggest that long-term domiciliary NIV had a different impact on the onset and duration of severe exacerbations and mortality, and could potentially be used to guide the development of recommendations regarding appropriate indications for long-term domiciliary NIV depending on the targeted outcomes (eg, prevention of exacerbations or improved survival).

Our analysis included a large number of mortality events (18 125 in total, of which 7805 occurred during a severe COPD exacerbation). Continuation versus cessation of long-term NIV was associated with a reduction in mortality both in the presence and absence of severe exacerbation. The reduction in mortality rate with NIV continuation versus cessation was about 15% in our study. A 2021 Cochrane review concluded that home NIV was likely to reduce all-cause mortality in stable COPD (adjusted HR 0.75, 95% CI 0.58 to 0.97) but did not significantly reduce mortality in a post-COPD exacerbation population (adjusted HR 0.97, 95% CI 0.74 to 1.28).⁵ However, those conclusions were based on data from only three studies with 405 participants (stable COPD; moderate-certainty evidence) or two studies with a total of 317 participants (post-exacerbation COPD; low-certainty evidence). In contrast, the number of individuals and events, and the data source used in the current analysis meant that our data provide a good reflection of the long-term effects of domiciliary NIV in a real-world setting. Outside of NIV continuation versus cessation, other predictors of mortality in our study were consistent with those reported in a recent review and meta-analysis (including cardiovascular comorbidity, age, male sex and use of long-term oxygen therapy).²¹

Overall, our analysis showed that long-term domiciliary NIV was not significantly associated with transitions to severe exacerbation (HR 0.98, 95% CI 0.05 to 1.00; $p=0.09$). Instead, transitions to exacerbations were primarily driven by well-known factors such

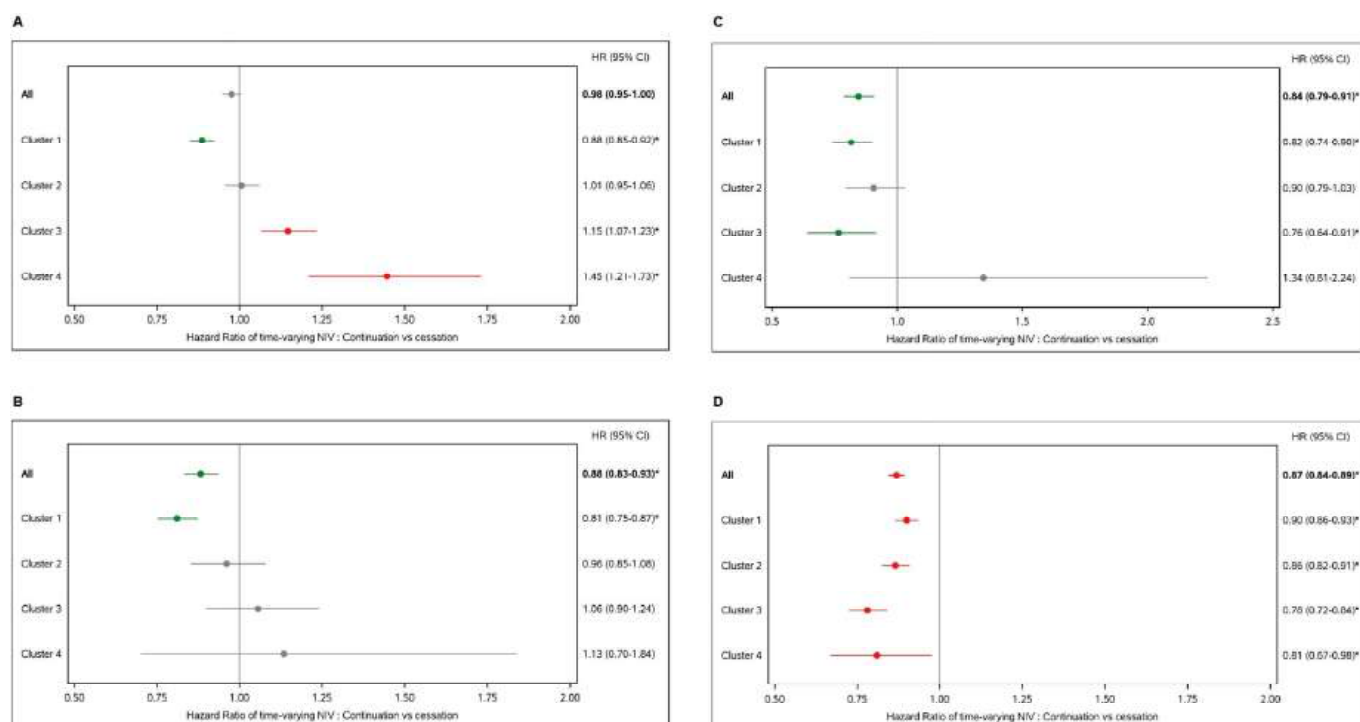


Figure 4 Multistate models for the adjusted risk of transition from: (A) without severe exacerbation to severe exacerbation; (B) without severe exacerbation to death; (C) severe exacerbation to death; and (D) severe exacerbation to without severe exacerbation (recovery) based on health trajectory cluster in the year before the initiation of non-invasive ventilation. Values are HR and 95% CI. * $p<0.05$. NIV, non-invasive ventilation.

as COPD severity and multimorbidity. Consistent with published literature,^{22–24} these factors included sex, comorbidities, anxiety/depression and the need for long-term oxygen therapy. The overall message from our analysis is that use of long-term domiciliary NIV in an unselected population of individuals with COPD does not appear to reduce incident severe disease exacerbations but could protect against death during a severe disease exacerbation. However, it is also important to note that the impact of long-term NIV therapy on the risk of transition to severe exacerbation could have been influenced by the fact that patients who discontinue NIV therapy may also decide not to accept other interventions, including hospital admission during a COPD exacerbation.

We found that recovery from severe exacerbation was longer in those who continued versus ceased long-term NIV therapy. This might appear counterintuitive, but probably reflects the NIV-associated reduction in mortality during severe COPD exacerbations. Survival gain during severe hospitalised exacerbation would result in a longer duration of recovery from that severe event. This is consistent with data on NIV use for management of acute COPD exacerbations in intensive care units.²⁵ Slower recovery from severe exacerbation may also reflect a more severe COPD phenotype.

Our group recently found considerable heterogeneity in the clinical course before domiciliary NIV initiation, and identified four different clusters of health trajectories before the start of NIV therapy.¹⁷ Applying our current multistate model analysis to these different clusters showed that the risk of transitioning to severe exacerbation was significantly lower with NIV continuation vs cessation only for patients in Cluster 1 (ie, those with less severe COPD who had early NIV initiation). In addition, reductions in mortality with NIV continuation versus cessation were primarily seen in individuals from Clusters 1 and 3. These findings suggest that early initiation of long-term domiciliary NIV could be a strategy that might help to prevent severe exacerbations and all-cause death. Other COPD profiles (or phenotypes) have also been identified, including a ‘respiratory COPD’ profile (severe airway obstruction, low or normal body mass index, few comorbidities) or a ‘systemic COPD’ profile (moderate airflow obstruction, obesity, high prevalence of cardiometabolic comorbidities).²⁶ Of these, ‘respiratory COPD’ was found to have a poorer prognosis than ‘systemic COPD’,²⁶ which is consistent with our finding that transitions from ‘without exacerbation’ to ‘severe exacerbation’ and from ‘without exacerbation’ to ‘death’ were less common in obese patients. Although it might seem logical to expect that the presence of obesity might increase the risk of transition from ‘without exacerbation’ to ‘death’ due to higher rates of cardiovascular disease, there is actually a large body of evidence to suggest that obese individuals with established cardiovascular disease have a better prognosis than lean patients with the same degree of cardiovascular disease.²⁷

Study strengths and limitations

Key strengths of the current analysis include the large and robust dataset used and the substantial number of events that could be included in the multistate model. The French SNDS is a large unbiased claims database that covers nearly the whole population of France (including public and private practices, across healthcare providers, insurers and devices), and the number of events included in the current model was larger than any previous studies by several orders of magnitude. In addition, analysis of the MONTANA cohort includes data that were captured before the start of the COVID-19 pandemic, eliminating any confounding related to the use of NIV to manage COVID-19 illness. Furthermore, the multistate modelling approach allowed us to determine the impact of long-term domiciliary NIV on different outcomes, including intermediate outcomes (severe exacerbations of COPD).

There are also several limitations that should be considered when interpreting the current study findings. First, the study had an observational design. However, the analytical approach provided reasonable control for potential confounders. Second,

the SNDS is an electronic records database, rather than one designed specifically for research or clinical purposes, and lacked information on some potentially relevant parameters (including smoking status, alcohol intake, body mass index and forced expiratory volume in 1 s), actual adherence to NIV therapy (daily usage), use of bronchodilators in patients hospitalised with an acute disease exacerbation, the details of NIV provision and the specific settings used for each patient and the degree of control of respiratory failure (eg, based on arterial carbon dioxide pressure before and after NIV therapy initiation). Third, there was no information about the specific reason for NIV cessation and it is possible that characteristics and covariates that are independently associated with mortality (other than those included in the multistate model) may also be associated with the decision to stop home NIV. In addition, we cannot exclude the possibility of misclassification based on disease/medication codes, meaning that some included individuals may not have only COPD as the primary respiratory diagnosis. Although not all patients had coding for use of inhaled COPD therapies, this may have been due to a focus on disease-related hospitalisation codes in patients hospitalised with COPD (meaning that not all patients receiving a bronchodilator would have this recorded in their medical record). Nevertheless, we feel confident that the clear exclusion criteria used in the study mean that we enrolled a true clinical COPD population. Furthermore, trajectories of patients with COPD–obstructive sleep apnoea overlap syndrome could be different from that in other COPD phenotypes, but this was not evaluated separately in the current study. Additionally, it is also important to note that only severe exacerbations of COPD were evaluated in our analysis because these could be consistently and reliably identified based on the need for hospitalisation, and are an important driver of direct costs in patients with COPD.²⁸ Finally, the results of our analysis are only applicable to a similar clinical population of individuals with COPD that clinicians have deemed suitable for a trial of home NIV.

CONCLUSION

Overall, the findings of this multistate model analysis showed that the use of long-term domiciliary NIV was associated with lower all-cause mortality in patients with chronic hypercapnic COPD, both during and outside a severe disease exacerbation. In contrast, NIV did not appear to significantly influence the number of incident severe exacerbations, except in individuals with less severe COPD who had early initiation of domiciliary NIV. These data are more robust, although less granular, than those from previous small randomised controlled trials, and provide novel and valuable insights that are supportive of the initiation of long-term domiciliary NIV early in the COPD disease course as a strategy to potentially reduce the occurrence of severe exacerbations and prevent all-cause death. Although additional research into real-world home NIV delivery is needed to better understand medium- and long-term outcomes, the current findings have the potential to impact on current recommendations and guidelines for the use of domiciliary NIV in individuals with chronic hypercapnic COPD.

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Acknowledgements Medical writing assistance was provided by Nicola Ryan, independent medical writer, funded by ResMed. Data management was conducted by Sacha Hiridjee and the initial study protocol was written by Arnaud Panes, both of whom are employees of Heva, funded by ResMed. The authors would also like to thank the Direction de la Stratégie, des Études et des Statistiques (DSES), Département Accès, Traitement et Analyse de la Donnée (DATAD), and Cellule de la CNAM en Charge de l’accompagnement des Demandes D’extraction (DEMEX) teams at the Caisse Nationale de l’Assurance maladie (CNAM) for the data extraction.

Collaborators The following individuals are part of the MedXcloud group: Atul Malhotra, Jean-Louis Pépin, Peter Cistulli, Adam Benjafield, Meredith Barrett, Jeff Armistead, Carlos Nunez, Kimberly Sterling, PharmD. Contributors Study procedures and analyses were undertaken by independent

third parties, HEVA (EH, HD, AS) and INSERM HP2 laboratory and artificial intelligence chair 'trajectories medicine' (director and principal investigator, JLP). The first draft of the manuscript was prepared by JLP, with the assistance of an independent medical writer funded by ResMed. The manuscript was reviewed and edited by all the authors (JLP, EH, HD, AJ, FL, AB, AM, JR, PC, AS, SB, APa, APr). All authors (JLP, EH, HD, AJ, FL, AB, AM, JR, PC, AS, SB, APa, APr) confirm that they had full access to all the data in the study and accept responsibility to submit for publication. JLP accepts full responsibility for the finished work and the conduct of the study, had access to the data and controlled the decision to publish.

Funding The MONTANA study was funded by ResMed (no grant number). JLP is supported by the French National Research Agency (ANR) in the framework of the "FRANCE 2030" program, the "e-health and integrated care" chair of Grenoble Alpes University Foundation and "Sleep Health-AI chair" in "MIAI Cluster" of artificial intelligence (ANR-23-IAEL-0006). Role of sponsors: Representatives of the study sponsor were involved in the design of the study. The first draft of the manuscript was prepared by JLP with the assistance of an independent medical writer funded by ResMed. The manuscript was reviewed and edited by all the authors. All authors made the decision to submit the manuscript for publication and assume responsibility for the accuracy and completeness of the analyses and for the fidelity of this report to the trial protocol.

Competing interests JLP has received lecture fees or conference travel grants from ResMed, Philips, AstraZeneca, Jazz Pharmaceuticals, Agiradom and Bioprojet, and has received unrestricted research funding from ResMed, Philips, GlaxoSmithKline, Bioprojet, Fondation de la Recherche Médicale (Foundation for Medical Research), Direction de la Recherche Clinique du CHU de Grenoble (Research Branch Clinique CHU de Grenoble), and fond de dotation 'Agir pour les Maladies Chroniques' (endowment fund 'Acting for Chronic Diseases'). AM is funded by the NIH. He reports income related to medical education from Livanova, Eli Lilly and ZOLL, and ResMed provided a philanthropic donation to UCSD. PC has an appointment to an endowed academic Chair at the University of Sydney that was established from ResMed funding, has received research support from ResMed and SomnoMed and is a consultant to ResMed, SomnoMed, Signifier Medical Technologies, Bayer and Sunrise Medical. AB, FL and AJ are employees of ResMed. EH, HD and AS are employees of HEVA and their participation in this study was funded by ResMed. APa has received consulting fees from ResMed. APr has received investigator fees for clinical trials funded by ResMed. SB and JR have no conflicts of interest to disclose.

Patient consent for publication Not applicable.

Ethics approval Specific approvals for this study were obtained from the Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé (CESREES; ref: 3904033) and the 'Commission Nationale Informatique et Liberté' (CNIL), the French information technology and personal data protection authority (DR 2021 162 and n° 921198).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. The data that support the findings of this study are under restricted access, granted by the Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé (CESREES; ref: 3904033) and from the French data protection authority (Comité National de l'Informatique et des Libertés, CNIL), and therefore are not publicly available.

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PM_{2.5} como fator de risco para dessaturação de oxigênio durante o sono na DPOC: identificação de indivíduos suscetíveis com base no tabagismo e em fenótipos inflamatórios

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/thorax-2025-223140>).

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Received 6 February 2025
Accepted 4 June 2025
Published Online First 20 June 2025



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To cite: Zhang W, Chen B, Shima M, et al. *Thorax* 2025;80:683–692.

RESUMO

Contexto A hipóxia noturna é prevalente na doença pulmonar obstrutiva crônica (DPOC) e contribui significativamente para um pior prognóstico. No entanto, os principais fatores de risco ambientais e os fenótipos suscetíveis permanecem pouco compreendidos.

Métodos Este estudo prospectivo com medidas repetidas incluiu 96 doentes com DPOC, com monitorização pessoal em tempo real da exposição a partículas finas (PM_{2.5}) e da saturação de oxigênio (SpO₂) durante o sono, totalizando 84 971 observações. O objetivo foi investigar a associação entre PM_{2.5} e dessaturação de oxigênio, e identificar indivíduos suscetíveis com base no tabagismo e em fenótipos inflamatórios. Os fenótipos inflamatórios foram determinados por biomarcadores exalados (óxido nítrico e sulfureto de hidrogênio) e leucócitos sanguíneos (neutrófilos e eosinófilos). Aplicaram-se modelos lineares mistos generalizados para estimar o risco de dessaturação associado ao PM_{2.5}.

Resultados A exposição pessoal ao PM_{2.5} esteve significativamente associada à diminuição da SpO₂ durante o sono, com efeitos observáveis em poucas horas. O maior risco de dessaturação foi observado em: Fumadores ativos: OR = 1,53 (IC 95%: 1,22–1,92), Ex-fumadores: OR = 1,14 (IC 95%: 1,02–1,28), Não fumadores: sem efeito significativo. Fumadores ativos apresentaram inflamação neutrofílica mais elevada, e aqueles com inflamação neutrofílica das vias aéreas foram mais suscetíveis à dessaturação induzida por PM_{2.5} (p interação <0,001). Entre os ex-fumadores, os que tinham inflamação eosinofílica das pequenas vias aéreas foram mais vulneráveis (p interação <0,001). Tanto ex-fumadores como fumadores ativos com fenótipo sistémico misto de granulócitos apresentaram maior risco de dessaturação. Além disso, indivíduos com inflamação crónica elevada foram mais suscetíveis à dessaturação induzida por PM_{2.5} do que aqueles sem inflamação.

Conclusão O PM_{2.5} atmosférico é um fator de risco importante para hipóxia noturna em doentes com DPOC, especialmente em indivíduos com historial de tabagismo e fenótipos inflamatórios específicos. **Número de registo do ensaio clínico:** NCT05076630.

INTRODUCTION

Oxygen is indispensable for aerobic respiration of all eukaryotic cells, depending on well-functioning pulmonary ventilation and gas exchange. Chronic obstructive pulmonary disease (COPD) is characterised by progressive airflow limitation, emphysema and damage to the pulmonary capillary bed,¹ affecting 212.3 million people worldwide.² Pulmonary abnormalities in patients with COPD predispose them to ventilation/perfusion mismatch and consequent hypoxaemia,^{1–3} which substantially contributes to a range of poor outcomes, including comorbidities and death.^{1–4} With diminished respiratory muscle contraction, increased airflow resistance, decreased chemoreceptor sensitivity and consequent hypoventilation during sleep, noctur-

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Fine particulate matter (PM_{2.5}) is a primary risk factor for chronic obstructive pulmonary disease (COPD). Given deteriorating pulmonary ventilation and gas exchange, patients with COPD are prone to experience hypoxaemia, particularly during sleep. However, the association of PM_{2.5} with nocturnal hypoxia among patients with COPD, as well as the susceptible phenotypes, remains unknown.

WHAT THIS STUDY ADDS

► This study provides the first scientific evidence linking personal PM_{2.5} exposure to acute decreases in oxygen saturation (SpO₂) levels and increased risks of oxygen desaturation during sleep, through precise real-time personal monitoring of PM_{2.5} and sleep SpO₂ in patients with COPD. In particular, smoking exacerbates the risk of oxygen desaturation associated with PM_{2.5}, with the most pronounced effect observed in current smokers, followed by former smokers. Individuals with high airway and systemic inflammation were more susceptible to PM_{2.5}-induced oxygen desaturation, and the specific susceptible inflammatory phenotypes differ between non-smokers and smokers.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► This study suggests that PM_{2.5} is an important environmental contributor to the development of nocturnal hypoxia in patients with COPD, which highlights the potential health benefits through mitigating particulate pollution during sleep. Moreover, this study identifies potential susceptible phenotypes to PM_{2.5}-induced oxygen desaturation, which underscores the need to develop personalised prevention and management strategies tailored to the specific phenotypes of patients with COPD in clinical and public health practice.

nal hypoxaemia is more pronounced and has become a considerable yet underappreciated aspect

of COPD.^{1,3} It has been reported that patients with COPD who spend over 10 min of sleep with oxygen desaturation (oxygen saturation (SpO_2) < 90%) have a higher risk of cardiovascular events and mortality (HR=1.91; 95% CI: 1.60 to 2.28).⁴ Despite this, there remains a considerable knowledge gap regarding the crucial and preventable contributors to oxygen desaturation during sleep in patients with COPD.

Air pollution, particularly fine particulate matter ($\text{PM}_{2.5}$), is a primary risk factor for COPD, accounting for 48% of global COPD deaths.⁵ To date, the impact of $\text{PM}_{2.5}$ on SpO_2 remains inconclusive, with some reporting negative associations^{6–9} while others observing non-significant results.^{10–14} This discrepancy is likely attributable to the substantial exposure measurement bias introduced by using outdoor concentrations of air pollutants as proxies for personal exposures. To date, only one study of 20 patients with COPD has investigated the effect of personal $\text{PM}_{2.5}$ exposure on real-time SpO_2 , and found that an increase of $17.2 \mu\text{g}/\text{m}^3$ in $\text{PM}_{2.5}$ within 0–3 hours was associated with a 0.42% (95% CI: –0.55% to –0.29%) decline in SpO_2 .⁹ Notably, even mild perturbations caused by $\text{PM}_{2.5}$ can easily result in oxygen desaturation in patients with COPD, as their SpO_2 levels often lie closer to the steep portion of the S-shaped oxyhaemoglobin dissociation curve, especially during sleep.³ However, the relationship between personal $\text{PM}_{2.5}$ exposure and the risk of oxygen desaturation during sleep in COPD has not been reported (first question shown in figure 1).

As is well-known, cigarette smoking is the most important behavioural risk factor for the pathological development of COPD. It has been reported that smoking is associated with decreased nocturnal SpO_2 ,¹⁵ which can be mitigated by smoking cessation.¹⁶ In particular, $\text{PM}_{2.5}$ exposure and smoking may exert synergistic effects on respiratory mortality.¹⁷ However, the potential interaction between $\text{PM}_{2.5}$ and smoking, two primary contributors to COPD, on nocturnal oxygen desaturation remains unclear (second question shown in figure 1). Furthermore, COPD is recognised as a heterogeneous chronic inflammatory condition, commonly featuring neutrophilic and eosinophilic phenotypes, which are closely linked to risk factors such as smoking.¹⁸ Biologically, excessive inflammatory responses can exacerbate the risk of hypoxaemia by damaging lung structure and affecting energy metabolism.^{18,19} However, determining which inflammatory phenotypes should be prioritised to mitigate $\text{PM}_{2.5}$ -induced hypoxia under different smoking conditions remains a critical and unresolved question (second question shown in figure 1).

To address these gaps, we performed this prospective repeated-measure panel study to investigate the acute effects of personal $\text{PM}_{2.5}$ exposure on real-time SpO_2 and the risk of oxygen desaturation during sleep, and to determine susceptible phenotypes based on smoking and inflammation status. Given that COPD is a chronic inflammatory condition, we finally examined whether individuals with constant inflammatory states are particularly susceptible

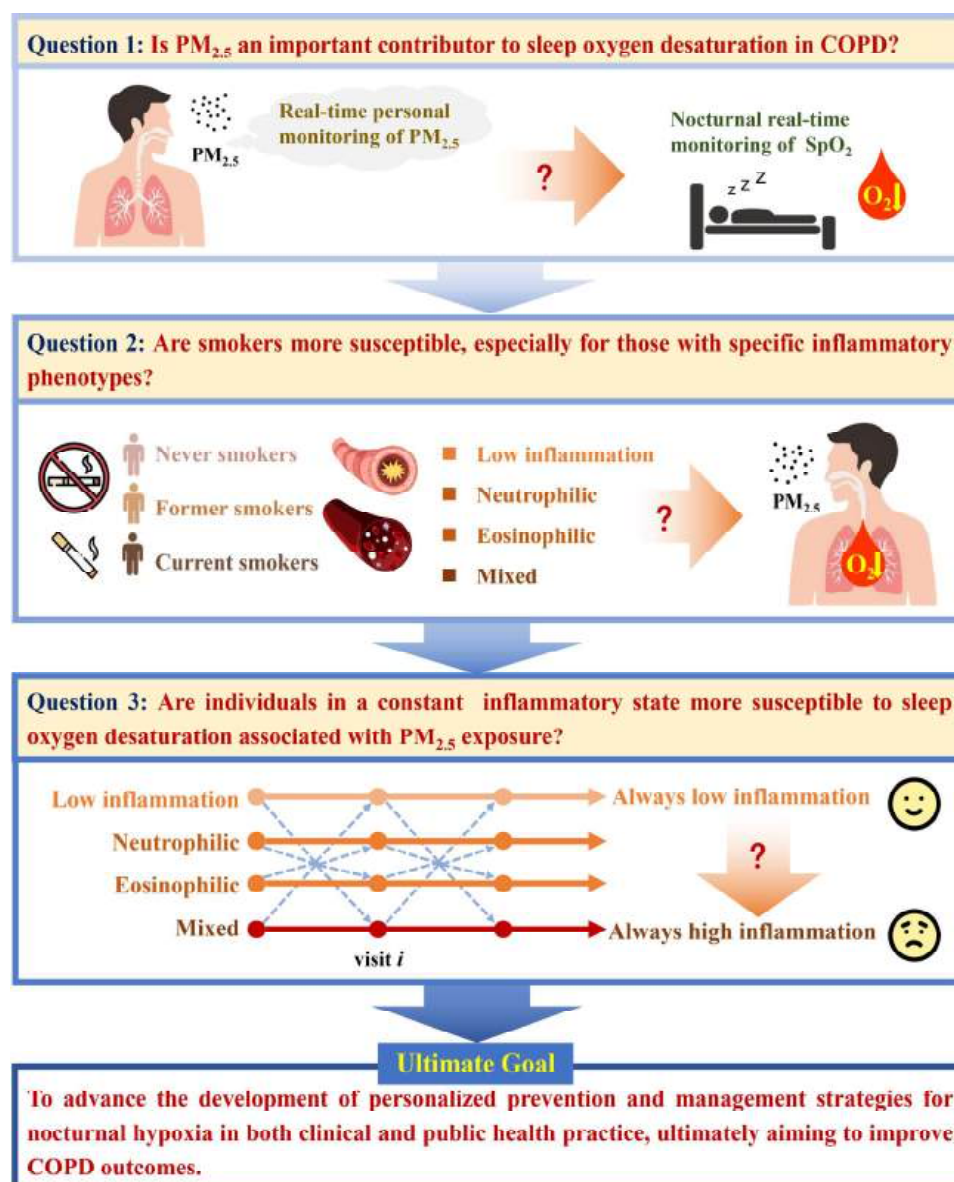


Figure 1 Schematic representation of research question and analytical procedure: A stepwise analytical framework to elucidate the interactive effects of personal $\text{PM}_{2.5}$ exposure, smoking and inflammatory phenotypes on oxygen desaturation during sleep in patients with COPD. COPD, chronic obstructive pulmonary disease; $\text{PM}_{2.5}$, fine particulate matter; SpO_2 , oxygen saturation.

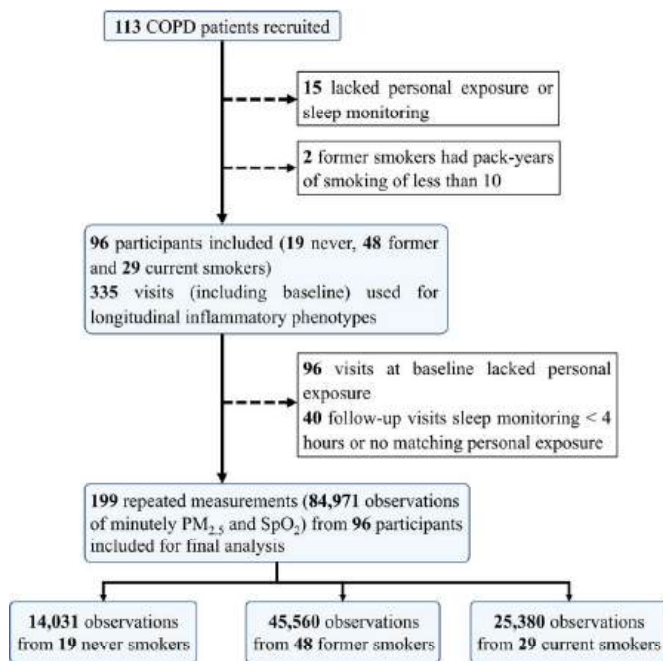


Figure 2 Flow diagram showing the study participant inclusion process. COPD, chronic obstructive pulmonary disease; PM_{2.5}, fine particulate matter; SpO₂, oxygen saturation.

ble to PM_{2.5}-related oxygen desaturation (third question shown in figure 1). This study seeks to promote the development and implementation of individualised management strategies targeting preventable risk factors for nocturnal hypoxia, ultimately aiming to improve COPD outcomes.

METHODS

Study design and participants

In this prospective repeated-measure panel study, stable patients with COPD were recruited from the Peking University Third Hospital and a nearby community health service centre between March 2021 and September 2023 in Beijing, China. Panel study designs have been widely applied in environmental epidemiology to assess the short-term effects of environmental exposures by repeated measurements of exposure and health variables from a panel of subjects.⁹ Participants were recruited based on the following criteria: (1) post-bronchodilator forced expiratory volume in 1 s (FEV₁)/forced vital capacity < 0.7; (2) no acute exacerbations within 4 weeks; (3) aged 40–80 years; and (4) residents of Beijing for over 1 year. Exclusion criteria included: (1) clinically diagnosed obstructive sleep apnoea, self-reported sleep apnoea or routine daytime sleepiness; (2) anaemia; (3) use of hypnotics or sedatives; and (4) taking oxygen therapy or continuous airway positive pressure.

The sample size was calculated using a programme designed for panel study (<https://corinne-riddell.shinyapps.io/mcgille-bohsamplesizecalculator/>).²⁰ For the entire project, a sample size of 95 was estimated based on the association between PM_{2.5} and FEV₁. This study included 96 patients with COPD, including 19 never, 48 former and 29 current smokers. We estimated a sample size of 19 to test the effect of PM_{2.5} on sleep SpO₂, with 80% power and a 0.05 significance. Therefore, the sample size is sufficient to ensure adequate power to test the associations of PM_{2.5} with SpO₂ changes within each smoking group. For each subject, 3 months elapsed between consecutive follow-ups. All follow-ups were conducted during periods of stable COPD. Participants' information, including demographic characteristics, smoking history, treatment, comorbidities and behavioural lifestyle, was collected at baseline. During each follow-up, participants underwent 24-hour real-time personal monitoring of PM_{2.5}, along with real-time sleep SpO₂ monitoring that night (online supplemental figure 1). The study was registered at ClinicalTrials.gov (NCT05076630).

Personal PM_{2.5} exposure

Personal exposure to PM_{2.5}, temperature and relative humidity (RH), was monitored in real-time using a MicroPEM monitor (online supplemental figure 1, RTI International, USA). This device is lightweight (less than 240 g) and portable, making it ideal for continuous monitoring. During single 24-hour visit follow-ups, participants received a calibrated MicroPEM device around 09:00, and then carried it for approximately 24 hours while going about their normal daily activities, returning it about 09:00 the next day. The median monitoring duration was 23.8 (IQR: 22.6–24.6) hours. Specifically, participants were given a portable backpack containing the MicroPEM monitor attached with a plastic tube near the breathing zone. They were instructed to carry the backpack when outdoors, place it on a table about 1.2 metres high in their main activity area (eg, living room) when at home, avoiding kitchens and windows, and position it near their bed while sleeping. The devices were calibrated regularly by professional technicians to ensure the accuracy of exposure assessment. Additional details can be found in the online supplemental methods.

Sleep oxygen saturation monitoring

Real-time SpO₂ during sleep was monitored by a ring pulse oximetry (online supplemental figure 1, Megahealth Medical, Zhejiang, China), which is designed to be worn like a ring with an adjustable fit for comfort and optimal oximetry signal quality. This oximeter records SpO₂ every second with 0.1% resolution, and its accuracy has been previously verified.²¹ Participants were instructed to wear the oximeter at bedtime and remove it on waking up the next day. The SpO₂ data were calculated into 1 min averaged values to match the minutely personal PM_{2.5} exposure. The SpO₂ < 90% was defined as oxygen desaturation.²² In addition, sleep quality was assessed by the Pittsburgh Sleep Quality Index. More details can be found in the online supplemental methods.

Definition of inflammatory phenotypes

At each visit, exhaled mediators were detected to characterise the airway inflammatory phenotypes. Exhaled nitric oxide at flow rates of 50 mL/s (FeNO₅₀) and 200 mL/s (FeNO₂₀₀) was measured using a Nano Coulomb Breath Analyzer (Sunvou-CA2122, Wuxi, China). We defined patients with large airway inflammation as FeNO₅₀ > 25 ppb,²³ and those with small airway inflammation as FeNO₂₀₀ > 10 ppb.^{24,25} Exhaled hydrogen sulfide (FeH₂S) was measured to reflect airway neutrophilic inflammation,²⁶ using another analyser (Sunvou-DA2130, Wuxi, China). Since the appropriate cut-off value for FeH₂S is unascertained, the median (23 ppb) was used for stratification of inflammation levels. FeH₂S > 23 ppb was classified as high airway neutrophilic inflammation.

Fasting peripheral blood was collected to count inflammatory cells, including white blood cell (WBC), eosinophil (EOS) and neutrophil (NEUT) in the hospital laboratory. An eosinophilic COPD was defined as a blood EOS count ≥ 150 cells/μL.^{27,28} A neutrophilic COPD was determined by a blood WBC count > 11 × 10⁹/L or a NEUT proportion > 65%.²⁹ Individuals that met both eosinophilic and neutrophilic COPD were categorised as mixed granulocytic COPD, while those that did not belong to any of these groups were classified into paucigranulocytic COPD.

In addition, based on longitudinal repeated measurements of inflammatory phenotypes, participants were further categorised into different subgroups with the same phenotype at all visits or fluctuating phenotypes. Additional details are in the online supplemental methods.

Statistical analyses

Linear mixed-effect (LME) models were applied to examine short-term effects of personal PM_{2.5} exposure on SpO₂ during sleep among individuals with different smoking status. SpO₂ was approximately normally distributed and included directly as a dependent variable. For oxygen desaturation, a binary outcome variable, generalised linear mixed model (GLMM) using the 'binomial' distribution with the 'logit' link was applied to estimate the OR of oxygen desaturation associated with PM_{2.5}. Participants' identity numbers were

Table 1 Descriptive statistics for individual characteristics of study participants

Variable	Never smokers (n=19)	Former smokers (n=48)	Current smokers (n=29)	All participants (n=96)
Basic information				
Age, years	69.6±6.8	70.2±6.3	66.6±5.7	69.0±6.3
Male, N (%)	8 (42.1)	48 (100)	29 (100)	85 (88.5)
BMI, kg/m ²	25.7±2.8	24.3±3.1	22.3±3.3	24.0±3.3
Neck circumference, cm	37.2±4.0	38.9±2.5	38.4±2.5	38.4±2.9
Pack-years	0±0	37.9±20.7	33.1±19.1	28.9±23.1
Comorbidities, N(%)				
Asthma	8 (42.1)	15 (31.3)	5 (17.2)	28 (29.2)
Hypertension	8 (42.1)	31 (64.6)	15 (51.7)	54 (56.3)
Diabetes	3 (15.8)	10 (20.8)	4 (13.8)	17 (17.7)
Lung function				
FEV ₁ , L	1.4±0.5	1.6±0.6	1.8±0.6	1.6±0.6
FEV ₁ %pred	59.0±14.3	56.7±18.1	60.7±19.1	58.4±17.8
FVC, L	2.4±0.8	2.8±0.7	3.0±0.8	2.8±0.8
FVC%pred	75.6±15.8	73.9±16.1	77.7±18.7	75.5±17.0
FEV ₁ /FVC, %	58.4±6.8	55.3±10.0	57.4±8.4	56.6±9.0
Respiratory symptoms				
mMRC	1.6±0.9	1.2±0.9	0.8±0.8	1.1±0.9
CAT	12.1±6.1	7.8±5.4	8.7±6.4	8.9±6.1
Airway inflammation				
FeNO _{50'} , ppb	23.2±17.6	23.0±17.4	18.4±18.2	21.6±17.8
FeNO _{200'} , ppb	11.0±7.8	10.8±6.9	8.9±7.8	10.2±7.4
FeH ₂ S, ppb	23.0±21.9	25.9±25.4	36.1±33.5	28.3±27.8
Blood leucocyte				
WBC, 10 ⁹ /L	6.10±1.53	6.59±1.93	7.29±2.43	6.73±2.08
NEUT, 10 ⁹ /L	3.66±1.04	4.14±1.56	4.69±1.90	4.24±1.64
NEUT%	59.66±7.72	61.82±8.70	63.41±7.43	61.97±8.22
EOS, 10 ⁹ /L	0.24±0.18	0.25±0.39	0.17±0.13	0.22±0.30
EOS%	3.83±2.77	3.39±3.30	2.40±1.84	3.15±2.86
Sleep monitoring				
SpO ₂ , %	94.1±2.3	94.3±2.5	94.7±2.2	94.4±2.4
T90, %	5.8±5.6	5.6±9.1	3.7±5.3	5.1±7.5
Sleep duration, hours	6.7±1.3	6.7±1.1	6.8±1.1	6.7±1.1
PSQI	7.1±3.0	5.8±2.9	6.1±2.6	6.1±2.9
Personal exposure monitoring				
PM _{2.5} during sleep, µg/m ³	19.3±24.9	18.0±16.8	25.3±28.3	22.4±27.3
24-hour average PM _{2.5} , µg/m ³	34.0±28.4	33.1±31.6	45.7±31.7	36.9±31.4
Temperature, °C	27.5±2.6	27.6±2.6	27.5±2.7	27.5±2.6
RH, %	21.0±7.4	21.4±7.0	20.7±7.2	21.1±7.1
Indoor duration, hours/day	21.8±2.1	21.0±2.2	21.2±2.1	21.2±2.1

Continued

Table 1 Continued

Variable	Never smokers (n=19)	Former smokers (n=48)	Current smokers (n=29)	All participants (n=96)
Categorical variables were presented as by N (%), and continuous variables were presented as mean±SD.				
BMI, body mass index; CAT, COPD Assessment Test; EOS, eosinophil; FeH ₂ S, exhaled hydrogen sulfide; FeNO _{50'} , exhaled nitric oxide at the flow rate of 50 mL/s; FeNO _{200'} , exhaled nitric oxide at the flow rate of 200 mL/s; FEV ₁ , forced expiratory volume in 1 s; FVC, forced vital capacity; mMRC, modified Medical Research Council; NEUT, neutrophil; PM _{2.5} , fine particulate matter; PSQI, Pittsburgh Sleep Quality Index; RH, relative humidity; SpO ₂ , oxygen saturation; T90, percent of time with oxygen saturation below 90%; WBC, white blood cell.				

treated as the random-effect term to account for within-participant correlation of repeated measurements. The model adjusted for the following covariates: (1) participants' characteristics, including age, sex, smoking status, neck circumference, body mass index (BMI) and FEV₁%pred; (2) time-related factors, including day-of-week, time since falling asleep and natural cubic splines with 3 degrees of freedom for calendar time; and (3) weather factors through natural cubic splines with 3 degrees of freedom for temperature and RH. To evaluate cumulative time-lag effects, personal PM_{2.5} concentrations were calculated over multiple moving averages, with lag periods ranging from lag 0–5 min to 0–7 hours, which represents the cumulative exposure to PM_{2.5} preceding the SpO₂ measurement. Generalised additive mixed models (GAMMs) were used to establish the exposure-response relationships of PM_{2.5} with SpO₂ changes and risks of oxygen desaturation.^{9–22} Furthermore, interaction models of PM_{2.5} and inflammatory phenotypes were constructed to explore whether PM_{2.5} exerts differential impacts in individuals with different airway and systemic inflammatory phenotypes. In addition, several sensitivity analyses were performed to test the robustness of our results. The results were presented as the estimated changes in SpO₂ and OR of oxygen desaturation per IQR increase in PM_{2.5}. Statistical significance was defined as *p*<0.05 (two-sided). R V.4.1.3 software with the 'lmerTest' and 'gamm4' package was used to fit LME, GLMM and GAMM models. Additional details are in the online supplemental methods.

RESULTS

Descriptive statistics

As illustrated in figure 2, 113 patients with COPD were recruited, 15 of whom were not included due to lack of personal exposure or sleep monitoring. Two former smokers with fewer than 10 pack-years of smoking were excluded. Finally, 96 participants, including 19 never, 48 former and 29 current smokers, were included in this study. After excluding sleep data with <4 hours of monitoring and no matching personal exposure, a total of 84 971 observations of minutely sleep SpO₂ from 199 nights of monitoring of 96 participants was included in the final analysis.

Among the 96 participants, 85 (88.5%) were male (table 1). The average age and BMI were 69.0±6.3 years and 24.0±3.3 kg/m², respectively. The mean SpO₂ during sleep was 94.4%, which was significantly lower than the pre-sleep SpO₂ of 97.1% (*p*<0.001, online supplemental figure 2). Online supplemental figure 3 illustrated the real-time changes in sleep SpO₂ for patients with COPD. The average concentrations of 24-hour PM_{2.5} exposure were 34.0±28.4 µg/m³ for never smokers, 33.1±31.6 µg/m³ for former smokers and 45.7±31.7 µg/m³ for current smokers (table 1). For the inflammatory profiles, current smokers exhibited higher airway and systemic neutrophilic inflammation, but lower eosinophilic inflammation, compared with never and former smokers (table 1).

Associations of PM_{2.5} with SpO₂ in patients with different smoking status

Personal PM_{2.5} exposure within hours was significantly associated with decreased sleep SpO₂ and increased risks of oxygen desaturation (figure 3), and no threshold was observed (figure 4). Among former and current smokers, significant declines in sleep SpO₂ associated with PM_{2.5} were observed at all cumulative lag periods,

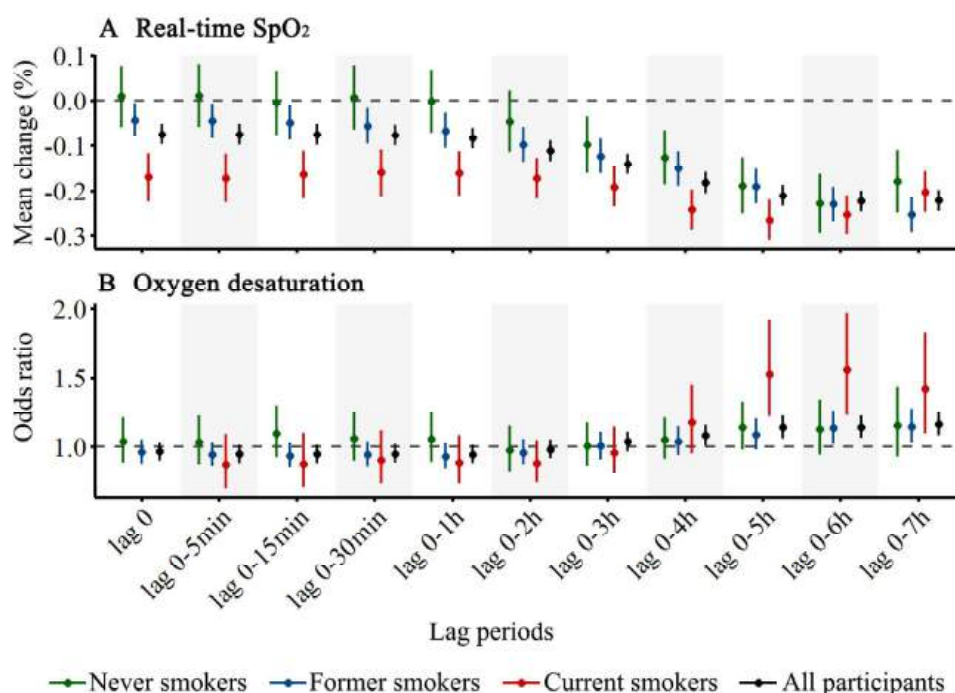


Figure 3 Estimated changes in (A) real-time SpO_2 and (B) ORs of oxygen desaturation per IQR increment of personal exposure to $\text{PM}_{2.5}$ at different cumulative lag periods in patients with COPD with different smoking status. IQR of $\text{PM}_{2.5}$: never: $16.8 \mu\text{g}/\text{m}^3$; former: $18.3 \mu\text{g}/\text{m}^3$; current: $27.6 \mu\text{g}/\text{m}^3$; all participants: $22.4 \mu\text{g}/\text{m}^3$. COPD, chronic obstructive pulmonary disease; $\text{PM}_{2.5}$, fine particulate matter; SpO_2 , oxygen saturation.

with current smokers exhibiting a higher risk of oxygen desaturation (figure 3). Specifically, an IQR increment of $27.6 \mu\text{g}/\text{m}^3$ in $\text{PM}_{2.5}$ at cumulative lag 0–5 hours was associated with a 0.27% (95% CI: -0.31% to -0.22%) decline in SpO_2 and an OR of 1.53 (95% CI: 1.22 to 1.92) for oxygen desaturation in current smokers. For former smokers, an IQR ($18.3 \mu\text{g}/\text{m}^3$) increase in $\text{PM}_{2.5}$ at cumulative lag 0–7 hours was associated with a 0.25% (95% CI: -0.29% to -0.22%) decline in SpO_2 and an OR of 1.14 (95% CI: 1.02 to 1.28) for oxygen desaturation. Among never smokers, a significant decrease in SpO_2 was observed after 0–3 hour cumulative lag, but the OR of oxygen desaturation was statistically non-significant. Notably, after excluding pre-sleep $\text{PM}_{2.5}$ exposure, $\text{PM}_{2.5}$ during sleep remains significantly associated with decreased SpO_2 ,

and increased risks of oxygen desaturation were observed among former and current smokers at cumulative lag 0–2 hours (online supplemental table 1). Sensitivity analyses indicated that these associations were robust (online supplemental figure 4).

Inflammation exacerbates $\text{PM}_{2.5}$ -induced oxygen desaturation

Online supplemental table 2 showed that patients with higher inflammatory levels tended to exhibit lower SpO_2 and higher oxygen desaturation index, though not all differences were statistically significant ($p < 0.05$). Interaction analyses suggested that higher airway and systemic inflammation generally exacerbated the $\text{PM}_{2.5}$ -associated decrease in sleep SpO_2 (online supplemental table 3). As mentioned above, patients with different smoking statuses showed

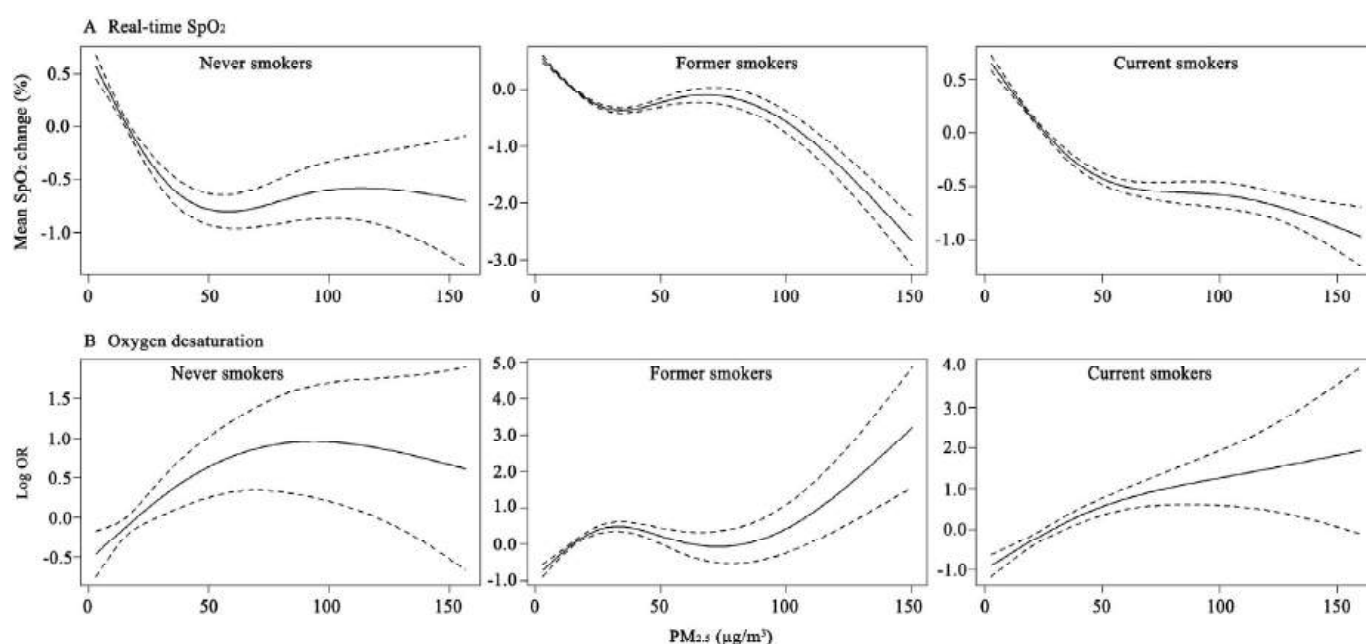


Figure 4 Exposure-response relationship of personal $\text{PM}_{2.5}$ exposure with (A) real-time SpO_2 and (B) risks of oxygen desaturation during sleep in patients with COPD with different smoking status. Generalised additive mixed models (GAMM) were used to establish the exposure-response relationships. The strongest cumulative lag effects were selected, with lag 0–6 hours for never smokers, lag 0–7 hours for former smokers and lag 0–5 hours for current smokers. COPD, chronic obstructive pulmonary disease; $\text{PM}_{2.5}$, fine particulate matter; SpO_2 , oxygen saturation.

Table 2 Effects of PM_{2.5} on SpO₂ and oxygen desaturation during sleep in never, former and current smokers with different airway inflammatory phenotypes

Airway inflammation	N	Real-time SpO ₂ (%)		Oxygen desaturation	
		Change (95% CI)	P _{interaction}	OR (95% CI)	P _{interaction}
Never smokers					
FeNO ₅₀					
≤25ppb	8668	−0.20 (−0.26 to −0.13)	Ref.	1.17 (0.97 to 1.40)	Ref.
>25ppb	4468	−0.68 (−0.96 to −0.40)	0.001	0.88 (0.54 to 1.42)	0.282
FeNO ₂₀₀					
≤10ppb	7349	−0.25 (−0.32 to −0.18)	Ref.	1.04 (0.85 to 1.27)	Ref.
>10ppb	4418	−0.78 (−1.04 to −0.51)	<0.001	1.14 (0.80 to 1.63)	0.648
FeH ₂ S					
≤23ppb	5937	0.00 (−0.06 to 0.07)	Ref.	0.94 (0.78 to 1.13)	Ref.
>23ppb	3816	−0.18 (−0.32 to −0.04)	0.018	1.03 (0.47 to 2.26)	0.816
Former smokers					
FeNO ₅₀					
≤25ppb	31 031	−0.34 (−0.38 to −0.29)	Ref.	1.27 (1.12 to 1.45)	Ref.
>25ppb	11 600	−0.42 (−0.51 to −0.32)	0.134	1.29 (1.00 to 1.65)	0.940
FeNO ₂₀₀					
≤10ppb	24 898	−0.22 (−0.28 to −0.16)	Ref.	0.95 (0.79 to 1.14)	Ref.
>10ppb	15 870	−0.47 (−0.52 to −0.42)	<0.001	1.60 (1.35 to 1.88)	<0.001
FeH ₂ S					
≤23ppb	17 607	0.04 (−0.04 to 0.13)	Ref.	0.91 (0.71 to 1.16)	Ref.
>23ppb	17 971	−0.39 (−0.43 to −0.34)	<0.001	1.28 (1.10 to 1.50)	0.015
Current smokers					
FeNO ₅₀					
≤25ppb	21 575	−0.26 (−0.30 to −0.21)	Ref.	1.74 (1.35 to 2.23)	Ref.
>25ppb	2413	−0.17 (−0.27 to −0.07)	0.089	1.11 (0.45 to 2.74)	0.396
FeNO ₂₀₀					
≤10ppb	20 182	−0.24 (−0.28 to −0.19)	Ref.	1.44 (1.10 to 1.87)	Ref.
>10ppb	3806	−0.32 (−0.43 to −0.22)	0.101	1.12 (0.63 to 2.00)	0.417
FeH ₂ S					
≤23ppb	8740	−0.10 (−0.16 to −0.03)	Ref.	0.94 (0.67 to 1.31)	Ref.
>23ppb	10 066	−0.58 (−0.70 to −0.47)	<0.001	2.37 (1.34 to 4.19)	<0.001
Note: interaction models of PM _{2.5} with airway inflammation levels were constructed and the effect estimates for patients with low and high airway inflammation were derived from the regression coefficients of PM _{2.5} and the interaction term. Results were presented as mean changes in SpO ₂ and ORs of oxygen desaturation per IQR increment of PM _{2.5} (never: 16.8 µg/m ³ ; former: 18.3 µg/m ³ ; current: 27.6 µg/m ³). The strongest cumulative lag effects were selected, with lag 0–6 hours for never smokers, lag 0–7 hours for former smokers and lag 0–5 hours for current smokers.					
FeH ₂ S, exhaled hydrogen sulfide; FeNO _{50r} , exhaled nitric oxide at the flow rate of 50 mL/s; FeNO _{200r} , exhaled nitric oxide at the flow rate of 200 mL/s; PM _{2.5r} , fine particulate matter; SpO ₂ , oxygen saturation.					

Note: interaction models of PM_{2.5} with airway inflammation levels were constructed and the effect estimates for patients with low and high airway inflammation were derived from the regression coefficients of PM_{2.5} and the interaction term. Results were presented as mean changes in SpO₂ and ORs of oxygen desaturation per IQR increment of PM_{2.5} (never: 16.8 µg/m³; former: 18.3 µg/m³; current: 27.6 µg/m³). The strongest cumulative lag effects were selected, with lag 0–6 hours for never smokers, lag 0–7 hours for former smokers and lag 0–5 hours for current smokers.

FeH₂S, exhaled hydrogen sulfide; FeNO₅₀, exhaled nitric oxide at the flow rate of 50 mL/s; FeNO₂₀₀, exhaled nitric oxide at the flow rate of 200 mL/s; PM_{2.5}, fine particulate matter; SpO₂, oxygen saturation.

different inflammatory characteristics. In particular, the susceptible inflammatory phenotypes varied among never, former and current smokers (table 2 and table 3). For never smokers, PM_{2.5} was associated with greater SpO₂ declines in those with eosinophilic and neutrophilic airway inflammation (p interaction<0.05, table 2), as well as systemic neutrophilic and mixed granulocytic phenotypes (p interaction<0.05, table 3). For former smokers, individuals with higher small-airway eosinophilic inflammation were more susceptible to PM_{2.5}-related oxygen desaturation (p interaction<0.001, table 2). For current smokers, those with higher neutrophilic airway inflammation were more susceptible (p interaction<0.001, table 2). Notably, individuals with a systemic mixed granulocyte phenotype had higher ORs for oxygen desaturation in former (OR=3.95, p interaction=0.002) and current smokers (OR=2.41, p interaction=0.034, table 3).

Higher susceptibility to PM_{2.5}-induced oxygen desaturation in states of constant inflammation

Given that COPD is a chronic inflammatory condition, interactive effects of PM_{2.5} and longitudinal inflammatory phenotypes were

further examined. We found that individuals with constantly high inflammation were typically at higher risk of oxygen desaturation (table 4), with effect estimates larger than those observed at a single time point (online supplemental table 3). ORs for oxygen desaturation in individuals with constant high FeNO₅₀, FeNO₂₀₀ or FeH₂S were 2.21 (95% CI: 1.50 to 3.26), 1.84 (95% CI: 1.38 to 2.45) and 1.46 (95% CI: 1.23 to 1.74), respectively, per IQR increase of 22.4 µg/m³ in PM_{2.5}, and these effects were significantly greater than in those with constantly low airway inflammation (p interaction<0.05, table 4). For systemic inflammatory phenotypes, patients with a constant mixed granulocyte phenotype (OR=2.32) showed the greatest susceptibility, followed by those with a constant neutrophilic phenotype (OR=1.39) and eosinophilic phenotype (OR=1.31).

DISCUSSION

To the best of our knowledge, this is the first study to link personal PM_{2.5} exposure with oxygen desaturation during sleep, through precise real-time personal monitoring of PM_{2.5} and sleep SpO₂ in patients with COPD. This prospective study also provides the first

Table 3 Effects of PM_{2.5} on SpO₂ and oxygen desaturation during sleep in never, former and current smokers with different systemic inflammation phenotypes

Inflammatory phenotype	N	Real-time SpO ₂ (%)	P _{interaction}	Oxygen desaturation	P _{interaction}
		Change (95% CI)		OR (95% CI)	
Never smokers					
Paucigranulocytic	2518	−0.11 (−0.20 to −0.01)	Ref.	1.01 (0.82 to 1.24)	Ref.
Neutrophilic	1703	−1.10 (−1.43 to −0.76)	<0.001	2.35 (0.92 to 5.99)	0.080
Eosinophilic	6749	−0.04 (−0.13 to 0.06)	0.268	0.97 (0.77 to 1.20)	0.772
Mixed granulocytic	2649	−0.47 (−0.76 to −0.19)	0.011	0.82 (0.57 to 1.16)	0.281
Former smokers					
Paucigranulocytic	13 624	−0.13 (−0.19 to −0.07)	Ref.	1.23 (1.00 to 1.50)	Ref.
Neutrophilic	8670	−0.33 (−0.38 to −0.27)	<0.001	0.93 (0.76 to 1.13)	0.037
Eosinophilic	19910	−0.35 (−0.48 to −0.21)	0.005	1.74 (1.13 to 2.69)	0.174
Mixed granulocytic	3356	−0.80 (−1.00 to −0.60)	<0.001	3.95 (1.95 to 8.01)	0.002
Current smokers					
Paucigranulocytic	6968	−0.21 (−0.28 to −0.15)	Ref.	1.22 (0.79 to 1.88)	Ref.
Neutrophilic	6662	−0.22 (−0.30 to −0.15)	0.882	0.94 (0.62 to 1.43)	0.401
Eosinophilic	5968	−0.34 (−0.45 to −0.23)	0.046	1.51 (0.95 to 2.41)	0.421
Mixed granulocytic	4119	−0.38 (−0.57 to −0.20)	0.079	2.41 (1.45 to 4.01)	0.034
Note: interaction models of PM _{2.5} with inflammation phenotypes were constructed, and the effect estimates for patients with different inflammation phenotypes were derived from the regression coefficients of PM _{2.5} and the interaction term. Results were presented as mean changes in SpO ₂ and ORs of oxygen desaturation per IQR increment of PM _{2.5} (never: 16.8 µg/m ³ ; former: 18.3 µg/m ³ ; current: 27.6 µg/m ³). The strongest cumulative lag effects were selected, with lag 0–6 hours for never smokers, lag 0–7 hours for former smokers and lag 0–5 hours for current smokers. PM _{2.5} , fine particulate matter; SpO ₂ , oxygen saturation.					

evidence that smoking and inflammatory phenotypes exacerbate COPD susceptibility to PM_{2.5}-associated nocturnal oxygen desaturation. Notably, individuals with constant high airway and systemic inflammation were more susceptible to PM_{2.5}-related oxygen desaturation risks. These findings provide novel insights into the development of personalised prevention and treatment strategies to alleviate nocturnal hypoxia in patients with COPD.

Several studies evaluated the association between PM_{2.5} and SpO₂, but the results were inconclusive. Some studies observed significant negative relationships,^{6–9} whereas others reported non-significant associations.^{10–14} This inconsistency can be attributed to several factors, including (1) substantial exposure measurement bias introduced by using outdoor concentrations of air pollutants as proxies for personal exposures; (2) difficulty in capturing acute changes in SpO₂ due to lack of continuous monitoring; and (3) small variation in daytime resting SpO₂. So far, only one panel study in Hong Kong (n=20) investigated the effect of personal PM_{2.5} exposure on SpO₂ with continuous real-time monitoring and observed acute declines of SpO₂ within hours of PM_{2.5} exposure,⁹ aligning with our findings. Nevertheless, the study did not specifically assess the effect on SpO₂ and the risk of oxygen desaturation during sleep, where hypoxaemia is often exacerbated and greatly affects COPD prognosis.^{13 4} Our findings reveal for the first time the significant impact of personal PM_{2.5} on the increased risks of sleep oxygen desaturation, highlighting potential sleep benefits in vulnerable populations through mitigating particulate pollution, as demonstrated in our recent indoor air purification intervention trial.³⁰

Smoking may also affect SpO₂ during sleep.^{15 16} Importantly, we found that PM_{2.5} and smoking, two primary risk factors for COPD, may work together to increase the risk of nocturnal oxygen desaturation. In alignment with our findings, previous studies have also indicated that smokers are more susceptible to the adverse respiratory effects of air pollution than non-smokers.^{14 17 31} The interaction of PM_{2.5} and smoking may involve several mechanisms. Smokers have higher lung deposition of fine particles than non-smokers.³² Moreover, smoking impairs lung clearance of inhaled particles by reducing function and ciliary activity.^{33 34} Additionally, smoking depletes antioxidants like glutathione, causes oxidative stress, and

activates mucus hypersecretion and multiple inflammatory pathways such as NF-Kb,³⁵ which may disrupt the redox balance and the adaptive energy metabolism in erythrocytes, thereby affecting oxygen delivery.^{36 37} We found smoking and inflammation were associated with altered erythrocyte parameters (online supplemental figure 5), which may increase susceptibility to PM_{2.5}-associated oxygen desaturation (online supplemental figure 6). Furthermore, excessive inflammation increases oxygen consumption and impairs lung ventilation and air exchange, thus exacerbating hypoxaemia risk.¹⁹ Therefore, individuals with higher airway and systemic inflammation, regardless of smoking status, are more susceptible to PM_{2.5}-induced oxygen desaturation during sleep. Importantly, the susceptible inflammatory phenotype varied slightly among never, former and current smokers, likely due to their distinct inflammatory profiles. Smoking primarily activates neutrophilic inflammation, especially in the airway, which increases the susceptibility to air pollution-related oxygen desaturation.¹⁴ In non-smokers, the eosinophilic phenotype may be more concerning, as PM_{2.5} was associated with larger lung function declines in those with eosinophilic COPD.²⁷ Another potential biological explanation may be related to the characteristics of NEUTs and EOSs, especially in terms of energy metabolism, as EOSs exhibit greater basal mitochondrial respiration and ATP-linked respiration than NEUTs.³⁸ The specific biological mechanisms require further experimental research to elucidate.

This prospective panel study addresses an important knowledge gap regarding the association of personal PM_{2.5} exposure with oxygen desaturation during sleep in patients with COPD. By employing precise real-time exposure and sleep monitoring over a follow-up period of approximately 1 year per participant, the study provides a unique opportunity to detect immediate declines in sleep SpO₂ following PM_{2.5} exposure. Moreover, the prospective repeated-measure design enables participants to serve as their own controls, enhancing statistical power and effectively managing potential confounding factors across individuals. More importantly, this study reveals for the first time the interactive effects of PM_{2.5} with smoking status and inflammatory phenotypes and identifies the potential susceptible phenotypes to PM_{2.5}-related oxygen desaturation. These findings underscore the need to develop person-

Table 4 Effects of PM_{2.5} on SpO₂ and oxygen desaturation during sleep in individuals with different longitudinal inflammatory phenotypes³

Longitudinal phenotype	N	Real-time SpO ₂ (%)	P _{interaction}	Oxygen desaturation	P _{interaction}
		Change (95% CI)		OR (95% CI)	
Large airway inflammation					
Always FeNO ₅₀ ≤25ppb	44 218	−0.11 (−0.15 to −0.08)	Ref.	1.18 (1.07 to 1.31)	Ref.
Always FeNO ₅₀ >25ppb	7678	−0.54 (−0.66 to −0.42)	<0.001	2.21 (1.50 to 3.26)	0.003
Fluctuating	30 966	−0.30 (−0.33 to −0.27)	<0.001	1.25 (1.11 to 1.40)	0.507
Small airway inflammation					
Always FeNO ₂₀₀ ≤10ppb	28 129	−0.03 (−0.07 to 0.00)	Ref.	1.07 (0.95 to 1.21)	Ref.
Always FeNO ₂₀₀ >10ppb	11 276	−0.50 (−0.54 to −0.45)	<0.001	1.84 (1.38 to 2.45)	<0.001
Fluctuating	42 997	−0.20 (−0.24 to −0.17)	<0.001	1.27 (1.15 to 1.41)	0.021
Airway neutrophilic inflammation					
Always FeH ₂ S≤23ppb	15 687	−0.02 (−0.07 to 0.03)	Ref.	1.16 (1.01 to 1.34)	Ref.
Always FeH ₂ S>23ppb	14 584	−0.53 (−0.58 to −0.47)	<0.001	1.46 (1.23 to 1.74)	0.035
Fluctuating	33 866	−0.15 (−0.19 to −0.11)	<0.001	1.25 (1.05 to 1.49)	0.515
Systemic inflammation phenotype					
Always paucigranulocytic	16 655	−0.03 (−0.07 to 0.01)	Ref.	1.17 (1.00 to 1.37)	Ref.
Always neutrophilic	8967	−0.48 (−0.54 to −0.42)	<0.001	1.39 (1.08 to 1.79)	0.258
Always eosinophilic	20 813	−0.27 (−0.31 to −0.22)	<0.001	1.31 (1.15 to 1.50)	0.273
Always mixed granulocytic	3486	−1.34 (−1.49 to −1.19)	<0.001	2.32 (1.28 to 4.19)	0.028
Fluctuating	34 757	−0.22 (−0.25 to −0.18)	<0.001	1.11 (0.99 to 1.25)	0.584
Note: participants were categorised into different subgroups based on longitudinal repeated measurements of inflammatory phenotypes. Interaction models of PM _{2.5} with longitudinal inflammatory phenotypes were constructed, and the effect estimates for patients with different inflammatory phenotypes were derived from the regression coefficients of PM _{2.5} and the interaction term. Results were presented as mean changes in SpO ₂ and ORs for oxygen desaturation per IQR increment of PM _{2.5} (22.4 µg/m ³) at cumulative lag 0–7 hours. FeH ₂ S, exhaled hydrogen sulfide; FeNO ₅₀ , exhaled nitric oxide at the flow rate of 50 mL/s; FeNO ₂₀₀ , exhaled nitric oxide at the flow rate of 200 mL/s; PM _{2.5} , fine particulate matter; SpO ₂ , oxygen saturation					

Note: participants were categorised into different subgroups based on longitudinal repeated measurements of inflammatory phenotypes. Interaction models of PM_{2.5} with longitudinal inflammatory phenotypes were constructed, and the effect estimates for patients with different inflammatory phenotypes were derived from the regression coefficients of PM_{2.5} and the interaction term. Results were presented as mean changes in SpO₂ and ORs for oxygen desaturation per IQR increment of PM_{2.5} (22.4 µg/m³) at cumulative lag 0–7 hours.

FeH₂S, exhaled hydrogen sulfide; FeNO₅₀, exhaled nitric oxide at the flow rate of 50 mL/s; FeNO₂₀₀, exhaled nitric oxide at the flow rate of 200 mL/s; PM_{2.5}, fine particulate matter; SpO₂, oxygen saturation.

alised prevention strategies tailored to the specific phenotypes of patients with COPD.

Nevertheless, several limitations warrant consideration. First, since induced sputum was not collected to count airway EOSs and NEUTs, airway inflammatory phenotypes may be misclassified to some extent. However, as exhaled mediators are recognised as convenient and reliable airway inflammation biomarkers, this misclassification is unlikely to significantly distort the true modification effects of airway inflammation phenotypes. Second, the modification effects of longitudinal inflammatory phenotypes were not analysed separately for never, former and current smokers due to the limited sample size. Third, carboxyhaemoglobin may cause an overestimation of measured SpO_{2.5} in current smokers, which might affect the effect estimates to some degree. Fourth, PM_{2.5} samples were not collected for chemical analysis and source apportionment, so we could not determine the key PM_{2.5} sources contributing to decreased SpO₂ during sleep. In addition, female patients with COPD are predominantly never smokers in China. It remains to be confirmed whether our findings are applicable to female smokers with COPD. Furthermore, considering the difficulty in obtaining biomarkers during sleep, the pathophysiologic mechanisms of PM_{2.5}-related oxygen desaturation need to be explored in the future.

CONCLUSION

This study provides the first scientific evidence linking personal PM_{2.5} exposure to acute decreases in SpO₂ levels and increased risks of oxygen desaturation during sleep in patients with COPD. Furthermore, our study reveals that smoking exacerbates the risk of oxygen desaturation associated with PM_{2.5}, with the most pronounced effect observed in current smokers, followed by former smokers. In particular, individuals with high airway and systemic inflammation, especially those with constant high-level inflammation, are more susceptible to PM_{2.5}-related oxygen desaturation compared with those at non-inflammatory status. Notably, the specific susceptible inflammatory phenotypes vary between non-

smokers and smokers. These findings highlight the significant impact of two major preventable COPD risk factors, PM_{2.5} and smoking, on oxygen desaturation during sleep and identify high-risk inflammatory phenotypes. This study suggests that personalised environmental and behavioural risk factor management strategies tailored to smoking status and inflammatory characteristics may have important implications for the effective prevention and treatment of nocturnal hypoxia in patients with COPD.

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Acknowledgements We are grateful to all participants for their patience, time and contributions to this study.

Contributors WZ were responsible for field implementation, data collection, statistical analyses and draft writing. BC, CZ and SL contributed to the field implementation and data collection. MS, LG, YY, SW and XG reviewed and revised the manuscript. FD and YC made substantial contributions to the conception, design and supervision of the work, and reviewed and revised the manuscript critically. All authors approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. FD is responsible for the overall content as guarantor. FD accepts full responsibility for the finished work and the conduct of the study, has access to the data and controls the decision to publish.

Funding This work was supported by the National Natural Science Foundation of China (No. 22376005, 22076006, 82090014, 91543112), the Capital Health Development Research Project (No. 2020-2Z-40917) and the Japan Society for the Promotion of Science KAKENHI (No. JP18KK0268).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study protocol was approved by the Institutional Review Board of Peking University Health Science Center (IRB number: 00001052-21085). 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.

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Combinação do teste cutâneo da tuberculina com teste subsequente de libertação de interferão-gama melhora significativamente o rastreio de contactos domiciliários

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/thorax-2024-222400>).

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Received 29 August 2024

Accepted 3 May 2025

Published Online First 30 May 2025



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To cite: Chan CK, Leung CC, Huang SS, et al. *Thorax* 2025;80:650–657.

RESUMO

Introdução Em Hong Kong, o teste cutâneo da tuberculina (TCT) com um ponto de corte de 15 mm era utilizado aos 0 e 3 meses para o rastreio de contactos, mas até metade dos casos futuros de tuberculose podiam não ser detetados. Foi então introduzido, num programa piloto, um teste subsequente de libertação de interferão-gama (IGRA) para indivíduos com reação tuberculínica entre 5–14 mm.

Métodos Trata-se de um estudo de coorte prospetivo. Todos os contactos domiciliários de casos de tuberculose bacilífera, com idades entre 12 e 64 anos, registados no Serviço de Tuberculose e Doenças Torácicas de Hong Kong entre 1 de julho de 2018 e 30 de junho de 2022, foram acompanhados prospectivamente através de registos clínicos e do sistema nacional de notificação de tuberculose até 31 de dezembro de 2022. **Resultados** Entre os contactos não tratados com reação tuberculínica de 5–14 mm, quer no teste inicial quer no segundo teste aos 3 meses, a taxa de tuberculose foi significativamente mais elevada nos indivíduos com IGRA reativo em comparação com os IGRA não reativos (12,44 vs 0,75 por 1000 pessoas-ano; risco relativo: 16,52; $p=0,003$). Após ajustamento para a eficácia do tratamento preventivo nos casos tratados, as proporções estimadas de casos de tuberculose detetados com base nos critérios do programa piloto (TCT ≥ 15 mm ou TCT 5–14 mm com IGRA reativo ou conversão do TCT) foram semelhantes às obtidas com pontos de corte de TCT de 5 mm ou 10 mm, apesar de apresentarem taxas de positividade mais baixas. Com uma taxa global de positividade de 54,5%, o programa piloto identificou 95,8% dos casos futuros estimados de tuberculose, com um risco relativo entre casos positivos e negativos de 19. **Conclusão** A combinação do TCT com IGRA subsequente em indivíduos com reação tuberculínica de 5–14 mm melhora significativamente o rastreio de contactos domiciliários em contextos de carga intermédia de tuberculose.

INTRODUCTION

The prevention of active tuberculosis (TB) through detection and treatment of latent tuberculosis infection (LTBI) in household contacts is one of the important strategies for TB control.¹ The WHO recommends that either a tuberculin skin test (TST) or interferon-gamma release assay (IGRA) be used to test for LTBI.² However, the discriminating values of these tests, when used alone as a single-step test, for predicting TB have been reported as only modest³ and a fairly large number of persons screened have to be treated to prevent one future TB case.⁴ Partly as a result of these, the public acceptance of screening and preventive treatment for LTBI is often far less than optimal and only around 20% of eligible persons actually completed the full cascade of care.⁵ The practice of screening LTBI among household contacts varies according to different national guidelines.^{6–10} Some guidelines from countries with low TB incidence recommend the use of IGRA to confirm the diag-

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Tuberculin skin test (TST) and interferon-gamma release assay (IGRA) are currently used to establish the diagnosis of latent tuberculosis infection (LTBI), but the relative tuberculosis (TB) risks between test-positive and test-negative subjects were very modest.

WHAT THIS STUDY ADDS

► Follow-on IGRA markedly reduced the number of missed cases among household contacts with an intermediate tuberculin reaction of 5–14 mm, while minimising the number needed to treat. Repeat LTBI testing after 3 months greatly outperformed single time point testing.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► The study lends support to the use of follow-on IGRA after TST in areas with high BCG vaccination coverage. Repeat LTBI testing after 3 months allows time for test conversion after recent exposure, and the high relative risk found between test-positive and test-negative subjects suggests a need to re-examine the need for LTBI testing among household contacts in a setting with low ongoing TB transmission.

nosis of LTBI in TST-positive subjects to allow better targeting of preventive therapy.^{8,9} The basis for the recommendation was mainly due to a higher specificity and predictive performance of IGRA compared with TST.^{11–13} In Hong Kong, a city with intermediate TB burden (TB notification rate 43.6 per 100 000 in 2022) and routine neonatal Bacilli Calmette-Guerin (BCG) vaccination with 99% coverage,¹⁴ screening for LTBI is performed mainly by TST (using two units of protein purified derivative RT 23) under the existing local guideline.¹⁵ For household contacts, TST is repeated after 3 months if the first test is negative to allow time for TST conversion after recent exposure. IGRA is considered a suitable alternative.¹⁵ Given the high BCG coverage, a TST cut-off of 15 mm induration (TST15) is used for household contacts aged ≥ 12 years to limit the proportion of contacts requiring treatment and to maximise potential cost-effectiveness.¹⁶ However,

using TST15, 56% of future TB cases were missed according to a previous local study.¹⁷ A pilot service programme that added a follow-on IGRA (either QuantiFERON-TB Gold Plus or T-Spot.TB) to TST-negative contacts (TST<15 mm and without TST conversion) with tuberculin reaction of 5–14 mm in either the initial test or second test at 3 months was launched under ongoing evaluation since July 2018 (online supplemental figure S1). Contacts with a positive test result were offered LTBI treatment after exclusion of active TB in line with local recommendations.¹⁵ This study aimed to evaluate the added value of IGRA for follow-on screening of household contacts with a tuberculin reaction of 5–14 mm under the above-mentioned programme.

METHODS

Definition of household contacts

The subjects of this prospective cohort study included all household contacts of smear-positive TB aged 12–64 registered in the pilot service programme of Tuberculosis and Chest Service under the Department of Health of Hong Kong from 1 July 2018 to 30 June 2022. Household contacts aged 65 and over were excluded as elderly subjects were generally more prone to side effects from LTBI treatment and thus were not tested as per the existing local guideline.¹⁵ Household contacts were defined as those living under the same roof as the index case for at least 1 month.

Scheduling of follow-up visits

Household contacts accepting LTBI investigation attended scheduled follow-up visits at chest clinics to undergo testing as per online supplemental figure S1. Contacts screened positive for LTBI and accepted LTBI treatment attended monthly follow-up visits or more frequent visits during treatment based on the

clinical condition. Contacts not electing for LTBI investigation or treatment (for those screened positive) were offered follow-up visits 6–12 monthly during the study period, or as considered appropriate by the attending doctor. Reminders through phone calls by specially trained nurses were made for defaulter cases when necessary.

Collection of data

Demographics, the screening tests received and the test results were extracted from the relevant clinical records. Treatment information, including the regimen used and the interval between the date of initiation of screening and the date of start of LTBI treatment, was also extracted for those screened positive for LTBI. A positive screening test result was defined as either a tuberculin reaction of ≥ 15 mm, tuberculin conversion (an increase from a first to second TST of ≥ 10 mm), or a reactive follow-on IGRA result according to the manufacturers' protocols. LTBI treatment completion was defined as taking $\geq 80\%$ of prescribed doses within the specified period for the respective regimen.¹⁸ Information on TB events was obtained from the prospectively maintained structured records and through tracking the territory-wide TB notification registry of Hong Kong Department of Health up to 31 December 2022. Diagnostic and clinical information of all identified TB cases was verified against the relevant medical records. Co-prevalent TB cases suspected at initial contact evaluation (symptoms/signs and chest X-ray) and diagnosed within 1 month were excluded.¹⁹ Only TB cases proven by isolation of *Mycobacterium tuberculosis* complex, or in the absence of bacteriological confirmation, disease diagnosed on clinical, radiological and/or histological grounds together with an appropriate response to anti-TB treatment were included.

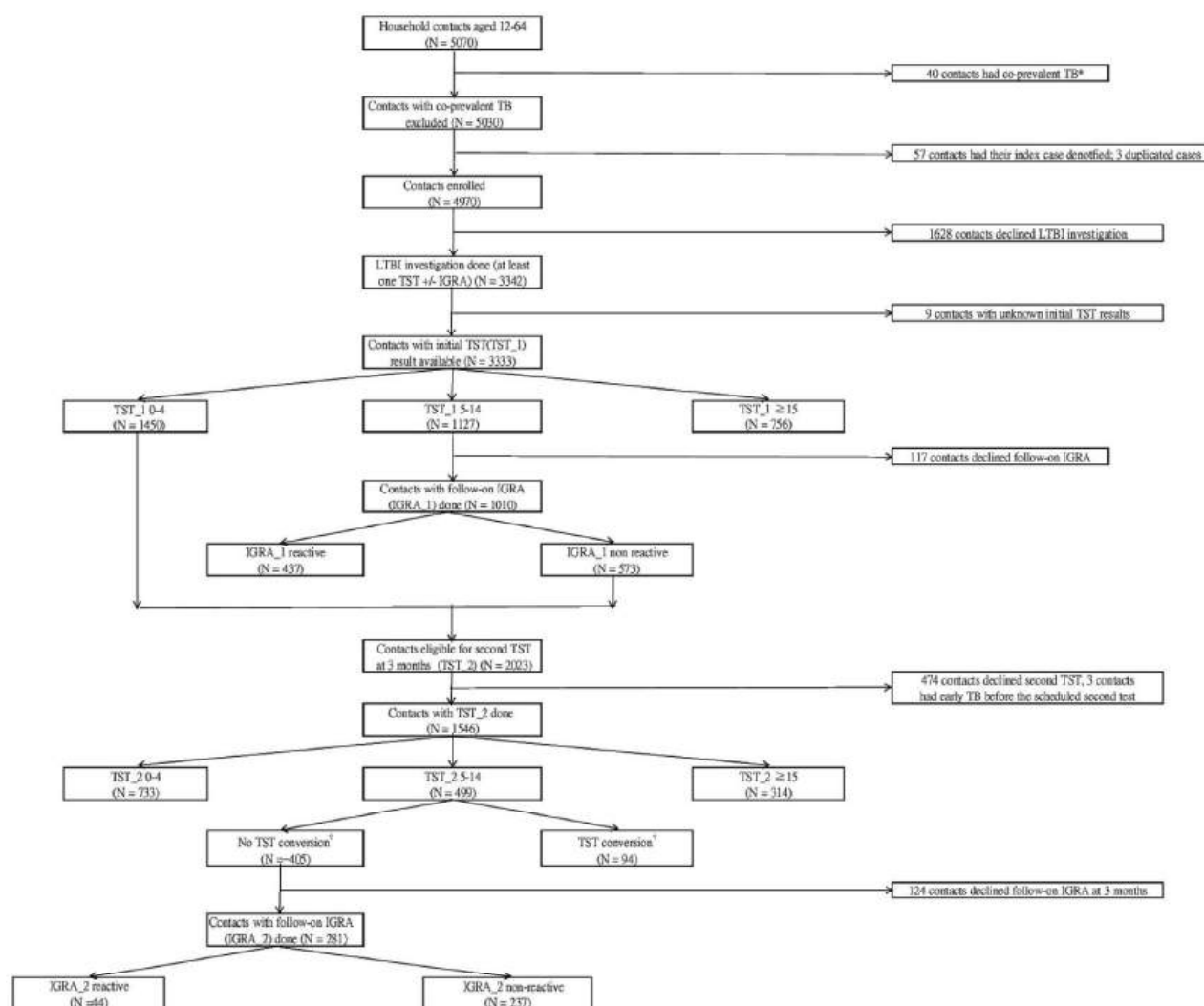


Figure 1 Flow diagram showing the study population and the number of contacts that underwent LTBI investigation at each stage.

Ethical considerations

Consent to use the collected personal data for research was included in the personal information collection form when personal data was collected on registration.

Data analysis

Analyses were conducted using the statistical software packages SPSS V.26 (IBM, Armonk (New York), USA) and MedCalc V.22 (MedCalc Software, Ostend, Belgium). Screening outcomes were analysed on a per contact basis. Baseline characteristics of contacts with tuberculin reaction of 5–14 mm who accepted and who declined follow-on IGRA were compared using Student's t-test for continuous variables and χ^2 or Fisher's exact test for categorical variables. Person-time at risk of TB was accrued from the date of initiation of contact screening until occurrence of active TB or 31 December 2022, whichever was earlier. The incident TB rates based on person-time accrued were compared between contacts with positive test results (stratified by LTBI treatment) and contacts with negative test results using χ^2 or Fisher's exact test as appropriate. Adjustment for sex, age and ethnicity was made using Cox regression analysis.²⁰ The test-positive rates for TST cut-off of 5 mm (TST5), 10 mm (TST10), 15 mm (TST15) and the pilot programme criterion of TST $\geq$ 15 mm/TST 5–14 mm and IGRA reactive/TST conversion in either the initial or second test at 3 months were compared using the Cochran Q test for related samples. To tackle potential bias from LTBI treatment, the theoretical number of TB cases (if left untreated) among treated contacts was estimated by multiplying the observed number of TB cases by the protective efficacy ratio of LTBI treatment as defined by the overall ratio of TB rates between untreated and treated test-positive contacts. The overall positive rate for contacts completing the initial and second test per pilot programme criterion was calculated by the formula 'initial test-positive rate + (1 – initial test-positive rate) x second test-positive rate'. The overall proportion of TB cases (after adjustment for LTBI treatment) captured by completing both initial and second test was estimated by the formula 'proportion of total TB cases captured by initial test + (1 – preceding proportion – proportion of early TB cases before scheduled second test) x proportion of TB cases captured by second test'. The relative risk between test-positive cases and test-negative cases was calculated by the formula '(overall captured proportion/overall positive rate)/[(1-overall captured proportion)/(1-overall positive rate)]'. The number needed to treat to prevent one case of TB (NNT) was calculated by the formula '(number of contacts screened X overall positive rate) / {total TB cases X overall proportion of TB cases captured X [(protective efficacy ratio-1)/protective efficacy ratio]}'. Sensitivity analyses were performed by using the protective efficacy ratio reported in a meta-analysis for adjustment²¹ and with restriction to bacteriologically confirmed TB cases. All statistical tests were conducted as two-sided, at the 5% significance level.

RESULTS

Study population, test coverage and baseline characteristics of contacts eligible for IGRA

A total of 5070 household contacts aged 12–64 (from 2523 smear-positive index cases) were identified from the pilot service programme during the study period. 100 cases were excluded from the analysis either because of duplicate entry (3), denotification of the index case (57) or TB suspected from initial contact evaluation (symptoms and signs plus chest X-ray) and started on treatment for active TB within 30 days from enrolment (40) (figure 1). Of the remaining 4970 contacts included in the analysis, 3342 (67.2%) had LTBI investigation (at least one TST and/or IGRA) done. The baseline characteristics of the 1532 contacts with tuberculin reaction of 5–14 mm and thus eligible for IGRA (either at baseline or at 3 months without TST conversion) were shown in table 1. The baseline characteristics of the contacts electing and not electing for IGRA were similar except that a slightly lower proportion in the former group had a history of BCG vaccination and/or presence of BCG scar compared with the latter among contacts with information available (810/1044 (77.6%) and 139/164 (84.8%), respectively, p=0.048) (table 1). Of 1291 contacts electing for IGRA, 1278 (99.0%) underwent the test with QuantiFERON-TB Gold Plus. Only about 1.0% of contacts were tested with T-Spot-TB as the IGRA test used was switched from T-Spot. TB to QuantiFERON-TB Gold Plus soon after the pilot programme was launched.

LTBI rate and treatment coverage

Results of baseline TST were available in 3333 out of the 3342 tested subjects. Nine contacts with missing data on baseline TST results were omitted from the analysis of LTBI rate and treatment coverage. The proportion of contacts completing and not completing the cascade of LTBI testing was shown in figure 2. LTBI was diagnosed among 1645 (49.4%), based on either initial TST $\geq$ 15 mm (756), reactive IGRA following initial TST 5–14 mm (437), second TST $\geq$ 15 mm (314), TST conversion (94) or reactive IGRA following second TST 5–14 mm without TST conversion (44). Of 1645 contacts screened positive for LTBI, 1105 (67.2%) accepted LTBI treatment (figure 2). The initial LTBI regimen used comprised either isoniazid monotherapy for 6 months (754, 68.2%), weekly isoniazid plus rifapentine for 12 weeks (342, 31.0%), rifampicin monotherapy for 4 months (9, 0.8%). 926 subjects (83.8%) completed LTBI treatment. The baseline characteristics of contacts with positive tests electing and not electing for LTBI treatment were similar (table 1).

Progression to TB among tested and untested contacts

A total of 78 subjects developed active TB. The median interval between the date of start of TB treatment and the date of enrolment was 5 months (IQR 2.2–17.4). Of the 78 TB cases,

Table 1 Baseline characteristics of contacts stratified by acceptance of IGRA and by acceptance of LTBI treatment

	Contacts with tuberculin reaction of 5–14 mm (N=1532)			Contacts screened positive for LTBI (N=1645)*		
	Subjects electing for IGRA† (N=1291 unless otherwise specified)	Subjects not electing for IGRA† (N=241 unless otherwise specified)	P value	Subjects electing for LTBI treatment (N=1105 unless otherwise specified)	Subjects not electing for LTBI treatment (N=540 unless otherwise specified)	P value
Male (N/%)	517 (40.0)	89 (36.9)	0.403	422 (38.2)	213 (39.4)	0.663
Age (mean $\pm$ SD)	40.82 $\pm$ 13.78	39.49 $\pm$ 14.00	0.170	42.02 $\pm$ 13.73	42.59 $\pm$ 14.22	0.435
Chinese (N/%)	1192 (92.3)	213 (88.4)	0.056	989 (89.5)	493 (91.3)	0.292
History of BCG vaccination and/or presence of BCG scar	810/1044 (77.6%)‡	139/164 (84.8%)‡	0.048	676/869 (77.8%)§	325/438 (74.2%)§	0.168

*A total of 1645 contacts were screened positive for LTBI, based on either initial TST $\geq$ 15 mm (756), reactive IGRA following initial TST 5–14 mm (437), second TST $\geq$ 15 mm (314), TST conversion (94) or reactive IGRA following second TST 5–14 mm without TST conversion (44).

†IGRA offered to 1532 contacts with either initial TST of 5–14 mm (at 0 month) (1127) or second TST of 5–14 mm without TST conversion at 3 months (405); IGRA was accepted by 1010 and 281 subjects, respectively.

‡Among contacts eligible for IGRA, information on BCG vaccination history and/or presence of BCG scar available in 1208/1532 contacts (78.9%).

§Information on BCG vaccination history and/or presence of BCG scar available in 1307 of 1645 contacts (79.5%) screened positive for LTBI.

BCG, Bacillus Calmette-Guérin; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; TST, tuberculin skin test.

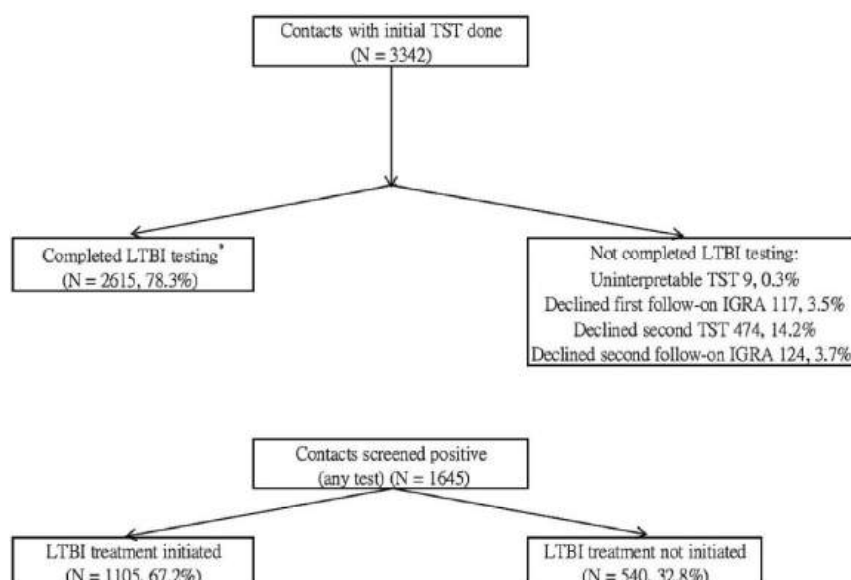


Figure 2 Flow diagram showing the proportion of contacts completing LTBI and initiating LTBI treatment.

33 occurred among 1628 contacts (2.0%) who declined LTBI investigation. 45 occurred among 3333 contacts (1.4%) who underwent LTBI investigation and/or treatment with a mean follow-up duration of 2.6 years. The overall TB rate among the tested contacts was 5.27 (95% CI 3.93 to 7.05) per 1000 person-years. The demographics and clinical manifestations of TB between patients accepting and declining LTBI testing were similar except that contacts with TB in the former were younger and a higher proportion had extrapulmonary involvement compared with those in the latter (table 2). Among the tested group, three TB cases (early TB cases) were diagnosed before the scheduled second test at 3 months among contacts screened negative in the initial test.

TB rates in different categories of test-positive and test-negative contacts, and overall protective efficacy of LTBI treatment

The observed TB rates among different categories of test-positive (with or without LTBI treatment) and test-negative contacts are shown in table 3. The TB rates were significantly higher among test-positive (TST $\geq$ 15 mm or TST 5–14 mm with a reactive follow-on IGRA or TST conversion) who declined treatment compared with test-negative contacts. Among untreated contacts with a TST of 5–14 mm in the initial or second test, the TB rates among those with a reactive follow-on IGRA and non-reactive IGRA were 12.44 (95% CI 4.04 to 29.04) and 0.75 (95% CI 0.02 to 4.20) per 1000 person-years, respectively (HR 25.0 (95% CI 2.78 to 100.0), $p=0.004$). Among test-

Table 2 Baseline characteristics and manifestations of incident TB among tested and untested subjects

	TB cases among untested subjects (N=33)	TB cases among tested subjects (N=45)	All TB cases (N=78)	P value
Baseline characteristics				
Male (N, %)	13 (39.4)	20 (44.4)	33 (42.3)	0.823
Age (mean, SD)	46.8 $\pm$ 13.5	32.2 $\pm$ 14.4	38.4 $\pm$ 15.8	<0.001
Chinese (N, %)	31 (93.9)	41 (91.1)	72 (92.3)	0.699
Comorbidity (N, %)*	12 (36.4)	10 (22.2)	22 (28.2)	0.263
Manifestations of TB				
Pulmonary and/or EPTB (N, %)	31 (93.9)	43 (95.6)	74 (94.9)	0.567
Extent of lung parenchymal lesion†				0.184
Minimal	24 (77.4)	39 (90.7)	63 (85.1)	
Moderate to extensive	7 (22.6)	4 (9.3)	11 (14.9)	
EPTB (N, %)‡	2 (6.1)	13 (28.9)	15 (19.2)	0.025
Mode of diagnosis of TB	25 (75.)	29 (64.4)	54 (69.2)	0.413
Bacteriological (positive smear and/or cult and/or molecular) (N, %)	8 (24.2)	16 (35.6)	24 (30.8)	
Histological/radiological clinical (N, %)				
Interval between contact date and date of start of TB treatment in months (median, IQR)§	5.7 (2.0–17.4)	4.7 (2.4–17.5)	5.0 (2.2–17.4)	0.797
*The most common comorbidities were diabetes mellitus (5), lung cancer (2) and alcoholism (2) among untested subjects with TB, and diabetes mellitus (3), nephritis (1) and alcoholism (1) among tested subjects with TB.				
†Among 31 contacts and 43 contacts with lung parenchymal lesions in the two groups, respectively; moderate to extensive lung lesion defined by lung parenchymal involvement more than the equivalent of a right upper lobe.				
‡The site of extrapulmonary involvement among the two untested contacts with EPTB was pleura (1), cervical lymph node (1); the site of extrapulmonary involvement among the 13 tested contacts with EPTB was pleura (7), hilar and/or mediastinal lymph node (4), cervical lymph node (2), chest wall mass (1) (one contact has more than one site of extrapulmonary involvement).				
§Interval between contact date and date of start of TB treatment was not available in one contact in either group (due to refusal of TB treatment/patient already left Hong Kong by the time sputum culture result became available, respectively).				
EPTB, extrapulmonary tuberculosis; TB, tuberculosis.				

Table 3 Breakdown of the TB rates among different categories of test positive (with or without LTBI treatment) and test negative household contacts under field conditions

Category	Number of contacts	Developed TB	Follow-up duration (PYs)	TB rate per 1000 PYs (95% CI)	Relative risk (unadjusted)*	P value	HR†	P value
TST without IGRA in first or second test								
TST≥15 mm or TST conversion, treated	769	4 (0.5%)	1934.39	2.07 (0.56 to 5.29)	0.08 (0.02–0.24)	<0.001	0.09 (0.03–0.25)	<0.001
TST≥15 mm, or TST conversion, untreated	395	24 (6.1%)	974.47	24.63 (15.78 to 36.65)	Reference	–	Reference	–
TST negative	1177	10 (0.8%)	3123.06	3.20 (1.54 to 5.89)	0.13 (0.06–0.28)	<0.001	0.12 (0.06–0.24)	<0.001
IGRA after TST 5–14 mm in first or second test								
IGRA positive, treated	336	1 (0.3%)	889.87	1.12 (0.03 to 62.61)	0.09 (0.002–0.81)	0.014	0.08 (0.01–0.64)	0.018
IGRA positive, untreated	145	5 (3.4%)	401.82	12.44 (4.04 to 29.04)	Reference	–	Reference	–
IGRA negative‡	511	1 (0.2%)	1327.72	0.75 (0.02 to 4.20)	0.06 (0.001–0.54)	0.003	0.04 (0.01–0.36)	0.004
Total	3333§	45 (1.3%)	8540.77	5.27 (3.93 to 7.05)				

*Comparison of rates using χ^2 test.
†Adjusted for age, sex, ethnicity using Cox regression analysis.
‡Excluding contacts with initial IGRA negative but subsequent tests positive (either second TST≥15 or TST conversion).
§Excluding nine contacts with unknown initial TST result.
IGRA, interferon gamma release assay; LTBI, latent tuberculosis infection; PY, person-years; TB, tuberculosis; TST, tuberculin skin test

positive contacts, the protective efficacy ratio of LTBI treatment estimated from the overall ratio of TB rates between test-positive cases accepting and not accepting treatment was 11.87 (95% CI 4.62 to 30.49) (table 3). Similar results were obtained when the analysis was restricted to contacts who underwent IGRA with QuantiFERON-TB Gold Plus only (online supplemental table S1).

Distribution of TB cases by TST cut-offs

Table 4 shows the observed and adjusted number (adjusted for protective efficacy of LTBI treatment) of TB cases by different TST cut-offs and the programme criterion of TST≥15 mm/TST 5–14 mm and IGRA reactive/TST conversion. Consistently lower proportions of adjusted TB cases were captured using TST15

Table 4 Number of observed and adjusted TB cases by TST cut-offs*

	TST cut-off ≥ (mm)			Programme criterion	P value
	5	10	15	15/conversion/IGRA+ve	
Initial test (N=3333)‡					
Test +ve: N (%)	1883 (56.5)	1362 (40.9)	757 (22.7)	1193 (35.8)	<0.001§
TB cases among test +ve	29 (3)	23 (3)	17 (2)	22 (3)	–
Adjusted TB cases¶ among test +ve	61.61	55.61	38.74	54.61	–
TB cases among test –ve††	16 (2)	22 (2)	28 (3)	23 (2)	–
Adjusted TB cases¶ among test –ve	37.74	43.74	60.61	44.74	–
Adjusted total TB cases	99.35	99.35	99.35	99.35	
Adjusted proportion of TB detected by +ve test	62.0%	56.0%	39.0%	55.0%	<0.001††
Second test (N=1546)					
Test+ve: N (%)	813 (52.6)	595 (38.5)	314 (20.3)	452 (29.2)	<0.001§
TB cases among test +ve	12 (2)	12 (2)	8 (2)	12 (2)	–
Adjusted TB cases¶ among test +ve	33.74	33.74	29.74	33.74	–
TB cases among test –ve**	1 (0)	1 (0)	5 (0)	1 (0)	–
Adjusted TB cases¶ among test –ve	1	1	5	1	–
Adjusted total TB cases	34.74	34.74	34.74	34.74	
Adjusted proportion of TB detected by +ve test	97.1%	97.1%	85.6%	97.1%	0.007††

*Adjustment for protective efficacy of LTBI treatment at any stage after enrolment and before the occurrence of active TB.

†Cochrane Q test for related samples.

‡Initial TST result not available in nine out of 3343 contacts.

§Comparing test positive rates between different cut-offs.

¶Figures in brackets denote the number of TB cases who had received LTBI treatment.

||Number of adjusted TB cases equals number of untreated+treated x protection efficacy ratio; protective efficacy ratio=overall ratio of TB rates between untreated/treated test-positive cases (11.87 in this study).

**Contacts with negative initial test results; received LTBI treatment subsequently due to either TST≥15 mm, TST conversion or reactive IGRA on second testing at 3 months.

††Comparing adjusted proportion of TB detected by positive test result between different cut-offs.

+ve, positive; LTBI, latent tuberculosis infection; TB, tuberculosis; TST, tuberculin skin test; –ve, negative.

than other TST cut-offs or the pilot programme criterion in the initial test and second test. The proportions of adjusted TB cases captured by the pilot programme criterion were similar to those captured using TST5 or TST10 in the initial and second test. The test-positive rates using the pilot programme criterion were lower than those using TST5 or TST10 in both tests. Similar findings were observed in a sensitivity analysis that used a lower protective efficacy ratio of 2.44 reported in a meta-analysis for calculating the adjusted TB rates for various cut-offs (online supplemental table S2)²¹ and in another sensitivity analysis restricted to bacteriologically confirmed TB cases (online supplemental table S3). The overall positive rate for contacts completing the initial and second test at 3 months per pilot programme criterion was calculated according to the formula stated in the method section to be 54.5% (table 4). As shown in table 4 and online supplemental table S2, the initial test alone missed a very substantial proportion of future TB cases by any of the listed cut-offs. The overall proportion of adjusted TB cases captured by completing both initial and second tests in our pilot programme was estimated by the formula as stated in the method section to be 95.8% using protective efficacy ratio of 11.87 (table 4), or 91.5% using protective efficacy ratio of 2.44 (online supplemental table S2). The corresponding relative risks between test-positive cases and test-negative cases were 19.0 (NNT=20.8) and 9.0 (NNT=64.4), respectively.

DISCUSSION

Key findings

In this study, a high TB rate of 12.44 per 1000 person-years was observed among untreated contacts with a reactive follow-on IGRA after an intermediate TST of 5–14 mm, which was 25-fold of that of similar contacts with a non-reactive follow-on IGRA (table 3). The risk of TB in untreated test-positive cases was 12.5-fold that of treated cases. The proportions of adjusted TB cases captured by the pilot programme criterion were higher than those captured by TST15 but similar to those captured by TST5 or TST10 in the initial and second test (table 4). However, the test-positive rates using the pilot programme criterion were lower than those using TST5 or TST10 in both tests (table 4). For contacts completing the initial and second test under the pilot programme, 54.5% were tested positive with 95.8% of estimated future TB cases captured. The estimated relative risk between test-positive cases and test-negative cases under the pilot programme was very high, irrespective of whether the observed protective efficacy ratio (table 4) or meta-analysis-reported protective efficacy ratio (online supplemental table S2) was used to adjust for the protective effect of LTBI treatment.

Comparison on the rate of LTBI with previous studies

The overall rate of LTBI among the screened household contacts was 49.4% in the present study, similar to the reported rate of 54.8% in a previous local study.¹⁷ Slightly lower LTBI rates were reported in a South Korean study in which contacts underwent both TST and IGRA (TST positivity rate 42.6% and IGRA positivity rate 45.7%, respectively).²² The relatively high LTBI rate in both local studies could have been due to the overcrowded living environment in Hong Kong. In populations exposed to a high burden of TB in the past few decades, remote infection could also have contributed partly to the LTBI rates detected among contacts. While some subjects tested positive for LTBI could have a false positive reaction to BCG or boosted TST reaction, the proportion of such false positive cases should be small as the contact screening in Hong Kong has been using a high cut-off of 15 mm for a positive TST and an increase of 10 mm from first to second test for TST conversion.

Comparison on incident TB rates and TB risk between positive and negative tests with previous studies

A totindex cases) were identified from the pilot service. The overall TB rate among tested household contacts of smear positive TB was 5.27 (95% CI 3.93 to 7.05) per 1000 person-years of follow-up. The rate was similar to that reported in the previous local study,

in which 25 cases of active TB were detected among a cohort of 1049 contacts with a total of 4910 person-years of follow-up (TB rate 5.09 (95% CI 3.44 to 7.53)).¹⁷ The rate was also similar to that reported among contacts of patients with TB in a large Brazilian cohort, but was higher than that reported among contacts in low incidence settings.^{23 24}

In contrast with the modest relative risks between test-positive and test-negative subjects of around two reported for a single TST or IGRA in a meta-analysis,³ a high relative risk of 16.52 (95% CI 1.85 to 781.4) was found between follow-on IGRA reactive and non-reactive untreated contacts with intermediate TST reaction of 5–14 mm in our study. While the CIs might partially overlap because of the modest number of active TB cases observed in this study as in other contact screening studies,²⁵ the lower risk of ongoing TB transmission in the local settings likely contributed to the higher relative risk.²⁶ The estimated relative risk between test-positive and test-negative contacts having completed the initial and second test in our pilot programme was also very high. Here, the use of a second test at 3 months was likely instrumental as shown by the high proportions of future TB cases missed by the initial test and very low proportions of future TB cases missed by the second test (table 4 and online supplemental table S2).

The observed protective efficacy ratio from LTBI treatment of 11.87 in our study was much higher than that of 2.44 reported in a meta-analysis.²¹ While lower ongoing TB transmission in the local setting²⁶ and use of alternative regimens other than 6 months of isoniazid might have contributed, self-selection of lower risk contacts for treatment could not be completely excluded. However, as eligibility for treatment was decided by a single programme criterion, such selection bias should not unduly affect comparison across alternative cut-offs in either the initial or second test. In any case, consistent findings were observed in the comparison across alternative cut-offs irrespective of whether the observed (table 4) or meta-analysis-reported protective efficacy ratio (online supplemental table S2) was used to adjust for the protective effect of LTBI treatment.

Implications

For screening and preventive treatment of LTBI to exert material impact on TB control, we need far more than the reported 20% of eligible subjects actually completing the full cascade of care. The low relative risk observed between test-positive and test-negative subjects in previous studies³ was likely because a single LTBI test cannot adequately cover subjects with recent and/or ongoing TB exposure. Such findings might not help to motivate either clinicians or patients for LTBI testing. Indeed, in its latest guideline on TB preventive treatment published in 2020, the WHO recommended that adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment.²⁷ LTBI testing was not a requirement for initiating preventive treatment. However, as clearly shown in this study, the discriminating value of LTBI testing could be very high when testing was repeated at 3 months for TB contacts with an initial negative test to allow time for tuberculin or IGRA conversion in a setting with good control of ongoing TB transmission. In sharp contrast to the first test, the second test barely missed any future TB cases. This clearly pointed to the window period for test conversion rather than ongoing transmission as the principle reason for the proportion of missed TB cases by the first test.

The high BCG vaccination coverage in Hong Kong also complicated the use of TST for LTBI testing. While our previously used treatment criterion of TST15 did identify contacts at higher risk in this study and the previous study,¹⁷ a follow-on IGRA helped to sharply reduce the risk among those with intermediate tuberculin reaction of 5–14 mm. Although adopting a lower TST cut-off to 5 or 10 mm may also help to minimise the risk of TB among test-negative subjects, this was achieved by putting more contacts on treatment not completely free of adverse effects.²⁸ As only a small proportion of infected subjects will ever develop active TB,²⁹

³⁰ minimising the number of contacts put on treatment is needed to achieve an optimal benefit: risk ratio. With the improved testing performance after the addition of follow-on IGRA for contacts with tuberculin reaction of 5–14 mm in our pilot programme, the estimated NNT was as low as 21, which compared very favourably with other published studies.⁴ It is hoped that these new findings can improve confidence in LTBI testing and promote acceptance of preventive treatment among household contacts in settings where ongoing TB transmission is under control.

Strengths and limitations

This study included a large cohort of contacts screened under a territory-wide pilot screening programme in a real-world setting. With a well-established notification system locally, it was possible to track incident TB cases even among those who did not return for follow-up. Among 1532 contacts with TST 5–14 (first and second test without TST conversion combined), a high proportion of 84.3% completed the test. The baseline characteristics of the contacts electing and not electing for IGRA were similar (table 1). Although a slightly lower proportion of the former group had a history of BCG vaccination and/or presence of BCG scar compared with the latter, this would go against self-selection of BCG-vaccinated contacts for IGRA testing. As subjects under evaluation were not immunocompromised and all were given the tests irrespective of other background factors not evaluated in this study, the latter were less likely to confound the association between the test results and the development of TB, especially for comparison of different tests or cut-offs within the same subjects. However, only 67.2% of household contacts accepted screening for LTBI, and only around three quarters of those with a negative initial test per pilot programme criterion completed the second test. Uncertainty could occur related to selection bias on extrapolation from tested subjects to untested subjects even though there was no major difference in their baseline characteristics. With the modest incident TB rates observed in our study as in other contact screening studies,²⁵ it was only possible to compare the TB rates by the overall programme TST positive criterion of TST $\geq$ 15 mm and/or TST conversion and follow-on IGRA after TST 5–14 mm. As eligibility for the second test was necessarily decided by the single pilot programme criterion, it was only possible to compare across alternative cut-offs among subjects having undertaken initial test and second test separately (table 4). With preventive treatment of detected LTBI being the standard of care, it was only possible to directly observe the future TB risk among untreated subjects. Adjustment for the protective effect of preventive treatment is needed to estimate the risk of TB among treated subjects if left untreated. As preventive treatment further reduced the observable numbers of TB among household contacts, the adjusted results as shown in table 4 and online supplemental table S2 were subject to considerable uncertainties. However, as discussed above, the key comparative findings across alternative cut-offs were consistent irrespective of whether a high or low protective efficacy ratio was used, thereby supporting their robustness even in the presence of such uncertainties. While studies have reported that IGRA has better sensitivity, better predict progression to active TB and has superior specificity in BCG-vaccinated persons, the discriminating value of IGRA when used alone as a single-step test for predicting TB is modest.³ The results from our study suggest that combining TST and IGRA at 0 and 3 months may improve the screening of household contacts in places with an intermediate TB burden and good infrastructure. Further studies to address the cost-effectiveness may help to confirm the usefulness of such a combined, serial-testing screening approach.

Acknowledgements We would like to thank all our colleagues in the Tuberculosis and Chest Service who, by their assistance and support, have made this paper possible. We would also like to express our gratitude to Ms Ida Ka Yun Mak for her dedicated effort in maintaining the database for the Pilot Service Programme and helping with the analysis.

Contributors CKC and CCL conceived and designed the study. CKC and SSH were responsible for data collection. CCL, CKC and SSH were responsible for analysis and interpretation of data. CKC and CCL were involved in manuscript writing. All authors (CKC, CCL, SSH, S-nML and L-bT) were involved in revision and final approval of the manuscript. CKC was the guarantor of this article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by The Ethics Committee of the Department of Health of Hong Kong (U/M 585/2023).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon 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.

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Epidemiologia e perfil clínico das infecções pediátricas por VSR: contributos de um estudo de coorte australiano de 6 anos

Vários estados australianos registaram padrões imprevisíveis de infecção por vírus sincicial respiratório (VSR) durante a pandemia de COVID-19. Compreender o perfil das crianças com infecções graves por VSR e as alterações ocorridas na era pandémica pode informar programas de prevenção contra o VSR. Embora tenhamos descrito anteriormente o aumento fora de época das infecções por VSR após o relaxamento das intervenções não farmacológicas (INFs)¹ e os preditores de infecção grave por VSR na era pré-pandémica², este artigo inclui dados adicionais e uma análise secundária. Os objetivos deste estudo foram descrever os impactos da pandemia de COVID-19 na (1) epidemiologia das infecções por VSR, (2) perfil clínico e (3) gravidade das infecções por VSR em crianças hospitalizadas num hospital pediátrico em Melbourne, Austrália.

Neste estudo de coorte retrospectivo, utilizámos dados de crianças (<2 anos) hospitalizadas com infecção por VSR confirmada laboratorialmente ao longo de seis épocas de VSR (entre 1 de janeiro de 2017 e 31 de dezembro de 2022). Os dados foram recolhidos como parte da vigilância do VSR da OMS³ e do estudo CAMEO-RSV² (Epidemiologia Clínica e Molecular e Características Imunológicas das Infecções por VSR em Crianças) no Royal Children's Hospital (RCH), Victoria.

Os dados extraídos dos registos médicos eletrónicos das crianças incluíram dados demográficos, idade, estado de prematuridade, idade gestacional, comorbilidades, tratamentos e desfechos clínicos. Apresentamos os resultados graficamente para ilustrar a sazonalidade do VSR ao longo dos anos e mostramos os resultados dos anos pré-pandémicos (2017–

Table 1 Demographic characteristics and severity indicators for children hospitalised for RSV infection during pre-pandemic versus pandemic NPI eras (N=1738)

Characteristic	Pre-pandemic			Pandemic NPI		
	2017	2018	2019	2020	2021	2022
	N=232 n (%)	N=354 n (%)	N=383 n (%)	N=36 n (%)	N=237 n (%)	N=496 n (%)
Age (months), median (IQR)	3.5 (1.3–10.3)	4.6 (1.8–12.7)	3.7 (1.4–10.1)	9 (2.2–17)	3.3 (1–13)	5.5 (2–12)
Sex, female	117 (50.4)	155 (43.8)	151 (39.4)	19 (52.8)	96 (40.5)	219 (44.2)
Any comorbidity	37 (16.0)	62 (17.5)	80 (20.9)	3 (8.3)	33 (13.9)	47 (9.5)
Cardiac comorbidity	14 (6.0)	22 (6.2)	31 (8.1)	3 (8.3)	18 (7.6)	24 (4.8)
Respiratory comorbidity*	7 (3.0)	17 (4.8)	25 (6.5)	0 (-)	9 (3.8)	12 (2.4)
Chronic lung disease of prematurity	4 (1.7)	9 (2.5)	6 (1.6)	0 (-)	2 (0.8)	11 (2.2)
Premature† born <37 weeks GA	46 (19.8)	78 (22)	80 (20.9)	6 (16.7)	34 (14.6)	69 (14.3)
Premature† born <34 weeks GA	15 (6.5)	32 (9.0)	29 (7.6)	1 (2.8)	10 (4.2)	35 (7.1)
Severity indicator						
Hospital LOS (days), median (IQR)	3.0 (1.2–5.0)	2.2 (1.1–4.1)	2.2 (1.2–4.1)	2.2 (1–6.4)	1.9 (1–4.2)	2 (1–3.5)
ICU admission	89 (38.6)	93 (26.3)	84 (21.9)	8 (22.2)	38 (16.0)	68 (13.7)
ICU LOS (days), median (IQR)	3.2 (2–5.2)	2.2 (1.2–5.1)	3.2 (1.2–6.1)	7.6 (4.0–9.2)	3.8 (2.6–5.8)	2.7 (1.9–5.4)
Antibiotics*	123 (53.0)	175 (49.4)	181 (47.5)	15 (41.6)	79 (33.3)	192 (38.7)
No respiratory support provided	85 (36.6)	181 (51.1)	198 (51.7)	26 (72.2)	151 (63.7)	210 (42.3)
Low-flow oxygen via nasal prongs	27 (11.6)	44 (12.4)	48 (12.5)	3 (8.3)	34 (14.3)	153 (30.9)
High-flow oxygen via nasal prongs	85 (36.6)	85 (24.0)	91 (23.8)	2 (5.6)	25 (10.5)	90 (18.2)
CPAP	21 (9.1)	31 (8.7)	30 (7.8)	1 (2.8)	18 (7.6)	30 (6.1)
Mechanical ventilation	14 (6.0)	13 (3.7)	16 (4.2)	4 (11.1)	9 (3.8)	13 (2.6)
Deceased	0 (-)	0 (-)	3 (0.8)	0 (-)	1 (0.4)	0 (-)

Level of respiratory support provided refers to the maximum level of supplemental oxygen or invasive support required, only one level per child. Of the four children who died over the study period, we did not investigate these deaths further and RSV may not have been the primary cause of death.
 *Not chronic lung disease of prematurity.
 †Data not recorded or unknown for 2021.
 CPAP, continuous positive airway pressure; GA, gestational age; ICU, intensive care unit; LOS, length of stay; NPI, non-pharmaceutical intervention; RSV, respiratory syncytial virus.

2019) e dos anos com INFs pandémicas (2020–2022).

A Figura 1 mostra uma redução dramática nas hospitalizações associadas ao VSR durante 2020, com um aumento acentuado de casos após o relaxamento das INFs. Isto incluiu casos fora de época em 2021, seguidos de um forte aumento sazonal em 2022. As características das crianças hospitalizadas mudaram ao longo do tempo, com menor taxa de prematuridade e

comorbilidades na era das INFs pandémicas (ver Tabela 1). A maioria das crianças (72,2%) não apresentava fatores de risco predisponentes para VSR. Verificou-se uma diminuição na proporção de admissões com antecedentes de prematuridade (de 19,8% para 14,3%) ou comorbilidades (de 16,0% para 9,5%) ao longo do período do estudo.

As alterações na epidemiologia do VSR associadas às INFs relacionadas com a pandemia foram sem precedentes. Victoria teve confinamentos rigorosos e prolongados, totalizando 262 dias entre 2020 e 2021. As INFs tiveram um impacto dramático na transmissão do VSR, com um aumento acentuado de casos após o levantamento das restrições, resultando numa duplicação das hospitalizações em 2022, ano em que as infecções regressaram ao pico habitual de inverno. Este aumento parece resultar tanto de uma melhor deteção, devido à testagem generalizada, como de uma verdadeira subida na incidência de bronquiolite no RCH, sugerindo um aumento real de infecções e não apenas uma melhoria na vigilância.

As características das crianças hospitalizadas evoluíram, com menor prevalência de prematuridade e comorbilidades na era pandémica em comparação com a era pré-pandémica. A gravidade clínica também diminuiu, com menores taxas de internamento em cuidados intensivos e menor utilização de oxigenoterapia por cânula nasal de alto fluxo.

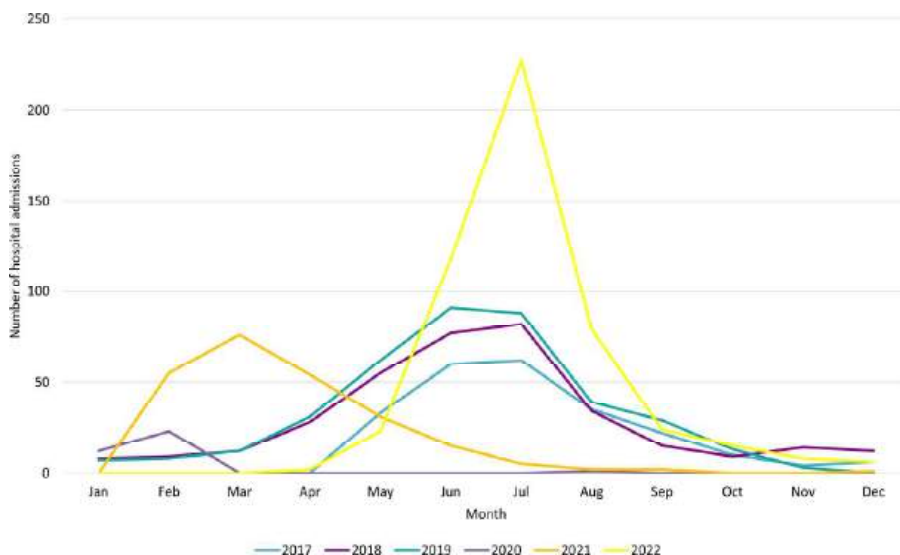


Figure 1 Number of respiratory syncytial virus admissions per month for years 2017–2022, N=1738.

Os nossos resultados ilustram variações na epidemiologia do VSR durante a pandemia de COVID-19, com uma tendência para um perfil clínico mais ligeiro na era das INFs em comparação com o período pré-pandémico. As razões para esta mudança permanecem incertas.

Embora este estudo descritivo forneça dados relevantes do período pandémico, é difícil prever como a epidemiologia do VSR evoluirá na era das medidas preventivas, como a vacinação materna e os anticorpos monoclonais em lactentes. Um Programa Nacional de Proteção Materna e Infantil contra o VSR foi iniciado na Austrália a 3 de fevereiro de 2025. Serão necessários estudos adicionais para acompanhar a evolução da epidemiologia do VSR.

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Contributors All authors contributed to the study conception and design. AA, DW, JA and HI contributed to data collection, with project administration led by AA. JT led the data analysis with verification from JA. JT led writing the original draft. All members of the RCH RSV Research Group contributed to the study conception and design, data interpretation and writing—review and editing of the final draft.

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 JT and DW are named on an investigator-led project grant sponsored by GlaxoSmithKline. DW has received consultancy fees from Merck Sharp and Dohme (MSD) and Praxhub, which have been directed to a research fund. AA, IB and NC have received funding from the Australian Department of Health for RSV hospitalisation surveillance in children under 2 years, as part of a WHO-led international RSV surveillance project. All other authors have no conflicts of interest to declare.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by RCH Human Research Ethics Committee (HREC #37185 and HREC#37024).

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data may be made available for use by future researchers from a recognized research institution whose proposed use of the data has been ethically reviewed and approved by an independent committee and who accept MCRI conditions for access.

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To cite Tuckerman J, Anderson J, Alafaci A, et al.

Arch Dis Child 2025;110:759–760.

Accepted 3 March 2025

Published Online First 15 March 2025

Arch Dis Child 2025;110:759–760.

doi:10.1136/archdischild-2025-328666

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