

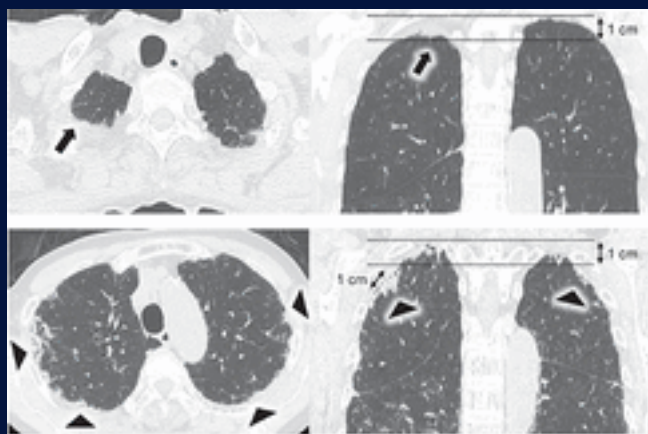
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Índice Volume 7 Número 4 Thorax com artigos do Archives of Disease in Childhood julho / agosto 2023

Edição Portuguesa N.º 4 julho / agosto 2023 - Volume 7

169 Editorial

171 Será que os “milhões de doentes desaparecidos” com DPOC querem ser encontrados?

172 Efeitos respiratórios da poluição atmosférica: é o momento de travar esta trajetória mortal

174 Artigo original

174 Otimização do salbutamol intravenoso em crianças: um estudo de fase 2

180 Condutividade no suor no diagnóstico de fibrose quística após rastreio positivo em recém-nascidos: estudo prospetivo da precisão dos testes de diagnóstico

185 Doença pulmonar pediátrica

185 Diferença de importância mínima em doenças pulmonares intersticiais infantis

192 Displasia broncopulmonar e fluxo aéreo expiratório aos 8 anos em crianças extremamente prematuras na era pós-surfactante

199 Doença pulmonar obstrutiva crónica

199 Terapêutica de manutenção e alívio com budesonida/formoterol vs. tratamento com dose fixa de fluticasona/salmeterol em pacientes com DPOC

206 Asma

206 As exacerbações da asma estão associadas a uma diminuição da função pulmonar: um estudo longitudinal de base populacional

215 Epidemiologia respiratória

215 A poluição atmosférica associada à incidência e trajetória da progressão de doenças pulmonares crónicas: um estudo de coorte de base populacional

222 Doença pleural

222 Diferenciação dos derrames pleurais malignos e benignos com base em inteligência artificial



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Editorial

Em pleno Verão escaldante, em que as preocupações ambientais e com a saúde dos residentes em Portugal estão em foco, este número da Edição de artigos das Revistas *Thorax* e *Archives of Disease in Childhood*, dedicados aos Sócios das Sociedades Científicas de Pneumologia, Alergologia e Imunologia Clínica, Medicina Geral e Familiar e Pediatria, apresenta uma série de artigos muito atuais e que incidem se quisermos em 3 vetores interrelacionados: o diagnóstico precoce das doenças ou das suas determinantes, o ambiente, e em particular a poluição atmosférica como gerador de doença e, por fim, as trajetórias das doenças e os fatores que as influenciam, nomeadamente o acesso aos serviços de saúde e/ou os métodos ativos de rastreio e a influência da literacia das populações na sua aceitação/adesão.

Este número da revista coloca ao nosso dispor 2 editoriais sobre as doenças pulmonares mais frequentes e/ou mortais em idade adulta: a DPOC e o cancro do pulmão. Descrevem a amplitude causal, da potencialidade atual de diagnóstico precoce e da associação entre ambas. Boa indução para uma reflexão e revisitação dos programas para as doenças respiratórias existentes em Portugal. Temos depois 8 artigos que descrevem estudos originais que revisitam a asma e a DPOC e a terapêutica, em crise ou de controlo. O artigo de Sandra Walsh *et al.* revisita a farmacocinética e farmacodinâmica do salbutamol por via ev na crise aguda de asma na criança e o de Susan Muiser *et al.* descreve os resultados do estudo comparativo entre budesonida/formoterol utilizado na estratégia MART (*symptom-driven maintenance and reliever therapy*) e fluticasona/salmeterol em dose fixa. Ainda bem que continuam a existir estudos farmacológicos que nos auxiliam, com as evidências, a nós prescritores...

Finalmente, mas não com menor importância, 3 artigos que incidem nas doenças raras mas de grande importância e impacto na saúde: métodos que aumentam a precisão no diagnóstico de fibrose quística com potencial utilização em Países com menos recursos, metodologias para monitorização da progressão da doença pulmonar intersticial na criança e resultados de estudos de função respiratória em crianças com displasia broncopulmonar. Este último artigo descreve os resultados funcionais respiratórios aos 8 anos de idade, mas alguns destes doentes são neste momento adultos com limitações funcionais relevantes!

E para terminar 2 artigos que espelham as nossas preocupações atuais: a influência da poluição atmosférica no desencadear de doença pulmonar e o potencial de modelos de inteligência artificial na discriminação de doença maligna através da análise de TC torácicas em derrames pleurais. O futuro está já no presente....

Boas leituras! Bom Verão! Boas Férias!

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Será que os “milhões de doentes desaparecidos” com DPOC querem ser encontrados?

David MG Halpin^{1,2}

Encontrar os “milhões de doentes desaparecidos” com DPOC tornou-se num mantra da política de saúde. No Reino Unido, 1,4 milhões de pessoas estão diagnosticadas com DPOC, mas estima-se que entre 50 e 65% das pessoas que vivem com DPOC não estão diagnosticadas. Esta situação agravou-se devido à pandemia da COVID-19, quando as novas taxas de diagnóstico caíram mais de metade. Num estudo recente com doentes com DPOC, 22% referiram que o período de espera para o diagnóstico após a identificação de sintomas é igual ou superior a cinco anos.¹ Em muitos casos, os doentes tiveram dificuldades em aceder ao teste de diagnóstico com espirometria. Contudo, uma em cada três pessoas referiu que se deveu ao facto de terem esperado pelo menos um ano até procurarem ajuda. O relatório concluiu que a obtenção do diagnóstico foi “frequentemente o culminar de um longo período de deterioração de sintomas e oportunidades perdidas”.

A detecção de casos nos grupos de alto risco para identificar a DPOC é recomendada^{2,3} e a inclusão da espirometria em rastreios de doença pulmonar (RDP) em fumadores ou ex-fumadores parece ser uma forma evidente de encontrar alguns dos milhões desaparecidos. Nesta publicação, Bradley *et al.* descrevem a sua experiência de incluir a espirometria pré-prova de resposta ao broncodilatador (PRBD) em RDP com tomografia computadorizada de dose baixa para rastreio do cancro do pulmão, em Yorkshire.⁴ Apesar de o programa de rastreio ter tido pouca adesão, a maior parte das pessoas que participaram concordou em realizar a espirometria. Das 2391 pessoas que realizaram a espirometria pré-prova de resposta ao broncodilatador (PRBD), 201 preencheram os critérios para uma avaliação mais aprofundada para possível DPOC não diagnosticada, mas, entre estas, 25% recusaram o encaminhamento. Não existiram diferenças na sintomatologia, taxas de tabagismo ou espirometria entre os que concordaram ser encaminhados e os que recusaram. Dos 151 convidados para avaliação mais aprofundada, um terço não compareceu, o que significa que apenas metade dos doentes elegíveis compareceram numa avaliação. Entre os doentes que não compareceram, verificou-se que 20% apresentavam valores de FEV₁/FVC após prova de resposta ao broncodilatador (PRBD) >0,7 e, como tal, não cumpriam os critérios de diagnóstico para DPOC. Após a avaliação, 32% dos que apresentaram obstrução do fluxo aéreo (OFA) após prova de resposta ao broncodilatador (PRBD) foram medicados com beta-agonistas de curta duração e 35% iniciaram terapêutica de controlo com broncodilatador duplo indicada pelo seu médico de família. Um quarto dos referidos doentes foram referenciados para reabilitação pulmonar, mas, destes, 75% recusaram. Os pontos fortes do estudo de Bradley *et al.* são a avaliação pormenorizada do que aconteceu aos pacientes após a participação

no programa de rastreio, bem como a natureza autêntica dos dados. Um ponto fraco diz respeito à ausência de informação sobre as razões pelas quais os participantes não aderiram a uma avaliação mais aprofundada.

No total, 2,5% dos doentes que realizaram espirometria no RDP receberam um novo diagnóstico de DPOC no seu registo do médico de família. Outros programas de RDP reportaram que cerca de 10% dos participantes apresentaram OFA sintomática não diagnosticada, com base na espirometria pré-prova de resposta ao broncodilatador (PRBD), mas não investigaram se estes indivíduos participaram noutra avaliação mais aprofundada ou se receberam tratamento.^{5,6} A aparente dificuldade em conseguir que as pessoas participem em mais investigações para confirmar ou recusar o diagnóstico de DPOC é motivo de preocupação. O aumento da privação e o tabagismo são fatores que permitiram prever a fraca aceitação do RDP, mas nenhum deles nem qualquer outro parâmetro avaliado pelos investigadores previram o envolvimento numa avaliação mais aprofundada. Todos os doentes com sintomas, incluindo aqueles que apresentavam apenas sintomas moderados, foram referenciados para uma avaliação mais aprofundada. Contudo, tal como referido pelos autores, se a referência estivesse limitada a doentes mais sintomáticos através da utilização de um limiar do *score* do Teste de Avaliação para DPOC, tal poderia levar a uma proporção de participação mais elevada. É importante que a espirometria pré-prova de resposta ao broncodilatador (PRBD), por si só, não seja utilizada para orientar o tratamento e que a terapia inalatória só tenha início após a espirometria pós-broncodilatador confirmar o diagnóstico, embora a cessação tabágica deva ter sido, e foi, recomendada a todos os fumadores que realizaram o rastreio.

Só será possível encontrar os “milhões desaparecidos” se eles quiserem. Os adultos competentes têm o direito de escolher se querem ou não realizar uma avaliação mais aprofundada, mas é essencial que compreendam as razões pelas quais foi recomendada uma avaliação mais profunda, bem como quais são as possíveis consequências de um atraso no diagnóstico. Os participantes podem ter tido problemas sociais ou de saúde que influenciaram o seu comportamento. Outros programas de rastreio médico constatarem também que, habitualmente, os doentes não dão seguimento a avaliações de diagnóstico, quando tal é indicado. Aspectos psicossociais, sintomas moderados, falta de conhecimento e consciência da doença, receio de investigações mais aprofundadas, preocupação com os resultados, falta de tempo e dificuldade de viajar para comparecer na consulta têm, todos eles, demonstrado que afetam a adesão a novos testes. No entanto, as pessoas com possível DPOC não diagnosticada tinham já concordado em realizar o rastreio do cancro do pulmão, despendido de tempo para participarem e se deslocarem até à consulta e realizado a espirometria. É possível que a preocupação em ter cancro e a tranquilização de que não tinham tido uma maior

relevância do que as preocupações em relação a terem DPOC, pois não tem o perfil que uma doença com este impacto e gravidade merece. Deve dar-se continuidade ao trabalho de sensibilização para a DPOC, incluindo para o facto de que esta doença mata mais pessoas do que o cancro do pulmão e incapacita muitas pessoas através do aumento progressivo da falta de ar, mas que é possível tratá-la e preveni-la.

Embora a produção de novos diagnósticos de DPOC em Yorkshire seja baixa, estes doentes são alguns dos “milhões desaparecidos”. De acordo com a previsão do *NHS England* (Serviço Nacional de Saúde de Inglaterra), até 2024/2025, serão convidados 1,5 milhões de pessoas para realizar um RDP. Se fossem replicados a nível nacional, os resultados do programa de Yorkshire, mesmo que as taxas de avaliação mais aprofundada permanecessem baixas, indicariam que mais de 35 000 pessoas iriam receber um diagnóstico precoce e correto de DPOC, em comparação com a previsão de 7700 novos diagnósticos de cancro do pulmão. Se pudesse ser feito mais para incentivar as pessoas que fizeram o rastreio a aceitar e realizar a avaliação mais aprofundada, assegurando, por exemplo, que compreendiam por que razão a avaliação é importante e enviando lembretes para a consulta, o número de pacientes com diagnóstico precoce de DPOC poderia ser muito superior. Os doentes querem que os diagnósticos sejam atempados e precisos.¹ Os diagnósticos tardios estão associados a uma taxa e a um risco mais elevados de exacerbações e hospitalizações.⁷ É importante encontrar os “milhões desaparecidos” mais cedo. Isto só poderá ser feito se as pessoas compreenderem porque é importante e quiserem ser encontradas. Devem continuar a envidar-se esforços para sensibilizar para a doença e facilitar o acesso a testes de diagnóstico.⁸ A inclusão da espirometria no RDP parece ser um passo em frente na direção certa.

Contributors DMGH is the sole author.

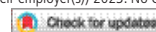
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Efeitos respiratórios da poluição atmosférica: é o momento de travar esta trajetória mortal

Sara De Matteis^{1,2}

O *Global Burden of Disease Study* estimou que mais de 500 milhões de indivíduos, cerca de 7% da população mundial, sofrem de doenças respiratórias crônicas, com custos significativos individuais e sociais associados a morbilidade, incapacidade e mortalidade.¹ A identificação e mitigação de fatores de risco potencialmente modificáveis são essenciais na prevenção dos impactos associados na saúde pública. A vasta literatura forneceu evidências convincentes de que a poluição atmosférica, especialmente as partículas finas em suspensão (PM)_{2,5} (diâmetro <2,5 µm), é um fator de risco importante para a incidência e mortalidade de doenças respiratórias agudas e crônicas, incluindo asma e doença pulmonar obstrutiva crônica (DPOC).^{2,3} Além disso, em 2013, a *International Agency for Research on Cancer* (Agência Internacional de Investigação sobre o Câncer) classificou a poluição atmosférica exterior como um conhecido agente cancerígeno para os pulmões.⁴

Um grande projeto multicêntrico recente, intitulado *Effects of Low-Level Air Pollution: A Study in Europe* (Efeitos da Poluição Atmosférica de Nível Baixo: um Estudo na Europa), demonstrou que os efeitos adversos no pulmão, incluindo a incidência de asma em adultos⁵ e DPOC⁶, ocorre mesmo quando existe exposição a níveis inferiores aos atuais valores-limite para a qualidade do ar da União Europeia. Além disso, as novas diretrizes da OMS sobre a qualidade do ar (2021) reduziram para metade — de 10 mg/m³ para 5 mg/m³ — a média recomendada anual para as concentrações de PM_{2.5} em ambientes exteriores.

Apesar da extensa literatura sobre a poluição atmosférica e os efeitos respiratórios, continuam sem resposta questões importantes sobre os mecanismos etiopatogénicos e as dinâmicas subjacentes à progressão de um estado sem doença pulmonar para as subseqüentes doenças pulmonares crônicas e, por fim, para a morte. Para elucidar, estas trajetórias mortais informariam e guiariam estratégias preventivas focadas, de acordo com uma moderna abordagem de saúde pública de precisão.

No estudo de Wang *et al.*, os autores procuraram esclarecer estas lacunas de conhecimento no grande biobanco populacional do Reino Unido, uma coorte de meio milhão de indivíduos com idade compreendida entre os 37 e os 73 anos, inscritos em 22 centros de saúde localizados em Inglaterra, na Escócia e no País de Gales, em 2006-2010.^{8,9} Os participantes disponibilizaram informação individual a partir de inquéritos em ecrã tátil e medições biológicas e físicas na admissão. Nesta análise, apenas foram incluídos e acompanhados os

indivíduos sem doenças pulmonares na linha de base e com informação sobre os fatores de confusão críticos (n= 265 506) até receberem o primeiro diagnóstico de asma, DPOC e/ou cancro do pulmão identificado através de uma ligação de registo com registos de saúde eletrónicos. Além disso, os dados da espirometria individual foram utilizados para integrar a definição de DPOC.

As estimativas das concentrações anuais de poluentes atmosféricos, incluindo PM₁₀, PM_{2.5}, PM_{2.5-10}, NO_x e NO₂, foram calculadas utilizando modelos conhecidos como *land-use regression* (LUR), provenientes do projeto *European Study of Cohorts for Air Pollution Effects* (Estudo Europeu de Coortes para os Efeitos da Poluição Atmosférica).¹⁰ Os modelos LUR permitem fazer uma estimativa das concentrações de poluentes ambientais, considerando diversas variáveis preditoras, selecionadas a partir do meio envolvente (por exemplo, tráfego, utilização do solo e topografia), obtidas a partir do sistema de informação geográfica. Os autores aplicaram modelos multiestado ajustados a vários potenciais fatores de confusão para examinar as associações da exposição à poluição atmosférica às trajetórias de progressão desde o estado sem doença pulmonar crônica até doença pulmonar crônica incidente, multimorbilidade de doenças pulmonares crônicas e morte por qualquer causa. Os modelos multiestado¹¹ são uma extensão do modelo de risco proporcional de Cox que aumenta o tempo para evento a partir de um *end-point* composto ou resumido, fornecendo uma compreensão pormenorizada das trajetórias da doença, tal como anteriormente relatado.¹²

Durante um seguimento médio de 12 anos, 13 863 participantes desenvolveram, pelo menos, uma doença pulmonar crônica, 1055 desenvolveram multimorbilidade de doenças pulmonares crônicas e 12 772 morreram. Curiosamente, os autores observaram associações diferenciais da poluição atmosférica com diferentes trajetórias de multimorbilidade de doenças pulmonares crônicas. As PM_{2.5} demonstraram a associação mais forte a todas as trajetórias de transição, com aumento de HR (96% IC) por 5 µg/m³ de 1,31 (1,22 para 1,42) e 1,27 (1,01 para 1,57) para transições de um estado saudável para um estado de doença pulmonar crônica incidente e de um estado de doença pulmonar crônica incidente para multimorbilidade de doenças pulmonares crônicas, e de 1,32 (1,21 para 1,45), 1,24 (1,01 para 1,53) e 1,91 (1,14 para 3,20) para risco de mortalidade relativo ao estado saudável, doença pulmonar crônica incidente e multimorbilidade de doenças pulmonares crônicas, respetivamente. É interessante notar que não se observaram associações significativas para PM_{2.5-10} com nenhuma trajetória.

A consistência dos resultados foi testada em várias análises de sensibilidade, incluindo estratificação por idade e sexo, que demonstraram efeitos mais fortes entre homens com idade superior a 55 anos. Importa referir que os autores utilizaram uma lista previamente reportada de profissões com risco de DPOC no biobanco do Reino Unido¹³ para fazer os ajus-

tes tendo em conta a exposição profissional. A estimativa de atenuação de efeito confirma o importante papel da exposição profissional no desenvolvimento de doença pulmonar e a necessidade de considerar este potencial fator de confusão na análise da poluição atmosférica.¹⁴

Os achados deste estudo estão em linha com a literatura sobre a associação positiva da exposição à poluição atmosférica com incidência, morbilidade e mortalidade devido a doenças respiratórias crônicas. Além disso, o aumento do risco de morte identificado entre os indivíduos “saudáveis” expostos sugere a hipótese de que a mistura complexa de gases e PM na poluição atmosférica pode causar danos aos pulmões, independentemente das doenças pulmonares preexistentes. Esta hipótese é apoiada pelos estudos toxicológicos que apresentaram vários caminhos etiopatogénicos, desde inflamação e stress oxidativo, até metilação do ADN, autofagia, apoptose, mudanças na capacidade de resposta das vias respiratórias, reduzida desobstrução das vias respiratórias e defesas do hospedeiro contra infeção com promotoras.^{15,16}

A hipótese de que doenças pulmonares anteriores podem aumentar o risco de cancro do pulmão não é nova,¹⁷ mas continuam a existir incertezas quanto aos processos fisiopatológicos que explicam a associação entre poluição atmosférica e cancro do pulmão. Este estudo apoia o papel da poluição atmosférica enquanto criador e promotor da progressão cancerígena de doenças pulmonares subjacentes, especialmente DPOC, conforme recentemente sugerido por outro estudo do biobanco do Reino Unido, o qual propôs a inflamação como o condutor mecanicista biológico.¹⁸

Os pontos fortes deste estudo são o tamanho grande da amostra, que permitiu várias análises de sensibilidade, a disponibilidade de informação individual sobre potenciais fatores de confusão e a análise longitudinal prospetiva com a utilização de um modelo multiestado para estimar o impacto da exposição à poluição atmosférica em cada fase de transição da trajetória de progressão da multimorbilidade de doenças pulmonares crônicas. São também várias as lacunas que impedem a interpretação causal: a exposição do indivíduo à poluição atmosférica baseou-se no endereço residencial, na linha de base. Contudo, os resultados foram confirmados em participantes restritos da coorte que não mudaram de residência após 2010. A informação sobre potenciais fatores de confusão, incluindo tabagismo, foi recolhida na linha de base. Alguns indivíduos apresentaram vários diagnósticos recebidos no mesmo dia, nos respetivos registos médicos. Contudo, utilizando diferentes intervalos e excluindo-os da análise, os resultados mantêm-se inalterados. Questões potenciais de truncamento à esquerda e viés de risco competitivo não foram abordadas.¹⁹ Por fim, a natureza voluntária da coorte do biobanco do Reino Unido, incluindo os participantes mais informados, os que nunca fumaram, os menos carenciados e os que pertencem a minorias étnicas, dificulta a possibilidade de generalização destas conclusões para outras populações mundiais com diferentes enquadramentos socioeconómicos e mistura populacional.

Idealmente, seriam necessários grandes estudos longitudinais com medições repetidas de poluição atmosférica (incluindo em ambientes interiores), potenciais fatores de confusão e

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multimorbilidade (não apenas respiratória) para analisar associações prospectivas. Além disso, os estudos toxicológicos que utilizam a mais recente abordagem “ômica” poderiam ajudar a esclarecer os mecanismos moleculares etiopatogênicos subjacentes com importantes implicações para a prevenção (especialmente entre grupos mais suscetíveis) e, potencialmente, para a terapia de doenças subsequentes.

Os estudos de intervenção demonstraram que a redução da exposição à poluição atmosférica, tanto a curto como a longo prazo, tem efeitos significativos na saúde,²⁰ pelo que, dado não existir qualquer limite seguro, as políticas ambientais deveriam esforçar-se por controlar a poluição atmosférica nos níveis mais baixos possíveis para a prevenção primária e secundária dos correspondentes impactos na saúde global.²¹

Já existem evidências suficientes: chegou o momento de travar a trajetória mortal da poluição atmosférica. Isto é eticamente obrigatório, dado que a poluição atmosférica é um fator de risco que pode ser modificado e prevenido.

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ARTIGO ORIGINAL

Otimização do salbutamol intravenoso em crianças: um estudo de fase 2

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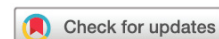
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RESUMO

Objetivo Os agonistas β_2 , como o salbutamol, são o pilar da gestão da asma. Faltam modelos farmacocinéticos e farmacodinâmicos que orientem a dosagem pediátrica. Exploramos a relação entre a dose de salbutamol, a concentração sérica, a eficácia e os efeitos adversos em crianças ao desenvolver um modelo PKPD.

Desenho Um estudo de coorte prospetivo com crianças admitidas em hospital com asma aguda, que receberam salbutamol por via intravenosa.

Contexto As crianças foram recrutadas para duas coortes: os serviços de urgência de dois hospitais de Londres ou as transportadas pelo Children's Acute Transport Service para três unidades de cuidados intensivos pediátricos de Londres.

Doentes Os doentes eram elegíveis se tivessem idades compreendidas entre 1 e 15 anos, tivessem sido admitidos devido a asma aguda e estivessem prestes a receber ou estivessem a receber salbutamol intravenoso.

Intervenções O tratamento seguiu as práticas locais. Foram recolhidos os níveis plasmáticos de salbutamol em série. Foram registadas as medições de eficácia com recurso ao Paediatric Asthma Severity Score (PASS). As medições de toxicidade incluíram lactato, pH, glicose, ritmo cardíaco, tensão arterial e arritmias. A modelação PKPD foi realizada recorrendo a modelo linear de efeitos mistos.

Principais resultados Foram recrutadas 58 crianças com 221 medições de concentração de salbutamol de 54 crianças. A média (intervalo) de idade foi de 2,9 (1,1 a 15,2) anos e o peso foi de 13,6 (8 a 57,3) kg. Foram obtidas 95 medições PASS e 2078 medições de toxicidade.

Resultados Um modelo PK bicompartimentado descreveu adequadamente o curso temporal das concentrações plasmáticas de salbutamol. Uma relação entre a concentração e o efeito EMAX (efeito máximo do medicamento) descreveu as medições de PASS e toxicidade. As simulações PKPD mostraram que uma infusão de 0,5 $\mu\text{g/kg/min}$ (máximo 20 $\mu\text{g/min}$) durante 4 horas após o bólus obtém uma broncodilatação máxima >90 % durante 12 horas.

Conclusões É descrito um modelo PKPD pediátrico para o salbutamol. Uma infusão de 0,5 $\mu\text{g/kg/min}$ após do bólus permite uma broncodilatação eficaz. As taxas mais elevadas estão associadas a mais taquicardia e hiperglicemia.

INTRODUCTION

A child is admitted to the hospital every 20 min with acute asthma.¹ The β_2 -adrenergic receptor agonists such as salbutamol form the mainstay of treatment. National guidelines from the British Thoracic Society recommend that intravenous salbutamol should be considered as second-line treatment in children who fail to respond to nebulised β_2 -agonists and steroids. An intravenous salbutamol bolus 15 $\mu\text{g/kg}$ body weight over 10 min followed by a maintenance infusion of 1–5 $\mu\text{g/kg/min}$ is recommended,² although the evidence for this dosing strategy is limited.³ Current paediatric salbutamol dosage regimens are extrapolated from adult pharmacokinetic studies and result in

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- There is limited evidence for the use of intravenous β_2 -agonists in children with asthma. Pharmacokinetic–pharmacodynamic (PKPD) models to guide paediatric salbutamol dose are lacking.
- Current paediatric salbutamol dosage regimens are extrapolated from adult PK studies and result in children receiving far more intravenous salbutamol (1–5 $\mu\text{g/kg/min}$) than the maximum adult dose (20 $\mu\text{g/min}$).
- Salbutamol is associated with adverse effects such as lactic acidosis, hyperglycaemia, ketosis and cardiac arrhythmias.

WHAT THIS STUDY ADDS

- A two-compartment disposition model described intravenous salbutamol pharmacokinetics. An E_{max} concentration–efficacy relationship described effectiveness and toxicity measures.
- Blood glucose and heart rate are useful toxicity measurements, with the salbutamol concentration required for maximal therapeutic effect surpassed before toxicity.
- Using the PKPD model, an infusion of 0.5 $\mu\text{g/kg/min}$ for 4 hours after 15 $\mu\text{g/kg}$ bolus over 10 min achieved >90% of maximum bronchodilation for 12 hours. A ceiling effect at 20 $\mu\text{g/min}$ is reported.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Current dosage schedules for intravenous salbutamol in children result in salbutamol concentration levels above those required for therapeutic bronchodilation, at the expense of adverse effects.
- This study provides a PKPD model on which to base future dosing schedules of intravenous salbutamol in children, thereby maximising effectiveness while minimising toxicity.

children receiving far more intravenous salbutamol (1–5 $\mu\text{g/kg/min}$) than the maximum adult dose (20 $\mu\text{g/min}$). Huge variations in clinical practice are reported.⁴

Data from pharmacokinetic/pharmacodynamic (PKPD) models on which to base paediatric salbutamol dose are lacking.⁵ Salbutamol use is associated with adverse effects such as lactic acidosis,

hyperglycaemia, ketosis and diastolic hypotension with myocardial injury and cardiac arrhythmias.^{6–9} Salbutamol beneficial effect and adverse effect ratios have not been explored.

We conducted a prospective cohort study to explore the relationship between salbutamol dose, plasma concentration, effectiveness and adverse effects in children by developing a population PKPD model. We anticipated this model could change dosing recommendations.

METHODS

Design

We conducted a prospective cohort study of children admitted to hospital with acute severe asthma, who received intravenous salbutamol during their clinical management. All children were treated according to local policy.

Serial salbutamol concentration levels, effectiveness scores and toxicity measurements were taken as described (see Data sources/measurements section). PKPD modelling was performed using non-linear mixed-effects models (NONMEM7.3, ICON Development Solutions, USA).

Setting

Patients were recruited in two cohorts between September 2014 and May 2017:

1. The emergency departments at two hospitals in London: St Mary's and the Royal London Hospitals (ED cohort).
2. Critically ill children retrieved by the Children's Acute Transport Service (CATS) to three tertiary paediatric intensive care units (PICUs): Great Ormond Street, St Mary's and the Royal London Hospitals (CATS cohort).

Participants

Patients were eligible if aged 1–15 years (inclusive), admitted to hospital for acute asthma (defined by the British Thoracic Society guidelines) and about to receive or receiving intravenous salbutamol. Participants were identified by the clinical teams and recruited by research nurses. Patients continued in the study until 8 hours after stopping salbutamol or hospital discharge.

We followed established procedures for obtaining deferred consent in emergency situations.^{10–12}

Data sources/measurements

Study data were collected using REDCap database hosted at University College London.¹³ Data collected included age, sex, ethnicity, renal function tests; asthma treatments and timing including nebulisers, steroids, magnesium sulfate, aminophylline and intravenous salbutamol; and hospital length of stay, PICU admission and use of mechanical ventilation.

Salbutamol concentrations: Serial blood samples to measure salbutamol concentrations were taken. In the ED cohort, samples were taken at t_0 (prior to starting intravenous salbutamol) and t_{end} (prior to stopping the salbutamol infusion). Other samples were taken with routine clinical sampling. We aimed for a minimum of three samples per patient. In the CATS cohort, salbutamol concentrations were taken at t_{CATS} (at first contact with the retrieval team, when the child was usually already on intravenous salbutamol). Further samples were taken via indwelling vascular catheters: prior to a dose change, 30 min after a dose change, once at tend and one in 8 hours after stopping intravenous salbutamol. Samples were analysed by ABS Laboratories, using an liquid chromatography–mass spectrometry method, validated according to European Medicines Agency and Food and Drug Administration regulatory authority criteria.^{14,15} This assay is validated to a lower limit of 0.1 ng/mL salbutamol.

Genotype data: Blood samples were taken for single nucleotide polymorphism analysis involving the three most common β -2 adrenoceptor genes (ADRB2): Arg16Gly, Gln27Glu and Thr164Ile to see if they influenced the PKPD model.

Effectiveness measurements were recorded in spontaneously breathing patients by the Paediatric Asthma Severity Score (PASS, 0–15), a validated scoring system incorporating wheezing,

prolonged expiration and work of breathing. This non-invasive scoring system correlates with peak expiratory flow rate and pulse oximetry.¹⁶ Serial measurements were recorded by the research nurse. We did not attempt to measure effectiveness in ventilated patients.

Toxicity-associated physiological measurements recorded included serum lactate, pH, base excess and blood glucose values. Toxicity-associated cardiovascular measurements were heart rate, blood pressure and cardiac arrhythmias.

Sample size

To characterise model parameter–covariate relationships, it is proposed that at least 50 subjects are required in a population PKPD study.¹⁷ We aimed to recruit 100 patients. Ethical approval by the Brent Research Ethics Committee (ref: 14/LO/2103).

Statistical methods

Population PKPD modelling

Sequential population PKPD modelling was performed with NONMEM (V.7.3), where a PK model was first developed and individual PK parameters were combined with a PD model to describe the time course of PD observations.¹⁸

One-compartment and two-compartment PK models were tested to describe intravenous salbutamol disposition. Nebulised salbutamol administered was included under the assumption that most drug was deposited in the lung over 5 min with estimated inhaled bioavailability (0.09) and absorption rate fixed at 16.7 per hour. An estimated baseline plasma concentration was also tested. Allometric size scaling with body weight on clearance and volume of distribution was added a priori, and a sigmoidal maturation function describing the change of clearance over age was tested.¹⁹

PASS scores were treated as continuous data and modelled with a regression model, where salbutamol plasma concentrations were linked with PASS scores.²⁰ Both linear, E_{MAX} and sigmoidal E_{MAX} concentration–effect relationships were tested. Raw data showed a flat concentration–response relationship indicating current clinical salbutamol concentrations achieve the maximum possible bronchodilation effect. As parameters could not be estimated due to O-gradients, EC_{50} and HILL were fixed to literature values from a dose-ranging study (online supplemental figure 9).²¹ Since these values were for R-salbutamol, our assay measured total salbutamol, and the salbutamol concentrations were converted to total by adding the R-salbutamol concentration to the predicted S-salbutamol concentrations from a recent study.²²

We examined whether any patient characteristics influenced the estimation of bronchodilation effect (PASS). Covariates analysed were aminophylline, corticosteroids, ipratropium, montelukast, antibiotics, serum creatinine and $MgSO_4$. β -2 adrenoceptor genotyping was visually inspected. The likelihood ratio test or Akaike information criterion were used, respectively, for nested and non-nested models to compare the goodness of fit.²³

The following markers of toxicity were modelled: lactate, pH, base excess, blood glucose, heart rate and diastolic blood pressure. Heart rate and diastolic blood pressures were standardised with age-appropriate Z-scores.^{24,25} Toxicity effects were estimated from circulating salbutamol with first-order equilibration with the plasma compartment. A sigmoidal E_{MAX} model was used to link salbutamol concentration with toxicity effects. Concomitant therapy with corticosteroids was investigated as a covariate on blood glucose PKPD model parameters E_{0^*} , E_{MAX} and EC_{50} .

PKPD models for plasma concentrations, PASS scores and toxicity measurements were evaluated by prediction-corrected visual predictive checks (pcVPCs) that were generated using Perl-speaks-NONMEM (V.4.8.1). For each pcVPC, 1000 simulations from the PKPD model were performed.²⁶ Whether the median, 2.5th and 97.5th percentiles of observed data lay within the 95% CI of simulated data was visually assessed.

Dose regimen simulation

Using our PKPD model, simulations were conducted in 2000 patients to determine the optimal dose of intravenous salbutamol

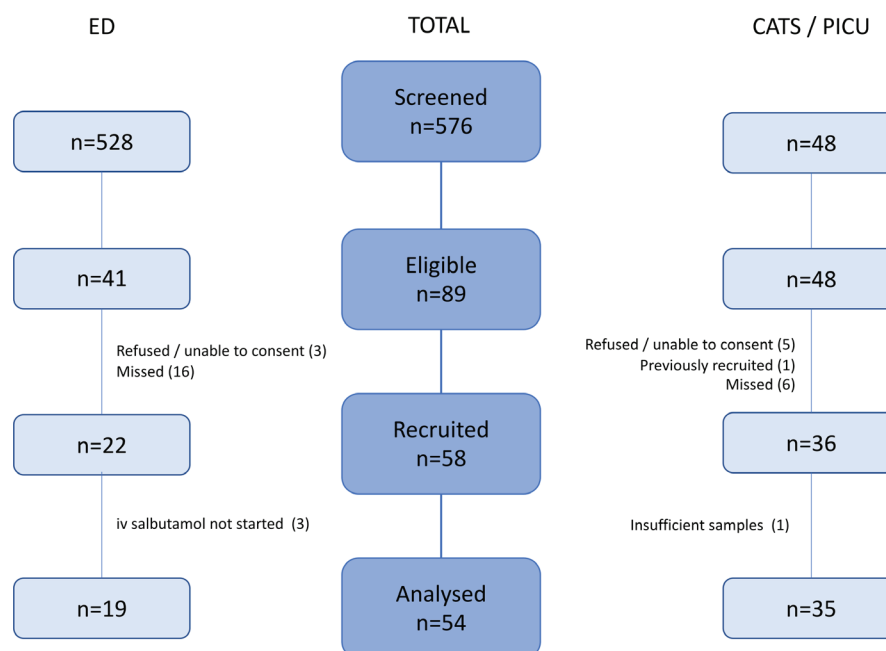


Figure 1 Flow chart of patient recruitment. CATS/PICU, Children's Acute Transport Service/Paediatric Intensive Care Unit cohort; ED, Emergency Department cohort; iv, intravenous.

in children. The simulated patient population had body weights ranging from 5 to 54 kg and were given a bolus dose of 15 µg/kg followed by an infusion of 0.25, 0.5, 1 and 5 µg/kg/min. The target was to propose an infusion dose that achieved >90% of the maximum bronchodilation effect for 12 hours in the majority of patients, with minimum clinical toxicity; in particular of hyperglycaemia (blood glucose >10 mmol/L) and tachycardia (heart rate >2 SD above baseline). We analysed infusion durations up to 24 hours but ultimately focused on a 4-hour infusion as it may obviate the need for out-of-hospital transfer. A 0.5 µg/kg/min infusion was further investigated with and without a maximum dosage of 20 µg/min using Monte Carlo simulations.

RESULTS

Participants

There were 576 patients screened. There were 89 eligible patients, 8 refused or were unable to consent, 1 was previously recruited and 22 were missed. There were 54 of 60 children included in the final analysis (figure 1).

Descriptive data

The median (range) age was 2.9 (1.1–15.2) years with 20 (37%) females. There were 40 (74%) children with a known history of asthma or viral-induced wheeze. There were 50 children (93%) given salbutamol inhalers/nebulisation prior to enrolment. In the CATS cohort, 16 children (47%) had received an intravenous salbutamol bolus and 11 children (32%) had commenced on salbutamol infusions prior to enrolment. The median (range) duration of these infusions was 5 (0.5–22.7) hours. At enrolment, the median (range) salbutamol concentrations were 86.65 (1.36–166) and 8.04 (2.47–24) ng/mL in the CATS and ED cohorts, respectively (table 1).

Following enrolment, 30 children (55%) received further salbutamol nebulisers/inhalers. There were 8 (24%) and 19 (95%) children who received an intravenous bolus in the CATS and ED cohorts, respectively. Salbutamol infusions were run at a median (range) rate of 1.0 (0.1–4) µg/kg/min in the CATS cohort and 1.0 (0.5–2) µg/kg/min in the ED cohort. Salbutamol infusion duration median (range) was 3.33 (0.183–196.2) hours and 5.5 (0.5–48.8) hours in the CATS and ED cohorts, respectively, after enrolment. Concomitant drugs used during the study period are outlined in table 2.

Outcome data

We obtained 221 salbutamol plasma concentrations from 54 patients. There were 95 PASS measurements, 280 lactate measurements, 295

pH measurements, 294 base excess measurements, 255 blood glucose measurements, 306 diastolic blood pressure measurements, 358 heart rate measurements (online supplemental figures 1–8) and 20 genotype samples. Mechanical ventilation was required in 34 children (97%) of the CATS cohort and 3 children (15.8%) in the ED cohort for a median duration of 91.6 hours and 99.1 hours, respectively. Median (range) length of hospital stay was 6 (3–34) days and 2 (1–9) days in the CATS and ED cohorts, respectively (table 2).

MAIN RESULTS

Population PK modelling

A two-compartment PK model adequately described the time course of salbutamol plasma concentrations. PK parameters were standardised to a 70 kg person using allometry. Our scaled estimated clearance was 16.3 L/hour/70 kg. Age had no impact on clearance. Other parameters included intercompartment clearance (8.58L/hour/70 kg), central volume (109 L/70 kg) and peripheral volume (69.4 L/70 kg) (table 3).

Population PD modelling

We found current salbutamol dosing results in salbutamol plasma concentrations that are above the 90% maximum drug effect (E_{MAX}). Parameter values from the E_{MAX} drug effect models are outlined in table 3 for PASS. The concentration that achieved a half maximum response (EC_{50}) and slope (HILL) parameters could not be reliably estimated and were subsequently fixed to literature-based forced expiratory volume in 1 s (FEV_1) estimates at 0.15 ng/mL and 3.2, respectively (online supplemental figure 9).

None of the covariates tested: aminophylline, corticosteroids, ipratropium, montelukast, antibiotics, serum creatinine and $MgSO_4$ were significant ($p>0.01$) on PASS score. As genotype samples were only obtained in 20 patients, no trends were identified.

Blood glucose and heart rate increased with increased salbutamol plasma concentrations. Parameter estimates for these toxicity measurements are outlined in table 3. For both these variables, the concentration–response curve demonstrates that maximum bronchodilation effect is achieved faster than the toxicity effects of hyperglycaemia and tachycardia. Concomitant therapy with corticosteroids or ventilation were not significant covariates on PKPD model parameters. Salbutamol plasma concentration did not correlate with lactate, base excess or diastolic blood pressure.

Model evaluation

Visual plots of PK and PD results (pcVPC) were reasonable for plasma concentrations, PASS and toxicity measurements, suggest-

Table 1 Descriptive data of study participants at enrolment

	All patients (N=54)	CATS cohort (n=35)	ED cohort (n=19)
Age (years), median (range)	2.9 (1.1–15.2)	2.7 (1.1–15.2)	3.5 (1.1–15.1)
Weight (kg), median (range)	13.6 (8–57.3)	13 (8.34–46)	14.4 (8.5–57.3)
Female, n (%)	20 (37)	9 (25.7)	11 (55)
Ethnicity, n (%)			
White	21 (38.9)	17 (48.6)	4 (21.1)
Asian	15 (27.8)	8 (22.9)	7 (36.8)
Black	8 (14.8)	5 (14.3)	3 (15.8)
Chinese	5 (9.3)	1 (2.9)	4 (21.1)
Mixed	1 (1.9)	0 (0)	1 (5.3)
Missed	4 (7.4)	4 (11.4)	0 (0)
Comorbid conditions, n (%)			
Known history of asthma	16 (9)	11 (31)	5 (14)
Previous viral-induced wheeze	24 (44)	15 (43)	9 (47)
Allergies nuts/eggs/wheat/soya	2 (4)	1 (3)	1 (5)
Eczema/hay fever	5 (9)	1 (3)	4 (21)
Trisomy 21	2 (4)	1 (3)	1 (5)
Tracheomalacia/bronchomalacia/laryngomalacia	2 (4)	2 (6)	–
Gastro-oesophageal reflux	3 (6)	3 (9)	–
Other	12 (22)	10 (29)	2 (10)
Medications prior to enrolment, n (%)			
Inhaled salbutamol	9 (17)	2 (6)	7 (35)
Nebulised salbutamol	41 (76)	27 (79)	14 (70)
Intravenous salbutamol bolus	16 (30)	16 (47)	–
Intravenous salbutamol infusion	11 (20)	11 (32)	–
Intravenous dose $\mu\text{g/kg/min}$, median (range)	1	1(1–5)	–
Intravenous duration hours, median (range)	5 (0.5–22.7)	5 (0.5–22.7)	–
Concomitant medications, n (%)			
Nebulised ipratropium	35 (65)	26 (74)	9 (47)
Corticosteroids	34 (63)	27 (77)	7 (37)
Intravenous magnesium	34 (63)	27 (77)	7 (37)
Intravenous aminophylline	20 (37)	19 (54)	1 (5)
Ketamine	8 (15)	8 (23)	–
Plasma salbutamol level at enrolment (ng/mL), median (range)	22.4 (1.36–166)	86.65 (1.36–166)	8.04 (2.47–24)

CATS, Children's Acute Transport Service; ED, Emergency Department.

ing that the developed PKPD models were adequate in describing the observed PKPD (online supplemental figure 10).

Other analyses

Using our PKPD model, we aimed to extrapolate a dose regimen for children. Our target was to achieve 90% of the maximum bronchodilation effect for >12 hours, with minimal toxicity. Using simu-

Table 2 Treatment and outcomes of study patients

	CATS (median (range))	ED (median (range))
Treatment during study period		
Salbutamol bolus dose ($\mu\text{g/kg}$)	13.1 (4.95–15)	13.9 (3.97–17.9)
Salbutamol infusion dose ($\mu\text{g/kg/min}$)	1 (0.1–4)	1 (0.5–2)
Salbutamol infusion duration (hours)	3.33 (0.183–196.2)	5.5 (0.5–48.8)
Salbutamol nebulised dose (mg)	2.5 (2.5–5)	2.5 (2.5–2.5)
Other medications		
Steroids, n (%)	28 (80)	13 (68)
Intravenous MgSO_4 , n (%)	18 (51)	5 (26)
Aminophylline infusion, n (%)	22 (63)	8 (53)
Ipratropium bromide, n (%)	20 (57)	12 (63)
Montelukast, n (%)	8 (23)	2 (13)
Ketamine infusion, n (%)	13 (37)	0 (0)
Outcome		
Mechanical ventilation, n (%)	34 (97)	3 (20)
Hours of mechanical ventilation	91.6 (10.9–294)	99.1 (96–147.2)
Length of stay in hospital, days	6 (3, 34)	2 (1, 9)

CATS, Children's Acute Transport Service; ED, Emergency Department.

lations in 2000 virtual patients after a bolus of 15 $\mu\text{g/kg}$, infusion rates of 0.25–5 $\mu\text{g/kg/min}$ for 4 hours were explored (figure 2). We found that a salbutamol infusion of 0.5 $\mu\text{g/kg/min}$ after bolus with a ceiling rate of 20 $\mu\text{g/min}$ achieved this (online supplemental figure 11).

Table 3 Parameter estimates from pharmacokinetic and pharmacokinetic–pharmacodynamic effectiveness and toxicity models

	Fixed effects	Random effects	Residual variability
Pharmacokinetic parameters			
Bioavailability (0–1)	0.0925	–	–
k_a (per hour)	16.7	–	–
CL (L/hour/70 kg)	16.3	0.522	–
V_c (L/70 kg)	109	1.79	–
Q (L/hour/70 kg)	8.58	–	–
V_p (L/70 kg)	69.4	6.45	–
$BASE$ (ng/mL)	1.04	–	–
Proportional error	–	–	0.0629
Additive error (ng/mL)	–	–	0.220
Effectiveness parameters			
E_0 (fraction of PASS score (0–9))	0.381	0.257	–
E_{MAX} (fraction of PASS score (0–9))	0.25	–	–
EC_{50} (ng/mL)	1.15 (fixed)	–	–
$HILL$	3.2 (fixed)	–	–
Additive on logit scale	–	–	0.461
Glucose parameters			
E_0 (mmol/L)	5.03	–	–
E_{MAX}	3.86	0.258	–
EC_{50} (ng/mL)	1.08	1.11	–
Proportional error	–	–	0.0747
Tachycardia parameters			
E_0 (Z-score)	3.08	0.809	–
E_{MAX}	4.16	–	–
EC_{50} (ng/mL)	385	0.732	–
Additive error (bpm)	–	–	1.41

bpm, beats per minute; CL , clearance; E_0 , measurement in the absence of salbutamol; EC_{50} , drug concentration producing 50% of the maximum effect; E_{MAX} , maximum drug effect; $HILL$, shape parameter in the E_{MAX} model (higher values indicate a steeper dose–response curve); k_a , absorption rate constant; PASS, Paediatric Asthma Severity Score; PK, pharmacokinetic parameters standardised to a 70-kg person using allometry; Q , intercompartmental clearance; V_c , apparent volume of distribution central compartment; V_p , apparent volume of distribution peripheral compartment.

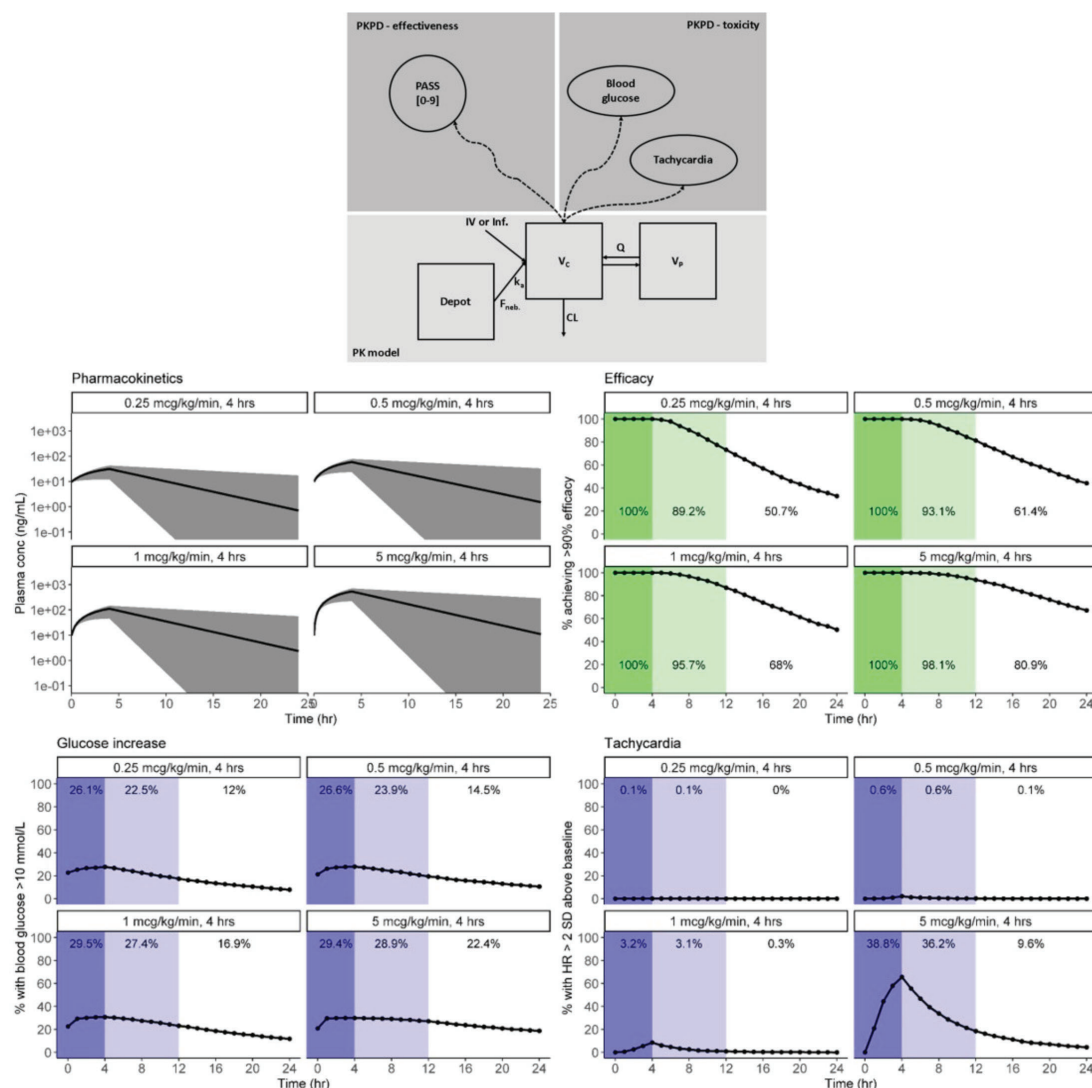


Figure 2 Schematic representation of PKPD models for salbutamol plasma concentration, PASS and individual toxicity measurement. Simulations to show the effect of 0.25, 0.5, 1 and 5 $\mu\text{g/kg/min}$ infusion for 4 hours after a bolus of 15 $\mu\text{g/kg}$, on the time course of salbutamol plasma concentration (pharmacokinetics), bronchodilation effect (efficacy) and the two important toxic effects (glucose increase and tachycardia). The virtual population of 2000 patients was weighing 5 to 54 kg. CL, clearance; F, absolute bioavailability; Inf., infusion; IV, intravenous; k_a , absorption rate constant; neb., nebulised; PASS, Paediatric Asthma Severity Score; PKPD, pharmacokinetic–pharmacodynamic; Q, intercompartmental clearance; V_c , apparent volume of distribution central compartment; V_p , apparent volume of distribution peripheral compartment.

DISCUSSION

Key results

A population PKPD model for intravenous salbutamol in children is reported. A two-compartment disposition model adequately described intravenous salbutamol PK. The clearance and volume of distribution estimates in children are comparable with those scaled from adult volunteers. This concurs with a published PK model.²² Dosing per body weight appears appropriate.

Our observed plasma concentrations were substantially higher than levels regarded as toxic in adults, but in-keeping with other reports of children receiving intravenous salbutamol according to current guidelines.^{22–27} Many patients had plasma salbutamol concentrations associated with near maximum possible effect before receiving any intravenous therapy.

PD modelling was performed for all toxicity variables, although correlation with salbutamol EC_{50} estimates were only demonstrated for heart rate Z-score and blood glucose. The blood glucose effect was independent of corticosteroids as a covariant. The concentration–response curve demonstrates that the maximum bronchodilation effect is achieved faster than the toxicity effects of hyperglycaemia and tachycardia.

The use of PKPD simulation is well established in drug development.²⁸ Using our PKPD model, simulations showed that after a bolus of 15 $\mu\text{g/kg}$, an infusion of 0.5 $\mu\text{g/kg/min}$ for 4 hours

achieved our target of >90% of the maximum bronchodilation effect for 12 hours in the majority of patients. We report a ceiling effect and a maximum infusion rate of 20 $\mu\text{g/min}$ is adequate. Higher infusion rates did achieve bronchodilation above 90%, but at the cost of increased toxicity.

Limitations

We aimed to recruit 100 patients but fewer patients received intravenous salbutamol, and research nurse availability contributed to recruitment failures. Fifty subjects were suggested for this population PKPD study and we stopped recruitment once that number was achieved. The requirement for three salbutamol concentration samples was also restrictive, with the protocol adjusted to include those with two samples after the first interim analysis (provided five clinical effectiveness measurements were available). The CATS cohort was more data-rich, but PASS scores were only obtained in non-ventilated patients. Height measurements were unavailable in most children (74.1%), which prevented the exploration of fat mass index on PK parameter estimates.

The high salbutamol concentrations at enrolment presented a mathematical challenge for EC_{50} modelling. This is a common phenomenon in pharmacology where a 10-fold range around the expected EC_{50} is desirable. The EC_{50} for effectiveness (ie, PASS)

could not be reliably estimated and was fixed to FEV₁ literature-based EC₅₀ estimate of 1.15 ng/mL.²⁹

Interpretation

A population PKPD model for intravenous salbutamol in children is described and can be used to inform future randomised controlled trials. Current dose regimens do achieve therapeutic bronchodilation but at the expense of adverse effects. A lower dose of 0.5 µg/kg/min after 15 µg/kg bolus would achieve the desired bronchodilation while minimising toxicity, with a ceiling effect at 20 µg/min. Demonstration that a 4-hour infusion sustained >90% maximum bronchodilation for 12 hours may obviate the need for high-dependency transfer. Understanding the salbutamol plasma–concentration effects on blood glucose and heart rate may allow the titration of ongoing salbutamol infusions to these variables.

Collaborators OSTRICH Study Group: Mark Peters, David Inwald, Ami Parikh, Ian Maconochie and Mario Cortina-Borja.

Contributors SW and PR created the study concept and design, sourced funding and MHRA approval. They formed a collaborative study group and assisted with patient recruitment and data collection. They provided clinical interpretation for the outcomes and wrote and approved the research paper. JFS, BJA, FK, YS and SP assisted with the study design. They performed the data analysis, PKPD modelling and simulation analysis and interpretation. They assisted with writing the research paper. The OSTRICH Study Group comprised the clinical leads for each research centre. They assisted with study design, patient recruitment and data collection. They edited and approved the final research paper. SW accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish, and will act as guarantor.

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ARTIGO ORIGINAL

Condutividade no suor no diagnóstico de fibrose quística após rastreio positivo em recém-nascidos: estudo prospectivo da precisão dos testes de diagnóstico

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RESUMO

Objetivos — Avaliar a precisão da condutividade no suor em recém-nascidos e crianças muito novas.

Desenho — Estudo prospectivo da precisão dos testes de diagnóstico com base na população.

Cenário — Programa Público de Rastreio de Recém-Nascidos de âmbito Estatal, em que a taxa de incidência de fibrose quística (FC) é $\approx 1:11\ 000$.

Pacientes — Recém-nascidos e crianças muito novas com tripsinogénio imunorreativo de dois níveis positivo.

Intervenções — Os testes de condutividade no suor e ácido de cloretos no suor foram realizados em simultâneo, no mesmo dia e na mesma instalação, por técnicos independentes, com valores-limite de 80 mmol/l e 60 mmol/l, respetivamente.

Medidas dos principais resultados — A sensibilidade, a especificidade, os valores preditivos positivos e negativos (VPP e VPN), a precisão global, os rácios de verossimilhança positivos e negativos (+RV, -RV) e a probabilidade após teste [condutividade no suor (CS)] foram calculados para avaliar o desempenho da CS.

Resultados — Foram incluídos 1193 participantes, 68 com FQ e 1108 sem FQ, e 17 com valores intermédios. A idade média (SD) foi 48 (19,2) dias, com intervalo entre 15 e 90 dias. A CS produziu sensibilidade de 98,5% (95% IC 95,7 para 100), especificidade de 99,9% (95% IC 99,7 para 100), VPP de 98,5% (95% IC 95,7 para 100) e VPN de 99,9% (95% IC 99,7 para 100), precisão global de 99,8% (95% IC 99,6 para 100), +RV de 1091,7 (95% IC 153,8 para 7744,9) e -RV de 0,01 (95% IC 0,00 para 0,10). Após um resultado de condutividade no suor positivo e negativo, a probabilidade de FQ do doente aumenta cerca de 350 vezes e cai virtualmente para zero, respetivamente.

Conclusão — A condutividade no suor apresentou uma precisão excelente na confirmação ou exclusão da FQ após tripsina imunorreactiva positivo entre recém-nascidos e crianças muito novas.

INTRODUCTION

Due to the limited availability and affordability of CFTR gene mutations analysis in resource-limited settings—where, like in Brazil, only cases with abnormal chloride values undergo DNA testing, after positive two-tier IRT sweat chloride determination is the strategy implemented by several newborn screening programmes for cystic fibrosis (CF) worldwide.^{1–3} It offers maximal accuracy but requires a specialised centre and skilled personnel.^{4–6} In addition, the time-consuming Gibson and Cooke's method is still used in those settings instead of the extensively recommended Macroduct system.^{3–7}

In its turn, sweat conductivity (SC) analysis is cheaper, commonly used in many settings throughout the world,⁸ including many laboratories in high-income Australasia countries,⁹ and

Key messages

What is the key question?

► Sweat conductivity is considered a screening test for cystic fibrosis (CF); accuracy studies are needed to assess its role as an alternative method to rule in/out CF.

What is the bottom line?

► Sweat conductivity showed an excellent diagnostic accuracy; for instance, positive and negative likelihood ratios were 1091.7 and 0.01, respectively.

► In settings where the incidence rate of CF is around 1:11 000, post-test probability increases 350 times the likelihood of CF after a positive sweat conductivity, while negative results virtually rule out CF.

Why read on?

► In settings with a shortage of chloride titration, sweat conductivity can expedite diagnosis and allow early prompt treatment, minimising family and parental distress due to a positive newborn blood-spot screening.

provides instant results^{1 3 5 7} like the more expensive chloridometer. Several studies comparing SC with conventional sweat test (ST) demonstrated that sensitivity, specificity, positive and negative predictive values (PPV and NPV) ranged from 83.3% to 100%.^{1 3 5 7 10 11} However, these studies had an underpowered sample size, although one recruited^{3 8 34} subjects, from newborns to adults.⁵ Currently, institutions such as Cystic Fibrosis Foundation (CFF) and the UK-based Association for Clinical Biochemistry & Laboratory Medicine consider SC a screening test.^{4 12–14}

Therefore, the present study aimed to assess the diagnostic accuracy of SC solely among newborns and infants younger than 3 months with positive IRT/IRT-based NBS. Our hypothesis was that SC has comparable accuracy to the classical coulometric titration of sweat chloride for diagnosing CF in newborns and young infants.

METHODS

Study design

We conducted this prospective, population-based, paired diagnostic test accuracy study between April 2013 and October 2020, following the Standards for Reporting Diagnostic Accuracy guidelines (STARD).¹⁵



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Participants and predefined inclusion and exclusion criteria

We included newborns and infants younger than 3 months, public Statewide Newborn Screening Programme participants, who presented two IRT positive results (ie, >70 mg/L) in our CF referral centre, located in Belo Horizonte, Brazil. To ensure blinding and to avoid interference of other clinical conditions on the result of SC and chloride titration if they were done on different days, participants underwent both tests on the same day and facility, conducted simultaneously, once only, by independent technicians.

Exclusion criteria were skin lesions of any aetiology, clinical instability and insufficient sweat quantity.

Test methods and procedures

Data collection and recording were completed immediately after performing SC and chloride determination.

Collection of sweat samples by Macroduct system and SC analysis (index test)

Sweat collection was performed as described by others.^{3 5 7 10 11} Briefly, the technician cleaned the patient's skin before placing the Macroduct coil. As recommended by the manufacturer, the sweat collection time was 30 min.¹⁶ Following the manufacturer's guidelines, after sweat collection, the catheter was separated from the disk and a syringe was connected to one end of the catheter. To measure conductivity, the other end was connected to the Sweat-Chek analyzer.

Collection of sweat samples by Gibson and Cooke's technique and chloride analysis (reference standard)

Gibson and Cooke's method was performed according to well-established standards in the contralateral forearm.^{12 14} After pilocarpine iontophoresis, chloride quantitation was carried out through a chloridometer.^{12 14}

Cut-off points for positive and negative results

For chloride concentration, we adopted the CFF and the reference values recommended by others, that is, results below 30 mmol/L and equal to or greater than 60 mmol/L, were considered negative and positive, respectively, indicating the definitive diagnosis of

non-CF and CF.^{4 12 14} For SC, we followed both the manufacturer's guidelines¹⁶ and the values reported by others.^{3 7} SC was considered negative when values were equal or lower than 60 mmol/L and positive when they were equal or greater to 80 mmol/L. Sweat chloride values of 30–59 mmol/L and SC values of 60–79 mmol/L were considered intermediate and analysed apart.

Statistics

Analysis

The primary analysis included only participants with positive and negative results for both methods; intermediate results were not accounted for at this stage. We conducted descriptive statistics and constructed a 2×2 contingency table to estimate sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios (+LR and -LR) and their respective 95% CI.

Intermediate values are expected to occur with chloride titration and SC. According to STARD guidelines,¹⁵ they can be ignored altogether, be reported but not accounted for or handled as a separate test result category. It is also possible to reclassify all such results as false positives or false negatives, depending on the reference standard result ('worst-case scenario') or as true positives and true negatives ('best-case scenario'). As suggested by STARD guidelines, we conducted secondary analyses to reassess SC performance using both scenarios.¹⁵

For the calculation of the post (sweat conductivity) test probability, we considered that in our setting, in the last 5 years, the average prevalence (pretest probability) of CF among newborns and young infants was at around 0.2%.

We also constructed the receiver operator characteristic (ROC) curve to estimate the area under the curve (AUC). Finally, we assessed the agreement between index and reference tests through Kappa coefficient.

Analyses were performed using SPSS software, V.23 (SPSS, USA).

Sample size

Sample size calculation was based on the classical equation, that is, $N = 4Z\alpha^2P(1 - P)/W^2$, in which $Z\alpha$ equals 1.96; P , a proportion that equals the sensitivity or specificity estimates and W , the width of the 95% CI.¹⁷

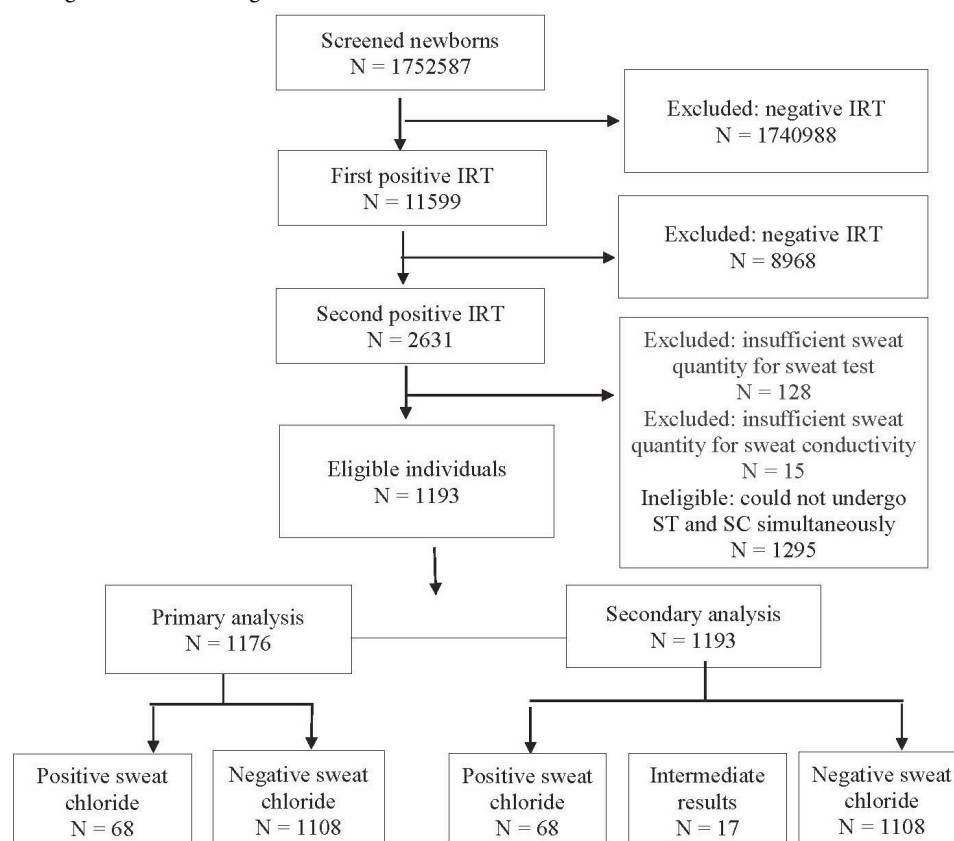


Figure 1 Flow diagram displaying the study cohort retrieval process. SC, sweat conductivity; ST, sweat test.

Table 1 General characteristics of the patients with CF and without CF included in the primary analysis

	Sweat chloride		P value*
	Positive	Negative	
	N (%)	N (%)	
Age-group			0.30
Newborns	13 (19.1)	161 (14.5)	
Infants	55 (80.9)	947 (85.5)	
Sex			0.86
Female	35 (51.5)	555 (50.1)	
Male	33 (48.5)	546 (49.3)	
Not recorded	0	7 (0.6)	
Region of residence			0.01
Urban area	8 (11.8)	277 (25.0)	
Rural area	60 (88.2)	831 (75.0)	
Gestational age (weeks)			0.03
<37	1 (1.5)	102 (9.2)	
≥37	61 (89.7)	999 (90.2)	
Not recorded	6 (8.8)	7 (0.6)	
Birth weight (g)			0.21
<2.500	5 (7.4)	142 (12.8)	
≥2.500	60 (88.2)	954 (86.1)	
Not recorded	3 (4.4)	12 (1.1)	
Weight at the tests day (g)			1.00
<2.000	zero	4 (0.4)	
≥2.000	36 (52.9)	1061 (95.8)	
Not recorded	32 (47.1)	43 (3.8)	

* χ^2 or Fisher's exact test.
CF, cystic fibrosis.

According to the published literature, the average sensitivity for SC is 98%; accepting a margin of error within 0.06 for the 95% CI, we would need a minimum of 83 patients with CF. Regarding specificity, the literature reports an average specificity of 99%;^{13 57 9 10} adopting a width of 0.02 for the 95% CI would require at least 380 individuals without CF. Thus, the final sample size would need at least 463 subjects.

RESULTS

Participants

During the study period, 1 752 587 newborns were screened. A total of 2631 newborns and young infants had two positive IRT tests. According to predefined criteria, we excluded 1 750 099 and considered ineligible 1295 participants; therefore, 1193 were recruited for the study. Among them, 17 subjects (17/1193, 1.4%) presented intermediate results for ST, SC or both tests (figure 1).

Table 1 compares the general characteristics of 1176 participants with positive and negative ST and SC.

There were no significant differences between the two groups, except that the CF group had a higher prevalence in rural areas and a lower proportion of preterm birth. (Gestational age<37 weeks).

The median age of the patients was 5 days old at the first IRT and 15 days of age for those in which the first dosage was higher than 70 mg/L, while the mean (SD) and median (IQR) age of the participants were 48 (19.2) and 43 days old (15-90), respectively. In the

Table 2 Diagnostic accuracy of SC among the 1176 participants without intermediate results (primary analysis)

		Sweat chloride		
		Positive	Negative	Total
		N (%)	N (%)	N (%)
Sweat conductivity	Positive	67 (98.5)	1 (0.1)	68 (5.8)
	Negative	1 (1.5)	1107 (99.9)	1108 (94.2)
	Total	68 (100)	1108 (100)	1176 (100)

SC, sweat conductivity.

CF group, the mean and median values were 100.2 (21.8) mmol/L and 98.1 (66–242) mmol/L for sweat chloride and 103.9 (14.3) mmol/L and 106.0 (25–131) mmol/L for SC. In the non-CF group, the mean and median values for sweat chloride and conductivity were 10.9 (4.4) mmol/L and 10.2 (2.4–29.7) mmol/L and 29.2 (6.0) and 29 (11–103), respectively (data are not shown in table 1).

Test results and estimates: diagnostic accuracy of SC

Table 2 shows the results of ST and SC among the 1176 patients with no intermediate values to chloride analysis and conductometry.

Sweat conductivity yielded a sensitivity of 98.5% (95% CI 95.7 to 100), a specificity of 99.9% (95% CI 99.7 to 100), a PPV of 98.5% (95% CI 95.7 to 100), a NPV of 99.9% (95% CI 99.7 to 100) and an overall accuracy of 99.8% (95% CI 99.6 to 100). Furthermore, the positive and negative LR were 1091.7 (95% CI 153.8 to 7744.9) and 0.01 (95% CI 0.0 to 0.1), respectively.

Post-test probability for positive and negative LR were 68.6 and 0.002, respectively, meaning that the patient's probability of CF increases from 0.2% to almost 70% (ie, around 350 times more) and drops from 0.2% to virtually zero, after a positive and negative SC result, respectively.

The ROC curve was plotted with the 1176 patients without intermediate values to assess the overall accuracy of SC (see figure 2). The AUC was 98.8% (95% CI 96.6 to 100; $p<0.001$), demonstrating that SC potentially has an accuracy close to perfect to distinguish individuals with and without CF. Finally, the kappa correlation coefficient was 0.99 (95% CI 0.97 to 1.0). Please, like in the text inside the Figure replace 96.6%–1.0% to 96.6%–100%

Table 3 summarises the results of 17 participants with intermediate values for either SC, sweat chloride or both. As shown, the overall rate of borderline values was 1.4%, and the number of individuals with intermediate SC results was slightly lower than that for sweat chloride testing, that is, 8%–0.7%, and 12%–1.0% out of 1193, respectively. Only three participants (0.25%) remained with intermediate values to both tests.

The secondary analyses included all 1193 studied participants. For the worst-case scenario, where true positives=67, false-positives=8, false-negatives=11 and true negatives=1107, sensitivity, specificity, PPV and NPV and positive and negative LR were 89.3% (95% CI 80.0 to 95.2), 99.0% (95% CI 98.2 to 99.5), 85.9% (95% CI 77.0 to 91.6), 99.2% (95% CI 98.6 to 99.6), 90.8 (95% CI 50.1 to 164.3) and 0.1 (95% CI 0.0 to 0.2), respectively. For the best-case scenario, where true positives=74, false-positives=1, false-negatives=1 and true negatives=1117, sensitivity, specificity, PPV

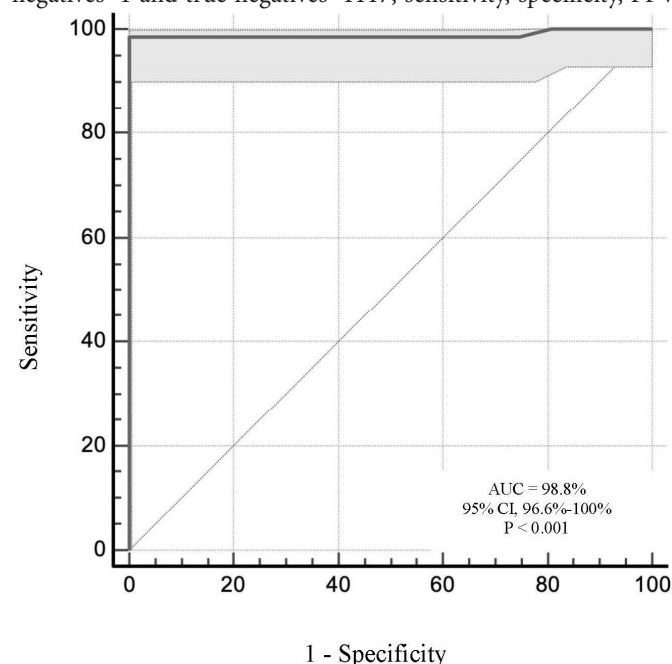


Figure 2 The ROC curve obtained for 1176 subjects. Solid black line: area under the curve for sweat conductivity. Shaded grey area: 95% CI. AUC, area under the curve; ROC, receiver operating characteristics.

Table 3 Sweat chloride and SC results among the 17 (out of 1193) participants with intermediate results

		Sweat chloride			Total N (%)
		Positive	Intermediate	Negative	
		N (%)	N (%)	N (%)	
Sweat conductivity	Positive	zero	3 (25)	zero	3 (17.6)
	Intermediate	4 (100)	3 (25)	1 (100)	8 (47.1)
	Negative	zero	6 (50)	zero	6 (35.3)

and NPV and positive and negative LR were 98.6% (95% CI 99.5 to 99.9), 99.9% (95% CI 99.5 to 100), 98.6% (95% CI 91.2 to 99.8), 99.9% (95% CI 99.3 to 99.9), 1.103,0 (95% CI 155.4 to 7.825,7), 0.01 (95% CI 0.0 to 0.1), respectively.

DISCUSSION

Chloride titration and SC are two sides of the same coin. An increase in chloride anion reflects a proportionate increase in the total electrolyte concentration, which is the basis of analysis by electrical conductivity.¹⁸

To date, this is the first study that demonstrated the excellent accuracy of SC as an alternative diagnostic test for CF among 1193 newborns and very young infants—the target age group of the NBS—compared with the classical ST.

All accuracy estimates obtained in the primary and secondary analyses evidenced the discriminatory diagnostic power of SC, specially the very high positive LR and very low negative LR. Positive and negative LR have unequivocal clinical relevance and are independent of disease prevalence offering a more practical way of interpreting SC accuracy. The higher the positive LR, the better the test result for ruling in the disease; conversely, the lower the negative LR, the better the test result is for ruling out the disease.¹⁷ Irrespective of the way that primary and secondary analyses were done, all accuracy indices for SC remained relatively stable. Moreover, post-test probability values mean that the likelihood of CF increases 350 times after a positive SC, while negative results virtually rule out CF.

The ROC curve is a useful summary of the overall accuracy of any test. The very large AUC (98.8%) and the near-perfect agreement between index and reference tests (Kappa=0.99) provide additional evidence for the accuracy of SC. The rate of the intermediate ST (1.0%) and SC (0.7%) results also demonstrated the comparability between them.

As the mean and median age of the included participants were lower than 50 days when they underwent ST and SC, the first clinical appointment was accomplished before completing the second month of life irrespective of their gestational age, birth weight and weight at the testing day. These data are comparable to those described by Leung et al reporting a mean age of 2.58 (SD 0.69) months at initial examination among 231 American CF children diagnosed exclusively through classical ST.¹⁹

We searched studies on SC, disregarding investigations carried out with its related Nanoduct, and found only one prospective study including newborns.³ That study assessed 534 subjects and had similar estimates for SC, that is, 100% sensitivity, 96.2% specificity, 83.3% PPV, 100% NPV, 31.7 positive LR, and zero negative LR.³ Other studies in different age groups found good to high estimates for sensitivity (83.3%–100%), specificity (97.3%–100%), PPV (90.9%–100%) and NPV (94.7%–100%).^{1,3,5,7,10,11} To note, the present study had the narrowest width of the 95% CI for all estimates, demonstrating the highest statistical precision.

As a result of multiple determinants, a glaring gap is evident in the median age of survival of patients with CF living in affluent and non-affluent countries. For instance, the life expectancy of individuals with CF in Canada, the USA and European Union countries are in the mid-40s or above, while only half of that in Brazil and even lower in some countries of the former Soviet Union.²⁰ It is widely recognised that individuals with CF in developed nations

are diagnosed earlier than their counterparts in developing ones and are likely to receive sooner standard CF care because of organisational factors, appropriate healthcare infrastructure and human resources.²⁰ Providing the cheaper and simple SC test in rural or remote settings could contribute to speeding up the diagnosis, bridging at least some of these critical gaps.

Then, in settings with a relative shortage of chloridimeters, implementing an SC network in close cooperation with CF referral centres labs could reduce their burden with negative sweat chloride testing after NBS and contribute to the earlier diagnosis of CF. For instance, the CF Referral Centre labs must retest sweat samples through a chloridimeter from either positive or negative SC results chosen randomly through a rigorous and periodical schedule. As shown, around 80% of our studied newborns and young infants resided in the countryside, that is, between 30 and 470 miles from our CF Centre, the sole facility for the whole State, which surface area is like that of France. A similar scenario seems to apply in similar settings worldwide.

We should pinpoint the limitations of our study. First, even though chloride titration is still considered a gold standard, it would be better if we had used a more robust gold standard, that is, the combination of sweat chloride plus DNA testing. That strategy would undoubtedly avoid the rate of intermediate results and would guide CFTR modulator therapies. Second, we recruited 72 out of 83 patients with CF, that is, 11 fewer than would be needed. However, the present work has enough power to assess the diagnostic accuracy of SC, given that the final sample size (n=1193) is much larger than that previously calculated (n=463). Finally, in terms of size and age group, this unparalleled sample may also have mitigated the ineligibility of the 1295 potential patients who could not simultaneously undergo both tests, one of the inclusion criteria.

In conclusion, SC demonstrated excellent reliability after two-tier IRT NBS. Therefore, it might be considered an alternative diagnostic tool for CF, especially in poor health infrastructure settings, because it contributes to early treatment and minimises family and parental distress due to a positive NBS.

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ARTIGO ORIGINAL

Diferença de importância mínima em doenças pulmonares intersticiais infantis

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RESUMO

Contexto A monitorização da progressão da doença pulmonar intersticial na infância (chILD) é essencial. Não está disponível qualquer informação sobre a diferença mínima importante (DMI), que é definida como a alteração mínima de um parâmetro percebido como importante para que o médico altere a terapêutica. Calculamos as DMI para os sinais vitais (ritmo respiratório, saturação periférica de oxigênio em ar ambiente, score de gravidade de Fan) e os resultados de qualidade de vida relacionada com a saúde (HrQoL).

Métodos Este estudo usou dados do Kids Lung Register, que é uma plataforma de gestão online que recolhe dados de distúrbios pulmonares pediátricos raros com foco na chILD. Foram recolhidos dados dos sinais vitais e resultados HrQoL (Health Status Questionnaire, questionário específico chILD e PedsQL V.4.0). Os DMI foram calculados de acordo com métodos de base distributiva (DP de um terço) e de base ancorada (com recurso ao volume expiratório forçado no primeiro segundo e à capacidade vital forçada como âncoras).

Resultados Foram usados dados iniciais de 774 crianças para calcular os DMI seguintes: taxa respiratória 1,3 (z-score), saturação periférica de oxigênio em ar ambiente de 3,0 %, score de gravidade de Fan 0,2-0,4, Health Status Questionnaire 0,4-0,8, questionário específico chILD 4,4%-8,3%, resultado do resumo de saúde física 7,8%-8,9%, resultado do resumo de saúde psicossocial 3,4%-6,9% e resultado total 5,1%-7,4%. Os resultados da análise de responsividade estiveram, em geral, de acordo com os DMI calculados.

Conclusões Pela primeira vez, fornecemos estimativas dos DMI para sinais vitais e dos valores HrQoL numa grande coorte de chILD com recurso a métodos diferentes.

INTRODUCTION

Childhood interstitial lung diseases (chILD) are a heterogeneous group of diffuse and mostly chronic respiratory disorders that mainly affect the lung parenchyma leading to impaired alveolar gas exchange.¹ This disease group is more diverse than interstitial lung diseases in adults, comprising at least 200 different conditions. In contrast to the broad diversity of underlying causes, the clinical presentation of chILD is non-specific and includes tachypnoea, crackles, hypoxaemia and failure to thrive.¹ The frequency of chILD is considered to be more than ten times smaller than in adults ILDs.¹ Reported were prevalences between 0.36/100 000 and 4.65/100 000 children^{2 3} and incidences between 0.13/100 000 and 10.76/100 000 children.^{2,4,5} As chILD-related mortality is high with estimates around 15%,^{4 6} evaluating disease progression is particularly important.

When monitoring the clinical course of patients, the smallest change in a parameter that is considered important and prompting a potential change in treatment is defined as the minimal important difference (MID).⁷⁻¹⁰ The MID provides a guide as to whether a change provides a minimum level of perceived benefit. The term was first described in 1989 and is now a well-established concept considered as a reliable method for calculating

Key messages

What is the key question?

► The minimal important difference (MID) is the smallest change in a clinically relevant parameter, which would indicate a change in treatment. In the design of randomised clinical trials, MIDs assist in determining the selection of endpoints and calculating the sample size. The concept of MID directly addresses the limitation that studies may find statistical relationships that only have little or no clinical significance for patients. So far, MIDs for essential clinical parameters are not yet established for childhood interstitial lung diseases (chILD).

What is the bottom line?

► This study introduced MIDs in respiratory rate, peripheral oxygen saturation in room air, Fan severity score and health-related quality of life (HrQoL) scores in patients with chILD.

Why read on?

► The MID computed in this study will help judge the clinical relevance of changes in vital signs and HrQoL scores, design future clinical trials and support cost-effectiveness analyses of potential therapies.

reference points for clinicians to consider altering a treatment and help interpreting the relevance of changes in parameters over time.¹¹⁻¹³ Also, in the design of randomised clinical trials (RCTs) MIDs assist in determining the selection of endpoints and calculate the sample size.^{14 15} Finally, the concept of MID directly addresses the limitation that studies may find statistical relationships that only have little or no clinical significance for patients.¹⁶ So far, MIDs for essential clinical parameters are not yet available for chILD.

There is no consensus yet as to how to calculate MIDs and several different methods defining MIDs have been introduced. It is recommended to include multiple approaches.^{17 18} The most widely used methods include distribution-based and anchor-based approaches.¹⁹ More commonly used is the distribution-based method.^{7 12} This approach is determining MIDs based on the statistical characteristics of a variable, e.g. one-third of the SD have been selected as MID.²⁰ A major advantage of this approach is the simplicity of use, as it does not require external criteria. However, a disadvantage is the dependence on the reference sample making the calculation less generalisable.²¹ The anchor-based approach to determine MIDs is generally considered superior and statistically more complex

Table 1 Baseline characteristics of the study cohort

Study cohort	
Total sample size	757 (100%)
Age (years)	7.3 (6.04; 0.1–18.0)
Sex	
Male	406 (53.6%)
Female	351 (46.4%)
Country the patient is treated in	
Germany	414 (54.7%)
UK	98 (12.9%)
Turkey	69 (9.1%)
Poland	39 (5.2%)
Italy	24 (3.2%)
Switzerland	21 (2.8%)
Spain	16 (2.1%)
Denmark	15 (2.0%)
Other*	61 (8.1%)
Disease category	
A1—DPLD-Diffuse developmental disorders	27 (3.6%)
A2—DPLD-Growth abnormalities deficient alveolarisation	52 (6.9%)
A3—DPLD-Infant conditions of undefined aetiology	139 (18.2%)
A4—DPLD related to alveolar surfactant region	185 (24.4%)
Ax—DPLD-unclear RDS in the mature neonate	14 (1.8%)
Ay—DPLD-unclear RDS in the almost mature neonate	14 (1.8%)
B1—DPLD related to systemic disease processes	81 (10.7%)
B2—DPLD-in the presumed immune intact host related to exposures	103 (13.6%)
B3—DPLD-in the immunocompromised host or transplanted	43 (5.7%)
B4—DPLD related to lung vessels structural processes	62 (8.2%)
B5—DPLD related to reactive lymphoid lesions	7 (0.9%)
Bx—DPLD-unclear RDS in the non-neonate	23 (3.0%)
By—DPLD-unclear non-neonate	8 (1.1%)

Data are presented as numbers (percent) or mean (range; SD).
*Belgium 13 (1.7%), Greece 10 (1.3%), Austria 8 (1.1%), Hungary 7 (0.9%), Portugal 5 (0.7%), Czech Republic 4 (0.5%), Netherlands 3 (0.4%), South Africa 3 (0.4%), Brazil 2 (0.3%), State of Palestine 1 (0.1%), Croatia 1 (0.1%), France 1 (0.1%), Luxembourg 1 (0.1%), Romania 1 (0.1%), Serbia 1 (0.1%).

compared with the distribution-based method.^{22–23} This method relates the change of a clinical or patient-reported outcome (PRO) score to an independent parameter, the anchor.²⁴ This second criterion can be an expert opinion, a clinically relevant test result or a score directly capturing the patient's preferences. The latter is considered optimal when calculating MID for health-related quality of life (HrQoL).²⁵ A detailed review characterising different methods used to calculate anchor-based MIDs in children has recently been published.²⁶

The scope of this study was to establish MIDs for clinical variables commonly used in chILD in order to provide tools to assess the clinical relevance of disease progression and design RCTs.

METHODS
Kids Lung Register and study design

This study used data obtained from the Kids Lung Register (www.kidlung.net). It is an observational, web-based management platform that prospectively collects clinical data of children diagnosed with chILD. Local physicians can participate as referring centre after all necessary contractual legal and ethical requirements have been fulfilled. Each patient and/or caregiver has to give age-appropriate assent and written informed consent. Clinical teams providing care are trained and provided with specific standard

operating procedures (SOPs) as to how variables are collected and entered into the case report forms of the register. Following inclusion (baseline visit) completeness of data is checked and in a common meeting the diagnosis made by multidisciplinary teams in accordance with the clinical guidelines of the American Thoracic Society²⁷ and the European management platform for interstitial lung diseases in children.²⁸ Following this expert review process, data about the clinical course of the included patients are prospectively collected at defined study visits and entered by participating centres. During the first year, visits are scheduled every 6 months, then annually. The implementation and use of the Kids Lung Register have been described in detail elsewhere.²⁸

Vital signs and Fan severity score

Vital signs included the respiratory rate, peripheral oxygen saturation (SpO₂) in room air and Fan severity score. The respiratory rate and oxygen saturation in room air were measured twice over 1 min in an awake patient after 5 min at rest. The measurements had to be at least 1 min apart. The stable average values were recorded. If the patient needed supplemental oxygen, the oxygen supplementation was withdrawn after 5 min at rest and the O₂-saturation was measured twice in the course of 1 min. If the SpO₂ fell below 80% oxygen is placed back and no value noted. Respiratory rate z-scores were derived from.²⁹ The severity of illness was analysed using the adapted disease Fan severity score and categorised as follows: (1) asymptomatic, (2) symptomatic with normal room air oxygen

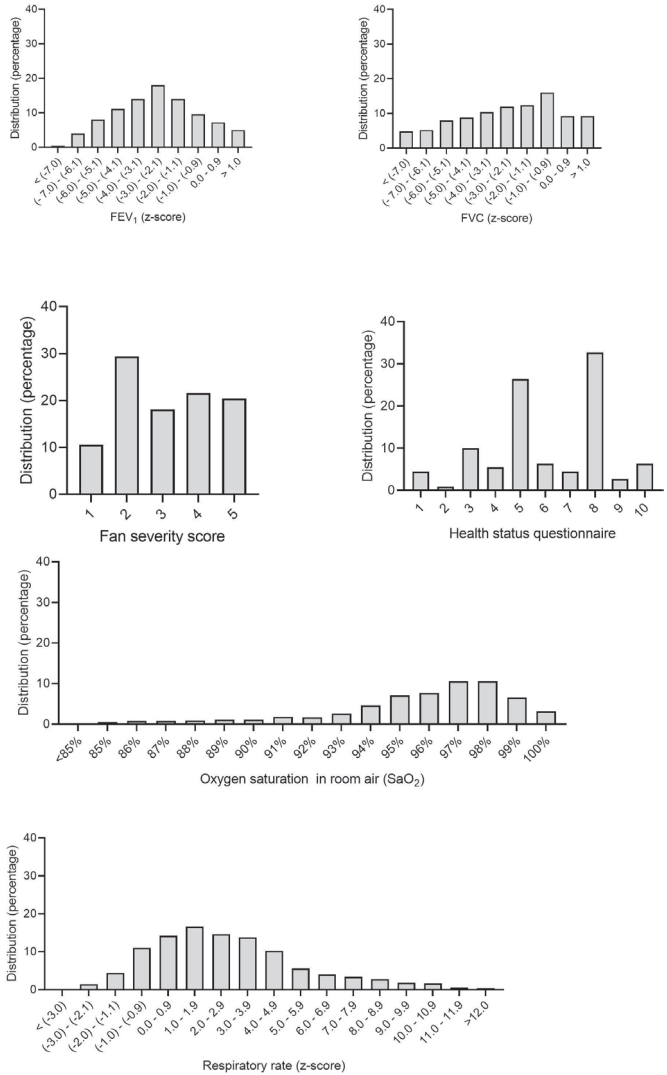


Figure 1 Distribution of FEV₁, FVC, Fan severity score, Health Status Questionnaire scores, oxygen saturation ratio in room air and respiratory rate (z-score) at baseline visit across patients with chILD. chILD, childhood interstitial lung diseases; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

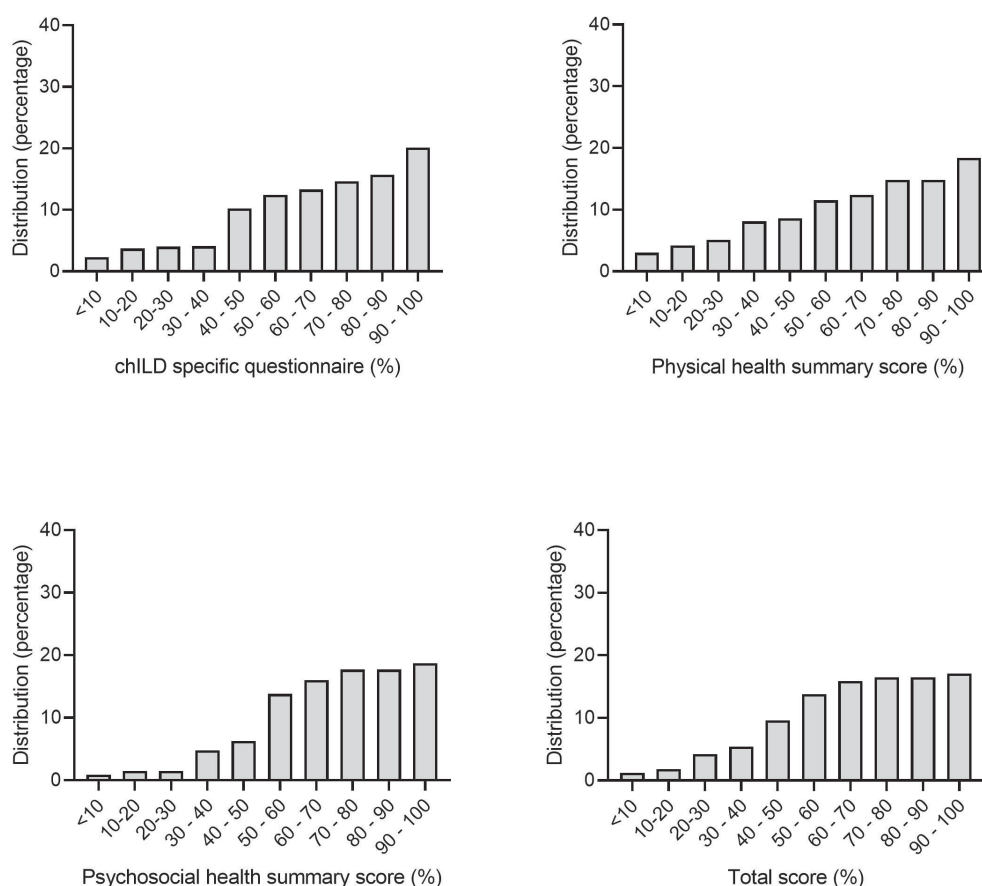


Figure 2 Distribution of chILD-specific questionnaire, Physical Health Summary score, Psychosocial Health Summary score and total score at baseline visit across patients with chILD. chILD, childhood interstitial lung diseases.

saturation under all conditions, (3) symptomatic with normal resting room air saturation, but abnormal saturation ($\text{SaO}_2 < 90\%$) with sleep or exercise, (4) symptomatic with abnormal resting room air saturation $< 90\%$ and (5) symptomatic with pulmonary hypertension.^{30 31}

Pulmonary function testing

All children older than 5 years were asked to perform lung function testing. Absolute litres of forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were recorded. Age-specific and sex-specific scores (z-scores) were calculated using the Global Lung Function Initiative reference values.³²

Table 2 Correlation between vital signs as well as HrQoL and possible anchors: FEV_1 (z-score) and FVC (z-score)

Variable	FEV_1 (z-score) spearman's correlation coefficient (p value)	FVC (z-score) spearman's correlation coefficient (p value)
Vital signs		
Respiratory rate (z-score)	-0.194 (0.011)	-0.221 (0.004)
O2 saturation on room air	0.108 (0.004)	0.136 (0.051)
Fan severity score	-0.351 (<0.001)	-0.375 (<0.001)
HrQoL		
Health Status Questionnaire	0.335 (0.017)	0.302 (0.068)
chILD-specific questionnaire	0.339 (<0.001)	0.300 (<0.001)
Physical Health Summary score	0.393 (<0.001)	0.399 (<0.001)
Psychosocial Health Summary score	0.300 (<0.001)	0.303 (<0.001)
Total score	0.359 (<0.001)	0.344 (<0.001)
chILD, childhood interstitial lung diseases; FEV_1 , forced expiratory volume in 1 s; FVC, forced vital capacity; HrQoL, health-related quality of life.		

Health-related quality of life

At every study visit, the caregivers were asked to estimate the children's medical condition on a scale from 0 (very bad) to 10 (perfect): the Health Status Questionnaire. Thereafter, caregivers were handed PROs. The questionnaires were filled by the caregivers (proxy-reported) including the chILD-specific questionnaire and PedsQL 4.0. The PedsQL 4.0 consists of three different subscales: physical health summary score, psychosocial health summary score and total score. All questionnaires were available in different languages and age versions. Feasibility, reliability and validity as well as internal consistency for chILD-specific questionnaire and PedsQL V.4.0 have been proven.³³

Statistics

The statistical evaluation of the data was done with SPSS software for statistical analyses (V.26.0) and GraphPad Prism (V.8.4.3). Demographic data are reported as means (range, SD) or numbers (per cent).

Calculation of MIDs and responsiveness analysis

As a combination of anchor-based and distribution-based methods is recommended to determine MIDs,^{17 20} both methods were used in this study assessing baseline visit scores. For the distribution-based method, the SD of the assessed scores was determined. The MIDs are defined by one third of the calculated values. This method has been suggested by Yost and Eton.¹⁹

The recommended statistical analysis to determine MIDs using the anchor-based method is more complex.⁷ We choose the same approach that has been recently published in a study defining MIDs in adults with a broad spectrum of ILDs.³⁴ First, we identified the pulmonary function as relevant to patients and lung function testing results (FEV_1 and FVC) as potential anchors. The relationship between the anchors and variables (respiratory rate, oxygen saturation on room air, Fan severity and HrQoL scores) was assessed using Spearman's correlation. As recommended, the anchors were only included in the final analysis if the calculation

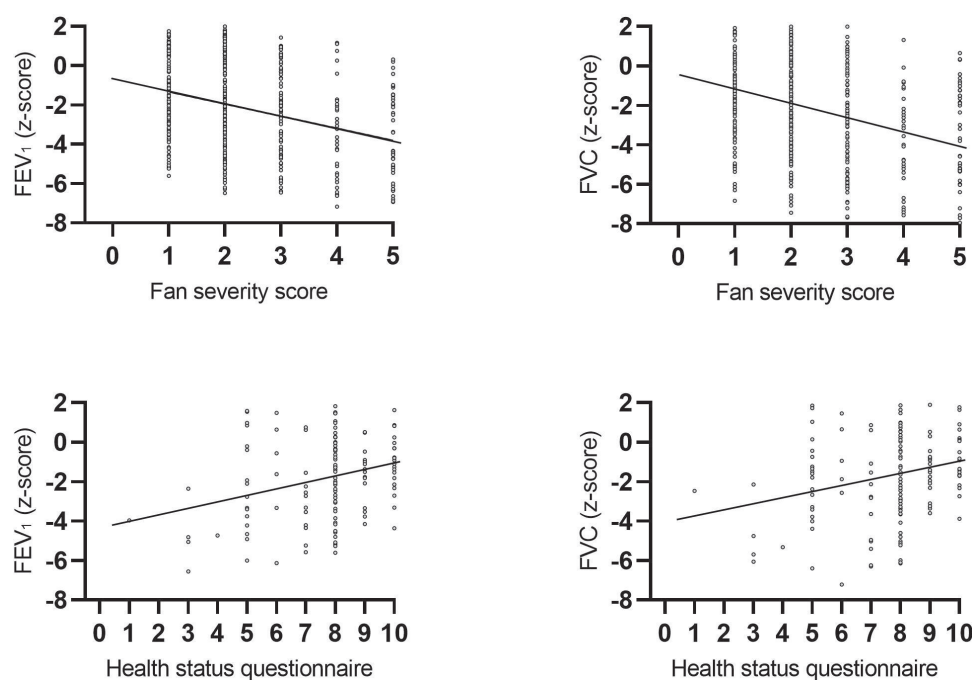


Figure 3 Association between Fan Severity Score and Health Status Questionnaire scores assessed from patients with FEV_1 (z-score) and FVC (z-score) as anchors. FEV_1 , forced expiratory volume in 1 s; FVC, forced vital capacity.

proved at least a moderate correlation between the anchors and the outcome variable (r value $r \geq |0.3|$).^{17 19} If an acceptable relationship was revealed, we performed an unadjusted linear regression between the anchors (independent variable) and the outcome variable (dependent variable). Finally, the MIDs were generated from the corresponding regression equations based on a z-score of 1.64 for FEV_1 and FVC, as this number was established for the lower limit of normal for spirometry.^{35 36}

To evaluate for possible changes of vital signs and HrQoL scores, a responsiveness analysis was performed at the follow-up visit. An absolute FEV_1 and FVC z-score change of 1.64 between baseline and the follow-up visit was considered significant, as this number is representing the lower, respectively upper 5% limit of normal. Children were categorised into three groups: group 1 (deteriorated) ΔFEV_1 or $\Delta FVC < -1.64$ (z-score), group 2 (same) -1.64 (z-score) $< \Delta FEV_1$ or $\Delta FVC < 1.64$ (z-score) and group 3 (improved) ΔFEV_1 or $\Delta FVC > 1.64$. The corresponding changes (means) for vital signs, Fan severity and PRO scores, were calculated. If the 6 months follow-up visit was missed, results were calculated using the 1-year follow-up.

RESULTS

Study population

A total of 757 children were included at baseline (table 1). Mean age was 7.3 years (SD 6.04; 0.1–18.0). Males (53.6%) and females (46.4%) were almost equally distributed. Most patients were treated in Germany (54.7%), UK (12.9%), Turkey (9.1%), Poland (5.2%), Italy (3.2%), Switzerland (2.8%), Spain (2.1%) and Denmark (2.0%). The spectrum of chILD categories and subcategories observed was broad. Characteristics of the study population are listed in table 1.

Vital signs and HrQoL

At baseline, respiratory rate of 535, oxygen saturation in room air of 490, Fan severity score of 742 and spirometry results of 242 children were available to calculate MIDs. There were no differences between children usually able to perform spirometry on an acceptable level (older than 5 years) with and without recorded PFT data regarding disease category ($p=0.053$) or being symptomatic ($p=0.285$). 364 HrQoL questionnaires were completed. The distribution of spirometry results was almost normal, Fan severity score, Health Status Questionnaire scores and oxygen saturation were skewed to the left. Respiratory rate (z-score) was tailed to

the right (figure 1), whereas the chILD-specific questionnaire and PedsQL V.4.0 scores had a ceiling effect (figure 2).

The correlation analysis between spirometry results and respiratory rate as well as oxygen saturation in room air revealed only a small association, whereas between spirometry results and Fan severity, Health Status Questionnaire, chILD-specific questionnaire and all PedsQL V.4.0 scores a moderate or better correlation was found (table 2, figures 3 and 4).

Estimates and responsiveness of MID

Estimates of the MIDs for respiratory rate (z-score), oxygen saturation in room air (per cent), Fan severity, Health Status Questionnaire, chILD-specific questionnaire and PedsQL V.4.0 scores are provided in table 3. Calculations of the distribution based MIDs were performed for all variables. For respiratory rate ($r=0.194$ for FEV_1 ; $r=0.221$ for FVC) and oxygen saturation in room air ($r=0.108$ for FEV_1 ; $r=0.136$ for FVC) no anchor-based MIDs were calculated; analyses revealed distribution-based MIDs of 1.3 and 3.0%, respectively. Distribution-based MIDs for Fan severity, Health Status Questionnaire, chILD-specific questionnaire and all PedsQL V.4.0 scores provided higher scores than anchor-based MIDs. The distribution-based MIDs calculated for Fan severity and Health Status Questionnaire score were 0.4 and 0.8, whereas the anchor-based scores ranged from 0.2 to 0.4 and 0.4 to 0.5, respectively. The distribution-based MIDs for chILD-specific questionnaire and PedsQL V.4.0 scores ranged from 6.9 to 8.9, whereas the anchor-based MIDs ranged from 3.4 to 8.3, depending on which anchor was used.

Results of the responsiveness analysis generally agreed with the MIDs previously calculated (table 4). A change of the z-score in FEV_1 or FVC above 1.64 between two study visits resulted in change of vital signs or HrQoL scores above the corresponding MIDs. In contrast to that, smaller z-score changes of the spirometry results revealed no meaningful changes of vital signs or HrQoL scores.

DISCUSSION

This is the first study of children diagnosed with chILD to provide estimates of MIDs for this population. No consensus has yet been reached as to which of the different methods, the distribution-based or anchor-based method, should be preferred.

This issue has been addressed before in other conditions. It is recommended to use both methods complementary to each other rather than separately with the resulting values narrowed down to

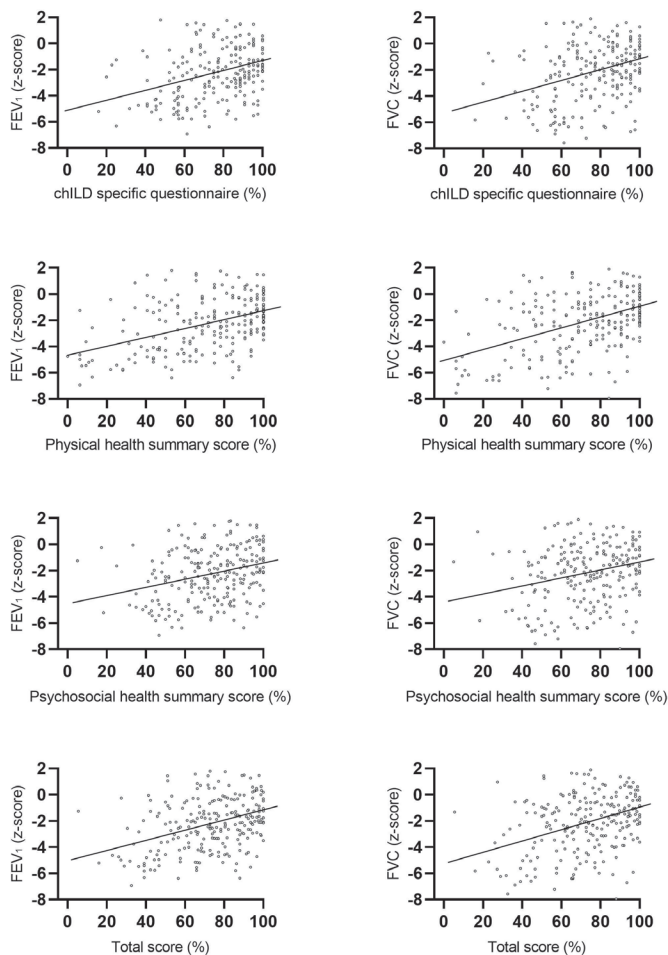


Figure 4 Association of chILD-specific questionnaire and Physical Health Summary score, Psychosocial Health Summary score and total score assessed from patients with FEV₁ (z-score) and FVC (z-score) as anchors. chILD, childhood interstitial lung diseases; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

a small range.^{18,37} The distribution-based method provided higher scores than the anchor-based method. This finding has been reported before and is likely a result of the distribution-based method using the statistical distribution of a heterogeneous population like chILD to calculate MIDs.^{34,38}

In this study, we analysed data of children diagnosed according to current guidelines of the American Thoracic Society²⁷ and the European management platform for interstitial lung diseases in children.²⁸ Whereas those classification systems include a broad spectrum of diseases with different pathophysiological mechanisms, the clinical presentation and symptoms are very similar across this large patient group.³⁹ In contrast to adult ILD, the frequency of chILD is more than ten times lower and most of the diseases are extremely rare.³⁹ Although, splitting diseases into smaller entities is key for precision medicine, conducting randomised control trials for specific, some extremely rare diseases does not seem feasible. Therefore, we believe that using this 'basket approach' to calculate MIDs will help clinicians to interpret changes and scientists to better design RCTs. As very recently done in interstitial lung diseases in adults, we selected results of lung function testing (FEV₁ and FVC) as appropriate anchors for this approach.³⁴ Of note, children under 5 years of age are usually not able to perform spirometry on an acceptable level. In consequence, one might argue that MIDs based on lung function data as anchor should not be used in infants. However, as the cooperation rather than any anatomical or structural issue, is preventing children under 5 years from performing acceptable spirometry manoeuvres, we argue that the anchor-based MIDs calculated in this study can be used across all age groups, particularly as we used age-independent z-scores of PFT results for this analysis.

Table 3 MID calculation (and 95% CIs) for vital signs and HrQoL

Variable	Distribution based MID (1/3 SD)	Anchor based MID (FEV ₁)	Anchor based MID (FVC)
Vital signs			
Respiratory rate (z-score)	1.3	.*	.*
O ₂ saturation on room air (percent)	3.0	.*	.*
Fan severity score	0.4	0.2 (0.2 to 0.3)	0.3 (0.2 to 0.3)
HrQoL			
Health Status Questionnaire	0.8	0.5 (0.3 to 0.6)	0.4 (0.2 to 0.5)
chILD-specific questionnaire (percent)	8.2	5.2 (3.2 to 7.0)	4.4 (2.7 to 6.0)
Physical Health Summary score (per cent)	8.9	8.3 (6.1 to 9.2)	7.8 (6.0 to 9.9)
Psychosocial Health Summary score (percent)	6.9	4.4 (2.6–6.3)	3.4 (2.0 to 5.1)
Total score (per cent)	7.4	5.8 (4.1 to 7.8)	5.1 (3.4 to 6.8)

*No anchor-based MIDs were calculated as Spearman's correlation coefficient did not indicate at least a moderate correlation (r value $\geq |0.3|$) between the variables and anchors.

chILD, childhood interstitial lung diseases; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; HrQoL, health-related quality of life; MID, minimal important difference.

Routine measurements of diffusion capacity for carbon monoxide (DLCO) for surveillance of fibrotic changes and disease progression is recommended in adult ILD.⁴⁰ This method provides a quantitative measure of gas transfer in the lungs defining respiratory status in patients with chronic lung diseases⁴¹ and have been used as anchor to calculate MIDs in adult ILD.³⁴ However, as lung fibrosis in chILD is rarely seen,⁴² DLCO in children is not widely used and current guidelines for chILD only recommend routine use for surveillance in children diagnosed with pulmonary haemorrhage.⁴³ As a result, only few DLCO data were entered into the register that are limited to children with pulmonary haemorrhage, and therefore, not used to calculate MIDs in this study.

For oxygen saturation in room air and respiratory rate (z-score) the distribution-based method revealed MIDs of 3.1% and 1.3, respectively. For these outcome parameters, we chose not to calculate the MIDs using the anchor-based method, as the statistical analysis did not find at least a moderate correlation between the scores and both anchors. For the Fan severity score, both methods were used. The MID ranged between 0.2 and 0.4. However, as only discrete changes of 1 or more on this 5-point severity illness scale are clinically meaningful, the MID for the Fan severity score may only be useful in changes of larger populations. As this illness score is chILD specific, no MIDs for the Fan severity score have been estimated in other respiratory conditions for comparison. The score is an independent measure of disease severity in chILD as it can be easily obtained across all age groups.

The MIDs for the HrQoL scores obtained in this study were consistent with published MIDs in other chronic conditions, ranging between 4% and 8%.^{12,44} PROs provide a better understanding of the patients' perspectives regarding treatment benefits as well as health status and are therefore commonly used.²⁶ The multidimensional construct helps assessing the different components of well-being, and can therefore yield a more comprehensive description of the medical condition than the reporting of clinical symptoms.⁴⁵ The questionnaires are frequently used for monitoring of the subjective health status and as outcome parameter in clinical trials.^{33,46,47} At the ceiling, however, the maximum possible improvement is limited and changes larger than the calculated MIDs might be needed for patients to be considered significant. A recent publication addressed this issue calculating MIDs for different degrees of disease severity across the same disease group. This allowed the authors to isolate the effects of the measures from the characteristics of the patients.⁴⁸ In this study, the MIDs calculated for different vari-

Table 4 Absolute change of vital signs and HrQoL scores across changes in FEV₁ and FVC between baseline and follow-up visit

Lung function change between visits	Deteriorated		Same		Improved	
	FEV ₁ < -1.64 (z-score)	FVC < -1.64 (z-score)	-1.64 < FEV ₁ < 1.64 (z-score)	-1.64 < FVC < 1.64 (z-score)	FEV ₁ > 1.64 (z-score)	FVC > 1.64 (z-score)
Δ Fan severity score	-0.3	-0.3	0.2	0.0	0.7	0.4
Δ Health Status Questionnaire	-1.0	-1.0	0.7	0.8	2.7	2.0
Δ chILD-specific questionnaire	-12.2	-15.5	4.5	5.1	19.4	16.1
Δ Physical Health Summary score	-12.9	-14.5	3.7	3.6	21.5	18.2
Δ Psychosocial Health Summary score	-11.3	-13.3	2.5	3.4	12.7	12.8
Δ Total score	-12.1	-13.8	2.7	3.4	16.0	14.3

An absolute FEV₁ and FVC z-score change of 1.64 between baseline and the follow up follow-up visit was considered significant defining the groups 'deteriorated', 'same' and 'improved'.

chILD, childhood interstitial lung diseases; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; HrQoL, health-related quality of life.

ables changed according to disease severity. However, the patient group with larger MID for one variable did not comprise patients with large MID for the other variable. The authors concluded that there is no need to specify different MID for different subgroups of patients and favoured a single MID for all patients. Nevertheless, conceptually for a rational use of MID a minimum level of disease severity must be present to perceive clinical improvement. Also, independent of the method used, MID represent a population average and might differ from individual patient's perception.

There are several limitations to consider when interpreting our findings. As no large randomised control trials in chILD exists, it was not possible to verify the MID calculated in this study. However, the response analysis that we performed was in agreement with the MID calculated. Also, we used PFT data as anchor to calculate MID. For a comprehensive MID calculation it is recommended using additionally scale-based instruments that directly capture a patient's perception of well-being (eg, Visual Analogue Scale), data that we did not capture and therefore not included in this analysis.

A second limitation is that this is not a population-based study and chILD is a group of individually very rare conditions. Still, we were able to recruit a representative cohort over several years to calculate MID. Also, chILD is an umbrella term covering more than 200 different entities and diseases so rare that only a few patients have been reported. However, the uniform clinical presentation of respiratory disorders affecting lung parenchyma may justify this joint approach, which has recently been used to calculate MID in adult ILD.³⁴

In this study, most variables were not normally distributed but skewed to one side, that is, more affected patients than healthy subjects were sampled. To overcome this issue, we calculated additionally anchor-based MID and used both methods in combination. Of note, the Kids Lung Register does not systematically assess why variables are not entered. It can only be speculated if PFT data were missed being recorded or participants were not able to perform spirometry for a certain reason (eg, due to sickness). However, for children able to perform spirometry on an acceptable level (older than 5 years) we did not find differences between participants with and without recorded PFT data regarding disease category or being symptomatic. Also, participating centres were trained and provided with specific SOPs regarding how variables were to be collected. However, we did not monitor if data were collected as required according to the SOPs. The ceiling effect seen in HrQoL scores suggests that it may not be a sensitive measure in mild forms of the disease, and therefore, limited to monitor disease progression for such children. Similar results have been found in adult ILD calculating MID for HrQoL scores.³⁴ In this study, only parent HrQoL data were analysed as proxy for the children.

In summary, we used a cohort of patients with chILD to determine MID for respiratory rate (z-score), oxygen saturation in room air, Fan severity score and HrQoL scores using both dis-

tribution-based and anchor-based methods. The MID provided here will assist clinicians to monitor disease progression and help researchers to design RCTs in chILD.

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Contributors ES developed the theoretical framework, processed the analytic calculations, performed the data interpretation, and took the lead in writing the manuscript. MG designed and organised the project, organised the platform and contributed to the manuscript providing critical feedback. Clinical principal site investigators of the project were ES, MG, NS, JC, MW, NK, NE, JL and KK. All participating centres contributing less than 2% of the analysed data were listed under the chILD-EU collaborators group, which is included as a contributing author.

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ARTIGO ORIGINAL

Displasia broncopulmonar e fluxo aéreo expiratório aos 8 anos em crianças extremamente prematuras na era pós-surfactante

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RESUMO

Contexto Não é claro que a displasia broncopulmonar (DBP) está independentemente associada à redução do fluxo expiratório em idade escolar.

Objetivo Determinar as associações independentes de DBP moderada a grave, DBP leve, idade gestacional e z score de peso à nascença com o fluxo ventilatório expiratório em crianças extremamente prematuras (EP; <28 semanas de gestação).

Métodos Todos os sobreviventes EP nascidos em Victoria, Austrália, em três eras (1991–1992, n=225; 1997, n=151 e 2005, n=170) foram recrutados à nascença e 418/546 (77%) possuíam dados de espirometria válidos aos 8 anos. A DBP foi classificada como moderada a grave (necessidade de oxigénio às 36 semanas pós-menstruais), leve (oxigénio >28 dias mas não às 36 semanas pós-menstruais). Foram medidas as variáveis de fluxo ventilatório expiratório, incluindo o volume expiratório forçado em 1 segundo (FEV₁), e os valores convertidos em z score.

Resultados Em comparação com ausência de DBP (n=94), a DBP moderada a grave (n=193) esteve associada a uma redução substancial do fluxo ventilatório expiratório (p. ex. diferença média de zFEV₁ -0,69, IC 95% -0,97 a -0,41; p<0,001), ao contrário da DBP leve (n=131) (diferença média de zFEV₁ 0,01, IC 95% -0,28 a 0,31; p<0,001). N análise multivariada, a DBP moderada a grave manteve-se fortemente associada ao fluxo ventilatório reduzido (diferença média de zFEV₁ -0,63, IC 95% -0,92 a -0,33; p<0,001), ao contrário da DBP leve (diferença média de zFEV₁ 0,04, IC 95% -0,26 a 0,34; p=0,27), da idade gestacional (aumento médio de zFEV₁ de 0,07 por semana, IC 95% -0,05 a 0,17; p=0,29) e da z score de peso à nascença (aumento médio de zFEV₁ de 0,07 por DP, IC 95% -0,06 a 0,20; p=0,28).

Conclusões Em crianças EP, a DBP moderada a grave, ao contrário da DBP leve, esteve independentemente associada à redução do fluxo expiratório.

INTRODUCTION

Survival rates for infants born extremely preterm (EP; <28 weeks' gestation) have increased dramatically with the advent of neonatal assisted ventilation and subsequent advances in perinatal care over the past 50 years. One of the major advances was the introduction of exogenous surfactant into clinical practice in the early 1990s to treat respiratory distress in infants born preterm who lacked their own surfactant after birth. Today, almost 9-in-10 live births at 22–27 weeks' gestation who are offered intensive care are expected to survive into adulthood.¹ Worryingly, adults born EP are destined for higher rates of chronic obstructive pulmonary disease than are adults born at term.²

Bronchopulmonary dysplasia (BPD) affects approximately 50% of survivors born EP,³ and is strongly associated with reduced expiratory airflow in later life in survivors born preterm.^{2,4–6} A recent report suggests that it is not BPD per se that is associated with reduced expiratory airflow, but it is increasing prematurity and fetal growth

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Bronchopulmonary dysplasia is associated with reduced expiratory airflow in children born preterm but recently it has been suggested that gestational age and fetal growth restriction are more important associations, and bronchopulmonary dysplasia itself is not.

WHAT THIS STUDY ADDS

► Moderate–severe bronchopulmonary dysplasia is independently associated with reduced expiratory airflow in 8-year-old children who were born extremely preterm (<28 weeks' gestation), whereas mild bronchopulmonary dysplasia and gestational age are not. The relationship with fetal growth is not so straightforward; expressed as a continuous variable it is not independently associated with reduced expiratory airflow, but expressed as a dichotomous variable (birth weight <10th centile) it is.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► This study confirms that focus should remain on preventing bronchopulmonary dysplasia if expiratory airflows are to improve in survivors born extremely preterm. It also clarifies why different conclusions about the independent associations of bronchopulmonary dysplasia with reduced expiratory airflow might arise, dependent on methodological issues, including sample selection, criteria for bronchopulmonary dysplasia, and the definition of reduced expiratory airflow.

restriction that are more important in infants born <35 weeks' gestation.⁷ If that is so, efforts to reduce BPD alone without reducing prematurity or fetal growth restriction are unlikely to improve long-term expiratory airflow. Moreover, the conclusions from that study seem to differ from reports of survivors born very preterm (<32 weeks' gestation) or very low birth weight (<1500 g) where BPD was clearly associated with reduced expiratory airflow in childhood, adolescence and adulthood.^{2,4,8,9} Such associations persisted after adjustment for gestational age and fetal growth restriction;² however, the studies included in the latter report predominantly arose from survivors born in the pre-surfactant era, when far fewer infants born EP survived.

The aim of this study was to determine the independent associations of BPD, including moderate-severe and mild BPD, gestational age and birth weight z-score with expiratory airflow in children born EP in Victoria, Australia, at 8 years of age in the years since exogenous surfactant has been available to treat surfactant deficiency in newborn infants. We hypothesised that moderate-severe BPD would be independently associated with reduced expiratory airflow, but that mild BPD, gestational age and birth weight z-score would not.

METHODS

The only four neonatal intensive care units in the state of Victoria, Australia, have collaborated with government data collection agencies and the state-wide transport service to obtain population-based data on long-term outcomes for discrete cohorts of infants born initially with birth weight <1000 g from the late 1970s, and since the early 1990s those born EP have been included. Antenatal corticosteroids have been used clinically in Victoria since the late 1970s, and exogenous surfactant was introduced into clinical care in 1991.

All survivors born EP in the state in three discrete eras 1991–1992 (24 months), 1997 (12 months) and 2005 (12 months) were recruited at birth and followed longitudinally. Perinatal data, including gestational age, birth weight and BPD were collected prospectively. Moderate-severe BPD was defined as dependence on oxygen at 36 weeks' postmenstrual age, as per the consensus definition of BPD.¹⁰ Mild BPD was defined as treatment with oxygen for at least 28 days but not after 36 weeks' postmenstrual age.¹⁰ Birth weight z-scores were computed relative to revised British Growth Reference data.¹¹

Respiratory function studies

At 8 years of age, corrected for preterm birth, expiratory airflow was measured by spirometry according to American Thoracic Society guidelines¹² in accredited respiratory function laboratories by respiratory scientists who were blinded to clinical details of the participants. Maximum expiratory flow-volume curves were recorded with the child seated. Flow was measured with a pneumotachograph, and volume obtained by integration of flow from the flow-versus-time data. Variables reflecting expiratory airflow included the forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), FEV₁/FVC, and forced expiratory flow from 25% to 75% of vital capacity (FEF_{25%–75%}). Results at body temperature and pressure saturated with water vapour were converted into z-scores, percentiles, and % predicted for age, height, sex and ethnicity.¹³ Poor expiratory airflow was defined as an FEV₁ <5th percentile (z-score equivalent <−1.645 SD; % predicted equivalent <80%).

Data on respiratory function at 8 years of age have been reported previously for all three cohorts,^{3 14 15} in some cases not only for children born EP, but also combined with those weighing <1000 g at birth.

Statistical analysis

Data were analysed using Stata V.17.0. The relationships of the expiratory flow variables as continuous z-scores with BPD (categorised as moderate-severe, mild or nil), gestational age and birth weight z-score were analysed by linear regression, first univariably, and then with all three variables in the model to assess the independent associations of each variable adjusted for the other two. We also evaluated univariable and multivariable associations of the proportions with poor expiratory airflow (FEV₁ <5th percentile) with BPD, gestational age and birth weight z-score by logistic regression.

In a supplementary analysis we explored associations of expiratory airflow with any BPD (mild + moderate-severe) and fetal growth restriction (birth weight <10th centile; birth weight z-score <−1.282), along with gestational age, using linear and logistic regression analyses, in order to replicate the methods of Hart et al.⁷

All regression models were fitted using generalised estimating equations with robust error estimates to account for clustering

within multiple births. Mean differences or ORs and 95% CIs were calculated, where appropriate. Data were interpreted based on magnitude of any differences and their 95% CIs, and not just on p values alone. We did not impute for missing data as it was unlikely that missing data occurred at random. Informed consent was provided by parents for the 2005 cohort but was not required for the earlier cohorts where follow-up to school age was considered to comprise usual clinical care.

RESULTS

Of 949 consecutive live births born between 22 and 27 completed weeks over the three eras combined, 546 (58%) survived to 8 years of age. Of the 546 survivors, 501 (92%) were seen at 8 years. Valid expiratory flow data were obtained from 418 (77%) of all survivors at a mean age of 8.3 years, corrected for prematurity (table 1). In the 418 with expiratory flow data, 46% (n=193) had moderate-severe BPD, 31% (n=131) had mild BPD only, and 22% (n=94) had no BPD; other perinatal characteristics are shown in table 1.

Perinatal characteristics between those with and without expiratory airflow data were mostly similar, although there were fewer who were from multiple pregnancies in those without expiratory airflow data (online supplemental table 1). At 8 years of age 45% (37/82) of those without expiratory airflow data had a major neurodevelopmental disability (IQ <−2 SD relative to normal birth weight controls, moderate/severe cerebral palsy, blindness or deafness) compared with 12% (49/417) of those for whom valid expiratory airflow data were available.

Associations of BPD with expiratory airflow

Mean expiratory airflow z-scores were substantially lower than the expected value of zero for all variables, regardless of whether the children had BPD or not (table 2). Overall, 21% (89/418) had an FEV₁ <5th percentile.

On univariable analysis, there was strong evidence that moderate-severe BPD was associated with substantial reductions in z-scores for FEV₁, FVC and FEF_{25%–75%}, but not FEV₁/FVC (figure 1), and with higher odds of having clinically important airway obstruction (figure 2). However, there was little to no evidence that mild BPD was associated with airway obstruction, expressed either continuously or dichotomously (figures 1 and 2).

On univariable analysis there was evidence that increasing gestational age was associated with increases in z-scores for FEV₁ and FVC, and lower odds for clinically important airway obstruction, but there was little evidence that increasing birth weight z-score

Table 1 Proportion with expiratory airflow data at 8 years, age when assessed, and perinatal characteristics for participants

Survivors to 8 years—n	546
Expiratory airflow data at 8 years—n (% survivors)	418 (77)
Corrected age when assessed—years—mean (SD)	8.3 (0.5)
Perinatal characteristics in the 418 with expiratory airflow data	
Antenatal glucocorticoids—n (%)	335 (80)
Multiple pregnancy—n (%)	117 (28)
Gestational age—completed weeks—mean (SD)	25.8 (1.1)
Birth weight—g—mean (SD)	867 (182)
Male—n (%)	207 (50)
Birth weight z-score—mean (SD)	−0.34 (0.85)
Fetal growth restriction*—n (%)	30 (7)
Exogenous surfactant—n (%)	276 (66)
Postnatal glucocorticoids—n (%)	144 (34)
Moderate-severe bronchopulmonary dysplasia†—n (%)	193 (46)
Mild bronchopulmonary dysplasia‡—n (%)	131 (31)
No bronchopulmonary dysplasia—n (%)	94 (22)
*Birth weight z-score <−1.282 (<10th centile).	
†In oxygen at 36 weeks.	
‡Oxygen for at least 28 days after birth but not at 36 weeks.	

Table 2 Descriptive data for expiratory airflow in relation to severity of bronchopulmonary dysplasia, and univariable associations with gestational age and birth weight z-score

Airflow variable	Bronchopulmonary dysplasia			Gestational age	Birth weight z-score
	Moderate–severe n=193	Mild n=131	None n=94		
Continuous	z-scores	z-scores	z-scores	Mean (95% CI) per 1 week increase	Mean (95% CI) per 1 SD increase
FEV ₁	–1.21 (1.23)	–0.53 (1.10)	–0.51 (1.13)	0.15 (0.04 to 0.25)	0.09 (–0.05 to 0.22)
FVC	–0.92 (1.30)	–0.26 (1.19)	–0.32 (1.11)	0.19 (0.08 to 0.30)	0.14 (–0.004 to 0.28)
FEV ₁ /FVC	–0.43 (1.49)	–0.37 (1.29)	–0.27 (1.33)	–0.07 (–0.19 to 0.05)	–0.08 (–0.22 to 0.06)
FEF _{25%–75%}	–1.55 (1.13) n=178	–1.23 (0.97) n=127	–1.07 (1.05) n=92	0.05 (–0.04 to 0.14)	0.08 (–0.04 to 0.19)
Dichotomous	n (%)	n (%)	n (%)	OR (95% CI) per 1 week increase	OR (95% CI) per 1 SD increase
Low airflow*	58 (30)	19 (15)	12 (13)	0.79 (0.64 to 0.97)	0.89 (0.67 to 1.20)

Data are mean (SD), unless otherwise specified.
*FEV₁ <5th centile.
FEF_{25%–75%} forced expiratory flow from 25%–75% of vital capacity; FEV₁, forced expired volume in 1 s; FVC, forced vital capacity.

was associated with any expiratory flow variables, or clinically important airway obstruction (table 2; figures 1 and 2).

On multivariable analysis, the strong evidence that moderate–severe BPD was associated with substantial reductions in z-scores for FEV₁, FVC and FEF_{25%–75%}, and with an increase in the odds of clinically important airway obstruction persisted, with little effect on the point estimates compared with the unadjusted analyses (figures 1 and 2). The lack of evidence for associations of mild BPD with airway flows or airway obstruction persisted on multivariable analysis. The evidence for an increase in zFEV₁ with increasing gestational age diminished, but persisted for FVC on multivariable analysis. The lack of evidence for associations of airflows with increasing birth weight z-score persisted.

In the supplementary analysis, there was evidence for associations of both any BPD and fetal growth restriction with reduced z-scores for FEV₁, FVC and FEF_{25%–75%}, as continuous variables, and for higher odds of clinically important airway obstruction on univariable analysis (online supplemental table 2, figures 1 and 2). Univariable associations with increasing gestational age were unchanged from table 2 (increases in z-scores for FEV₁ and FVC, and lower odds for clinically important airway obstruction). On multivariable analyses of the continuous variables, the evidence for associations of any BPD with reduced FEV₁ and FEF_{25%–75%} persisted, but weakened for FVC, whereas the evidence for associations of gestational age and fetal growth restriction was unchanged from the univariable analyses (online supplemental table 2, figures 1 and 2). The evidence for higher odds of clinically important airway obstruction persisted for fetal growth restriction, but weakened for both any BPD and gestational age.

DISCUSSION

The major findings in the present study of school-age children born EP in the post-surfactant era are that moderate–severe BPD

was associated with lower expiratory airflow and higher rates of poor expiratory airflow in the clinically important range. Importantly, adjustment for gestational age and birth weight z-scores had little effect on the strength of the evidence concerning the associations of moderate–severe BPD with poor expiratory airflow. Although there were some associations of better expiratory airflow with increasing gestational age, the strength of the evidence diminished on some multivariable analyses. The relationships with fetal growth were not straightforward; as a continuous variable there was little evidence that birth weight z-scores were associated with expiratory airflow, but there was evidence that fetal growth restriction (birth weight <10th centile), as a dichotomous variable, was associated with reduced expiratory airflow. There was no evidence that mild BPD was associated with expiratory airflow on either univariable or multivariable analysis. These results were consistent with our hypotheses.

A systematic review in 2013 reported that preterm survivors with and without BPD had substantial reductions in expiratory airflow compared with term-born controls; some studies defined BPD as oxygen dependency at 28 days after birth, and other studies as oxygen dependency at 36 weeks’ postmenstrual age.¹⁶ Regardless of how BPD was defined, expiratory airflow was reduced more in survivors with BPD compared with term-born controls than it was in preterm survivors who had no BPD compared with controls. In the majority of the 59 studies included in the review the participants were born before the 1990s, but some were born in the 1990s when surfactant was clinically available. In the systematic review, there was no adjustment of associations of expiratory airflow with BPD for gestational age or fetal growth restriction.

Our results with respect to the associations of expiratory airflow with the severity of BPD are similar to other studies of survivors born preterm in the surfactant era. Ronkainen et al¹⁷ reported the results of a systematic review of six studies with FEV₁ results published between 2000 and 2013; compared with term-born controls, survivors born preterm had an increasing reduction in

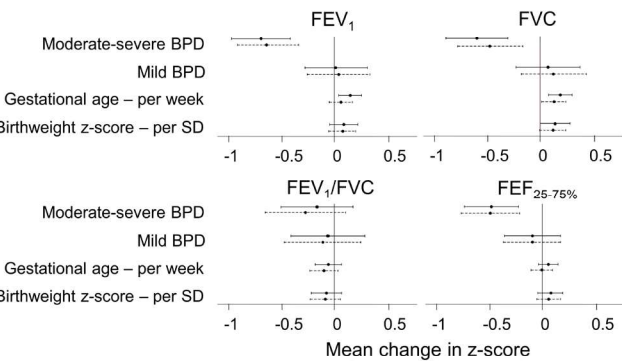


Figure 1 Mean differences and 95% CIs for associations of expiratory airflow with bronchopulmonary dysplasia (BPD), gestational age and birth weight z-score—univariable (solid line) and multivariable (dashed line) analyses. FEF, forced expiratory flow; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

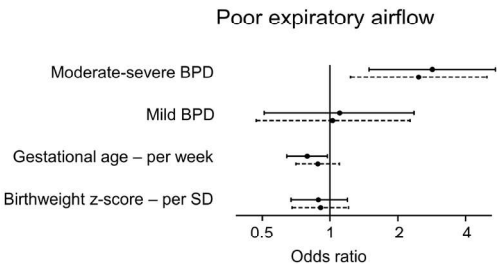


Figure 2 ORs and 95% CIs for poor expiratory airflow (forced expiratory volume in 1 s <5th centile) with bronchopulmonary dysplasia (BPD), gestational age and birth weight z-score—univariable (solid line) and multivariable (dashed line) analyses.

FEV₁, from -7.4% predicted for no BPD, to -10.5% predicted for any BPD, to -17.8% for moderate-severe BPD. In a cohort of 35 survivors born EP in Norway in 1991-1992, Vollsæter et al¹⁸ reported that those who had moderate-severe BPD had worse expiratory airflow than those who had mild BPD, who in turn had worse expiratory airflow than those who had no BPD, at mean ages of 10.5 and 17.8 years. In a study of infants born <27 weeks' gestation in Sweden between 2004 and 2007, Thunqvist et al¹⁹ reported that expiratory airflow at 6½ years was lower in 17 children who had severe BPD compared with 65 children who had moderate BPD. They did not report results for children with mild or no BPD but there cannot have been many because overall 90% of their cohort had either moderate or severe BPD. Although they also reported that children born 22-24 weeks' gestation had worse expiratory airflow than those born 25-26 weeks' gestation, there were no substantial differences in airflow between those with birth weight z-score ≤ -2 SD compared with those with birth weight z-score > -2 SD.

A recent study from the pre-surfactant era reported reductions in expiratory airflow at 26 years of age in survivors born <1500 g birth weight who had BPD (oxygen at 36 weeks' postmenstrual age; moderate-severe) compared with no BPD, which persisted after correction for gestational age and growth restriction, among other variables.⁵ They did not report relationships relative to severity of BPD, however. Another recent study of survivors born <26 weeks' gestation in the post-surfactant era also showed reductions in airflow at 19 years of age in those who had BPD (oxygen dependency after 36 weeks' postmenstrual age; moderate-severe) compared with those who did not, but they did not adjust for gestational age or growth restriction, and neither was the relationship with severity of BPD explored.⁶

Our findings might seem to differ from those of Hart et al⁷ who reported that although any BPD, lower gestational age and fetal growth restriction were all associated with poorer expiratory airflow at 7-12 years of age in survivors born <35 weeks' gestation on univariable analysis, on multivariable analysis the association with BPD disappeared, but persisted for both lower gestational age and fetal growth restriction. In our study it was the strong associations with moderate-severe BPD that persisted, and associations with lower gestational age diminished on multivariable analysis; there was little evidence for associations with birth weight z-score. However, in our supplementary analysis designed to mirror the methods of Hart et al, our conclusions were more similar to theirs; all of any BPD, gestational age and fetal growth restriction were associated with poor expiratory airflow on univariable analysis, but only fetal growth restriction was independently related to poor expiratory airflow on multivariable analysis, with associations with both any BPD and gestational age weakening. In our other supplementary analysis, associations of any BPD with expiratory airflow continuous variables were weaker than with moderate-severe BPD, but they did persist on multivariable analysis for both FEV₁ and FEF_{25%-75%} as continuous variables. There are several reasons why our study might have reached different conclusions to Hart et al. First, the upper gestational age for our study was only 27 completed weeks, and hence we had a higher proportion of survivors with moderate-severe BPD (46%) than did Hart et al (12%; 68/544); since it is the moderate-severe BPD group that are largely responsible for the associations with expiratory airflow, Hart et al would have had less power to find any associations with any BPD than we did. Second, Hart et al analysed associations only with low expiratory airflow as a dichotomous outcome, which reduces power to find associations compared with expressing expiratory airflows as continuous variables. Third, they chose a cut-off for poor expiratory airflow at <85% predicted for FEV₁, rather than a more typical cut-off of <5th centile, which is <80% predicted. Fourth, they only examined associations with FEV₁, whereas we also included FVC, FEV₁/FVC and FEF_{25%-75%}. We chose to report outcomes for both mild and moderate-severe BPD separately because moderate-severe BPD is a more important clinical outcome than mild BPD, consistent with the strong independent associations of moderate-severe BPD with expiratory airflow obstruction in our study.

The strengths of our study include recruiting complete geographical cohorts of children born EP, which encompasses any potential differences in care between individual units and hence our results are more generalisable to similar geographical cohorts elsewhere. We also had high follow-up rates into mid-childhood, measured expiratory airflow in approved respiratory function laboratories according to accepted international guidelines, and obtained satisfactory expiratory flow data in most participants.

Limitations include that we were unable to obtain expiratory flow data on all participants; the high rate of major disability in those without valid expiratory flow data are one reason why such data were unavailable for some children who were assessed at 8 years; they were unable to complete satisfactory spirometry. Another limitation is that we did not record the precise inspired oxygen concentration or requirements for assisted ventilation at 36 weeks' postmenstrual age for all infants in all eras, and hence we could not classify moderate-severe BPD into categories of moderate and severe separately. Of note the workshop report that proposed the categorisation of different levels of severity of BPD was published in 2001,¹⁰ after two of the three cohorts in the current study had been born and relevant data on respiratory and oxygen requirements in the newborn period had already been collected. A large study of expiratory flows across all grades of severity of BPD would be worthwhile. We corrected age for prematurity because children were assessed in multiple areas other than expiratory airflow, including IQ. Failure to correct IQ for prematurity results in a known bias in test scores at school age in children born EP.²⁰ Had we not corrected age for prematurity, our conclusions would have likely have been unaltered as correction for prematurity has little effect on expiratory airflow z-scores.²¹

In conclusion, our results demonstrate that moderate-severe BPD is strongly independently associated with reduced expiratory airflow and having higher odds of clinically important reductions in expiratory airflow in school-age children who were born EP, whereas mild BPD is not associated with expiratory airflow in these children. Such knowledge may inform counselling of families with children born EP, particularly those who develop moderate-severe BPD, as well as informing clinical follow-up, and potential interventions.

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Informações essenciais compatíveis com o Resumo das Características do Medicamento

Bevespi Aerosphere 7,2 microgramas/5 microgramas, suspensão pressurizada para inalação. Cada dose única (dose libertada que sai do aplicador bucal) contém 9 microgramas de brometo de glicopirrônio, equivalente a 7,2 microgramas de glicopirrônio, e 5 microgramas de fumarato de formoterol di-hidratado. Isto corresponde a uma dose calibrada de 10,4 microgramas de brometo de glicopirrônio, equivalente a 8,3 microgramas de glicopirrônio, e 5,8 microgramas de fumarato de formoterol di-hidratado. **Indicações terapêuticas:** Bevespi Aerosphere é indicado como tratamento broncodilatador de manutenção para o alívio de sintomas em doentes adultos com doença pulmonar obstrutiva crônica (DPOC). **Posologia e modo de administração:** **Posologia:** A dose recomendada é duas inalações duas vezes por dia (duas inalações de manhã e duas inalações à noite). Os doentes devem ser aconselhados a não fazer mais de 2 inalações duas vezes por dia. Se for omitida uma dose, esta deve ser tomada assim que for possível e a dose seguinte deve ser tomada no horário habitual. Não deve tomar-se uma dose a dobrar para compensar uma dose esquecida. **Populações especiais:** **Idosos:** Não é necessário qualquer ajuste de dose em doentes idosos. **Compromisso renal:** Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, só deve ser utilizado se o benefício esperado for superior ao risco potencial. **Compromisso hepático:** Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Não existem dados relevantes sobre a utilização de Bevespi Aerosphere em doentes com compromisso hepático grave e o medicamento deve ser utilizado com precaução nestes doentes. **População pediátrica:** Não existe utilização relevante de Bevespi Aerosphere em crianças e adolescentes (com idade inferior a 18 anos) para a indicação de DPOC. **Modo de administração:** Utilização por via inalatória. **Instruções de utilização:** Ao acionar Bevespi Aerosphere, um volume de suspensão é expelido do recipiente pressurizado a alta velocidade. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes devem ser instruídos sobre a técnica de inalação correta. É importante instruir o doente para: Ler com atenção as instruções de utilização no folheto informativo, que se encontra dentro da embalagem de cada inalador. Não utilizar o inalador se o agente excicante, contido na bolsa de alumínio, tiver vazado da sua embalagem. Preparar o inalador agitando-o e acionando-o quatro vezes para o ar antes da primeira utilização ou duas vezes quando o inalador não tenha sido utilizado há mais de sete dias, tenha sido exposto a temperaturas baixas ou tenha caído. Para obter uma deposição pulmonar adequada das substâncias ativas, o carregamento da dose tem de ser coordenado com a inalação. Doentes com dificuldade em coordenar o carregamento da dose com a inspiração podem utilizar Bevespi Aerosphere com uma câmara expansora para garantir a administração adequada do produto. Foi demonstrada compatibilidade com a câmara expansora Aerochamber Plus Flow-Vu. **Contra-indicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** **Asma:** Bevespi Aerosphere não deve ser utilizado no tratamento da asma. **Broncospasmo paradoxal:** Se ocorrer broncospasmo paradoxal, o tratamento com o medicamento deve ser interrompido e devem ser considerados outros tratamentos. **Não indicado para utilização em situações agudas:** Bevespi Aerosphere não é indicado para o tratamento de episódios agudos de broncospasmo, isto é, como terapêutica de alívio. **Efeitos cardiovasculares:** Podem ser observados efeitos cardiovasculares, após a administração de antagonistas dos receptores muscarínicos e simpaticomiméticos, incluindo glicopirrônio 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 tirotóxicose 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 glicose 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. **Compromisso renal:** Como o glicopirrônio 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. **Compromisso hepático:** 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 glicopirrônio 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 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 esteróides orais e inalados. **Hipocalcemia induzida por fármacos:** O tratamento concomitante com derivados da metilxantina, esteróides 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_2 -adrenérgicos:** Os bloqueadores β_2 -adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito dos agonistas β_2 -adrenérgicos, tal como o formoterol. O uso simultâneo de bloqueadores β_2 -adrenérgicos não seletivos ou seletivos deve ser evitado, a não ser que existam razões determinantes para a sua utilização. Se forem necessários bloqueadores β_2 -adrenérgicos (incluindo colírios), dá-se preferência a bloqueadores β_2 -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 glicopirrônio 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, Insónia, 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/submissaoar> (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 agosto 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 comparticipação no regime geral e 84% de comparticipação no regime especial). Versão 1.0 (agosto 2022).**

Informações essenciais compatíveis com o Resumo das Características do Medicamento

Riltrava Aerosphere 5 microgramas/7,2 microgramas/160 microgramas, suspensão pressurizada para inalação. Cada dose única (dose libertada que sai do aplicador bucal) contém 5 µg de fumarato de formoterol di-hidratado, 9 µg de brometo de glicopirrónio, equivalente a 7,2 µg de glicopirrónio e 160 µg de budesonida. Isto corresponde a uma dose calibrada de 5,3 µg de fumarato de formoterol di-hidratado, 9,6 µg de brometo de glicopirrónio, equivalente a 7,7 µg de glicopirrónio e 170 µg de budesonida. **Indicações terapêuticas:** Riltrava Aerosphere é indicado como tratamento de manutenção em doentes adultos com DPOC moderada a grave, que não estão adequadamente tratados com uma associação de um corticosteroide inalado e um agonista beta2 de longa duração de ação ou uma associação de um agonista beta2 de longa duração de ação e um antagonista muscarínico de longa duração de ação. **Posologia e modo de administração:** **Posologia:** A dose recomendada e máxima é 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 FlowVu. **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 broncospasma, isto é, como terapêutica de alívio. **Broncospasma paradoxal:** A administração de formoterol/glicopirrónio/budesonida pode produzir broncospasma paradoxal com sibilos e dispneia imediatamente após a administração e pode ser potencialmente fatal. O tratamento com este medicamento deve ser imediatamente interrompido se ocorrer broncospasma 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. fibrilação auricular e taquicardia, após a administração de antagonistas dos receptores muscarínicos e simpaticomiméticos, incluindo glicopirrónio e formoterol. Este medicamento deve ser utilizado com precaução em doentes com doença cardiovascular grave não controlada e clinicamente significativa, tal como cardiopatia isquémica instável, enfarte agudo do miocárdio, cardiomiopatia, arritmias cardíacas, e insuficiência cardíaca grave. Recomenda-se também precaução ao tratar doentes com prolongamento do intervalo QTc (QTc > 450 milissegundos para homens ou > 470 milissegundos para mulheres), conhecido ou suspeito, quer seja congénito ou induzido por medicamentos. **Efeitos sistémicos com corticosteroides:** Podem ocorrer efeitos sistémicos com qualquer corticosteroide inalado, particularmente em doses elevadas prescritas por longos períodos de tempo. Estes efeitos são muito menos prováveis de ocorrer com o tratamento por inalação do que com corticosteroides orais. Os efeitos sistémicos possíveis incluem síndrome de Cushing, manifestações Cushingoides, supressão suprarrenal, diminuição da densidade mineral óssea, cataratas e glaucoma. Devem ser considerados efeitos potenciais na densidade óssea especialmente com a administração de doses elevadas durante longo período de tempo em doentes com fatores de risco coexistentes para osteoporose. **Perturbações visuais:** Podem ser notificadas perturbações visuais com a utilização sistémica e tóxica de corticosteroides. Se um doente apresentar sintomas tais como visão turva ou outras perturbações visuais, o doente deve ser encaminhado para um oftalmologista para avaliação de possíveis causas que podem incluir cataratas, glaucoma ou doenças raras, tais como CRSC, que foram notificadas após a utilização de corticosteroides sistémicos e tópicos. **Transfusão de terapêutica oral:** Recomenda-se atenção especial nos doentes que fazem a transição de esteróides 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 acalçamentos 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, esteróides e diuréticos. **Hiperglicemia:** A inalação de doses elevadas de agonistas β₂-adrenérgicos pode provocar o aumento da glucose 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 tireotoxicose. **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 farmacodinâmicas:** 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 cobicistate, 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 β₂-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 β₂-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 cardiosseletivos. **Outras interações farmacodinâmicas:** O tratamento concomitante com quinidina, disopiramide, 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 beta2-simpaticomiméticos. O tratamento concomitante com inibidores da monoamina oxidase, incluindo medicamentos com propriedades semelhantes como furazolidona e procabazina, pode dar origem a reações hipertensivas. Existe um risco elevado de arritmias em doentes a receberem anestesia concomitante com hidrocarbonetos halogenados. **Fertilidade, gravidez e aleitamento:** A administração deste medicamento a mulheres grávidas só deve ser considerada se o benefício esperado para a mãe justificar o potencial risco para o feto. A administração deste medicamento a mulheres que estão a amamentar só deve ser considerada se o benefício esperado para a mãe for superior a qualquer possível risco para a criança. Considera-se pouco provável que este medicamento administrado na dose recomendada, afete a fertilidade no ser humano. **Efeitos indesejáveis:** **Frequentes:** Candidíase oral; Pneumonia; Hiperglicemia; Ansiedade; Insónia; 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 (fibrilação auricular, taquicardia supraventricular e extrasístoles); Irritação da garganta; Broncospasma; Boca seca; Equimose; Retenção urinária; Dor torácica. **Muito raros:** Sinais ou sintomas de efeitos sistémicos de glucocorticóides, por exemplo supressão suprarrenal; Comportamento anormal. **Desconhecido:** 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/submissaoar> (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 comparticipação no regime geral e 84% de comparticipação no regime especial). 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ARTIGO ORIGINAL

Terapêutica de manutenção e alívio com budesonida/formoterol vs. tratamento com dose fixa de fluticasona/salmeterol em pacientes com DPOC

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RESUMO

Contexto A terapêutica de manutenção e alívio (TMA) com corticosteroide inalado (CEI)/formoterol reduz efetivamente as exacerbações na asma. Procuramos investigar a sua eficácia em comparação com fluticasona/salmeterol de dose fixa na doença pulmonar obstrutiva crônica (DPOC).

Métodos Os pacientes com DPOC e exacerbação ≥ 1 nos 2 anos anteriores foram aleatoriamente divididos em TMA sem oclatuação (2 inalações de budesonida/formoterol Spiromax 160/4,5 µg duas vezes por dia +1 PRN) ou terapêutica de dose fixa (combinação de 1 inalação de propionato de fluticasona /salmeterol Diskus (CFS) 500/50 µg + salbutamol 100 µg PRN) durante 1 ano. O resultado primário foi a taxa de exacerbações moderada/grave, definido pelo tratamento com prednisolona oral e/ou antibióticos.

Resultados Ao todo, 195 pacientes foram randomizados (TMA Bud/Form n=103; dose fixa CFS n=92). Não existiu qualquer diferença significativa entre as terapias TMA e CFS nas taxas de exacerbação (1,32 vs. 1,32/ano, respetivamente, rácio de taxas 1,05 (IC 95% 0,79 a 1,39); p=0,741). Não foram observadas quaisquer diferenças nos parâmetros da função pulmonar ou no estado de saúde. A dose de CEI total foi significativamente mais baixa com TMA do que com terapêutica CFS (equivalente a budesonida 928 µg/dia vs. 1747 µg/dia, respetivamente, p<0,05). Proporções semelhantes de pacientes reportaram eventos adversos (TMA Bud/Form: 73% vs. dose fixa CFS: 68%, p=0,408) e pneumonias (TMA: 5% vs. CFS: 1%, p=0,216).

Conclusões O primeiro estudo de TMA em DPOC concluiu que a TMA com budesonida/formoterol poderá ser similarmente eficaz à terapêutica de dose fixa de fluticasona/salmeterol em pacientes com DPOC moderada a grave numa dosagem de CEI diária mais baixa. São necessárias mais evidências sobre a segurança a longo prazo.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently the third-leading cause of death worldwide and its morbidity and mortality are still rising.^{1,2} The mainstay of COPD treatment is the use of bronchodilators, particularly long-acting bronchodilators (ie, long-acting beta-2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs)). Bronchodilators improve airway patency and reduce air trapping with beneficial effects on symptoms and exercise capacity,^{3,4} and reduce COPD exacerbations.⁵ In addition, the use of inhaled corticosteroids (ICS) reduces the number of exacerbations and mortality, especially in patients with higher blood eosinophil counts.⁶⁻⁸ The downside of ICS use is the increased risk of side effects, including pneumonia, particularly in patients with more severe COPD and with higher doses of ICS.^{9,10}

Key messages

What is the key question?

► Symptom-driven maintenance and reliever therapy (MART) with inhaled corticosteroid (ICS)/formoterol is a frequently used treatment strategy in asthma which effectively reduces asthma exacerbations at a lower cumulative ICS dose. No studies have investigated the efficacy and safety of ICS/formoterol MART in patients with chronic obstructive pulmonary disease (COPD).

What is the bottom line?

► This was the first study of MART in COPD. We found that budesonide/formoterol MART might be similarly effective and safe to fluticasone/salmeterol fixed-dose therapy in moderate to severe patients with COPD. The similar effects of the two treatments were achieved at a much lower total daily standardised ICS dose with MART compared with fixed-dose therapy, which is an important finding as the use of higher ICS doses is associated with an increased risk of developing pneumonia or systemic adverse effects.

Why read on?

► This study demonstrates the potential that budesonide/formoterol MART could be a successful treatment strategy, not only in asthma but also in patients with moderate to severe COPD. These results need to be replicated in a non-inferiority trial of sufficient size.

Symptom-driven maintenance and reliever therapy (MART) is a frequently used treatment strategy in asthma.^{11,12} With MART, patients use a maintenance dose of an ICS (eg, budesonide or beclomethasone) combined with formoterol, a rapid-onset LABA. In addition, patients use low dose ICS-formoterol as needed for symptom relief, instead of a short-acting beta 2-agonist (SABA) such as salbutamol, which is why rapid onset is important. It has been shown that MART significantly reduces the number of severe asthma exacerbations when compared with the same or higher dose of a fixed combination ICS/LABA plus as-needed SABA,¹³ and compared with conventional best practice.^{14,15} Besides that, larger

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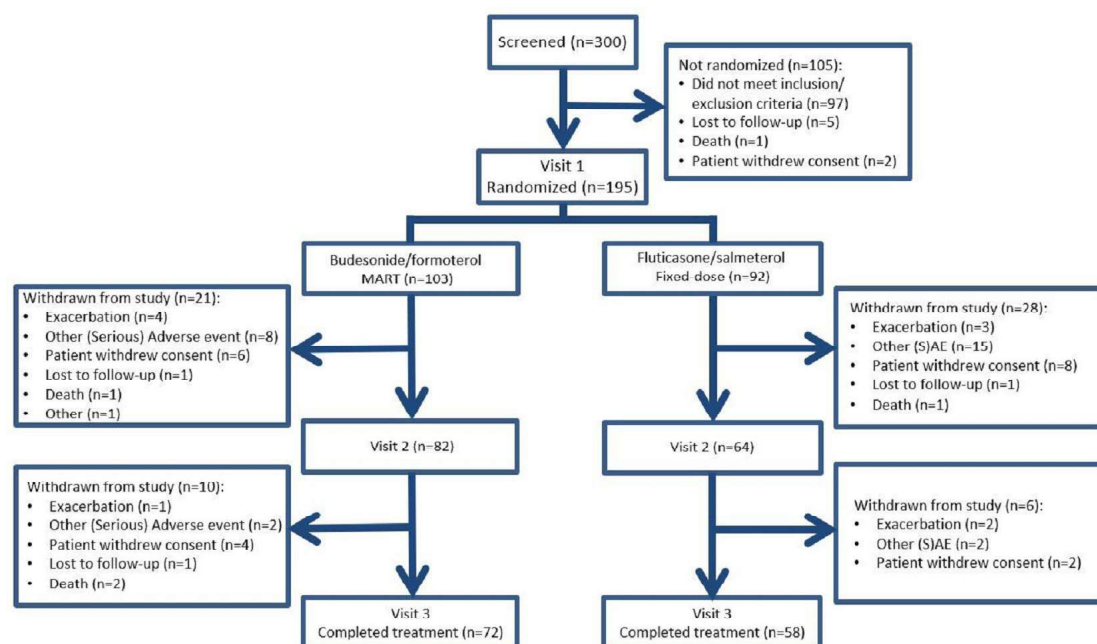


Figure 1 Patient flow chart. Patients were withdrawn from the study when: (1) Informed consent was withdrawn by the patient, (2) A patient experienced more than three COPD exacerbations or (3) It was considered to be in the best interest of the patient's health by the research physician. (S)AE, (serious) adverse event.

improvements in lung function and symptoms have been observed with MART.^{16–18} One study has investigated use of regular and as-needed formoterol in patients with COPD,¹⁹ finding higher lung function than with maintenance formoterol plus SABA reliever. However, no studies have investigated the efficacy and safety of ICS/formoterol MART in patients with COPD.

We aimed to compare the efficacy and safety of budesonide/formoterol MART versus fixed-dose fluticasone/salmeterol in patients with moderate to severe COPD.

METHODS

Study design

This was an open-label, randomised, parallel-group, 52-week, multicentre study, comprising three centres in the Netherlands. In this study, we evaluated the efficacy and safety of budesonide/formoterol (160/4.5 µg dry powder via Spiromax, TEVA, corresponding to 200/6 µg metered dose) used as MART ('MART Bud/Form') two inhalations twice daily plus additional inhalations as needed, compared with fixed-dose fluticasone/salmeterol combination (FSC) (500/50 µg dry powder via Diskus, GSK, 'fixed-dose FSC') one inhalation twice daily plus salbutamol 100 µg as needed. Patients in both groups were instructed to use no more than eight inhalations of their as-needed inhaler on a single day.

Patients and randomisation

A detailed overview of inclusion and exclusion criteria and study design is available in online supplemental 1–3. In brief, eligible patients were between 40 and 80 years of age, had a clinical diagnosis of COPD and a postbronchodilator forced expiratory volume in 1 s (FEV₁) <80% predicted, were current or ex-smokers with a smoking history of at least 10 pack-years, and had a history of at least one COPD exacerbation in the previous 2 years. Patients already using a LAMA at the start of the study could continue this at a stable dose during the study, or a LAMA could be commenced during the study in patients with FEV₁ <50% predicted. Participants with a history of asthma in their medical records were excluded.

Eligible patients were randomly assigned in a 1:1 ratio to receive either open label MART Bud/Form or fixed-dose FSC over a period of 52 weeks. Randomisation was stratified according to smoking status (current or past), postbronchodilator FEV₁ (<50% or ≥50% of predicted), and number of exacerbations requiring oral prednisolone during the last year (<2 or ≥2 exacerbations), and was performed using www.randomizer.org. After the screening visit, patients were seen at the outpatient clinic of the hospital

for three visits (visit 1 (T=0 months), visit 2 (T=6 months), visit 3 (T=12 months)), and when they presented with an exacerbation. In between scheduled visits, patients received phone calls, at 3 and 9 months, during which exacerbations, adverse events and concomitant medication were reviewed. In addition, patients completed a diary twice daily recording the number of inhalations.

End points

The primary outcome was the number of moderate and severe exacerbations expressed as the annualised rate. A moderate exacerbation was defined as any increase in dyspnoea, cough and/or sputum production for which treatment with oral prednisolone and/or antibiotics was given and that was not accompanied by a pneumonia. An exacerbation was defined as severe when hospital admission was required or when it resulted in death. An exacerbation was considered to be ongoing if the time between two consecutive prednisolone treatments was less than 6 days.

Patients were instructed to visit the study centre in case of worsening symptoms consistent with an exacerbation or pneumonia. Subsequently, the event was defined by one of the site investigators as either an exacerbation or a pneumonia or neither based on symptoms and physical examination, inflammatory markers in blood (total leucocytes, differential cell counts and C reactive protein) and chest X-ray (online supplemental table S1). If a patient was not able to visit the study centre due to the illness, classification of the event by the study investigators was based on documentation from the general practitioner or, in case of admission to another hospital, documentation from the relevant hospital. When all the aforementioned data (ie, symptoms and physical examination, inflammatory markers, chest X-ray) were available, the episode was classified by the study investigators as a confirmed pneumonia or COPD exacerbation as appropriate. When no chest X-ray was performed but the attending physician diagnosed the episode as pneumonia, the episode was classified as a probable pneumonia.

Statistical analysis

The sample size calculation was based on an annual exacerbation rate of 1.3 exacerbations per patient.^{20,21} With an α of 0.05, a β of 0.2 and a SD of 0.7, a sample size of 115 patients per treatment group was required to detect a reduction of 20% in the annual exacerbation rate. Due to financial issues, TEVA withdrew funding of the study before inclusion of the required 230 patients was reached. Since 195 patients (85% of the target number) were already randomised, the investigators decided to continue follow-up with

Table 1 Baseline characteristics

Characteristic	MART Bud/Form n=103	Fixed-dose FSC n=92
Male, n*	63 (61.2%)	73 (79.4%)
Age, years	65 (7.83)	65 (6.98)
Body mass index, kg/m ²	27.0 (23.5–30.2)	27.3 (24.1–31.6)
Smoking, pack-years	45 (31–71)	51 (30–70)
Smoking status		
Current	34 (33%)	24 (26.1%)
Past	69 (67%)	68 (73.9%)
Exacerbations during last 12 months		
0	18 (17.5%)	18 (19.6%)
1	44 (42.7%)	41 (44.6%)
2	24 (23.3%)	19 (20.7%)
>2	17 (16.5%)	14 (15.1%)
ICS use at entry, n	84/100 (84%)	74/91 (81.3%)
ICS dosage/day µg/day budesonide equivalents at entry	800 (640–800)	800 (760–1600)
200–400, n	4 (3.9%)	0
>400–800, n	63 (61.2%)	48 (52.2%)
>800, n	17 (16.5%)	26 (28.3%)
LAMA use at entry, n	80/100 (80%)	72/91 (79.1%)
FEV ₁ , % predicted (prebronchodilator)	45.8 (36.0–55.7)	49.3 (35.4–62.7)
FEV ₁ , % predicted (postbronchodilator)	52.6 (39.8–62.6)	52.6 (41.6–66.4)
FEV ₁ /FVC ratio (postbronchodilator)	52.9 (43.9–66.9)	57.7 (44.8–73.3)
N (%) with ratio less than 0.7	102 (99%)	87 (94.6%)
RV, % predicted	143.6 (121.9–176.4)	137.2 (107.5–173.1)
TLC, % predicted	117.1 (15.9)	113.1 (19.9)
RV/TLC, % predicted	118.4 (100.2–133.9)	109.5 (97.3–128)
IOS R ₂₀ , kPa/L/s	0.34 (0.29–0.38)	0.32 (0.28–0.40)
IOS R ₅ –R ₂₀ , kPa/L/s	0.18 (0.09–0.25)	0.15 (0.09–0.22)
IOS AX, Hz-kPa/L/s	1.73 (0.81–3.20)	1.54 (0.71–2.75)
Blood eosinophils, 10 ⁹ /L	0.18 (0.12–0.26)	0.22 (0.12–0.32)
Blood eosinophils >300 cells/µL, n (%)	18 (17.4%)	24 (26.1%)
CCQ total score (baseline)	1.9 (1.3–2.8)	2.0 (1.4–2.8)
CAT total score (baseline)	17.5 (5.9)	18.0 (7.3)
SGRQ total score (baseline)	41.3 (15.1)	43.7 (16.8)

Data presented as median (IQR), n (%) or mean±SD.

*P value <0.05

AX, area of reactance; CAT, COPD assessment test; CCQ, Clinical COPD Questionnaire; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FSC, fluticasone/salmeterol combination; FVC, forced vital capacity; IOS, impulse oscillometry; LAMA, long-acting muscarinic antagonist; MART, maintenance and reliever therapy; R5, resistance at 5 Hz; R20, resistance at 20 Hz; RV, residual volume; SGRQ, St. George's Respiratory Questionnaire; TLC, total lung capacity.

support of limited funding from the University Medical Centre Groningen; this resulted in slightly lower power of 73.5% instead of 80%. The primary and secondary endpoints were analysed by intention-to-treat, that is, including all randomised subjects who received at least one dose of study medication. The primary endpoint of annual exacerbation rate (moderate and severe combined) was analysed using a Poisson regression with the logarithm of time (in days) during which treatment was given as offset variable. The same approach was used when analysing moderate and severe exacerbations separately and for number of pneumonias. Time to first moderate or severe exacerbation was analysed with a Kaplan-Meier log rank test. Average daily ICS dosage was calculated using data from the pharmacy (containing information about the number of inhalers that were dispensed during the study and the number of inhalations that was left in the inhaler when returned to the pharmacy), divided by the number of study participation days, and converted to delivered budesonide equivalents (conversion factor for fluticasone=1.6, ie, 250 µg of fluticasone corresponds to 400 µg of budesonide).²² Average reliever usage was

Table 2 Moderate and severe exacerbations and exacerbation rates

Variable	MART Bud/Form n=103	Fixed-dose FSC n=92	P value
Total no of patient years of study treatment (= patient-year)	85	66	
Patients with exacerbation, n	59 (57.3%)	54 (58.7%)	0.842
Total no of exacerbations	112	87	
Total no of exacerbations per patient-year	1.32	1.32	0.984*
Exacerbations per patient during study			0.368
0	44 (42.7%)	38 (41.3%)	
1	25 (24.3%)	32 (34.8%)	
2	17 (16.5%)	12 (13.0%)	
>2	17 (16.5%)	10 (10.9%)	
Total no of moderate exacerbations	99	78	
Total no of moderate exacerbations per patient-year	1.16	1.18	0.963*
Moderate exacerbations per patient during study			0.439
0	47 (45.6%)	41 (44.6%)	
1	26 (25.2%)	33 (35.9%)	
2	18 (17.5%)	9 (9.8%)	
>2	12 (11.7%)	9 (9.8%)	
Total no of severe exacerbations	13	9	
Total no of severe exacerbations per patient-year	0.15	0.14	0.936*
Severe exacerbations per patient during study			0.570
0	92 (89.3%)	83 (90.2%)	
1	9 (8.7%)	9 (9.8%)	
2	2 (1.9%)	0 (0%)	

Data presented as n (%). Patient-years were based on exposure time to study medication. Moderate exacerbation was defined as any increase in dyspnoea, cough and/or sputum production for which treatment with oral prednisolone and/or antibiotics was given. An exacerbation was defined as severe when admission to the hospital was required or when it resulted in death. P value based on χ^2 test unless stated otherwise.

*P value based on Mann-Whitney U test.

FSC, fluticasone/salmeterol combination; MART, maintenance and reliever therapy.

calculated using data from the patient diaries, that is, number of daily inhalations, corrected for the number of study participation days and analysed by χ^2 test for trend. The changes from baseline in lung function parameters, inflammatory cell counts in sputum and scores on health status questionnaires were analysed using a linear mixed effects model for repeated measures. A post hoc subgroup descriptive analysis by baseline blood eosinophils (ie, <300

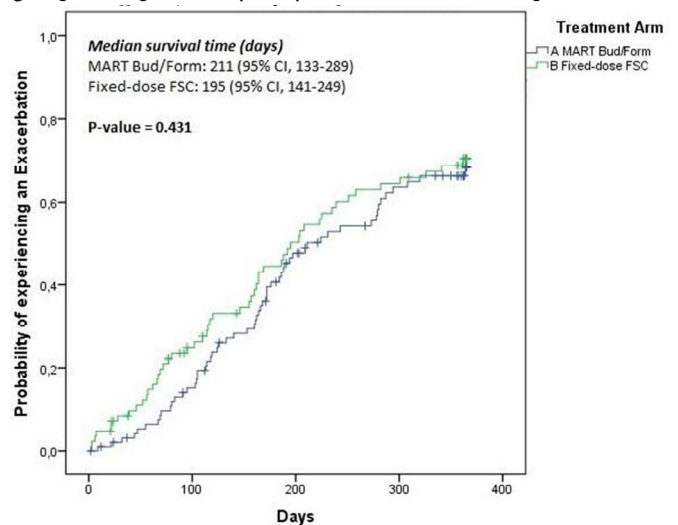


Figure 2 Kaplan-meier survival analysis of time to first exacerbation (moderate or severe) in both treatment arms. Analysis based on full dataset. Vertical lines indicate when patients were censored. FSC, fluticasone/salmeterol combination; MART, maintenance and reliever therapy.

Table 3 (Serious) adverse events and study discontinuation

Variable	MART Bud/Form n=103	Fixed-dose FSC n=92	P value
Patients with at least one adverse event, n*	75 (73%)	62 (67%)	0.408
Serious adverse events, n*	21 (20%)	17 (19%)	0.857
Hospitalisation due to exacerbation	8	9	
Hospitalisation due to pneumonia	5	0	
Other	8	8	
Patients with confirmed pneumonia (including on chest X-ray), n (%)†‡			0.216†
0	98 (95%)	91 (99%)	
1	5 (5%)	1 (1%)	
Patients with confirmed or probable pneumonia, n*			0.068‡
0	96 (93%)	91 (99%)	
1	6 (6%)	1 (1%)	
2	1 (1%)	0	
ICS dosage/day µg/day budesonide equivalents	928 (798–1168)	1747 (1643–1877)	<0.001§
Premature discontinuation, n	31 (30%)	34 (37%)	0.31
Reason for premature discontinuation			0.263‡
Exacerbation	5 (5%)	5 (5%)	
Adverse effect	7 (7%)	13 (14%)	
Serious adverse event	3 (3%)	4 (4%)	
Subject's decision	10 (10%)	10 (11%)	
Lost to follow-up	2 (2%)	1 (1%)	
Death	3 (3%)	1 (1%)	
Discontinuations due to adverse effects, specified			
Increased dyspnoea	0	5	
Cough, sore throat	1	2	
Tremor	0	1	
Myalgia	3	0	
Joint pain	0	1	
Xerostomia	0	1	
Palpitations	1	0	
Increased sputum	0	1	
Flushes	1	0	
Chest pain/angina pectoris	1	0	
Hypersensitivity of skin	0	1	
Dissatisfied with use	0	1	
PASAPQ total score (end of study)	70 (64–74)	70 (62–77)	0.916§

Data presented as n (%) or median (IQR). P value based on χ^2 test unless stated otherwise. Budesonide equivalents for fluticasone were calculated with a conversion factor of 1.6.

*n is based on all patients taking ≥ 1 dose of study medication.

†P value based on Fisher's exact test.

‡P value based on χ^2 test for trend.

§P value based on Mann-Whitney U test.

¶All patients with pneumonia confirmed on chest X-ray were hospitalised.

FSC, fluticasone/salmeterol combination; ICS, inhaled corticosteroids; MART, maintenance and reliever therapy; PASAPQ, Patient Satisfaction and Preference Questionnaire.

RESULTS

Patients

The study ran from May 2015 to June 2019. In total, 300 patients were screened of whom 195 were randomised; 103 patients in budesonide/formoterol MART and 92 patients in fluticasone/salmeterol fixed-dose (figure 1). Baseline characteristics are presented in table 1. There were no significant differences between treatment groups except for a lower proportion of males in MART Bud/Form (63 (61.2%)) compared with fixed-dose FSC (73 (79.4%), $p=0.006$). Similarly high proportions of patients were taking ICS at entry into the study (84% and 81.3% respectively), but with a slightly higher ICS dose in the fixed-dose group (table 1). A total of 72 patients (70.0%) in MART Bud/Form and 58 (63.0%) in fixed-dose FSC completed all study visits. Withdrawals in fixed-dose FSC mostly occurred

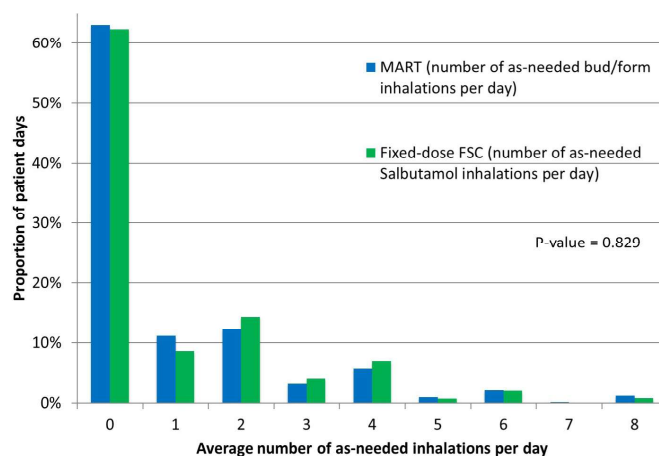


Figure 3 Proportion of patient days by frequency of as-needed inhalations in MART Bud/Form versus fixed-dose FSC. Analysis based on full patient diary dataset. P value based on χ^2 test for trend. FSC, fluticasone/salmeterol combination; MART, maintenance and reliever therapy.

between visit 1 (randomisation) and visit 2 (6 months, figure 1), explaining the substantial difference in number of patient-years (based on exposure time to study medication) between the treatment arms (MART Bud/Form: 85 patient-years; fixed-dose FSC: 66 patient-years). Only 4 patients started using a LAMA during the study (three in fixed-dose FSC and one in MART Bud/Form).

Exacerbations

No difference was found between MART and fixed-dose therapy in the primary endpoint of moderate/severe exacerbation rate: 1.32 vs 1.32 /year, respectively, rate ratio 1.05 (95% CI 0.79 to 1.39), $p=0.741$. The rates of moderate and severe exacerbations separately were also similar (table 2). In addition, there was no significant difference between treatment groups in time to first moderate or severe exacerbation (figure 2). The median time to first exacerbation was 211 days in MART Bud/Form (95% CI, 133 to 289) and 195 days in fixed-dose FSC (95% CI, 141 to 249), $p=0.431$. In a post hoc analysis, there was no significant effect of sex on the results (online supplemental 3.2). The treatment type per exacerbation, that is, prednisolone, antibiotics or both, was not different between MART and fixed-dose therapy (online supplemental table S4).

ICS exposure and as-needed medication use

Average adherence to diary completion was 76.1% of days over the 12 month study. Patients in MART used significantly less total ICS per day (budesonide-equivalent) compared with fixed-dose patients (928 µg/day vs 1747 µg/day, $p<0.001$) (table 3). No significant difference was found in the frequency of as-needed medication use per day ($p=0.829$, figure 3). Patients in MART Bud/Form reported no reliever use on 63.1% of days, similar to that by patients with fixed-dose FSC (62.4% of days, figure 3). In only 1.2% of study days MART patients were excessive users of ICS/LABA as needed puffs, that is, 8 or more additional puffs, compared with 0.8% of days with fixed-dose.

Lung function and health status

The change in lung function parameters from baseline was minimal and similar in both treatment groups (figure 4A–C). Interestingly, hyperinflation as reflected by residual volume (RV)/total lung capacity (TLC%) tended to improve more with MART Bud/Form compared with fixed-dose FSC (difference in change from baseline: -3.58% (95% CI, -7.21 – 0.05), $p=0.053$). The change from baseline in health status scores was also similar in both treatment arms (total CAT score MART Bud/Form vs fixed-dose FSC difference in change from baseline: 1.44 points (95% CI, -0.24 – 3.12), $p=0.092$, figure 4D).

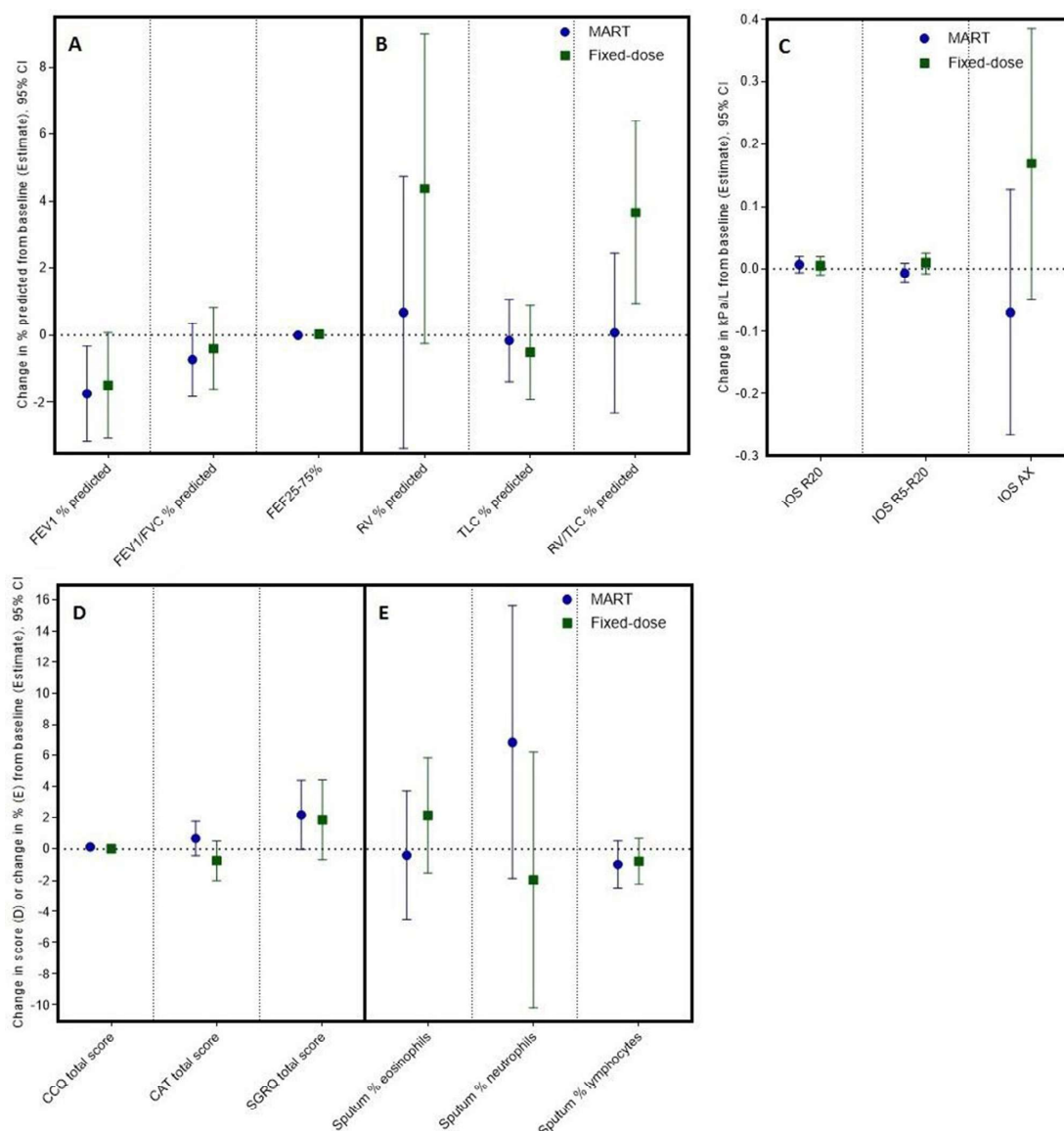


Figure 4 Change from baseline in lung function parameters, health status questionnaires and inflammatory cell counts in induced sputum analysed by linear mixed effects models for repeated measures. The figures show the estimates for the change from baseline with the corresponding 95% CI. (A) Change in postbronchodilator spirometry % predicted outcomes. (B) Change in postbronchodilator % predicted body box outcomes. (C) Change in postbronchodilator impulse oscillometry outcomes. (D) Change in scores on health status questionnaires. (E) Change in inflammatory cell counts in induced sputum. CAT, COPD assessment test; CCQ, clinical COPD questionnaire; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IOS, impulse oscillometry; MART, maintenance and reliever therapy; RV, residual volume; SGRQ, St. George's Respiratory Questionnaire; TLC, total lung capacity.

Safety

Similar proportions of patients reported one or more adverse events (MART Bud/Form: 72.8% vs fixed-dose FSC: 67.5%, $p=0.408$) (table 3) and serious adverse events (MART Bud/Form: 20% vs fixed-dose FSC: 19%, $p=0.857$). There were five confirmed pneumonias in MART vs one event in fixed-dose (rate ratio 4.07 (95% CI 0.48 to 34.85), $p=0.200$). When combining the number of confirmed or probable pneumonias we found eight pneumonias in MART vs one in fixed-dose (rate ratio 7.33 (95% CI 0.93 to 57.85), $p=0.059$). Of these patients, most were men (MART Bud/Form: 5 (71%) vs fixed-dose FSC: 1 (100%)) with mean ages of 67 years and 64 years respectively, and a higher calculated budesonide-equivalent dose per day with fixed-dose FSC compared with MART Bud/Form (1634 $\mu\text{g/day}$ vs 1060 $\mu\text{g/day}$, respectively; online supplemental table S2). The calculated daily ICS dose in these MART patients was slightly higher compared with the general population of MART patients (1060 $\mu\text{g/day}$ vs 928 $\mu\text{g/day}$, respectively). However, it should be noted that average adherence to diary completion was only 46% of study days in MART patients with pneumonia; for the fixed-dose patient with pneumonia it was 50% of study days. In a post hoc analysis, there was no significant effect of sex on the results (online supplemental 3.2).

Study discontinuation and side effects

The percentage of patients who prematurely discontinued from the study was slightly higher with fixed-dose FSC, although this difference was not significant (MART Bud/Form: 30% vs fixed-dose FSC: 37%, $p=0.310$). Reasons for premature discontinuation were similar in both groups ($p=0.263$, table 3). In MART, 7 patients withdrew due to reported adverse events compared with 13 patients in fixed dose. Adverse effects included increased dyspnoea, cough/sore throat and myalgia. At the end of the study, patients in both treatment arms were equally satisfied with the inhaler, according to the total scores on the patient Satisfaction and Preference Questionnaire (table 3).

Blood eosinophilia

Categorisation of patients by baseline blood eosinophils <300 or ≥ 300 cells/ μL showed a similar rate of exacerbations per patient-year in both treatment arms (table 4, online supplemental table S3). However, due to the small sample sizes we did not formally test statistical differences. Time to first exacerbation did not differ by baseline blood eosinophil categories (online supplemental figure S1 and S2).

Table 4 Exacerbations and adverse events in patients with baseline blood eosinophils <300 and ≥300 cells/μL

Characteristic	MART Bud/Form <300; n=85	MART Bud/Form ≥300; n=18	Fixed-dose FSC <300; n=68	Fixed-dose FSC ≥300; n=24
Total no of patient years of study treatment (= patient-year)	69	16	49	17
Patients with exacerbation, n	46 (54.1%)	12 (66.7%)	38 (55.9%)	16 (66.7%)
Total no of exacerbations per patient-year	1.32	1.31	1.33	1.29
Exacerbations during study				
0	38 (44.7%)	6 (33.3%)	30 (44.1%)	8 (33.3%)
1	18 (21.2%)	7 (38.9%)	21 (30.9%)	11 (45.8%)
2	16 (18.8%)	1 (5.6%)	8 (11.8%)	4 (16.7%)
>2	13 (15.3%)	4 (22.2%)	9 (13.2%)	1 (4.2%)
Total no of moderate exacerbations per patient-year	1.17	1.00	1.14	1.29
Moderate exacerbations during study				
0	40 (47.1%)	7 (38.9%)	33 (48.5%)	8 (33.3%)
1	19 (22.4%)	7 (38.9%)	22 (32.4%)	11 (45.8%)
2	17 (20%)	1 (5.6%)	5 (7.4%)	4 (16.7%)
>2	9 (10.6%)	3 (16.7%)	8 (11.8%)	1 (4.2%)
Total no of severe exacerbations per patient-year	0.14	0.17	0.18	0
Severe exacerbations during study				
0	76 (89.4%)	16 (88.9%)	59 (86.8%)	24 (100%)
1	8 (9.4%)	1 (5.6%)	9 (13.2%)	0
2	1 (1.2%)	1 (5.6%)	0	0
Patients with confirmed pneumonia, n (%)	4 (4.7%)	1 (5.6%)	0	1 (4.2%)
Patients with confirmed or probable pneumonia, n*	6 (7.1%)	1 (5.6%)	0	1 (4.2%)
Patients with at least one adverse event, n*	60 (70.6%)	15 (83.3%)	47 (69.1%)	15 (62.5%)
Patients with at least one serious adverse event, n*	18 (21.2%)	3 (16.7%)	14 (20.6%)	3 (12.5%)

Post hoc subgroup analysis by baseline blood eosinophils: <300 or ≥300 cells/μL. No statistical tests were performed because of underpower due to the small sample sizes of the subgroups. Data presented as n (%).

*n is based on all patients taking ≥1 dose of study medication.

FSC, fluticasone/salmeterol combination; MART, maintenance and reliever therapy.

Inflammatory cell counts in sputum

Sputum induction was performed in a subset of patients (MART Bud/Form: n=18; fixed-dose FSC: n=25). No difference was found between MART Bud/Form and fixed-dose FSC with respect to the change in cell counts over the course of the study (figure 4E).

DISCUSSION

In the first study investigating the use of ICS-formoterol MART in COPD, we found that budesonide/formoterol MART was similarly effective as fluticasone/salmeterol fixed-dosing in patients with moderate to severe COPD. We observed similar moderate and severe exacerbation rates in both treatment groups. Importantly, the similar effects of the two treatments were achieved at a much lower total daily standardised ICS dose with MART Bud/Form compared with fixed-dose FSC. Use of lower ICS doses could be beneficial, as higher ICS doses are associated with an increased risk of developing pneumonia or systemic adverse effects.^{23,24} However, it is important to consider that the dose-response relationship of the different ICS types in COPD is uncertain. Therefore, we cannot rule out that we might have obtained similar results with, for example, a MART regimen of Bud/Form 160/4.5 μg two inhalations twice daily versus fixed-dose fluticasone/salmeterol 250/50 μg one inhalation twice daily.^{24,25}

We did not observe differences in effects on lung function, inflammatory markers in induced sputum and symptoms. Although we found increased hyperinflation (RV/TLC%) over the course of the study with fixed-dosing, indicating a possible advantage of MART over fixed-dosing, this difference was not statistically significant. In contrast, we found more symptoms (CAT score) with MART Bud/Form, but the difference was non-significant and less than the minimal clinically important difference of 2. It is important to stress that all aforementioned differences between the treatment arms concern only minimal differences between the treatment groups and without adjustment for multiple analyses. Overall, we consider these differences not only to be non-significant, but also clinically unimportant.

No difference in the number of (serious) adverse events was found between MART Bud/Form and fixed-dose FSC. However,

we did find an unexpected non-significant higher incidence of confirmed or probable pneumonia with MART. Importantly, the MART patients that had a pneumonia in our study had only a minimally higher average daily budesonide dose compared with the remaining MART patients, and had excessive use of ICS (>8 puffs on a day) on 0% of days compared with 1.2% of days in the MART patients without pneumonia. Our results are unexpected, since previous studies showed the increased risk of pneumonia with ICS to be associated with higher ICS doses, and more likely with fluticasone propionate than budesonide,^{6,8,26} although an increase was also found with budesonide in the ETHOS study.⁷ Literature suggests that lower Body Mass Index (BMI ≤25 kg/m²) and older age (≥55 years) can increase the risk of developing pneumonia,²⁷ but we did not find a significant difference overall between both treatment arms with respect to BMI and age. Altogether, we could not identify a factor that could explain the higher number of pneumonias with MART compared with fixed dosing. Since numbers were relatively small, it could potentially be a coincidental finding and we cautiously conclude that the use of MART Bud/Form in patients with COPD is similarly safe as fixed-dose FSC.

Current international guidelines recommend the use of ICS/LABA for symptomatic patients with COPD with a history of exacerbations, especially when there is evidence of eosinophilic inflammation, defined as blood eosinophils >300 cells/μL.²⁸ In our study, all patients had a history of exacerbations, similarly high proportions of patients received ICS at entry (although MART patients used slightly lower ICS doses at entry (table 1), and all received maintenance ICS as part of their randomised treatment. The median blood eosinophil counts at baseline were 180 cells/μL in MART Bud/Form and 220 cells/μL in fixed-dose FSC, with 18% and 26%, respectively, having blood eosinophils ≥300 cells/μL. It could be speculated that symptom-driven increase of ICS may be especially effective in those with higher baseline levels of eosinophilic inflammation (although this was not observed in mild asthma patients²⁹). Therefore, we performed a post hoc subgroup analysis in patients with blood eosinophils <300 or ≥300 cells/μL. This subgroup analysis showed a slightly lower moderate exacerbation rate and a higher severe exacerbation with MART Bud/Form.

Form ≥ 300 compared with fixed-dose FSC ≥ 300 , but the number of patients in these subgroups was very small (MART Bud/Form: $n=18$; fixed-dose FSC: $n=24$).

A limitation of our study is the prespecified sample size that was not reached due to early termination of external funding. Although the study had a smaller sample size than calculated beforehand, we still had a reasonable power of 73.5% suggesting that the primary results of our study are still informative. Second, the reported as-needed medication use was based on patient-reported data, but diary data are not always complete and in some cases could have led to retrospective completion and recall bias. However, as many patients filled out large proportions of the diary, we are confident that it still represents a fairly complete dataset. Lastly, by chance there were significantly more women in MART Bud/Form. Literature suggests that women have a higher chance of experiencing COPD exacerbations and pneumonia.^{30–32} It could be speculated that this contributed to a higher number of exacerbations and pneumonia with MART Bud/Form. However, during post hoc analyses, we did not find a significant effect of sex on the results. Besides, out of seven MART patients with a probable or confirmed pneumonia only two were female.

The results of this study demonstrate the potential of budesonide/formoterol MART as a successful treatment strategy in moderate to severe patients with COPD. The next step should be replication of these results in a non-inferiority trial with a large sample size. Besides that, further evidence is needed about long-term safety.

In conclusion, in moderate to severe patients with COPD budesonide/formoterol used as MART might be similarly effective and safe as fluticasone/salmeterol fixed-dose therapy, at a considerably lower daily dosage of ICS.

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ARTIGO ORIGINAL

As exacerbações da asma estão associadas a uma diminuição da função pulmonar: um estudo longitudinal de base populacional

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RESUMO

Fundamentação — A diminuição progressiva da função pulmonar (FP) em pacientes com asma contribui para piores resultados. Considera-se que as exacerbações da asma contribuem para esta diminuição. Contudo, a evidência é limitada com resultados heterogêneos.

Métodos — Este estudo de coorte histórico de uma vasta população de pacientes com asma na Optimum Patient Care Research Database examinou os pacientes com asma com mais de 3 registros elegíveis (análise primária) de taxa de pico de fluxo expiratório (PFE) ou registros de volume expiratório forçado em 1 segundo (FEV₁) (análise de sensibilidade), após completarem 18 anos. Os modelos de crescimento linear ajustados testaram a associação entre a taxa de exacerbação anual (TEA) média e a trajetória da FP.

Resultados — Estudamos 109 182 pacientes com seguimento entre os cinco e os 50 anos, dos quais 75 280 apresentavam dados para todas as variáveis incluídas na análise ajustada. Para cada exacerbação adicional, perdeu-se uma estimativa adicional de 1,34 l/min PFE por ano (95% IC -1,23 para -1,50). Os pacientes com TEA >2/ano e com idade compreendida entre os 18 e os 24 anos na linha de base perderam um acréscimo de -5,95 l/min PFE/ano (95% IC -8,63 para -3,28), em comparação com aqueles com TEA 0. Estas diferenças na taxa de diminuição de FP entre os grupos com TEA tornou-se progressivamente mais pequena à medida que a idade na linha de base aumentava. Os resultados utilizando FEV₁ foram consistentes com os acima indicados.

Conclusão — De acordo com o nosso conhecimento, este estudo inclui a maior coorte a nível nacional deste tipo e demonstra que as exacerbações da asma estão associadas a uma diminuição mais rápida da FP. Isto foi mais visível em pacientes mais jovens, mas foi evidente em pacientes mais velhos quando esteve relacionado com uma FP inicial mais baixa, sugerindo um fenótipo de deterioração persistente que se desenvolve na idade adulta, ao longo do tempo. A intervenção precoce com gestão apropriada em pacientes mais novos com asma poderia ser importante para prevenir a diminuição excessiva da FP.

INTRODUCTION

Many patients with asthma experience significant irreversible deterioration of their lung function over time,¹ which is associated with features of severe disease including persistent dyspnoea, poor quality of life (QoL), increased healthcare costs and premature death.^{1,2} Childhood factors such as starting lung function and environmental factors, like cigarette smoke and lifestyle choices, can play a part in predicting lung function and the speed of decline in lung function in adulthood.^{3,4} However, symptomatic asthma and particularly exacerbations severe enough to require oral corticosteroids (OCS) or resulting in hospitalisation are thought to be major, potentially modifiable causes of lung function decline over time. The causal pathways arise

Key messages

What is already known on this topic

► Previous studies have assessed the link between exacerbations and accelerated lung function decline in asthma with variable results. Most studies included small numbers of patients often with severe disease and/or short follow-up times that may not adequately capture lung function status.

What this study adds

► This study provides the most robust estimate of year-on-year loss of lung function with increasing exacerbation burden for the average adult patient with asthma. This association and speed of lung function decline were stronger in younger patients aged 18–39 years, persisted even in patients on higher average daily inhaled corticosteroid doses and was consistent for trajectories based on either PEF or FEV₁.

How this study might affect research, practice or policy

► Our findings underline the need for earlier intervention (before 40 years of age) in the management of asthma, particularly in frequently exacerbating patients who are at risk of accelerated lung function decline.

from the inflammatory processes underlying exacerbation episodes, which can lead to permanent structural changes in lung tissue known as airway remodelling, described extensively elsewhere.⁵ Exacerbations may also contribute to other deterioration pathways including mucus hypersecretion and emphysema.^{6,7}

While a handful of studies have assessed the link between exacerbations and accelerated lung function decline in asthma, these studies have mostly included small numbers of patients often with severe disease and/or with short follow-up times that may not adequately capture true underlying lung status.^{8–12} The results have been mixed, and even where an association was found, estimates of the additional exacerbation-associated loss in lung function were highly variable between studies.^{8–12} This highlights the need for large-scale, robust studies that can track the course of lung function in a representative population of patients over the



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long term. Such studies can indicate whether early intervention with measures that prevent exacerbations, including targeted lifestyle management and newer classes of asthma medications, may have an impact on slowing or reversing accelerated lung function decline. Crucially, lung function develops over time, increasing in children, then plateauing in adolescence and slowly declining in adulthood. The long-term impact of exacerbations during adulthood is, therefore, thought to be phase dependent, with the largest impact in older patients whose lung function is in the decline phase⁸; however, no study has investigated this assumption.

Using primary care electronic medical record (EMR) data are one way to answer this question given the availability of long-term clinical and therapy information for patients with chronic conditions, including lung function test results for asthma and patients with chronic obstructive pulmonary disease (COPD). In the UK, the Quality Outcomes Framework (QoF), a performance-based incentive programme for general practitioners, requires annual recording of peak expiratory flow rate (PEF) in patients with asthma,^{13 14} making PEF ideal for longitudinal lung function studies. The aim of our study was to test the hypothesis that exacerbation burden is associated with age-specific, long-term lung function trajectory. We used PEF data from anonymised primary care EMR data for patients with asthma from 650 primary care practices covering England, Scotland, Wales and Northern Ireland in the Optimum Patient Care Research Database (OPCRD). There is no equivalent QoF requirement for lung function monitoring using forced expiratory volume in 1 s (FEV₁), which is infrequently measured in patients with asthma beyond diagnostic spirometry or testing for obstruction in older patients.¹⁵ Nonetheless, studies suggest that PEF and FEV₁ values are highly correlated,^{16 17} thus as an exploratory objective, this study additionally assessed the association of exacerbations and FEV₁ decline in a sensitivity analysis in patients with FEV₁ data available.

METHODS

Study design

This was an observational, historical, UK-wide cohort study of patients with active asthma, managed in primary care. All patient data for this study were extracted from the UK OPCRd between June and November 2019.

Data source

The OPCRd is one of the largest enhanced healthcare databases providing deidentified data from over 800 general practices and approximately 12 million patients in the UK. It was established in 2005, contains regularly inputted data from 1988 and retrospectively inputted data from 1950 and is maintained by Optimum Patient Care (UK), a UK-based social enterprise.^{18 19 20} The index date (starting point) for each patient was the first eligible lung function record at, or after their 18th birthday, and lung function trajectories were constructed using all eligible lung function readings following this point.

Baseline variables included demographic, clinical and medication data and were measured in the 2-year period prior to the index date unless specified otherwise (online supplemental table 1).

Patients

Patients were required to have a QoF diagnostic Read code for asthma and ≥ 2 prescriptions for asthma medication, made on ≥ 2 separate occasions, at any point during the baseline line year or follow-up period, which ran for a total of 69 years from 1950 to 2019. This was done not as a measure of asthma severity, but as an indicator of active disease, in line with the work of Nissen et al²¹ Only those with at least three lung function measurements (of the same type) that covered a period of at least 5 years after age 18 were included. We focused on patients aged ≥ 18 years in order to assess the relationship with exacerbation burden once lungs reached close to full development; childhood-only trajectories or trajectories that traverse childhood and adulthood may not be reliably modelled with the linear statistical approach used in this analysis.

Those with COPD or other chronic respiratory conditions at baseline were excluded.

Outcome

The primary outcome was PEF measured in litres per minute and a feasibility analysis of the correlation between PEF and FEV₁ measured on the same date was performed (online supplemental table 2). A supplementary analysis using per cent predicted PEF based on formulas in Hankinson et al²² and using FEV₁ was also performed (online supplement).

Lung function trajectory

Lung function trajectory was assessed by measuring the slope created by multiple recordings of PEF over time. Lung function readings within 14 days of an exacerbation were dropped. Trajectories were smoothed by retaining the highest absolute values of PEF within each subsequent 1-year period (or highest FEV₁ in each 6-month period) starting from the index date (online supplement).

Asthma exacerbations

The annual exacerbation rate (AER) was assessed using all exacerbations from the start of the baseline period until the end of the follow-up period. An asthma exacerbation was defined according to the ERS/ATS task force definition,²³ that is, an asthma-related hospital attendance/admission and/or primary care consultation and/or an asthma-related Accident and Emergency (A&E) attendance and/or an acute OCS course of ≥ 3 days. Only one exacerbation per 14-day period was included in the calculation of AER.^{11,12} The AER is presented as a continuous variable and additionally categorised into annual rates as described in the Analytical methods section.

Age, gender and inhaled corticosteroid usage

The relationship between AER and lung function decline was assessed according to patient age at first lung function reading (18–24, 25–39 and 40+ years) and mean annual inhaled corticosteroid (ICS) dosage (using tercile cut points: 147.1 $\mu\text{g/day}$ and 463.7 $\mu\text{g/day}$). To be entirely predictive of overall ICS usage throughout the follow-up period, we calculated yearly dosage of ICS based on both baseline and follow-up data and used the average of all yearly doses to categorise patients into the above terciles. All ICS dosages were converted to beclomethasone dipropionate equivalent dosages, and tercile cut-points were identified on the combined sample of all patients. An additional gender-stratified analysis was performed (adjusted for covariates excluding gender as outlined in the analytical methods section below) and included in the online supplemental file 1.

Sensitivity analyses

A sensitivity analysis was performed using FEV₁ (absolute volume and % predicted) to investigate lung function trajectory in patients with longitudinal FEV₁ records fitting the same eligibility criteria (3+ readings over 5+ years of follow-up).

Two additional sensitivity analyses restricted the cohort to (1) patients with first eligible lung function reading on or after 1990 in order to coincide with the digitisation of medical records where patterns of data input may have changed and (2) with first reading on or after 2005 following scale changes to UK peak flow metres.²⁴

Analytical methods

Baseline characteristics are presented as percentages (categorical indicators) or medians/means with IQR or SDs (continuous indicators). Linear growth models were used to assess the association of AER and lung function trajectory, achieved by estimating the interaction between AER (continuous and categorical) and time in the model, while also allowing for random variation in trajectories of lung function at the patient level. This method of trajectory estimation was used for ease of interpretation and for consistency with similar published studies.^{8–10} Cut-offs for AER in the categorical model were 0/year, >0 –1/year, >1 –2/year and >2 /year. Final models are adjusted for age at baseline, gender, smoking status at baseline, smoking status during follow-up, body mass index (BMI) at baseline, length of follow-up, lung function at baseline and time-varying

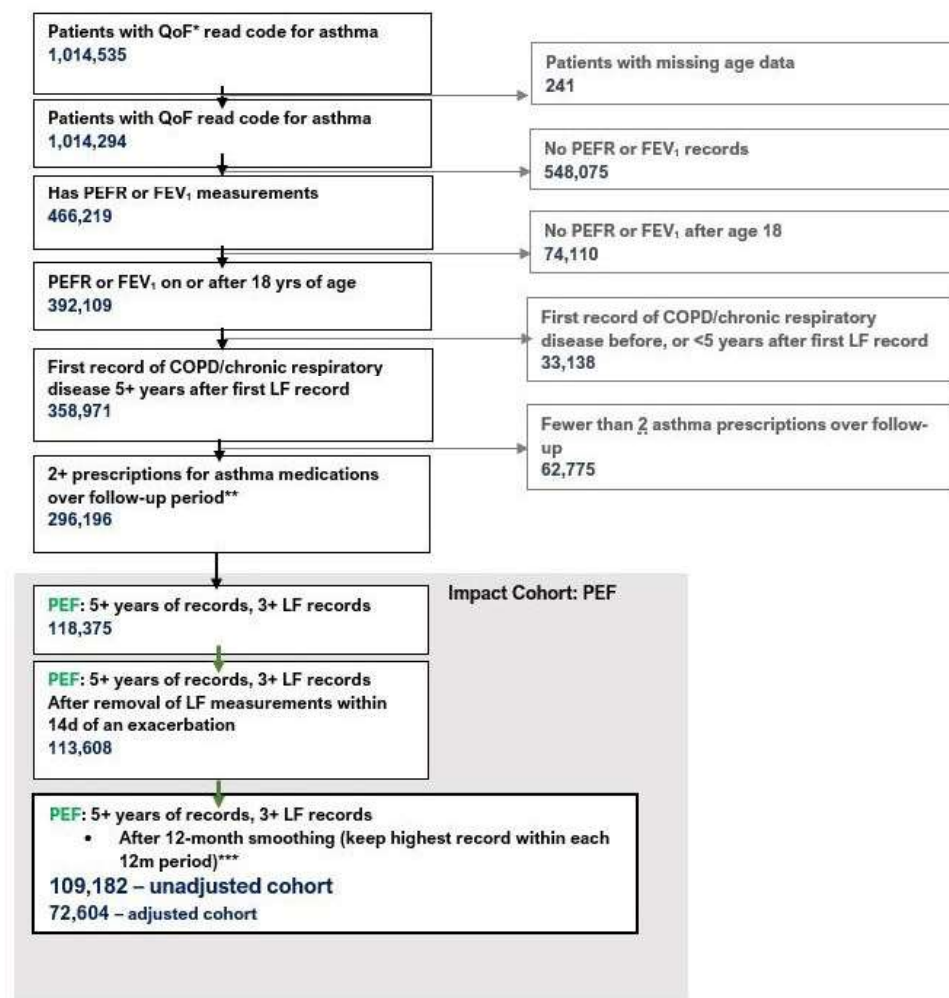


Figure 1 Patient disposition. COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in one second; LF, lung function; PEF(R), peak expiratory flow rate; QoF, quality outcome framework-defined asthma diagnosis read codes. **≥2 separate prescriptions on ≥occasions during follow-up. ***Smoothing methods described in online supplement.

height (where the outcome is absolute PEF or FEV₁). Definitions for all covariates are provided in online supplemental table 1. These adjustments were made because these covariates are thought to be independently associated with lung function and may be unevenly distributed within our sample particularly by exacerbation burden. Crude (unadjusted) models for all analyses are also available in the supplementary data file. Patients with missing data (for smoking or BMI) were excluded from the adjusted analysis.

RESULTS

Patient disposition and characteristics

A total of 109 182 patients followed for a median of 10.4 years were eligible for inclusion in the PEF cohort (figure 1, table 1 and online supplemental table 3) and were included in the unadjusted analyses. Approximately 30% of patients did not have smoking status/BMI recorded (this proportion remained consistent across exacerbation categories), 72 604 patients with full data were included in the adjusted analyses. See online supplemental figure 1 and online supplemental table 4 for patient disposition and baseline characteristics, respectively, for the FEV₁ cohort. Patients with higher AER started with lower lung function at baseline and had more frequent asthma symptoms or severe disease at time of first recorded lung function (table 1 and online supplemental table 3). These patients were characterised by higher eosinophil counts, older age, higher BMI, more short-acting β₂ agonist and OCS prescriptions and higher total dosages of ICS at baseline. There was no clear trend of smoking status or age at first asthma diagnosis in patients with higher compared with lower AERs. The overall trajectory of PEF with time in all patients was negative with a loss of −3.73 L/min/year (95% CI −3.77 to −3.69) of PEF or 0.27% predicted points of PEF/year (95% CI 0.25 to 0.29).

Association between AER and PEF decline

There was a significant acceleration in PEF decline associated with every additional exacerbation per year, estimated as −0.21%-predicted PEF/year (95% CI −0.25 to −0.18; p<0.0001) and −1.34 L/min/year (95% CI −1.2 to −1.5; p<0.001). Patients with exacerbation rates of >0–1/year, >1–2/year, and >2/year all had significant, additional yearly loss of lung function compared with those with an exacerbation rate of 0/year, whether assessed as the absolute change in PEF (figure 2A) or % predicted PEF (figure 2B). This ranged from an additional −0.81 L/min/year decline (95% CI −0.93 to 0.70; p≤0.001) for those with AER>0–1/year to an additional −2.46 L/min/year decline (95% CI −3.06 to −1.85; p≤0.001) for those with AER>2 compared with those with none (figure 2A). Online supplemental figure 2 shows the model-predicted crude (unadjusted) association of exacerbations on (A) PEF (L) and (B) %-predicted PEF, illustrating the difference between exacerbation categories in baseline lung function. Those with the highest exacerbation burden had the lowest starting per cent-predicted lung function (table 1 and online supplemental table 3). Those who smoked (either sustained smoker or mixed smoker/ex-smoker) and even sustained ex-smokers had a significantly greater PEF decline (both % predicted and absolute flow) compared with those who had never smoked (online supplemental table 5).

Exacerbations and PEF decline by baseline age

The association between exacerbation rate and PEF (L) decline persisted as above for patients stratified by age at baseline (figure 3). The largest effect occurred in patients aged 18–24 and 25–39 years at baseline. The rate of lung function decline in patients in these age groups experiencing 2+ exacerbations/year was 3–6 times

greater than the non-exacerbators; these differences were much greater than the same group of patients with 2+ exacerbations/year versus none aged ≥ 40 years (figure 3). Unadjusted results (online supplemental figure 3) further indicate that baseline lung function was lower in patients with higher AERs, but only in older patient groups (aged ≥ 25 years). A similar pattern of accelerated decline with increasing AER was observed for % predicted PEF, stratified by age at baseline (adjusted: online supplemental figure 4; unadjusted: online supplemental figure 5).

Exacerbations and PEF decline by yearly average ICS dosage

The association between exacerbation rate and PEF (L) decline persisted as above for patients stratified by mean yearly ICS as -0.21 dose (figure 4). Higher average ICS dose/year was associated with declining PEF trajectories, irrespective of AER. Higher AER consistently resulted in a faster decline in PEF trajectory in patients in the medium and highest mean yearly ICS dosage terciles. Small numbers of patients with AER >2 in the lowest ICS dosage group resulted in large errors around the point estimates of lung function decline; these patients did not experience a significantly accelerated decline compared with those with an exacerbation rate of 0/year (figure 4). Unadjusted results are provided in online supplemental figure 6. A similar pattern of accelerated decline with increasing AER was observed for % predicted PEF stratified by mean annual ICS dose (adjusted: online supplemental figure 7; unadjusted: online supplemental figure 8).

Exacerbations and lung function decline in males and females

Male and female-specific trajectories for both PEF and FEV₁ are included in the supplementary file (online supplemental tables 6

and 7). Lung function decline measured by PEF tended to be faster in women compared with men, irrespective of exacerbation category. However, the impact of exacerbations on lung function trajectories was more marked in men (men: >2 AER vs 0 AER/year: -3.35 L/min/year (95% CI -4.59 to -2.11); women: >2 AER vs 0 AER: -1.62 L/min/year (95% CI -2.25 to -0.99); online supplemental table 6). FEV₁-measured decline in lung function did not demonstrate this trend, and the majority of the between exacerbation group comparisons were not significant (online supplemental table 7).

Sensitivity analysis with FEV₁

There were 10 943 patients in the FEV₁ cohort (online supplemental figure 1) followed for a median of 8.1 years (online supplemental table 4) who were included in the unadjusted analyses, and 8172 with data on all covariates included in the adjusted analysis. Compared with the PEF cohort, patients in the FEV₁ cohort were older at baseline with shorter follow-up times, were more likely to be diagnosed with asthma as older adults, have a higher prevalence of COPD diagnosed later in follow-up and were in generally poorer health as assessed by a number of metrics (online supplemental table 4). Being older on average and with shorter follow-up, the FEV₁ cohort had already experienced significant decline by the index date in contrast to the PEF cohort. The association between AER and FEV₁ trajectories showed the same overall pattern of accelerated decline in patients with higher AERs (online supplemental figure 9). As with PEF, the overall FEV₁ trajectory decreased over time: 25.5 mL/year (95% CI -26.3 to -24.6) and -0.13% /year (95% CI -17.0 to 10.4) for FEV₁ volume and percent predicted, respectively. Unadjusted results are shown in online supplemental figure 10.

Table 1 Characteristics of 109 182 patients in the PEF cohort—overall and by annual exacerbation rate (AER)

Patient characteristics	Overall (n=109 182)	AER 0/year (n=44 107)	AER>0–1/year (N=60 927)	AER>1–2/year (N=3236)	AER>2/year (N=912)
Baseline lung function					
Median years of follow-up (IQR)	10.4 (7.5–14.1)	9.3 (6.9–12.8)	11.2 (8.1–15.1)	10.9 (7.9–14.7)	10.6 (7.7–14.1)
Mean baseline % predicted PEF (SD)	94.8 (18.6)	95.7 (17.7)	94.5 (19.0)	90.9 (21.1)	87.1 (21.2)
Vital statistics					
Median age at baseline (IQR)	42 (30–55)	39 (28–53)	43 (32–57)	50 (37–61)	47 (37–60)
Male, N (%)	44 697 (40.9)	20 791 (47.1)	22 577 (37.1)	1007 (31.1)	322 (35.3)
Median eosinophil count at baseline cells/mm ³ (IQR)*	225 (148–350)	213 (140–335)	230 (150–350)	250 (156–400)	287 (180–433)
Asthma status at baseline					
Median age of onset of asthma (IQR)	35 (18–51)	32 (16–48)	37 (21–53)	42 (25–56)	39 (22–53)
Median years with asthma prior to index date (IQR)†	4.5 (0.1–14.2)	5.1 (0.1–14.7)	4.0 (0.1–13.7)	5.6 (0.6–15.7)	7.1 (0.9–18.4)
Median number of exacerbations at baseline (IQR)	0.2 (0.6)	0.00 (0–0)	0.0 (0–0)	0.0 (0–1)	1.0 (0–3)
Non-smoker, n (%)	38 287 (35.1)	16 637 (37.7)	20 388 (33.5)	983 (30.4)	279 (30.6)
Ex-smoker, n (%)	20 120 (18.4)	7865 (17.8)	11 436 (18.8)	637 (19.7)	20.0 (182)
Current smoker, n (%)	16 873 (15.5)	6381 (14.5)	9818 (16.1)	524 (16.2)	150 (16.5)
Smoking status not recorded, n (%)	33 902 (31.1)	13 224 (30.0)	19 285 (31.7)	1092 (33.8)	301 (33.0)
Median SABA prescriptions in baseline year (IQR)	2 (1–4)	2 (1–4)	2 (1–5)	3 (2–7)	5 (2–9)
Median ICS dosage/day over follow-up in mcg (IQR)	260.5 (91.8–556.96)	161.8 (48.63–79.7)	322.7 (133.7–633.5)	783.5 (446.4–1241.9)	1054.7 (599.6–1586.8)
Median OCS prescriptions/year over follow-up (IQR)	0.3 (0.1–0.6)	0.1 (0.1–0.2)	0.3 (0.1–0.5)	2.1 (1.6–2.9)	4.3 (3.3–5.8)
Asthma severity: GINA step at baseline‡					
Step 0 (no prescriptions), n (%)	8723 (14.69)	8781 (19.91)	10 665 (17.5)	375 (11.6)	82 (15.0)
Step 1 (SABA only), n (%)	7952 (13.4)	9760 (22.1)	10 389 (17.1)	280 (8.7)	67 (7.4)
Step 2 (low dose ICS), n (%)	11 675 (19.7)	15 349 (34.8)	19 517 (32.0)	709 (21.9)	121 (13.3)
Step 3 (low dose ICS +LABA), n (%)	12 805 (21.7)	7267 (16.5)	12 912 (21.2)	840 (26.0)	210 (23.0)
Step 4 or 5 (med/high dose ICS +LABA + add ons), n (%)	18 228 (30.7)	2950 (6.7)	7444 (12.2)	1032 (31.9)	432 (47.4)

*Most recent eosinophil reading within 5 years of baseline and up to second year of follow-up.

†See online supplemental appendix 2 for more information on calculation of age of onset of asthma.

‡GINA step: Based on 2018 guidelines for stepped therapy for asthma (GINA).⁴⁸

BMI, body mass index; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; OCS, oral corticosteroid; PEF, peak expiratory flow rate; SABA, short-acting β_2 agonist.

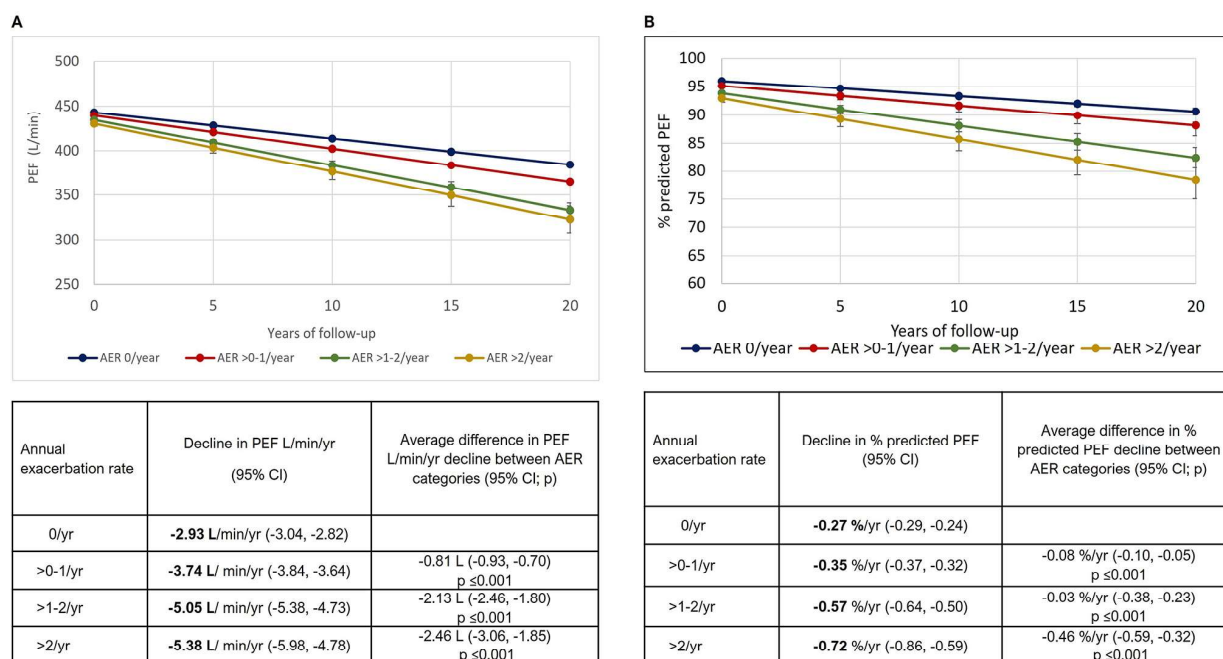


Figure 2 (A) Adjusted 20-year PEF trajectories (L/year) by annual exacerbation rate (AER; n=109 182). (B) Adjusted 20-year per cent-predicted PEF trajectories (%/year) by annual exacerbation rate (AER; n=109 182). Final models are adjusted for age at baseline, gender, fixed smoking status at baseline, time-varying smoking status during follow-up, BMI at baseline, length of follow-up, lung function at baseline and time-varying height. AER, annual exacerbation rate; BMI, body mass index; PEF, peak expiratory flow.

Because of low patient numbers, patients aged 18–39 years were combined into a single stratum; the association between exacerbations and FEV₁ (L) decline was greatest for patients in this age group (online supplemental figure 11). Patients with AER >2 lost an additional –39.3 mL FEV₁ per year compared with patients with no exacerbations (95% CI –65.2 to –13.4; p=0.008). In patients aged ≥40 years, there was no significant association of AER on the lung function trajectories. Results were similar for %-predicted FEV₁ (online supplemental figure 12). Because of low numbers, patients in the lowest two terciles for ICS dosage/year were combined into a single stratum (terciles 1+2). The relationship between exacerbations and FEV₁ (L) decline persisted in patients in the highest tercile of ICS dosage/year (online supplemental figure 13). Patients with ex-

acerbation rate >2/year lost an additional 7.9 mL/year FEV₁ V1 compared with patients with no exacerbations (95% CI –16.1 to 0.2; p=0.056). Results were similar for %-predicted FEV₁ (online supplemental figure 14).

Sensitivity analyses of subsample cohorts with post age 18 years lung function records starting post-1990 and post-2004

There were 108 958 patients with their first post-age 18 years PEF reading on or after 1 January 1990 (unadjusted cohort) and 72 576 in the adjusted cohort. This represented a loss of 0.2% of patients from the full 1950–2019 cohort. Post-1990 PEF trajectories and the relationship with exacerbations were practically identical to the results of the full cohort (online supplemental table 8). The post-1990 FEV₁ trajectories (representing 99.95% of patients from

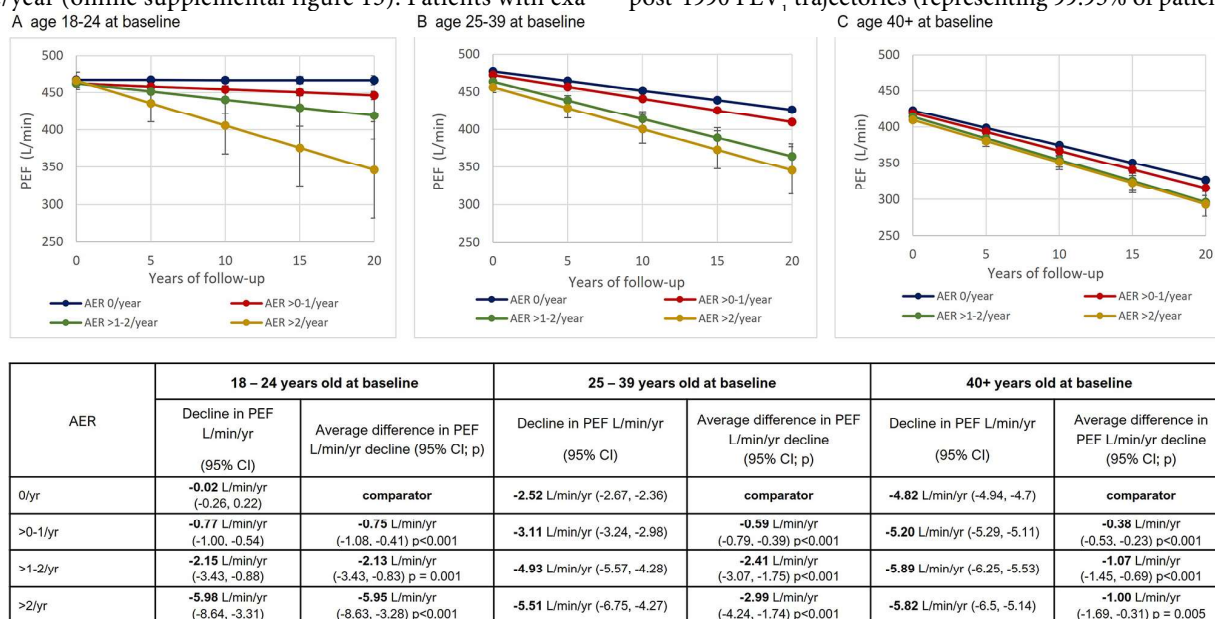


Figure 3 Adjusted 20-year PEF trajectories (L/year) by annual exacerbation rate (AER) stratified by patient age at baseline (18–24 years, n=16 482; 25–39 years, n=32 892; ≥40 years, n=59 808). Final models are adjusted for age at baseline, gender, fixed smoking status at baseline, time-varying smoking status during follow-up, BMI at baseline, length of follow-up, lung function at baseline, and time-varying height. AER 0/year- no exacerbations, AER >0-1/yr - greater than 0 and up to 1 exacerbation per year, AER >1-2/yr - greater than 1 and up to 2 exacerbations per year, AER >2/yr - greater than 2 exacerbations per year. BMI, body mass index; PEF, peak expiratory flow rate.

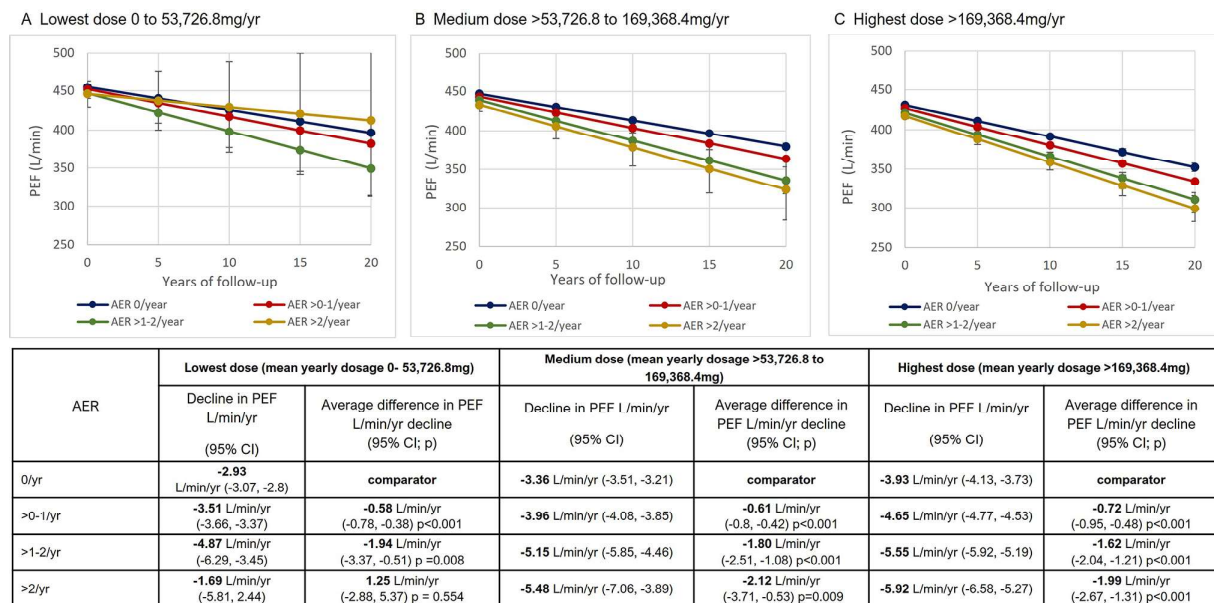


Figure 4 20-year PEF trajectories (L/year) by annual exacerbation rate (AER) stratified by mean daily ICS dose (33.3% centiles); lowest dose: $n=37\,652$; medium dose: $n=37\,770$; highest dose: $n=33\,760$. Final models are adjusted for age at baseline, gender, fixed smoking status at baseline, time-varying smoking status during follow-up, BMI at baseline, length of follow-up, lung function at baseline, and time-varying height. AER 0/year, no exacerbations; AER >0-1/yr, greater than 0 and up to 1 exacerbation per year; AER >1-2/yr, greater than 1 and up to 2 exacerbations per year; AER >2/yr, greater than 2 exacerbations per year; BMI, body mass index; PEF, peak expiratory flow.

the full 1950–2019 cohort) were identical to the results of the full cohort (online supplemental table 9).

To account for change in PEF measurement practices in 2004, an additional sensitivity analysis of the PEF cohort was performed on a subsample of 37 029 (unadjusted) and 26 873 (adjusted) patients with first lung function reading on or after 1 January 2005 (online supplemental table 8). Follow-up in this group was markedly shorter than in the full cohort (median 7.6 years IQR 6.1–9.6). However, the association between exacerbations and lung function decline was, again, similar to the full 1950–2019 cohort, although the additional loss of lung function in patients experiencing more exacerbations versus none was slightly attenuated (>2 AER vs 0 AER: -1.929 L/year (-3.29 to -0.57) $p=0.0054$; online supplemental table 8).

DISCUSSION

To our knowledge, this is the first study to show, in a broad asthma cohort including over 100 000 patients across the UK tracked for 5–60 years, that more frequent exacerbations are associated with long-term lung function decline. Our study provides the most robust estimate of year-on-year loss of lung function with increasing exacerbation burden for the average adult patient with asthma. We observed that the greater the AER, the lower the starting lung function and the more negative the trajectory over time. After adjustment for key confounders including starting lung function, this association persisted and was stronger in younger patients aged 18–39 years than in patients aged 40+ years, which was consistent for trajectories based on either PEF or FEV_1 . This finding underlines the need for a review of the management of patients at risk of accelerated decline before reaching 40 years of age; patients with fastest decline tended to already be on the highest Global Initiative for Asthma (GINA) therapies (ie, GINA 3+), suggesting that many may be less responsive to ICS or to OCS, the long-term use of which are associated with significant negative side effects in asthma and COPD.^{25–26} Such patients would benefit from earlier intervention/review of therapy and lifestyle to consider alternatives. Our study also demonstrates the potential value of using PEF to compare long-term lung function trajectories in groups of patients with asthma, in contrast to previous studies of exacerbations and lung function decline that use FEV_1 .^{8–10,12} The barriers to the availability of frequent, long-term recording of FEV_1 in routinely collected primary care data make

the potential for longitudinal studies using PEF more attractive and feasible.

The relationship between accelerated lung function decline and exacerbations of COPD has been studied extensively and demonstrated reliably, in relatively large populations.^{27–30} However, evidence of this relationship in asthma prior to this study has been less conclusive. Six published studies have used FEV_1 to assess lung function and exacerbations mostly in very severe or difficult-to-treat patients and showed considerable variation in association.^{2,8–12} Nonetheless, even in this small evidence base a general trend of greater decline with increasing exacerbation burden was more commonly than not observed, with declines of between 25 and 50 mL FEV_1 per year in exacerbating patients. Two of these previous studies made the reasonable case that use of ICS may diminish the association of exacerbations on decline, and, therefore, focused on ICS-naïve patients.^{8,11} As a result, these studies tended to show some of the larger effect sizes seen across the previous literature on this subject; one reporting excess loss of 30.2 mL FEV_1 per year in 93 ICS-naïve patients,⁸ and the other an additional loss of 1.34% predicted FEV_1 per year in 3368 ICS-naïve patients.¹¹ This second study found no difference in decline in patients on ICS. Such studies are ethically impossible to reproduce prospectively, and difficult to reproduce in observational cohorts as large numbers of long-term ICS-naïve yet frequently exacerbating patients do not naturally occur. Results from our heterogeneous asthma population may be more applicable to primary care as we observed that fastest decliners were usually already on the highest dosages of ICS medication, suggesting that increasing dosage of ICS and other medications because of disease severity does not entirely protect some patients from the associated faster decline in lung function with exacerbations, or from faster lung function decline in general.

The value of our study within the context of this background literature is in the evaluation of a very large and heterogeneous asthma cohort, with long-term follow-up, and a focus on trajectories stratified by patient age. Bai et al study of 93 patients with asthma all aged <40 years speculated that the greatest association of exacerbation rate and lung function may be seen in older patients whose lung function would be in the decline phase.⁸ Our study demonstrates that, in fact, the opposite is true; lung function declines more quickly in younger adults compared with older patients who have had the same number of exacerbations. The corollary is that in the under 18 age group, patients with exacerbations

should show an even greater decline in lung function. This has not been extensively investigated, but recent studies suggest that function deteriorates more rapidly in children who have exacerbations^{31 32} and may be attenuated by preventative asthma medication.³² Others have found that childhood impairment of lung function and male sex was the most significant predictors of both abnormal longitudinal patterns of lung function growth and of decline.³³ Comparative studies of lung function decline with exacerbations in childhood and adulthood could shed further light on the life course impacts of exacerbations.

In adults, we observed that patients with asthma aged 18–39 years at baseline who have exacerbations experience an additional loss of PEF, that is, 10–120 additional L/min in absolute terms or 2.25% expressed as change in per cent-predicted PEF over 20 years compared with patients with no exacerbations over the same period. Contrasted with this are patients aged ≥ 40 years at baseline who experienced a mean total loss of up to 20 L/min of PEF (or 7 percentage points of predicted PEF) over 20 years. The results in our FEV₁ sensitivity cohort were consistent with this. A meta-analysis of 27 trials estimated that each 10% drop in predicted FEV₁ is associated with an approximate 2-point drop in patient QoL using the Asthma Quality of Life questionnaire (AQLQ)³⁴; this is four times the minimal clinical difference for the AQLQ.³⁵ The difference in per cent-predicted PEF and FEV₁ in frequent exacerbators versus those without exacerbations in younger exacerbating patients in our study was more than eight times the minimal clinical difference for QoL after 20 years, highlighting the real-life implications of accelerated lung function deterioration in this group.

Faced with these findings, potential key questions for clinicians managing patients with asthma in primary care are: when to intervene to minimise the potential long-term negative impact of exacerbations on lung function; what early intervention should look like and in which patients. While we allow that further studies are required, to fully quantify the causal relationship between exacerbations and decline if any, many healthcare professionals will find it encouraging that the majority of patients with asthma in this study experienced little to no acceleration in lung function decline. We estimated that the overall rate of decline in non-exacerbating patients was 2.93 L/year PEF or 20.2 mL/year FEV₁ (irrespective of age or ICS dosage) making this group comparable with patients without asthma who are estimated to experience an average decline of 22.4 mL FEV₁/year, as reported in a recent meta-analysis of 16 cohort studies of more than 30 000 patients with no known chronic respiratory disease.³⁶ In patients who do exacerbate, however, our study highlights the potential value of addressing exacerbation burden when patients are still in the growth and plateau phases of lung trajectory before 40 years of age. Our unadjusted results suggest that younger patients often start with similar lung function, irrespective of exacerbation burden at baseline, while patients who were older at the time of their first lung function reading and who had higher exacerbation burdens had relatively poorer baseline lung function. This indicates that at the population level, an earlier adult-period history of exacerbations and other factors play a big part in decline, above childhood factors. Our findings, thus, strongly suggest that the group who are likely to experience the greatest gain from earlier intervention for long-term benefit are those aged below 40 years. This may include a more proactive approach to lifestyle changes and trigger avoidance as well as a review of ICS-based therapy or consideration of newer classes of biologic therapy.^{37–41} Currently, anti-IL-5, anti-IL-13/14 and anti-IgE biologic medications are only indicated for subgroups of patients with severe asthma,⁴¹ who are often in later life. Patients with frequent exacerbations may benefit from earlier targeted therapy. To our knowledge, there are, as yet, no longitudinal studies of exacerbations and lung function trajectory in patients on biologic medications.

This large-scale study covering all four countries of the UK provides insights into lung function decline in patients with asthma followed for up to 60 years within the period 1950–2019. Our findings are robust, not simply due to the large sample size but also due to the inclusion of a broad UK-wide group of adult patients with

asthma, which is likely more generalisable to the general population than previous studies.^{2 8–12} Additionally, our long follow-up time spanning 69 years of recording (one of the longest maximum follow-up periods of any of the previous studies discussed), enabled us to quantify the long-term association between exacerbations and lung function in sufficient numbers of patients, even in subgroup analyses. Notably, this allowed for rate of decline comparisons in younger, middle and older aged adults with good levels of certainty (including >10 000 patients/age group), highlighting the possible effect of age on this relationship. We have controlled for variation in individual patient trajectories and other key factors that may independently impact lung function, including baseline lung function, which may be viewed as a proxy for severity and for earlier life factors which were not directly measured in this study.

Our study intended to estimate the long-term association of exacerbations and lung function trajectory in a disease characterised by short-term variability in lung function; therefore, we did not include patients with short-term trajectories (<5 years of lung function data) that may impact the representativeness of our results. However, we argue that inclusion of such patients would not keep within the aim of our study to assess long-term association between exacerbation burden and lung function. We included patients with eligible data from as early as 1950. While digitisation of medical records was not introduced until the early 1990s, OPCR, the Clinical Practice Datalink and other primary care databases store electronic records of patient outcomes from prior to this era due to the retrospective digitisation of paper-based patient records by many practices.⁴² Such records use Read Codes later selected for QoF monitoring. Importantly this enabled us to include a subsample of patients with longer term trajectories (>20 years) including two patients born in the early 1920s with first PEF readings dated in 1950 and 1956. Commercial peak flow metres were not widely available until the early 1960s however earlier models were in general use,⁴³ and so we saw no reason to exclude older patients such as these, with otherwise excellent data (who represented 0.002% of the dataset). Nonetheless, our sensitivity analyses excluding patients with readings prior to 1990 or prior to 2005 (to coincide with scale changes in UK PEF metres) had small to negligible impacts on point estimates (which in the case of the 2004 cohort are likely to be partially due to the shorter follow-up times) and no impact on the overall inferences.

While our study demonstrated a clear link between exacerbations and lung function decline, we highlight the need for studies to fully quantify the chronology of this relationship and assess causality. This could be achieved either with causal modelling approaches, which would include the inputs of a range of additional potential confounders that could impact the results over the course of follow-up and/or interventional studies of treatments which target exacerbations and track lung function over time.

We restricted the cohorts to adult lung function to focus on the relationship between exacerbations and decline once lungs reach their development peak and begin the natural decline phase. This results in a tendency towards later median age at onset of asthma, as childhood asthma may well resolve or attenuate before adulthood. Lung function trajectories that traverse childhood and adulthood are not linear and, therefore, require different modelling approaches to the linear models used in this paper. However, previous studies have highlighted the importance of childhood factors, including childhood exacerbations, smoking and childhood asthma diagnosis among others^{31 44 45}; undoubtedly lung capacity by early adulthood will be influenced by these factors. While we have not included childhood risk factors, we have allowed for varying starting adult lung function and the impact of this on subsequent adult lung function trajectory. Nonetheless, the specific association (if any) of exacerbations and lung function in children is an area of great importance that warrants further investigation. Although patients with missing data for smoking or BMI were excluded from the adjusted analyses, the amount of missing data was typical of routinely collected primary care record data in the UK (especially data with such a long look-back as that presented in the current study) and less than previously published.^{46,47} We also ex-

cluded patients with a COPD diagnosis at baseline.⁸ However, it is possible that some older patients will have had either undiagnosed or unrecorded but diagnosed COPD at the start of their lung function recording period. Patients who already had significant obstruction at baseline may not be as sensitive to further changes in AER, and, therefore, the estimated effect sizes in the overall cohort may be underestimated. Finally, although EMR data are prone to misclassification (eg, lack of information on prebronchodilator or postbronchodilator status of lung function tests, lack of location data and potential underreporting of exacerbations), these issues are most likely to cumulatively bias the results towards the null. However, after applying noise reduction techniques and adjustment for known confounders, we still observed highly significant associations, suggesting not only the advantages of sample size and duration of this dataset but also the strength of the relationship between exacerbations and lung function. Overall, this highlights the value of the use of routine data for large-scale, long-term analyses of this type.

In conclusion, we have demonstrated the association between exacerbations and lung function decline, after adjusting for, and stratifying by, possible alternative causes of decline that might confound the relationship including starting lung function, BMI, gender, smoking status and other key variables. We do this while addressing key evidence gaps in sample size, patient representativeness, duration of follow-up and analysis methodology. Future analyses that further explore these associations under a causal framework and within other key subgroups of gender, ethnicity, location and other lifestyle factors will be highly valuable to address remaining evidence gaps. A key new finding is that the greatest association of exacerbations is found in younger patients with lung function in the plateau or start of decline phase, and that while the association is much more modest in older patients, many have also already experienced significant decline in lung function, particularly those with higher exacerbation burdens. This finding has important implications for earlier therapeutic intervention in frequently exacerbating patients prior to middle age before permanent deterioration in lung function has occurred.

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Patient consent for publication Not applicable.

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ARTIGO ORIGINAL

A poluição atmosférica associada à incidência e trajetória da progressão de doenças pulmonares crônicas: um estudo de coorte de base populacional

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RESUMO

Enquadramento — Nenhum estudo anterior examinou os efeitos da poluição atmosférica na progressão do estado saudável para a doença pulmonar crônica, subsequente multimorbidade de doenças pulmonares crônicas e, por fim, para a morte.

Métodos — Utilizamos dados do biobanco do Reino Unido de 265 506 adultos sem doença pulmonar crônica na data de admissão. A multimorbidade de doenças pulmonares crônicas foi definida como a coexistência de, pelo menos, duas doenças pulmonares crônicas, incluindo asma, doença pulmonar obstrutiva crônica e cancro do pulmão. As concentrações de poluentes do ar foram calculadas utilizando modelos de regressão de ocupação. Os modelos multiestado foram aplicados para avaliar o efeito da poluição atmosférica na progressão da multimorbidade de doenças pulmonares crônicas.

Resultados — Durante um seguimento médio de 11,9 anos, 13 863 participantes desenvolveram, pelo menos, uma doença pulmonar crônica, 1055 desenvolveram multimorbidade de doenças pulmonares crônicas e 12 772 morreram. Observamos associações diferenciais de poluição atmosférica com diferentes trajetórias de multimorbidade de doenças pulmonares crônicas. As partículas finas demonstraram a associação mais forte com todas as cinco trajetórias, com aumento de HR (95% IC) por 5 µg/m³ de 1,31 (1,22 para 1,42) e de 1,27 (1,01 para 1,57) para transições de um estado saudável para doença pulmonar crônica incidente e de doença pulmonar crônica incidente para multimorbidade de doenças pulmonares crônicas, e de 1,32 (1,21 para 1,45), 1,24 (1,01 para 1,53) e 1,91 (1,14 para 3,20) para risco de mortalidade relativo ao estado saudável, à doença pulmonar crônica incidente e à multimorbidade de doenças pulmonares crônicas, respetivamente.

Conclusão — O nosso estudo apresenta a primeira evidência de que a poluição atmosférica pode afetar a progressão de um estado livre de doença pulmonar crônica para doença pulmonar crônica incidente, multimorbidade de doenças pulmonares crônicas e morte.

INTRODUCTION

Chronic lung diseases, including asthma, chronic obstructive pulmonary disease (COPD) and lung cancer, are important public health concerns.¹ The Global Burden of Disease estimated that 141.8 million disability-adjusted life-years and 5.8 million deaths were attributable to respiratory diseases worldwide in 2019.² Since life expectancy has increased in recent decades and with the long course of the disease, patients with one chronic lung disease are more prone to develop chronic lung multimorbidity, defined as the coexistence of two or three chronic lung diseases.^{3,4} Patients with chronic lung multimorbidity have more severe respiratory symptoms and an increased risk of hospital admission, exacerbation and death compared with those with single chronic lung disease.^{5,6} It is

Key messages

What is already known on this topic

- Air pollution is associated with an increased risk of chronic lung disease, however, no prior study has examined the impact of air pollution on the progression from healthy to chronic lung disease, subsequent chronic lung multimorbidity and further to death.

What this study adds

- Based on a large-scale prospective cohort of UK adults, we found that air pollution has adverse effects on the progression from free of chronic lung disease to subsequent chronic lung disease, chronic lung multimorbidity and death. Among the five air pollutants included in the analysis, particulate matter with aerodynamic diameter ≤ 2.5 µm showed the largest associations with the progression trajectory of chronic lung multimorbidity.

How this study might affect research, practice or policy

- From a clinical perspective, our findings have indicated the serious health concerns arise due to high-level air pollution following incident chronic lung disease. From a public health perspective, efforts to reduce ambient air pollution can have positive impacts on ameliorating the health burden of respiratory multimorbidity.

thus essential to identify risk factors that can accelerate the progression from chronic lung disease to chronic lung multimorbidity.

Air pollution has been deemed a significant risk factor for chronic lung diseases. There is convincing epidemiological evidence that exposure to air pollutants is associated with an increased risk of respiratory diseases.^{7–12} For instance, recent systematic reviews have concluded that air pollution, including particulate matter with aerodynamic diameter ≤ 10 µm (PM₁₀), ≤ 2.5 µm (PM_{2.5}), between 2.5 and 10 µm (PM_{2.5–10}), nitrogen oxides (NO_x) and nitrogen dioxide (NO₂) were associated with increased prevalence and incidence of chronic lung diseases.^{7,9} Mechanistic evidence suggests that exposure to ambient air pollutants might involve airway inflammation, airway remodelling, changes in airway responsiveness, reduced airway clearance,

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impaired host defenses against infection and oxidative DNA damage, which may contribute to the development of asthma, COPD and lung cancer.^{13–14} However, prior research has primarily examined the effects of air pollution on the first occurrence of a single chronic lung disease. Limited evidence exists on the role of air pollution in the progression from chronic lung disease to chronic lung multimorbidity and subsequent death. Evidence on these specific associations may allow for more precise public health recommendations that would prevent the development of chronic lung multimorbidity from chronic lung disease.

To address this gap in research, we conducted this study with the intention of examining the associations of air pollution with different phases of chronic lung multimorbidity progression. Specifically, we used multistate models to estimate the effects of air pollution on the transition from free of chronic lung disease to incident chronic lung disease, subsequently to chronic lung multimorbidity and further to death.

METHODS

Study population

We used data from the UK Biobank (UKB), a prospective cohort study in the UK. Details of the UKB have been described elsewhere.¹⁵ The extensive and large-scale UKB study obtained health information from approximately 500 000 individuals aged 37–73 years from 22 health measurement centres across England, Scotland and Wales from 2006 to 2010. During the baseline survey, participants provided individual-level information through touch-screen questionnaires and provided biological and physical measurements.¹⁶

Inclusion and exclusion criteria

Among the 502 461 participants initially recruited at baseline, we excluded participants if they: (1) had asthma/COPD/lung cancer or self-reported use of medication (bronchodilators, inhalants or corticosteroids) for chronic lung diseases at baseline ($n=140\,917$) and (2) had missing air pollution data ($n=30\,924$) or missing covariates ($n=65\,114$). After exclusion, 265 506 participants remained in the final analyses (figure 1).

Follow-up and outcomes

Participants were followed up from recruitment until one of the following events occurred: all-cause death, lost to follow-up or the end date of follow-up (31 October 2015 for Scotland and 31 July 2019 for England and Wales). Outcome events of interest (asthma, COPD, lung cancer and death) were obtained through linking to the Patient Episode Database for Wales, Hospital Episode Statistics for England, Scottish Morbidity Record, National Cancer Registries data, National Health Service (NHS) Information Centre and the NHS Central Register Scotland.^{16–19}

In the current analyses, diseases were diagnosed in accordance with the International Classification of Diseases 10th revision: asthma: J45 and J46; COPD: J41–J44 and lung cancer: C33 and C34.20–21 Additionally, participants with a forced expiratory volume in 1 s/forced vital capacity ratio below the Global Lung Function Initiative 2012 reference values for the lower limit of normal²² were also defined as COPD.

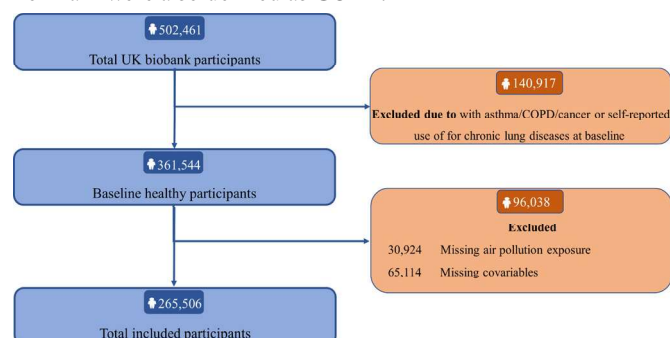


Figure 1 The flow chart of the UK Biobank participants included and excluded in the study. COPD, chronic obstructive pulmonary disease.

Assessment of air pollution exposure

The annual concentrations of air pollutants, including PM_{10} , $PM_{2.5}$, $PM_{2.5-10}$, NO_x and NO_2 , were estimated with land-use regression (LUR) models derived from the European Study of Cohorts for Air Pollution Effects project.¹¹ The LUR models estimate the ambient pollutant concentrations by considering several predictor variables selected from the surrounding environment, such as traffic, land use and topography, obtained from the geographic information system.²³ The LUR models for $PM_{2.5}$, PM_{10} , NO_2 and NO_x performed satisfactorily during leave-one-out cross-validation, with cross-validation R^2 of 71%, 77%, 82% and 78%, respectively, however, only moderate performance for $PM_{2.5-10}$ (cross-validation $R^2=68\%$).^{24–25} Individual air pollution exposure was determined by the residential addresses provided during the baseline visit.

In the UKB, the annual concentrations of $PM_{2.5}$, $PM_{2.5-10}$ and NO_x only had single-year data (2010), while PM_{10} and NO_2 were available for several years (2007 and 2010 for PM_{10} ; 2005–2007 and 2010 for NO_2), we thus averaged the values of different years to get the average estimated concentrations of NO_2 and PM_{10} in our analyses.

Covariates

A series of covariates were obtained through the baseline questionnaire survey, including demographic characteristics (age, sex and ethnicity), socioeconomic status (annual household income and education), smoking status, pack-years of smoking, body mass index (BMI), occupational exposure and family history of chronic lung multimorbidity. Ethnicity was categorised as white and non-white. Annual household income was classified into four levels (<£18 000, £18 000–£100 000, >£100 000 and unknown). Educational attainment was divided into four levels (college or above, high school or equivalent, less than high school and others). Smoking status had three levels (never, previous or current smoking). Pack-years of smoking were calculated using the following formula: pack-years of smoking=number of cigarettes smoked per day/20 *(age stopped smoking – smoking start age). BMI was calculated by dividing the weight in kilograms by the height in metres squared and further grouped into underweight, normal, overweight and obese according to the standard set by the WHO.^{26–27} Participants reporting baseline occupational exposure (UK Biobank Data Field 20277) for 1 of 14 jobs associated with an increased risk (prevalence ratio ≥ 1.30) for chronic lung disease identified by De Matteis et al (online supplemental table S4)²⁸ were classified as having an ‘at-risk’ occupation. Family history of chronic lung multimorbidity was defined as participants who reported having at least one parent or sibling with two or more chronic lung diseases.

Statistical analysis

We used multistate models to examine the associations of air pollution exposure with the progression trajectory from free of chronic lung disease to incident chronic lung disease, chronic lung multimorbidity and all-cause death. The multistate model is a probabilistic model that incorporates multiple states enabling modelling of the rate of transitions between states.^{29–30} The extension of the Cox

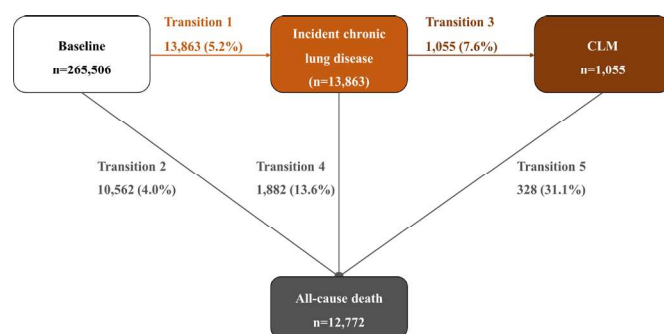


Figure 2 Numbers (percentages) of participants in transition pattern A from baseline to incident chronic lung disease, chronic lung multimorbidity (CLM) and all-cause death.

proportional hazards model to a multistate model expanded the time to event from a single or a summarising composite endpoint to multiple endpoints, providing in-depth insight into the disease trajectory.³¹ Specifically, five transitions (transition pattern A, figure 2) were established in the model: (1) free of chronic lung disease to incident chronic lung disease; (2) free of chronic lung disease to all-cause death; (3) incident chronic lung disease to chronic lung multimorbidity; (4) incident chronic lung disease to all-cause death and (5) chronic lung multimorbidity to all-cause death. If participant responses indicated various diagnoses/events on the same day, we measured the theoretical entry date of the prior state as the entry date of the latter state minus half a day.³² For instance, if participants died from incident chronic lung disease, the dates of the incident chronic lung disease equal the date of death minus half a day. In our analyses, the directed acyclic graph (DAG) was applied to identify the minimal sufficient adjustment set following previous literature.^{33,34} The minimally sufficient adjustment set represents covariates such that the adjustment for this set of variables will minimise confounding bias when estimating the association between the exposure and the outcome.³⁵ The minimally sufficient adjustment set was determined using the DAGitty software (<http://dagitty.net/>). We carefully reviewed previous studies to select a few candidate variables and then introduced them into the DAG (online supplemental figure S1). Specifically, the minimal sufficient adjustment set in our analyses includes age, sex, ethnicity, annual household income, education, smoking status, pack-years of smoking, BMI, occupational exposure and family history of chronic lung multimorbidity. However, the large amount of missing data on occupational exposures (more than 160 000 missing values) may affect the stability of the results, so it was not included in the main models.

We also evaluated the association of air pollution exposure with different transitions from free of chronic lung disease to chronic lung multimorbidity and to all-cause death. In this analysis, incident chronic lung diseases were defined as three individual diseases (asthma, COPD and lung cancer), yielding 11 possible transitions (transition pattern B, figure 3). Given that the chronology of disease onset could not be determined in this pattern, participants who were diagnosed with more than one chronic lung disease on the same date were excluded, leaving 265 493 participants in this analysis.

Subgroup analyses

To investigate potential effect modifications, we conducted subgroup analyses by sex and age based on the multistate analyses

of transition pattern A. The cross-product term of the stratifying covariate with air pollution was implemented to test differences between subgroups.³⁶

Sensitivity analyses

Several sensitivity analyses were conducted to test the robustness of the findings of transition pattern A. First, we excluded participants experiencing events in the first 2 years from the baseline survey to mitigate the potential issue of reverse causality. Second, since it was not possible to confirm the exact time of the prior event for participants who had various diagnoses/events on the same day, we used different time intervals (0.5, 1, 3 and 5 years) for participants who experienced different states on the same day. Third, we excluded participants who experienced different states on the same day. Fourth, we additionally adjusted for occupational exposures in the models. Lastly, we restricted our cohort participants to those who did not move their residential addresses after 2010 to minimise the misclassification of long-term air pollution exposures.

The associations are presented as HRs and 95% CIs corresponding to a 5 µg/m³ increase in air pollution concentration. All analyses were conducted using statistical computing environment R V.4.0.5, and the multistate model was performed using the 'mstate' package. A $p < 0.05$ was considered statistically significant.

RESULTS

Descriptive results

A total of 265 506 participants (55.0% females) with a mean age of 55.8 years were included in the final analysis (table 1). Overall, the annual average concentration of PM_{2.5}, PM_{2.5-10}, PM₁₀, NO₂ and NO_x were 9.98 µg/m³, 6.42 µg/m³, 19.29 µg/m³, 29.12 µg/m³ and 43.79 µg/m³ among all participants, respectively. Baseline characteristics were generally similar between those who were included and those excluded in the study, however, included participants had a higher income and were more likely to have never smoked (shown in online supplemental table S1).

During a median follow-up of 11.9 years, 13 863 individuals developed at least one chronic lung disease, 1055 developed chronic lung multimorbidity and 12 772 died (10 562 without chronic lung disease, 1882 from incident chronic lung disease and 328 from chronic lung disease) in transition pattern A (figure 2). In transition pattern B, 6317 participants (2.4% of the baseline participants without chronic lung disease) developed asthma, 6520 (2.5%) developed COPD, and 1011 (0.4%) developed lung cancer (figure 3). Participants who developed lung cancer first ($n=1011$) were more

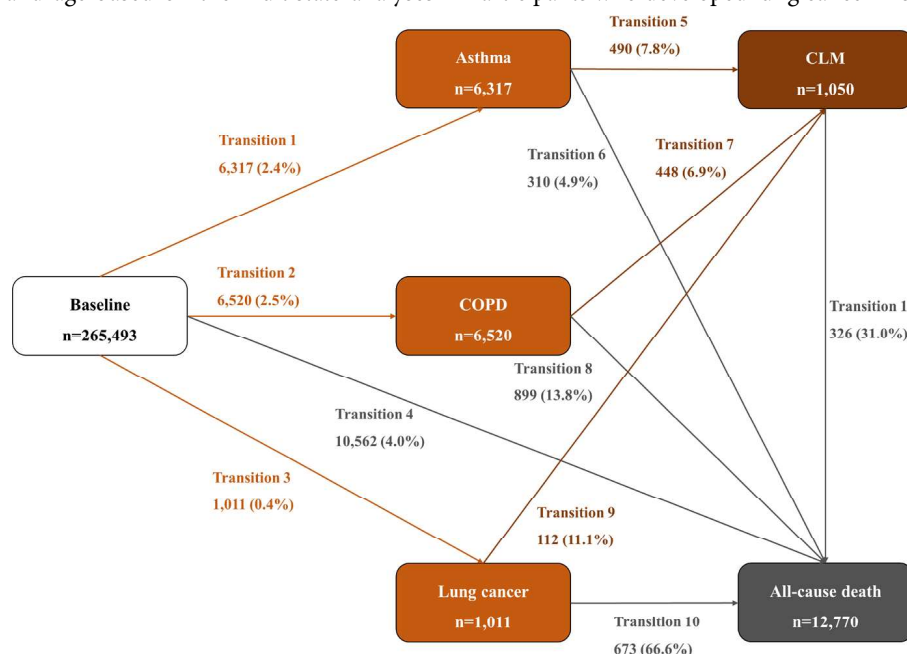


Figure 3 Numbers (percentages) of participants in transition pattern B from baseline to incident chronic lung disease, chronic lung multimorbidity (CLM) and all-cause death. COPD, chronic obstructive pulmonary disease.

Table 1 Summary of baseline characteristics of participants by disease status during follow-up

	Overall (N=2 65 506)	Incident chronic lung disease survivor (N=10 926)	Chronic lung multimorbidity survivor (N=727)	Death with incident chronic lung disease (N=1882)	Death with chronic lung multimorbidity (N=328)	Death without incident chronic lung disease (N=10 562)	Free of incident chronic lung disease (N=2 41 081)
Pollutants ($\mu\text{g}/\text{m}^3$), mean (SD)							
PM _{2.5}	9.98 (1.05)	10.05 (1.07)	10.15 (1.07)	10.18 (1.10)	10.33 (1.06)	10.03 (1.07)	9.97 (1.05)
PM _{2.5-10}	6.42 (0.90)	6.41 (0.88)	6.48 (0.96)	6.45 (0.90)	6.49 (0.89)	6.42 (0.89)	6.43 (0.90)
PM ₁₀	19.29 (1.94)	19.26 (1.90)	19.41 (1.81)	19.46 (1.88)	19.67 (1.83)	19.27 (1.88)	19.29 (1.95)
NO ₂	29.12 (9.16)	29.44 (9.05)	30.28 (8.76)	30.23 (8.96)	31.67 (8.80)	29.14 (8.87)	29.09 (9.18)
NO _x	43.79 (15.52)	44.68 (15.32)	46.05 (16.28)	46.42 (16.39)	48.94 (17.19)	44.42 (15.99)	43.69 (15.49)
Age (year)	55.84 (8.07)	57.64 (7.72)	59.16 (7.23)	61.47 (6.18)	62.01 (5.73)	60.92 (6.78)	55.47 (8.05)
Sex, n (%)							
Female	145 958 (55.0)	6182 (56.6)	391 (53.8)	758 (40.3)	133 (40.5)	4239 (40.1)	134 255 (55.7)
Male	119 548 (45.0)	4744 (43.4)	336 (46.2)	1124 (59.7)	195 (59.5)	6323 (59.9)	106 826 (44.3)
Ethnicity, n (%)							
White	249 303 (93.9)	10246 (93.8)	690 (94.9)	1810 (96.2)	313 (95.4)	10117 (95.8)	226 127 (93.8)
Non-white	16 203 (6.1)	680 (6.2)	37 (5.1)	72 (3.8)	15 (4.6)	445 (4.2)	14 954 (6.2)
BMI level, n (%)							
Normal	85 244 (32.1)	3075 (28.1)	167 (23.0)	490 (26.0)	84 (25.6)	2646 (25.1)	78 782 (32.7)
Underweight	1197 (0.5)	42 (0.4)	2 (0.3)	19 (1.0)	1 (0.3)	56 (0.5)	1077 (0.4)
Overweight	114 909 (43.3)	4452 (40.7)	302 (41.5)	751 (39.9)	125 (38.1)	4610 (43.6)	104 669 (43.4)
Obese	64 156 (24.2)	3357 (30.7)	256 (35.2)	622 (33.0)	118 (36.0)	3250 (30.8)	56 553 (23.5)
Education level, n (%)							
College or above	126 518 (47.7)	4593 (42.0)	225 (30.9)	549 (29.2)	70 (21.3)	4311 (40.8)	116 770 (48.4)
High school or equivalent	81 788 (30.8)	3107 (28.4)	186 (25.6)	476 (25.3)	84 (25.6)	2769 (26.2)	75 166 (31.2)
Less than high school	15 698 (5.9)	720 (6.6)	54 (7.4)	174 (9.2)	18 (5.5)	763 (7.2)	13 969 (5.8)
Other	41 502 (15.6)	2506 (22.9)	262 (36.0)	683 (36.3)	156 (47.6)	2719 (25.7)	35 176 (14.6)
Annual household income, n (%)							
< £ 18 000	48 191 (18.2)	2749 (25.2)	242 (33.3)	695 (36.9)	150 (45.7)	3120 (29.5)	41 235 (17.1)
£ 18 000–£ 100 000	168 637 (63.5)	6153 (56.3)	331 (45.5)	813 (43.2)	127 (38.7)	5538 (52.4)	155 675 (64.6)
≥ £ 100 000	12 834 (4.8)	349 (3.2)	8 (1.1)	32 (1.7)	2 (0.6)	232 (2.2)	12 211 (5.1)
Unknown	35 844 (13.5)	1675 (15.3)	146 (20.1)	342 (18.2)	49 (14.9)	1672 (15.8)	31 960 (13.3)
Smoking status, n (%)							
Never	178 418 (67.2)	5837 (53.4)	249 (34.3)	521 (27.7)	40 (12.2)	5961 (56.4)	165 810 (68.8)
Previous	64 987 (24.5)	3353 (30.7)	269 (37.0)	762 (40.5)	146 (44.5)	3355 (31.8)	57 102 (23.7)
Current	22 101 (8.3)	1736 (15.9)	209 (28.7)	599 (31.8)	142 (43.3)	1246 (11.8)	18 169 (7.5)
Smoking pack-years, mean (SD)	6.94 (13.93)	13.20 (19.89)	22.30 (24.66)	26.25 (26.02)	35.54 (28.26)	11.96 (19.61)	6.20 (12.75)
Family history of CLM, n (%)							
No	259 748 (97.8)	10 616 (97.2)	693 (95.3)	1822 (96.8)	310 (94.5)	10 312 (97.6)	235 995 (97.9)
Yes	5758 (2.2)	310 (2.8)	34 (4.7)	60 (3.2)	18 (5.5)	250 (2.4)	5086 (2.1)

BMI, body mass index; CLM, chronic lung multimorbidity; NO₂, nitrogen dioxide; NO_x, nitrogen oxides; PM₁₀, particulate matter with diameters ≤10 μm .

likely to develop chronic lung multimorbidity (n=112 (11.1%)) or died (n=673 (66.6%)) compared with individuals who first developed asthma (n=6317, 7.8% develop chronic lung multimorbidity; 4.9% died) or COPD (n=6520, 6.9% develop chronic lung multimorbidity; 13.8% died).

Multistate analyses

The multistate analyses demonstrated long-term air pollution exposure could increase the risk of disease transition to varying extents in the five different transition options for chronic lung disease (table 2). With the exception of PM_{2.5-10}, all pollutants were consistently associated with an increased risk of the transition from free of chronic lung disease to incident chronic lung disease, the transition from free of chronic lung disease to death, the transition from incident chronic lung disease to chronic lung multimorbidity and the transition from free of incident chronic lung disease

to death. In detail, among the five air pollutants included in the analysis, PM_{2.5} showed the largest associations with all five transitions. The HRs (95% CIs) per 5 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} were 1.31 (1.22 to 1.42) for baseline healthy to incident chronic lung disease, 1.27 (1.01 to 1.57) for incident chronic lung disease to chronic lung multimorbidity, 1.32 (1.21 to 1.45) for baseline to death, 1.24 (1.01 to 1.53) for incident chronic lung disease to death and 1.91 (1.14 to 3.20) for chronic lung multimorbidity to death. Significant positive associations of PM₁₀ on the transition from baseline healthy to incident chronic lung disease and death, and the transition from incident chronic lung disease and chronic lung multimorbidity to death were observed in our analyses, with HRs (95% CIs) of 1.10 (1.05 to 1.15), 1.06 (1.01 to 1.11), 1.18 (1.05 to 1.33) and 1.55 (1.13 to 2.11), respectively. We also found similar significant and positive associations for NO₂ and NO_x in all five transitions. No significant associations for PM_{2.5-10} were observed with any trajectory.

Table 2 HR (95% CIs) for each transition in transition pattern A by ambient air pollutants

	HR (95% CI), per 5 µg/m ³				
	PM _{2.5}	PM _{2.5-10}	PM ₁₀	NO ₂	NO _x
Baseline → incident chronic lung disease	1.31 (1.22 to 1.42)	0.94 (0.85 to 1.03)	1.10 (1.05 to 1.15)	1.02 (1.01 to 1.03)	1.01 (1.01 to 1.02)
Incident chronic lung disease → chronic lung multimorbidity	1.27 (1.01 to 1.57)	1.22 (0.88 to 1.68)	1.14 (0.97 to 1.35)	1.05 (1.01 to 1.08)	1.02 (1.00 to 1.04)
Baseline → death	1.32 (1.21 to 1.45)	0.98 (0.88 to 1.09)	1.06 (1.01 to 1.11)	1.02 (1.01 to 1.03)	1.02 (1.01 to 1.02)
Incident chronic lung disease → death	1.24 (1.01 to 1.53)	1.09 (0.85 to 1.41)	1.18 (1.05 to 1.33)	1.03 (1.00 to 1.06)	1.01 (1.00 to 1.03)
Chronic lung multimorbidity → death	1.91 (1.14 to 3.20)	1.17 (0.64 to 2.13)	1.55 (1.13 to 2.11)	1.11 (1.04 to 1.18)	1.04 (1.01 to 1.07)

Bold values denote statistically significant results.

NO₂, nitrogen dioxide; NO_x, nitrogen oxides; PM₁₀, particulate matter with diameter ≤10µm.

After dividing chronic lung diseases into three specific conditions (including asthma, COPD and lung cancer), PM_{2.5} and NO_x were significantly associated with the occurrence of each chronic lung disease, the transition from free of chronic lung disease to death, the transition from asthma to chronic lung multimorbidity and the transition from COPD to subsequent death (table 3). PM₁₀ and NO₂ were significantly associated with the transition from free of chronic lung disease to COPD or lung cancer, the transition from asthma to chronic lung multimorbidity, and the transition from chronic lung multimorbidity to death. Furthermore, among the three conditions examined in the transition of incident chronic lung disease to chronic lung multimorbidity, the only observed significant association with air pollution was the transition from asthma to chronic lung multimorbidity. Aside from the transition from COPD to death, non-significant associations were observed between air pollution and the transitions from incident chronic lung disease to death.

Subgroup analyses

Online supplemental table S2 shows the results of multistate analyses stratified by age and sex. We observed that the effects of air pollution on all five transitions appeared to be stronger among males than females, although most of the effects were statistically insignificant. Notably, a significant interaction between PM₁₀ and sex on the transition from free of chronic lung disease to death was observed and the association was stronger among males (HR 1.10, 95% CI 1.03 to 1.18) than females (HR 0.98, 95% CI 0.90 to 1.06). We also found significant interactions between PM₁₀, NO₂ and NO_x and age strata on the transition from free of chronic lung disease to incident chronic lung disease, with stronger associations among older individuals.

Sensitivity analyses

Online supplemental table S3 shows the results of the sensitivity analyses. The results were not substantially altered when we excluded individuals who developed chronic lung disease within 2 years of follow-up. There were no apparent differences after using different time intervals (0.5, 1, 3 and 5 years) to calculate the entry date of the prior state for those who entered different states on the same day. When we excluded participants who experienced different states on the same day, the analysis yielded similar results. In sensitivity analyses excluding participants who moved their residential addresses after 2010, overall patterns did not change considerably, although the HRs (95% CIs) per 5 µg/m³ increase of PM₁₀ was 1.04 (0.98 to 1.10) in the transition from the baseline healthy to death. Associations were similar in sensitivity models additionally adjusted for occupational exposures, however, the effects of PM_{2.5}, NO₂ and NO_x on the transition from chronic lung multimorbidity to death and the impact of PM₁₀ on the transition from baseline healthy, incident chronic lung disease and chronic lung multimorbidity to death were not statistically significant.

DISCUSSION

Based on this large prospective cohort of UK participants, we applied multistate models to examine the impact of air pollution on the transition trajectory of chronic lung disease, from baseline healthy to incident chronic lung disease, to subsequent chronic lung multimorbidity and further to death. Air pollution exposure was associated with all five transition trajectories to varying degrees. Among the five air pollutants included in the analysis, PM_{2.5} had the strongest impact in all trajectories. Additionally, air pollution had a larger impact on serious disease transition (transition from chronic lung multimorbidity to death) than early stages

Table 3 HR (95% CIs) for each transition in transition pattern B by ambient air pollutants

	HR (95% CI), per 5 µg/m ³				
	PM _{2.5}	PM _{2.5-10}	PM ₁₀	NO ₂	NO _x
Baseline → incident chronic lung disease					
Baseline → asthma	1.18 (1.05 to 1.33)	0.93 (0.81 to 1.06)	1.03 (0.96 to 1.10)	1.01 (0.99 to 1.02)	1.01 (1.00 to 1.02)
Baseline → COPD	1.42 (1.27 to 1.59)	0.95 (0.83 to 1.09)	1.19 (1.11 to 1.26)	1.03 (1.02 to 1.04)	1.02 (1.01 to 1.03)
Baseline → lung cancer	1.43 (1.07 to 1.91)	0.94 (0.66 to 1.33)	1.17 (1.02 to 1.34)	1.05 (1.01 to 1.08)	1.02 (1.00 to 1.04)
Incident chronic lung disease → chronic lung multimorbidity					
Asthma → chronic lung multimorbidity	2.01 (1.32 to 3.08)	1.01 (0.60 to 1.71)	1.35 (1.03 to 1.77)	1.12 (1.06 to 1.18)	1.05 (1.02 to 1.07)
COPD → chronic lung multimorbidity	0.99 (0.63 to 1.54)	1.44 (0.87 to 2.39)	1.08 (0.83 to 1.39)	1.01 (0.95 to 1.09)	1.00 (0.98 to 1.03)
Lung cancer → chronic lung multimorbidity	0.69 (0.26 to 1.84)	0.81 (0.29 to 2.28)	0.90 (0.54 to 1.49)	0.96 (0.86 to 1.08)	0.97 (0.91 to 1.05)
Baseline → death	1.32 (1.21 to 1.45)	0.98 (0.88 to 1.09)	1.05 (1.00 to 1.11)	1.02 (1.01 to 1.03)	1.02 (1.01 to 1.02)
Incident chronic lung disease → death					
Asthma → death	1.10 (0.65 to 1.89)	1.45 (0.81 to 2.60)	1.24 (0.90 to 1.70)	1.02 (0.95 to 1.09)	1.01 (0.98 to 1.05)
COPD → death	1.55 (1.15 to 2.07)	1.07 (0.74 to 1.55)	1.30 (1.09 to 1.54)	1.01 (0.96 to 1.07)	1.03 (1.01 to 1.04)
Lung cancer → death	0.85 (0.57 to 1.27)	1.01 (0.67 to 1.53)	0.82 (0.66 to 1.01)	0.97 (0.93 to 1.01)	1.00 (0.97 to 1.03)
Chronic lung multimorbidity → death	1.89 (1.12 to 3.19)	1.18 (0.64 to 2.17)	1.53 (1.12 to 2.09)	1.10 (1.04 to 1.17)	1.04 (1.01 to 1.07)

Bold values denote statistically significant results.

COPD, chronic obstructive pulmonary disease; NO₂, nitrogen dioxide; NO_x, nitrogen oxides; PM₁₀, particulate matter with diameter ≤10µm.

(transition from baseline healthy to incident chronic lung disease/death or transition from incident chronic lung disease to chronic lung multimorbidity/death).

Consistent with previous studies,^{37–38} we found that air pollution exposure was associated with an increased risk of incident chronic lung diseases (including asthma, COPD and lung cancer), which has provided further evidence in support of the adverse effects of air pollution on chronic lung diseases. Several underlying mechanisms have been theorised for the association between long-term air pollution exposure and chronic lung diseases. For example, long-term air pollution exposure can cause inflammation that may lead to oxidative stress, and as a result, chronic lung diseases.⁷ Air pollutants may also induce DNA methylation, autophagy and apoptosis, leading to the development of chronic lung diseases.¹⁴ Additionally, exposure to air pollutants might contribute to changes in airway responsiveness, reduced airway clearance and impaired host defenses against infection, which may also lead to the development of chronic lung diseases.¹³

Although it has been widely recognised that chronic lung diseases may be influenced by exposure to air pollution, limited studies have identified and quantified the risk of chronic lung multimorbidity. Our study has provided evidence that long-term exposure to air pollution may contribute to the development of chronic lung multimorbidity in individuals with chronic lung disease. We found that $PM_{2.5}$ had the strongest association with the transition from chronic lung disease to chronic lung multimorbidity compared with other air pollutants, suggesting that $PM_{2.5}$ plays a pivotal role in disease progression. A better understanding of the relationship between air pollution exposure and chronic lung multimorbidity can support the development or modification of air pollution management strategies.

These findings highlight the key role of air pollution in the risk of mortality in both participants with and without chronic lung disease. In those that were considered healthy and free of chronic lung disease, air pollution exposure was associated with an increased risk of death. It was also noteworthy that $PM_{2.5}$, PM_{10} , NO_2 and NO_x could increase the risk of death in all stages of disease progression. This study confirms the influence of air pollution on the increased risk of death, and further provides evidence that improving air quality may help in the primary and secondary prevention of both chronic lung disease and chronic lung multimorbidity.

We observed significantly adverse effects of $PM_{2.5}$ and PM_{10} on progression trajectory of chronic lung diseases, however, no such associations were found for $PM_{2.5-10}$. The underlying reasons might be that, compared with $PM_{2.5-10}$, $PM_{2.5}$ tended to have relatively larger surface areas and were capable of carrying more toxic substances into the lungs. These substances may cause lung inflammation and oxidative stress.³⁹ Another possible explanation was that $PM_{2.5}$ had smaller diameters and they can travel into and deposit on the surface of the deeper parts of the lungs compared with $PM_{2.5-10}$.⁴⁰

Clinical and public health perspectives

The findings of this study have important implications for both clinical and public health prevention strategies for respiratory diseases. The results indicate that elevated levels of ambient air pollution are important and modifiable environmental factors that contribute to each transition stage of the progression trajectory of chronic lung disease. From a clinical perspective, we recommend the development of evidence-based clinical guidelines for the treatment and prevention of respiratory health effects associated with air pollution exposure. In this respect, it is recommended that once an individual develops a chronic lung disease, they should take some measures, such as wearing masks, using air purifiers or reducing outdoor exercise, during periods of high-level air pollution. From the public health perspective, efforts to reduce ambient air pollution can have positive impacts on ameliorating the health burden of respiratory diseases, whether concentrations are below or above the current limit value.

Subgroup analyses

Evidence of interactions between sex and age in transitions from baseline to incident chronic lung disease and death were observed

in trajectory pattern A. The impact of PM_{10} on the transition from healthy baseline to death was higher in males than females. It is possible that females and males have differences in biological and behavioural factors, such as time-activity patterns that result in differential susceptibility.⁸ The impacts of PM_{10} , NO_2 and NO_x with the transition from baseline healthy to incident chronic lung disease were higher in the older population (age ≥ 55). This difference may be explained by older participants having generally poorer health simply due to age, and as a result, a reduced capacity to cope biologically with high levels of air pollution.^{39–41}

Strengths and limitations

Our study has a few strengths, including a large sample size, standardised data collection protocol and sufficient covariate information. To our knowledge, this is the first prospective study to examine the association between air pollution exposure and the risk of chronic lung multimorbidity. Notably, the primary advantage of our study is the use of a multistate model, which distinguishes the impact of air pollution exposure on each transition stage of the progression trajectory of chronic lung multimorbidity.

Several limitations should be noted. First, air pollution exposure in this study was assessed according to the residential address reported at baseline, which might result in exposure misclassification. Second, potential changes in time-varying factors at the time of transition could not be accounted for in this investigation. Third, due to a small proportion of available follow-up data on relevant confounders, we only used the information provided at baseline in our study. Fourth, though the clinical condition of participants may involve resolution or remission,²⁹ disease progression is represented only using a one-way traffic approach in our study due to data limitations. Lastly, we used an interval of 0.5 days to calculate the occurrence date of incident chronic lung disease for participants who had the same diagnosis date for two or three chronic lung diseases, which may have resulted in inaccurate associations. However, observed sensitivity analyses using several time intervals yielded comparable results.

CONCLUSION

In summary, based on a large-scale prospective cohort of UK adults, we provide evidence that air pollution has adverse effects on the progression from free of chronic lung disease to subsequent chronic lung disease, chronic lung multimorbidity and death. Our findings suggest that air pollution mitigation strategies can play a vital role in chronic lung disease and chronic lung multimorbidity prevention.

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ARTIGO ORIGINAL

Diferenciação dos derrames pleurais malignos e benignos com base em inteligência artificial

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RESUMO

Introdução Este estudo pretendeu construir modelos de inteligência artificial com base em TC torácicas para realizar a segmentação e classificação do derrame pleural benigno (EPB) e do derrame pleural maligno (EPM).

Métodos Um total de 918 pacientes com derrame pleural foram incluídos inicialmente, sendo que 607 casos selecionados aleatoriamente foram usados como coorte de treino e os restantes 311 como coorte de teste interno. Foi utilizada uma outra coorte de teste externo independente com 362 casos. Desenvolvemos um modelo de segmentação do derrame pleural (M1) ao combinar U-Net 3D com ponderação espacial com a U-Net 2D clássica. De seguida, foi construído um modelo de classificação (M2) para identificar EPB e EPM utilizando o volume de TC e a sua máscara de derrame pleural 3D como valores de entrada.

Resultados O coeficiente de semelhança de Dice, o coeficiente de Jaccard, a precisão, a sensibilidade, a distância de Hausdorff médias 95% (HD95) e os indicadores de distância de superfície médios em M1 foram de $87,6 \pm 5,0\%$, $82,2 \pm 6,2\%$, $99,0 \pm 1,0\%$, $83,0 \pm 6,6\%$, $6,9 \pm 3,8$ e $1,6 \pm 1,1$, respetivamente, que foram melhores do que os da U-Net 3D e da U-Net 3D com ponderação espacial. No que diz respeito a M2, a área sob a curva de características do recetor operativo, a sensibilidade e a especificidade obtidas com máscaras de concatenação de volume como input foram de 0,842 (IC 95% 0,801 a 0,878), 89,4% (IC 95% 84,4% a 93,2%) e 65,1% (IC 95% 57,3% a 72,3%) na coorte de teste externa. Estas métricas de desempenho foram significativamente melhoradas quando comparadas com outros padrões de input.

Conclusões Aplicámos um modelo de aprendizagem profunda à segmentação dos derrames pleurais e o modelo mostrou um desempenho encorajador no diagnóstico diferencial de EPB e EPM.

INTRODUCTION

Effusions, including pleural effusions, ascites, pericardial effusions and abscesses, are commonly observed in many diseases, such as infections and various cancers. The most common effusions are malignant pleural effusions (MPEs) caused by lung cancer, breast cancer, lymphoma and so on, and benign pleural effusions (BPEs) caused by *Mycobacterium tuberculosis* infection, heart failure, parapneumonic infections and so on.^{1–3} The most common conditions leading to ascites are liver disease, cirrhosis and cancer.⁴ Because pleural effusions are representative effusions, we chose MPE and BPE as our study objects. The gold standard in the diagnosis of MPE and BPE depends on pleural effusion pathogenic/cytological examinations and thoracentesis with pleural biopsy.^{5–6} However, the low positivity rates for pathogenic diagnosis, the invasiveness and high costs of pleural biopsy, and the risk of complications represent the limitations of these gold-standard techniques, although their high specificity is their most important advantage.^{7–8} These limitations suggest opportunities for

Key messages

What is already known on this topic

- The limitations of the gold standard in the diagnosis of benign pleural effusion (BPE) and malignant pleural effusion (MPE) suggest opportunities for more convenient, highly sensitive and non-invasive methods to improve diagnostic performance. Although many previous studies have explored other examinations to help diagnose pleural effusion, no available studies have focused on the differential diagnosis of pleural effusion based on thoracic CT image analysis using deep learning algorithms.

What this study adds

- The artificial intelligence (AI) model proposed in this study showed encouraging performance in the segmentation of pleural effusion areas and differential diagnosis of BPE and MPE based on thoracic CT images.

How this study might affect research, practice or policy

- In the present study, we proposed an AI model to implement the segmentation of pleural effusion regions. It would be worthwhile to apply these segmentation and classification deep learning models to other sorts of effusions.

more convenient, highly sensitive and non-invasive methods to improve the diagnostic performance of BPE and MPE.

Thoracic CT is an appropriate method for the further assessment of pleural effusion.⁹ Because the features extracted from images by radiologists are limited, artificial intelligence (AI) deep learning algorithms are helpful tools for automatically analysing complex medical images thanks to their strong feature-learning ability.¹⁰ However, no available studies have focused on the differential diagnosis of pleural effusion based on thoracic CT image analysis using deep learning algorithms.

U-Net, a convolutional neural network, has become an increasingly important basis for many deep learning models in medical image analysis.¹¹ It can achieve remarkable generalisation performance when trained with a limited number of images, which makes it especially suitable for our research.¹² In previous studies, U-Net was used for the segmentation of solid organs and lesion

regions, such as pancreas segmentation,¹³ 3D cardiac segmentation¹⁴ and automatic ground-glass nodule detection.¹⁵ In our study, we applied U-Net to the segmentation of effusion regions, and specifically pleural effusions. We combined the 3D spatially weighted U-Net with the 2D classical U-Net for pleural effusion segmentation in thoracic CT images to obtain fine masks. The high precision of pleural effusion segmentation identifies predictive features which can be subsequently used to train deep learning models for lesion classification. We thus proposed a deep learning algorithm, based on the global and partial analysis of thoracic CT image features to diagnose BPE and MPE, which can potentially play a critical role in improving patients' clinical prognosis.

MATERIALS AND METHODS

Patients and study design

In this consecutive study, 918 pleural effusion cases retrospectively collected from Wuhan Union Hospital between January 2016 and December 2021 were enrolled, with 311 cases randomly selected as the internal testing cohort and the other 607 as the training cohort. Another independent cohort including 362 patients with pleural effusion collected from Renmin Hospital of Wuhan University between January 2020 and May 2022 was used as the external testing cohort. Patients who met the following inclusion criteria were enrolled: (1) diagnosed with pleural effusion by CT scan of the chest and (2) underwent pleural effusion pathogenic/cytological examinations and diagnostic thoracentesis with or without pleural biopsy. The exclusion criteria were (1) pleural effusion whose cause could not be determined, (2) under the age of 18 and (3) unavailable clinical information. The diagnostic criteria for MPE and BPE adopted in this study are based on our previous studies,^{16,17} and the criteria are further described in online supplemental methods.

Two professional physicians, HX and WC, collected clinical information, including demographic characteristics, radiological features and laboratory testing results of the enrolled patients from electronic medical records. The volume of pleural effusion was

classified as mild (<500 mL), moderate (500–1000 mL) or severe (>1000 mL). The parameters of the CT scanner are presented in online supplemental methods.

Architecture of the pleural effusion segmentation model (M1)

The pleural effusion segmentation model (M1) is a cascaded two-step deep-learning model (figure 1A). The initial coarse segmentation results are obtained from the spatial attention information based on the 3D spatially weighted U-Net. We used a 3D spatial attention mechanism to capture large-scale contextual information, thus enhancing the representative ability of the model (figure 1C). However, owing to the huge amount of information per sample for 3D U-Net, the region of interest needs to be cropped into small image patches to be used as inputs. Using this method, natural contour information may be lost to some degree. Therefore, the model's learning of natural contour information was enhanced through the 2D classical U-Net. The concatenation of 3D spatially weighted U-Net and 2D classical U-Net helps obtain a fine segmentation of pleural effusion. Details about the algorithms of the coarse and fine segmentation models are shown in online supplemental methods.

Architecture of the pleural effusion classification model (M2)

We developed a 3D deep convolutional neural network to identify patients with MPE from thoracic CT volumes. As shown in figure 1B, this classification model (M2) uses CT volume and its 3D pleural effusion masks as inputs (details in online supplemental methods). The 3D pleural effusion fine masks are obtained by assembling 2D fine masks generated by the fine segmentation model. This component takes advantage of both stacked bottleneck blocks and squeeze-and-excitation (SE) blocks. The bottleneck block is introduced to extract deeper features from the CT volumes and to solve the problem of degradation in the network training process. The SE block is introduced to improve the representational power of the network by enabling it to perform dynamic channel-wise feature recalibration (figure 1D; online

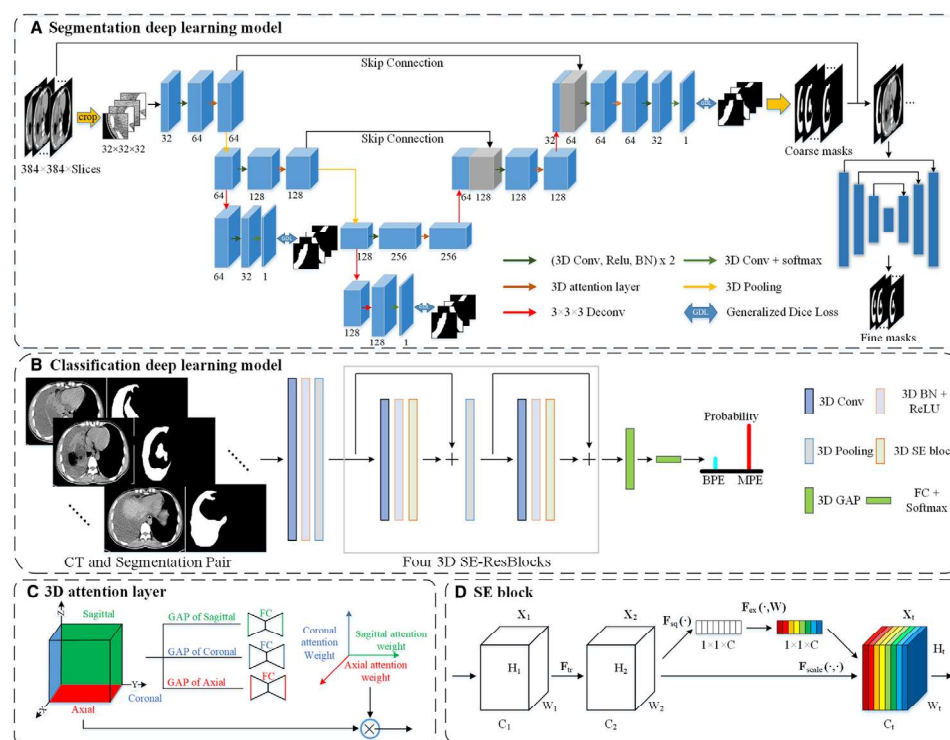


Figure 1 Classification architecture for the differential diagnosis of BPE and MPE based on AI-processed CT images. In order to diminish the effects of unrelated image regions, we first extract the results of the pleural effusion segmentation models (the coarse segmentation model based on the 3D spatially weighted U-Net and the fine segmentation model based on the 2D classical U-Net). Differential diagnosis is then achieved by the pleural effusion classification model based on the residual blocks and SE blocks. (A) Schematic flowchart of the proposed algorithm for pleural effusion segmentation. (B) Schematic flowchart of the proposed algorithm for predicting the probability of pleural effusion being MPE. (C) Architecture of the 3D attention layer in the segmentation model. (D) Architecture of the SE block in the classification model. BPE, benign pleural effusion; MPE, malignant pleural effusion; SE, squeeze-and-excitation.

Table 1 Patient characteristics in the training, internal testing and external testing cohorts

Characteristics	Training cohort		P value	Internal testing cohort		P value	External testing cohort		P value
	MPE (n=341)	BPE (n=266)		MPE (n=179)	BPE (n=132)		MPE (n=204)	BPE (n=158)	
Gender			<0.001			<0.001			<0.001
Female	177 (51.9%)	81 (30.5%)		101 (56.4%)	37 (28.0%)		108 (52.9%)	39 (24.7%)	
Male	164 (48.1%)	185 (69.5%)		78 (43.6%)	95 (72.0%)		96 (47.1%)	119 (75.3%)	
Age, median (IQR), years	60.0 (50.0–68.0)	61.0 (48.0–71.0)	0.694	59.0 (52.0–68.0)	57.0 (46.0–68.0)	0.115	64.0 (56.3–71.0)	65.0 (53.8–75.0)	0.755
Unilateral pleural effusion	179 (52.5%)	127 (47.7%)	0.246	107 (59.8%)	63 (47.7%)	0.035	152 (74.5%)	71 (44.9%)	<0.001
Bilateral pleural effusion	162 (47.5%)	139 (52.3%)		72 (40.2%)	69 (52.3%)		52 (25.5%)	87 (55.1%)	
Volume of pleural effusion			0.750			0.627			0.763
Mild	236 (69.2%)	186 (69.9%)		124 (69.3%)	97 (73.5%)		112 (54.9%)	81 (51.3%)	
Moderate	60 (17.6%)	50 (18.8%)		33 (18.4%)	19 (14.4%)		40 (19.6%)	35 (22.1%)	
Severe	45 (13.2%)	30 (11.3%)		22 (12.3%)	16 (12.1%)		52 (25.5%)	42 (26.6%)	

Data shown are the number and percentage of patients, with the exception of age (median and IQR). Statistical comparisons were performed for each clinical variable between the two groups (MPE vs BPE). P values were computed using the Mann-Whitney U test for age as a continuous variable and the χ^2 test or Fisher's exact test for categorical variables, as appropriate.

BPE, benign pleural effusion; MPE, malignant pleural effusion.

supplemental methods). Inputting the 3D fine masks of pleural effusion according to the 3D thoracic CT volume helps reduce the effects of background information and improves the classification of BPE and MPE. Details about the training process of the pleural effusion segmentation and classification model are shown in online supplemental methods.

Quantitative assessment indicators

For the pleural effusion segmentation model, the Dice similarity coefficient (DSC) and Jaccard coefficient were used to evaluate the spatial overlap between the model-generated contour (M) and the ground truth contour (G). In our study, G means the sets defined by these boundaries of pleural effusion area drawn by a professional radiologist (15 years of experience) on CT images; M means the sets defined by these boundaries of pleural effusion area generated by the AI model. Precision and sensitivity measure the detection capability for identifying the correct regions. The Hausdorff distance 95% (HD95) and average surface distance (ASD) measure the boundary similarity between the model-generated contour and the ground truth contour. Details about the above indicators are described in online supplemental methods.

The area under the receiver operator characteristic (ROC) curve (AUC), sensitivity and specificity were used to evaluate the

predictive performance of M2 as a pleural effusion classification model.

Statistical analysis

Implementation details are described thoroughly in online supplemental methods. Statistical analyses were performed using SPSS Statistics (V.22). Comparisons were performed using the Mann-Whitney U test for continuous variables and χ^2 or Fisher's exact test for categorical variables, as appropriate. ROC curves were generated to evaluate the classification performance. Statistical significance was defined as a two-sided p value <0.05.

RESULTS

Baseline characteristics of patients

The baseline characteristics of the enrolled patients are presented in table 1. We compared the distribution of sex, age, volume of pleural effusion (mild/moderate/severe) and unilateral/bilateral pleural effusion between the two groups (BPE vs MPE). There was no significant difference between the two groups in any of the three cohorts in terms of age and volume of pleural effusion. However,

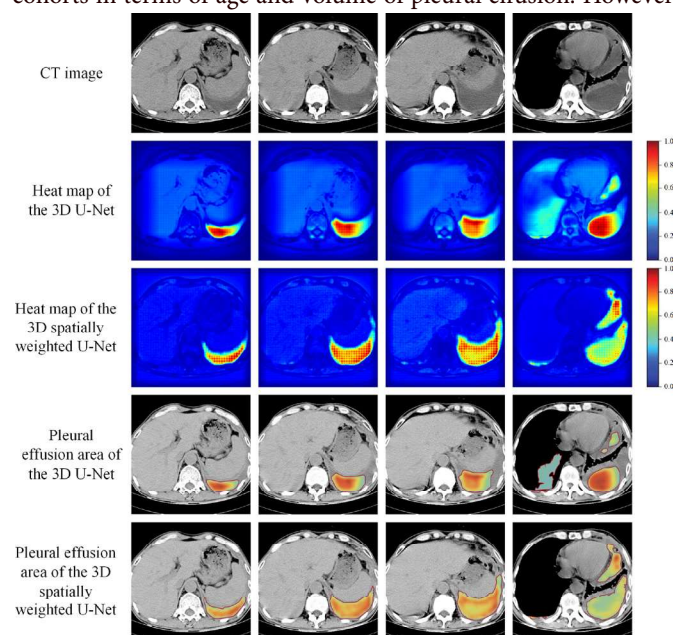


Figure 2 Pleural effusion area discovery. The cut-off value used to acquire the high-response area in heatmaps was 0.5. The second and third rows show the heatmap of 3D U-Net and the 3D spatially weighted U-Net, respectively. The fourth and fifth rows show the pleural effusion area discovered by 3D U-Net and the 3D spatially weighted U-Net, respectively.

Table 2 Causes of pleural effusion in the training, internal testing and external testing cohorts

Causes	Training cohort (n=607)	Internal testing cohort (n=311)	External testing cohort (n=362)
Malignant effusions	341 (56.1%)	179 (57.6%)	204 (56.3%)
Lung cancer	147 (24.2%)	77 (24.7%)	146 (40.3%)
Breast cancer	91 (15.0%)	46 (14.8%)	20 (5.5%)
Lymphoma	64 (10.5%)	36 (11.6%)	2 (0.6%)
Gastrointestinal cancer	28 (4.6%)	13 (4.2%)	24 (6.6%)
Ovarian	4 (0.6%)	4 (1.3%)	7 (1.9%)
Others	7 (1.2%)	3 (1.0%)	5 (1.4%)
Benign effusions	266 (43.9%)	132 (42.4)	158 (43.7%)
Parapneumonics	111 (18.3%)	60 (19.3%)	88 (24.3%)
Heart failure	59 (9.7%)	25 (8.0%)	11 (3.1%)
Tuberculous pleuritis	83 (13.7%)	43 (13.8%)	36 (10.0%)
Pulmonary embolism	3 (0.5%)	0 (0.0%)	3 (0.8%)
Pericardial diseases	1 (0.2%)	1 (0.3%)	3 (0.8%)
Others	9 (1.5%)	3 (1.0%)	17 (4.7%)

Data shown are the number and percentage of patients.

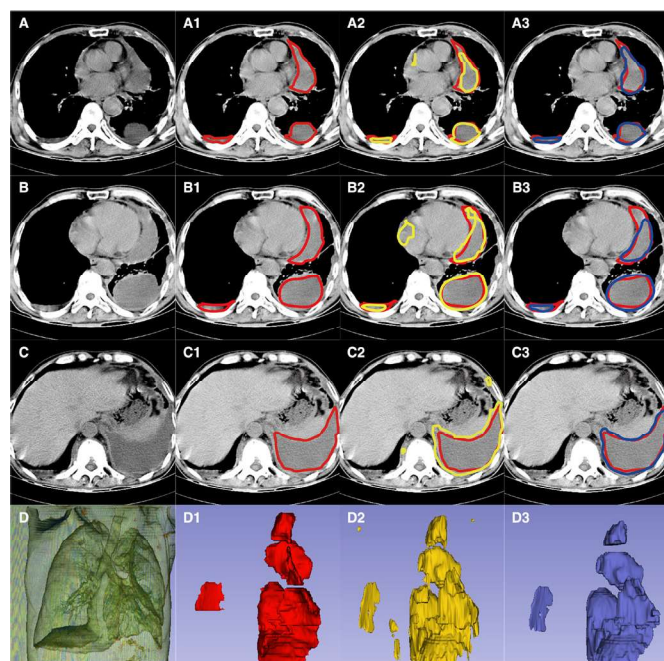


Figure 3 Comparison of the segmentation results of a patient using the ground truth contour, 3D spatially weighted U-Net (one-step method) and M1 (two-step method: 3D spatially weighted U-Net and 2D classical U-Net) in 2D and 3D views. The first column shows the images in three different CT slices (A–C) and the 3D (D) view of a patient's thoracic CT scan. The second column (a1, b1, c1 and d1) shows the corresponding experts' ground truth contour (pleural effusion outline highlighted in red). The third column (a2, b2, c2 and d2) shows the pleural effusion segmentation results (pleural effusion outline highlighted in yellow) using 3D spatially weighted U-Net. The fourth column (a3, b3, c3 and d3) shows the pleural effusion segmentation results (pleural effusion outline highlighted in blue) using M1.

the distribution of gender in patients with MPE and BPE was significantly distinct ($p < 0.001$) in all three cohorts. Lung cancer was the leading cause of MPE (24.2% in the training cohort, 24.7% in the internal testing cohort, 40.3% in the external testing cohort), while parapneumonics was the leading cause of BPE (18.3% in the training cohort, 19.3% in the internal testing cohort, 24.3% in the external testing cohort; table 2).

3D spatially weighted attention mechanism in coarse segmentation for pleural effusion area discovery

To highlight the importance of the attention mechanism inserted in 3D U-Net, figure 2 depicts the pleural effusion areas delineated by 3D U-Net and 3D spatially weighted U-Net, respectively, and displays heatmaps to indicate the importance of each part of the pleural effusion areas. The cut-off value used to acquire the high-response area was 0.5. It can be clearly observed that the high-response areas were mainly concentrated at the pleural effusion boundary when using 3D spatially weighted U-Net, while they were gathered in the pleural effusion inner part when using 3D U-Net, showing that the attention mechanism significantly improved the accuracy of the pleural effusion area segmentation. Compared with 3D U-Net segmentation, the results of 3D spatially weighted U-Net segmentation better fit the ground truth.

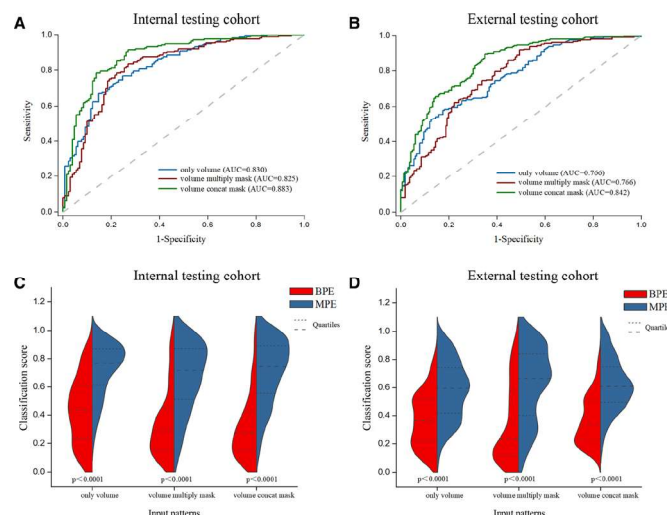


Figure 4 Predictive performance of the classification deep learning model shown by ROC curves and violin plots. (A, B) ROC curves for different input patterns in the internal (A) and external (B) testing cohort. (C, D) Deep learning score difference between BPE and MPE with different input patterns in the internal (C) and external (D) testing cohorts. AUC, area under the ROC curve; BPE, benign pleural effusion; MPE, malignant pleural effusion; ROC, receiver operating characteristic.

Comparison among 3D U-Net, 3D spatially weighted U-Net and segmentation deep learning model (M1)

For visual demonstration, representative pleural effusion area segmentation results of M1 (two-step method: 3D spatially weighted U-Net and 2D classical U-Net) are compared with the results of 3D spatially weighted U-Net (one-step method). Figure 3A1–C1 show an example of the radiologist's ground truth contours at three different CT slices, with the outline of contours shown by red lines. Figure 3A2–C2 show the contours (yellow lines) obtained using only 3D spatially weighted U-Net, while figure 3A3–C3 show the contours (blue lines) obtained using M1. For 3D illustration, figure 3D1–D3 show the 3D views of the pleural effusion area discriminated by the radiologist, one-step method and two-step method, respectively. Compared with the one-step method, the segmentation results of the two-step method better fit the ground truth.

For quantitative assessment of the segmentation results, six indicators were used to evaluate the similarity, difference and segmentation performance of 3D U-Net, 3D spatially weighted U-Net and M1. The average DSC, Jaccard coefficient, precision, sensitivity, HD95 and ASD indicators for M1 were 87.6%, 82.2%, 99.0%, 83.0%, 6.9 and 1.6, respectively, which were better than those of 3D U-Net and 3D spatially weighted U-Net (table 3).

Diagnostic validation of the classification deep learning model (M2)

The proposed M2 model with volume concat mask as input consistently achieved the highest accuracy across the internal and external testing cohorts (figure 4A,B). In addition, the classification score indicated a notable distinction between BPE and MPE with different input patterns in the internal and external testing cohorts (all $p < 0.001$). The input with volume concat mask bore the most significant distinction between BPE and MPE in both the internal and external testing cohorts, as revealed by the violin plots (figure 4C,D).

Table 3 Comparison of the proposed segmentation model (M1) with the 3D U-Net and 3D spatially weighted U-Net in terms of similarity, difference and positioning performance

Methods	DSC (%)	Jaccard (%)	Precision (%)	Sensitivity (%)	HD95	ASD
3D U-Net	30.2±4.9	26.7±6.3	76.2±4.1	29.4±7.8	197.6±14.7	4.3±0.4
3D spatially weighted U-Net	67.1±2.4	69.8±2.7	81.0±3.3	83.8±5.3	72.7±11.2	4.7±0.8
M1	87.6±5.0	82.2±6.2	99.0±1.0	83.0±6.6	6.9±3.8	1.6±1.1

Data shown are mean±SD.
ASD, average surface distance; DSC, Dice similarity coefficient; HD95, Hausdorff distance 95%; M1, two-step method (3D spatially weighted U-Net and 2D classical U-Net).

Table 4 Comparison about classification performance with different inputting patterns of the classification model (M2) in the internal and external testing cohorts

Input	Testing cohort	AUC (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)
Only volume	Internal	0.830 (0.783 to 0.871)	67.1 (59.6 to 73.9)	85.4 (78.1 to 91.0)
	External	0.766 (0.719 to 0.808)	58.0 (50.9 to 64.8)	82.5 (75.9 to 88.0)
Volume multiply mask	Internal	0.825 (0.778 to 0.866)	83.5 (77.2 to 88.7)	73.1 (64.6 to 80.5)
	External	0.766 (0.720 to 0.808)	91.8 (87.2 to 95.1)	50.6 (42.7 to 58.4)
Volume concat mask	Internal	0.883 (0.841 to 0.916)	78.4 (71.6 to 84.2)	86.2 (79.0 to 91.6)
	External	0.842 (0.801 to 0.878)	89.4 (84.4 to 93.2)	65.1 (57.3 to 72.3)

Data are presented as % (95% CI).
AUC, area under the receiver operating characteristic curve.

AUC, sensitivity and specificity were used as the main indicators for evaluating the diagnostic performance of M2. The three indicators for input with volume concat mask were 0.883 (95% CI 0.841 to 0.916), 78.4% (95% CI 71.6% to 84.2%) and 86.2% (95% CI 79.0% to 91.6%) in the internal testing cohort, and 0.842 (95% CI 0.801 to 0.878), 89.4% (95% CI 84.4% to 93.2%) and 65.1% (95% CI 57.3% to 72.3%) in the external testing cohort, which were significantly improved compared with those for input with only volume and input with volume multiply mask (table 4). The similar AUC values of the internal and external testing cohorts suggested an encouraging level of generalisability of M2 for diagnosing BPE and MPE in new patients. The input with the volume concat mask significantly improved the classification performance of M2, while, notably, the decrease in the speed of the network compared with the other two input patterns was negligible.

Comparison of the heatmaps between typical MPE and BPE

Comparison of the activation heatmaps generated by M2 between two randomly selected patients with MPE (one with lung cancer, one with breast cancer) and two randomly selected patients with BPE (one with tuberculous pleuritis, one with heart failure) is shown in figure 5. The activation heatmaps indicated the importance of different parts of the pleural effusion regions and suggested that different areas drew the attention of M2 to various degrees. The important areas found by M2, which were considered closely

associated with the nature of pleural effusion (BPE or MPE), varied in different patients. The difference in features between high-importance pleural effusion areas and other pleural effusion areas requires further research.

DISCUSSION

In this study, we proposed a new architecture for the differential diagnosis of BPE and MPE based on pleural effusion segmentation of thoracic CT images. This deep learning architecture was trained using 607 CT images, and its performance was validated in an internal testing cohort (311 pleural effusion cases) and an external testing cohort (362 pleural effusion cases) from Wuhan Union Hospital and Renmin Hospital of Wuhan University. The encouraging diagnostic performance of the deep learning model was shown in both the internal (AUC 0.883, 95% CI 0.841 to 0.916) and external (AUC 0.842, 95% CI 0.801 to 0.878) testing cohorts. In addition, we combined this AI model with some clinical data, including gender, age, unilateral/bilateral pleural effusion and volume of pleural effusion, to predict BPE and MPE. The results showed that combining clinical indicators could improve the AUC in all three cohort (training cohort: 0.903 vs 0.896, internal testing cohort: 0.895 vs 0.882, external testing cohort: 0.868 vs 0.842) (online supplemental figure S1). This deep learning model discovered suspect pleural effusion areas and produced fine segmentations in the first step, then identified BPE and MPE by holistically and partially analysing thoracic CT image features, revealing that the features of thoracic CT images were closely related to the nature of pleural effusions. Our study provides an alternative, easy-to-use method to achieve non-invasive and efficient diagnosis of BPE and MPE from original CT images without human assistance. Previous studies have demonstrated that thoracic CT image features, such as fluid loculation, pleural lesions, pleural nodules and extrapleural fat, can help discriminate MPEs from BPEs.^{18 19}

Pleural nodules and nodular pleural thickening were reported to be associated to MPE, while circumferential pleural thickening was more common in tuberculous pleural effusion (TPE).^{18 20} Zhang et al revealed that spectral CT imaging features combined with patient age and disease history could differentiate BPEs from MPEs with a sensitivity of 100% and a specificity of 71.4%, as well as an AUC of 0.933.²¹

Pleural effusions can be divided into transudates and exudates. Although no CT feature can accurately distinguish transudates from exudates, Abramowitz et al indicated that fluid loculation and pleural thickening were more common in exudates than in transudates.²² Discrimination of a pleural effusion as transudate or exudate is important for further evaluation and treatment. Some causes of BPE, such as heart failure and cirrhosis, generate transudates. However, some causes of BPE, such as infections and pulmonary embolism, generate exudates, as does MPE.^{3 23} The immunological microenvironment and inflammatory responses in MPE are two important factors that lead to the production of different components. In addition to neoplastic cells, cytokines and chemokines produced by immune cells, signalling molecules generated by tumour-associated macrophages, and fibroblasts are the main components of the surviving environment of tumour cells in pleural effusions.²⁴ In early-stage TPE, lymphocyte

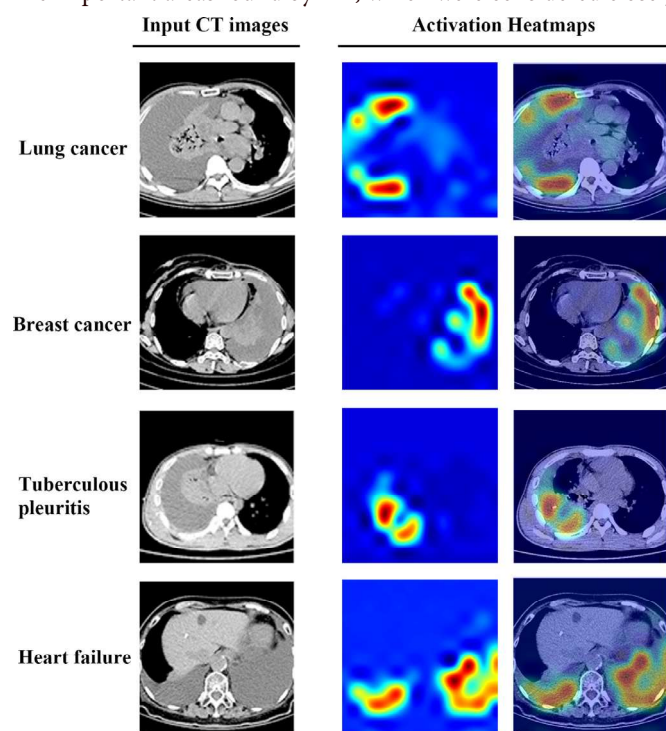


Figure 5 Comparison of the activation heatmaps generated by the pleural effusion classification model between four randomly selected patients with lung cancer, breast cancer, tuberculous pleuritis and heart failure, respectively.

predominance characterises a large proportion of the fluid; in the meantime, a higher mycobacterial burden appears in effusions that have loculations.²⁵ Li et al identified different peptide profiles between BPE and MPE through proteomic analysis and established a model to discriminate between BPE and MPE.²⁶ The different pleural effusion components for BPE and MPE may be a crucial cause of different thoracic CT image features, making it feasible to classify BPE and MPE using a deep learning model based on thoracic CT image features.

In the present study, we proposed an AI model to implement the segmentation of pleural effusion regions. The deep learning model for segmentation proposed in our study successfully integrated 3D spatially weighted U-Net and 2D classical U-Net. Our results showed that the cascaded segmentation architecture combining 3D spatially weighted U-Net with 2D classical U-Net (M1) was superior to the other two segmentation methods (only 3D U-Net and only 3D spatially weighted U-Net). Applying the spatial attention mechanism to 3D U-Net not only focuses the deep learning model on the regions of interest for input thoracic CT images, avoiding the interference of background information, but also extracts both shallow-level and deep-level attention information, which can improve the feature extraction ability of the model.^{15,27} However, in order to reduce the cubically growing number of network parameters caused by 3D convolution, using patches (crop region of interest into small image patches) as input may lose some natural contour information. 3D spatially weighted U-Net cascaded by a 2D classical U-Net can be conducive to supplementing natural contour information and excluding most error information about the pleural effusion region. In addition, in the deep learning model for pleural effusion classification, we input the holistic thoracic CT image and the fine segmentation region of pleural effusion generated by M1 at the same time. On the one hand, this approach stresses the features within the pleural effusion areas; while on the other hand, it does not neglect the related information within the areas outside the pleural effusion.

It has been reported that the primary tumour cannot be found in approximately 10% of MPEs.²⁴ Therefore, it is of vital importance to identify MPEs of unknown origin in a timely and non-invasive manner. It would be worthwhile to apply these segmentation and classification deep learning models to other sorts of effusions. Since the causes of ascites and abscess vary depending on the type of tumour and pathogen infection, a single AI model able to determine which type of cancer or bacteria is the reason for effusion production would represent remarkable progress. Further research and efforts are required to achieve this goal.

Although the proposed deep learning model of pleural effusion segmentation and classification showed encouraging performance, our study has several limitations. First, the data source only derived from two hospitals which may have limited the generalisability and robustness of the deep learning model. Second, high model interpretability of deep learning networks is considered valuable,²⁸ but the association between the imaging representations and the nature feature of pleural effusions cannot be fully understood in our study because of the end-to-end learning strategy. Third, despite the advantages of the proposed model, which uses exclusively thoracic CT images, in terms of convenience and time-saving, the predictive performance may be improved by combining this model with other clinical models; however, this point was not clarified in this study. Future large-scale external validations from multiple centres are necessary to provide convincing evidence of the generalisability of the deep learning model proposed in this study.

In conclusion, our research proposed an original deep learning model: a combination of 3D spatially weighted U-Net and 2D classical U-Net were used for the segmentation of pleural effusion. Subsequently, a deep learning model was established for the differential diagnosis of BPE and MPE based on thoracic CT images with masks. The non-invasiveness and high efficiency of the segmentation and classification models suggest their potential clinical utility. Our work shows the potential of AI to assist radiologists in identifying malignant disease and thereby improving patient care.

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