

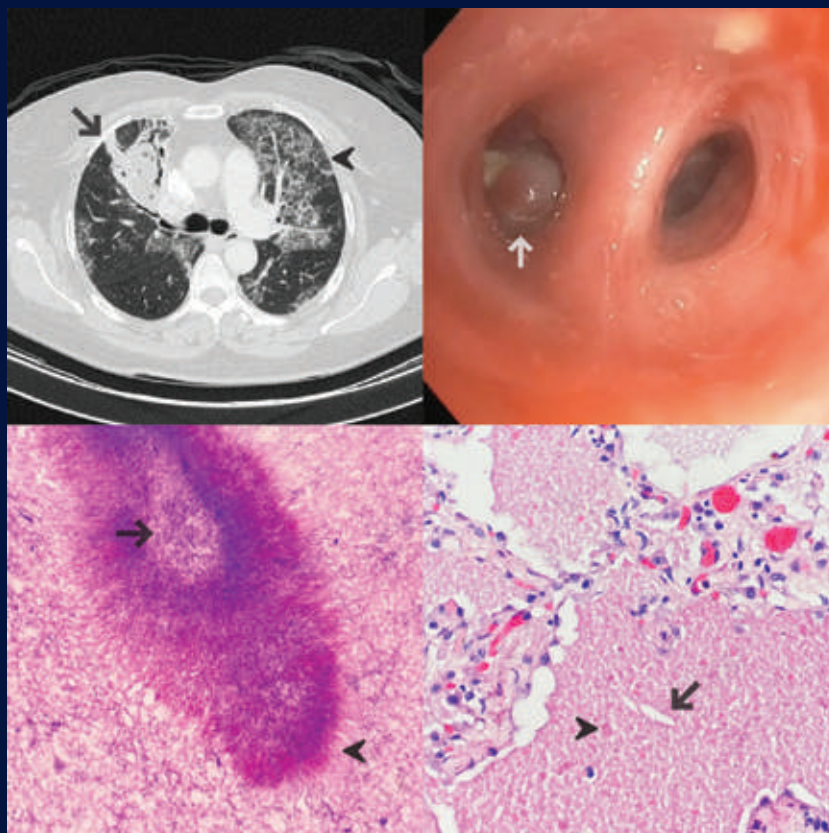
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ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

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1 INALAÇÃO¹



1 VEZ AO DIA¹



1 DISPOSITIVO¹

+171mL
(p<0,001)

MELHORIA SUPERIOR E CLINICAMENTE SIGNIFICATIVA DA FUNÇÃO PULMONAR vs. BUD/FOR Turbohaler²

-34%
(p<0,001)

REDUÇÃO SIGNIFICATIVA DA TAXA ANUAL DE EXACERBAÇÕES POR DPOC, ASSOCIADAS A HOSPITALIZAÇÕES vs. LAMA/LABA³

-42%
(p=0,01)

REDUÇÃO SIGNIFICATIVA DA MORTALIDADE POR TODAS AS CAUSAS (on-treatment) vs. LAMA/LABA^{3*}



Não foram registados novos dados de segurança relativos ao uso da associação entre um ICS, um LAMA e um LABA.³

ELEBRATO
FUROATO DE FLUTICASONA | UMECLIDÍNIO | VILANTEROL | ELLIPTA
ELE RESPIRA

Referências: 1. RCM Elebrato Ellipta, julho de 2022; 2. Lipson DA et al. Am J Respir Crit Care Med 2017; 196:438–446; 3. Lipson DA et al. N Engl J Med 2018 378:1671–1680.

BUD: Budesonida; DPOC: Doença pulmonar obstrutiva crônica; FOR: Formoterol; ICS: Corticosteroide inalado; LABA: Agonista β2 de longa duração de ação; LAMA: Antagonista muscarínico de longa duração de ação.

*A mortalidade por todas as causas foi um endpoint exploratório do estudo IMPACT. Aqui, estão apresentados os dados on-treatment. Os eventos on-treatment são os que ocorreram desde o início de tratamento e até 7 dias após o seu término.

INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM O RCM

NOME DO MEDICAMENTO Elebrato Ellipta **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA** Cada inalação disponibiliza uma dose administrada de 92 microgramas de furoato de fluticasona, 65 microgramas de brometo de umecliclínio equivalente a 55 microgramas de umecliclínio e 22 microgramas de vilanterol (como trifrenatato). Isto corresponde a um recipiente unido de 100 microgramas de furoato de fluticasona, 74,2 microgramas de brometo de umecliclínio equivalente a 62,5 microgramas de umecliclínio e 25 microgramas de vilanterol (como trifrenatato). Excipiente com efeito conhecido: cada dose administrada contém aproximadamente 25 mg de lactose mono-hidratada. **FORMA FARMACÉUTICA** Pó para inalação em recipiente unido **INDICAÇÕES TERAPÊUTICAS** Tratamento de manutenção em doentes adultos com doença pulmonar obstrutiva crônica (DPOC) moderada a grave, que não estejam adequadamente tratados com uma associação de um corticosteroide para inalação e um agonista beta-2 de longa duração de ação ou uma associação de um agonista beta-2 de longa duração de ação e um antagonista muscarínico de longa duração de ação (ver RCM para informação sobre efeitos sobre o controlo dos sintomas e prevenção das exacerbações). **POSOLOGIA E MODO DE ADMINISTRAÇÃO** A dose máxima recomendada é uma inalação 1x/dia, em cada dia à mesma hora. **Idosos, Compromisso renal e Compromisso hepático** Não é necessário ajustar a posologia. Utilizar com precaução em doentes com compromisso hepático moderado a grave. **População pediátrica** A utilização não é relevante na população pediátrica (<18 anos) para a indicação de DPOC. **Modo de administração** Via inalatória. **CONTRAINDICAÇÕES** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **EFEITOS INDESEJÁVEIS** As reações adversas mais frequentemente notificadas são nasofaringite, cefaleia e infeção das vias respiratórias superiores. **Infeções e infestações** Frequentes: Pneumonia, infeção das vias respiratórias superiores, bronquite, faringite, rinite, sinusite, gripe, nasofaringite, candidíase da boca e da garganta e infeção do trato urinário. **Pouco frequentes:** Infeção viral das vias respiratórias superiores. **Doenças do sistema imunitário** Raras Reações de hipersensibilidade, incluindo anafilaxia, angioedema, urticária e erupção cutânea. **Doenças do sistema nervoso** Frequentes: Cefaleia. **Pouco frequentes:** Disgeusia. **Afeções oculares** Pouco frequentes: Visão turva, Glaucoma, Dor ocular. **Raros:** Tensão intraocular aumentada. **Cardiopatas** Pouco frequentes: Taquiarritmia supraventricular, taquicardia e fibrilhação auricular. **Doenças respiratórias, torácicas e do mediastino** Frequentes: Tosse e dor orofaríngea. **Pouco frequentes:** Disfonia. **Doenças gastrointestinais** Frequentes: Obstipação. **Pouco frequentes:** Boca seca. **Afeções musculoesqueléticas e dos tecidos conjuntivos** Frequentes: Artralgia e dorsalgia. **Pouco frequentes:** Fraturas. **TITULAR DA AIM** GlaxoSmithKline Trading Services Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda. **DATA DA REVISÃO DO TEXTO** julho 22. **APRESENTAÇÃO:** Elebrato Ellipta 92 mcg+55 mcg+22 mcg, 30 doses. **Regime de Participação:** Escalão B. Regime Geral 69%; Regime Especial 84%. Está disponível informação pormenorizada sobre este medicamento no sítio da internet da Agência Europeia de Medicamentos <http://www.ema.europa.eu/>. Consultar o RCM completo para informação detalhada. Medicamento sujeito a receita médica. Para mais informações e em caso de suspeita de um acontecimento adverso ou de outra informação de segurança, contactar o departamento médico da GlaxoSmithKline - +351 214129500. Para mais informações contactar o representante local do titular da AIM: Bial-Portela & Cª, S.A., À Av. da Siderurgia Nacional, 4745-457 S. Mamede do Coronado; NIF: 500220913. As Marcas Registradas são propriedade ou licenças das empresas do grupo GSK. ©2022 empresas do grupo GSK ou sob licença. DMgMA_PT220726

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Editorial

Último trimestre do ano, outono / inverno, regressam em força as infeções respiratórias virais. E este ano com uma intensidade que está a afetar imenso a população de todos os grupos etários. E este impacto já o estamos a sentir na nossa prática clínica. SARS-CoV-2, influenza, VSR, et al. estão por cá, sós e associados, sempre com as bactérias a espreitar... é tempo de tratar e, em especial, de prevenir. Vacinar, vacinar, vacinar! Sem hesitações. A pandemia teve e vai continuar a ter muitas consequências...

Neste número da revista trazemos ao Vosso conhecimento um interessante conjunto de artigos que realçam a abordagem de diferentes condições clínicas, em todos os grupos etários, do diagnóstico ao tratamento, incluindo a importância da vacinação contra a COVID-19 desde a idade pediátrica.

Mas gostaríamos aqui de destacar o artigo “Aplicação em telessaúde de um espirómetro ultrassónico domiciliário” de Doumit e colaboradores. Encontrou esta equipa de investigação australiana uma excelente fiabilidade entre medições deste dispositivo validando a sua utilização em telessaúde, mas realçando a existência de amplos limites de concordância com os equipamentos de laboratório, o que pode limitar a interpretação de resultados colhidos em diferentes contextos.

Importa realçar que a pandemia COVID-19 nos abriu e permitiu aprofundar toda uma nova área de atuação para a telemedicina. Ela já existia, expandiu-se imenso e temos de a promover e manter. Não pode ser guardada no armário do esquecimento.

A telemedicina pode ser definida como o uso de informações, comunicações ou tecnologias eletrónicas usadas por profissionais de saúde para apoiar e fornecer cuidados clínicos a pessoas que não se encontram nas instituições de saúde, independentemente da distância.

Se pensarmos nas doenças respiratórias crónicas obstrutivas, não transmissíveis, como é o caso da DPOC e da asma, que como sabemos têm elevadas prevalências, a telemedicina está cá para ajudar. Telerreabilitação, educação em saúde, telemonitorização, deteção precoce de agudizações, apoio psicossocial e cessação do tabagismo com recurso a programas de telemedicina permitem a prestação de cuidados de saúde de qualidade a pessoas com DPOC, em especial para os que têm maior limitação no acesso aos serviços de saúde presenciais. Em pessoas com asma, a telemedicina é eficaz para melhorar a técnica inalatória, aumentar a adesão à medicação e à autogestão da doença, bem como na promoção da educação em saúde.

É indiscutível a importância das consultas virtuais e o uso de ferramentas móveis e/ou baseadas na web para gestão / monitorização dos doentes, mas as limitações técnicas ainda são frequentes, a literacia digital ainda não atinge valores desejáveis e, com a utilização destes métodos, privacidade e segurança continuam a ser preocupações muito significativas. Mas temos de avançar, aprofundar conhecimentos, influenciar as decisões pois a telemedicina tem de ser assumida como uma área prioritária no nosso sistema de saúde.

Boas leituras,

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Bronquiectasias infantis, o pouco que se sabe

Siobhán B Carr,^{1,2} Stefan A Unger^{3,4}

As bronquiectasias infantis, não relacionada com a fibrose quística (FC), ainda são classificadas como uma doença órfã. Historicamente, está pouco investigada, ficando para trás na literatura adulta e de outras doenças pulmonares crônicas pediátricas, tais como a asma e a FC. Nos últimos anos, as bronquiectasias adultas tem registado um crescimento significativo com a formação de vários grandes registos, como o EMBARC (*European Multicentre Bronchiectasis Audit and Research Collaboration*) e o *BronchUK* (www.bronchiectasis.eu/ registo, www.bronch.ac.uk). Estes registos demonstraram que as bronquiectasias infantis e as bronquiectasias adultas podem ter etiologias semelhantes, por exemplo pós-infecção e secundária à imunodeficiência, mas também demonstraram causas e comorbilidades potenciais diferentes, tal como a doença pulmonar obstrutiva crónica presente em cerca de 15% dos casos adultos.¹ Tanto nas bronquiectasias adultas como nas bronquiectasias pediátricas permanece uma grande população com etiologia desconhecida, especialmente na literatura pediátrica, onde a prevalência parece elevada nas comunidades autóctones.²

Thomas *et al*³ exploram uma possível etiologia da bronquiectasias examinando a sua associação com a traqueomalácia. Numa coorte histórica num único centro pediátrico terciário, o grau de traqueomalácia, definida durante a realização de broncoscopia flexível, foi comparado em crianças com ou sem evidência de bronquiectasias em imagiologia de TC convencional de alta resolução (c-HRCT). O relatório inclui um aumento da proporção de qualquer traqueomalácia observada na coorte das bronquiectasias. Com recurso a uma análise multivariável, demonstraram um aumento adicional da significância da associação quando a traqueomalácia foi definida como >50% de redução expiratória no lúmen traqueal transversal.

Com este artigo e outros, as bronquiectasias estão finalmente a ganhar destaque na medicina pediátrica. A *European Respiratory Society* (ERS) criou recentemente um grupo de trabalho sobre bronquiectasias pediátricas que contribuiu para a criação de uma rede global de clínicos, pais e crianças: a *Child-BEARNet* (*Children's Bronchiectasis Education Advocacy and Research Network*) (www.improvebe.org). Esta rede visa impulsionar o desenvolvimento de diretrizes, um registo e investigação. A primeira publicação de diretrizes para a prática clínica da ERS constitui uma referência aspiracional para todos os centros que cuidam de crianças com bronquiectasias.⁴ Vários países já criaram as suas próprias redes de bronquiectasias não-FC, incluindo o Reino Unido.

Através de inquéritos internacionais, o grupo de pacientes da Fundação Europeia do Pulmão (*European Lung Foundation | ELF | Homepage*) tem trabalhado com crianças e jovens (CYP) com bronquiectasias e com os

seus prestadores de cuidados para compreender o impacto desta doença crónica na qualidade de vida. Este trabalho prosseguiu dando prioridade às 10 principais áreas de investigação, tanto para CYP como para equipas clínicas multidisciplinares.⁵ Este “mapa” inclui uma melhor compreensão da etiologia da doença, mas, sobretudo, concentra-se nas áreas com maior impacto sobre a vida diária, incluindo a fisioterapia e o tratamento de agudizações.

Como pediatras especialistas nas doenças respiratórias, tendemos a confiar fortemente na riqueza da investigação dentro da literatura sobre a FC para orientar as estratégias de tratamento em crianças com bronquiectasias. No entanto, em primeiro lugar, temos de reconhecer que a FC e a sua etiologia são muito diferentes da miscelânea que são as bronquiectasias não-FC. Em segundo lugar, temos de garantir que estamos todos de acordo relativamente às definições que utilizamos.

No essencial, as bronquiectasias são uma definição imagiológica da dilatação das vias aéreas observada em c-HRCT. Foi postulado que deve ser utilizada uma definição de *cut-off* diferente na dilatação das vias aéreas em pediatria, utilizando um rácio broncoarterial de >0,8 em vez do rácio de 1,0 utilizado em adultos. Contudo, as recentes diretrizes da ERS⁴ destacaram que a evidência para a utilização deste rácio é de qualidade inferior, havendo necessidade de mais estudos e consenso entre radiologistas e clínicos respiratórios, bem como de assegurar a uniformização da aquisição de imagens do tórax por TC. Por outro lado, e quase mais importante, as características radiológicas podem ajudar a definir o ‘estado de pré-bronquiectasias’ ou, potencialmente, prever a progressão no contexto da sintomatologia clínica ou de achados como a traqueomalácia?

As bronquiectasias podem ser vistas como a fase final radiográfica de muitas condições. Está associada ou pode conduzir a sintomas respiratórios recorrentes e/ou persistentes, frequentemente uma tosse produtiva e crises frequentes de infecção respiratória, referidas como agudizações. Existe uma base de evidência emergente sobre como tratar estas agudizações,⁶ mas muito poucas evidências adicionais sobre as estratégias de tratamento. Ao agruparmos muitas doenças sob o termo geral de bronquiectasias, existe o perigo de esquecermos as diferenças na etiologia e mecanismo e, essencialmente, as diferenças potenciais na forma de tratamento. Uma criança com bronquiectasias causada por um insulto estático único, tal como a pós-tuberculose ou a inalação de um corpo estranho, é na verdade extremamente diferente de uma criança com uma condição genética congénita, por exemplo, discinesia ciliar primária (DCP). Também devemos ter presente que nem todas as crianças dentro de uma categoria etiológica como a DCP sofrerão de bronquiectasias.

Qualquer estratégia de tratamento ou investigação futura devem focar-se tanto nas bronquiectasias já estabelecidas como na prevenção do estabelecimento de bronquiectasias. Com uma intervenção precoce, pode ser possível prevenir mais danos, potencialmente inverter a dilatação precoce das vias aéreas e até interferir com o processo de dilatação pré-brônquica. Para tal, é necessário compreender a progressão em termos de como e quando é que uma criança

atravessa esse limiar de lesão significativa das vias aéreas.

Na edição original da *Thorax* de junho, os autores destacam a traqueomalácia como um exemplo potencial de um mecanismo causal. Parece lógico que uma fraca desobstrução das vias respiratórias possa causar infeções recorrentes, conduzindo por sua vez a uma inflamação persistente e, eventualmente, a lesões das vias respiratórias. No entanto, nem todas as crianças com traqueomalácia apresentam sintomas respiratórios ou desenvolvem bronquiectasias. É necessário estabelecer uma verdadeira prevalência neste grupo de crianças e explorar outros fatores que contribuam para esta situação. O impacto da traqueomalácia na desobstrução das vias respiratórias parece diminuir com a idade à medida que as vias respiratórias crescem.

Dadas estas novas descobertas, existem outros mecanismos que podem conduzir a uma fraca desobstrução das vias aéreas que necessitam de mais atenção, especialmente considerando este estado de ‘pré-bronquiectasias’. Isto inclui tosse fraca, certas malformações congénitas das vias respiratórias pulmonares e broncomalácia, bem como traqueomalácia. Ao realçar as maiores probabilidades de detetar traqueomalácia quando uma criança apresenta bronquiectasias, alertamos os pediatras para uma maior vigilância no tratamento e monitorização destas crianças, concentrando-se numa boa limpeza das vias respiratórias e no tratamento precoce de potenciais infeções. Por outro lado, também devemos ser mais proativos na investigação precoce de traqueomalácia em crianças que apresentem tosse produtiva persistente ou recorrente, mesmo na ausência de bronquiectasias. No futuro, as melhores intervenções precoces irão necessitar de uma avaliação estruturada com ensaios clínicos e definições acordadas para recolher mais dados comparáveis, por exemplo para explorar a traqueomalácia como uma causa potencial de bronquiectasias.

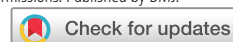
Embora as bronquiectasias infantis ainda estejam classificadas como uma doença órfã negligenciada de que sabemos tão pouco, é através de esforços como os de Thomas *et al*³ que esta pode deixar de ser uma doença órfã em breve.

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Corticosteroides inalados na DPOC: risco e benefícios

Christer Janson

A DPOC é uma doença progressiva em que a inflamação das vias aéreas desempenha um papel importante. Anteriormente, havia uma grande expectativa de que o tratamento anti-inflamatório regular com corticosteroides inalados (ICS) pudesse ajudar a travar a progressão da doença. Em 2007, foi publicado o muito aguardado resultado do estudo *Towards a Revolution in COPD Health* (TORCH).¹ O principal objetivo de TORCH era perceber se a combinação do beta-agonista de ação prolongada (LABA) com a ICS reduziria a mortalidade entre os pacientes com DPOC. O estudo não encontrou um benefício de sobrevivência estatisticamente significativo do tratamento ICS/LABA comparativamente ao placebo. No entanto, de forma algo inesperada, foi descoberto que a pneumonia era mais comum nos braços de tratamento que tinham recebido ICS. No grupo com ICS/LABA, 20% dos pacientes apresentaram pelo menos um evento de pneumonia em comparação com 12% no grupo com placebo. O facto de a ICS aumentar o risco de pneumonia na DPOC tem sido confirmado em muitos ensaios aleatorizados controlados (RCT) e estudos observacionais subsequentes.²⁻⁴

Num estudo observacional publicado na revista, Eklöf *et al* relatam que o tratamento com ICS está associado a um risco aumentado de apresentar uma cultura positiva de *Pseudomonas aeruginosa* em pacientes com DPOC.⁵ No estudo, os autores relacionaram dados de múltiplos registos nacionais com dados microbiológicos. O estudo incluiu mais de 21 000 pacientes com DPOC, dos quais 763 (4%) apresentaram uma cultura positiva. Os autores encontraram uma associação relacionada com a dose entre a utilização de ICS e a cultura positiva com um aumento do risco de mais do triplo (HR 3,54, IC 95% 2,72 a 4,60) nos pacientes com a dose mais elevada de ICS. Outros fatores de risco identificados foram a idade avançada, o sexo masculino, o IMC reduzido e a função pulmonar reduzida. Outros estudos descobriram que o uso de ICS está associado a um risco mais elevado de infecções micobacterianas não tuberculosas^{2,6} e a tuberculose activa.²

Os dados acima baseiam-se em estudos observacionais e é difícil descartar a confusão residual. Por exemplo, no estudo de Eklöf *et al*, foi efetuado um ajuste para os casos em que os antibióticos haviam sido administrados no ano anterior, mas não para a frequência com que foram prescritos. Também é de notar que o resultado do estudo foi qualquer isolamento de *P. aeruginosa*, e isto não implica necessariamente colonização. No entanto, no seu conjunto, estes estudos mostram que o uso de ICS aumenta indubitavelmente o risco de infecções respiratórias na DPOC. Isto é problemático pois a pneumonia, as infecções por

P. aeruginosa e as infecções micobacterianas estão associadas a um maior risco de hospitalização e mortalidade na DPOC.^{2,6}

Alguns estudos encontraram uma diferença intraclassas entre os ICS no risco de infecções respiratórias, com um risco mais elevado do propionato de fluticasona do que da budesonida.^{6,7} Por exemplo, a taxa de eventos de pneumonia por 100 pacientes-anos para fluticasona/salmeterol foi de 11.0 vs. 6.4 nos pacientes com DPOC tratados com budesonida/formoterol no estudo PATHOS.⁷ Resultados semelhantes foram relatados por Brode *et al*, onde a utilização de ICS foi associada a infecções micobacterianas não tuberculosas.⁶ Esta associação foi estatisticamente significativa para o propionato de fluticasona (OR ajustado 2.09, IC 95% 1.80 a 2.43), mas não para a budesonida (OR ajustado 1.19, IC 95% 0.97 a 1.45). No estudo de Eklöf *et al*, não se verificou, contudo, qualquer diferença entre os diferentes compostos de ICS no que diz respeito ao risco de apresentar uma cultura positiva de *P. aeruginosa*.⁵

Provavelmente, o mecanismo por trás do aumento do risco de infecções respiratórias em pacientes tratados com ICS é o efeito imunossupressor, com uma diminuição da função das células T, macrófagos e neutrófilos no pulmão.² O tratamento com ICS na DPOC está associado a outros efeitos secundários, tais como candidíase orofaríngea, afinamento da pele e hematomas fáceis.⁸ Também existem indícios de que a utilização de ICS aumenta o risco de osteoporose.^{8,9} Como exemplo, num estudo observacional publicado recentemente, a prevalência de eventos relacionados com a osteoporose (fratura, diagnóstico e/ou medicação para a osteoporose) foi de 25% em pacientes com DPOC tratados com doses elevadas de ICS comparativamente a 19% em pacientes com DPOC tratados com ICS.⁹

Contudo, os efeitos secundários indesejados dos ICS na DPOC devem ser equilibrados com os benefícios que este tipo de tratamento tem em muitos pacientes com DPOC. Estes benefícios incluem um risco reduzido de agudizações^{3,4} e a melhoria do estado de saúde e da função pulmonar.^{1,3} Dois RCT recentes também relataram uma menor mortalidade em pacientes tratados com ICS em combinação com LABA e antagonistas muscarínicos de ação prolongada (LAMA) comparativamente a pacientes a receber LAMA/LABA.^{3,4} Por exemplo, no estudo *Efficacy and Safety of Triple Therapy in Obstructive Lung Disease*, a mortalidade foi 46% mais baixa nos pacientes tratados com ICS/LABA/LAMA do que nos pacientes tratados com LAMA/LABA.⁴

Ao usar ICS na DPOC, o desafio é identificar os pacientes em que os benefícios ultrapassam os riscos. Numa revisão de 2018¹⁰, que também foi incluída na Iniciativa Global para a Doença Pulmonar Obstrutiva <https://www.gold.org/>, Agusti *et al* dividiram os pacientes com DPOC em três grupos: pacientes em que os ICS devem ser evitados, pacientes em que os ICS podem ser considerados e pacientes em que há um forte apoio aos ICS.¹⁰ Os pacien-

tes em que os ICS devem ser evitados foram aqueles com eventos repetidos de pneumonia, níveis de eosinófilos sanguíneos (B-Eos) abaixo de 100 células/ μ L ou um histórico de infecções micobacterianas. Contrariamente, existe um forte apoio aos ICS nos pacientes que têm um histórico de asma, nos pacientes com agudizações repetidas e nos pacientes com um B-Eos superior a 300 células/ μ L. Este é um excelente começo, mas são necessárias ferramentas de risco-benefício mais sofisticadas. Atualmente, apenas um biomarcador, o B-Eos, é utilizado na prática clínica da DPOC. A categorização futura do risco-benefício pode incluir outros biomarcadores que avaliem a função dos neutrófilos, dos linfócitos e dos macrófagos. Outras ferramentas para esta avaliação podem ser a TC torácica (classificação de enfisema, espessamento brônquico e bronquiectasias), espirometria, manifestações clínicas (tosse produtiva ou não produtiva, nível de dispneia), capacidade física, estado nutricional e comorbilidades.

O artigo de Eklöf *et al* mostra uma associação dependente da dose entre o risco de infecções por *P. aeruginosa* e o tratamento com ICS na DPOC.⁴ Este resultado apoia ainda mais que os ICS não devem ser utilizados de forma acrítica na DPOC. O desafio que se coloca é o de trabalhar mais arduamente na identificação dos pacientes com DPOC que poderão beneficiar de ICS e daqueles em que o tratamento com ICS deve ser evitado.

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Dá ritmo à vida^{2,3*}

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

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

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

NOTA: Antes de prescrever consulte o RCM do medicamento. APRESENTAÇÃO: Pó para inalação, cápsula (pó para inalação). Cada cápsula contém 150 microgramas de indacaterol, 50 microgramas de glicopirrônio e 160 microgramas de furoato de mometasona. Cada dose libertada (a dose libertada através do aplicador bucal do inalador) contém 114 microgramas de indacaterol (na forma de acetato), 8 microgramas de brometo de glicopirrônio equivalente a 46 microgramas de glicopirrônio e 136 microgramas de furoato de mometasona. **Excipiente(s) com efeito conhecido:** Cada cápsula contém 25 mg de lactose mono-hidratada. **INDICAÇÕES:** Zimbus Breezhaler está indicado como terapêutica de manutenção da asma em doentes adultos não controlados adequadamente com uma associação de um agonista beta₂ de ação prolongada e uma dose alta de corticosteroide inalado em regime de manutenção que experimentaram uma ou mais exacerbações da asma no ano anterior. **POSOLOGIA: Adultos:** A dose recomendada é uma cápsula inalada uma vez por dia. A dose máxima recomendada é de 114 µg/46 µg/136 µg uma vez por dia. **Doentes pediátricos (< 18 anos):** Não recomendado em doentes com menos de 18 anos de idade. **Populações especiais: População idosa:** Não é necessário ajuste de dose em doentes idosos (65 anos de idade ou mais). **Compromisso renal:** Não é necessário ajuste de dose em doentes com compromisso renal ligeiro a moderado. Deve ter-se precaução em doentes com compromisso renal grave ou doença renal terminal que necessitem de diálise. **Compromisso hepático:** Não é necessário ajuste de dose em doentes com compromisso hepático ligeiro a moderado. Não existem dados disponíveis sobre a utilização deste medicamento em doentes com compromisso hepático grave, como tal deve ser utilizado nestes doentes apenas se o benefício esperado superar o risco potencial. **Modo de administração:** Apenas para utilização por via inalatória. As cápsulas não podem ser engolidas. Os doentes que não sintam melhorias na sua respiração devem ser questionados se estão a engolir o medicamento em vez de o inalar. As cápsulas têm de ser administradas usando apenas o inalador Zimbus Breezhaler. O tratamento deve ser administrado à mesma hora do dia todos os dias. Pode ser administrado independentemente da hora do dia. Após a inalação, os doentes devem lavar a boca com água sem engolir. Se for omitida uma dose, esta deve ser tomada assim que possível. Os doentes devem ser instruídos a não tomarem mais do que uma dose por dia. As cápsulas de Zimbus Breezhaler devem ser sempre conservadas no blister para proteger da luz e humidade, e só podem ser removidas do blister imediatamente antes da utilização. **CONTRAINDICAÇÕES:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **ADVERTÊNCIAS/PRECAUÇÕES:** ♦ **Asma Aguda:** não deve ser utilizado para tratar sintomas agudos de asma, incluindo episódios agudos de broncospasma, para os quais é necessário um broncodilatador de curta ação. ♦ **Hipersensibilidade:** Se ocorrer uma reação de hipersensibilidade, Zimbus Breezhaler deve ser descontinuado imediatamente e deverá ser instituída terapêutica alternativa. ♦ **Broncospasma paradoxal:** Tal como com outra terapêutica inalatória, a administração deste medicamento pode resultar em broncospasma paradoxal, o qual pode colocar a vida em risco. Se tal ocorrer, o tratamento deve ser interrompido imediatamente e deverá ser instituída terapêutica alternativa. ♦ **Efeitos cardiovasculares:** Tal como outros medicamentos contendo agonistas adrenérgicos beta₂, este medicamento pode produzir um efeito cardiovascular clinicamente significativo em alguns doentes conforme avaliado através de aumentos na frequência cardíaca, pressão arterial e/ou sintomas, alterações do electrocardiograma (ECG). Este medicamento deve ser usado com precaução em doentes com patologias cardiovasculares (doença arterial coronária, enfarte agudo do miocárdio, arritmias cardíacas, hipertensão, suspeita ou confirmação de prolongamento do intervalo QT, distúrbios convulsivos ou tirotóxicose e em doentes com resposta aumentada aos agonistas adrenérgicos beta₂). ♦ **Hipocalcemia:** Os agonistas adrenérgicos beta₂ podem causar uma hipocalcemia significativa em alguns doentes, o que potencialmente pode levar a reações adversas cardiovasculares. Em doentes com asma grave, a hipocalcemia pode ser potenciada pela hipoxia e pela terapêutica concomitante, o que pode aumentar a suscetibilidade a arritmias cardíacas. ♦ **Hiperglicemia:** A inalação de doses elevadas de agonistas adrenérgicos beta₂ e corticosteroides pode produzir um aumento da glicose plasmática. Nos doentes diabéticos, ao iniciar o tratamento, a glicose plasmática deve ser monitorizada mais cuidadosamente. ♦ **Efeitos anticolinérgicos:** Tal como com outros medicamentos anticolinérgicos, este medicamento deve ser utilizado com precaução em doentes com glaucoma de ângulo fechado ou retenção urinária. ♦ **Doentes com compromisso renal grave:** Nos doentes com compromisso renal grave (taxa de filtração glomerular estimada inferior a 30 mL/min/1,73 m²), incluindo aqueles com doença renal terminal que necessitam de diálise, deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. ♦ **Prevenção de infeções orofaríngeas:** De modo a reduzir o risco de infeção orofaríngea por *Candida albicans*, os doentes devem ser aconselhados a lavar a boca ou a gargarejar com água, sem a engolir, ou a lavar os dentes após inalar a dose prescrita. ♦ **Efeitos sistémicos dos corticosteroides:** Podem ocorrer efeitos sistémicos dos corticosteroides inalados, principalmente no caso de doses elevadas prescritas por períodos prolongados. Os efeitos sistémicos possíveis podem incluir: síndrome de Cushing, manifestações Cushingóides, supressão adrenal, atraso do crescimento em crianças e adolescentes, diminuição da densidade mineral óssea, cataratas, glaucoma e, mais raramente, uma série de efeitos psicológicos ou comportamentais incluindo hiperatividade psicomotora, distúrbios do sono, ansiedade, depressão ou agressão (especialmente em crianças). Como tal, é importante que a dose de corticosteroide inalado seja titulada para a dose mais baixa na qual o controlo efetivo da asma é mantido. Podem ser notificados distúrbios visuais como o uso de corticosteroides sistémicos ou tópicos (incluindo intranasais, inalados ou intraoculares). Doentes que apresentem sintomas como visão turva ou outros distúrbios visuais, devem ser considerados para encaminhamento para um oftalmologista para avaliação de possíveis causas dessas perturbações visuais, as quais podem incluir cataratas, glaucoma ou doenças raras como a coriorretinopatia central serosa (CRCS), que foram notificadas após o uso de corticosteroides sistémicos ou tópicos. Este medicamento deve ser administrado com precaução em doentes com tuberculose pulmonar ou em doentes com infeções crónicas ou não tratadas. ♦ **Gravidez:** Este medicamento deve ser utilizado durante a gravidez apenas se o benefício esperado para o doente justificar o potencial risco para o feto. ♦ **Amamentação:** Tem que ser tomada uma decisão sobre a descontinuação da amamentação ou a descontinuação/abstenção da terapêutica, tendo em conta o benefício da amamentação para a criança e o benefício da terapêutica para a mulher. ♦ **Trabalho de parto:** Como outros medicamentos contendo agonistas adrenérgicos beta₂, o indacaterol pode inibir o trabalho de parto devido a um efeito relaxante no músculo liso uterino. **INTERAÇÕES:** ♦ **Bloqueadores adrenérgicos beta:** este medicamento não deve ser administrado com bloqueadores adrenérgicos beta₂ (incluindo gotas para os olhos) a menos que existam razões importantes para a sua utilização. ♦ **Medicamentos conhecidos por prolongarem o intervalo QTc:** este medicamento deve ser administrado com precaução a doentes que estejam a ser tratados com inibidores da monoamina oxidase, antidepressivos tricíclicos ou medicamentos conhecidos por prolongar o intervalo QT. ♦ **Tratamento hipocalémico:** O tratamento hipocalémico concomitante com derivados da metilxantina, esteróides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocalémico dos agonistas adrenérgicos beta₂. ♦ **Interação com inibidores do CYP3A4 e da glicoproteína P:** A inibição do CYP3A4 e da glicoproteína P (gp-P) não tem impacto na segurança de doses terapêuticas de Zimbus Breezhaler. ♦ **Outros antimuscarínicos de ação prolongada e agonistas adrenérgicos beta:** a coadministração deste medicamento com outros medicamentos contendo antagonistas muscarínicos de ação prolongada ou agonistas adrenérgicos beta₂ de ação prolongada não foi estudada e não é recomendada. ♦ **Cimetidina ou outros inibidores do transporte de catiónes orgânicos:** Não é esperada qualquer interação medicamentosa clinicamente relevante. **EFEITOS INDESEJÁVEIS:** ♦ **Frequentes (≥1% a <10%) e potencialmente graves:** hipersensibilidade. ♦ **Muito frequentes:** asma (exacerbação), nasofaringite. ♦ **Frequentes (≥1% a <10%):** infeção do trato respiratório superior, candidíase, infeção do trato urinário, cefaleia, taquicardia, dor orofaríngea, tosse, disfonia, gastroenterite, dor musculoesquelética, espasmos musculares, piroxia. ♦ **Pouco frequentes (≥0,1% a <1%):** hiperglicemia, cataratas, boca seca, erupção cutânea, prurido, disúria. Para mais informações, consultar o titular de autorização de introdução no mercado ou o representante local do titular de autorização de introdução no mercado. Medicamento sujeito a receita médica. **Escalação de comparticipação:** Escalão B. **Titular da AIM:** Novartis Europharm Limited. **Representante local:** Laboratório Medinfar - Produtos Farmacêuticos, S.A. - Rua Henrique de Paiva Couceiro, N° 29, Venda Nova, 2700-451 Amadora. Informações Essenciais Compatíveis com o Resumo das Características do Medicamento (ZIM_RCM2010422_JEC_v2).

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LABORATÓRIO

Cuidado, o uso de cigarros eletrônicos próximo de crianças está a ter um impacto negativo na sua saúde pulmonar

Ana Lucia Fuentes,^{1,2} Laura E Crotty Alexander^{1,2}

Os cigarros eletrônicos são dispositivos manuais que aquecem e aerossolizam líquidos que normalmente consistem em propilenoglicol, glicerol, aromatizantes químicos e nicotina (ou tetrahydrocannabinol).¹ Estes dispositivos foram inicialmente comercializados como substitutos de nicotina de menor risco, mas as evidências no sentido contrário são cada vez maiores. Mais preocupante ainda é que o marketing tem visado a população adolescente vulnerável, com 78% dos estudantes do ensino médio e secundário expostos a pelo menos um anúncio de cigarros eletrônicos entre 2014 e 2016.² De interesse é a forma como estas estratégias de marketing provavelmente contribuíram para a desinformação em torno dos cigarros eletrônicos. Pepper *et al* exploraram o entendimento dos adolescentes relativamente aos cigarros eletrônicos e descobriram percepções erradas sobre a nicotina e os líquidos eletrônicos entre os participantes.³ Descobriram que 62% dos utilizadores de *vaping* sem nicotina e 49% dos utilizadores de *vaping* com nicotina pensavam que a nicotina nos líquidos eletrônicos era feita artificialmente e não a partir do tabaco. Isto pode indicar que existe uma percepção errada de que algumas formas de nicotina são mais seguras do que outras. Adicionalmente, descobriram que os adolescentes que acreditavam estar a usar cigarros eletrônicos sem nicotina apresentavam um conhecimento geral mais fraco sobre os cigarros eletrônicos, o que pode levar a confusão sobre quais os compostos que estão realmente a consumir.

Alguns podem sentir-se confortáveis com os estudos que argumentam que o uso de nicotina não tem aumentado com o aumento do *vaping*. Por exemplo, Miech *et al.* descobriram que mais estudantes do ensino secundário relataram que consomem *vaping* apenas aromatizado e não com nicotina.⁴ Contudo, é importante notar que o conteúdo de nicotina referido nos rótulos dos produtos e o que é quimicamente medido pode variar muito. Foi detetada nicotina em vários produtos rotulados como “nicotina zero”, com estudos que mostram até 23,9 mg/ml de nicotina encontrados nos cigarros eletrônicos “sem nicotina”.⁵ Isto significa que os utilizadores podem não ter consciência do que estão realmente

a consumir e, portanto, correm o risco de se tornarem involuntariamente viciados em nicotina. Adicionalmente, Marynak *et al.* descobriram que 99% das vendas de produtos de cigarros eletrônicos em 2015 continham nicotina, levando à conclusão de que os consumidores (incluindo jovens e adolescentes) estão muito provavelmente a utilizar produtos que contêm nicotina.⁶

Infelizmente, verificou-se um aumento dramático no uso de cigarros eletrônicos em adolescentes e jovens adultos.⁷ O uso de cigarros eletrônicos aumentou 900% entre os estudantes do ensino secundário entre 2011 e 2015.⁸ Os dispositivos de *vaping* são agora o produto de tabaco mais usado entre os jovens nos EUA.⁸ É difícil provar o grau em que as estratégias de marketing agressivas utilizadas pela indústria do tabaco contribuíram para este rápido aumento no uso de cigarros eletrônicos, mas uma empresa, a JUUL, perdeu recentemente um processo judicial de 40 milhões de dólares na Carolina do Norte devido ao impacto das suas práticas de marketing enganosas no uso de dispositivos eletrônicos com elevado teor de nicotina por parte de adolescentes. É lamentável que quaisquer cigarros eletrônicos tenham sido comercializados como “mais seguros” antes de existirem dados suficientes para que essa determinação se tornasse realidade.

Felizmente, dispomos agora de evidências sólidas sobre os impactos negativos do uso do cigarro eletrónico na saúde. Consequentemente, a *US Food and Drug Administration* aumentou a regulamentação dos cigarros eletrônicos à base de cartuchos aromatizados e aumentou a idade de venda do tabaco para 21.⁹ Embora seja estimulante e reconfortante saber que os cigarros eletrônicos estão finalmente a ser regulados pelos organismos apropriados, continua a ser dececionante que os produtos possam entrar e permanecer no mercado até que se prove que não são seguros, em vez de serem comprovadamente seguros antes de serem vendidos a crianças e adultos.

Embora as evidências relativas aos impactos negativos na saúde do *vaping* estejam a aumentar diariamente, existe uma escassez de dados relativos aos efeitos na saúde da exposição ao *vaping* com nicotina em segunda mão (SHNV). Esta ausência de evidências incentiva os *vapers* a utilizar os cigarros eletrônicos junto a amigos, familiares e conhecidos de modo negligente. Tal como os cigarros eletrônicos, parece que a exposição ao SHNV precisa de ser comprovada como sendo insegura antes de serem tomadas medidas para proteger o público. Felizmente, nesta edição da *Thorax*, com

artigos da ADC, edição portuguesa, Islam *et al* reportam dados que demonstram um aumento dos sintomas brônquicos e de falta de ar em indivíduos expostos a aerossóis de cigarros eletrônicos em segunda mão.¹⁰

Em contraste com a exposição a SHNV, existem evidências significativas sobre os riscos de saúde associados ao fumo de cigarros em segunda mão. Isto levou a campanhas generalizadas de proibição do fumo de cigarros em locais públicos. Infelizmente, isto não se traduziu na exposição ao SHNV. De facto, estudos demonstraram que os pais apresentavam mais probabilidades de adotarem políticas antitabaco do que políticas anti-*vaping*, o que apoia a percepção de que a exposição ao SHNV é menos prejudicial.¹¹

Devido a esta percepção e ao potencial nocivo, os achados relatados por Islam *et al* são de importância crítica. Embora associação não constitua causa, este estudo é o primeiro a descrever os efeitos negativos da exposição a SHNV em sintomas respiratórios. É necessário realizar mais estudos para provar que esta exposição causa danos diretamente. Em última análise, trata-se de uma preocupação de saúde pública que - se não for abordada - tem o potencial de afetar negativamente a nossa população, incluindo aqueles que são mais vulneráveis.

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Patient consent for publication Not applicable.

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Taxas nacionais e disparidades na vacinação infantil e doenças evitáveis por vacinação durante a pandemia de COVID-19: Estudo retrospectivo da base de dados da rede sentinela inglesa

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RESUMO

Objetivos Descrever as taxas e as variações na administração de vacinas contra pneumococos e sarampo, papeira e rubéola (MMR) em crianças e alterações associadas em doenças evitáveis pela vacinação (VPD) na primeira e segunda vagas da pandemia de COVID-19.

Métodos Estudo retrospectivo de base de dados de todas as crianças com idade <19 anos registradas numa unidade de medicina geral e familiar na rede de vigilância sentinela nacional inglesa do *Oxford Royal College of General Practitioners Research and Surveillance Centre* entre 2 de novembro de 2015 e 18 de julho de 2021.

Resultados A cobertura da dose de reforço da vacina pneumocócica diminuiu de 94,5% (95% IC 94,3% a 94,7%) no seu pico à semana 47 (2020) da Organização Internacional de Normalização (ISO) para 93,6% (95% IC 93,4% a 93,8%) até ao final do estudo. A cobertura da segunda dose de MMR diminuiu de 85,0% (95% IC 84,7% a 85,3%) no seu pico à semana 37 (2020) da ISO para 84,1% (95% IC 83,8% a 84,4%) até ao final do estudo. O ponto de rutura nas tendências para MMR foi à semana ISO 34 (2020) (95% IC semanas 32-37 (2020)), enquanto que, para a vacina pneumocócica, o ponto de rutura ocorreu mais tarde, à semana 3 ISO (2021) (95% IC semana 53 (2020) a semana 8 (2021)). A cobertura de vacinação para crianças de etnia branca apresentava menos probabilidades de diminuir relativamente a outras etnias. As taxas de consulta para VPD reduziram e permaneceram baixas desde agosto de 2020.

Conclusão As taxas de vacinação infantil começaram a reduzir antes do início da segunda vaga. Esta queda está a acentuar as disparidades étnicas, socioeconómicas e geográficas na utilização de vacinas e corre o risco de aumentar as disparidades sanitárias. O distanciamento social e o encerramento de escolas podem ter contribuído para taxas mais baixas de VPD associadas, mas pode existir um risco acrescido à medida que estas medidas forem levantadas.

INTRODUCTION

The UK national childhood immunisation programme aims to protect against serious diseases.¹ The programme has achieved high vaccination coverage in the population. This is important especially for measles, mumps and rubella (MMR) and pneumococcal vaccinations since these infections have high transmission rates in unvaccinated populations, and a wide range of potentially serious effects in those infected including pneumonia, meningitis and death.²⁻⁷

Through 2020/2021 there have been three waves of the COVID-19 pandemic in the UK with varying levels of social distancing, school closure and lockdowns in place.^{8,9} A systematic review of 17 observational studies during 2020 to assess the impact of the pandemic on childhood vaccination coverage found that there was a decline in the total number of vaccines administered and consequent reduction in coverage, with many children missing out on their vaccine doses.¹⁰ Results from a study in over 2600 primary care practices and >35 child health providers found that in the first 3 weeks of

Key messages

What is the key question?

► During the first wave of the COVID-19 pandemic in the UK, transient declines in preschool vaccinations were observed.

What is the bottom line?

► This study covering the impact of the second and third national lockdowns in the UK showed a small but significant decrease in coverage of measles, mumps and rubella and pneumococcal vaccines over the course of the study. This decrease in vaccine coverage varied by ethnicity, socioeconomic status and location.
► Consultations for vaccine-preventable diseases in primary care also decreased to negligible rates from August 2020.

Why read on?

► It is important to continue to monitor trends in childhood vaccination coverage during the pandemic, especially among children from ethnic minorities and lower socioeconomic groups, as reductions in coverage may lead to widening health disparities.

social distancing in 2020 in the UK, MMR vaccination counts were 19.8% lower (95% CI –20.7% to –18.9%) than for the same period in 2019.^{11,12} There were signs of a recovery by April 2020.¹³

We carried out this research to report any impact of the pandemic on vaccine uptake in children, especially MMR and pneumococcal vaccines, exploring any disparities in coverage over the duration of the pandemic, and to see if there was an impact on vaccine-preventable diseases (VPDs). We report on the first two completed waves, with the third wave ongoing.

METHODS

Study design, setting and data sources

We undertook a retrospective study nested within the English national influenza sentinel surveillance network run by the Oxford Royal College of General Practitioners Clinical Informatics Digital Hub (ORCHID). Previous studies demonstrated that the age-sex distribution of patients in the network is broadly similar to the English national census distribution.¹⁴ ORCHID data have been used for previous childhood vaccine research.¹⁵ The VPDs studied have been reported by the network in its weekly and annual reports for over 50 years.¹⁶

Participants

The study included data from all children aged <19 who were registered with a general practitioner

Table 1 Cross-sectional profile of population at start and end of the study compared with midyear population estimates from the Office for National Statistics

	Week 45 (2015)	ONS midyear 2015 population estimates for England ⁴⁹	Week 28 (2021)	ONS midyear 2020 population estimates for England ⁴⁹
Children included (n)	1 094 150	12 338 887	1 043 968	12 699 899
Ethnicity	White—593 032 (54.2%) Black—35 446 (3.2%) Asian—78 692 (7.2%) Other—12 148 (1.1%) Missing/unclassified—344 307 (31.5%)	White—8 903 313 (78.5%)* Black—562 333 (5.0%)* Asian—1 136 293 (10.0%)* Other—145 004 (1.3%)* Missing/unclassified—NA*	White—500 162 (47.9%) Black—34 008 (3.3%) Asian—71 753 (6.9%) Other—15 555 (1.5%) Missing/unclassified—390 766 (37.4%)	NA
IMD quintile	1 (most deprived)—233 093 (21.3%) 5 (least deprived)—242 733 (22.2%)	1 (most deprived)—2 962 565 (24.0%) 5 (least deprived)—2 301 477 (18.7%)	1 (most deprived)—226 230 (21.7%) 5 (least deprived)—218 708 (20.9%)	1 (most deprived)—3 018 135 (23.8%) 5 (least deprived)—2 352 108 (18.5%)
Living in urban/rural settings	Conurbation—407 092 (37.2%) Urban—506 868 (46.3%) Rural—180 173 (16.5%)	Conurbation and urban—10 505 165 (80.8%)† Rural—2 500 562 (19.2%)†	Conurbation—405 644 (38.9%) Urban—455 314 (43.6%) Rural—182 948 (17.5%)	Conurbation—5 835 864 (43.1%)† Urban—4 948 489 (36.6%)† Rural—2 994 260 (22.1%)†

*From 2011 census for ages 0–17 years.⁵⁰
†From statistical digest of rural England for ages 0–19 years.⁵¹
IMD, Index of Multiple Deprivation; NA, not applicable; ONS, Office for National Statistics.

between 2 November 2015 and 18 July 2021. We compared any change in birth rate with that reported by the Office for National Statistics (ONS).¹⁷

Variables

We extracted data on age, gender and ethnicity which were recorded using an ontology to maximise identification,¹⁸ socioeconomic status measured using the Index of Multiple Deprivation (IMD)^{19 20} and rurality using the ONS classification based on individual-level postcode.²¹ We have used practice postcode to assign IMD and household setting where no valid patient postcode was available (~3%).

We also extracted vaccination status and consultations for VPDs from the pseudonymised vaccination record and computerised medical records of all children <19 within the network using the Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT).²²

Statistical analysis

Calculation of childhood vaccination rates and rates of VPDs

Weekly vaccination coverage for the first dose of MMR was calculated by dividing the number of children <2 who had been given one dose of MMR by the number of children <2 registered within the ORCHID network that week. Coverage for the second dose of MMR was calculated similarly for children <5 who had been given two doses.

Weekly vaccination coverage for the first dose of pneumococcal vaccine was calculated by dividing the number of children <1 who had been given one dose of pneumococcal vaccine by the number of children <1 registered within the ORCHID network that week. Coverage for the booster dose of pneumococcal vaccine was calculated similarly for children <2 who had been given two doses. To account for the change from a three-dose schedule in 2020,²³ our definition of pneumococcal vaccine coverage prior to 1 January 2020 counted children who had had three doses of pneumococcal

vaccine. The second/third dose of pneumococcal vaccine will be referred to as booster dose of pneumococcal vaccine henceforth.

Weekly VPD rates were calculated by dividing the total number of consultations for VPDs per week by the number of children registered within the ORCHID network. The list of vaccines, VPDs and their associated SNOMED-CTs used for this study is included in online supplemental appendix 1.

Data are presented graphically by the International Organization for Standardization (ISO) week.²⁴

Segmental linear regression analysis and examination of inequalities in vaccination trends

Linear regression was used to model trends in vaccination coverage and to identify inequalities by ethnicity, IMD and urban/rural location.

Segmental linear regression analysis was used to identify any break points in the vaccination trends. This regression analysis uses an iterative process to estimate the slopes and break points in generalised linear models which have one or more segmented relationships in the predictor.²⁵

Inequalities in coverage following break points in the vaccination trend were of particular interest, thus an interaction term between ethnicity and break point was added to the regression model. Similar analysis was undertaken to examine the inequalities by IMD and urban/rural location.

Statistical analyses were undertaken using R V.3.5.1.

Ethical considerations

This study was classified as a service evaluation (measuring what standard of care is achieved) by the Medical Research Council/Health Research Authority decision tools²⁶ so did not require formal ethics approval; it was approved by the RCGP Approval Committee (data request ORC_05_2020). This study does not include patients who opted out of record sharing, approximately 2%.

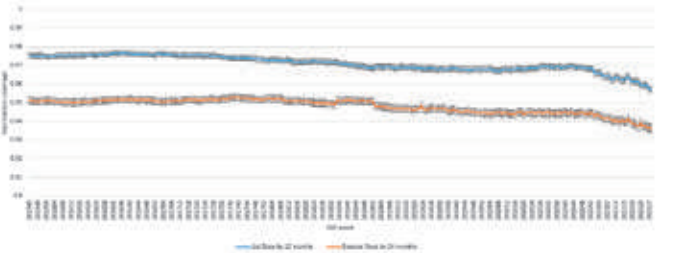


Figure 1 Trends in weekly pneumococcal vaccination rates (and 95% CI) over the last 5 years. ISO, International Organization for Standardization.

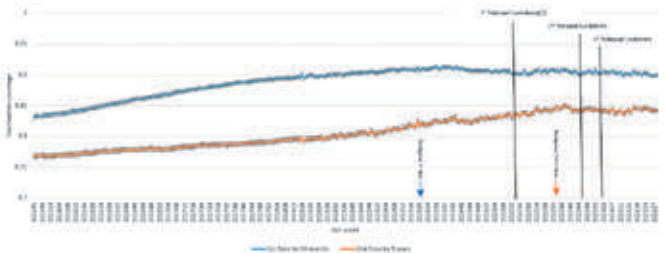


Figure 2 Trends in weekly measles, mumps and rubella (MMR) vaccination rates (and 95% CI) over the last 5 years. ISO, International Organization for Standardization.

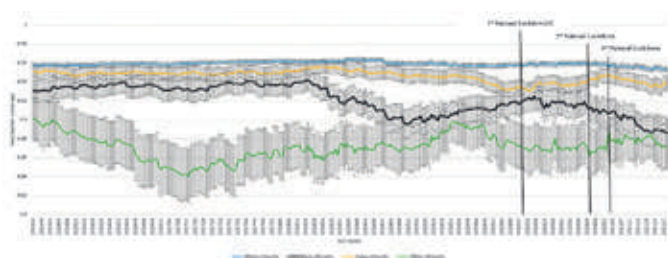


Figure 3 Trends in weekly rates of coverage of booster dose of pneumococcal vaccine (and 95% CI) over the last 5 years by ethnicity. ISO, International Organization for Standardization.

RESULTS

The population

The number of registered children <19 whose data contributed to the analysis reduced from 1 094 150 in 2015 to 1 043 968 in 2021 (see table 1). This fall of 4.6% is smaller than the decrease in the proportion of live births over this period of 11.8% reported by ONS.^{27 28} There was a 6.3% lower proportion of children of white ethnicity over the course of the study, while the proportion of births of children of white ethnicity decreased by 3.7% between 2015 and 2019.^{27 29}

Trends in childhood vaccinations

Coverage of pneumococcal booster doses decreased from 94.5% (95% CI 94.3% to 94.7%) on ISO week 47 (2020) to 93.6% (95% CI 93.4% to 93.8%) by the end of the study. In turn, coverage of the second dose of MMR decreased from 85.0% (95% CI 84.7% to 85.3%) on ISO week 37 (2020) to 84.1% (95% CI 83.8% to 84.4%) by the end of the study (see figures 1 and 2).

Segmental linear regression analysis showed that the break point in trends for booster dose of pneumococcal vaccine was at ISO week 3 (2021) (95% CI ISO week 53 (2020) to week 8 (2021)), while the break point for trends in the second dose of MMR was at ISO week 34 (2020) (95% CI ISO weeks 32–37 (2020)). The segmental regression analysis showed that the break point in trends for the first dose of MMR was at ISO week 21 (2019) (95% CI ISO week 18 (2019) to week 23 (2019)), while the break point in trends for the first dose of pneumococcal vaccine was at ISO week 53 (2020) (95% CI ISO week 49 (2020) to week 4 (2021)).

Vaccination coverage had reduced for children of all ethnicities (see figures 3 and 4). Coverage declined less in children of white ethnicity than other ethnic groups following the break point, especially for the second doses of MMR. Compared with children of white ethnicity, coverage of the second dose of MMR following the break point reduced by −0.041 (95% CI −0.045 to −0.038) per week for children of black ethnicity and −0.002 (95% CI −0.005 to −0.0009) per week for children of Asian ethnicity.

The reduction in coverage of pneumococcal booster doses per week following the break point was −0.0071 (95% CI −0.0097 to −0.0045) for children of black ethnicity compared with children of white ethnicity. In contrast, coverage of pneumococcal booster doses increased by 0.0084 (95% CI 0.0104 to −0.0068) per week for children of Asian ethnicity compared with children of white ethnicity (see table 2). Similar inequalities were observed for coverage by urban/rural location (see table 3 and figures 5 and 6).

For each quintile increase in IMD, the average rate of change in second dose of MMR coverage was 0.0099 (95% CI 0.0092 to 0.0105),

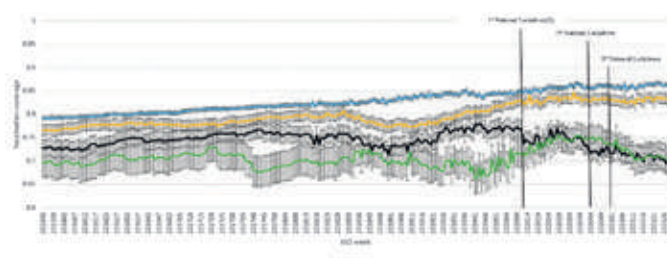


Figure 4 Trends in weekly rates of coverage of second dose of measles, mumps and rubella (MMR) (and 95% CI) over the last 5 years by ethnicity. ISO, International Organization for Standardization.

while the average change in coverage of pneumococcal booster doses was 0.0014 (95% CI 0.00091 to 0.0018) (see figures 7 and 8).

Trends in VPDs over the last 5 years

Presentation of VPDs had reduced to negligible rates by week 32 (2020). Figure 9 showed that the break point in trends for mumps disease rates was within 1 week of the first national lockdown. The break points in trends for VPD rates were less clearly associated with the national lockdowns.

DISCUSSION

Principal findings

The COVID-19 pandemic has had a small but significant effect on coverage of childhood pneumococcal and MMR vaccinations.

Coverage for pneumococcal booster doses at the end of our study was 93.6% (95% CI 93.4% to 93.8%). This is comparable to data published by Public Health England (PHE) which showed that pneumococcal conjugate vaccine coverage in children 12 months of age was 93.4% in the first quarter of 2021.³⁰

In turn, the coverage for second dose of MMR at the end of our study was 84.1% (95% CI 83.8% to 84.4%), which is lower than the published data which showed MMR coverage in children 24 months of age was 89.3% in the first quarter of 2021.³⁰

There were significant ethnic, socioeconomic and urban/rural differences in vaccination coverage, especially for MMR.

In our study, so far, there have been no recorded increases in VPDs among children, with negligible consultation rates for most VPDs. This may have been confounded by cases not presenting to healthcare or by cases presenting to parts of the National Health Service (NHS) other than general practice, with a subsequent delay in reporting and recording in the primary care record. Data from the WHO for all four nations of the UK showed that between 2019 and 2020, the number of cases of measles had reduced by 91.3%, mumps by 31.2% and rubella by 100%. In contrast, globally between 2019 and 2020, measles cases reduced by 82.8%, mumps increased by 157.8% and rubella reduced by 79.3%.³¹

Strengths and weaknesses

The strengths of our study include its large sample size from a nationally representative sentinel network, the long period covered with weekly vaccine coverage rates, including data covering the second and third national lockdowns; and that we covered trends in both vaccine coverage and VPD rates.

A limitation of our study involves the quality of recording in routinely collected data. Our sentinel network has been involved in monitoring respiratory infections and vaccinations for over 50

Table 2 Average reduction in vaccine coverage per week following the break point by ethnicity (95% CI)

Ethnicity	Booster dose of pneumococcal vaccine Break point: week 3 (2021) (95% CI week 53 (2020) to week 8 (2021))	Second dose of MMR vaccine Break point: week 34 (2020) (95% CI weeks 32–37 (2020))
White	Reference group	Reference group
Black	−0.0071 (95% CI −0.0097 to −0.0045)	−0.041 (95% CI −0.045 to −0.038)
Asian	0.0084 (95% CI 0.0063 to 0.0105)	−0.002 (95% CI −0.005 to −0.0009)
Other	0.0156 (95% CI 0.0129 to 0.0184)	−0.011 (95% CI −0.015 to −0.0071)

MMR, measles, mumps and rubella.

Table 3 Average reduction in vaccine coverage per week following the break point by urban/rural location (95% CI)

Urban/rural location	Booster dose of pneumococcal vaccine Break point: week 3 (2021) (95% CI week 53 (2020) to week 8 (2021))	Second dose of MMR vaccine Break point: week 34 (2020) (95% CI weeks 32–37 (2020))
Urban	Reference group	Reference group
Conurbation	0.0016 (95% CI 0.000 to 0.0031)	–0.0209 (95% CI –0.0229 to –0.0188)
Rural	–0.0020 (95% CI –0.0038 to –0.0002)	0.0049 (95% CI 0.0025 to 0.0073)

MMR, measles, mumps and rubella.

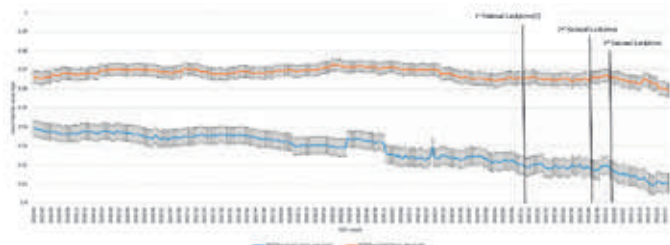


Figure 5 Trends in weekly rates of coverage of booster dose of pneumococcal vaccine (and 95% CI) over the last 5 years by Index of Multiple Deprivation (IMD). ISO, International Organization for Standardization.

years and has had regular feedback on data quality.^{14 16} Another limitation relates to the duration of our study, which covered a number of changes to the childhood vaccination schedule, including the change to a two-dose pneumococcal conjugate vaccine schedule in 2020. Changes to the two-dose pneumococcal vaccine schedule have been taken into account in this study, although the broader changes in the childhood vaccination programme have not been adjusted for in this analysis. Our study only covered two vaccinations as these infections have high transmission rates in unvaccinated populations, and the resulting VPDs associated with low vaccine coverage are likely to be the first to become apparent. However, the trends in these two vaccinations may not reflect the trend in all childhood vaccination rates, especially those provided outside primary care.

It is important to note that changes in coverage associated with marked reductions in vaccine administrations will be delayed.³² For example, most children who turn 2 years of age during the early months of the pandemic will have received the first dose of MMR and the pneumococcal booster well before the start of the pandemic. Therefore, changes in coverage that occur because of decreased vaccine administrations during the pandemic will not be seen until weeks when a substantial proportion of children have turned 2 years old. Our methodology for calculating vaccination coverage has allowed us to compare our results directly with national published statistics.³⁰ However, as our study takes in a larger window of observation than stipulated by the NHS vaccination schedule, it may be less sensitive to secular trends in coverage.³²

Finally, our definition of VPDs included pneumonia or pneumonitis, not all of which are vaccine-preventable cases. Conversely, in the setting of COVID-19, care-seeking patterns might be quite different for respiratory illnesses in particular, and some cases of COVID-19 (particularly among adolescents) might be classified as 'pneumonia or pneumonitis' under the definition that we have used.

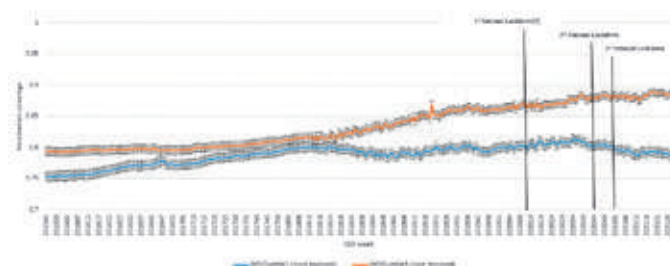


Figure 6 Trends in weekly rates of coverage of second dose of measles, mumps and rubella (MMR) (and 95% CI) over the last 5 years by Index of Multiple Deprivation (IMD). ISO, International Organization for Standardization.

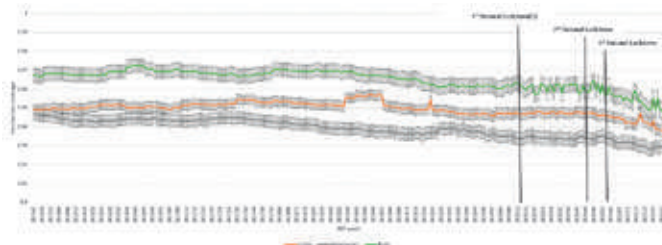


Figure 7 Trends in weekly rates of coverage of booster dose of pneumococcal vaccine (and 95% CI) over the last 5 years by rural/urban location. ISO, International Organization for Standardization.

Interpretation, unanswered questions and need for further work

It is reassuring that this large representative data set indicates general practice delivery of childhood immunisations has remained good, especially during the first lockdown. Our study is comparable to data from WHO and PHE,^{30 31 33 34} although the coverage rates for MMR are lower in our data set than the PHE. This may be the result of some vaccinations being given in community settings not attached to a general practitioner.

Our results show that pneumococcal vaccine coverage has been declining steadily over time and accelerated in the pandemic. In contrast, MMR coverage seemed to be increasing but this plateaued in the pandemic. There are a number of possible explanations for this observed decline in these childhood vaccination rates, including the pivotal role general practice has played in the national COVID-19 vaccine implementation.³⁵ Early studies showed that general practice-led sites delivered two in three of all COVID-19 vaccinations in England between December 2020 and April 2021,³⁶ this may have impacted capacity for routine vaccinations during the period of our study.

There are a number of possible explanations for the differential decline in coverage by ethnicity, socioeconomic status and geographical location. Ethnic and socioeconomic differences in parents' perception of the importance of immunisations, whether immunisations were permitted or culturally acceptable and their understanding of immunisation schedules have been shown to affect immunisation decisions.^{37 38} Recent research on COVID-19 vaccines have found a marked difference in vaccine hesitancy by race/ethnicity,^{39–41} with a much greater proportion of ethnic minority populations expressing concern about side effects and the long-term effects of vaccines on health. Some have capitalised on this lack of trust in vaccines to spread misinformation.⁴² This differential decline in coverage may also reflect access barriers,

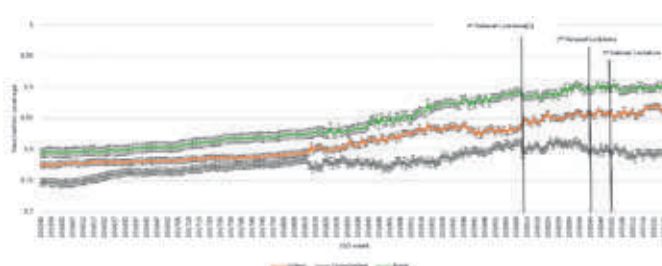


Figure 8 Trends in weekly rates of coverage of second dose of measles, mumps and rubella (MMR) (and 95% CI) over the last 5 years by rural/urban location. ISO, International Organization for Standardization.

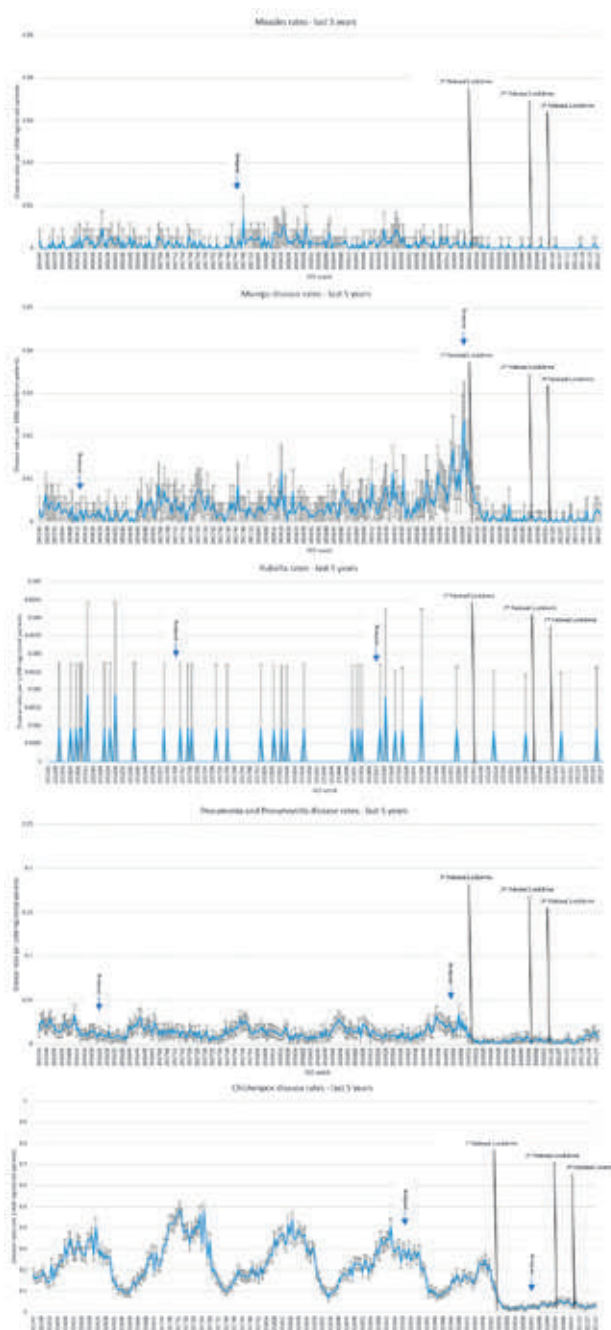


Figure 9 Trends in weekly vaccine-preventable disease (VPD) rates over the last 5 years. ISO, International Organization for Standardization.

including difficulties in accessing vaccination appointments during the pandemic.^{43–45} Thus, it is important to continue to monitor these trends to record any reduction in coverage from the second and third lockdowns, especially among ethnic minority groups and lower socioeconomic groups which will lead to widening health disparities.^{38 46}

These data show that there may be an increasing risk of preventable serious childhood diseases if the modest reductions in vaccination rates are not rapidly reversed especially in those populations with greater rates of decline.^{47 48} The drive to offer COVID-19 booster vaccinations in adults and the expansion of COVID-19 vaccinations for children should not be at the expense of routine childhood immunisation rates.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was classified as a service evaluation (measuring what standard of care this service achieved) by the Medical Research Council/Health Research Authority decision tool so did not require formal ethics approval; it was approved by the Royal College of General Practitioners (RCGP) Approval Committee (data request number: ORC_05_2020). This study does not include patients who opted out of record sharing, approximately 2%.

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Aplicação em telessaúde de um espirômetro ultrassônico doméstico

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RESUMO

Objetivo Investigar a validade e a utilização doméstica de um espirômetro ultrassônico pessoal.

Métodos Foi realizada uma espirometria supervisionada com recurso a equipamento de laboratório e a um espirômetro ultrassônico pessoal. Adicionalmente, foi avaliada a capacidade de as crianças para realizarem uma espirometria aceitável durante as consultas supervisionadas de telessaúde em casa.

Resultados 59 crianças completaram a espirometria em ambos os dispositivos. Verificou-se um elevado coeficiente de correlação intraclasse (ICC) entre os dispositivos para volume expiratório forçado em 1s (FEV₁) e a capacidade vital forçada (FVC): ICC 0,991 (95% IC 0,985 a 0,995) e 0,989 (95% IC 0,981 a 0,993), respetivamente. A análise Bland-Altman revelou a média de enviesamento e os limites de concordância de -0,01 (-0,22 a 0,24) L para FEV₁, e de -0,02 (-0,30 a 0,33) L para FVC. 125 de 140 (89%) sessões de espirometria em telessaúde supervisionada foram aceitáveis.

Conclusão Verificou-se uma excelente fiabilidade entre medições do dispositivo. Contudo, os limites de concordância foram amplos. Por conseguinte, é necessário ter atenção no caso de o dispositivo ser utilizado alternadamente com equipamento de laboratório. As elevadas taxas de sucesso das sessões de espirometria em telessaúde indicam que o dispositivo é adequado para esta aplicação.

INTRODUCTION

Outpatient assessment and management of children with chronic lung disease has traditionally been performed face-to-face during outpatient reviews. Telehealth is an alternative model of care which allows the child to remain at home. Telehealth utilisation increased in response to the SARS-CoV-2 pandemic and increased use is likely to continue.¹ Increased utilisation of telehealth presents challenges to healthcare teams in ensuring safe and effective healthcare delivery.

An example of a challenge to ensuring best care with increased telehealth use is the assessment of respiratory function using spirometry. Regular spirometry is recommended in children with chronic respiratory diseases such as asthma and cystic fibrosis, as the results assist with diagnosis, disease monitoring and treatment modifications. Valid assessment is reliant on accurate, usable devices. The accuracy of personal spirometers which use turbine technology has been established.² Recently, ultrasonic sensor technology has been incorporated into personal spirometers. Ultrasonic spirometers are advantageous over turbine spirometers as they use an ultrasonic transmitter and receiver to measure flow and volume, which eliminates the need for device recalibration or replacement of precalibrated turbine heads. However, the accuracy and usability of personal ultrasonic spirometers are yet to be established.

The first aim of this study was to determine the accuracy of spirometry results recorded using a personal ultrasonic spirometer. Second, this study aimed to assess the ability of children to perform acceptable and reproducible (A&R) spirometry in the home environment during supervised telehealth consultations.

What is already known on this topic?

- ▶ There has been an increased utilisation of telehealth for respiratory medicine consultations since the onset of the SARS-CoV-2 pandemic.
- ▶ Serial measurement of lung function is an important assessment tool in children with chronic lung disease.

What this study adds?

- ▶ A new, personal ultrasonic spirometer correlates well with laboratory equipment; however, the limits of agreement are wide, suggesting different devices should not be used interchangeably.
- ▶ A high percentage of children can perform successful spirometry at home when remotely supervised during telehealth consultations.

METHODS

Participants

This prospective study in children with chronic respiratory diseases was conducted at Sydney Children's Hospital, Australia, from May to December 2020. For the device validation part of the study, children were eligible if they were attending face-to-face appointments and required spirometry. For the home spirometry part of the study, children were eligible if they had a telehealth appointment, were in possession of a personal ultrasonic spirometer and required spirometry as part of their assessment. Children were excluded if they had not previously performed A&R spirometry according to international standards.³ Informed consent was obtained.

Study design

Part 1: device validation

Children performed spirometry on two systems in randomised order: conventional laboratory equipment (Vyntus Spiro, Carefusion, Yorba Linda, California) and a personal ultrasonic spirometer (SpiroHome, Inofab, Turkey). Output from both systems included absolute values for forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC), as well as per cent predicted values (%predicted) and z-scores, calculated using the Global Lung Initiative reference equations.

Part 2: telehealth spirometry

Home spirometry was performed on the SpiroHome device with a respiratory scientist supervising and coaching the forced expiratory manoeuvres via telehealth (PEXIP Infinity Connect, eHealth Conferencing Services). During testing, the participant would show the respiratory



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Table 1 Correlation and agreement between laboratory equipment and personal device

	ICC (95% CI)	Mean difference between devices	LOA
FEV ₁ absolute value (L)	0.991 (0.985 to 0.995)	0.01	-0.22 to 0.24
FVC absolute value (L)	0.989 (0.981 to 0.993)	-0.02	-0.30 to 0.33
FEV ₁ %predicted	0.972 (0.953 to 0.983)	-0.4	-8.6 to 9.4
FVC %predicted	0.956 (0.926 to 0.974)	0.6	-9.1 to 10.3

Mean difference between devices was calculated by subtracting laboratory spirometry from personal spirometry results.

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ICC, intraclass correlation coefficient; LOA, limits of agreement.

scientist their screen after each manoeuvre, allowing for interpretation of flow-volume loops and continual feedback. The results were also available for review by the respiratory scientist via an online portal on completion of the testing session. Acceptability and reproducibility were determined based on international standards.³

Statistical analysis

Intraclass correlation coefficient (ICC) was calculated to determine the strength of relationship of measurements between devices. Agreement between spirometers was calculated and expressed as mean difference with limits of agreement and presented in Bland-Altman plots. A >10% difference in FEV₁ %predicted and/or a difference in volume of 0.15 L between devices for FEV₁ or FVC were considered significant, as these differences indicate a significant clinical change⁴ or unacceptable reproducibility,³ respectively. Linear regression was performed to investigate the association between age or height and the difference between device measurements. Age of children who were successful and unsuccessful in performing home spirometry was compared using an unpaired t-test. Sample size was determined pragmatically, with consecutive children recruited until the personal spirometer supply was exhausted.

RESULTS

Fifty-nine children (26 male, mean age 12.3 years, SD 3.3) with a mean (SD) FEV₁ %predicted of 86% (19) participated in the device validation study. Diagnoses included cystic fibrosis (n=43), asthma (n=9) and bronchiectasis (n=7). ICC was high and mean between-device differences were low across all measures, indicating excellent reliability between measurements obtained using the two devices (table 1). However, between-device differences exceeded acceptable limits in some children. In 13 (22%) children, there was a between-device difference in FEV₁ and/or FVC of greater than 0.15 L (figure 1A,B). In four (7%) of these children, FEV₁ %predicted was ≥10% lower on SpiroHome than on the laboratory equipment (figure 1C).

There was no systematic bias evident on analysis of the plots for absolute or %predicted values of FEV₁ or FVC. There was also no association between age or height and differences between measurements obtained by the two devices ($r < 0.2$ and $p > 0.7$ for all measures).

Eighty children (41 male, mean age 12.3 years, SD 3.3) performed spirometry using the SpiroHome on a total of 140 occasions during supervised telehealth consultations. Overall, A&R spirometry results were obtained on 125 of 140 (89%) occasions. Children who were able to produce A&R telehealth spirometry were significantly older than those unable to produce A&R spirometry (mean (SD) age 13.1 (2.8) years vs 9.9 (3.5) years; $p < 0.05$).

DISCUSSION

This study has demonstrated good reliability between the spirometry indices measured using a personal ultrasonic spirometer and conventional laboratory equipment. In addition, supervised home use during telehealth resulted in a higher percentage (89%) of A&R results compared with previous studies of unsupervised attempts at home spirometry,² indicating the importance of supervision during telehealth consultations.

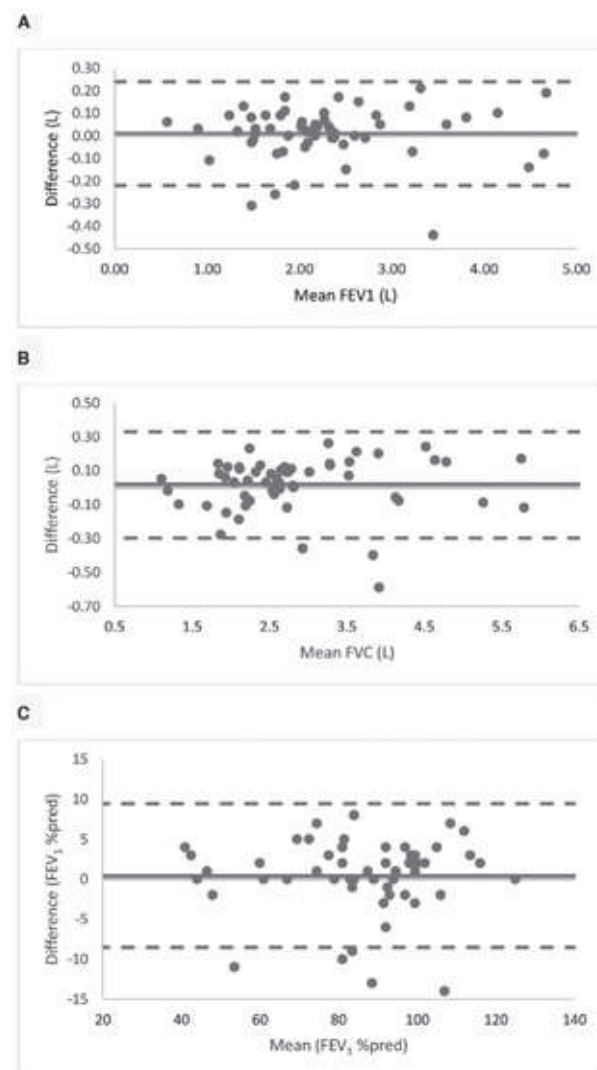


Figure 1 Bland-Altman plots displaying the difference between measurements on the devices (portable spirometer minus conventional spirometer) plotted against the mean value obtained using the two devices for (A) absolute forced expiratory volume in 1 s (FEV₁), (B) absolute forced vital capacity (FVC) and (C) FEV₁ per cent predicted (FEV₁ %pred). Solid lines represent the mean bias and dotted lines represent the upper and lower limits of agreement.

While between-device correlation was high, differences in measurements were unacceptable in a subset of children. FVC and/or FEV₁ differences exceeded 0.15 L in 13 of 57 (22%) children. In four of these children, this translated to the personal device indicating a >10% difference in FEV₁ %predicted compared with laboratory equipment. Previous research using a personal turbine device found an even higher proportion (15%) of participants exhibiting a >10% difference in FEV₁ %predicted compared with laboratory equipment.⁵ Between-device differences of this magnitude are problematic in the scenario of a personal device being used interchangeably with laboratory equipment to monitor lung function over time, such as when hospital laboratory equipment is used during face-to-face reviews than a personal device during telehealth. In this circumstance, a false change in lung function between clinical reviews may be perceived when no true change has occurred. One strategy to overcome this issue would be for patients to use their personal spirometer for hospital and home assessments.

This study had limitations. First, this study tested a single device in children who were familiar with spirometry. The results, therefore, are not necessarily able to be generalised to other devices or children with little spirometry experience. In addition, there were a relatively low number of children with moderate-severe airway obstruction. While there was no evidence of systematic bias based

on severity of airway obstruction, the small number of children included limits conclusions regarding the accuracy of the device in this group.

In conclusion, the SpiroHome, a personal ultrasonic spirometer, is a valid alternative to laboratory equipment for assessing spirometry outcomes. However, the limits of agreement between measurements are wide and beyond acceptable in a small percentage of children. Therefore, using the device interchangeably with laboratory equipment is problematic. Children were able to perform A&R spirometry on a large majority of occasions, indicating the device is suitable for home use during supervised telehealth consultations.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Sydney Children's Hospitals Network Human Research Ethics Committee (reference number: 2019/ETH10536). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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Novos desafios, novas respostas nos cuidados de proximidade FDR Xair, a Radiologia além (de todas as) fronteiras

Leve, compacto e ultraportátil: três características que nunca foram tão importantes como atualmente, no que aos equipamentos médicos diz respeito.

Além de fácil de transportar, o FDR Xair, um equipamento único no mercado de sistemas médicos, é simples de manusear e operar, sendo que a sua portabilidade permite o diagnóstico em vários e diferentes ambientes médicos, mas não só. É possível atender pacientes com mobilidade limitada e em qualquer local, nomeadamente hospitais, clínicas, centros médicos, domicílios, lares, estabelecimentos prisionais, locais de desastres naturais, hospitais de campanha, instalações médicas desportivas, entre outros cenários que exijam uma resposta rápida e eficiente.

O FDR Xair é alimentado por bateria de polímero de lítio com capacidade de autonomia para capturar até 100 imagens, sem uma fonte de energia estável. E tudo isto com um design moderno, elegante e prático. Este dispositivo portátil de raios-X é fácil de manusear e é bastante intuitivo. Aliás, os botões estão localizados em redor do ecrã, permitindo que o técnico opere o equipamento facilmente enquanto o segura.

O equipamento pode ser usado em combinação com o detetor Fujifilm FDR D-EVO II para um exame radiológico de alta qualidade e de baixa dose

O FDR Xair combina tecnologia de inteligência artificial (IA) com a herança de processamento de imagem da Fujifilm, garantindo uma elevada qualidade de imagem.

Além disso, o sistema FDR Xair pode ser conectado à unidade GPU compacta “Ex mobile”, para fornecer a compatibilidade com uma aplicação baseada em IA, que auxilia na deteção de consolidações e nódulos. Isto é algo essencial para o diagnóstico de tuberculose nas radiografias de tórax, permitindo, assim, a análise no local.

O combate à tuberculose tem agora um potente aliado

Por todos estes motivos, a inovadora unidade de raio-X da Fujifilm FDR Xair foi adicionada recentemente ao “Catálogo de Dispositivos Médicos de Diagnóstico”, que é publicado pela Global Drug Facility (GDF)¹ sob o título “Stop TB Partnership”², como um elemento fundamental e preponderante para o diagnóstico de tuberculose.

Afinal, a tuberculose é uma das três principais doenças infecciosas do mundo³, que afeta mais de 10 milhões de pessoas por ano, tendo sido responsável pela morte de 1,4 milhões de pessoas em 2019, em todo o mundo. Aproximadamente 90% dos casos concentram-se em países em desenvolvimento de África, sudeste da Ásia e outras regiões⁴. No entanto, este é um número que se estima estar muito aquém da realidade. Supõe-se que mais de três milhões de pacientes com tuberculose não são diagnosticados todos os anos, o que destaca a importância do rastreio da doença.

Além disso, e num contexto mais atual e no âmbito da pandemia da COVID-19, o FDR Xair System foi particularmente usado como um dispositivo de raio-X de tórax para o diagnóstico de pneumonia.

Notas

1 - O GDF é o braço de compras da Stop TB Partnership

2 - A Parceria Stop TB é uma parceria multissetorial de vários parceiros para a implementação de medidas contra a TB, estabelecida em 2001 pela OMS em Genebra, Suíça.

3 - Tuberculose, SIDA e malária

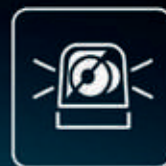
4 - Global Tuberculosis Report 2020, emitido pela OMS

FUJIFILM
Value from Innovation

Leve
Compacto
Ultraportátil



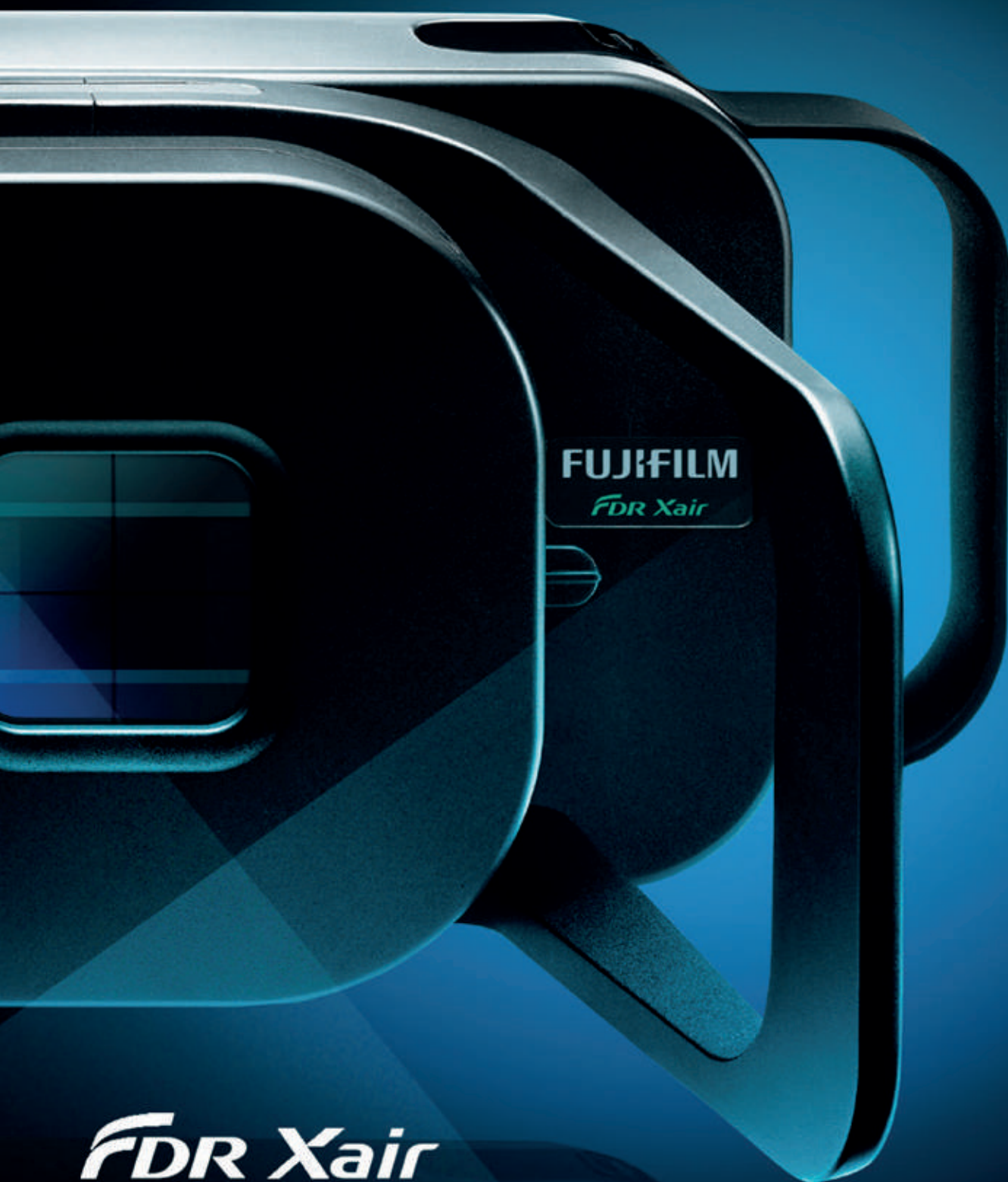
Domícios
Lares



Locais
remotos



Hospitais
Clínicas



FDR Xair

Pressão positiva contínua nas vias aéreas em crianças em ambientes com recursos limitados, efeito na mortalidade e eventos adversos: revisão sistemática e meta-análise

Kristen L Sessions,¹ Andrew G Smith,² Peter J Holmberg,³ Brian Wahl,⁴ Tisungane Mvalo,^{5,6} Mohammad J Chisti,⁷ Ryan W Carroll,⁸ Eric D McCollum^{4,9}

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/archdischild-2021-323041>).

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RESUMO

Objetivo Determinar a ventilação não-invasiva com resultados da pressão positiva contínua nas vias aéreas (CPAP) para problemas respiratórios pediátricos em países de baixos e médios rendimentos (LMIC).

Desenho Revisão sistemática e meta-análise.

Cenário Hospitais LMIC.

Doentes Crianças entre um mês e 15 anos de idade com problemas respiratórios.

Intervenções Pesquisamos na Medline, Embase, LILACS, Web of Science e Scopus a 7 de Abril de 2020. Os estudos incluídos avaliaram a segurança, eficácia ou eficiência da CPAP. Foram incluídos todos os tipos de estudos, tendo sido excluídos apenas os estudos neonatais. Foram extraídos dados por dois revisores e foi avaliado o envio-mento. Foi avaliada a certeza da evidência e foram produzidos rácios de risco (RR) para meta-análises. (protocolo PROSPERO CRD42018084278).

Resultados Foram analisados 2174 artigos, sendo 20 incluídos na revisão sistemática e 3 incluídos em duas meta-análises separadas de mortalidade e eventos adversos. Os estudos adequados para meta-análise foram ensaios aleatorizados controlados (RCT) do Bangladesh, Gana e Maláui. Para as meta-análises de comparação de mortalidade ou eventos adversos entre CPAP e recetores de oxigénio de fluxo reduzido, não encontramos qualquer efeito claro da CPAP na mortalidade (RR 0,75, IC 95% 0,33 a 1,72) ou em eventos adversos (RR 1,52, IC 0,71 a 3,26). Reduzimos a certeza da evidência tanto para os resultados de mortalidade como de eventos adversos para 'reduzida' devido a questões de conceção e discrepâncias de resultados entre os RCT.

Conclusões A evidência da eficácia da CPAP contra a mortalidade e eventos adversos apresenta pouca certeza e é dependente do contexto. Os hospitais que introduziram a CPAP precisam de ter mecanismos implementados para otimizar a segurança no contexto em que está a ser utilizada. Isto inclui a localização (uma área de alta dependência ou de cuidados intensivos), um número adequado de pessoal treinado em CPAP, monitorização próxima e mecanismos de escalada, supervisão médica direta diária, equipamento adequado à idade e de fácil utilização e monitorização contínua dos resultados e da qualidade dos cuidados.

INTRODUCTION

Significant progress has been made in reducing the global mortality burden for children during the last 20 years. Despite this, nearly 5.4 million children worldwide below 5 years old died in 2017.¹ Reflecting historical mortality trends, lower respiratory infections (LRIs) are disproportionately represented, accounting for more deaths among 1–59 month olds than any other illness.¹ Various efforts, including WHO treatment guidelines and the Millennium and Sustainable Development Goals, have contributed to child mortality reductions from LRIs.¹ However, large respiratory mortality disparities persist in low-income and middle-income countries (LMICs).²

Current management of LRIs and respiratory distress include medical therapies in addition to

What is already known on this topic?

- Lower respiratory infections (LRIs) like pneumonia are the leading infectious cause of paediatric death globally despite antibiotics and oxygen treatment.
- Non-invasive ventilation (NIV) with continuous positive airway pressure (CPAP) is an accepted paediatric treatment modality in high-income countries and for severely ill neonates in low-income and middle-income countries (LMICs).
- The most up-to-date research evaluating the efficacy, effectiveness and safety of CPAP NIV for severe LRI of non-neonates has been reported but not systematically assessed and evaluated by meta-analysis.

What this study adds?

- This systematic review and meta-analysis synthesises the most updated body of evidence for non-neonates treated with CPAP NIV in LMICs.
- We provide key evidence-based recommendations for hospitals in LMICs who have already implemented CPAP NIV for the management of non-neonates with severe respiratory illnesses like LRIs.

respiratory support. In many LMICs, the highest level of respiratory support is conventional low-flow oxygen. Larger hospitals may have some capacity for more intensive management, including non-invasive ventilation (NIV) with continuous positive airway pressure (CPAP) and intubation with invasive mechanical ventilation (IMV), but the necessary equipment, medications and human resource capacity makes this infrequent.

CPAP NIV provides positive airway pressure to a spontaneously breathing individual to improve lung compliance, ventilation-perfusion mismatch, gas exchange and work of breathing.³ In high-income countries, CPAP is a standard of care for paediatric respiratory patients with respiratory distress and can reduce IMV and mortality. In LMICs, 'bubble CPAP' (bCPAP) may particularly benefit neonatal respiratory distress (<28 days old). bCPAP, unlike conventional CPAP, generates pressure according to the depth the circuit's expiratory limb is submerged below water.³ A systematic review of neonatal bCPAP in LMICs demonstrated a 30%–50% reduction in IMV but without a mortality change.⁴ Similarly, a systematic review of high flow nasal cannula oxygen found that, when compared with CPAP, CPAP had a lower treatment failure risk among infants with younger age, hypoxemia or respiratory distress.⁵ No

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Table 1 Search strategy

PICO term	Description
Population	Patients 1 month to 15 years of age with respiratory distress including, but not limited to, pneumonia or bronchiolitis in low-income and middle-income countries
Intervention	Non-invasive ventilation including bCPAP, positive end-expiratory pressure and CPAP used in the acute hospital setting for treatment of respiratory distress
Comparison	High or low-flow oxygen therapy through nasal cannula, mechanical ventilation or no respiratory support
Outcome	Mortality, treatment failure, adverse events

bCPAP, bubble continuous positive airway pressure.

mortality difference was found. CPAP NIV safety concerns include possible excessive oxygen delivery, skin and/or nasal septal damage, aspiration and, rarely, pneumothorax.

While neonatal bCPAP in LMICs is widely considered beneficial and safe, CPAP efficacy, effectiveness and safety for non-neonates in LMICs has been a recent focus. A systematic review of the literature through 2018 concluded bCPAP was safe and effective in LMICs.⁶ However, recent research has raised new questions regarding CPAP for non-neonates. This study's main objective was to systematically review the literature to determine through meta-analyses if CPAP is efficacious, effective, and safe for 1 month to 15 years olds with respiratory distress in LMICs.

METHODS

The development and reporting of this work are per the Preferred Reporting Items for Systematic Reviews (PRISMA) statement.⁷ The protocol was registered on PROSPERO (CRD42018084278).

Data sources and search strategies

A search of Medline, Embase, LILACS, Web of Science and Scopus was performed on 7 April 2020 (table 1). There were no language, age, publication date or type restrictions. The World Bank LMIC classification was applied. The search strategy was facilitated by a medical reference librarian (online supplemental appendix 1). The references of included studies were also searched.

Inclusion and exclusion criteria for systematic review

All studies published in peer-reviewed journals on NIV efficacy, effectiveness or safety in the population of interest were included. We defined NIV as bCPAP or CPAP. Editorials, letters, narratives, systematic reviews and errata were excluded. Included studies assessed hospital CPAP efficacy, effectiveness or safety for 1 month to 15 years old with respiratory distress in LMICs. Studies on neonates (<28 days old) only were excluded.

Data collection and extraction for systematic review

Search keywords are in online supplemental appendix 1. The online Covidence platform for data extraction and quality assessments

was used. Two independent reviewers screened each study by title and abstract. Eligible studies underwent a full review. Disagreements at the title and abstract stage were resolved by a third blinded author; disagreements at the manuscript review stage were resolved by consensus. A data extraction tool was created in Covidence to collect author, funding, setting, study design, population, interventions and outcomes data.

Risk of bias assessment for studies included in systematic review

Data extraction and risk of bias assessments were performed by two independent reviewers and discrepancies were adjudicated by consensus. Comparative studies, including all randomised control trials (RCTs), were evaluated using Cochrane recommended criteria.⁸ Studies with no comparator group were evaluated using criteria proposed by Murad *et al* to evaluate selection, ascertainment, causality and reporting domains.⁹

Data synthesis, assessment of reporting biases and assessment of heterogeneity

The feasibility of meta-analyses was assessed using clinical and methodological characteristics for all study designs. Random-effects models summarised study findings using an inverse variance method. For dichotomous outcomes, risk ratios (RR) or ORs and 95% CIs estimated the treatment effect. We used difference in means for continuous outcomes. We created and evaluated a funnel plot to evaluate for reporting biases. We estimated statistical heterogeneity using the χ^2 test and the I^2 statistic. The latter describes the proportion of variation across studies due to heterogeneity rather than sampling error. All statistical analyses were done using Stata V.16.1 (Stata, College Station, Texas, USA).

Certainty of evidence assessment

For studies contributing data to meta-analyses, we used GRADEpro GDT software (GRADEpro GDT 2015) to apply the Cochrane-recommended GRADE domains of study limitations, consistency of effect, imprecision, indirectness and publication bias to evaluate evidence quality.¹⁰ When appropriate limitations were identified, we downgraded evidence according to guidelines.



Figure 1 Study selection. LMICs, low-income and middle-income countries; NIV, non-invasive ventilation.

Table 2 Characteristics of included studies

Author, Year	Country and setting	Study design	Sample size and population	Intervention and equipment	Comparison	Outcomes of interest
Randomised control trials						
Cam, 2002 ⁹	Vietnam Referral hospital Intensive care unit	Randomised control trial	N=37 Age 0–15 years, dengue shock syndrome with respiratory failure despite nasal cannula oxygen	CPAP (n=18) Via Beneveniste valve	Oxygen mask (n=19)	Mortality Adverse events Success of treatment at 30 min* and 24 hours
Chisti, 2015 ¹⁰	Bangladesh Center for Diarrhoeal Disease Research Intensive care unit	Randomised control trial	N=225 Age 0–5 years, severe pneumonia and hypoxemia	Locally constructed bCPAP (n=79)	Low flow oxygen (n=67) High flow oxygen (n=79)	Mortality treatment failure* (clinical failure, mechanical ventilation or death) Duration of hospital stay Duration of symptoms
Lal, 2018 ¹¹	India Referral hospital	Randomised control trial	N=72 Age 1–12 months, acute bronchiolitis with wheezing	bCPAP via Gregory circuit (n=36)	Standard of care with oxygen mask (n=36)	Mortality Adverse events Need for mechanical ventilation Change in vital signs* and MP5NZ-SS+ and SA score+
McCollum, 2019 ¹²	Malawi District Hospital General ward	Randomised control trial	N=644 Age 0–59 months, severe pneumonia and one or more high risk conditions (HIV infection or exposure, Hypoxemia, severe malnutrition)	bCPAP via Fisher and Paykel healthcare CPAP system (n=321)	Low-flow oxygen (n=323)	Mortality* Adverse events Duration of respiratory support
Morales, 2004 ¹⁵	Mexico National Institute of Respiratory Disease Intensive care unit	Prospective comparative study†	N=26 Age 0–14 years, acute respiratory failure, Glasgow Coma Score >8	NIV via quantum ventilator (n=14)	Orotracheal intubation (n=12)	Mortality Adverse events Treatment success* (vital sign stabilisation after 2 hours) Vital sign changes Duration of hospital stay
Wilson, 2013 ¹³	Ghana Four district hospitals General wards	Crossover randomised control trial	N=69 Age 3 months to 5 years, tachypnoea and retractions or nasal flaring	Hudson RCI CPAP nasal cannula and DeVilbiss IntelliPAP CPAP machine	Immediate CPAP use (n=31) delayed CPAP use (n=38)	Mortality Change in vital signs*
Wilson, 2017 ¹⁴	Ghana District hospital and Municipal hospital General wards	Crossover cluster Randomised control trial	N=2200 Age 1 month-5 years, tachypnoea and retractions or nasal flaring	Hudson RCI CPAP nasal cannula and DeVilbiss IntelliPAP CPAP machine (n=1025)	Oxygen via non-rebreather face mask (n=1175)	Mortality* Adverse events Duration of CPAP
Non-comparative studies						
Balfour-Lynn, 2014 ¹⁶	Ghana District hospital General ward	Observational implementation study ²⁰	N=106 Age 0–5 years, respiratory distress based on respiratory rate, SpO ₂ , intercostal retractions and grunting	NIV via Nippy Junior paediatric pressure controlled portable ventilator	N/A	Mortality* Adverse events
Bjorkland, 2019 ¹⁷	Uganda Referral hospital Acute care unit	Prospective, non-blinded, non-randomised interventional study	N=83 Age 30 days - 5 years, moderate or severe respiratory distress based on a calculated respiratory score (Tal score >3) or hypoxia despite low-flow oxygen	SEAL-bCPAP with nasal prong adaptation from ear plug material	N/A	Mortality* Adverse events* Change in respiratory rate, oxygen saturation and Tal score†
Bonora, 2011 ¹⁸	Argentina Referral hospital Intensive care unit	Retrospective observational study	N=154 Age 1–18 years, patients needing NIV for >30 min to attempt to avoid intubation	Neumovent graph, neumovent graph net or harmony devices for NIV	N/A	Mortality Need for intubation* Duration of NIV Duration of hospital stay
Brown, 2013 ²⁷	Malawi Referral hospital	Case report	N=1 Age 6 months, respiratory distress	Low cost bCPAP device developed by authors	N/A	Mortality Adverse events Vital sign changes after 1 hour Length of hospital stay
Figuera, 2017 ¹⁹	Argentina Provincial hospital Intermediate care unit	Retrospective descriptive study	N=120 Age 1–24 months, weight <12 kg, Tal score >5	Hudson RCI-CPAP	N/A	Mortality Adverse events Success of CPAP (15% decrease in RR) Changes in vital signs and Tal score† Duration of NIV Duration of ICU stay

Continued

Table 2 Continued

Author, Year	Country and setting	Study design	Sample size and population	Intervention and equipment	Comparison	Outcomes of interest
Ghiggi, 2000 ²⁰	Argentina Referral hospital Intensive care unit	Prospective observational study	N=42 Age 1 month- 5 years, Acute respiratory failure from pulmonary cause with indication for mechanical ventilation	Nasopharyngeal CPAP via Sechrist IV100 B respirators	N/A	Mortality Adverse events Need for mechanical ventilation* Change in vital signs Duration of NIV
Kinikar, 2011 ²¹	India Referral hospital Intensive care unit	Case-control study	N=36 Age 0–12 years, influenza like illness, moderate to severe respiratory distress or respiratory failure	Locally constructed nasal bubble CPAP	N/A	Mortality Adverse events Changes in vital signs in first 6 hours*
Lum, 2011 ²²	Malaysia Referral hospital Intensive care unit	Prospective observational study	N=129 Age 0–16 years, patients deemed likely to require intubation based on vital signs and work of breathing	NIV via Mapleson F breathing system	N/A	Mortality Adverse events Length of NIV Length of PICU stay Treatment success* (intubation avoided) Vital Sign changes
Machen, 2015 ²³	Malawi Referral hospital Acute care unit	Prospective observational study	N=79 Weight<10 kg, respiratory distress, bCPAP deemed appropriate by physician	bCPAP	N/A	Mortality* Duration of bCPAP Duration of hospital stay Change in RISC score†
McCollum, 2011 ²⁸	Malawi Referral hospital	Case report	N=1 3 month old, respiratory distress	Hudson RCI -bCPAP	N/A	Mortality Adverse events Duration of bCPAP Change in vital signs
Myers, 2019 ²⁴	Malawi Referral hospital Critical care zone, emergency zone	Prospective observational study	N=117 Age 0–59 months, severe respiratory distress	Diamedica "Baby CPAP"	N/A	Mortality* Adverse events
Pulsan, 2019 ²⁵	Papua New Guinea Referral hospital Intensive care unit, Special care nursery	Prospective observational study	N=64 Children with severe acute lower respiratory infection, with hypoxaemia or severe respiratory distress despite standard oxygen therapy	Diamedica-modified Airsep intensity bCPAP	N/A	Mortality Change in respiratory distress score*†
Walk, 2016 ²⁶	Malawi Referral hospital High dependency unit, emergency ward	Prospective observational study	N=77 Age 1 week to 14 years, progressive acute respiratory failure despite oxygen and antimicrobial therapy	Locally constructed CPAP	N/A	Mortality* Adverse events Treatment failure (death or intubation) Duration of CPAP Changes in vital signs

*Primary outcome.

†Scoring tool to evaluate illness severity

‡Non-randomised comparative study.

bCPAP, bubble continuous positive airway pressure; CPAP, continuous positive airway pressure; HIV, immunodeficiency virus; ICU, intensive care unit; MPSNZ-SS, Modified paediatric society of New Zealand severity score; NIV, non-invasive ventilation; PICU, paediatric intensive care unit; RISC score, respiratory index of severity in children.

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There was no direct funding. The corresponding author had full access to all study data and final responsibility for submission.

RESULTS

Systematic review

A total of 2174 studies were screened and 20 were included in the systematic review (figure 1). These included 5 RCTs,^{11–15} 1 cluster RCT,¹⁶ 1 non-randomised comparative study¹⁷ and 13 observational studies^{18–28} (table 2). Most studies evaluated bCPAP or conventional CPAP and were small. Ten studies also included neonates. Sixteen studies were at tertiary referral or provincial hospitals and included intensive care or high acuity units. Four studies, including RCTs in Malawi¹⁴ and Ghana,¹⁶ were at district hospitals in a general paediatric ward. The Ghana RCT had daily physician oversight while the Malawi RCT did not. Mortality was the primary endpoint in seven studies. In the Bangladesh RCT, bCPAP was delivered in an intensive care unit (ICU) under paediatric intensive care physician supervision.¹²

RCTs and mortality

For the five RCTs, CPAP mortality varied from 0% to 22% (table 3). Mortality or treatment failure served as primary endpoints for all. In the Bangladesh RCT, children on bCPAP compared with low-flow oxygen had lower mortality (4% bCPAP vs 15% oxygen: RR 0.25, 95% CI 0.07 to 0.89; $p=0.022$).¹² The study was stopped early by the data safety monitoring board for benefit. A second RCT in Ghana used a cluster crossover design in which CPAP was available at one hospital at a time, while the other hospital was the control.¹⁶ Children at the intervention hospital received CPAP and at both hospitals, supplemental oxygen was provided as needed to maintain oxygenation >92%. The proportion of controls receiving oxygen was not reported. This trial found no difference in all-cause mortality between CPAP (3%) and controls (4%) (RR 0.67, 95% CI 0.42 to 1.08; $p=0.11$). An exploratory adjusted analysis demonstrated decreased mortality for <1 year olds on CPAP (3%) compared with controls (7%) (RR 0.40, 95% CI 0.19 to 0.82; $p=0.01$).¹⁶ Another RCT in Malawi comparing bCPAP to low-flow oxygen found higher mortality in the bCPAP arm (17% and 11%, RR 1.52; 95% CI 1.02 to 2.27; $p=0.036$).¹⁴ This study was stopped early due to both futility and the possibility of harm from bCPAP. In an open, prospective

Table 3 Outcomes for randomised control trials

Author, year	Total sample size	Mortality	Findings	Adverse events	Reported limitations	Reported conclusions
Cam, 2002 ⁹	37	CPAP: 4/18 (22%) Oxygen: 0/19 (0%)	Stabilisation of patient with PaO ₂ >80 mm Hg after 30 min: CPAP: 14/18 (78%) Oxygen: 6/19 (32%) 13/19 oxygen patients were transitioned to CPAP after failure on oxygen, all improved	0 (0%)	Small sample size compared with calculated sample size	Nasal CPAP is useful in improving management of acute respiratory failure in children with dengue shock syndrome
Chisti, 2015 ¹⁰	225	bCPAP: 3/79 (4%) Low-flow oxygen: 10/67 (15%) High-flow oxygen: 10/79 (13%) Total: 23/225 (10%)	Treatment failure: bCPAP: 5/79 (6%) Low-flow oxygen: 16/67 (24%) High-flow oxygen: 10/79 (13%) Length of hospital stay (days; median (IQR)): bCPAP: 5 (3–7) Low-flow oxygen: 4 (3–7) High-flow oxygen: 5 (3–7)	bCPAP: 17/79 (22%) Oxygen: 14/67 (21%) AEs included abdominal distension, and newly recognised heart failure.	Trial was stopped early before full recruitment	Bubble CPAP therapy could be beneficial in hospitals in developing countries where the only respiratory support is standard flow oxygen.
Lal, 2018 ¹¹	72	Not reported	Decrease in RR at 1 hour (mean, SD): bCPAP: 8 (6) Supplemental oxygen via facemask or hood: 5 (4) Need for mechanical ventilation: bCPAP: 2/36 (5%) Standard of care: 1/36 (3%)	0 (0%)	Study duration was only 1 hour, functional outcomes including need for invasive ventilation and duration of hospital stay were not evaluated	CPAP significantly decreases respiratory rate in patients with acute bronchiolitis in the first hour of treatment
Morales, 2004 ¹⁵	26	0 (0%)	Duration of Hospital stay (days, mean (SD)): NIV: 8.2 (2.8) Intubation: 19 (11) Success of intervention: NIV: 12 (86%) Intubation: 12 (100%)	NIV: 11 (79%) Intubation: 11 (92%) Complications included aerophagia, erythema, septal necrosis, pericardial effusions, infections	Limitations not reported	NIV is useful in reducing the possibility of orotracheal intubation and decreases the length of hospital stay compared with mechanical ventilation
McCollum, 2019 ¹²	644	bCPAP: 53/321 (17%) Oxygen: 35/323 (11%)	Duration of respiratory support (days, mean (SD)): bCPAP: 4.5 (1.9) oxygen: 3.9 (2.1)	bCPAP: 11/321 (3%) Oxygen: 1/323 (<1%) AE included aspiration events, probable pneumothorax and skin breakdown	Trial stopped early before full recruitment, no access to radiographic imaging, designed to reflect real-world setting but staff augmented,	bCPAP in a paediatric ward without daily physician supervision did not reduce mortality among high-risk Malawian children with severe pneumonia, compared with oxygen.
Wilson, 2013 ¹³	70	Immediate CPAP: 3/31 (10%) Delayed CPAP: 0/38 (0%)	Decrease in RR at 1 hour (mean (CI)): Immediate CPAP: 16 (10, 21) Delayed CPAP: 1 (-2, 5) Percent change in RR at 2 hours: Immediate CPAP: data missing Delayed CPAP: 13 (8, 19)	Not reported	Study design not powered to evaluate mortality, Active study was only 2 hours long, not blinded, 100% consent rate, limited diagnostic testing	CPAP is a safe and effective method to decrease respiratory rates in children presenting with nonspecific respiratory distress
Wilson, 2017 ¹⁴	2200	CPAP: 26/995 (3%) Control: 44/1160 (4%)	Duration of CPAP (median (IQR)): CPAP: 12 (7.2–19.8) Control: 0 (0)	CPAP related AE: CPAP: 28/1021 (3%) Control: 24/1160 (2%) CPAP related AE included vomiting, nasal trauma, skin trauma, aspiration and eye trauma Other AE: CPAP: 70/1021 (7%) Control: 85/1160 (7%) Other AE included fever, cough, diarrhoea, rash, skin or mucosal complaints, respiratory distress, rhinitis, swelling, seizure, anaemia or malaria	Allocation by site rather than patient leading to concealment and enrolment bias, limited diagnostic abilities, possibly underpowered	CPAP did not decrease all-cause 2-week mortality in children 1 month to 5 years with undifferentiated respiratory distress. After adjustments for key variables, 2-week mortality in CPAP group vs control group was decreased for children under 1 year of age. CPAP improved respiratory rate.

AE, adverse events; bCPAP, bubble continuous positive airway pressure; CPAP, continuous positive airway pressure; RR, respiratory rate in breaths per minute.

RCT from Vietnam involving 37 children with respiratory distress from dengue, 18 received CPAP and 19 received oxygen. Mortality was 22% after CPAP compared with 0% for controls ($p=0.03$).⁹

Observational studies and mortality

Among the 11 observational studies, CPAP mortality ranged from 0% to 55% (table 4). Four tertiary hospital studies reported

Table 4 Outcomes for non-randomised control trials

Author, year	Total sample size	Mortality	Additional findings	Adverse events	Reported limitations	Reported conclusions
Balfour-Lynn, 2014 ¹⁶	106	2 (2%)	N/A	0 (0%)	Possibility of missing data	NIPPV can be a simple and cost-effective way to treat patients with acute respiratory failure
Bjorklund, 2019 ¹⁷	83	8 (10%)	Patients with severe illness based on Tal score: 0 hours: 64/83 (77%) 2 hours: 12/83 (15%)	Severe: 0 Mild: 5 (6%) Mild AE included nasal tissue irritation and abdominal distension	Evaluations for complications based only on clinical exam, not powered to evaluate effectiveness, differences in pretrial and trial patients	SEAL-bCPAP is safe for treatment of respiratory distress in non-neonatal children in LMIC with a trend towards decreased mortality
Bonora, 2011 ¹⁸	154	Avoided intubation: 3.8% Required intubation: 38.8%	No need for intubation: 80/154 (52%) Duration of NIV (days, median (IQR)): 4 (2.25–6) Avoided intubation: 4 (2.25–6) Required intubation: 2 (1–4) Duration of hospital stay (days, median (IQR)): 6 (5–9) Avoided intubation: 13 (9–24) Required intubation: 13 (9–24)	Skin breakdown noted but number of adverse events not reported	Retrospective study design with no control group, no rigid protocol to determine when therapies should be escalated or discontinued	NIV avoided mechanical ventilation in a high proportion of children
Brown, 2013 ²⁷	1	0 (0%)	Duration of bCPAP: 4 days Duration of hospital stay: 6 days	0 (0%)	Limitations not reported	A low-cost bCPAP could reduce child mortality in Africa
Figueroa, 2017 ¹⁹	120	Not reported	Success of bCPAP: 72% Duration of bCPAP (hours, mean (CI)): 75 (65–85) Duration of ICU stay (days, mean (CI)): 10 (9–11)	4 (3%) Complications included abdominal bloating and pneumothorax	Limitations not reported	A reduction in respiratory rate, heart rate and TAL scores at 2 hours after starting intervention were predictors of success
Ghiggi, 2000 ²⁰	42	2 (5%)	Duration of nasopharyngeal CPAP (days, mean (SD)): 4.12 (3.71) Need for mechanical ventilation: 13/42 (31%)	8 (19%) Complications included tube obstructions and apnoea due to excessive sedation	Small sample size	Nasopharyngeal CPAP was useful to avoid mechanical ventilation
Kinikar, 2011 ²¹	36	0 (0%)	Duration of ICU stay (days, median (range)): 2 (2–5) Duration of hospital stay (days, median (range)): 7 (6–11) Decrease in mean RR after 6 hours: H1N1 positive: 20 H1N1 negative: 17	0 (0%)	Limitations not reported	Indigenous NB-CPAP improves hypoxemia and signs and symptoms in hemodynamically stable children with acute respiratory failure due to influenza-like injury
Lum, 2011 ²²	129	19 (15%)	Duration of NIV (days, median (IQR)): 4 (2–8) Duration of PICU stay (days, median (IQR)): 4.5 (2–9) Avoided mechanical ventilation for ≥5 days: 98 (76%)	29 (22%) Complications included pneumonia while on NIV, pressure from mask and problems with mask fitting	Not an RCT, no routine use of blood gas sampling, shortage of NIV machines	NIV represents a viable strategy that provided effective respiratory support and prevented intubation in majority of patients
Machen, 2015 ²³	79	23 (29%)	Duration of CPAP (days, mean): 3.12 Duration of hospitalisation (days, mean): 8.41 Had lower RISC score after 24 hours: 63 (80%)	Not reported	Clinical diagnoses could have led to misclassification	bCPAP was most beneficial to patients with bronchiolitis
McCollum, 2011 ²⁸	1	0 (0%)	Duration of bCPAP (days): 7	0 (0%)	Limitations not reported	bCPAP was successful in treating an infant with PJP pneumonia secondary to HIV infection
Myers, 2019 ²⁴	117	38 (33%)	Required intubation: 15/115 (13%) Duration of treatment (hours, median (IQR)): 24 (24–60)	13 (11%) Complications included blocked nostrils or nasal prongs, interruption of oxygen supply, nasal septum lesions and aspiration	Observational study design, small sample size, limited human resources and some missing data points	It is feasible to use bCPAP in the hospital management of critically ill children in resource-limited settings
Pulsan, 2019 ²⁵	64	35 (55%)	RDS (mean (IQR)): Pre-CPAP: 11 (10–12) 1 hour: 9 (8–11) 84 hours: 6.5 (6–8)	Not reported	Observational study design, bCPAP only used when oxygen failed	bCPAP improves oxygenation and reduces respiratory distress in some children but children with comorbidities continue to do poorly
Walk, 2016 ²⁶	77	36 (47%)	Duration of treatment (days, median (IQR)): 3 (3–5)	13 (17%)	Non-randomised and uncontrolled, small sample size, understaffing, missing vital sign data	bCPAP can be feasibly implemented into a tertiary African hospital with high-risk patients

AEs, adverse events; bCPAP, bubble continuous positive airway pressure; CPAP, continuous positive airway pressure; RR, respiratory rate in breaths per minute.

Author, Year	Selection: Random Sequence Generation	Selection: Allocation Concealment	Outcomes: Blinding of Participants or personnel	Outcomes: Blinding of Outcome Assessment	Outcomes: Incomplete Outcome Data	Outcomes: Reporting Bias/ Selective Reporting	Other Sources of Bias
Christi, 2015	●	●	●	●	●	●	●
Cam, 2002	●	●	●	●	●	●	●
Lal, 2018	●	●	●	●	●	●	●
Morales, 2004	●	●	●	●	●	●	●
Wilson, 2013	●	●	●	●	●	●	●
Wilson, 2017	●	●	●	●	●	●	●
McCollum, 2019	●	●	●	●	●	●	●

Figure 2 Risk of bias assessment for RCT and prospective comparative studies.

mortality >30%.^{20–28} Mortality was the primary endpoint for five prospective observational studies and was 2%,¹⁸ 10%,¹⁹ 29%,²⁵ 33%²⁶ and 47%.²⁸ Results from several studies suggested multiple comorbidities may detrimentally influence outcomes. Specifically, two studies with high all-cause mortality among CPAP recipients reported fewer deaths among HIV-uninfected patients with very severe pneumonia and single organ failure.^{26,28}

Non-fatal adverse events (AEs)

Sixteen studies reported non-fatal AEs (table 3A,B). Six of these reported no AEs. AEs in the other seven studies were 3%–22%. One study reported a 79% AE rate including infections.¹⁷ When infections were excluded, the AE rate was 22%. Most AEs were mild and included trauma to the nasal septum, skin and eyes, vomiting and abdominal distension.^{14–16–17–19–21–26} A few serious AEs including the development of heart failure, aspiration and pneumothorax were reported.^{12–14–16–21}

Risk of bias assessment for systematic review

Due to the inability to blind the respiratory therapy intervention, no RCT was blinded from participants, personnel or outcome assessors (figure 2). One study was not randomised¹⁷ and another RCT used a cluster crossover design and randomised at the hospital level.¹⁵ All seven studies had low risk of incomplete data or reporting bias.

Five observational studies had unclear or high risk of selection bias due to inconclusive reporting (online supplemental file 1).^{18–25–27–29–30} All studies were considered low risk of ascertainment bias. Due to

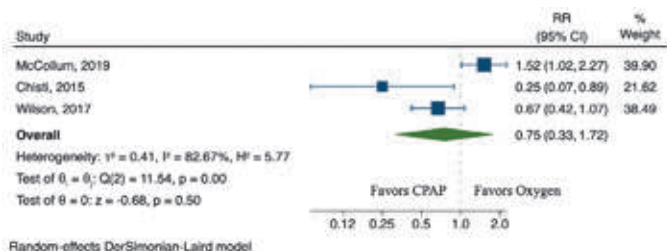


Figure 3 Meta-analysis of trials assessing CPAP against mortality in children less than 5 years. CPAP, continuous positive airway pressure.

the observational design, 10/13 studies were considered unclear or high risk of causality bias. Risk of causality bias was assigned based on potential alternate causes, presence of a challenge/rechallenge phenomenon and appropriate follow-up duration.⁹

Meta-analysis

The RCTs in Bangladesh, Ghana and Malawi were found suitable for inclusion in a meta-analysis for the efficacy of CPAP against mortality and adverse events (figure 1). Meta-analyses for other trial endpoints or with observational studies were not suitable due to incomparability of endpoints and populations, and high

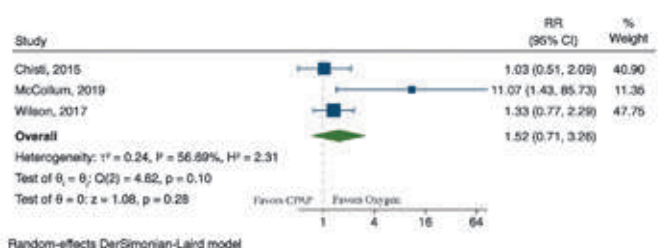


Figure 4 Meta-analysis of trials assessing CPAP against adverse events in children less than 5 years. CPAP, continuous positive airway pressure.

Table 5 Meta-analysis study selection

Outcome	Study	Included (yes/no)	Explanation
Death	Cam (2002) ¹¹	No	Non-comparable age group, non-comparable case definition (dengue)
	Christi (2015)	Yes	
	Lal (2018) ¹³	No	Non-comparable age group, outcome not reported
	McCollum (2019) ¹⁴	Yes	
	Morales (2004) ¹⁷	No	Non-comparable age group, non-comparable control group (invasive mechanical ventilation)
	Wilson (2013) ¹⁵	No	Non-comparable age group, non-comparable study design (all participants received CPAP intervention)
	Wilson (2017) ¹⁶	Yes	
Treatment failure	Cam (2002) ¹¹	No	Non-comparable age group, non-comparable case definition (dengue)
	Christi (2015)	Yes	
	Lal (2018) ¹³	No	Non-comparable age group, outcome not reported
	McCollum (2019) ¹⁴	No	Non-comparable outcome
	Morales (2004) ¹⁷	No	Non-comparable age group, non-comparable control group (invasive mechanical ventilation)
	Wilson (2013) ¹⁵	No	Non-comparable age group, non-comparable study design (all participants received CPAP intervention)
	Wilson (2017) ¹⁶	No	Outcome not reported
Adverse events	Cam (2002) ¹¹	No	Non-comparable age group, non-comparable case definition (dengue)
	Christi (2015)	Yes	
	Lal (2018) ¹³	No	Non-comparable age group
	McCollum (2019) ¹⁴	Yes	
	Morales (2004) ¹⁷	No	Non-comparable age group, non-comparable control group (invasive mechanical ventilation)
	Wilson (2013) ¹⁵	No	Non-comparable age group, non-comparable study design (all participants received CPAP intervention)
	Wilson (2017) ¹⁶	Yes	

CPAP, continuous positive airway pressure.

Table 6 Certainty of evidence (GRADE)

Certainty assessment		No. of patients			Effect							
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	Usual care (oxygen)	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Death												
3	Randomised trials	Serious*	Serious†	Not serious	Not serious	None	79/1395 (5.7%)	89/1550 (5.7%)	RR 0.75 (0.33 to 1.72)	14 fewer per 1000 (from 38 fewer to 41 more)	⊕⊕○○ Low	CRITICAL
Adverse events												
3	Randomised trials	Serious*	Serious†	Not serious	Not serious	None	17/79 (21.5%)	14/67 (20.8%)	RR 1.52 (0.71 to 3.26)	109 more per 1000 (from 61 fewer to 472 more)	⊕⊕○○ Low	IMPORTANT

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ARTIGO ORIGINAL

Rastreo da função pulmonar entre os 10 e 35 anos após nascimento extremamente prematuro ou com peso à nascença extremamente baixo

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RESUMO

Contexto Permanecem desconhecidas as consequências pulmonares ao longo da vida de um indivíduo após nascimento extremamente prematuro ou com um peso à nascença extremamente baixo. O nosso objetivo foi descrever trajetórias da função pulmonar em indivíduos entre os 10 e os 35 anos de idade que tenham nascido extremamente prematuros e abordar os efeitos de coorte potenciais ao longo de um período que englobasse grandes mudanças nos cuidados perinatais.

Métodos Realizámos espirometria repetida em três coortes populacionais nascidas em idade gestacional ≤ 28 semanas ou com peso à nascença ≤ 1000 g durante 1982-85, 1991-92 e 1999-2000, referidos como extremamente prematuros, e em controlos nascidos no termo com correspondência a nível de idade e sexo. Foram efetuados exames aos 10, 18, 25 e 35 anos. Os dados longitudinais foram analisados com recurso a regressão de modelos mistos, sendo os indivíduos extremamente prematuros estratificados por displasia broncopulmonar (BPD).

Resultados Recrutámos 148/174 (85%) indivíduos nascidos extremamente prematuros e 138 nascidos no termo. Em comparação com os indivíduos nascidos no termo, os que nasceram extremamente prematuros apresentaram pontuações z para volume expiratório forçado em 1s (FEV₁) mais baixas na maioria das avaliações. As principais exceções ocorreram nos grupos sem BPD nas duas coortes mais jovens. Em grande parte, as trajetórias FEV₁ foram semelhantes para os nascidos extremamente prematuros e para os nascidos no termo, também durante o período de 25-35 anos, que inclui o início do declínio da função pulmonar relacionada com a idade. Os indivíduos nascidos extremamente prematuros apresentaram um pico de função pulmonar inferior aos dos indivíduos nascidos no termo, mas os valores de z- FEV₁ melhoraram por cada década consecutiva de nascimento ($p=0,009$). Os critérios espirométricos para doença pulmonar obstrutiva crónica foram mais preenchidos pelos indivíduos nascidos extremamente prematuros do que pelos indivíduos nascidos no termo, 44/148 (30%) vs. 7/138 (5%), $p<0,001$.

Conclusões A função pulmonar dos indivíduos que nasceram extremamente prematuros foi paralela à dos indivíduos nascidos no termo, mas significativamente abaixo das trajetórias dos indivíduos nascidos no termo entre os 10-35 anos, incluindo o declínio incipiente relacionado com a idade que ocorre entre os 25 e os 35 anos. Os défices em relação aos indivíduos nascidos no termo foram diminuindo a cada década de nascimento entre 1980 e 2000.

INTRODUCTION

Rarely in the history of medicine were the 'frontiers of the possible' pushed further and faster than in our neonatal intensive care units (NICU) during the 1980s and 1990s.¹ By the turn of the millennium, survival approached 80%–90% for 28 weeks' gestation, the cut-off for being labelled extremely premature.² In high-income countries, extremely

Key messages

What is the key question?

► Extremely premature birth is associated with airway obstruction during childhood, adolescence and young adulthood. Survival was uncommon in these infants before the 1980s and their lifetime health prospects are therefore unknown.

What is the bottom line?

► This is the first population-based longitudinal study to describe lung function trajectories well into adulthood in extremely preterm-born survivors, describing persistent airway obstruction beyond peak function in early adult life and throughout the onset of the age-related decline from 25 to 35 years.

Why read on?

► Chronic obstructive pulmonary disease roots in early life, and extremely premature birth represents an important precursor that needs to be acknowledged by chest physicians and targeted by the research community.

preterm-born infants currently account for one in 200 children growing up.³ They are born at a time when the lungs normally undergo complex developmental processes in a protected intrauterine environment. In contrast, the lungs of infants born at this early stage are exposed to lifesaving, but also harmful, intensive care. Survivors are at increased risk of chronic lung disease as well as premature death from a range of causes.⁴

Lung function normally increases through childhood and adolescence, reaches a peak in the mid-20s, and then gradually declines with age.⁵ The trajectory is modulated by genetic mechanisms, antenatal factors, and multiple early events and exposures.⁶ For most people, the adult decline proceeds unrecognised as symptoms only appear if lung function reaches very low levels.⁷ For infants born extremely preterm, this lifespan perspective represents uncharted territory, as their high survival rates are recent achievements.

Most extremely preterm-born do not appear to reach their expected peak adult lung function.⁸ A few longitudinal studies have traced their lung function up to the mid-20s, finding both



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deterioration or tracking in parallel although at lower levels, when compared with subjects born at term.^{9–13} To date, no longitudinal studies have traced lung function of extremely preterm-born past 25 years of age, and thus we lack information regarding the nature of their age-related decline. Given their common early morbidities, the decline might start at a younger age or be steeper than in the general population, and early chronic obstructive pulmonary disease (COPD) is a feared scenario.¹⁴ Bronchopulmonary dysplasia (BPD) is a respiratory complication affecting approximately 50% of extremely preterm-born neonates, primarily characterised by prolonged requirement for supplemental oxygen in the neonatal period.² BPD is associated with subsequent airway obstruction and bronchial hyper-responsiveness, and there are concerns for additional negative impact on adult pulmonary health.^{5,14}

We have previously reported lung function data from three population-based cohorts born extremely preterm or with extremely low birth weight (BW) (hereafter referred to as extremely preterm-born) during the early 1980s, 1990s and 2000s.^{12–15,16} With the present extension of these studies, we aimed to describe their lung function trajectories well into adulthood, and to address potential cohort effects over almost twenty years of inclusion, a period that encompassed major changes in perinatal care. We hypothesised that lung function in subjects born extremely preterm tracked in parallel, but below the level of matched term-born controls, and that differences decreased with succeeding decade of birth.

MATERIALS AND METHODS

Subjects and study design

Three regional population-based cohorts born during 1982–1985 (82–85 cohort), 1991–1992 (91–92 cohort) and 1999–2000 (99–00 cohort) at gestational age (GA) ≤ 28 (82–85 and 91–92 cohort) or ≤ 27 weeks (99–00 cohort), or with BW ≤ 1000 g were included. For each extremely preterm-born, the temporally closest individual born at term at the same hospital and of the same sex with BW 3–4 kg (Norwegian 10–90 percentiles)¹⁷ was recruited as a control. The cohorts were assessed at three (two for the 99–00 cohort) study-visits performed in 2001–2002, 2008–2011 and 2018–2020 at, respectively, 18, 25 and 35 years; 10, 18 and 25 years; and 10 and 18 years (figure 1). Inclusion and study design has been described previously.^{12–15,16} The subjects completed the International Study of Asthma and Allergy in Childhood¹⁸ questionnaire at each visit.

BPD was defined as need for supplemental oxygen or respiratory support at postmenstrual age ≥ 36 weeks. The mode of determination of GA, and the definitions of small for GA (SGA), smoking status, atopy and asthma have been described previously,^{12–15,16} and is also provided in the online supplemental file.

Lung function measurements

Spirometry without prior administration of bronchodilator was performed and reviewed according to standard criteria¹⁹ in a lung physiology laboratory with experienced test-personnel, using a Vmax spirometer (SensorMedics, Anaheim, California, USA) for the first two study visits, and a Vyntus pneumo spirometer (Vyaire, Hoechst, Germany) for the last. Forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), the ratio FEV₁/FVC and forced expiratory flow at 25%–75% of FVC (FEF_{25–75%}) were recorded. Raw data were normalised for age, sex, ethnicity and height.²⁰ The lower limit of normal (LLN) was defined as z-score ≤ -1.645 . The Global lung function initiative (GLI) equations were used to estimate peak expected lung function at 20 and 22 years for females and males, respectively, defining participants' final height as measured at 18 or 25 years, whichever was highest. The spirometry criteria for COPD was defined as FEV₁/FVC z-score $\leq$ LLN.

Statistical methods

Descriptive data are reported as means, SD, ranges, counts and/or percentages, as appropriate. Questionnaire data are presented as at least one positive response at any visit. Welch's one-way analysis of variance (ANOVA)/t-tests, Kruskal-Wallis, Wilcoxon-Mann-Whitney and Pearson's χ^2 tests, were performed to compare exposure variables between cohorts and between extremely preterm and term-born subjects within cohorts, as appropriate. We fitted linear mixed-effects longitudinal models to estimate, for each time point, mean z-scores for FEV₁, FVC, FEV₁/FVC and FEF_{25–75%}, and FEV₁ as percentage of expected adult peak. The explanatory variables were cohort, age group and subject category (term-born vs extremely preterm-born without BPD vs extremely preterm-born with BPD). For maximal flexibility, all possible interactions of these explanatory variables were included, and subjects were included as a random intercept. The use of mixed-effects models allows inclusion of subjects with incomplete follow-up data, reduces bias caused by missing data, and increases the precision of the estimates.²¹

We fitted simplified versions of the full model to test for cohort effects and parallel longitudinal patterns, and we compared the

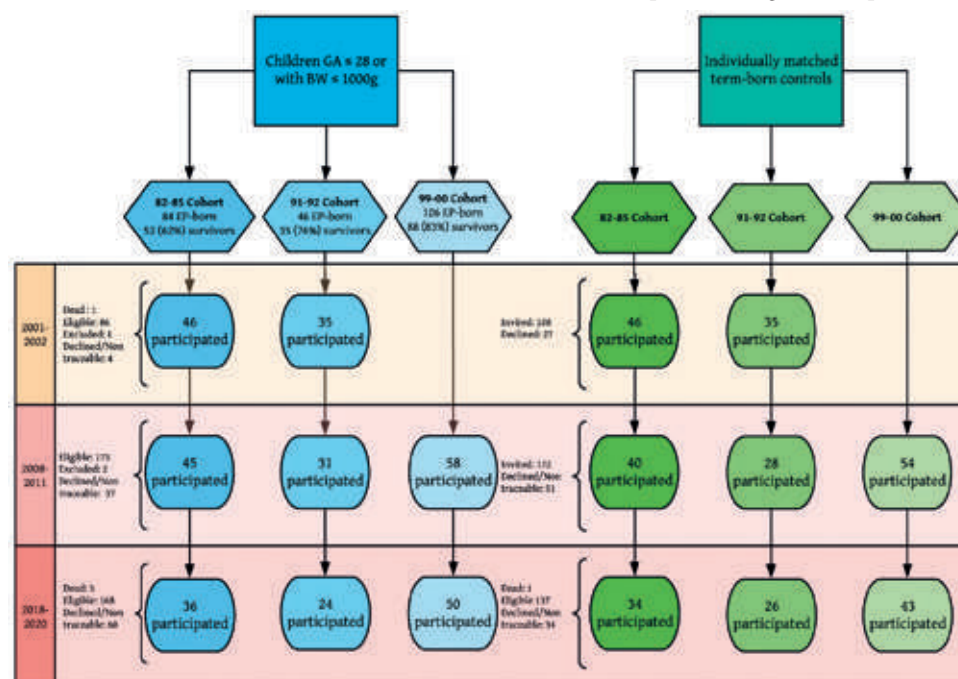


Figure 1 Patient inclusion. The inclusion procedure for the extremely preterm (EP)-born (born at gestational age ≤ 28 weeks or birth weight ≤ 1000 g) and their matched term-born controls. BW, Birth weight; GA, gestational age.

Table 1 Perinatal data

	82–85 cohort		91–92 cohort		99–00 cohort		P value
Term-born, participated/eligible	46/46		35/35		57/57		–
EP-born, participated/eligible	49/51		35/35		64/88		–
Perinatal data of term-born and EP-born subjects							
Birth weight in grams, mean (range)							
Term-born	3441	(3000–4000)	3564	(3010–4000)	3696	(2990–4500)	0.003
EP-born	1005	(580–1480)	933	(570–1400)	844	(450–1250)	<0.001
EP no BPD	1047	(580–1480)	976	(620–1400)	862	(450–1250)	0.001
EP BPD	888	(670–1080)	851	(570–1200)	827	(520–1100)	0.39
Maternal smoking during pregnancy, n (%)							
Term-born	10	(22)	9	(26)	–	(26)*	0.72
EP-born	22	(48)	13	(38)	15	(25)	0.06
Perinatal data of the EP-born subjects							
Gestational age in weeks, mean (range)	27.5	(23–34)	26.7	(23–31)	26.7	(24–31)	0.03
SGA, n (%)	9	(18)	5	(14)	23	(36)	0.03
Birth weight Z score, mean (SD)	–0.5	(1.2)	–0.3	(0.9)	–0.8	(1.3)	0.13
Postnatal days with oxygen treatment, median (quartiles)†	42	(26–56)	49	(26–71)	61	(40–78)	0.05
Days on CPAP, median (quartiles)	3	(0–14)	8	(1–28)	29	(19–42)	<0.001
Ventilator days, median (quartiles)	8	(1–16)	4	(1–12)	5	(2–9)	0.04
BPD n (%)	13	(27)	12	(34)	33	(52)	0.02
Antenatal steroids, n (%)	17	(35)	15	(44)	52	(81)	<0.001
Surfactant, n (%)	0	(0)	17	(49)	54	(84)	<0.001
Postnatal steroids, n (%)	4	(8)	10	(29)	20	(31)	0.01
PDA closure, medical or surgical, n (%)	13	(27)	17	(49)	14	(22)	0.02

Cohort differences were tested using Welch's one-way ANOVA for continuous variables and Pearson's χ^2 test for categorical variables.

*Data not recorded for term-born from this cohort; the reported value represents percentage of smoking mothers of all births in the region, from the medical birth registry of Norway. The corresponding p value is based on comparison of the two earliest cohorts.

†Cohort differences were tested using Kruskal-Wallis test due to skewed data.

ANOVA, analysis of variance; BPD, bronchopulmonary dysplasia (supplemental oxygen or respiratory support at postmenstrual age ≥ 36 weeks); CPAP, continuous positive airway pressure; EP, subjects born extremely preterm or with extremely low birth weight (gestational age ≤ 28 weeks or birth weight ≤ 1000 g); PDA, persistent ductus arteriosus; SGA, small for gestational age (BW <10th percentile for GA according to Norwegian growth curves).

full and simplified models using likelihood ratio tests. To compare cohorts of extremely preterm-born subjects, we omitted the age variable, as FEV₁ z-scores were stable over time. To assess the effects of neonatal variables, we fitted a multiple regression model for z-FEV₁ at 18 years, the only age where all cohorts had measurements. Explanatory variables were cohort, BPD status, GA, BW z-score, maternal smoking and treatment with surfactant and antenatal steroids. We evaluated the effect of current smoking at 18 years on z-FEV₁ for the 82–85 and 91–92 cohorts by Welch's t-test (data missing for the 99–00 cohort).

All models were fitted using R V.4.0.2, and the mixed-effects models by using the R package 'lme4' V.1.1–25. Values of $p \leq 0.05$ were characterised as statistically significant.

The study was originally designed in 2001 to have 90% power to detect differences exceeding 7.5 percentage points in FEV₁ between the extremely preterm-born and term-born groups, given normally distributed data, a within-group SD of 10 percentage points, and a two-sided significance level of 0.05. This required a sample-size of 39 in each group.

RESULTS

Subjects

In total, 217 extremely preterm-born were admitted to the two NICUs during the three inclusion periods; 174 (80%) were alive at first follow-up. Survival rates at hospital discharge were 62%, 76% and 83% in the 82–85, 91–92 and 99–00 cohorts, respectively. During the follow-up period, three died and three were excluded due to inability to perform spirometry. In total, 148/174 (85%) participated at least once, 122/174 (70%) at two or more visits, and 99/171 (58%) participated at all possible visits (three for the 82–85

and 91–92 cohort, two for the 99–00 cohort) (figure 1). Sixteen subjects were included solely on the BW criterion, six in the 82–85 cohort (mean GA 31 weeks), two in the 91–92 cohort (GA 30 and 31 weeks), and eight in the 99–00 cohort (mean GA 29.6 weeks).

To recruit a full 1:1 control group, we approached 1.3 term-born subjects per extremely preterm-born in the 82–85 and 91–92 cohorts, and 1.6 in the 99–00 cohort. Altogether 138 controls were included, one died during the study period. In total, 93/137 (68%) participated at all possible visits and 115/138 (83%) at two or more visits.

Perinatal characteristics

For term-born participants, mean BW increased with birth-decade. For extremely preterm-born, mean BW and GA decreased, and the proportion born SGA increased with birth-decade. Days on oxygen supplementation and the proportion with BPD increased with birth-decade, as did the use of CPAP, surfactant and antenatal as well as postnatal steroids, whereas the number of ventilator days decreased. Exogenous surfactant was unavailable for the 82–85 cohort, available as synthetic surfactant (Exosurf) provided according to the OSIRIS study protocol for the 91–92-cohort,²² and as porcine-derived surfactant (Curosurf) provided according to existing guidelines to the 99–00 cohort. Details on neonatal management have been described previously.^{15–16} Maternal smoking decreased with birth-decade. Perinatal characteristics did not differ between participants and non-participants in the 99–00 cohort, except that more non-participants were exposed to maternal smoking during pregnancy (56% vs 25%; online supplemental table E1). Non-participation rates for the two oldest cohorts were negligible (table 1).

Table 2 Background variables (n=286)

Cohort		82–85 cohort			91–92 cohort			99–00 cohort		
Participated/eligible*	Term-born	46/46	(100)	–	35/35	(100)	–	57/57	(100)	–
	EP-born	49/51	(96)		35/35	(100)		64/88	(73)	
Female sex, n (%), p value	Term-born	21	(46)	–	22	(63)	–	27	(47)	–
	EP-born	21	(43)		22	(63)		31	(48)	
Final Height in cm, mean (SD), p value	Term-born	174	(8)	0.04	171	(9)	0.09	177	(10)	<0.001
	EP-born	170	(8)		167	(9)		168	(10)	
Adult Weight in kg, mean (SD), p value	Term-born	73	(14)	0.73	73	(14)	0.34	73	(14)	0.02
	EP-born	74	(18)		69	(14)		66	(14)	
Self-reported smoking, n (%), p value	Term-born	16	(35)	0.42	8	(23)	0.04	–†	–	–
	EP-born	21	(43)		2	(6)		2	(6)	
Atopy, n (%), p value	Term-born	20	(43)	0.13	8	(23)	0.78	20	(40)	0.04
	EP-born	13	(28)		9	(26)		12	(22)	
Wheeze last 12 months, n (%), p value	Term-born	17	(38)	0.27	15	(43)	0.34	7	(13)	0.10
	EP-born	24	(49)		19	(54)		15	(24)	
Asthma med. last 12 months, n (%), p value	Term-born	6	(13)	0.34	4	(13)	0.17	3	(5)	0.25
	EP-born	10	(20)		9	(26)		7	(11)	
Asthma ever, n (%), p value	Term-born	9	(20)	0.06	10	(29)	0.14	5	(9)	<0.001
	EP-born	18	(37)		16	(46)		22	(35)	
Current asthma, n (%), p value	Term-born	6	(13)	0.10	8	(23)	0.29	4	(7)	0.31
	EP-born	13	(27)		12	(34)		8	(13)	

The listed variables 'Allergy', 'self-reported smoking', 'wheeze last 12 months' and 'asthma med. last 12 months' refer to the number (fraction) with a least one positive response or finding at any visit. 'Current asthma' refers to a combination of wheeze in the last 12 months plus a positive response to the questions 'asthma ever' or 'asthma medication last 12 months' on minimum one visit. P value refers to comparisons between EP and term-born (Welch's t-test for continuous data and Pearson's χ^2 test for categorical data).

*At least one visit (all percentage and p values are based only on visits where the subject participated).

†Data not presented due to large amount of missing data.

Adult weight, weight at 25 years (or 18 years if not applicable); Asthma med, asthma medication; EP, subjects born extremely preterm or with extremely low birth weight (gestational age ≤ 28 weeks or birth weight ≤ 1000 g); Final height, the height achieved at 18 or 25 years, whichever was highest.

Anthropometric measurements and information from questionnaires

Adult extremely preterm-born attained a lower height than term-born. Questionnaires revealed no significant differences between the extremely preterm-born and term-born participants regarding wheeze, use of asthma medication or current asthma. Significantly more extremely preterm-born responded 'yes' to the question 'Have you ever had asthma', although atopy tended to be more common in term-born. Smoking became less common from the 82–85 to the 91–92 cohort for extremely preterm-born but not term-born ($p < 0.001$ and $p = 0.24$, respectively). Complete questionnaire data from each visit are available in online supplemental table E2 (table 2).

Lung function

For term-born controls, mean z-scores for spirometry variables were close to zero at most assessments (table 3). Notably, for the next-to last visit of the 99–00 cohort, mean z-FEV₁ was -0.3 and the 95% CI did not include zero (table 3), thus, development was not completely stable over time (likelihood ratio test comparing a full model to a model without age effect for term-born, $p = 0.005$, figure 2).

For extremely preterm-born, mean z-scores for FEV₁, FEV₁/FVC and FEF_{25–75%} were significantly below zero and below those of term-born at most assessments, with a few exceptions for the non-BPD group in the 91–92 and 99–00 cohorts (table 3). The deficits were largest for the BPD groups in the 82–85 and 91–92 cohorts. Within each of the extremely preterm-born cohorts, z-FEV₁ remained stable from childhood to adulthood (likelihood ratio test comparing a full model to a model without age effect for extremely preterm-born, $p = 0.27$, figure 2).

Significantly more extremely preterm-born than term-born had z-scores for FEV₁, FEV₁/FVC and FEF_{25–75%} below LLN at minimum one visit (table 4). Notably, 44 (30%) extremely preterm-born compared with 7 (5%) term-born fulfilled the COPD

spirometry criteria ($p < 0.001$), with respectively 20 and 5 also reporting wheeze. The fraction below LLN for extremely preterm-born with vs without BPD were 24 (41%) vs 20 (22%), respectively.

Lung function differences across three decades

Across the three birth cohorts, z-FEV₁ for extremely preterm-born increased (likelihood ratio test comparing a model with a cohort effect for extremely preterm-born to one without a cohort effect, $p = 0.009$), and approached the term-born in the last cohort. The improvements occurred in the subgroup without BPD from the 1980s and in the subgroup with BPD from the 1990s (figure 2). When exploring effects from neonatal variables, only birth cohort and BW z-score had a significant impact on z-FEV₁ at 18 years ($p = 0.03$ and 0.006 , respectively), not maternal smoking, GA, BPD status, or the use of surfactant or antenatal steroids (online supplemental table E3). Current smoking was not associated with z-FEV₁ at 18 years ($p = 0.15$ and 0.92 for term and extremely preterm-born, respectively).

Development of FEV₁ as percentages of peak expected values

FEV₁ expressed as percentages of expected adult peak values revealed parallel trajectories for term- and extremely preterm-born in the 82–85 and 91–92 cohorts (global test for lack of parallelism for these two cohorts, $p = 0.33$). In the 99–00 cohort, the trajectories diverged between the term- and extremely preterm-born (global test for lack of parallelism for all three cohorts, $p = 0.03$), with term-born developing marginally better. The two extremely preterm-born cohorts who had reached 25 years of age did not achieve their expected peak lung function, mean FEV₁% of expected adult peak (95% CI) were 99% (96% to 101%) for term-born; 89% (84% to 94%) and 86% (83% to 90%) for extremely preterm-born in the 91–92 and 82–85 cohorts, respectively (figure 3).

From 25 to 35 years of age (82–85 cohort), FEV₁ declined for both term-born and extremely preterm-born. Relative to their expected peak values, the decline did not differ significantly between the groups

Table 3 Spirometric lung function data comparing term-born with extremely preterm subjects (n=286 subjects)

82–85 cohort*				91–92 cohort				99–00 cohort				19.8 (18.2–21.4)		
Age (mean, range)	17.7 (15.3–19.9)		24.9 (22.5–27.0)		34.5 (32.1–37.6)		10.6 (9.7–11.5)		17.8 (17.0–19.2)		27.1 (26.1–28.4)		11.6 (10.1–13.8)	
n/eligible														
Term-born	46/46	40/46	34/46	35/35	28/35	26/34	54/57	43/57						
EP no BPD	34/38	32–33/38	25–26/36	23/23	19/23	15/23	26/43	27/43						
EP BPD	12/13	12/13	9–10/12	12/12	12/12	9/12	32/45	23/45						
FEV ₁ z-score	Mean	95% CI	P value	Mean	95% CI	P value	Mean	95% CI	P value	Mean	95% CI	P value	Mean	95% CI
	95% CI	95% CI	P value	95% CI	95% CI	P value	95% CI	95% CI	P value	95% CI	95% CI	P value	95% CI	95% CI
Term-born (ref)	0.0	–0.3 to 0.3	–	–0.1	–0.4 to 0.3	–	–0.2	–0.6 to 0.1	–	0.1	–0.2 to 0.5	–	–0.3	–0.6 to –0.1
EP no BPD	–1.1	–1.5 to –0.8	<0.001	–0.9	–1.2 to –0.5	0.07	–0.6	–1.1 to –0.2	0.17	–0.4	–0.8 to 0.1	0.08	–0.6	–0.9 to –0.2
EP BPD	–1.5	–2.1 to –1.0	<0.001	–1.6	–2.2 to –1.0	<0.001	–1.5	–2.1 to –0.9	<0.001	–1.4	–2.0 to –0.9	<0.001	–0.7	–1.1 to –0.4
FVC z-score	Mean	95% CI	P value	Mean	95% CI	P value	Mean	95% CI	P value	Mean	95% CI	P value	Mean	95% CI
	95% CI	95% CI	P value	95% CI	95% CI	P value	95% CI	95% CI	P value	95% CI	95% CI	P value	95% CI	95% CI
Term-born (ref)	–0.2	–0.5 to 0.1	–	0.2	–0.2 to 0.5	–	–0.1	–0.5 to 0.2	–	–0.2	–0.6 to 0.2	–	0.4	0.1 to 0.8
EP no BPD	–0.9	–1.3 to –0.6	0.003	–0.4	–0.7 to 0.0	0.11	–0.3	–0.7 to 0.0	0.05	–0.5	–1.0 to –0.1	0.17	–0.4	–0.9 to 0.0
EP BPD	–1.1	–1.6 to –0.5	0.01	–0.6	–1.2 to 0.0	0.07	–0.9	–1.5 to –0.3	0.002	–0.7	–1.2 to –0.1	0.15	–0.2	–0.8 to 0.4
FEV ₁ /FVC z-score	Mean	95% CI	P value	Mean	95% CI	P value	Mean	95% CI	P value	Mean	95% CI	P value	Mean	95% CI
	95% CI	95% CI	P value	95% CI	95% CI	P value	95% CI	95% CI	P value	95% CI	95% CI	P value	95% CI	95% CI
Term-born (ref)	0.4	0.1 to 0.6	–	–0.2	–0.4 to 0.1	–	0.1	–0.2 to 0.4	–	–0.1	–0.5 to 0.2	–	–0.3	–0.6 to 0.0
EP no BPD	–0.3	–0.7 to 0.0	0.002	–0.9	–1.3 to –0.6	<0.001	–0.9	–1.3 to –0.5	0.004	0.0	–0.4 to 0.4	0.73	–0.3	–0.7 to 0.3
EP BPD	–0.7	–1.2 to –0.1	0.001	–1.0	–1.6 to –0.5	0.007	–1.2	–1.8 to –0.6	0.003	–1.4	–2.0 to –0.8	<0.001	–1.7	–2.3 to –1.2
FEF _{25–75%} z-score	Mean	95% CI	P value	Mean	95% CI	P value	Mean	95% CI	P value	Mean	95% CI	P value	Mean	95% CI
	95% CI	95% CI	P value	95% CI	95% CI	P value	95% CI	95% CI	P value	95% CI	95% CI	P value	95% CI	95% CI
Term-born (ref)	0.2	–0.1 to 0.5	–	–0.1	–0.4 to 0.2	–	–0.2	–0.6 to 0.1	–	–0.3	–0.7 to 0.0	–	–0.4	–0.8 to –0.1
EP no BPD	–1.0	–1.3 to –0.7	<0.001	–1.2	–1.6 to –0.9	<0.001	–0.8	–1.2 to –0.4	0.05	–0.6	–1.0 to –0.2	0.32	–0.7	–1.1 to –0.3
EP BPD	–1.5	–2.0 to –0.9	<0.001	–1.5	–2.0 to –0.9	<0.001	–1.6	–2.2 to –1.1	<0.001	–1.9	–2.5 to –1.4	<0.001	–2.1	–2.7 to –1.5

All results are based on longitudinal mixed-effects models. The p values compare EP subjects with controls.

* Two of the eligible non-participants could not be classified according to BPD status, but are presented in the non-BPD group.

BPD, bronchopulmonary dysplasia (supplemental oxygen or respiratory support at postmenstrual age ≥36 weeks); EP, subjects born extremely preterm or with extremely low birth weight (gestational age ≤28 weeks or birth weight ≤1000 g); FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ref, reference level.

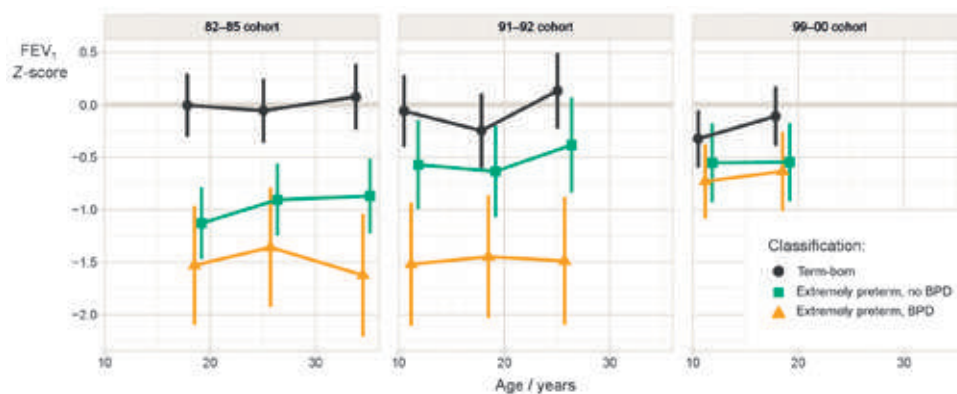


Figure 2 Estimated mean FEV₁ z-scores with 95% CIs in three cohorts of extremely preterm-born (born at gestational age ≤ 28 weeks or birth weight ≤ 1000 g) with or without BPD, and individually matched controls. BPD, bronchopulmonary dysplasia; FEV₁, forced expiratory volume in 1 s.

(from 98.8% to 95.2% in term-born and 86.3% to 81.0% in extremely preterm-born, mean absolute difference in decline 1.7%, 95% CI (-2.2% to 5.7%), $p=0.4$). FEV₁ % of expected peak values stratified by BPD status are presented in online supplemental figure E1.

DISCUSSION

This is the first longitudinal population based study to report lung function trajectories from childhood to the mid-30s for extremely preterm-born cohorts, including also the incipient age-related physiological decline. FEV₁ tracked in parallel, but significantly below the trajectories of term-born controls, including a parallel peak and onset of the age-related decline from 25 to 35 years. Lung function deficits were most pronounced for those born extremely preterm in the early 1980s, and successively smaller for each succeeding decade of birth. One in three extremely preterm-born participants met the spirometry criteria for COPD, although without prior administration of bronchodilator.

Development of lung function from childhood to 35 years of age

Population studies underline the importance of intrauterine and early life events for adult peak lung function,²³ the starting point for physiological age-related decline. Even subtle reductions in adult FEV₁ are associated with cardiovascular disease, poor respiratory health, COPD, and overall mortality.²⁴ There is increasing awareness that COPD is a heterogeneous condition that originates early

in life.²⁵ Until now, lifelong lung function trajectories for extremely preterm-born have represented uncharted territory, as no longitudinal studies have presented data beyond 25 years of age. This study highlights that a disturbingly high proportion individuals born extremely preterm commence their journey towards old age with FEV₁ levels significantly below normal, and that childhood and adolescent airway obstruction follow stable trajectories well into adulthood. This is in accordance with most longitudinal studies of younger extremely preterm-born cohorts,^{9 10 13} although an Australian study reported deterioration of lung function from 8 to 18 years, most prominent in the BPD subgroup.¹¹ We observed an apparent decline in FEV₁ z-score from 25 to 35 years in our 82–85 BPD subgroup (figure 2), but this was not significant, possibly due to small sample size.

Extremely preterm-born harbour numerous risk factors known to be implicated in the development of COPD, such as bronchial hyper-responsiveness and early life lung infections.^{23 25} As our spirometries were performed without prior bronchodilator and the questionnaires were not validated for assessing COPD symptoms, we could not classify COPD. Nevertheless, 30% of extremely preterm-born had FEV₁/FVC below LLN, and 45% of these also reported wheeze in the ISAAC questionnaire. It was encouraging that the onset of the physiological lung function decline from 25 to 35 years did not differ between extremely preterm-born and term-born, suggesting that further age-related decline may not be as steep as reported for other high-risk groups.⁵

Table 4 Spirometry variables below the lower limit of normal at any time

Cohort		82–85 cohort			91–92 cohort			99–00 cohort		
Z-FEV ₁ below LLN at any time, n (%), p value	Term-born (ref.)	3	(7)	–	3	(9)	–	6	(11)	–
	EP no BPD	10	(28)	0.01	4	(17)	0.31	7	(23)	0.13
	EP BPD	7	(54)	<0.001	6	(50)	0.002	8	(24)	0.08
Z-FVC below LLN at any time, n (%), p value	Term-born (ref.)	3	(7)	–	0	(0)	–	4	(7)	–
	EP no BPD	8	(22)	0.04	2	(9)	0.08	1	(3)	0.46
	EP BPD	2	(15)	0.31	1	(8)	0.08	4	(12)	0.41
Z-FEV ₁ /FVC below LLN at any time, n (%), p value	Term-born (ref.)	1	(2)	–	5	(14)	–	1	(2)	–
	EP no BPD	8	(22)	0.004	3	(13)	0.89	9	(29)	<0.001
	EP BPD	5	(38)	<0.001	9	(75)	<0.001	10	(30)	<0.001
Z-FF _{25–75%} below LLN at any time, n (%), p value	Term-born (ref.)	2	(4)	–	6	(17)	–	6	(11)	–
	EP no BPD	11	(31)	0.001	3	(13)	0.67	9	(29)	0.03
	EP BPD	7	(54)	<0.001	9	(75)	<0.001	12	(36)	0.003
Any variable below LLN at any time, n (%), p value	Term-born (ref.)	5	(11)	–	7	(20)	–	8	(14)	–
	EP no BPD	17	(47)	<0.001	6	(26)	0.59	12	(39)	0.008
	EP BPD	9	(69)	<0.001	10	(83)	<0.001	15	(45)	<0.001

The presented data are the number (fraction) of subjects with at least one value $\leq$ LLN at least one visit.

P value refers to comparisons between term-born and EP-born groups using Pearson's χ^2 test.

EP, subjects born extremely preterm or with extremely low birth weight (gestational age ≤ 28 weeks or birth weight ≤ 1000 g); FF_{25–75%}, forced expiratory flow at 25–75% of FVC; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; LLN, Lower limit of normal (z-score ≤ -1.645); ref., reference level.

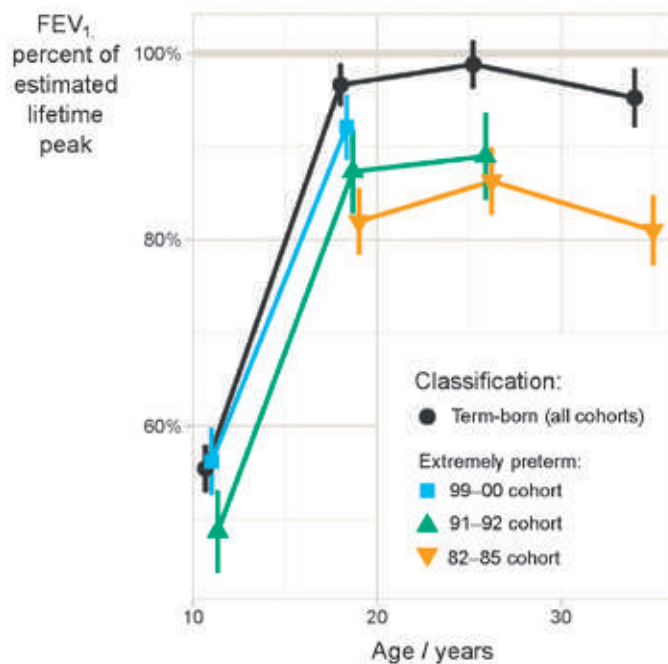


Figure 3 Mean measured FEV_1 as fraction of expected peak FEV_1 (with 95% CIs) in three population based cohorts born extremely preterm (born at gestational age ≤ 28 weeks or birth weight ≤ 1000 g) during three different decades (blue, green and yellow lines), and aggregated data for their individually matched term-born controls (black line), based on mixed-effects longitudinal model. Expected peak FEV_1 was calculated for each individual using the GLI reference equation. FEV_1 : forced expiratory volume in 1 s; GLI, global lung function initiative.

Cohort effects associated with improved perinatal care

Neonatal intensive care improved substantially during the recruitment period, with more extensive use of prenatal steroids, introduction of surfactant, better respiratory care, and generally improved perinatal management.¹ Improvements in care may have contributed to increased survival for the most immature, but the long-term effects on morbidity are less obvious,^{26,27} since a greater number of immature survivors conceivably could lead to poorer outcomes. The scarce literature on these matters is inconsistent. Doyle *et al* assessed three cohorts at 8 years of age born extremely preterm during 1991–2005, and found the poorest airflow patterns in the most recent cohort.²⁸ They argued this could be due to decreased use of postnatal corticosteroids or increased use of CPAP. We also observed increasing use of CPAP with birth cohort, however, no decrease in the use of postnatal steroids, which may have contributed to the differing results. Contrasting Doyle *et al* and in line with our findings, a meta-analysis addressing the effect of preterm birth on FEV_1 % suggested improvements with year of birth from 1980 to 1995.²⁹ One may even read a dose-response effect into our data-set, as improvements from the 1980s primarily occurred in those without BPD, presumably with the least traumatic neonatal history, whereas improvement from the 1990s also encompassed the BPD group (figure 2).

Prospects for the future

Advanced NICUs have facilitated survival in high numbers of immature infants for more than 30 years, paralleled by continuously refined treatment tools.² In our data set, these developments were paralleled by an apparent diminishing long-term significance of BPD. Instead, antenatal factors became more evident, reflected by negative effects from low BW z-scores, findings also reported in a recent Finnish study.³⁰ Preterm birth happens for a reason, and the pathology that leads to early deliveries are likely implicated in the causal pathways that lead to subsequent pulmonary disease—irrespective of optimal postnatal care.

Huge efforts and resources are invested in acute perinatal care of extremely preterm-born compared with the resources spent on the

long-term respiratory challenges that face adult NICU-graduates, with little evidence supporting that therapeutic interventions improve the pulmonary prognosis of BPD after discharge.³¹ Notably, premature birth is not listed as a risk factor for COPD in authoritative statements, and data suggest that few pulmonologists inquire about early life factors.^{32,33} Almost one in three extremely preterm-born participants met the post-bronchodilator spirometry criteria for COPD, and their upcoming age-related lung function decline will inevitably be a concern for adult pulmonologists. Thus, COPD after preterm birth appears to be a neglected condition, reflected even by the taxonomy; we still use the *neonatal* term BPD to label their adult lung disease—decades after their NICU discharge.

Strengths and limitations

Strengths of this study were enrolment of three population-based cohorts born in three different decades, the longitudinal approach, relatively high follow-up rates, and free access to healthcare for all children in the recruitment area, reducing the risk of socioeconomic bias. Similar growth patterns drawn from multiple visits of three cohorts born in eras with different treatment opportunities, support the notion that lung function trajectories in extremely preterm-born parallel those of term-born. The same and unselected control groups throughout the study period minimised risks of selection bias. The senior NICU staff and senior members of the research group were largely the same throughout the study periods.

The main limitation was a relatively low number of participants; however, the population-based design ensured unbiased inclusion. The initial power analysis did not account for stratifying data by BPD or comparisons across cohorts, making subgroup analyses vulnerable to type II errors. GA was assessed by the last menstrual period during 1982–85 and by early ultrasound thereafter. We have previously shown that the different methods probably did not introduce significant bias.³⁴ Our extremely preterm-born cohorts were relatively mature at birth when compared with participants of other recent studies, such as the EPICure.¹⁰ This was probably related to our inclusion criteria, also allowing participation of individuals with BW at or below 1000 g irrespective of GA, resulting in inclusion of more mature SGA infants. Thus, our outcome data are not directly generalisable to all extremely preterm-born cohorts. Categorising the long-term lung disease of preterms by their neonatal BPD status is debated. The definitions of BPD have varied historically and between institutions, with no specific information on anatomy, mechanics, inflammation or pathology in the respiratory organs.³⁵ Due to the longitudinal design, we opted to stick with the ISAAC questionnaire throughout the study, although it is validated for children, not adults.¹⁸ The 99–00 cohort were asked to respond to the questionnaires electronically at the last study-visit, unfortunately with lower response rates. Participation rates decreased over time and with more recent birth cohorts, but attrition did not exceed similar follow-up studies.³⁶ A higher rate of maternal smoking during pregnancy for those lost to follow-up in the 99–00 cohort may suggest that average outcomes were somewhat better in the participants. The spirometry results of the control groups largely confirmed that the GLI equations fitted our population, except the next-to-last visit for the youngest cohort where 95% CI for mean z- FEV_1 did not include zero. We have no clear explanation for this finding. This finding was most likely not attributable to the upgrading of spirometry equipment, as it did not apply to all control-cohorts. We therefore consider the risk of bias due to upgrading of equipment to be small, as laboratory standards were otherwise unchanged during the complete course of the study, and as spirometry is a robust technique.

CONCLUSION

This is the first longitudinal study to describe lung function trajectories from childhood and well into adulthood for population-based cohorts of extremely preterm-born survivors. Spirometry variables tracked in parallel, but significantly below the trajectories of matched term-born controls, including a parallel peak and onset of

the age-related decline from 25 to 35 years. On average, lung function deficits were most pronounced for participants born extremely preterm in the early 1980s, and successively smaller for each decade of birth. Irrespective of birth decade, almost one in three had spirometry values that met the spirometry criteria for COPD.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by reference number: REK nr. 2017-00628. For each study visit, approval was obtained from the Regional Committee for Research Ethics in Western Norway, and signed informed consents from all participants and/or guardians. Participants gave informed consent to participate in the study before taking part.

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O fardo global e regional da doença pulmonar intersticial e da sarcoidose pulmonar entre 1990 e 2019: resultados do estudo *Global Burden of Disease 2019*

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RESUMO

Contexto A doença pulmonar intersticial (ILD) e a sarcoidose pulmonar são doenças respiratórias comuns com uma distribuição heterogênea em todo o mundo. O fardo global e as tendências temporais da DPI e da sarcoidose são raramente exploradas.

Métodos Utilizando a classificação “ILD e sarcoidose pulmonar” do conjunto de dados *Global Burden of Disease 2019*, descrevemos as taxas normalizadas por idade da incidência, mortalidade, anos-vida ajustados à incapacidade (DALY) e a sua variação percentual anual média entre 1990 e 2019 por sexo, Índice Sociodemográfico (SDI) e região.

Resultados Em 2019, a incidência global e mortalidade da ILD e da sarcoidose pulmonar foi de 24,2 milhões e de 169 833 casos, respetivamente. Entre 1990 e 2019, a incidência global, as mortes e os DALY devido a ILD e sarcoidose pulmonar aumentaram 118,6%, 166,63% e 122,87%, respetivamente. A incidência global de ILD e sarcoidose pulmonar foi mais elevada nos homens e concentrou-se principalmente entre pessoas com idades entre os 70-79 anos de ambos os sexos. Foram observadas diferenças regionais significativas no fardo da ILD e da sarcoidose pulmonar: desde 2006, as regiões com SDI elevado apresentaram taxas de incidência normalizadas por idade mais elevadas, mas taxas de mortalidade normalizadas por idade mais reduzidas em comparação com as regiões com um SDI reduzido.

Conclusões O nosso estudo sugere que a incidência, a mortalidade e os DALY da ILD e da sarcoidose pulmonar estão a aumentar a nível global. De modo a reduzir o fardo existente desta condição, são vitais o diagnóstico precoce e o tratamento e devem ser estabelecidas estratégias mais direcionadas e específicas em regiões de fardo elevado. As diferenças na incidência e mortalidade entre regiões podem refletir a influência de fatores genéticos, ambientais, de diagnóstico, farmacoterapêuticos e do sistema de saúde

INTRODUCTION

Interstitial lung disease (ILD) is a group of more than 200 heterogeneous pulmonary disorders and can be categorised into four subgroups, including ILD of known cause, idiopathic interstitial pneumonia (IIP), granulomatous ILD and other forms of ILD.^{1–2} Pulmonary sarcoidosis belongs to the granulomatous ILD group. Accurate diagnosis of ILD is challenging and requires a multidisciplinary approach.^{3,4} Treatment options for ILD are limited, and the prognosis after diagnosis is poor.^{5,6} For example, idiopathic pulmonary fibrosis (IPF) is the most common type of IIP,^{3,7} and historically, the median survival of untreated patients with IPF after diagnosis was 2–3 years. While recent studies show significantly higher survival after antifibrotic treatment,^{8,9} pirfenidone and nintedanib have only been demonstrated to slow down the decline of pulmonary function in IPF, and treatment is not curative.^{10–12} Lung transplantation remains the only treatment option to improve survival and quality of life for many of these patients.¹³

National-level studies suggest the disease burden and outcome vary among different regions

Key messages

What is the key question?

► How do the global incidence, mortality and disability-adjusted life-years (DALYs) of interstitial lung disease (ILD) and pulmonary sarcoidosis change over time?

What is the bottom line?

► Incidence, mortality and DALYs of ‘ILD and pulmonary sarcoidosis’ have increased in recent decades, particularly among the ageing population; ILD and pulmonary sarcoidosis require more accurate diagnosis and early treatments to intervene and improve the life span of affected patients.

Why read on?

► This study used the most comprehensive and timely data from *Global Burden of Disease 2019*, and systematically analysed the temporal and geographical trends of incidence, deaths and DALYs for ILD and pulmonary sarcoidosis. This in-depth analysis helps global medical professionals and healthcare researchers better understand the burden of ILD and pulmonary sarcoidosis in their regions.

and different types of ILD. For example, data from US National Vital Statistics System¹⁴ demonstrated the age-standardised death rate (ASDR) related to IPF increased from 18.81 per 100000 persons in 2000 to 20.66 in 2017; similarly, in the UK, the ASDR of IPF increased substantially from 1.66 per 100000 individuals in 1979 to 8.29 in 2016.¹⁵ Northern Europeans and African-Americans are the two ethnic groups consistently reported to be most affected by sarcoidosis.¹⁶ In the USA, the prevalence of sarcoidosis per 100000 has been reported as 141 among African-Americans and 49.8 among Caucasians,^{17,18} whereas in Sweden, the prevalence of sarcoidosis was reported to be 160 cases per 100000 people.¹⁹

To date, however, few studies have reported comprehensive data on ILD incidence, mortality and disability-adjusted lifeyears (DALYs) trends at a global level. Among them, the global burden of ILD has been described in publications on chronic respiratory disease (CRD) based on the *Global Burden of Disease (GBD) 2017* dataset. These studies suggested an increasing mortality rate due to ILD.^{20,21} The newly released *GBD 2019* dataset (released on 15 October 2020) not only included nine more countries and territories than the *GBD 2017* dataset but also has improved estimates of disease burden based on more recent vital

statistics tables, improved case definitions and improved access to country-level information through collaborations with the WHO. An updated analysis of ILD and pulmonary sarcoidosis based on the newly released GBD 2019 dataset, however, is lacking. In this article, we shed light on the temporal and geographical trends of incidence, deaths and DALYs of the CRD subtype 'ILD and pulmonary sarcoidosis' by sex, region and regional Sociodemographic Index (SDI) globally from 1990 to 2019 using data from the GBD 2019 study.

MATERIAL AND METHODS

Data source

The GBD 2019 study, conducted by the Institute of Health Metrics and Evaluation, involved 21 geographical regions composed of 204 countries and territories from 1990 to 2019. The original input data for ILD and pulmonary sarcoidosis, as well as the modelling strategy for death and non-fatal outcomes, were described in detail previously²² and can be accessed through the Global Health Data Exchange (GHDx) online data source (<http://ghdx.healthdata.org/gbd-2019/data-input-sources>). Nonfatal and death data sources for various countries are detailed in online supplemental tables 1 and 2 and supplemental figure 1. Data sources for the disease burden of ILD and pulmonary sarcoidosis were obtained from the GHDx online data source query tool according to instructions on the website. We extracted the annual case data and age-standardised rates (ASRs) of the incidence, mortality and DALYs of ILD and pulmonary sarcoidosis from 1990 to 2019 according to sex, geographical region, country and territory. The 204 countries and territories were divided into five categories based on the SDI in 2019: high, high-middle, middle, low-middle and low-SDI regions. SDI is a composite indicator of a country's lag-distributed income per capita, average years of schooling and the fertility rate in women under the age of 25 years; it ranges from 0 (less developed) to 1 (most developed).²³ We also analysed the global trends in ILD and pulmonary sarcoidosis according to the following GBD age categories: 0–9, 10–24, 25–49, 50–75 and ≥75 years. Access to and use of GHDx data did not require informed patient consent.

Case definition

ILD and pulmonary sarcoidosis are a composite of chronic respiratory diseases that impair lung function and oxygen uptake through scarring and/or inflammation. The International Classification of Diseases (ICD), 10th revision codes included under this heading are D86–D86.2, D86.9 and J84–J84.9 (box 1), and the ICD, ninth revision codes are 135–135.9, 515 and 515.9–516.9. Notably, the category of ILD and pulmonary sarcoidosis here did not include lung diseases due to external agents, drug-induced interstitial lung disorders, or ILDs due to systemic or rheumatological disease.

Statistical analyses

The standardised approach for estimating the sex-specific and age-specific incidence, mortality and DALYs from the GBD 2019 dataset has been previously described.^{22–24–25} Briefly, the cause of death ensemble model, spatiotemporal Gaussian process regression and a Bayesian metaregression modelling tool, DisMod-MR V.2.1, were used to ensure consistency between incidence, excess mortality and cause-specific mortality. To evaluate the trends in incidence, mortality and DALYs of ILD and pulmonary sarcoidosis, we extracted the ASRs for incidence and mortality per region and calculated their change over time. The ASR, available in the GHDx, was considered as the objective index for quantifying trends of disease. Trends in ASRs are determined first by calculating the annual per cent change (APC), which is the slope of the sampled ASRs for a given location across an interval, followed by calculating the average annual percentage change (AAPC), which is a weighted average of the APCs.²⁶ The APCs and AAPCs were calculated by the Joinpoint Regression program, V.4.8.0.1.

Pearson correlation analysis was used to measure the strength and direction of the association between covariates. Derivative analysis and plots were completed using R program V.3.6.3, with *p* values of <0.05 considered significant.

Box 1 International Classification of diseases-10 codes of diseases included in the current study

D86 sarcoidosis

- ▶ D86.0 Sarcoidosis of lung.
- ▶ D86.1 Sarcoidosis of lymph nodes.
- ▶ D86.2 Sarcoidosis of lung with sarcoidosis of lymph nodes.
- ▶ D86.9 Sarcoidosis, unspecified.

J84 other interstitial pulmonary diseases

- ▶ Excludes 1: drug-induced interstitial lung disorders (J70.2–J70.4).
- ▶ Interstitial emphysema (J98.2).
- ▶ Excludes 2: lung diseases due to external agents (J60–J70).

J84.0 Alveolar and parietoalveolar conditions

J84.1 other interstitial pulmonary diseases with fibrosis

- ▶ Excludes 1: pulmonary fibrosis (chronic) due to inhalation of chemicals, gases, fumes or vapours (J68.4).
- Pulmonary fibrosis (chronic) following radiation (J70.1).

J84.2 lymphoid interstitial pneumonia

- ▶ Lymphoid interstitial pneumonitis.

J84.8 other specified interstitial pulmonary diseases

- ▶ Excludes 1: exogenous lipid pneumonia (J69.1).
- Unspecified lipid pneumonia (J69.1).

J84.9 Interstitial pulmonary disease, unspecified

- ▶ Interstitial pneumonia -not otherwise specified.

RESULTS

Global burden of ILD and pulmonary sarcoidosis

Globally, 24232080 incident cases (95% uncertainty interval (UI) 19 609 750–29 463 387) and 169833 (95% UI 118 756–204 802) deaths due to ILD and pulmonary sarcoidosis occurred in 2019 (table 1 and online supplemental table 3), which accounted for 31.2% of the total incidence and 4.3% of the total deaths among all chronic respiratory diseases (online supplemental figure 2). Among the 21 geographical regions, South Asia had the highest incident case number (7 349 426) of ILD and pulmonary sarcoidosis in 2019, while Oceania had the lowest (34 323). Worldwide, more ILD and pulmonary sarcoidosis cases in 2019 were observed in India, China and the USA (online supplemental table 4). The highest age-standardised incidence rate (ASIR) in 2019 occurred in Peru (779.16, 95% UI 595.7–958.27 per 100000 individuals), which was followed by the USA (747.41, 95% UI 613.16–905.73 per 100000 individuals; figure 1A and online supplemental table 5). According to geographical regions, North America had the highest ASIR (720.9, 95% UI 591.85–872.44 per 100000 individuals) in 2019, whereas Western Europe had the lowest ASIR (37.26, 95% UI 30.5–45.46 per 100000 individuals). The highest ASDR (9.73, 95% UI 6.72–12.47 per 100000 individuals) and ASR of DALYs (168.85, 95% UI 122.93–212.42 per 100000 individuals) were observed in Andean Latin America, and the lowest ASDR (0.33, 95% UI 0.26–0.49 per 100000 individuals) and ASR of DALYs (12.43; 95% UI 10.03–16.67 per 100000 individuals) were documented in Eastern Europe (online supplemental tables 3 and 6 and online supplemental figures 3 and 4). Among the five SDI quintiles, the high-SDI regions had the most incident cases (5 938 102) of ILD and pulmonary sarcoidosis in 2019, and the low-SDI regions had the lowest incident case number (1 790 724). Notably, the low-middle SDI regions had not only the highest ASIR (375.14 per 100000 individuals) but also the highest ASDR (3.75, 95% UI 2.51–5.15 per 100000 individuals) and ASR of DALYs (78.56, 95% UI 54.31–107.04 per 100000 individuals) in 2019. However, the high-middle SDI regions had the lowest ASIR (225.93, 95% UI 182.2–275.46 per 100000 individuals), ASDR (1.14, 95% UI 0.81–1.34 per 100000 individuals) and ASR of DALYs (26, 95% UI 20.53–30.04

Table 1 Incident cases and ASIRs of ILD and pulmonary sarcoidosis among regions in 1990 and 2019 and temporal trends from 1990 to 2019

Characteristic	1990		2019		1990–2019	
	Incident cases, n×10 ³ (95% ul)	Aslr per 100 000, n (95% ul)	Incident cases, n×10 ³ (95% ul)	Aslr per 100 000, n (95% ul)	Change in incidence number, n (%)	AAPC, n (95%CI)
Overall						
Sex	11 085.07 (8941.89-13 600.03)	258.12 (206.97-317.1)	24 232.08 (19 609.75-29 463.39)	294.41 (238.46-356.61)	118.6	0.47 (0.4 to 0.55)
Male	5457.31 (4410.98-6652.15)	267.77 (215.02-327.1)	11 932.37 (9628.22-14 464.32)	304.91 (246.47-368.41)	118.65	0.49 (0.37 to 0.61)
Female	5627.76 (4530.43-6922.09)	252.13 (202.72-311.48)	12 299.71 (9911.07-15 038.09)	287.17 (232.29-350.12)	118.55	0.47 (0.42 to 0.52)
SDI						
High	2715.51 (2165.31-3359.74)	275.16 (220.14-341.96)	5938.1 (4739.16-7303.99)	358.45 (293.09-437.55)	118.67	0.96 (0.65 to 1.27)
High–middle	2478.75 (1997.86-3045.35)	220.33 (177.93-270.06)	4379.07 (3494.56-5390.95)	225.93 (182.2-275.46)	76.66	0.09 (0.04 to 0.15)
Middle	2555.65 (2063.93-3119.95)	216.19 (173.36-265.08)	6276.72 (5005.6-7674.76)	246.55 (198.86-299.64)	145.6	0.47 (0.32 to 0.62)
Low–middle	2516.08 (2031.01-3060.35)	367.22 (292.45-447.07)	5437.88 (4381.26-6587.09)	375.14 (302.44-452.56)	116.13	0.09 (0.05 to 0.13)
Low	816 (671.3-971.79)	275.13 (222.51-332.08)	1790.72 (1470.4-2127.33)	277.21 (225.9-331.61)	119.45	0.07 (0.02 to 0.12)
Region						
Andean Latin America	100.69 (82.78-118.87)	469.63 (377.83-559.81)	385.45 (301.74-464.03)	687.2 (533.52-831.6)	282.82	1.33 (1.27 to 1.39)
Australasia	64.47 (51.7-78.85)	279.04 (225.56-339.97)	151.8 (116.88-188.16)	331.9 (260.05-406.6)	135.45	0.6 (0.42 to 0.78)
Caribbean	39.6 (32.52-47.42)	140.01 (114.49-169.04)	87.54 (72.04-104.76)	171.3 (141.45-204.12)	121.06	0.71 (0.66 to 0.76)
Central Asia	143.47 (118.67-170.78)	276.29 (226.29-329.28)	223.69 (182.82-269.11)	264.4 (219.43-313.7)	55.92	−0.15 (−0.22 to −0.08)
Central Europe	506.68 (412.15-615.97)	356.74 (291.41-431.82)	666.36 (547.25-797.47)	390.32 (321.96-465.23)	31.51	0.35 (0.19 to 0.51)
Central Latin America	302.31 (246.71-365.26)	319.76 (258.22-388.68)	825.57 (674.57-992.2)	346.2 (282.08-415.45)	173.09	0.27 (0.24 to 0.3)
Central sub-Saharan Africa	59.66 (50.51-70.58)	183.13 (152.76-215.55)	4147.24 (3206.6-5286.12)	207.33 (172.66-243.73)	168.78	0.43 (0.4 to 0.47)
East Asia	1658.89 (1308.13-2107.99)	170.75 (133.49-216.49)	788.97 (624.57-995.41)	197.76 (154.5-248.13)	150	0.52 (0.48 to 0.56)
Eastern Europe	873.01 (699.72-1075.48)	330.18 (266.72-404.86)	427.41 (359.39-513.11)	286.03 (230.06-359.39)	−9.63	−0.48 (−0.58 to −0.38)
Eastern sub-Saharan Africa	173.95 (146.54-207.19)	152.81 (126.12-181.62)	989.57 (749.28-1260.53)	169.4 (139.16-201.59)	145.71	0.37 (0.31 to 0.42)
High-income Asia Pacific	543.26 (422.55-689.14)	272.29 (213.53-343.64)	4096.08 (3309.71-5045.98)	260.19 (204.6-326.05)	82.16	−0.18 (−0.33 to −0.03)
High-income North America	1833.1 (1453.69-2280.51)	557.22 (443.25-698.38)	1606.02 (1316.89-1936.7)	720.9 (591.85-872.44)	123.45	0.95 (0.76 to 1.14)
North Africa and Middle East	522.23 (438.98-620.84)	227.42 (187.56-270.29)	34.32 (28.77-42.18)	311.3 (255.19-369.71)	207.53	1.1 (1.05 to 1.16)
Oceania	12.98 (10.92-15.57)	302.61 (250.5-364.97)	7349.43 (5905.51-8892.48)	353.11 (294.59-432.73)	164.35	0.54 (0.52-0.56)
South Asia	3150.83 (2521.09-3856.37)	490.86 (391.15-597.17)	750.43 (590.46-924.4)	493.6 (396.1-598.49)	133.25	0.02 (0 to 0.04)
Southeast Asia	281.25 (226.41-339.99)	94.32 (75.82-114.93)	181.7 (142.39-226.24)	116.83 (93.16-142.16)	166.82	0.74 (0.72 to 0.77)
Southern Latin America	91.79 (72.87-112.78)	194.65 (154.88-240.11)	235.75 (191.99-282.95)	226.77 (179.78-280.63)	97.95	0.51 (0.41 to 0.62)
Southern sub-Saharan Africa	132.37 (108.19-156.99)	397.13 (321.49-478.77)	363.56 (291.66-439.84)	364.8 (295.02-438.42)	78.1	−0.28 (−0.31 to −0.24)
Tropical Latin America	234.21 (189.29-287.66)	219.69 (176.23-270.13)	260.68 (208.9-321.88)	150.64 (121.51-181.32)	55.23	−1.29 (−1.43 to −1.16)
Western Europe	151.23 (122.16-185.55)	30.83 (25.01-38)	500.17 (416.77-605.44)	37.26 (30.5-45.46)	72.37	0.69 (0.61 to 0.77)
Western sub-Saharan Africa	209.1 (175.0w7-249.79)	164.61 (134.74-197.85)		162.94 (133.41-198.4)	139.21	0.01 (−0.11 to 0.13)

AAPC, average annual percentage change; ASIR, age-standardised incidence rate; ILD, interstitial lung disease; SDI, Sociodemographic Index; UI, uncertainty interval.

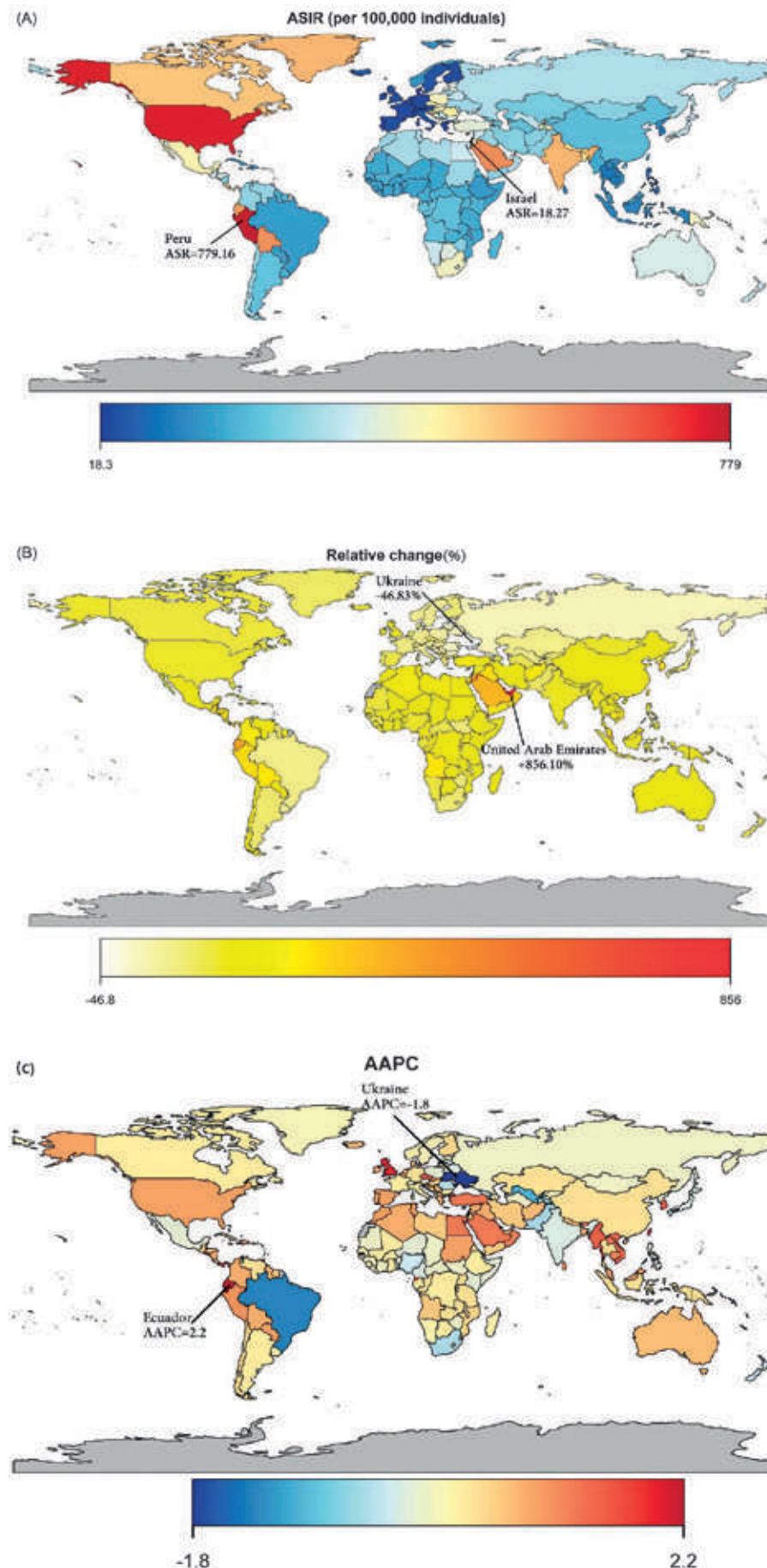


Figure 1 Global incidence of ILD and pulmonary sarcoidosis in 204 countries and territories. (A) ASIRs (per 100 000 individuals) of ILD and pulmonary sarcoidosis in 2019. (B) Relative changes in incident cases of ILD and pulmonary sarcoidosis between 1990 and 2019. (C) AAPCs of ILD ASIRs from 1990 to 2019. Countries with an extreme value for the case number or change were annotated. AAPC, average annual percentage change; ASIR, age-standardised incidence rate; ASR, age-standardised rate; ILD, interstitial lung disease.

per 100000 individuals). As for the age and sex compositions of ILD and pulmonary sarcoidosis, men had higher ASIR, ASDR and ASR of DALYs than women in 2019 (table 1 and online supplemental tables 3 and 6), and the incidence rate was mainly concentrated in people aged 70–79 years in both women and men (figure 2A).

Change in the incidence of ILD and pulmonary sarcoidosis

From 1990 to 2019, the incidence of ILD and pulmonary sarcoidosis increased by 118.6% globally, and the ASIR increased from 258.12 to 294.41 per 100000 individuals. The AAPC of ASIR (0.47, 95%CI 0.4 to 0.55) likewise increased during those 30 years. Among 21 geographical regions, Andean Latin America not only had the most significant increase in case numbers (relative change 282.82%) but also had the highest AAPC of ASIR (1.33, 95%CI 1.27 to 1.39), while Eastern Europe had the largest drop in incident cases (relative change –9.63%). The lowest AAPC of ASIR occurred in Tropical Latin America (–1.29, 95%CI –1.43 to –1.16; table 1). Among 204 countries and territories, the Eastern European country Ukraine had the largest decline in the number of cases (relative change –46.83%) and the lowest AAPC of ASIR (–1.76, 95%CI –1.83 to –1.7). Ecuador (2.19, 95%CI 2.08 to 2.3), UK (1.85, 95%CI 1.7 to 2.01) and Equatorial Guinea (1.78, 95%CI 1.72 to 1.83) were the three countries with the highest AAPC of ASIR (figure 1B,C and online supplemental table 7).

Globally, the ASIR of ILD and pulmonary sarcoidosis had two periods of rapid growth: 2005–2010 (APC=2.85, $p<0.05$) and 2014–2017 (APC=1.43, $p<0.05$). However, this growth trend has been in decline since 2017 (figure 3A and online supplemental figure 5). The ASIR of ILD and pulmonary sarcoidosis increased dramatically in high-SDI regions from 2006 to 2009, with an APC of 12.07 for this period ($p<0.05$), making it the region with the highest incidence since then. Most of the time between 1990 and 2019, low–middle SDI regions had higher ASIR, while middle and high–middle SDI regions had lower ASIR (figure 3A and online supplemental figure 4). From 1990 to 2019, ASIR was positively associated with SDI in most geographical regions except Western sub-Saharan Africa and Eastern Europe (figure 4). According to Pearson correlation analysis, the AAPC of ASIR weakly positively correlated with the SDI in 2019 ($R=0.16$, 95%CI 0.02 to 0.29, $p<0.05$; figure 5A).

From 1990 to 2019, the AAPC of ASIR of ILD and pulmonary sarcoidosis among men and women had a similar trend, 0.47 and 0.49, respectively. The ASIR of men was always higher than that of women (figure 6A and online supplemental figure 5). The AAPCs of ASIR among the age groups under 75 years old varied from 0.25 to 0.42, while the AAPC of people over 75 was 1.35 ($p<0.05$). Hence, the most pronounced increase in incidence was found in people over 75 years old, especially those aged 80–94 (figure 2B and online supplemental figure 6 and supplemental table 8).

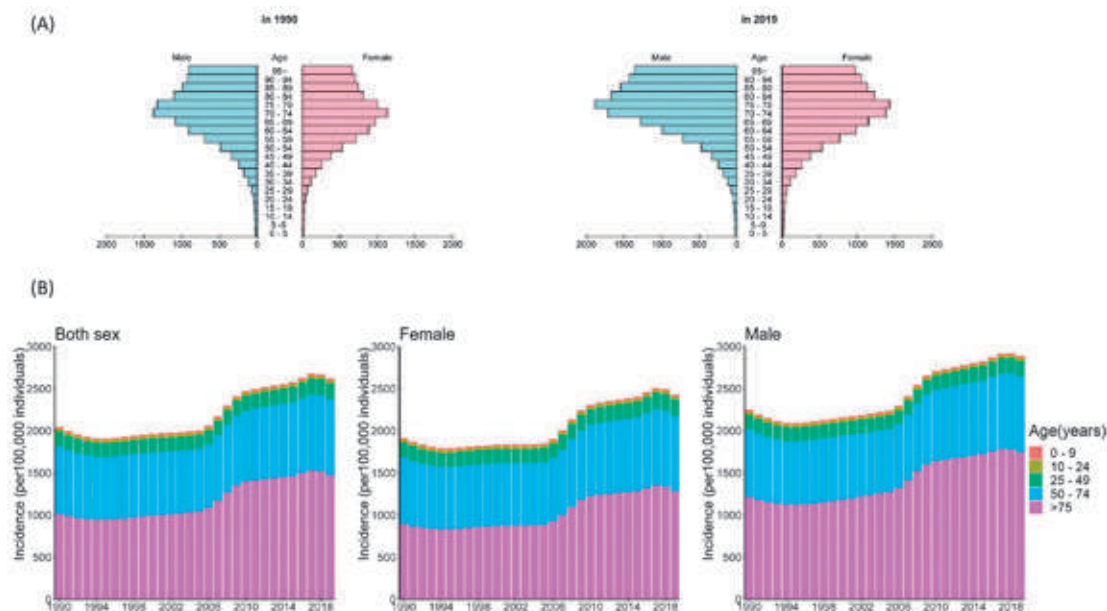


Figure 2 Incidence rate of ILD and pulmonary sarcoidosis by sex and age groups in 1990 and 2019 and temporal trends from 1990 to 2019. (A) Incidence rate (per 100 000 individuals) of ILD and pulmonary sarcoidosis by sex and 20 age groups in 1990 and 2019. (B) Incidence rate (per 100 000 individuals) of ILD and pulmonary sarcoidosis by sex and five age groups from 1990 to 2019. ILD, interstitial lung disease.

Change in ILD and pulmonary sarcoidosis mortality and DALYs

Worldwide, from 1990 to 2019, the number of ILD and pulmonary sarcoidosis deaths increased by 166.63%, with an AAPC of ASDR of 0.78 (95% CI 0.72 to 0.84). Concordantly, the DALYs increased by 122.87%, with an AAPC of DALYs of 0.41 (95% CI 0.35 to 0.41, online supplemental tables 3 and 6). Greece had the highest AAPC of ASDR as well as AAPC of DALYs (online supplemental table 7 and online supplemental figures 3 and 4). Both men and women demonstrated a slowly increasing trend in ASDR and ASR of DALYs; however, men always had higher ASDR and ASR of DALYs from 1990 to 2019 (figure 6B,C).

Among the five SDI quintiles, low-middle SDI regions had the highest ASDR and ASR of DALYs of the past 30 years, and high-middle SDI regions had the lowest ASDR and ASR of DALYs (figure 3B,C).

The ASDR and ASR of DALYs were positively associated with the SDI value in high-SDI regions, but not in the low and middle SDI regions. The ASDR and ASR of DALYs in Andean Latin America increased dramatically between 1996 and 2013, then dropped sharply between 2013 and 2019 (online supplemental figures 8 and 9). Worldwide, the AAPC of ASDR positively correlated with the SDI in 2019 ($R=0.39$, 95%CI 0.26 to 0.5, $p<0.001$; figure 5B). The AAPC of DALYs was positively correlated with the SDI in 2019 ($R=0.37$, 95%CI 0.24 to 0.48, $p<0.001$; figure 5C).

DISCUSSION

In this work, we summarised the incidence, mortality and DALYs of ILD and pulmonary sarcoidosis in 204 countries and territo-

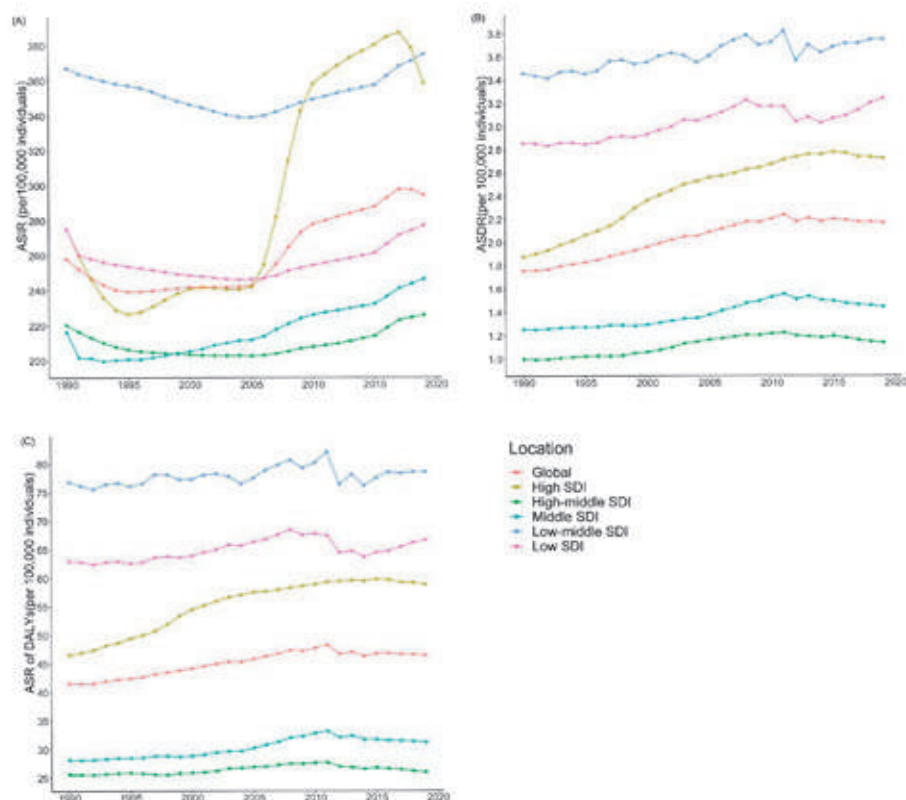


Figure 3 ASR of ILD and pulmonary sarcoidosis by SDI regions from 1990 to 2019. (A) Incidence, (B) death and (C) DALYs. ASDR, age-standardised death rate; ASIR, age-standardised incidence rate; ASR, age-standardised rate; DALYs, disability-adjusted life-years; ILD, interstitial lung disease; SDI, Sociodemographic Index. ASIR, age-standardised incidence rate; ASR, age-standardised rate; ILD, interstitial lung disease.

ries from 1990 to 2019 using data from the latest GBD 2019 data release. The results of this work help characterise trends in ILD and pulmonary sarcoidosis.

The current study characterises trends for incidence, mortality and DALYs of ILD and pulmonary sarcoidosis. In particular, as shown in online supplemental figure 2, among all chronic respiratory diseases captured by GBD, ILD and pulmonary sarcoidosis had the second-highest incidence rate, following asthma and the third-highest mortality rate, following COPD and asthma.

There are several potential reasons for the observed increases in ILD and pulmonary sarcoidosis globally. First, IPF, the dominant subtype of the IIPs, is an age-related disease, and ageing of the global population could be a key contributor to increases in the ILD and pulmonary sarcoidosis diagnostic group. The 2019 World Population Ageing Report showed that the share of the global population aged 65 years or over increased from 6% in 1990 to 9% in 2019; the number of persons aged 80 years or older nearly tripled between 1990 and 2019. In our study, the increase in ILD and pulmonary sarcoidosis incidence was mainly concentrated in people over 75 years old, and the peak onset age of ILD has moved up by 5 years since 1990. The global proportion of people over 65 years old is projected to rise further to 16% in 2050, so it is very likely that the burden of ILD will continue to increase in the future. Second, besides ageing, environmental factors such as air pollution, occupational exposures and smoking may also contribute to the increased incidence of ILD and pulmonary sarcoidosis.^{27,28} The AAPCs of ASIR among the age groups under 75 years old varied from 0.25 to 0.42. This indicates the incidence of ILD and pulmonary sarcoidosis was also significant in younger populations, presumably due to various environmental factors. Third, evolving diagnostic guidelines for ILD in recent decades have impacted the classification of these diseases and therefore their epidemiological profile. For example, in 2002, the American Thoracic Society/European Respiratory Society (ATS/ERS) published the first international diagnostic criteria and classification of IIP; the historical 'gold standard' of histological diagnosis was replaced by a 'dynamic integrated approach' using multidisciplinary discussion.² In 2013, the ATS/ERS IIP classification was updated, and several specific diagnostic criteria were revised in this version.³ Consistently, our results indicate the global ASIR of ILD and pulmonary sarcoidosis had two periods of rapid growth after each version of ATS/ERS IIP classifications were published: 2005–2010 (AAPC=2.85) and 2014–2017 (AAPC=1.43). In addition, the high-SDI regions had an even greater increase of ASIR from 2006 to 2009 (AAPC=12.07). We can infer that the publica-

tion and dissemination of IIP classification and diagnostic criteria improved the global recognition of ILD, especially in high-SDI regions. Last but not least, the improvement of diagnostic ability through wider availability of CT scans and specialist radiology training may also have contributed to the increasing trends seen in ILD and pulmonary sarcoidosis incidence.

In this study, we also found that incidence and mortality of ILD and pulmonary sarcoidosis could be inversely correlated in certain regions. For example, since 2006, high-SDI regions had higher ASIR but lower ASDR compared with the low-SDI regions. In particular, in 2019, high-income North America had the highest ASIR, whereas Andean Latin America, South Asia and South Latin America were in the top three of ASDR and ASR of DALYs. This is likely due to the fact that people living in more developed areas have better access to high-quality medical care leading to early diagnosis and timely treatments;^{29,30} it remains unknown whether differences in calculated mortality rates reflect earlier detection or the benefits of early treatment. Nevertheless, these observations support the importance of early referral and therapy to improve outcomes for patients with ILD and pulmonary sarcoidosis.³¹

We compared our results with other important studies. One previous study published in European Respiratory Journal (ERJ) systematically reviewed the global incidence and mortality of IPF, using data from 21 countries from 1968 to 2012.²⁸ They found the incidence of IPF was higher in Europe and North America and lower in East Asia and South America. In our study, among the 21 geographical regions, we also found North America had the highest ASIR of ILD and pulmonary sarcoidosis in 2019, consistent with the ERJ study. However, the lowest ASIR occurred in Western Europe, which differs from the ERJ study. We think such discrepancy may be due to a broader sampling of countries and a greater range of source data included in GBD 2019, differences in adjustment methods for demographics among countries between those two studies, and the use of the composite diagnosis of ILD and pulmonary sarcoidosis in the current study in contrast to the ERJ study focusing only on IPF. In addition, within our study, both North America and Western Europe are high-SDI regions with similar healthcare resources; their great disparity in ILD incidence may be caused by differences in health service systems and reporting requirements for various disease entities.

Despite providing comprehensive estimates of incidence, mortality and DALYs of ILD and pulmonary sarcoidosis by age, sex, SDI and region for the period of 1990–2019, this study should be interpreted with caution, as our analyses have some inevitable

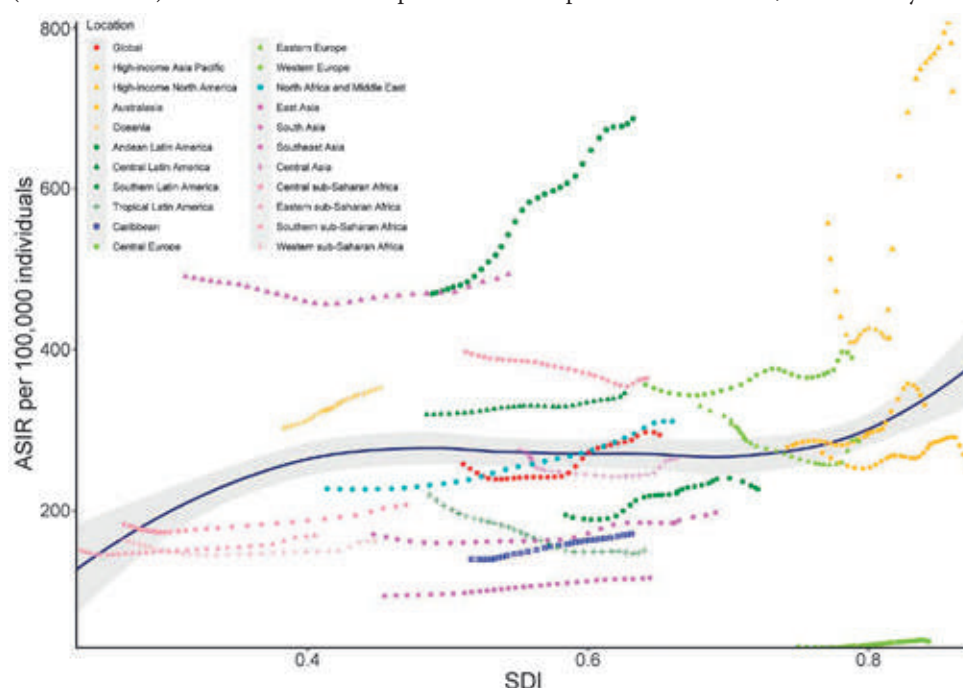


Figure 4 ASIRs of ILD and pulmonary sarcoidosis per 100 000 individuals among regions based on the SDI of each year. ASIR, age-standardised incidence rate; ILD, interstitial lung disease; SDI, Sociodemographic Index.

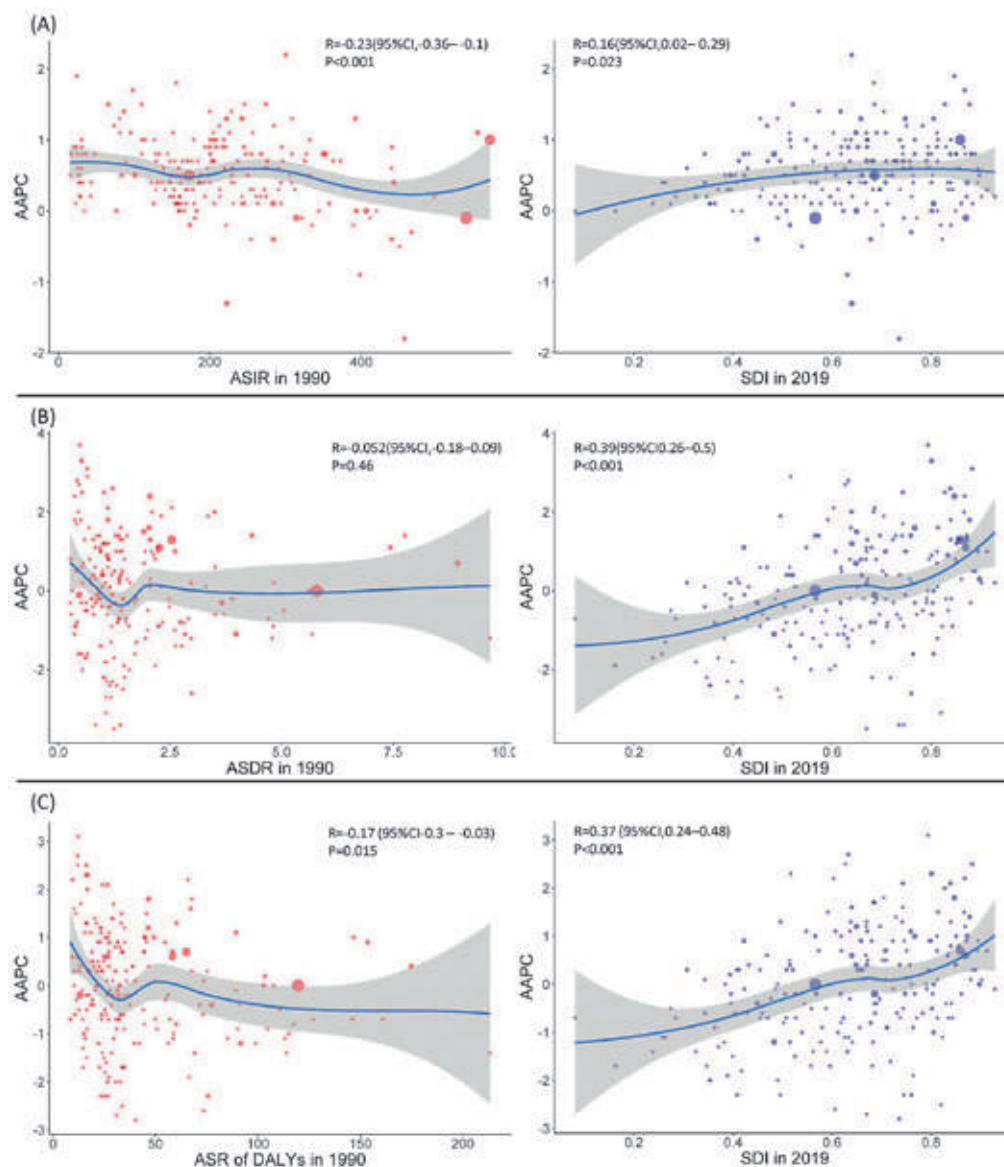


Figure 5 Correlation between the AAPC and the ILD and pulmonary sarcoidosis ASR in 1990 and SDI in 2019: (A) incidence, (B) death and (C) DALYs. The circles represent countries for which SDI data were available. The size of the circles increases with the cases of ILD and pulmonary sarcoidosis in 2019. The R indices and p values presented were derived from a Pearson correlation analysis. AAPC, average annual percentage change; ASDR, age-standardised death rate; ASIR, age-standardised incidence rate; ASR, age-standardised rate; DALYs, disability-adjusted life-years; ILD, interstitial lung disease; SDI, Sociodemographic Index.

limitations. First, our study is limited by the availability of primary data. Where data are not available, the results depend on the effectiveness of the out-of-sample prediction and imputation methods employed by GBD. When data are available, they rely heavily on ICD coding and may not be well adjudicated or may not meet preferred case definitions. Nonetheless, the clearer identification of the preferred and alternative measurement methods for each result, as well as the deviation mapping from alternative methods to reference methods, have led to better stability in GBD 2019 data adjustments than those used in prior releases.²² Second, despite improvements, the GBD 2019 data used for the current analysis may still underestimate the total ILD disease burden. In the GBD 2019 data, the category of ILD and pulmonary sarcoidosis excluded ICD-10 and ICD-9 codes associated with extrinsic causes of ILD, drug-induced ILD and ILD due to systemic (rheumatological) disease. For example, pneumoconiosis, a disease often considered as an occupational ILD, was treated separately from the ILD and pulmonary sarcoidosis in the GBD 2019 study. Hypersensitivity pneumonitis and connective tissue disease-associated are also very common types of ILD which were excluded.²⁷ In future GBD reports, those important subtypes of ILD should be included to truly reflect the disease burden of ILD. Lastly, ILD is an area where case definition and origin of source data are challenging and may differ between countries; the

intrinsic heterogeneity of the classification of ILD and pulmonary sarcoidosis complicates the interpretation of these results. Pulmonary sarcoidosis, in particular, is a cryptogenic, immunosuppressant-responsive disease whose incidence varies widely. Whereas pulmonary sarcoidosis accounts for a large proportion of total ILD in European countries,²⁸ it accounts for very little of ILD in East Asia.⁷ In the next cycle of the GBD study, a broader and detailed classification of ILD will help us better understand its disease burden.

Regardless of the aforementioned limitations, our results revealed clear global trends of increased disease burden of ILD and pulmonary sarcoidosis, perhaps underscoring the importance of demographic trends in driving disease burden. Our study also demonstrated a strong relationship between two periods of rapid growth of incidence of ILD and pulmonary sarcoidosis and publication of ATS/ERS IIP classifications, suggesting the relevance of case definitions for recognition of disease. Moreover, our results also uncovered higher ASIR and lower ASDR of ILD and pulmonary sarcoidosis in high-SDI regions, supporting the notion that more developed regions of the world may benefit from early diagnosis and better treatments. This observation emphasises the need to improve access to care in less developed countries for patients with ILD and pulmonary sarcoidosis. To the authors' knowledge, the current study is the most comprehensive and timely report of

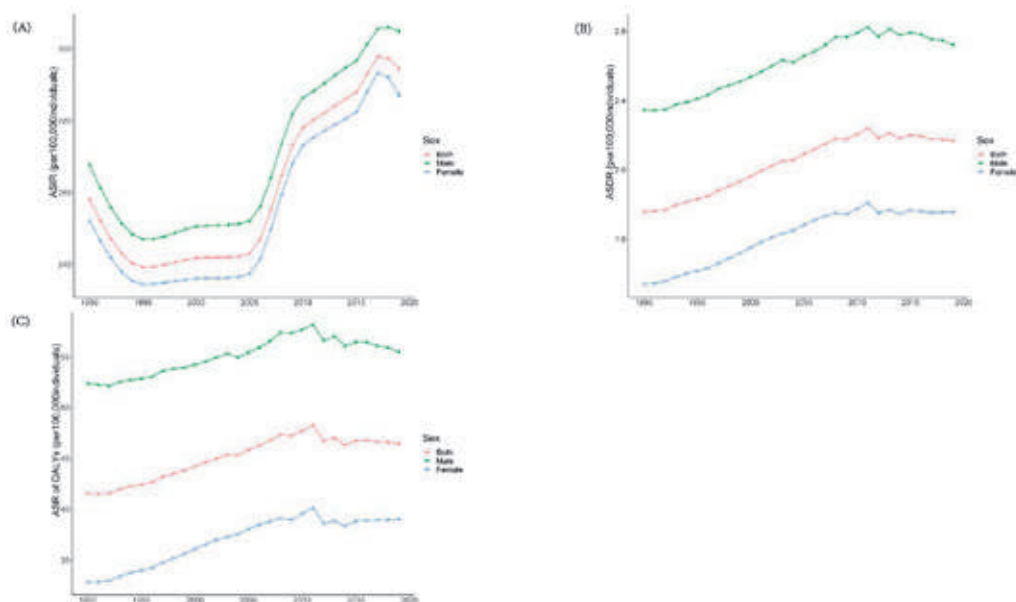


Figure 6 ASR per 100 000 individuals of ILD and pulmonary sarcoidosis in men, women, and both sexes from 1990 to 2019. (A) incidence, (B) death and (C) DALYs. ASR, age-standardised rate; ASDR, age-standardized standardised death rate; ASIR, Age age-standardised incidence rate; ILD, interstitial lung disease.

the global disease burden of ILD and pulmonary sarcoidosis yet published, providing a solid foundation for improved outcomes research and management of the disease in the future.

CONCLUSIONS

Data from this study suggest that the burden of ILD and pulmonary sarcoidosis is increasing with the ageing of the world population. We note considerable heterogeneity in the epidemiology of ILD and pulmonary sarcoidosis across countries and territories, SDI, sex and age. Our findings help policy-makers and medical professionals understand the burden of ILD and pulmonary sarcoidosis in their regions and suggest areas for future research, including the relationship between high incidence and low mortality of ILD and pulmonary sarcoidosis in high-SDI countries.

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ARTIGO ORIGINAL

Vaping de nicotina passivo em casa e sintomas respiratórios em jovens adultos

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RESUMO

Motivo Apesar da elevada prevalência do uso de cigarros eletrônicos (*vaping*), pouco se sabe atualmente sobre os efeitos para a saúde da exposição ao *vaping* de nicotina passivo.

Objetivo Investigar se a exposição ao *vaping* de nicotina passivo está associada a efeitos adversos na saúde respiratória entre jovens adultos.

Método Investigamos o efeito da exposição ao *vaping* de nicotina passivo na pieira, sintomas brônquicos e falta de ar reportados anualmente na coorte prospectiva do *Southern California Children Health Study*. Foram recolhidos dados dos participantes no estudo (n=2097) através de inquéritos anuais consecutivos entre 2014 (idade média: 17,3 anos) e 2019 (idade média: 21,9 anos). Utilizamos uma regressão logística de efeitos mistos para avaliar a associação entre o *vaping* de nicotina passivo e os sintomas respiratórios após controlo para confundidores relevantes.

Resultados A prevalência de *vaping* de nicotina passivo aumentou de 11,7% para 15,6% durante o período do estudo nesta população. A prevalência de pieira, sintomas brônquicos e falta de ar variou entre 12,3% e 14,9%, entre 19,4% e 26,0% e entre 16,5% e 18,1%, respetivamente, durante o período do estudo. Foram observadas associações entre a exposição ao *vaping* de nicotina passivo e os sintomas brônquicos (OR 1,40, 95% IC 1,06 a 1,84) e a falta de ar (OR 1,53, 95% IC 1,06 a 2,21) após controlo para *vaping*, exposição ativa e passiva a tabaco ou a canábis e para características demográficas (idade, sexo, raça/etnia e educação parental). Foram observadas associações mais significativas quando a análise foi limitada a participantes não fumadores nem *vapers*. Não se observaram associações a pieira após o ajustamento para confundidores.

Conclusão A exposição ao *vaping* de nicotina passivo esteve associada a um aumento do risco de sintomas brônquicos e de falta de ar entre jovens adultos.

INTRODUCTION

The prevalence of e-cigarette use (*vaping*, largely with nicotine) increased from 11% to 25.4% among 12th graders in the USA between 2017 and 2019.¹ Therefore, secondhand nicotine vape exposure is likely to be common. Although there is increasing evidence that e-cigarette use is associated with adverse health outcomes, there has been little study of health effects of secondhand nicotine vape exposure.² A recent cross-sectional study reported an association between asthma exacerbation and secondhand nicotine vape exposure³; however, to our knowledge, there has been no longitudinal study investigating the chronic effect of secondhand nicotine vape exposure on respiratory health outcomes. This is an important question because, unlike active smoking, secondhand nicotine vape exposure is not a voluntary exposure. Evidence of adverse health effects of secondhand nicotine vape would provide a compelling rationale for reducing home exposure to secondhand nicotine vape, and for restricting *vaping* in public places, just

Key messages**What is the key question?**

► Is secondhand vape exposure detrimental to respiratory health in young adults?

What is the bottom line?

► Secondhand vape exposure was associated with increased risk of bronchitic symptoms and shortness of breath in young adults, even after accounting for active smoking and *vaping*.

Why read on?

► Primary and secondhand exposure to *vaping* is highly prevalent among the adolescents and young adults but there has been little research investigating the effects of secondhand vape exposure on respiratory health.

as adverse health effects of secondhand smoking resulted in regulation of smoking in public places.

Parents often have more relaxed ‘vape-free’ policies at home than ‘smoke-free’ policies.^{4,5} In a recent survey, smoking inside the home was allowed in 37.4% of homes of current and former smokers, while *vaping* inside the home was allowed in 60.4% of homes of vapers, as secondhand nicotine vape exposure was perceived to be less harmful than secondhand smoking.⁶ Although secondhand exposure to particulate matter from e-cigarettes is lower than from combustible cigarettes,⁷ the ultrafine particle concentration in e-cigarette aerosol can be higher than in cigarette smoke, potentially delivering toxins to the distal airways and alveoli.⁸ E-cigarette aerosol also contains volatile aldehydes and oxidant metals,^{9–14} compounds that are known to cause lung toxicity.

Based on the known toxicity of *vaping* aerosols, we hypothesised that secondhand nicotine vape exposure would be associated with adverse respiratory symptoms such as wheezing, bronchitic symptoms and shortness of breath. We addressed this question in the Southern California Children’s Health Study,¹⁵ a cohort with detailed annual information on self-reported active *vaping* and secondhand nicotine vape exposure, combusted tobacco and cannabis smoke exposure, and self-reported respiratory health outcomes.

METHODS**Study design**

A baseline (wave 1) population of 2097, 11–12th grade Children Health Study participants (mean age 17.3 years, SD 0.6 years), were enrolled in this study from a cohort from schools throughout Southern California.¹⁵ Detailed exposure and health data were collected using self-completed



paper questionnaires in classrooms for wave 1 and online using research electronic data capture (REDCap)¹⁶ tools hosted at the University of Southern California across three additional waves of follow-up through 2019. The current analysis was limited to 2090 participants who provided data on secondhand nicotine vape exposure in at least one of the four waves. The total number of participants was 2090 in wave 1 (year 2014), 1609 in wave 2 (year 2015), 1502 in wave 3 (year 2017) and 1637 (78.3% of the original sample) in wave 4 (year 2018). An initial loss of 481 participants (23%) in wave 2 occurred during the transition from classroom to online collection after completing high school, some of whom participated in later follow-up. Those who were lost to follow-up at wave-2 were more likely to be male, Hispanic whites and parents not having any college education, compared with those who remained in the study (online supplemental table S1). The prevalence of secondhand nicotine vape exposure, bronchitic symptoms and wheeze did not differ substantially between those who were lost to follow-up in wave 2 and those who remained at wave 2. Additional description of the cohort has been reported previously.^{15,17}

Measures

Respiratory symptoms

Respiratory symptoms assessed, based on prior reports of effects of vaping,^{15,18} were bronchitic symptoms, wheeze and shortness of breath during the previous year. Bronchitic symptoms (bronchitis, cough or phlegm bronchitic symptoms) were based on reported (1) bronchitis in the previous 12 months, (2) daily cough in the morning for 3 months in a row, (3) daily cough at other times of the day for 3 months in a row or (4) congestion or phlegm other than when accompanied by a cold. Participants were considered to have bronchitic symptoms if they responded yes to any of the four symptoms.^{15,18} Wheeze was based on a report of wheezing or whistling in the chest during the previous 12 months. Shortness of breath was based on a report of having been troubled by shortness of breath when hurrying on level ground or walking up a slight hill. Information on shortness of breath was collected starting in wave 2 of the study.

SECONDHAND VAPING AND SMOKING EXPOSURE

Detailed information on secondhand exposure to e-cigarette aerosol and cigarette smoke was collected at each wave. Secondhand nicotine vape exposure at each wave was defined based on participants' reports that anyone in the household (other than the participant) used 'e-cigarette or other electronic nicotine delivery devices'. Secondhand smoking exposure at each wave was defined based on reports of secondhand exposure to combustible tobacco. Secondhand cannabis exposure at each wave was defined based on participants' responses that anyone in the household 'smoked or vaped cannabis'. Information on secondhand cannabis was available only in waves 3 and 4.

Primary vaping or smoking was defined based on participants' reports of any active vaping or smoking of nicotine or cannabis in the previous 30 days (yes/no) at each wave. Use of cannabis was available only in waves 3 and 4.

Sociodemographic information

Information was available on participants' gender, ethnicity (Hispanic white, non-Hispanic white, Asian, African American and other (ie, Pacific Islander, native American/Alaska Native, multi-racial or not defined)), and highest parental educational level, as previously described.¹⁵

Statistical analysis

Mixed effect logistic regression models were used to evaluate the association between secondhand nicotine vape exposure in each wave and each respiratory symptom (bronchitic symptoms, wheeze and shortness of breath) in that wave. All models included a participant-level intercept (random effect) to account for multiple observations over time, with adjustment (fixed effect) for sex, race/ethnicity, baseline age and parental education. All models were additionally adjusted for primary vaping or smoking and se-

condhand smoking/secondhand cannabis exposure. To assess the impact of the timing of exposure, we also fitted a model containing a four-level categorical exposure variable based on the joint distribution of 1-year lagged and current secondhand nicotine vape exposure: no secondhand nicotine vape exposure in the previous and current year (reference group), secondhand nicotine vape exposure in previous year only, secondhand nicotine vape exposure in current year only and secondhand nicotine vape exposure in both previous and current year. As sensitivity analyses, we additionally restricted the sample to participants (1) without primary vaping or smoking, (2) who were not lost to follow-up in wave 2 and (3) who reported no history of physician diagnosed asthma at wave 1. Statistical analyses were conducted using SAS V.9.4 (SAS Institute).

RESULTS

Study population

Among the 2090 study participants, about half were Hispanic white (51.8%) and male (50.4%; table 1). The distribution of the demographic factors of participants with respiratory symptoms was largely similar to that of the overall population, except that participants with shortness of breath were more likely to be female (shortness of breath participants: 70.2% female versus non-shortness of breath participants: 43.4% female, $p<0.01$).

Prevalence of vaping and smoking exposure

The prevalence of secondhand nicotine vape exposure increased from 11.7% to 15.6% from wave 1 to wave 4 in the study population (figure 1), while the prevalence of secondhand smoking decreased from 26.6% to 20.6%. Past 30-day use of cigarettes, e-cigarettes and cannabis (wave 3 to wave 4) increased over the study period. None of those changes were statistically significant except for the observed increase of primary vaping or smoking from 12.1% in wave 1 to 34.0% in wave 4 ($p<0.001$).

A majority of the participants (76.0%–93.1%) who had secondhand nicotine vape exposure during any of the study waves was also likely to have personal use of tobacco or cannabis products or secondhand exposure to combustible products (online supplemental table S2). For example, during wave 4, out of the participants who reported secondhand nicotine vape ($n=223$), only 6.9% had no other vaping or smoking related exposures, while 11.5% had primary vaping or smoking, but no secondhand smoking exposure, 33.2% had secondhand smoking, but no primary vaping or smoking exposure, and 48.4% had both secondhand smoking and primary vaping or smoking exposure.

Prevalence of respiratory symptoms

Over the study period, an increase in the prevalence of wheeze and bronchitic symptoms was observed in the study population (not statistically significant). The prevalence increased from 12.3% to 14.9% for wheeze and 19.4% to 26.0% for bronchitic symptoms (figure 2). The prevalence of shortness of breath did not show any clear trend over time, with prevalence of 16.5% in wave 2, 18.1% in wave 3 and 17% in wave 4.

Effect of secondhand nicotine vape exposure on respiratory symptoms

Compared with unexposed participants, participants with secondhand nicotine vape exposure had increased odds of reporting wheeze during the same year (OR 1.56, 95% CI 1.12 to 2.17), bronchitic symptoms (OR 1.90, 95% CI 1.48 to 2.44) and shortness of breath (OR 1.87, 95% CI 1.33 to 2.63), after controlling for age, sex, race/ethnicity and parental education (table 2: model 1). After additionally adjusting for secondhand smoking, secondhand cannabis, and primary vaping or smoking, the secondhand nicotine vape exposure associations with bronchitic symptoms (OR 1.40, 95% CI 1.06 to 1.84) and shortness of breath (OR 1.53, 95% CI 1.06 to 2.21) were attenuated, and the association between secondhand nicotine vape exposure and wheeze was not statistically significant (table 2: model 2). We observed no statistically significant modifying effect of race/ethnicity, sex, and age on the association between secondhand nicotine vape exposure and respiratory outcomes.

Table 1 Demographic characteristics of participants and those who reported wheeze, bronchitic symptoms, shortness of breath or secondhand nicotine vape exposure during the study period*

	Total	Wheeze†	Bronchitic symptoms†	Shortness of breath†	Secondhand nicotine vape exposure†
	N=2090	N=510	N=811	N=480	N=542
Race					
Asian	72 (3.4)	16 (3.1)	27 (3.3)	19 (4.0)	17 (3.1)
Black	31 (1.5)	9 (1.8)	12 (1.5)	2 (0.4)	6 (1.1)
Hispanic white	1081 (51.8)	214 (42.0)	378 (46.7)	254 (53.0)	241 (44.5)
Non-hispanic white	732 (35.1)	222 (43.5)	320 (39.5)	168 (35.1)	237 (43.7)
Others	172 (8.2)	49 (9.6)	73 (9.0)	36 (7.5)	41 (7.6)
Parental education at baseline					
Completed grade 12 or less	574 (27.5)	113 (22.2)	185 (22.8)	142 (29.6)	128 (23.6)
Some college	648 (31.0)	164 (32.2)	268 (33.0)	154 (32.1)	208 (38.4)
Completed college or more	622 (29.8)	183 (35.9)	279 (34.4)	136 (28.3)	153 (28.2)
Missing	246 (11.8)	50 (9.8)	79 (9.7)	48 (10.0)	53 (9.8)
Sex					
Female	1036 (49.6)	258 (50.6)	419 (51.7)	337 (70.2)	264 (48.7)
Male	1054 (50.4)	252 (49.4)	392 (48.3)	143 (29.8)	278 (51.3)

*² tests were performed comparing the demographic characteristics of participants with wheeze, bronchitic symptoms, shortness of breath, secondhand nicotine vape exposure to participants without the specific respiratory outcome or secondhand nicotine vape. N (%) is shown in the table. Significant differences ($p < 0.05$) are shown in bold.

†Total number of participants reporting wheeze, bronchitic symptoms, shortness of breath or secondhand nicotine vape exposure, at least once, over the study period (waves 1–4).

Sensitivity analysis

We restricted the analysis to the participants who reported no primary vaping or smoking in past 30 days ($n=1181$) in order to reduce potential for confounding by personal use. A stronger association was observed between secondhand nicotine vape exposure and respiratory symptoms in this sub-population (table 3: sensitivity analysis 1). The odds of reporting wheeze, bronchitic symptoms and shortness of breath were 2.27 (95% CI 0.74 to 6.95), 3.10 (95% CI 1.52 to 6.35) and 2.05 (95% CI 1.01 to 4.19), respectively, among those who reported past 30-day exposure to secondhand nicotine vape, compared with those not reporting current secondhand nicotine vape exposure, after adjusting for demographic factors and secondhand smoking/secondhand cannabis. To assess the potential influence of lost to follow-up in wave 2, we removed those participants from the analysis (table 3: sensitivity analysis 2). The estimates of association between

secondhand nicotine vape exposure and respiratory symptoms were similar to those in the corresponding table 2: model 2. To address the possibility that the effect of secondhand nicotine vape exposure was largely among participants with asthma, we restricted the analysis to participants without any history of physician diagnosed asthma at wave 1 (table 3: sensitivity analysis 3). The effect estimate remained largely unchanged from table 2: model 2.

Among ever reporters of secondhand nicotine vape exposure, 75.5% reported secondhand nicotine vape in at least two consecutive waves (eg, waves 1 and 2; waves 2 and 3 or waves 3 and 4). Therefore, we investigated whether the timing and consistency of exposure (previous, current and both) had different effects on respiratory symptoms in a subpopulation ($n=1609$) who had exposure and respiratory symptom information in at least two consecutive waves (online supplemental table S3). After adjusting for demographic factors, primary vaping or smoking, secondhand smoking and secondhand cannabis, no substantial difference was observed in the strength of association of secondhand nicotine

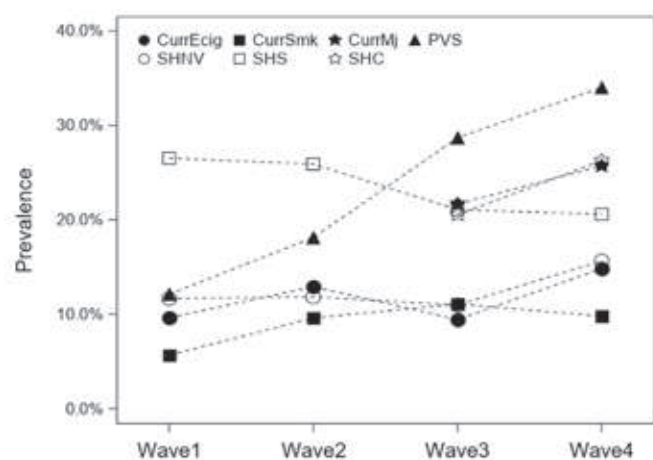


Figure 1 Prevalence of personal and secondhand tobacco and cannabis smoking and nicotine vaping during the study period (waves 1–4). CurrEcig, e-cigarette use in past 30 days; CurrMj, smoking or vaping cannabis in past 30 days; CurrSmk, smoking cigarette, cigar or cigarillos in past 30 days; PVS, personal vaping or smoking of nicotine or cannabis products in the previous 30 days; SHNV, secondhand vape exposure (nicotine); SHS, secondhand smoke exposure (tobacco); SHC, secondhand cannabis (vape or smoke) exposure.

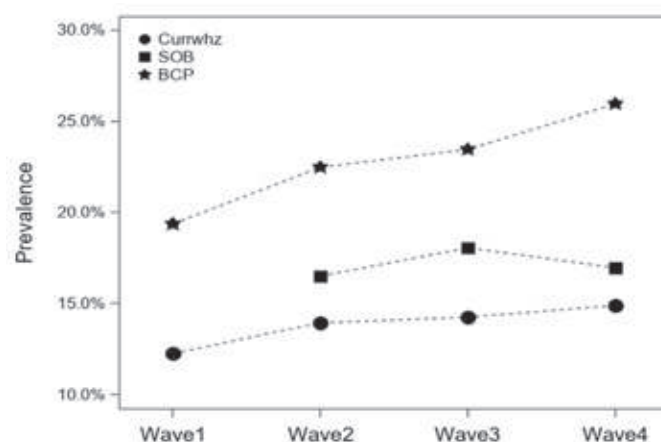


Figure 2 Prevalence of wheeze, bronchitic symptoms (BCP) and shortness of breath (SOB) during the study period (waves 1–4). BCP, Bronchitic symptoms reported in previous 12 months; Currwhz, wheeze reported in 12 months; SOB, shortness of breath reported in previous 12 months.

Table 2 Effect of past 30-day secondhand nicotine vape exposure on wheeze, bronchitic symptoms and shortness of breath; N=2090*

	Wheeze	Bronchitic symptoms	Shortness of breath
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Model 1†	1.56 (1.12 to 2.17)	1.90 (1.48 to 2.44)	1.87 (1.33 to 2.63)
Model 2‡	1.21 (0.84 to 1.72)	1.40 (1.06 to 1.84)	1.53 (1.06 to 2.21)

*Model 1: OR and 95% CI is based on mixed-effect logistic regression with personspecific random intercept and adjustment (fixed effect) for wave, age, sex, race and parental education.

†Model 2: OR and 95% CI is based on mixed-effect logistic regression similar to model 1 with additional adjustment (fixed effect) for primary smoking or vaping of nicotine or cannabis, and secondhand smoking or cannabis smoking or vaping exposure.

‡The OR and 95% CI for wheeze, bronchitic symptoms and shortness of breath is based on mixed-effect logistic regression models.

vape exposure, based on timing and consistency of exposure, with respiratory symptoms (online supplemental table S3).

DISCUSSION

To our knowledge, this is the first report of effects of secondhand nicotine vape exposure on respiratory symptoms among adolescents and young adults from a prospective study. We show associations of exposure to secondhand nicotine vape with bronchitic symptoms and shortness of breath, after controlling for sociodemographic characteristics, past 30-day active vaping and smoking of tobacco or cannabis products, and secondhand cigarette or cannabis smoke exposure. These results have important public health implications for the population exposed to secondhand nicotine vape. Unlike active vaping and smoking, secondhand nicotine vape exposure is not a voluntary exposure. Therefore, if the associations we observed are causal, prohibiting e-cigarette use in public places is warranted, just as secondhand tobacco smoke exposure has been prohibited in public spaces for decades, and reducing use indoors would reduce the burden of respiratory illness in the households of e-cigarette users. Further epidemiological study is needed to assess the replicability and generalisability of these findings to other age groups. Experimental studies are needed to help determine whether the effects are causal.

Secondhand nicotine vape exposure reported at the time of symptom reporting was associated with statistically significant 40% greater odds of bronchitic symptoms and 53% greater odds of shortness of breath, but not with wheeze, compared with individuals with no currently reported secondhand nicotine vape

Table 2 Effect of past 30-day secondhand nicotine vape exposure on wheeze, bronchitic symptoms and shortness of breath in sensitivity analyses restricted to participants with no past 30-day primary vaping or smoking of nicotine or cannabis§

	Wheeze	Bronchitic symptoms	Shortness of breath
	OR (95%CI)	OR (95%CI)	OR (95%CI)
Sensitivity analysis 1*	2.27 (0.74 to 6.95)	3.10 (1.52 to 6.35)	2.05 (1.01 to 4.19)
Sensitivity analysis 2†	1.30 (0.90 to 1.87)	1.39 (1.05 to 1.84)	1.56 (1.08 to 2.26)
Sensitivity analysis 3‡	1.15 (0.74 to 1.80)	1.63 (1.16 to 2.31)	1.47 (0.93 to 2.32)

*Sensitivity analysis 1: Analysis was restricted to participants without any reported primary vaping or smoking of nicotine or cannabis in the past 30 days (primary vaping or smoking) (n=1181).

†Sensitivity analysis 2: Participants were included if they participated in both wave 1 and wave 2 (n=1609), adjusted additionally for primary vaping or smoking.

‡Sensitivity analysis 3: Participants who reported no history of physician diagnosed asthma at wave 1 (n=1463), adjusted additionally for primary vaping or smoking.

§OR and 95% CI are based on mixed-effect logistic regression model with personspecific random intercept and adjustment (fixed effect) for wave, age, sex, race, parental education and secondhand smoking or cannabis (smoking or vaping secondhand cannabis) exposure.

exposure, after controlling for confounders and coexposures. Because this is the first study of effects of secondhand nicotine vape exposure on wheeze, bronchitic symptoms and shortness of breath, we cannot directly compare our results to previous findings. The observed association between secondhand nicotine vape exposure and wheeze (OR 1.21, 95%CI 0.84 to 1.72) in the current study was similar to the association between secondhand nicotine vape exposure and asthma exacerbation in a recent cross-sectional study (OR 1.27, 95%CI 1.11 to 2.47).³ The estimated effects of secondhand nicotine vape exposure on bronchitic symptoms in this study were similar in magnitude to those of secondhand smoking. For example, in a recent study of bronchitic symptoms among Chinese adolescents, the OR for secondhand smoking, compared with adolescents with no secondhand smoking exposure, was 1.53 (95%CI 1.25 to 1.87).¹⁹ Bronchitic symptoms are a response to irritant exposures such as secondhand smoking, active smoking and ambient particulate matter, among others.

Increased risk of shortness of breath has also been associated with secondhand smoking.²⁰ The interpretation of shortness of breath associated with secondhand nicotine vape exposure is not clear, but shortness of breath is a central feature of bronchiolitis obliterans that has been reported in workers heavily exposed to diacetyl and 2, 3-pentanedione, which are flavourings that have also been measured in e-cigarette liquids.^{9 13 21–24} There is a growing body of evidence that vaping is associated with a number of pulmonary diseases, including bronchiolitis obliterans,²⁵ acute respiratory distress syndrome²⁶ and acute eosinophilic pneumonia.²⁷ A recently published report described a case of hypersensitivity pneumonitis with secondhand nicotine vape exposure.²⁸ While only 3 years of data were collected in the current analysis to assess the effect of secondhand nicotine vape exposure on shortness of breath, the observed associations were both moderately strong and robust to confounders. Further study is warranted to determine potential causes of shortness of breath associated with secondhand nicotine vape exposure.

Many study participants with secondhand nicotine vape exposure were also exposed to a variety of other tobacco and cannabis products (online supplemental table S2). Disentangling the effect of secondhand nicotine vape exposure on respiratory symptoms from effects of other products was challenging. However, the models provided stable estimates of secondhand nicotine vape effects after adjustment for coexposures. We also observed stronger effects of secondhand nicotine vape exposure on respiratory symptoms among study participants who reported no past 30-day use of e-cigarette or combustible products (comparing table 3, sensitivity analysis 1 with table 2, model 2).

A potential explanation for the observed association between secondhand nicotine vape exposure and respiratory symptoms is selection bias due to the lost to follow-up of 481 participants following high-school graduation (at wave 2). However, those who remained in the study at wave 2 and those who were lost to follow-up had similar secondhand nicotine vape exposure and respiratory symptoms (online supplemental table S1). There were some modest differences in sociodemographic characteristics between those retained and those lost to follow-up, but all analyses were adjusted for those factors. Furthermore, secondhand nicotine vape exposure effect estimates in analyses restricted to participants not lost to follow-up at wave-2 (table 3, model 2) were similar to the estimates in the entire population (table 2). Therefore, selection bias is not likely to explain the associations with secondhand nicotine vape exposure we observed.

We also assessed whether the associations between secondhand nicotine vape exposure and respiratory symptoms were due to secondhand nicotine vape exposure induced asthma exacerbation.³ However, when we restricted the analysis to participants without any history of asthma at study entry, the secondhand nicotine vape exposure effect estimates (table 3, sensitivity analysis 3) were similar to effects in the entire sample (table 2, model 2). Asthma status of the subjects did not substantially affect the effect estimates observed between secondhand nicotine vape ex-

posure and the respiratory outcomes (online supplemental table S4).

Measurement error due to self-reported exposure and respiratory outcomes could have occurred. Because respiratory health outcomes were reported for last 12 months, it is possible that the participants under-reported symptoms occurring many months back. Exposure misclassification was likely to be small as exposure was assessed for the previous 30 days and seems unlikely to have been substantially differential with respect to outcome that could have biased the estimated effects of exposure.

CONCLUSION

We observed associations of secondhand exposure to e-cigarettes in the home with bronchitic symptoms and shortness of breath, after accounting for coexposures to other tobacco and cannabis products. The study satisfies several criteria of causation, including prospective assessment of the temporal relationship, relatively strong associations and biological plausibility. However, these findings need to be replicated in other study populations and in study designs including secondhand nicotine vape exposure challenge studies, and merit study in animal models, to establish a causal association between secondhand nicotine vape exposure and respiratory symptoms. If causal, reduction of secondhand e-cigarette exposure in the home would reduce the burden of respiratory symptoms and would provide a compelling rationale for regulation of e-cigarette use in public places.

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Contributors TSI was involved in the planning, conducting, drafting and reporting the study and is accountable for findings reported in the manuscript. JB was involved in the drafting and revising. SPE was involved in the data analysis and drafting. FL was involved in data analysis. APT was involved in interpretation and revising. MR was involved in interpretation and revising. JB-T was involved in the acquisition, interpretation and revising, and RM was involved in acquisition, revising, interpretation and final approval of the study.

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Data availability statement No data are available, however, data might be requested through USC TCORS.

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