

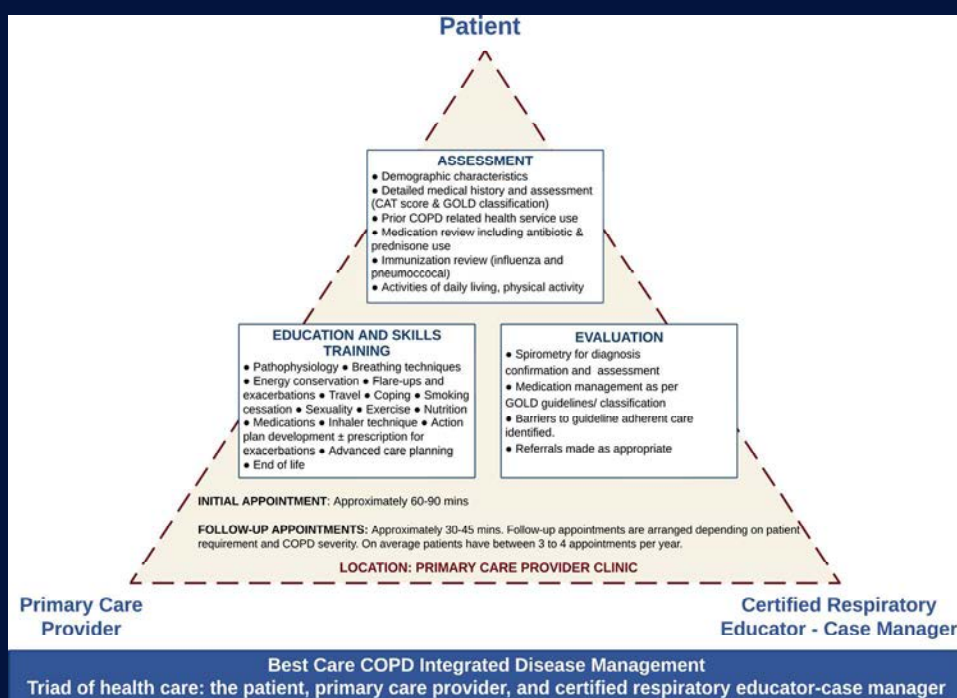
Thorax

ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

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CHILDHOOD

Edição Portuguesa





* **Beyfortus® é indicado para a prevenção de doença das vias respiratórias inferiores causada pelo RSV em:**

i) recém-nascidos e lactentes durante a sua primeira época do RSV;

ii) crianças até aos 24 meses de idade que permanecem vulneráveis a doença grave pelo RSV durante a sua segunda época do RSV.¹

Beyfortus® deve ser utilizado de acordo com as recomendações oficiais.¹

Contraindicações: hipersensibilidade à substância ativa ou a qualquer um dos excipientes.¹

** Beyfortus® proporciona pelo menos 5 meses de proteção contra a doença do trato respiratório inferior causada pelo RSV, com base em dados clínicos e farmacocinéticos.¹

† Para lactentes durante a sua primeira época do RSV, a dose recomendada é uma dose única de 50 mg para lactentes com peso corporal <5 kg e uma dose única de 100 mg para lactentes com peso corporal ≥5 kg, administrada por via intramuscular. Para crianças que permanecem vulneráveis a doença grave pelo RSV durante a sua segunda época do RSV, a dose recomendada é uma dose única de 200 mg administrada sob a forma de duas injeções intramusculares (2 x 100 mg). Para crianças submetidas a cirurgia cardíaca com *bypass* cardiopulmonar, pode ser administrada uma dose adicional logo que se verifique estabilização da criança após cirurgia, para garantir níveis séricos adequados de nirsevimab.¹ Consulte o Resumo das

Características do Medicamento para obter informações completas sobre a dosagem nesta circunstância.

† Com base nos resultados de dois ensaios multicêntricos aleatorizados, em dupla ocultação e controlados por placebo.³ O *endpoint* primário foi a incidência de ITRI medicamente assistida (incluindo hospitalização), causada por RSV confirmado por RT-PCR. Eficácia demonstrada até 150 dias após a administração.¹⁻³

– **Ensaio de fase 2b:** A população do estudo incluiu 1453 crianças grande prematuras e prematuras moderadas (IG ≥ 29 e < 35 semanas) que entravam na sua primeira época de RSV. As crianças receberam uma dose única intramuscular de 50 mg de Beyfortus® (n=969) ou placebo (n=484). Redução do risco relativo (RRR) em ITRI-RSV MA de 70,1% (IC de 95%: 52,3-81,2; p < 0,001). A incidência foi de 2,6% com

Informações essenciais compatíveis com o Resumo das Características do Medicamento

▼ Este medicamento está sujeito a monitorização adicional. Isto irá permitir a rápida identificação de nova informação de segurança. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas. Para saber como notificar reações adversas, ver secção “Efeitos Indesejáveis”.

Nome do medicamento Beyfortus 50 mg solução injetável em seringa pré-cheia e Beyfortus 100 mg solução injetável em seringa pré-cheia.

Composição Qualitativa e Quantitativa Cada seringa pré-cheia contém 50 mg de nirsevimab em 0,5 ml (100 mg/ml) e 100 mg de nirsevimab em 1 ml (100 mg/ml), respetivamente. Nirsevimab é um anticorpo monoclonal humano imunoglobulina G1 kappa (IgG1k) produzido em células de ovário de hamster Chinês (CHO) por tecnologia de ADN recombinante. Lista completa de excipientes, ver secção 6.1 do RCM completo. **Forma**

Farmacêutica: Solução injetável (injetável). Solução transparente a opalescente, incolor a amarela, pH 6,0. **Indicações terapêuticas:** Beyfortus é indicado para a prevenção de doença das vias respiratórias inferiores causada pelo Vírus Sincicial Respiratório (VSR), em: i. Recém-nascidos e lactentes durante a sua primeira época do VSR; ii. Crianças até aos 24 meses de idade que permanecem vulneráveis a doença grave pelo VSR durante a sua segunda época do VSR (ver secção 5.1 do RCM completo). Beyfortus deve ser utilizado de acordo com as recomendações oficiais.

Posologia e modo de administração: Posologia: *Lactentes durante a sua primeira época do VSR* - A dose recomendada é uma dose única de 50 mg administrados por via intramuscular para lactentes com peso corporal <5 kg e uma dose única de 100 mg administrados por via intramuscular para lactentes com peso corporal ≥5 kg. Beyfortus deve ser administrado desde o nascimento em lactentes nascidos durante a época do VSR. Para outros nascidos fora da época, Beyfortus deve ser administrado idealmente antes da época do VSR. A posologia em lactentes com um peso corporal entre 1,0 kg a <1,6 kg é baseada em extrapolação, não existem dados clínicos disponíveis. Prevê-se que a exposição em lactentes com <1 kg produza exposições mais elevadas do que naqueles que pesam mais. Devem ser considerados cuidadosamente os benefícios e riscos da

utilização de nirsevimab em lactentes <1 kg. Os dados disponíveis em lactentes prematuros extremos (Idade Gestacional [IG] <29 semanas) com menos de 8 semanas de idade, são limitados. Não existem dados clínicos disponíveis em lactentes com idade pós-menstrual (idade gestacional ao nascimento mais idade cronológica) com menos de 32 semanas (ver secção 5.1 do RCM completo). *Crianças que permanecem vulneráveis a doença grave pelo VSR durante a sua segunda época do VSR* - A dose recomendada é uma dose única de 200 mg administrada sob a forma de duas injeções intramusculares (2x100 mg). Beyfortus deve ser administrado, idealmente, antes do início da segunda época do VSR. Em indivíduos submetidos a cirurgia cardíaca com *bypass* cardiopulmonar, pode ser administrada uma dose adicional logo que se verifique estabilização do indivíduo após cirurgia, para garantir níveis séricos adequados de nirsevimab. Se estiverem dentro dos 90 dias, após receberem a primeira dose de Beyfortus, a dose adicional durante a primeira época do VSR deve ser de 50 mg ou 100 mg de acordo com o peso corporal, ou de 200 mg durante a segunda época do VSR. Se decorrerem mais de 90 dias desde a primeira dose, a dose adicional pode ser uma dose única de 50 mg independentemente do peso corporal, durante a primeira época do VSR, ou 100 mg durante a segunda época do VSR, para cobrir a época do VSR remanescente. A segurança e eficácia de nirsevimab em crianças com idade compreendida entre os 2 e os 18 anos não foram estabelecidas. Não existem dados disponíveis. **Modo de administração:** Beyfortus é apenas para injeção intramuscular. É administrado por via intramuscular, preferencialmente na zona anterolateral da coxa. O músculo glúteo não deve ser utilizado por rotina como um local de injeção, devido ao risco de lesão no nervo ciático. Se forem necessárias duas injeções, devem ser utilizados locais de injeção diferentes. Para instruções sobre requisitos especiais de manuseamento (ver secção 6.6. do RCM completo) **Contraindicações:** Hipersensibilidade à substância ativa ou a qualquer um dos excipientes mencionados na secção 6.1 do RCM completo. **Efeitos indesejáveis:** Resumo do perfil de segurança A reação adversa mais frequente foi erupção cutânea (0,7%), que ocorreu dentro de 14 dias após a administração. A maioria dos casos foi de intensidade ligeira a moderada. Adicionalmente, piroxia e reações no local da injeção foram notificadas com uma taxa de 0,5% e 0,3% dentro de

A Sanofi e a AstraZeneca estão a colaborar no desenvolvimento e comercialização de Beyfortus®.

SANOFI PRODUTOS FARMACÊUTICOS, LDA, Sede Social Empreendimento Lagoas Park, Edifício 7 – 3º Piso, 2740-244 Porto Salvo, Portugal. Capital social: € 26.815.015,00 matriculada na CRC de Cascais, sob o número único de matrícula e identificação de pessoa coletiva 500 134 960, Tel.: +351 21 3589400, email: geral.pt@sanofi.com - www.sanofi.pt

O poder de reduzir o caos na época do RSV

sanofi

Beyfortus® é um anticorpo de ação prolongada e direta **desenvolvido para proteger todos os recém-nascidos e lactentes***, contra a doença do trato respiratório inferior (DTRI) provocada pelo vírus sincicial respiratório (RSV).^{1,2}

Uma **única dose** reduziu o risco de infeção do trato respiratório inferior por RSV que requer assistência médica (ITRI-RSV MA) vs. placebo em recém-nascidos e lactentes.^{1,2,3,4}

Beyfortus®
(nirsevimab)

DISPONÍVEL
NA ÉPOCA 2024/25 PARA AS
CRIANÇAS ELEGÍVEIS*



Beyfortus® versus 9,5% com placebo.^{1,2} Os tipos e as frequências dos acontecimentos adversos foram semelhantes nos grupos de Beyfortus® e de placebo.²

– **Ensaio MELODY de fase 3:** A população do estudo incluiu 3012 crianças de termo e prematuras tardias (IG ≥ 35 semanas) que entravam na sua primeira época de RSV. As crianças receberam uma dose única intramuscular de 50 mg de Beyfortus®, se peso corporal <5 kg ou 100 mg de Beyfortus® se peso corporal ≥5 kg no momento da administração de Beyfortus® (n=2009), ou de placebo (n=1003). RRR em ITRI por RSV medicamente assistida de 76,4% (IC de 95%: 62,3-85,2). A incidência foi de 1,2% com Beyfortus® versus 5,4% com placebo.^{1,3} Os tipos e as frequências dos acontecimentos adversos foram semelhantes nos braços de Beyfortus® e placebo.^{3,4}

§ As reações adversas notificadas em crianças que receberam Beyfortus® em ensaios clínicos, foram erupção cutânea, reação no local da injeção e piroxia. A ocorrência foi pouco frequente (≥ 1/1.000 a < 1/100).¹

IC, intervalo de confiança; **IG**, idade gestacional; **DTRI**, doença do trato respiratório inferior; **ITRI**, infeção do trato respiratório inferior; **MA**, medicamente assistida; **RRR**, redução do risco relativo; **RSV**, vírus sincicial respiratório; **RT-PCR**, reação em cadeia da polimerase via transcriptase reversa.

1. Beyfortus®. Resumo das Características do Medicamento (RCM) de Beyfortus. Agosto 2024 **2.** Griffin MP et al. N Engl J Med 2020; 383(5): 415–425. **3.** Muller WJ et al. N Engl J Med 2023; 388(16): 1533–1534. **4.** Hammitt LL et al. N Engl J Med 2022; 386(9): 837–846.

7 dias após a administração, respetivamente. As reações no local da injeção não foram graves.

Lista tabelada de reações adversas A tabela 1 apresenta as reações adversas notificadas em 2966 lactentes de termo e pré-termo (IG ≥29 semanas) que receberam nirsevimab em ensaios clínicos. As reações adversas notificadas a partir de ensaios clínicos controlados são classificadas por Classe de Sistema de Órgãos (CSO) MedDRA. Dentro de cada CSO, os termos preferenciais são apresentados por frequência decrescente e em seguida por ordem decrescente de gravidade. As frequências de ocorrência de reações adversas são definidas como: muito frequentes (≥1/10); frequentes (≥1/100 a <1/10); pouco frequentes (≥1/1000 a <1/100); raros (≥1/10 000 a <1/1000); muito raros (<1/10 000) e desconhecido (não pode ser calculado a partir dos dados disponíveis). **REAÇÕES ADVERSAS FREQUÊNCIA Afeções dos tecidos cutâneos e subcutâneos** Erupção cutânea^a – Pouco frequentes; **Perturbações gerais e alterações no local de administração** Reação no local de injeção^b; piroxia – Pouco frequentes. ^aErupção cutânea foi definida pelos seguintes grupos de termos preferenciais: erupção cutânea, erupção maculopapular, erupção macular. ^bReação no local da injeção foi definida pelos seguintes grupos de termos preferenciais: reação no local da injeção, dor no local da injeção, endurecimento no local da injeção, edema no local da injeção, inchaço no local da injeção. Lactentes com risco mais elevado de doença grave pelo VSR na sua primeira época: A segurança foi avaliada no MEDLEY em 918 lactentes com risco mais elevado de doença grave por VSR, incluindo 196 lactentes extremamente prematuros (IG <29 semanas) e 306 lactentes com doença pulmonar crónica por prematuridade, ou doença cardíaca congénita hemodinamicamente significativa a entrar na sua primeira época do VSR, que receberam nirsevimab (n=614) ou palivizumab (n=304). O perfil de segurança de nirsevimab em lactentes que receberam nirsevimab na sua primeira época do VSR foi comparável ao comparador palivizumab e consistente com o perfil de segurança de nirsevimab em lactentes de termo e pré-termo com IG ≥29 semanas (D5290C00003 e MELODY). **Lactentes que permanecem vulneráveis a doença grave pelo VSR na sua segunda época:** A segurança foi avaliada no MEDLEY em 220 crianças com doença pulmonar crónica da prematuridade ou com doença cardíaca congénita hemodinamicamente significativa

que receberam nirsevimab ou palivizumab na primeira época do VSR e que continuaram a receber nirsevimab na sua segunda época do VSR (180 participantes receberam nirsevimab nas épocas 1 e 2; 40 receberam palivizumab na época 1 e nirsevimab na época 2). O perfil de segurança de nirsevimab em crianças que receberam nirsevimab na sua segunda época do VSR foi consistente com o perfil de segurança de nirsevimab em lactentes de termo e pré-termo com IG ≥29 semanas (D5290C00003 e MELODY). A segurança foi também avaliada no MUSIC, um ensaio em regime aberto, não controlado, de dose única em 100 lactentes e crianças imunocomprometidos com ≤24 meses, que receberam nirsevimab na sua primeira ou segunda época do RSV. Isto incluiu participantes com pelo menos uma das seguintes condições: imunodeficiência (combinada, anticorpos ou outra etiologia) (n=33); corticoterapia sistémica de dose elevada (n=29); transplante de órgão ou de medula óssea (n=16); a receber quimioterapia imunossupressora (n=20); outra terapia imunossupressora (n=15) e infeção por VIH (n=8). O perfil de segurança de nirsevimab foi consistente com o esperado para uma população de crianças imunocomprometidas e com o perfil de segurança de nirsevimab em lactentes de termo e pré-termo com IG ≥29 semanas (D5290C00003 e MELODY). O perfil de segurança de nirsevimab em crianças durante a sua segunda época do VSR foi consistente com o perfil de segurança de nirsevimab observado durante a sua primeira época do VSR. **Notificação de suspeitas de reações adversas** A notificação de suspeitas de reações adversas após a autorização do medicamento é importante, uma vez que permite uma monitorização contínua da relação benefício-risco do medicamento. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas diretamente ao INFARMED, I.P.: Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaooram> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos, Parque da Saúde de Lisboa, Av. Brasil 53, 1749-004 Lisboa, Tel: +351 21 798 73 73. Linha do Medicamento: 800222444 (gratuita) E-mail: farmacovigilancia@infarmed.pt **Data de revisão do texto:** agosto 2024. Medicamento sujeito a receita médica. Para mais informações, contactar o Representante Local do Titular da Autorização de Introdução no Mercado.

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Editorial

Editorial: Promovendo Avanços no Conhecimento em Saúde Respiratória

Nesta edição apresentamos uma compilação diversificada de artigos que abordam desafios contemporâneos na medicina respiratória em todos os grupos etários, começando por referir um estudo que aborda disparidades de disponibilidade, custo e acesso a medicamentos essenciais para doenças respiratórias crônicas em países de baixo e médio rendimento.

Destacamos igualmente um artigo que analisa práticas de alta hospitalar em casos de asma e sibilância aguda em crianças. Este estudo alerta para a necessidade de uniformizar as orientações na alta, garantindo maior segurança para os pacientes pediátricos. Complementando esta discussão, aborda-se igualmente o impacto do género na abordagem da asma grave, um tema muitas vezes negligenciado, mas essencial para personalizar os cuidados de saúde.

Na área da epidemiologia, a investigação sobre as trajetórias da função pulmonar desde a infância até à idade adulta revela determinantes críticos para a saúde respiratória ao longo da vida.

Já no campo da DPOC, é apresentada uma análise sobre os benefícios sustentáveis de uma gestão integrada a nível dos cuidados primários, evidenciando como uma intervenção precoce, eficaz, poderá aliviar pressões sobre os sistemas de saúde.

A poluição atmosférica e os seus efeitos na função pulmonar de crianças prematuras destacam o bem conhecido impacto ambiental na saúde pediátrica, num artigo que sublinha a urgência de políticas públicas mais robustas, que devem ser consideradas inadiáveis, para mitigar esses riscos.

Finalmente, artigos sobre o consumo de cigarros por jovens, incluindo com recurso a dispositivos eletrónicos, refletem um tema de crescente preocupação global. As estratégias de marketing direcionadas, especialmente nas redes sociais, demonstram a necessidade de uma regulamentação mais rigorosa para proteger este grupo muito vulnerável.

Em conclusão, neste número estimula-se a reflexão sobre como traduzir o conhecimento adquirido em ações práticas e políticas públicas. Acreditamos que estas contribuições podem ser inspiradoras de mudanças no cuidado que é dedicados às doenças respiratórias, reforçando a nossa missão de melhorar a saúde global.

Convidamos uma vez mais os nossos estimados Colegas a explorar os artigos apresentados, desejando-lhes boas leituras.

Mário Morais de Almeida

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Reforçar a base de evidências para apoiar uma regulamentação mais rigorosa da publicidade nas redes sociais a produtos de cigarros eletrónicos destinados a jovens

Kim L Lavoie

Apesar da promessa inicial dos cigarros eletrónicos serem um potencial instrumento de cessação tabágica, o verdadeiro motivo da adoção destes produtos tem sido fonte de muita controvérsia. Tem havido preocupações crescentes sobre o aumento exponencial do uso de cigarros eletrónicos e produtos de *vaping* entre jovens e adolescentes, dado que a proporção de pessoas com 11-15, 16-17 e 18 anos de idade na Grã-Bretanha que usam cigarros eletrónicos mais do que duplicou entre 2021 e 2023, atingindo 4,6%, 15,0% e 18%, respetivamente.¹ O 2023 *US Annual National Youth Tobacco Survey* reportou mais de 2,1 milhões de utilizadores atuais de cigarros eletrónicos nos EUA, dos quais 25% são utilizadores diários.²

Os cigarros eletrónicos são os produtos tabágicos mais populares entre os jovens americanos pelo décimo ano consecutivo, alimentando preocupações crescentes das agências de saúde pública em todo o mundo sobre os potenciais efeitos dos cigarros eletrónicos na saúde deste grupo demográfico vulnerável. Numa era em que a publicidade direta ao tabaco dirigida aos jovens há muito que foi proibida, e em que uma regulamentação rigorosa levou a que o consumo de cigarros de combustão tenha saído de moda entre os jovens,³⁻⁵ coloca-se a questão: por que razão os cigarros eletrónicos são tão populares entre este grupo demográfico? Para além dos fatores óbvios relacionados com o facto de a nicotina ser viciante e de os cigarros eletrónicos serem discretos, baratos e fáceis de obter, a resposta poderá estar nas formas subtis e criativas como os fabricantes de cigarros eletrónicos conseguiram chegar aos jovens e seduzi-los a experimentar os produtos de *vaping*.

Em primeiro lugar, os cigarros eletrónicos têm sido comercializados como uma alternativa menos nociva aos cigarros de combustão, com slogans como “Tem um sabor e uma sensação melhores do que um cigarro verdadeiro”,⁶ o que pode ser apelativo para os fumadores que querem deixar de fumar, mas também para os jovens não fumadores que podem ser seduzidos a experimentar graças a esta mensagem. O receio é que os jovens comecem a fumar através dos cigarros eletrónicos, podendo estes

tornar-se uma via para os cigarros de combustão. Existem atualmente cada vez mais evidências de que este é de facto o caso, com duas meta-análises que associam o uso de cigarros eletrónicos a um risco quase 3,0-3,5 vezes superior de iniciação ao consumo de cigarros entre jovens e adolescentes, mesmo após o ajuste para fatores de risco demográficos, psicossociais e comportamentais conhecidos.^{7,8}

Em segundo lugar, se visitarmos as lojas ou os websites de produtos de *vaping*, iremos encontrar uma seleção de vaporizadores coloridos, cápsulas, cartuchos e frascos cheios de líquidos para cigarros eletrónicos ou “vape de sumo” com sabores destinados a atrair os jovens, tais como “granizado de ananás”, “blue razz berry” e “leite de banana”.⁹ Entre os sabores de sumos de vape mais populares vendidos pela Hangsen, o maior fabricante e distribuidor de sumos de vape do mundo, encontram-se categorias de sabores como “sobremesas e doces”, “frutos” e “bebidas”. Existem dados que sugerem que esta estratégia está a funcionar, com um estudo de 2019 a mostrar que os sabores preferidos dos cigarros eletrónicos entre os adolescentes são os de fruta e doces, sendo que os adolescentes e os jovens têm uma probabilidade três a quatro vezes superior de usar cigarros eletrónicos com sabores de fruta e doces em comparação com os adultos.¹⁰ Os estudos também confirmaram que os próprios jovens estão bem cientes do facto de que os anúncios de líquidos de vape com sabores doces lhes são direcionados.

McKelvey *et al*¹¹ exibiram a um grupo de adolescentes oito anúncios com vários sabores e pediram-lhes que indicassem o grupo etário a que os anúncios se destinavam: mais novo, da mesma idade, um pouco mais velho ou muito mais velho. Os resultados mostraram que a maioria dos jovens (93,7%) indicou que o anúncio com sabor a cupcake se destinava a crianças mais novas e 63% e 68% indicaram que os anúncios a *smoothie* e a cereja se destinavam ao seu grupo etário (adolescentes), não tendo nenhum dos anúncios com sabores como alvo o público mais velho. Por último, a popularidade dos cigarros eletrónicos entre os jovens também pode ser explicada pelos mecanismos inteligentes que os fabricantes estão a utilizar para chegar aos jovens com a sua publicidade. Um desses mecanismos é através das redes sociais, que são muito consumidas pelos jovens e muito difíceis

de controlar e regulamentar.^{12,13} De facto, existem provas que sugerem que as empresas de cigarros eletrónicos estão a solicitar ativamente a celebridades e utilizadores que promovam os seus produtos através das redes sociais e que isso está a ter um efeito positivo nas atitudes dos jovens em relação ao *vaping*.¹⁴⁻¹⁶ Esta situação levou o público a apelar a uma melhor regulamentação da publicidade online de produtos de cigarros eletrónicos a jovens e adolescentes, mas para isso são necessárias evidências que associem a exposição às redes sociais a um maior consumo de cigarros eletrónicos.

Curiosamente, o estudo de Hopkinson *et al*,¹⁶ publicado nesta edição, concluiu que uma utilização mais frequente das redes sociais entre os jovens com idades entre os 10 e os 25 anos no Reino Unido estava associada a uma probabilidade quase três vezes superior de utilização de cigarros eletrónicos. Isto verificou-se mesmo depois de ajustadas as covariáveis, designadamente o sexo, a idade, a etnia, o rendimento do agregado familiar e os fumadores no domicílio. As implicações políticas deste documento são importantes, sobretudo no que diz respeito à regulamentação da publicidade e dos algoritmos destinados a utilizadores menores de idade. O facto de investigações anteriores indicarem que os jovens são efetivamente visados por este conteúdo, que este conteúdo chega aos jovens (32% dos jovens afirmam ter visto publicidade *online* a produtos de *vaping*)¹ e que as suas atitudes são afetadas é mais uma evidência da necessidade de reforçar a regulamentação. No entanto, este estudo também revela várias lacunas na investigação, que devem ser objeto de investigação futura. Os autores não avaliaram a exposição real a produtos de cigarros eletrónicos nos meios de comunicação social, nem avaliaram a medida em que a ligação entre a exposição aos meios de comunicação social e o *vaping* poderia ser mediada/moderada por variáveis como a disfunção parental, o isolamento social, a pressão dos pares ou o sofrimento psicológico. Adicionalmente, ainda não existe uma conclusão sobre os efeitos a longo prazo do *vaping* na saúde dos jovens, mas existem várias razões para nos mantermos vigilantes. Existem preocupações óbvias quanto à criação de uma nova geração de viciados em nicotina, o que poderá facilitar a transição para o consumo de cigarros de combustão, bem como vários casos de EVALI (lesão pulmonar associada ao uso de cigarros eletrónicos/*vaping*) em jovens como resultado do uso de produtos de *vaping*, e o agravamento da asma pré-existente (incluindo broncoconstrição aguda e disfunção das vias aéreas pequenas, aumento da inflamação das vias aéreas)¹⁷ entre os jovens adultos.

É evidente que é necessária mais investigação para compreender os mecanismos que ligam a exposição a produtos de *vaping* nas redes sociais e o consumo de cigarros eletrónicos, uma vez que nem todos os jovens expostos a estes produtos começam

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a consumi-los. Também precisamos de mais investigação para compreender não só os efeitos a longo prazo para a saúde, mas também os efeitos psicológicos e comportamentais a curto e médio prazo do *vaping*, sendo que as atuais evidências já apontam para um aumento dos riscos de luta física, consumo de substâncias e aumento da atividade sexual entre os adolescentes que consomem produtos de *vaping*, fumam cigarros de combustão ou ambos comparativamente a adolescentes que não o fazem.¹⁸

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REFERÊNCIAS

- 1 Action on Smoking and Health (ASH). Use of e-cigarettes (vapes) among young people in Great Britain. 2023. Available: <https://ash.org.uk/uploads/Use-of-vapes-amongyoung-people-GB-2023-v2.pdf>
- 2 Birdsey J, Cornelius M, Jamal A, et al. Tobacco product use among U.S. middle and high school students — national youth tobacco survey. *MMWR Morb Mortal Wkly Rep* 2023;72:1173–82.
- 3 Jamal A, Gentzke A, Hu SS, et al. Tobacco use among middle and high school students — United States, 2011–2016. *MMWR Morb Mortal Wkly Rep* 2017;66:597–603.
- 4 Eastwood B, Dockrell MJ, Arnott D, et al. Electronic cigarette use in young people in Great Britain 2013–2014. *Public Health* 2015;129:1150–6.
- 5 Greenhalgh E, Bain E, Winstanley M. 1.6 prevalence of smoking—teenagers. In: Greenhalgh E, Scollo M, Winstanley M, eds. *Tobacco in Australia: Facts and issues*. Melbourne: Cancer Council Victoria, 2023.
- 6 Truth in Advertising. O2Pur free e-cigarette starter kit. 2017. Available: <https://truthinadvertising.org/articles/o2pur-free-e-cigarette-starter-kit/>
- 7 Soneji S, Barrington-Trimis JL, Wills TA, et al. Association between initial use of e-cigarettes and subsequent cigarette smoking among

adolescents and young adults: a systematic review and meta-analysis. *JAMA Pediatr* 2017;171:788–97.

- 8 Chan GCK, Stjepanović D, Lim C, et al. Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation. *Addiction* 2021;116:743–56.
- 9 Vape club. The 10 best e-liquids of 2023. 2023. Available: <https://www.vapeclub.co.uk/e-liquids/guides/best-e-liquids>
- 10 Soneji SS, Knutzen KE, Villanti AC. Use of flavored e-cigarettes among adolescents, young adults, and older adults: findings from the population assessment for tobacco and health study. *Public Health Rep* 2019;134:282–92.
- 11 McKelvey K, Baiocchi M, Ramamurthi D, et al. Youth say ads for flavored e-liquids are for them. *Addict Behav* 2019;91:164–70.
- 12 O'Brien EK, Hoffman L, Navarro MA, et al. Social media use by leading US e-cigarette, cigarette, smokeless tobacco, cigar and hookah brands. *Tob Control* 2020;29:e87–97.
- 13 Kong G, LaVallee H, Rams A, et al. Promotion of vape tricks on YouTube: content analysis. *J Med Internet Res* 2019;21:e12709.
- 14 Phua J, Jin SV, Hahm JM. Celebrity-endorsed e-cigarette brand Instagram advertisements: effects on young adults' attitudes towards e-cigarettes and smoking intentions. *J Health Psychol* 2018;23:550–60.
- 15 Smith MJ, Buckton C, Patterson C, et al. User-generated content and influencer marketing involving e-cigarettes on social media: a scoping review and content analysis of YouTube and Instagram. *BMC Public Health* 2023;23:530.
- 16 Hopkinson N, Vrinten C, Parnham J. Association of time spent on social media with youth cigarette smoking and e-cigarette use in the UK: a national longitudinal study. *Thorax* 2024;79:662–9.
- 17 Kotoulas S-C, Pataka A, Domvri K, et al. Acute effects of e-cigarette vaping on pulmonary function and airway inflammation in healthy individuals and in patients with asthma. *Respirology* 2020;25:1037–45.
- 18 Demissie Z, Everett Jones S, Clayton HB, et al. Adolescent risk behaviors and use of electronic vapor products and cigarettes. *Pediatrics* 2017;139:e20162921.

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

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

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

Informações essenciais compatíveis com o Resumo das Características do Medicamento

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

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ARTIGO ORIGINAL

Práticas de alta hospitalar em serviço de urgência para crianças com pieira e asma agudas: um inquérito sobre práticas de alta hospitalar e uma análise das instruções de redes de segurança no Reino Unido e na Irlanda

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RESUMO

Objetivo A recuperação de crises agudas de pieira e de asma deve ser apoiada por uma rede de segurança, incluindo aconselhamento terapêutico. Avaliámos as práticas de alta hospitalar em serviço de urgência (SU) para crises agudas de pieira/asma na infância para descrever a variação na rede de segurança e na dosagem de broncodilatadores de recuperação.

Desenho do estudo Estudo bifásico entre junho de 2020 e setembro de 2021, incluindo (1) inquérito sobre as práticas de alta hospitalar nos serviços e (2) análise das instruções de alta hospitalar escritas para os prestadores de cuidados.

Contexto Serviços de Urgência secundários e terciários em zonas rurais e urbanas da Paediatric Emergency Research in the UK and Ireland (PERUKI)).

Principais resultados Descrever a prática e a variação nas recomendações de alta hospitalar, as recomendações de tratamento e a oferta de redes de segurança.

Resultados Dos 66/71 (93%) centros participantes, 62/66 (93,9%) referiram fornecer informações escritas sobre redes de segurança. 52/66 (78,8%) avaliaram "quase sempre" a técnica do inalador/espaçador. A revisão de rotina da medicação (21/66; 31,8%) e a adesão (16/66; 21,4%) foram menos frequentes. Na fase II, 61/66 (92,4%) apresentaram os seus documentos de alta hospitalar. 50/66 (81,9%) incluíram planos de broncodilação. 11/66 (18,0%) forneceram Planos de Ação Personalizados para a Asma como única informação de alta hospitalar. 45/50 (90%) forneceram regimes de dosagem de broncodilatadores "fixos". A redução gradual da dose foi comum (38/50; 76,0%). A dose inicial média foi de 10 inalações de 4 em 4 horas (27/50, 54,0% e a duração média foi de 4 dias (29/50, 58,0%). 13/61 (21,3%) não forneceram aconselhamento sobre broncodilatadores em caso de deterioração aguda. Quando fornecido, 42/48 (87,5%) recomendaram 10 inalações imediatamente. As subsequentes dosagens variaram consideravelmente. Os sinais de alerta mais comuns incluíram a incapacidade de falar (52/61, 85,2%), inaladores que não duravam 4 horas (51/61, 83,6%) e dificuldade respiratória (49/61, 80,3%).

Conclusões Existem variações na dosagem de broncodilatadores e no conteúdo das redes de segurança para a recuperação após crises agudas de pieira e asma. Isto reflete falta de evidências, afirmando a necessidade de mais estudos multicêntricos sobre estratégias de recuperação com broncodilatadores e aconselhamento adequado sobre redes de segurança.

INTRODUCTION

Acute wheeze and asthma are among the the most common reasons for urgent healthcare utilisation in children and young people (CYP). Up to half

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- There Acute wheezing attacks are a common reason for childhood hospital attendance, with many discharged following a short period of intense treatment to recover at home.
- Caregivers should be supported with robust safety netting advice during recovery.
- There is scant evidence to inform optimal bronchodilator dosing strategy during recovery from wheeze attacks and lack of information about current practices.

WHAT THIS STUDY ADDS

- There is variation in content and presentation of safety netting information for children discharged home from emergency departments following acute wheeze episodes.
- There is disparity in provision of normal and abnormal recovery advice and poor distinction in separating advice for de novo attacks.
- There is variation in bronchodilator treatment dose, duration and parent-led control, including dosing for managing unexpected deterioration.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Further research is warranted to inform optimal advice for caregivers about recovery bronchodilator administration.
- Opportunities are present to develop standardised safety netting advice for wheeze recovery.
- The format of written safety netting advice should reflect input from all stakeholders, including patients. Widely used Personalised Asthma Action Plans should be modified to allow their use as documents supporting recovery from acute wheezing.

of children experience an episode before their sixth birthday¹ and more than 25 000 CYP are admitted to hospital annually,² resulting in a significant healthcare burden.³ Most CYP presenting to emergency departments (EDs) with acute wheeze rapidly improve with high dose inhaled bronchodilators±oral corticosteroids; most are subsequently discharged within 4–24 hours. Recovery continues over several days, though up to 5% re-attend due to relapsing symptoms.⁴ Current management in the UK is based on British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) Asthma Guidance,^{5,6} which recommends a discharge bundle to optimise management. This includes review of triggers, medication and adherence, inhaler technique, planned follow-up, and a written Personalised Asthma Action Plan (PAAP). The latter typically includes regular preventer regimes alongside intensification treatment for acute symptoms; PAAPs are regarded as best practice for long-term asthma management, reducing hospital admissions and improving health outcomes.^{2,7,8}

Safety netting to support safe discharge is a crucial element of care, empowering caregivers to manage recovery and recognise evolving deterioration or serious illness.^{9–11} The National Institute for Health and Care Excellence (NICE), which provides recommendations for other childhood conditions, recommends that advice includes symptoms to watch for, how to access further care, likely time course of illness, and how to provide care at home.¹² Similar advice for ongoing management of acute wheeze episodes following discharge is lacking, particularly regarding the use of inhaled bronchodilators, resulting in practice variation and suboptimal clinical care.

In this cross-sectional survey and leaflet review study we evaluated discharge practices for children with acute asthma/wheeze presenting to EDs in the UK and Ireland. We focused on variation in safety net advice, step-down treatment plans, and advice on how to recognise and manage deterioration safely.

METHODS

This two-phase study was performed between June 2020 and September 2021 across Paediatric Emergency Research in the UK and Ireland (PERUKI),¹³ including tertiary and secondary care sites in rural and urban settings. The aim of phase I was to evaluate typical discharge practices including concordance with the BTS asthma discharge recommendations. The aim of phase II was to evaluate written discharge materials provided to caregivers.

Phase I consisted of a survey of departmental discharge practices. Between 22 June and 22 July 2020, site leads from all 71 PERUKI sites were invited to provide one response on typical departmental discharge practices for childhood acute asthma/wheeze (online supplemental file 1), with three reminders before closing. Survey content was developed from evidence underpinning discharge for asthma/wheeze, national clinical practice guidelines (CPGs), the National Asthma and COPD Audit Programme (NACAP) audit tool, and the BTS asthma discharge bundle.^{5,6,14,15} Study authors with expertise in survey methodology completed item generation and reduction, survey pretesting, and pilot testing for acceptability, flow and ease of administration. Questions included Likert Scales, matrices and multiple-choice options. Responses were submitted using Research Electronic Data Capture tools,¹⁶ and stored on a secure server in University Hospitals Bristol and Weston National Health Service Foundation Trust.

In phase II, site leads were asked to submit written discharge materials routinely provided to caregivers for childhood asthma/wheeze; up to three reminders were sent prior to closing. All written materials returned to the researchers were codified for advice content. A data collection tool (online supplemental file 2) was developed from national CPGs, and literature regarding good practice in written safety netting information for an acute condition.^{5,17,18} Evaluation of bronchodilator prescriptions included dose, duration and plan ‘type’ defined as (1) ‘fixed’ hospital-derived plan (hospital stipulates specific number/frequency of puffs to administer over a set timeframe), (2) ‘caregiver-determined’ plan (caregiver chooses dose, and/or frequency and duration according to child’s status; maximum dosing limits set by hospital) or (3) ‘hybrid’ plan (fixed dose and

Table 1 Survey-reported discharge practices

	Total (%) (n=66)*
Written information provided	
Safety netting discharge information	62 (93.9)
Red flags described	61 (92.4)
Bronchodilator dosing information including maximal dose/frequency	56 (84.8)
Bronchodilator advice	
‘Fixed’ plan	47 (71.2)
‘Hybrid’ plan	13 (19.7)
‘Caregiver-determined’ plan	5 (7.6)
No plan/dosing advice	1 (1.5)
GP follow-up	
Caregiver to arrange within 48 hours	40 (60.6)
At parent’s discretion	9 (13.6)
Hospital requests GP follow-up directly from primary care within 48 hours	3 (4.5)
Caregiver to arrange GP within 7 days	1 (1.5)
Caregiver to arrange GP within 14 days	1 (1.5)
Other follow-up arrangements	
Open access 48–72 hours	4 (6)
Community nursing team support available	4 (6)
*‘Total’ represents combined site responses, including sites with identical discharge practices for asthma/wheeze and the mean results for the two sites with differing practices for asthma/wheeze.	

timeframe advised only if child is symptomatic; guidance on symptoms provided). Data were abstracted by three researchers (RH, JYP, RJPGC) independently, each blinded to responses until completion. Differences were discussed between reviewers; where consensus could not be reached, a fourth reviewer (MDL) aided resolution.

Data were analysed using Microsoft Excel (V.2008). Results are presented using descriptive statistics; categorical data are summarised as numbers and percentages, and continuous variables are presented using means (and SD) or medians (and IQRs) as appropriate.

As this study did not include patient-level identification data, and participants were approached via a professional network, formal ethics approval was not required according to the Health Research Authority decision tool.¹⁹

RESULTS

In total 66/71 (93%) sites responded in phase I (table 1), with 48/66 (73%) reporting practice reflecting BTS/SIGN recommendations; 61 (86%) provided written discharge documents for analysis. Identical discharge practice and written instructions existed for asthma and wheeze at all sites, except two which advised General Practitioner (GP) follow-up only for children with asthma, and two which did not provide written safety netting or bronchodilator plans for wheeze.

Consistently reported actions included provision of recovery bronchodilator instructions (65/66; 98.5%), with maximal dosing information provided in 56/66 (84.8%) and written safety netting advice (62/66; 93.9%), including red flag signs of deterioration (61/66; 92.4%). Inhaler/spacer technique was ‘nearly always’ assessed in 52/66 (78.8%). Infrequently reported elements were peak expiratory flow rate which was ‘never’ assessed in 18/66 (27.3%) and smoking cessation support which was ‘nearly always’ offered by 10/66 (15.1%). Findings of the survey are presented in figure 1.

In phase II (table 2), 50/61 (81.9%) provided safety netting plans detailing ‘normal’ recovery; half (31/61; 50.8%) included signs marking abnormal recovery including deterioration. Thirty-three (54.1%) provided PAAPs for future episodes in addition to recovery information, while 11/61 (18.0%) provided PAAPs as the sole discharge information. For sites providing recovery-specific advice and PAAPs, 31/33 (93.9%) described recognition and management of deterioration within the PAAP (working upwards from a symptom-free baseline), rather than in the context of weaning treatment during recovery from an acute attack.

Other information (table 2) included explanation of the condition (23/61; 37.7%), and how medications work (19/61; 31.1%), but

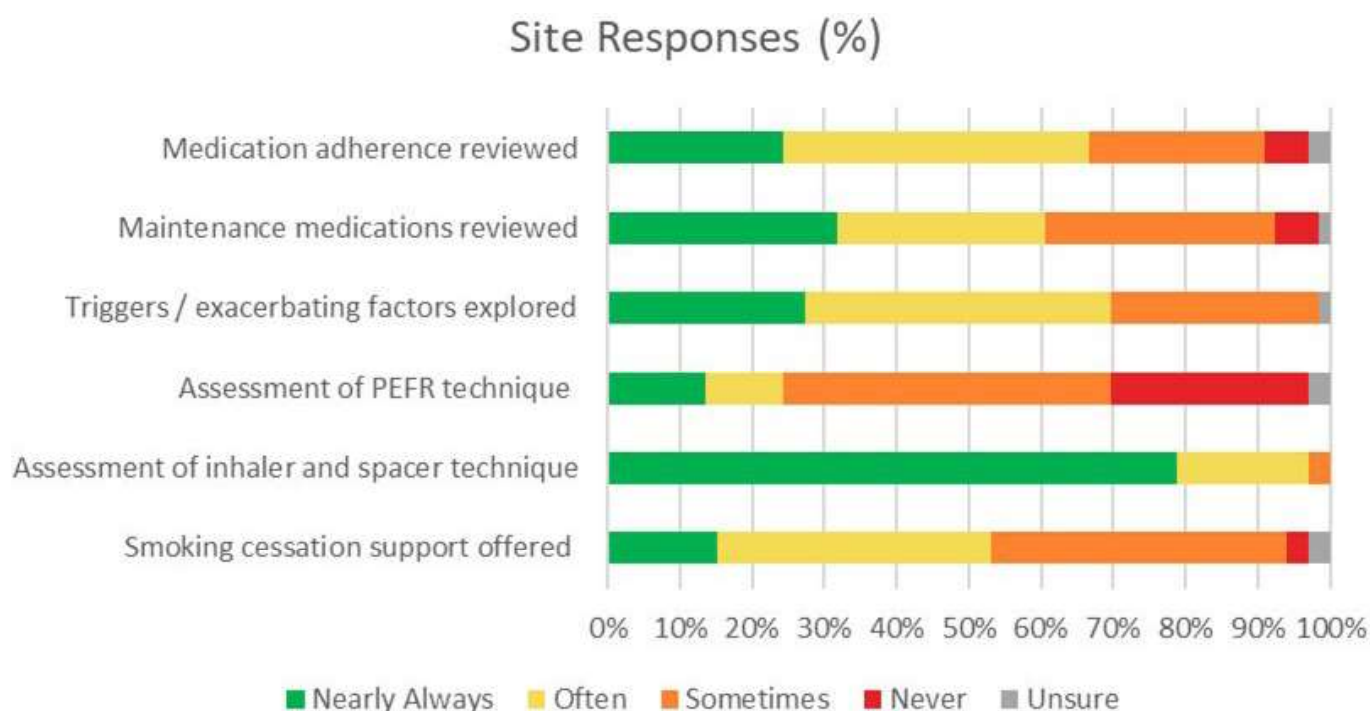


Figure 1 PredischARGE practices. PEFR, peak expiratory flow rate.

rarely side effects (3/61; 4.9%), whether to treat sleeping children (16/61; 26.2%) and signs indicating improvement (7/61; 11.5%).

Discharge bronchodilator plans were provided by 50/61 (81.9%) sites (table 3). Most (45/50; 90%) used 'fixed' hospital-derived plans; 10 contained free-text tailored prescribing. Seven (14%) recommended giving two to four bronchodilator actuations 'as required' for an unspecified duration following 'fixed' dosing. The median starting dose was 10 puffs every 4 hours (27/50; 54.0%), with dose tapering advised by 38/50 (76.0%) sites. Median plan duration was 4 days (29/50; 58.0%, range 2 to >6 days). 'Hybrid' plans were used by three sites (6.0%) and two (4.0%) provided fully 'caregiver-determined' plans.

Thirteen (21.3%) did not provide written advice for emergency bronchodilator use during acute deterioration; where provided, 87.5% (42/48) recommended 10 puffs immediately, with subsequent dosages varying considerably (table 4). Advice to access healthcare if deteriorating included calling emergency services 45/61 (73.7%), contacting primary care 47/61 (77.1%) and re-attending hospital 25/61 (40.9%); 7 (11.5%) did not provide any advice. The most common red flag features were inability to speak (52/61, 85.2%), inhalers not lasting 4 hours (51/61, 83.6%) and respiratory distress (49/61, 80.3%) (table 2); 'caregiver worry' was infrequently included (8/61, 13.1%).

Primary care follow-up was advised by 38/61 (62.3%), usually within 48 hours (28/38; 73.7%). Other arrangements included outpatient specialist nurses, asthma services, or general paediatrics. Open access and community nursing team input were detailed at three sites (4.9%).

DISCUSSION

In this review of ED discharge practices and supporting written resources for children with acute wheeze or asthma, we found substantial practice variation. This highlights potential for improvement and standardisation, and areas requiring further research. While most provided written discharge safety netting, the content, design and language varied considerably. Advice to 'wean' bronchodilator doses was widespread, and recommended treatment during convalescence or unexpected deterioration was diverse; primarily in dosage, timing and duration of bronchodilator use. This variation may negatively impact outcomes in the index and future attacks. This includes adverse effects of undertreatment or overtreatment, caregiver confusion, and delays in hospital attendance and treatment escalation.

Safety netting is best practice in emergency care, supporting safe recovery and prompting appropriate action for deterioration. ED environments present unique challenges to delivering patient education,²⁰ with comprehension affected by factors including health literacy, readability, emotions and tiredness.²¹ Written information should be reinforced with clear verbal instructions, and clinicians should check and clarify understanding. Although most sites provided safety netting, content varied as seen in other settings.²² Standardised care processes bring many benefits, including economic advantages and improved clinical outcomes. Standardising asthma discharge education including red flag signs and emergency escalation advice would ensure patients receive consistent advice between visits and different health providers, minimising potential caregiver confusion.

Establishing dose-response data for inhaled salbutamol in young children is challenging due to obstacles including disease heterogeneity and disagreement on thresholds for clinically significant bronchodilator responsiveness.^{23 24} International recommendations for bronchodilator dosing during acute asthma attacks are typically consensus-based and differ slightly,^{7 25-28} contributing to variation in acute management including type, route and dosage of bronchodilators and steroid usage.^{29 30}

This variation is reflected in international guidance for recovery dosing. The Global Initiative for Asthma (GINA) recommends 'as needed' dosing, with no further instructions other than recommending caregivers record daily dosing to ensure reduction to preattack levels.²¹ Canadian Thoracic Society guidelines do not provide recovery dosing advice,³¹ while the Canadian Paediatric society advises 4-hourly short-acting β_2 agonists until symptoms resolve, then 'as needed'.³² Neither BTS/SIGN asthma guidelines nor the BTS asthma discharge bundle provide dosing recommendations for the recovery phase following acute wheeze.^{5 15} It is not surprising that variation existed across sites in discharge bronchodilator dosing, with only 10 (16%) offering tailored personalised plans. In our cohort, only two advised fully caregiver-driven 'as needed'/'as required' recovery dosing plans. Due to wheeze phenotypes and differences in individual bronchodilator responsiveness,^{33 34} written PAAPs are a key recommendation of the BTS/SIGN discharge bundle and The National Review of Asthma Deaths for acute and maintenance asthma management;^{2 5} it seems intuitive that the principle of personalisation should also apply to recovery plans. Caregiver-led, symptom-guided, individualised management requires specific instructions and careful educa-

Domain	Characteristic	N (%)
Leaflet type	Combined discharge and PAAP	33 (54.1)
	Describing normal (expected) and abnormal (unexpected/deterioration) recovery	17 (27.9)
	Describing normal (expected) recovery	16 (26.2)
	Discharge only	17 (27.9)
	Describing normal (expected) recovery and abnormal (unexpected/deterioration) recovery path	14 (22.9)
	Describing normal (expected) recovery	3 (4.9)
	PAAP/plan for future episodes only	11 (18.0)
General Information provided*	Inhaler and spacer technique	33 (54.1)
	Overview of wheeze	23 (37.7)
	How inhalers work	19 (31.1)
	Expected time course for recovery	18 (29.5)
	Advice on what to do overnight	16 (26.2)
	Do not wake to give inhalers overnight	9 (56.3)
	Continue to administer overnight (wake if sleeping)	6 (37.5)
	Administer only if felt required	1 (1.6)
	Signs of improvement	7 (11.5)
	Inhaler side effects	3 (4.9)
	Unable to speak	52 (85.2)
	Respiratory distress	51 (83.6)
	Inhalers not lasting 4 hours	49 (80.3)
Advice on red flags*	Audible wheeze	40 (65.6)
	Coughing	37 (60.7)
	Fast breathing or short of breath	36 (59.0)
	Poor feeding or drinking	32 (52.5)
	Looks pale	31 (50.8)
	Not improving after specified period	26 (42.6)
	Drowsiness	25 (40.9)
	Caregiver is worried	8 (13.1)
	Contact GP	47 (77.1)
	Call 999	45 (73.7)
	Call/reattend hospital	25 (40.9)
	Call 111	19 (31.1)
	No advice given	7 (11.5)
Location of red flag and escalation advice	Within PAAP/future episodes information only	31 (52.5)
	Within discharge recovery information	28 (47.5)
	None described	2 (3.3)
GP follow-up recommended	GP follow-up (any)	38 (62.3)
	Within 48 hours	28 (45.9)
	Within 1 week	4 (6.6)
	Within 72 hours	3 (4.9)
	Other timeframe	3 (4.9)
Other support*	Smoking cessation support offered	15 (24.6)
	Specialist nurse	8 (13.1)
	Asthma clinic	4 (6.6)
	Open access	3 (4.9)
	Community nursing team	3 (4.9)
	General paediatric clinic	1 (1.6)
Written Information standards	Clear language used	61 (100)
	Traffic light system used for safety netting	38 (62.3)
	Signposts to further sources of information	33 (54.1)
	Terminology explained	25 (40.9)
	Contact number provided	18 (29.5)
	Invites feedback	2 (3.3)

*Percentages may be greater than 100% as more than one could be selected.
PAAP, Personalised Asthma Action Plan.

tion, ensuring comprehension and interpretation. Though more time-consuming and requiring clinician training, this may ensure patients at greater risk of deterioration receive tailored dosing advice, and reduce unnecessary bronchodilator administration from 'fixed' plans. Four (8%) sites used a dosing plan with parallel pathways for children who were either 'improving/symptom-free' or 'not improving/deteriorating'. Though still 'fixed' dosing in nature, these appeared to provide alternative flexible dosing

Bronchodilator dosing	N (%)	Median	IQR
Nature of plan (n=61)			
No recovery plan provided	11 (18.0)	—	—
'Fixed' plan	45 (73.8)		
'Hybrid' plan	3 (4.9)		
'Caregiver-determined' plan	2 (3.3)		
Starting dose (number of puffs to be given at a time) in sites that provide a recovery plan (n=50)		10 puffs	8–10 to 10 puffs
3–4	1 (2.0)		
5	2 (4.0)		
6	1 (2.0)		
8	4 (8.0)		
8–10	4 (8.0)		
10	27 (54.0)		
12	1 (2.0)		
Clinician-specified (free-text)	10 (20.0)		
Starting frequency in sites that provide a recovery plan (n=50)		4 hourly	4 hourly
3–4 hourly	3 (6.0)		
4 hourly	29 (58.0)		
4–6 hourly	3 (6.0)		
6 hourly	3 (6.0)		
'As needed' (no timing specified)	2 (4.0)		
Clinician-specified (free-text)	10 (20.0)		
Weaning dosing schedule (n=50)		—	—
Weaning dosage specified	38 (76.0)		
No weaning schedule advised	7 (14.0)		
Unable to determine (clinician-specified dosing in free-text boxes)	5 (10.0)		
Total plan duration (in days) (n=50)		4 days	3–5 days
2	2 (4.0)		
3	11 (22.0)		
4	15 (30.0)		
5	9 (18.0)		
6	3 (6.0)		
>6	2 (4.0)		
Unspecified	8 (16.0)		

according to clinical status, accommodating individual differences in treatment response and recovery trajectory.

Most plans adopted gradual dose tapering over specified timeframes regardless of clinical status, despite a lack of evidence to support this practice and its absence from BTS and GINA guidance. Potential advantages to weaning (including maintaining bronchodilation as the child overcomes illness and providing caregivers with clear tapering schedules) must be balanced with concerns that life-threatening deterioration may be masked.³⁵ In addition, as over two-thirds of young children with a wheeze attack will have no ED re-attendances within a year (and often experience just a one-off episode),³⁶ prolonged bronchodilator courses may be excessive. In our cohort, median duration was 4 days, though a tenth prescribed bronchodilators for six or more days. While bronchodilator adherence improves when written action plans are provided,³⁷ this topic is underinvestigated. It is plausible that lengthier bronchodilator plans are not completed, akin to inadequate adherence to steroid and antibiotic prescriptions.^{38–39} Greater understanding of caregiver behaviour regarding bronchodilator administration during recovery is therefore needed to inform optimal discharge prescribing practice.

One in 10 sites did not provide emergency escalation advice, and over a fifth did not provide bronchodilator instructions for unexpected deterioration. While most advised 10 salbutamol puffs, administration timescale and escalation strategies varied, including '10 puffs every minute until help arrives', give 'as often as needed' or 'no further advice'. Inadequate communication or ambiguous

Table 4 Emergency bronchodilator dosing for deterioration during recovery

Instructions given for initial and subsequent doses (n=48)	N (%)
Give 10 puffs then:	
Repeat 10 puffs every 10 min	9 (18.8)
Give as often as needed	5 (10.4)
Repeat once after 15 min	4 (8.3)
Repeat 10 puffs every 15 min	4 (8.3)
Give 1 puff every minute	3 (6.3)
No further dosing	3 (6.3)
Give 1 puff every 30 s	2 (4.2)
Repeat 10 puffs every 20 min	2 (4.2)
Repeat once	1 (2.1)
Repeat 10 puffs every minute	1 (2.1)
Give 2 puffs every 2 min	1 (2.1)
Repeat up to 10 puffs	1 (2.1)
Repeat every 3–4 hours	1 (2.1)
No further guidance offered	5 (10.4)
Give 1 puff then:	
Give 1 puff every minute	1 (2.1)
Give 1 puff every 5 breaths	1 (2.1)
Give 2 puffs then:	
Give 2 puffs every 2 min	1 (2.1)
Give 1 puff every minute	1 (2.1)
Give 6 puffs then:	
Give 6 puffs every 6 min	1 (2.1)
Give 12 puffs then:	
Repeat once	1 (2.1)
No emergency dosing plan	13 (21.3)

instructions may result in unrecognised deterioration⁴⁰ and delay timely review. Creating uncertainty for caregivers risks either inadequate or overzealous bronchodilator dosing with potential for iatrogenic complications.

Finally, format and context of written information matters. Clear distinction should be made between treatment step-down and safety netting during recovery (including recognition of deterioration), and actions during subsequent attacks; it is critical caregivers understand that each situation requires a different approach. PAAP content typically relates to longer-term disease control, and initial management of new-onset attacks rather than step-down care following acute attacks. With a fifth of sites in our study using PAAPs as their sole discharge document, consideration must be given to either (1) Expanding and modifying PAAPs to differentiate between recovery and subsequent attacks, or (2) Strengthening guidance that recovery plans should be separate entities to PAAPs. To ensure usability and clarity, step-down action plans should be developed with stakeholders including families and patients.

Recommendations for policy and research

Given the potential for negative impact on patient outcomes, national standards and practices should be developed to minimise this variation in care, as outlined above. While these will initially be consensus driven (and challenging to deliver due to strength of views in this area), future research should aim to provide evidence on best practice. An international consortium is currently developing a Core Outcome Set for use in childhood asthma trials, in conjunction with CYP and their families.⁴¹ These validated outcomes will lead the way to robust trial performance, including possible randomised controlled trials of 'fixed' vs 'caregiver-led' bronchodilator regimes, and trials focusing on dose difference or durations designs. Preparatory research should be undertaken now, including observational research (including treatment adherence, and pragmatic measurement of outcomes with existing regimes), and qualitative research to explore the views, experience, and behaviour of young people and parents during the recovery phase from acute asthma and wheeze attacks.

Strengths and limitations

This study encompasses practice from participating PERUKI sites including mixed and stand-alone paediatric EDs in a range of hospitals, but does not capture individual clinician variation. There is potential for responder bias and possibly a reluctance to report suboptimal discharge practices, potentially overestimating concordance with BTS discharge bundle recommendations; however, a strength of this study was objective blinded analysis of written materials as provided to families, to minimise this bias. In addition, this study provides the only measurement of discharge practices specifically from EDs in our setting, as other resources such as NACAP focus on children who are admitted to hospital only. Finally, for pragmatic reasons, the authors did not seek patient and public involvement to contribute to leaflet analysis, though development of all data extraction tools were underpinned by review of existing evidence and guidance.

CONCLUSIONS AND FUTURE WORK

This national study of discharge practices and written safety netting information for children with acute wheeze/asthma being discharged from EDs demonstrated a wide variety of practices and variable information quality. Further research is required to determine optimal recovery bronchodilator dosing, and to understand caregiver behaviour during recovery. There is a need for nationally consistent and clear discharge advice for children following acute wheezing and asthma attacks supporting caregivers to de-escalate treatment safely, and empowering them to recognise and respond to deterioration appropriately.

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REFERENCES

- Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;332:133–8.
- RCP London. Why asthma still kills. 2015. Available: <https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills> [Accessed 08 Jul 2023].
- Stevens CA, Turner D, Kuehni CE, et al. The economic impact of preschool asthma and wheeze. *Eur Respir J* 2003;21:1000–6.
- Thyng J, Cunningham L, McKinley S, et al. The impact of changing from prednisolone to dexamethasone for the management of wheeze in children- a service evaluation. *JAMMR* 2021;44–6.
- Asthma, British Thoracic Society. Better lung health for all. Available: <https://www.britthoracic.org.uk/quality-improvement/guidelines/asthma/> [Accessed 09 Jul 2023].
- NICE. Overview | asthma: diagnosis, monitoring and chronic asthma management | guidance. 2017. Available: <https://www.nice.org.uk/guidance/ng80> [Accessed 08 Jul 2023].
- Global Initiative for Asthma - GINA. 2022 GINA main report. Available: <https://ginasthma.org/gina-reports/> [Accessed 08 Jul 2023].
- Adams RJ, Smith BJ, Ruffin RE. Factors associated with hospital admissions and repeat emergency department visits for adults with asthma. *Thorax* 2000;55:566–73.
- Gray SJ, Wacogne ID, Roland D. Fifteen-minute consultation: safety netting effectively. *Arch Dis Child Educ Pract Ed* 2019;104:226–30.
- Almond S, Mant D, Thompson M. Diagnostic safety-netting. *Br J Gen Pract* 2009;59:872–4.
- Jones D, Dunn L, Watt I, et al. Safety netting for primary care: evidence from a literature review. *Br J Gen Pract* 2019;69:e70–9.
- NICE. Overview | fever in under 5s | quality standards. 2014. Available: <https://www.nice.org.uk/guidance/qs64> [Accessed 08 Jul 2023].
- Lyttle MD, O'Sullivan R, Hartshorn S, et al. Pediatric emergency research in the UK and Ireland (PERUKI): developing a collaborative for multicentre research. *Arch Dis Child* 2014;99:602–3.
- National asthma and COPD audit programme. Available: <https://www.nacap.org.uk/nacap/welcome.nsf/reportsPA.html> [Accessed 08 Jul 2023].
- BTS Asthma care bundles, British Thoracic Society. Better lung health for all. Available: <https://www.brit-thoracic.org.uk/quality-improvement/clinical-resources/asthma/btsasthma-care-bundles/> [Accessed 08 Jul 2023].
- Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
- NHS England. The information standard principles. Available: <https://www.england.nhs.uk/tis/the-info-standard/> [Accessed 08 Jul 2023].
- NICE. Overview | fever in under 5s: assessment and initial management | guidance. 2019. Available: <https://www.nice.org.uk/guidance/ng143> [Accessed 08 Jul 2023].
- Is my study research? Available: <https://www.hra-decisiontools.org.uk/research/> [Accessed 08 Jul 2023].
- Pétre B, Margat A, Servotte JC, et al. Patient education in the emergency department: take advantage of the teachable moment. *Adv in Health Sci Educ* 2020;25:511–7.
- Curran JA, Gallant AJ, Zemek R, et al. Discharge communication practices in pediatric emergency care: a systematic review and narrative synthesis. *Syst Rev* 2019;8:83.
- Chan M, Gray M, Burns C, et al. Assessment of variation in care following hospital discharge for children with acute asthma. *J Asthma Allergy* 2021;14:797–808.
- Tse SM, Gold DR, Sordillo JE, et al. Diagnostic accuracy of the bronchodilator response in children. *J Allergy Clin Immunol* 2013;132:554–9.
- Guezguez F, Ben Saad H. What constitutes a “clinically significant” bronchodilator response in children. *Eur Respir J* 2020;55:2000207.
- Bacharier LB, Boner A, Carlsen K-H, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008;63:5–34.
- NHLBI, NIH. National asthma education and prevention program coordinating committee (NAEPPCC). Available: <https://www.nhlbi.nih.gov/science/national-asthmaeducation-and-prevention-program-coordinating-committee-naeppcc> [Accessed 08 Jul 2023].
- Brand PLP, Caudri D, Eber E, et al. Classification and pharmacological treatment of preschool wheezing: changes since 2008. *Eur Respir J* 2014;43:1172–7.
- Gaillard EA, Kuehni CE, Turner S, et al. European respiratory society clinical practice guidelines for the diagnosis of asthma in children aged 5–16 years. *Eur Respir J* 2021;58:2004173.
- Koldewey C, Appelbaum N, Rodriguez Gonzalez C, et al. Mind the gap: mapping variation between national and local clinical practice guidelines for acute paediatric asthma from the United Kingdom and the Netherlands. *PLOS ONE* 2022;17:e0267445.
- Lee MO, Sivasankar S, Pokrajac N, et al. Emergency department treatment of asthma in children: a review. *J Am Coll Emerg Physicians Open* 2020;1:1552–61.
- Yang CL, Hicks EA, Mitchell P, et al. Canadian thoracic society 2021 guideline update: diagnosis and management of asthma in preschoolers, children and adults. *Can J Respir Crit Care Sleep Med* 2021;5:348–61.
- Canadian Paediatric Society. Managing an acute asthma exacerbation in children. Available: <https://cps.ca/en/documents/position/managing-an-acute-asthmaexacerbation> [Accessed 09 Jul 2023].
- Coverstone AM, Bacharier LB, Wilson BS, et al. Clinical significance of the bronchodilator response in children with severe asthma. *Pediatr Pulmonol* 2019;54:1694–703.
- Grunwell JR, Nguyen KM, Bruce AC, et al. Bronchodilator dose responsiveness in children and adolescents: clinical features and association with future asthma exacerbations. *J Allergy Clin Immunol Pract* 2020;8:953–64.
- Re: conflicting asthma guidelines cause confusion in primary care. 2023. Available: <https://www.bmj.com/content/360/bmj.k29/rr-9> [Accessed 08 Jul 2023].
- Davies G, Paton JY, Beaton SJ, et al. Children admitted with acute wheeze/asthma during november 1998–2005: a national UK audit. *Arch Dis Child* 2008;93:952–8.
- Ducharme FM, Zemek RL, Chalut D, et al. Written action plan in pediatric emergency room improves asthma prescribing, adherence, and control. *Am J Respir Crit Care Med* 2011;183:195–203.
- Butler K, Cooper WO. Adherence of pediatric asthma patients with oral corticosteroid prescriptions following pediatric emergency department visit or hospitalization. *Pediatr Emerg Care* 2004;20:730–5.
- Youngster I, Gelernter R, Klainer H, et al. Electronically monitored adherence to short-term antibiotic therapy in children. *Pediatrics* 2022;150:e2022058281.
- Cabral C, Ingram J, Hay AD, et al. “They just say everything’s a virus”—parent’s judgment of the credibility of clinician communication in primary care consultations for respiratory tract infections in children: a qualitative study. *Patient Educ Couns* 2014;95:248–53.
- Craig S, Babl FE, Dalziel SR, et al. Acute severe paediatric asthma: study protocol for the development of a core outcome set, a pediatric emergency research networks (PERN) study. *Trials* 2020;21:72.



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

1 vez dia¹

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

NOVA
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LABA/LAMA
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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 beta, de ação prolongada e uma dose alta de corticosteroide inalado em regime de manutenção que experimentaram uma ou mais exacerbações da asma no ano anterior. **POSOLOGIA: Adultos:** A dose recomendada é uma cápsula inalada uma vez por dia. A dose máxima recomendada é de 114 µg/46 µg/136 µg uma vez por dia. **Doentes pediátricos (< 18 anos):** Não recomendado em doentes com menos de 18 anos de idade. **Populações especiais: População idosa:** Não é necessário ajuste de dose em doentes idosos (65 anos de idade ou mais). **Compromisso renal:** Não é necessário ajuste de dose em doentes com compromisso renal ligeiro a moderado. Deve ter-se precaução em doentes com compromisso renal grave ou doença renal terminal que necessitem de diálise. **Compromisso hepático:** Não é necessário ajuste de dose em doentes com compromisso hepático ligeiro a moderado. Não existem dados disponíveis sobre a utilização deste medicamento em doentes com compromisso hepático grave, como tal deve ser utilizado nestes doentes apenas se o benefício esperado superar o risco potencial. **Modo de administração:** Apenas para utilização por via inalatória. As cápsulas não podem ser engolidas. Os doentes que não sintam melhorias na sua respiração devem ser questionados se estão a engolir o medicamento em vez de o inalar. As cápsulas têm de ser administradas usando apenas o inalador Zimbus Breezhaler. O tratamento deve ser administrado à mesma hora do dia todos os dias. Pode ser administrado independentemente da hora do dia. Após a inalação, os doentes devem lavar a boca com água sem engolir. Se for omitida uma dose, esta deve ser tomada assim que possível. Os doentes devem ser instruídos a não tomarem mais do que uma dose por dia. As cápsulas de Zimbus Breezhaler devem ser sempre conservadas no blister para proteger da luz e humidade, e só podem ser removidas do blister imediatamente antes da utilização. **CONTRAINDICAÇÕES:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **ADVERTÊNCIAS/PRECAUÇÕES:** ♦ **Asma Aguda:** não deve ser utilizado para tratar sintomas agudos de asma, incluindo episódios agudos de 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 beta, este medicamento pode produzir um efeito cardiovascular clinicamente significativo em alguns doentes conforme avaliado através de aumentos na frequência cardíaca, pressão arterial e/ou sintomas, alterações do electrocardiograma (ECG). Este medicamento deve ser usado com precaução em doentes com patologias cardiovasculares (doença arterial coronária, enfarte agudo do miocárdio, arritmias cardíacas, hipertensão, suspeita ou confirmação de prolongamento do intervalo QT, distúrbios convulsivos ou tirototoxicose e em doentes com resposta aumentada aos agonistas adrenérgicos beta). ♦ **Hipocalcemia:** Os agonistas adrenérgicos beta, podem causar uma hipocalcemia significativa em alguns doentes, o que potencialmente pode levar a reações adversas cardiovasculares. Em doentes com asma grave, a hipocalcemia pode ser potenciada pela hipoxia e pela terapêutica concomitante, o que pode aumentar a suscetibilidade a arritmias cardíacas. ♦ **Hiperglicemia:** A inalação de doses elevadas de agonistas adrenérgicos beta, e corticosteroides pode produzir um aumento da glicose plasmática. Nos doentes diabéticos, ao iniciar o tratamento, a glicose plasmática deve ser monitorizada mais cuidadosamente. ♦ **Efeitos anticolinérgicos:** Tal como com outros medicamentos anticolinérgicos, este medicamento deve ser utilizado com precaução em doentes com glaucoma de ângulo fechado ou retenção urinária. ♦ **Doentes com compromisso renal grave:** Nos doentes com compromisso renal grave (taxa de filtração glomerular estimada inferior a 30 ml/min/1,73 m²), incluindo aqueles com doença renal terminal que necessitam de diálise, deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. ♦ **Prevenção de infeções orofaríngeas:** De modo a reduzir o risco de infeção orofaríngea por *Candida albicans*, os doentes devem ser aconselhados a lavar a boca ou a gargarejar com água, sem a engolir, ou a lavar os dentes após inalarem a dose prescrita. ♦ **Efeitos sistémicos dos corticosteroides:** Podem ocorrer efeitos sistémicos dos corticosteroides inalados, principalmente no caso de doses elevadas prescritas por períodos prolongados. Os efeitos sistémicos possíveis podem incluir: síndrome de Cushing, manifestações Cushingoides, 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 com o uso de corticosteroides sistémicos ou tópicos (incluindo intranasais, inalados ou intraculares). Doentes que apresentem sintomas como visão turva ou outros distúrbios visuais, devem ser considerados para encaminhamento a um oftalmologista para avaliação de possíveis causas dessas perturbações visuais, as quais podem incluir cataratas, glaucoma ou doenças raras como a coriorretinopatia central serosa (CRCS), que foram notificadas após o uso de corticosteroides sistémicos ou tópicos. Este medicamento deve ser administrado com precaução em doentes com tuberculose pulmonar ou em doentes com infeções crónicas ou não tratadas. ♦ **Gravidez:** Este medicamento deve ser utilizado durante a gravidez apenas se o benefício esperado para o doente justificar o potencial risco para o feto. ♦ **Amamentação:** Tem que ser tomada uma decisão sobre a descontinuação da amamentação ou a descontinuação/abstenção da terapêutica, tendo em conta o benefício da amamentação para a criança e o benefício da terapêutica para a mulher. ♦ **Trabalho de parto:** Como outros medicamentos contendo agonistas adrenérgicos beta, o indacaterol pode inibir o trabalho de parto devido a um efeito relaxante no músculo liso uterino. **INTERAÇÕES:** ♦ **Bloqueadores adrenérgicos beta:** este medicamento não deve ser administrado com bloqueadores adrenérgicos beta (incluindo gotas para os olhos) a menos que existam razões importantes para a sua utilização ♦ **Medicamentos conhecidos por prolongarem o intervalo QT:** 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 prolongarem 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 beta. ♦ **Interação com inibidores do CYP3A4 e da glicoproteína P:** A inibição do CYP3A4 e da glicoproteína P (gp-P) não tem impacto na segurança de doses terapêuticas de Zimbus Breezhaler. ♦ **Outros antimuscarínicos de ação prolongada e agonistas adrenérgicos beta, de ação prolongada:** A coadministração deste medicamento com outros medicamentos contendo antagonistas muscarínicos de ação prolongada ou agonistas adrenérgicos beta, de ação prolongada não foi estudada e não é recomendada. ♦ **Cimetidina ou outros inibidores do transporte de catiões orgânicos:** Não é esperada qualquer interação medicamentosa clinicamente relevante. **EFEITOS INDESEJÁVEIS:** ♦ **Frequentes (≥1% a <10%) e potencialmente graves:** hipersensibilidade. ♦ **Muito frequentes:** asma (exacerbação), nasofaringite. ♦ **Frequentes (≥1% a <10%):** infeção do trato respiratório superior, candidíase, infeção do trato urinário, cefaleia, taquicardia, dor orofaríngea, tosse, disfonia, gastroenterite, dor musculoesquelética, espasmos musculares, plexia. ♦ **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 Medifar - Produtos Farmacêuticos, S.A. - Rua Henrique de Paiva Couceiro, N° 29, Venda Nova, 2700-451 Amadora Informações Essenciais Compatíveis com o Resumo das Características do Medicamento (ZIM_RCM20210422_IEC_v2).

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ARTIGO ORIGINAL

Impacto do sexo em asma grave: uma análise retrospectiva transversal dos cuidados primários e especializados do Reino Unido

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RESUMO

Introdução Após a puberdade, as mulheres são mais propensas a desenvolver asma e de forma mais grave do que os homens. As associações entre asma e sexo são complexas com múltiplos fatores intrínsecos e externos.

Objetivo Avaliar as diferenças sexuais nas características e tratamento de doentes com asma grave (SA) num mundo real definição.

Método As características demográficas, clínicas e de tratamento para os doentes com SA no Reino Unido Severe Asthma Registry (UKSAR) e Optimum Patient Care Research Database (OPCRD) foram analisadas retrospectivamente por sexo utilizando análises univariadas e multivariáveis de regressão logística ajustadas para o ano, idade e hospital/prática.

Resultados Foram incluídos 3.679 (60,9% do sexo feminino) do UKSAR e 18 369 doentes (67,9% do sexo feminino) do OPCRD com SA. As mulheres eram mais propensas a ser sintomáticas com o aumento do Questionário de Controlo de Asma-6 (UKSAR ajustado OR (aOR) 1,14, IC 95% 1,09 a 1,18) e Royal College of Physicians-3 pontuações de perguntas (OPCRD aOR 1,29, IC 95% 1,13 a 1,47). No entanto, tiveram um maior volume expiratório forçado em 1 por cento (FEV₁%) previsto (UKSAR 68,7% vs 64,8%, $p < 0,001$) sem diferença significativa no fluxo de pico expiratório. Os biomarcadores do tipo 2 IgE (UKSAR 129 UI/mL vs 208 UI/mL, $p < 0,001$) e FeNO (UKSAR 36ppb vs 46ppb, $p < 0,001$) foram mais baixos nas mulheres, sem diferença significativa em eosinófilos sanguíneos ou terapia biológica. As mulheres tinham menos probabilidade de estar em tratamento com corticoides orais de manutenção (UKSAR aOR 0,86, IC 95% 0,75 a 0,99), mas tinham mais probabilidade de serem obesas (UKSAR aOR 1,67, IC 95% 1,45 a 1,93; OPCRD SA aOR 1,46, IC 95% 1,34 a 1,58).

Conclusões As mulheres apresentaram sintomas aumentados e eram mais propensas a serem obesas, apesar do FEV₁% previsto mais alto e dos biomarcadores tipo 2 mais baixos, com diferenças consistentes e clinicamente importantes em ambos os conjuntos de dados.

INTRODUCTION

Asthma has an estimated global prevalence of over 350 million¹ with 15.6% of the UK population being diagnosed in their lifetime.² This includes approximately 3%–10% with severe asthma (SA),³ many of whom are potentially hidden in primary care.⁴ Despite its relatively small proportion, SA accounts for the majority of morbidity and economic costs associated with asthma.⁵ SA is defined by the European Respiratory Society/American Thoracic Society (ERS/ATS) as asthma requiring treatment with high-dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it

Key messages

What is the key question?

► Severe asthma is more common in females. It is associated with different disease characteristics between the sexes, including females having a higher symptom burden and lower expression of type 2 biomarkers.

What is the bottom line?

► Males and females with severe asthma have significant clinical differences in their asthma symptoms, healthcare utilisation, type 2 biomarkers and associated comorbidities. These differences have been demonstrated in large well-characterised and robust real-world cohorts across both specialist and primary care adding understanding to the sex differences of specific clinical characteristics in severe asthma.

Why read on?

► Understanding the different characteristics associated with severe asthma between males and females is essential in establishing personalised care for patients and focusing future research on the mechanisms underlying the differences seen.

from becoming ‘uncontrolled’ or which remains ‘uncontrolled’ despite this therapy.³

Asthma, which is characterised by chronic airway inflammation, remodelling and hyper-responsiveness with variable airflow obstruction and respiratory symptoms, is a heterogeneous disease in both pathogenesis and clinical characteristics. While asthma prevalence of all severities is higher in males at prepuberty, the switch to a female predominance by adulthood is well established.^{7,8}

Furthermore, females are more likely to develop asthma in their lifetime and in a more severe form than their male counterparts.¹ The associations between asthma and sex are, however, complex. Shifts in the sex prevalence of asthma coincide with changes in sex hormones suggesting a potential role in asthma pathogenesis,^{9,10} however, epidemiological studies have been inconclusive.¹¹ Further factors, including sex-associated and gender-associated exposures and behaviours such as

occupation, smoking, healthcare utilisation and access, alongside genetic and epigenetic factors also influence the relationship between asthma and sex.⁸

Despite a growing understanding of the complex and important relationship between the intrinsic and external factors associated with sex and asthma, there is little understanding of the real-world differences seen in clinical practice. Previous studies have attempted to phenotype patients with SA through multivariate cluster analysis, identifying clusters supporting the complex and heterogeneous relationship between asthma and sex.¹² Analysis from the UBIO-PRED cohort identified a cluster of predominantly obese female patients with SA who had frequent exacerbations but near-normal lung function.¹³ Type 2 (T2) asthma, which is driven by allergic and/or eosinophilic pathways, has been found to have a male predominance in further SA cohorts,^{14–16} and a male predominant cluster with SA, nasal polyps, eosinophilia and high-dose corticosteroid use was previously identified from the SARP programme.¹⁷ These T2 pathways, which can be identified through biomarkers such as FeNO, IgE and blood eosinophils respond to corticosteroid therapy and can be targeted through biological therapy in uncontrolled SA.¹⁸ It is, therefore, important to understand the differences in disease characteristics and T2 markers between males and females for diagnostic and personalised treatment pathways to be developed in SA.

The effect of T2 biomarker guided therapy can also be impacted by sex. A post hoc analysis by sex of the Refractory Asthma Stratification Programme (RASP-UK) biomarker study found a greater proportion of females with SA were able to reduce their corticosteroid dose using a T2 biomarker algorithm when compared with standard care, a difference not seen in males.¹⁹ This study found a dissociation between the sexes in symptoms and T2 biomarkers with a higher proportion of females to be symptom high/T2 biomarker low while males were symptom low/T2 biomarker high. The differences in self-reported symptoms were also shown to be mediated by obesity or a history of depression/anxiety. Such findings demonstrate the importance of understanding sex differences in the delivery of SA therapy. However, the current literature does not address the need to provide real-world comparison of the differences in the disease and treatment between males and females with SA.

This study aims to evaluate the sex differences in disease characteristics, symptom control, exacerbations, biological phenotypes and treatment in patients with SA using a retrospective epidemiological approach.

METHODS

Study population

This is a retrospective epidemiological study using cohorts from two datasets. The UK Severe Asthma Registry (UKSAR) is a national database containing demographic, clinical and treatment characteristics on patients referred to specialist UK SA centres with SA.²⁰ Patients have undergone systematic assessment and those diagnosed with SA according to the ERS/ATS criteria²¹ were included in this analysis.

The Optimum Patient Care Research Database (OPCRD) is a UK nationally representative pseudonymised dataset of 18 million patients registered at 1000 general practices within the UK (24% of the UK population).²² The OPCRd is approved by the UK National Health Service for clinical research use (15/EM/0150). It contains information on patient demographics, clinical diagnoses, medication prescriptions and referrals coded through the Read and SNOMED classification systems. To prevent time-window bias,²³ a standard 1-year window was used to assess outcomes for all patients. Those with less than 1 year of eligible follow-up time were excluded from the study. A 1-year ascertainment period was randomly chosen for patients with more than 1-year eligible follow-up time. To increase the comparability of our cohort, those with an alternative respiratory diagnosis in the 3 years prior to inclusion were also excluded.

SA in the OPCRd cohort was defined according to GINA (global initiative for asthma) 2018²⁴ criteria as those who remained uncontrolled (≥ 2 exacerbations within a year) on step 4 treatment or who require maintenance oral corticosteroids (OCS) to achieve control.

Exposures, outcomes and covariates

The primary outcomes of interest were T2 biomarkers (blood eosinophils, fractional exhaled nitric oxide (FeNO) and IgE), lung function (forced expiratory volume in the 1 s (FEV₁), forced vital capacity (FVC) and peak expiratory flow (PEF)), asthma control, asthma phenotype (atopy), asthma medications (treatment adherence, maintenance OCS use, biological therapy use), healthcare utilisation (exacerbations, emergency department (ED) attendance, hospital admission, asthma review and respiratory referral) and comorbidities. Outcome measurements were all taken at baseline prior to the initiation of biological therapy.

Lung function recordings were taken as raw measurements and per cent predicated calculated using the formula by Knudson et al²⁵ for PEF and Global Lung Function Initiative²⁶ for FEV₁ and FVC. Asthma control was measured by the Asthma Control Questionnaire-6 (ACQ6)²⁷ in the UKSAR and Royal College of Physicians-3 Questions (RCP 3Q)²⁸ in the OPCRd. Treatment adherence was assessed using the fixed medication possession ratio (MPR) of ICS during the ascertainment period. Good adherence was defined as an MPR of greater than or equal to 70%. Obesity was defined as a body mass index (BMI) of 30 kg/m² or greater. Comorbidities in the OPCRd cohort were identified through Read codes, which were used to identify a list based on the Charlson Comorbidity Index,²⁹ depression/anxiety and those related to systemic corticosteroid exposure.³⁰ Full details of the variables used in the analysis, including the time period in which they were assessed, are provided in online supplemental table 1. UKSAR baseline data were collected at the time of registration, prior to biological therapy being started and follow-up data collected annually.

Statistical analysis

This was a complete-case analysis using all available data from the UKSAR and OPCRd. We calculated descriptive statistics and compared the demographic and clinical characteristics of male and female patients. Various statistical models were used depending on the distribution of the outcome variable including logistic (eg, atopy, maintenance OCS use, any ED attendance, uncontrolled asthma) and Poisson (eg, number of exacerbations) models. To aid interpretation and comparability across outcomes, all results are shown as ratios (continuous variables), ORs (binary variables) or risk ratios (count variables). Consequently, we used gamma generalised linear models with a log link function to analyse continuous outcomes. Multivariable analyses adjusted for demographic factors were conducted accounting for age (5-year categories) and year. The UKSAR analysis additionally adjusted for hospital site, while the clustering of patients within GP practices in the OPCRd was accounted for using cluster robust SEs. We chose this limited set of adjustment variables to prevent any overadjustment bias, whereby adjustment is made for variables which lie on the causal path between sex and outcomes, to ensure that we captured the full magnitude of any sex disparities.³¹ For example, adjustment for socioeconomic status within our models could lead us to exclude gender disparities driven by socioeconomic disadvantage among females. We accounted for clustering within hospitals using fixed-effect in the UKSAR, and clustering within practices in the OPCRd using cluster robust standard errors, while fixed-effects were used to account for clustering within hospitals in the UKSAR due to a much smaller number of sites.³

Sensitivity and supplementary analysis

Sensitivity analysis was performed using patients with mild to moderate asthma from the OPCRd cohort to assess the potential impact of disease severity on our findings. Mild/moderate asthma was defined as patients with a diagnosis of asthma on GINA steps 2–3 therapy.²⁴ Those patients who had required OCS within the last 12 months were excluded from the mild/moderate asthma group to provide a clear comparator, avoiding patients with underlying SA whose therapy had not been stepped up. All patients with alternative respiratory diagnoses were excluded. We investigated potential mediation due to BMI (categorised as <25, 25–30, ≥ 30 kg/m²), depression/anxiety and smoking status using the methods

of Baron and Kenny³² to understand the extent to which they may mediate gender disparities. A directed acyclic graph displaying the assumed relationships between the variables included within our mediation analysis is provided in online supplemental figure 1.

RESULTS
Cohort demographics

The UKSAR analysis contained 3679 patients (2242 (60.9%) females) with SA from 17 specialist secondary care clinical centres, while the OPCRd analysis contained 18 369 patients (12 468 (67.9%) females) with SA within primary care. Details of the study flow diagram can be seen in online supplemental figure 2. Patients in the UKSAR cohort were on higher doses of ICS than SA patients from the OPCRd cohort (median 2000ug vs 1000ug BDP equivalent). Patient demographics and clinical characteristics are shown in tables 1 and 2, while details of the multivariable analysis are in online supplemental tables 2 and 3.

Asthma clinical characteristics and outcomes

Females from the UKSAR database had an earlier average age of onset of symptoms (22.8 years vs 29.5 years; p<0.001), and average age of first assessment at a UKSAR centre than males (48.9 years in vs 54.0 years, p<0.001). In adjusted analyses, uncontrolled asthma were higher among females than males (figure 1, tables 1 and 2) as measured using the ACQ6 in UKSAR (adjusted OR (aOR) 1.8, 95% CI 1.47 to 2.19) or the RCP 3Q in OPCRd SA (aOR 1.29, 95% CI 1.13 to 1.47). Females in the UKSAR cohort had higher ACQ6 scores 6 (UKSAR aOR 1.14, 95% CI 1.09 to 1.18), demonstrating increased symptoms and lower asthma control, across all domains with a clinically significant, unadjusted difference of 0.5 (3.1 vs 2.6, p<0.001). Exacerbation rates were higher in females than males across all cohorts (UKSAR IRR 1.13, 95% CI 1.10 to 1.17; OPCRd IRR 1.06, 95% CI 1.00 to 1.12). Secondary healthcare utilisation was also increased with females in the UKSAR dataset more likely to report a hospital admission (aOR 1.46, 95% CI 1.26 to 1.70) or ED attendance (aOR 1.37, 95% CI 1.17 to 1.60) in the last year. In primary care there was no evidence of differences in asthma reviews (OPCRd SA aOR 1.07, 95% CI 0.99 to 1.16) or differences in asthma referrals (OPCRd SA aOR 1.09, 95% CI 0.94 to 1.2). FEV₁ per cent predicted was higher in females with SA (UKSAR adjusted ratio 1.05, 95% CI 1.03 to 1.07) representing a difference of 3.9% in absolute terms (68.7% vs 64.8%, p<0.001). In primary care, there was no evidence of significant differences in PEF (adjusted ratio 1.01, 95% CI 1.00 to 1.03).

Type 2 biomarkers

Multivariable analysis found no evidence of a difference between sexes in baseline blood eosinophil count in the UKSAR dataset (adjusted ratio 0.94, 95% CI 0.88, 1.01), however, eosinophil counts were lower in females for the OPCRd SA dataset (adjusted ratio 0.85, 95% CI 0.82 to 0.89 (figure 1, tables 1 and 2). Similarly, eosinophil counts were lower in females when looking specifically at prevalence of eosinophils greater than 0.3×10⁹/L in the OPCRd SA (25.3% vs 33%) cohort but did not differ significantly in the UKSAR dataset. Female UKSAR patients also had lower levels of the T2 biomarkers IgE (adjusted ratio 0.63, 95% CI 0.56 to 0.72) and FeNO (adjusted ratio 0.79, 95% CI 0.74 to 0.85). In absolute terms, FeNO levels in females were on average 10ppb less than males (36ppb vs 46ppb, p<0.001), while IgE was 79 IU/mL lower (129 IU/mL vs 208 IU/mL, p<0.001).

Corticosteroid and biological therapy

In multivariable analysis, females in the UKSAR cohort were less likely to be on maintenance OCS (aOR 0.86, 95% CI 0.75 to 0.99). No evidence of a difference in treatment adherence was found (UKSAR aOR 1.20, 95% CI 0.97 to 1.49; OPCRd SA aOR 0.96, 95% CI 0.88 to 1.04). Fixed MPR of ICS between females and males was similar in the OPCRd SA (48.8% vs 49.9%, p<0.001) group (figure 1, tables 1 and 2). There was no evidence of a difference in the proportion of females and males on biological treatment (OR 1.07, 95% CI 0.89 to 1.29).

Table 1 Comparison of female and male patients with severe asthma in the UK Severe Asthma Registry

Characteristic	Female (n=2242)	Male (n=1437)	P value
Age at baseline assessment*	48.9 (15.3)	54.0 (14.1)	<0.001
<35	464 (20.7%)	157 (10.9%)	
35–54	907 (40.5%)	535 (37.3%)	
55–74	792 (35.4%)	668 (46.5%)	
75+	77 (3.4%)	76 (5.3%)	
Ethnicity†			0.094
Caucasian	1808 (81.8%)	1189 (83.7%)	
Southeast Asian	83 (3.8%)	58 (4.1%)	
Northeast Asian	43 (1.9%)	30 (2.1%)	
African	73 (3.3%)	25 (1.8%)	
Mixed	15 (0.7%)	11 (0.8%)	
Other	187 (8.5%)	107 (7.5%)	
Age at onset of symptoms*	22.8 (18.4)	29.1 (21.5)	<0.001
FEV ₁ (% predicted)*	68.7 (21.1)	64.8 (21.0)	<0.001
FVC (% predicted)*	83.6 (19.2)	84.4 (19.2)	0.248
FEV ₁ /FVC ratio†			<0.001
<70%	1182 (56.6%)	988 (73.3%)	
>70%	907 (43.4%)	359 (26.7%)	
KCO (% predicted)*	94.7 (32.9)	102.6 (20.4)	<0.001
ACQ6 score*	3.1 (1.3)	2.6 (1.4)	<0.001
Uncontrolled asthma (ACQ6>1.5)†	1528 (85.6%)	850 (75.7%)	<0.001
Courses of rescue steroids in last year†			<0.001
0	178 (8.2%)	185 (13.4%)	
1	142 (6.6%)	106 (7.7%)	
2	163 (7.5%)	107 (7.8%)	
3	205 (9.5%)	161 (11.7%)	
≥4	1477 (68.2%)	820 (59.5%)	
ED attendances for asthma (last year)‡	0 (0, 1)	0 (0, 1)	<0.001
Any ED attendance (last year)‡	808 (38.3%)	383 (28.7%)	<0.001
Any hospital admissions (last year)‡	884 (40.9%)	417 (30.5%)	<0.001
On maintenance OCS†	1045 (46.9%)	747 (52.3%)	0.001
Maintenance OCS (mg)‡	10 (8, 20)	10 (8, 15)	0.026
ICS dose (BDP equivalent-ug)‡	2000 (1600, 2000)	2000 (1600, 2000)	0.074
Treatment adherent†	1713 (81.5%)	1081 (80.6%)	0.491
On biological therapy†	1608 (72.4%)	1044 (73.3%)	0.553
Anti-IL5/5RA	1184 (80.9%)	804 (84.9%)	
Anti-IgE	274 (18.7%)	140 (14.8%)	
Anti-IL4/13	5 (0.3%)	3 (0.3%)	
Other	1 (0.1%)	0 (0.0%)	
FeNO (ppb)‡	36 (18, 66)	46 (26, 81)	<0.001
IgE (IU/mL)‡	129 (42,347)	208 (75,524)	<0.001
Blood eosinophil count (10 ⁹ /L)‡	0.37 (0.20, 0.60)	0.40 (0.20, 0.61)	0.1
Highest blood eosinophil count (10 ⁹ /L)†			0.394
<0.150	483 (22.3%)	295 (21.2%)	

Continued

Comorbidities and lifestyle

A higher proportion of female patients were found to be obese (figure 1, tables 1 and 2) in both the UKSAR (aOR 1.67; 95% CI 1.45 to 1.93) and OPCRd SA (aOR 1.46, 95% CI 1.34 to 1.58) cohorts.



Table 1 Continued

Characteristic	Female (n=2242)	Male (n=1437)	P value
0.150–0.300	328 (15.1%)	197 (14.2%)	
>0.300	1359 (62.5%)	900 (66.7%)	
BMI (kg/m ²)*	31.5 (7.8)	29.5 (5.8)	<0.001
Normal/underweight (<24.9)	453 (21.1%)	278 (20.4%)	
Overweight (25–29.9)	559 (26.1%)	538 (39.4%)	
Obese (≥30 kg/m ²)	1132 (52.8%)	548 (40.2%)	
Smoking status†			<0.001
Never smoked	1483 (67.5%)	861 (61.3%)	
Ex-smoker	603 (27.5%)	500 (35.6%)	
Current smoker	110 (5.0%)	44 (3.1%)	
Comorbidities‡			
Atopic disease	1210 (55.6%)	739 (52.9%)	0.113
Depression/anxiety	219 (9.8%)	90 (6.3%)	<0.001
Nasal polyps	249 (11.1%)	242 (16.8%)	<0.001

*Mean (SD) using t-test.

†Count (%) with χ^2 .

‡Median (IQR) with Man-Whitney U.

ACQ-6, Asthma Control Questionnaire-6; BDP, Beclomethasone dipropionate; BMI, body mass index; ED, emergency department; FeNO, Fractional exhaled nitric oxide; FEV₁, forced expiratory volume in the 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroids; IgE, Immunoglobulin E; OCS, oral corticosteroids.

In terms of smoking, females were significantly less likely to have smoked (UKSAR aOR 0.78, 95% CI 0.67 to 0.90; OPCRD SA aOR 0.71, 95% CI 0.65 to 0.76). However, a higher proportion of females were current smokers in both the UKSAR (5% vs 3.1%, $p<0.001$) and OPCRD SA (18.6% vs 15.7%, $p<0.001$) groups. Females were less likely to have nasal polyps compared with males in both datasets (UKSAR: 11.1% vs 16.8%; OPCRD: SA 1.3% vs 3.2%, $p<0.001$). There was no significant difference in atopic disease in the UKSAR (aOR 0.96, 95% CI 0.83 to 1.11) or OPCRD SA (aOR 1.04, 95% CI 0.94 to 1.15) groups. Allergic rhinitis was, however, more common in females (OPCRD SA 11.5% vs 10.2%, $p=0.005$).

Females were more likely than males to be suffering from depression and/or anxiety in both datasets (UKSAR aOR 1.55, 95% CI 1.18 to 2.02; OPCRD SA aOR 1.88, 95% CI 1.65 to 2.14). Females in OPCRD SA had a higher prevalence of osteoporosis (3% vs 1.1%, $p<0.001$); however, no significant sex difference was seen with other corticosteroid associated comorbidities, including diabetes or cataracts.

Sensitivity and supplementary analysis

The OPCRD analysis included 54 150 (30 946 (57.1%) females) with mild/moderate asthma (online supplemental figure 3). Results from this mild/moderate OPCRD cohort (online supplemental table 4) were generally in line with the SA cohorts (online supplemental tables 2 and 3), revealing similar disparities. However, females were significantly more likely to have asthma reviews (aOR 1.13, 95% CI 1.09 to 1.17) and atopic disease (aOR 1.17, 95% CI 1.11 to 1.22) in the sensitivity analysis with no significant difference in the OPCRD SA cohort. Furthermore, females in the mild/moderate group were also more likely to have exacerbations (IRR 1.38, 95% CI 1.31 to 1.46), which was also seen with SA in the UKSAR but was not significant in the OPCRD SA group.

Mediation analysis found the disparities in asthma control, exacerbations and ED attendance to persist even after adjustment for BMI, smoking status and coexisting depression/anxiety (online supplemental figure 4).

DISCUSSION

The analysis of these cohorts across two independent data sources and spanning UK primary and secondary care found females with asthma to have worse symptoms of asthma control, increased exacerbation rates and obesity compared with their male counterparts. The inclusion of the OPCRD demonstrates the applicability of the UKSAR to a wider unselected population of patients with SA.

Table 2 Comparison of female and male patients with severe asthma in the Optimum Patient Care Research Database

Characteristic	Female (N=12 468)	Male (N=5901)	P value
Age (years)*	56.1 (16.4)	57.2 (15.8)	<0.001
<35	1393 (11.2%)	549 (9.3%)	
35–54	4507 (36.1%)	2049 (34.7%)	
55–74	4779 (38.3%)	2475 (41.9%)	
75+	1789 (14.3%)	828 (14.0%)	
Ethnicity†			0.275
White	8404 (95.4%)	3920 (94.7%)	
Mixed	22 (0.2%)	12 (0.3%)	
Asian	309 (3.5%)	160 (3.9%)	
Black	43 (0.5%)	22 (0.5%)	
Other	32 (0.4%)	25 (0.6%)	
Index of Multiple Deprivation (quintile)‡			0.072
5 (least deprived)	2563 (20.7%)	1281 (21.9%)	
4	2420 (19.5%)	1200 (20.5%)	
3	2275 (18.4%)	1075 (18.4%)	
2	3378 (27.3%)	1513 (25.8%)	
1 (most deprived)	1743 (14.1%)	788 (13.5%)	
Peak flow (% predicted)‡	77.2 (62.7, 91.4)	76.4 (59.4, 91.5)	0.007
Uncontrolled (RCP three questions)†	2255 (56.0%)	950 (51.2%)	<0.001
Exacerbations‡	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	<0.001
Any exacerbations†	7018 (56.3%)	3109 (52.7%)	<0.001
Prior exacerbations†			0.007
0	0 (0.0%)	0 (0.0%)	
1	0 (0.0%)	0 (0.0%)	
2	7000 (56.1%)	3458 (58.6%)	
3	2545 (20.4%)	1146 (19.4%)	
4+	2923 (23.4%)	1297 (22.0%)	
ICS dose (BDP equivalent-ug)‡	1000 (1000, 2000)	1000 (1000, 2000)	<0.001
Treatment step (GINA 2018)†			0.055
4	10 343 (83.0%)	4962 (84.1%)	
5	2125 (17.0%)	939 (15.9%)	
Asthma review†	5695 (45.7%)	2646 (44.8%)	0.287
Respiratory referral†	936 (7.5%)	416 (7.0%)	0.267
Medication possession ratio fixed (%)‡	48.8 (24.6, 82.0)	49.9 (27.3, 82.0)	<0.001
Treatment adherent (MPR≥70%)†	3841 (31.6%)	1930 (33.5%)	0.014
Blood eosinophil count (10 ⁹ /L)‡	0.20 (0.10, 0.31)	0.23 (0.13, 0.40)	<0.001
Highest blood eosinophil count (10 ⁹ /L)†			<0.001
<0.150	2180 (32.8%)	686 (26.8%)	
0.150–0.300	2778 (41.9%)	1029 (40.2%)	
>0.300	1679 (25.3%)	843 (33.0%)	
BMI (kg/m ²)*	30.0 (7.0)	28.8 (5.5)	<0.001
Underweight (<18.5)	174 (1.7%)	47 (1.0%)	
Normal weight (18.5–24.9)	2578 (24.5%)	1182 (24.1%)	
Overweight (25–29.9)	3143 (29.8%)	1927 (39.3%)	
Obese (≥30)	4640 (44.0%)	1742 (35.6%)	

Continued

Disparities were consistent across both SA cohorts and the sensitivity analysis in the mild/moderate asthma cohort, suggesting that many of the sex differences seen in SA also exist in patients with mild/

Table 2 Continued

Characteristic	Female (N=12 468)	Male (N=5901)	P value
Smoking status†			<0.001
Never smoked	6511 (53.4%)	2639 (45.6%)	
Ex-smoker	3415 (28.0%)	2236 (38.7%)	
Current smoker	2273 (18.6%)	910 (15.7%)	
Comorbidities‡			
Atopic dermatitis	1540 (12.4%)	777 (13.2%)	0.120
Atopic disease	2217 (17.8%)	1048 (17.8%)	0.971
Allergic rhinitis	1439 (11.5%)	599 (10.2%)	0.005
Cataracts	314 (2.5%)	129 (2.2%)	0.170
Depression/anxiety	1990 (16.0%)	512 (8.7%)	<0.001
Diabetes	1150 (9.2%)	591 (10.0%)	0.087
Nasal polyps	157 (1.3%)	189 (3.2%)	<0.001
Osteoporosis	373 (3.0%)	62 (1.1%)	<0.001

*Mean (SD) using t-test.
†Count (%) with χ^2 .
‡Median (IQR) with Man-Whitney U.
BDP, Beclomethasone dipropionate; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; MPR, medication possession ratio; RCP, Royal College of Physicians.

moderate asthma. More patients with SA were females (UKSAR: 60.9%; OPCRD SA 67.9%), consistent with findings from other SA cohorts and registries.^{14 16} Asthma control, as measured by self-reported symptoms scores on both ACQ6 and RCP 3Q questionnaires, was statistically and clinically worse in females. However, females were less likely to have indicators of T2 inflammation with reduced FeNO and IgE levels in the UKSAR and lower blood eosinophil counts in the OPCRD cohort. Aligning with the findings of a recent RASP-UK biomarker study post hoc analysis by sex which found the majority of females to be T2 biomarker low but high in their ACQ6 symp-

tom scores with the converse seen in males.¹⁹ Interestingly, females had a higher per cent predicted FEV₁ than males despite their worse asthma control scores. In prior cluster analyses, a similar group of females with poor asthma control and near normal lung function has previously been identified.¹³ Females from the UKSAR were also found to be significantly more likely to report hospital admissions and/or ED attendance within the last year. These findings were consistent with the SARP study where hospitalisations had a bimodal distribution, which mapped changes in asthma prevalence in the sexes, with males more likely to use healthcare for their asthma during childhood and females later in life.³³ Similarly, females in the RASP-UK biomarker study¹⁹ were significantly more likely to have asthma exacerbations and attend primary care within the last year. While, Trawick et al found females have also been found to be twice as likely as their male counterparts to have repeated asthma related hospital admissions.³⁴ More generally, sex has been found to affect healthcare utilisation with females to be more likely to seek and use healthcare, even when female specific illnesses are accounted for.^{35 36} Variations in symptoms between the sexes are also likely to influence clinical presentation, interpretation, healthcare access and utilisation.^{37 38} While caution should be applied when interpreting self-reported outcomes, a dissociation between T2 biomarkers and symptom reporting has been noted in both sexes.¹⁹ The RASP-UK biomarker study post hoc analysis, which was also based on UK SA centres, was able to eliminate sex differences in symptom reporting from the ACQ by adjusting for differences in obesity and depression/anxiety.¹⁹ However, we were unable to replicate this mediation affect in our cohorts perhaps in part due to the RASP-UK biomarker study selection criteria, including a baseline FeNO of less than 45 ppb to enrich for T2 biomarker low participants, compared with our real-world cohort. Other studies have suggested other contributory factors for the discrepancy. One study examining acute moderate and SA exacerbations found males less likely to report symptoms or activity limitations despite clinically similar levels of PEF with inappropriately low healthcare utilisation by males.³⁸

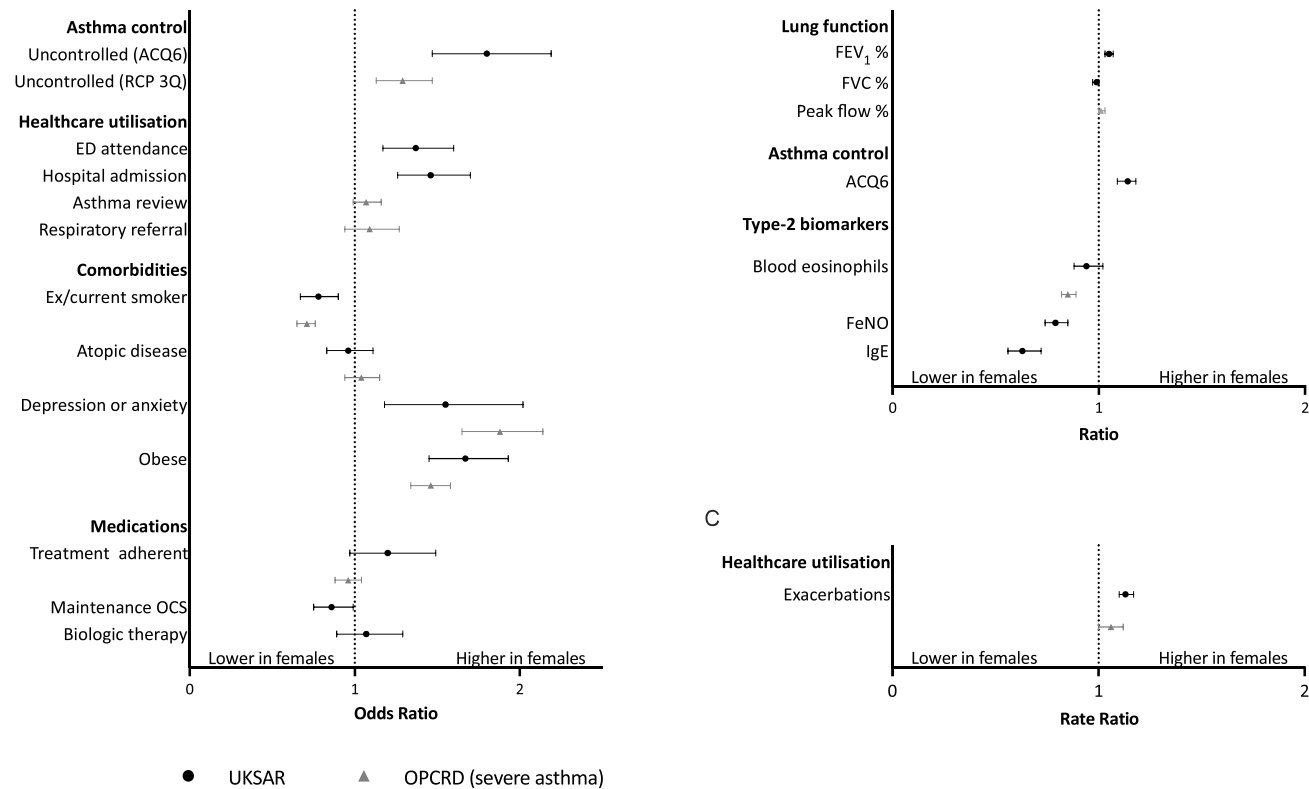


Figure 1 Summary of multivariable regression results comparing males and females with severe asthma in the UK Severe Asthma Registry (UKSAR) and Optimum Patient Care Research Database (OPCRD). Adjusting for year, age (5-year categories) and hospital in UKSAR and practice in OPCRD. (A) Odds Ratio (B) Ratio and (C) Rate Ratio comparing males and females with severe asthma in the UKSAR and OPCRD. ACQ, Asthma Control Questionnaire; ED, emergency department; FeNO, Fractional exhaled nitric oxide; FEV₁, forced expiratory volume in the 1 s; FVC, forced vital capacity; IgE, Immunoglobulin E; OCS, oral corticosteroids; RCP, Royal College of Physicians

Females are also recognised to have an enhanced somatosensory response, including a heightened cough reflex sensitivity,³⁹ which may play a role in SA. This raises the possibility of differential item functioning in the reporting and experience of asthma symptoms between males and females, and it is an area that is currently under active research.

As previously reported in the UKSAR, males were more likely to have raised T2 biomarkers, such as FeNO and total IgE, suggestive of T2 asthma, which can in turn be targeted through biological therapies.²⁰ While baseline blood eosinophils were not statistically different between sexes in the UKSAR, eosinophil counts greater than $0.3 \times 10^9/L$ were significantly higher in males compared with females in OPCRd cohorts. Blood eosinophilia in moderate to SA has previously been associated with male sex.¹⁵ There was no significant difference between the proportion of males and females receiving biological therapy. There was no clear differentiation between medication adherence in males and females, however, medicine possession ratio is notoriously difficult to interpret as it is subject to significant reporting bias and multiple other confounders. There are, however, numerous studies investigating the relationship between sex and adherence with most finding no association, in line with our results.⁴⁰

Females with SA were more likely to be obese across both independent cohorts. The association with obesity and asthma has multiple underlying mechanisms, including altered lung mechanics and airway inflammation.^{41–42} Obesity is associated with poor asthma control,⁴³ hospitalisation⁴⁴ and asthma severity.⁴⁵ A number of studies have found the increased risk of asthma with obesity^{46–48} and poor asthma control^{19–49} to be associated with females and not males. Furthermore, obesity may influence other parameters, for example, FeNO has been found to be lower in asthmatic patients who are obese, despite raised sputum eosinophils suggestive of T2 inflammation.⁵⁰ Depression/anxiety, which was also more common in females, is associated with obesity and poor asthma control.⁵¹ Despite the potential confounding influence of obesity, depression/anxiety and smoking, mediation analysis showed the disparities to persist even taking these factors into account, suggesting another mechanistic role for the sex differences seen in SA.

The sensitivity analysis in the mild/moderate OPCRd cohort aligned closely with the observations made in the SA cohorts. Although females exhibited a greater tendency to have atopic disease and undergo asthma reviews within the mild/moderate group, the notable disparity in comparison to the SA groups could potentially stem from the larger sample sizes. The sensitivity analysis thus reinforces the strength of the findings derived from the SA cohorts, while also indicating that the disparities are unlikely to stem solely from variations in disease severity. Specialist care could inherently influence outcomes; however, referral rates from primary to specialist care did not exhibit any sex-based differences. Moreover, in the UKSAR group, who are receiving specialist care, females continued to have increased exacerbations, ED attendances and hospital admissions.

The UKSAR is a large well-characterised cohort of patients with SA, as defined by ERS/ATS criteria.²¹ It provides high-quality and real-world data using robust standardised biomarker and spirometry measurements across multiple UK SA centres. It is important to note that the patients on the UKSAR have been referred to specialist care and may have more severe disease than the overall OPCRd population. Many patients are referred for biological therapy, which focuses on T2 disease and may therefore bias the population towards those with T2 disease. Selection bias was minimised by examining two distinct data sources with the OPCRd providing an additional validity data source to UKSAR in the wider unselected population and a sensitivity analysis comparator for mild to moderate asthma. This study, however, has several potential limitations. First, using retrospective datasets, it has been assumed that the diagnosis of SA is correct. While patients in the UKSAR will have undergone specialist multidisciplinary team assessment of their diagnosis, the OPCRd subjects were selected as those who remained uncontrolled (≥ 2 exacerbations within a year) on GINA 201824 step 4 treatment and not subject to the same diagnostic scrutiny. Second, as an observational study, it is open to confounding influences such as unmeasured or poorly measured variables. Data used in the analysis, such as asthma

control in the OPCRd dataset, was frequently missing and the timing of outcomes in relation to treatment can be difficult to account for. However, these factors are unlikely to have acted differentially based on sex. Further measures, such as health-seeking behaviour, which may mediate the effect seen between the sexes, and spirometry in primary care, which would provide a more robust comparison of lung function variables between datasets and is now recommended,³ were not measured and would benefit from further research.

In conclusion, this real-world data show consistent and clinically important differences in the characteristics of males and females with SA, with the use of two distinct data sets demonstrating the applicability of the UKSAR to the wider unselected SA population. Females had worse asthma control, increased exacerbations and were more likely to be obese despite higher FEV₁ per cent predicted, similar baseline blood eosinophils, lower FeNO and reduced total IgE compared with their male counterparts. Although related to sex the reasons and mechanisms behind these disparities are likely to be related to multiple factors such as hormonal, immunological, comorbidity and behavioural (both patient and healthcare professional) influences which were not measured in our dataset.

Further prospective epidemiological studies with high-quality linked datasets and measure of other potential mediating factors such as symptom perception, alongside mechanistic studies are required to understand the drivers behind these sex differences and provide tailored and personalised care to people with SA.

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REFERENCES

- GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: a systematic analysis for the global burden of disease study 2015. *Lancet Respir Med* 2017;5:691–706.
- Mukherjee M, Stoddart A, Gupta RP, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Med* 2016;14:113.
- Global Initiative for Asthma. Global strategy for asthma management and prevention (2022 update). 2022. Available: <https://ginasthma.org/reports/>
- Ryan D, Heatley H, Heaney LG, et al. Potential severe asthma hidden in UK primary care. *J Allergy Clin Immunol* 2021;9:1612–23.
- Sullivan PW, Slejko JF, Ghushchyan VH, et al. The relationship between asthma, asthma control and economic outcomes in the United States. *J Asthma* 2014;51:769–78.
- Chippes BE, Zeiger RS, Borish L, et al. Key findings and clinical implications from the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) study. *J Allergy Clin Immunol* 2012;130:332–42.
- Soriano JB, Kendrick PJ, Paulson KR, et al. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the global burden of disease study 2017. *The Lancet Respiratory Medicine* 2020;8:585–96.
- Chowdhury NU, Guntur VP, Newcomb DC, et al. Sex and gender in asthma. *Eur Respir Rev* 2021;30:210067.
- Fuseini H, Newcomb DC. Mechanisms driving gender differences in asthma. *Curr Allergy Asthma Rep* 2017;17:19.
- van den Berge M, Heijink HJ, van Oosterhout AJM, et al. The role of female sex hormones in the development and severity of allergic and non-allergic asthma. *Clin Exp Allergy* 2009;39:1477–81.
- McCleary N, Nwaru BI, Nurmatov UB, et al. Endogenous and exogenous sex steroid hormones in asthma and allergy in females: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2018;141:1510–3.
- Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218–24.
- Lefaeux D, De Meulder B, Loza MJ, et al. U-BIOPRED clinical adult asthma clusters linked to a subset of sputum omics. *J Allergy Clin Immunol* 2017;139:1797–807.
- Senna G, Latorre M, Bugiani M, et al. Sex differences in severe asthma: results from severe asthma network in Italy-SANI. *Allergy Asthma Immunol Res* 2021;13:219–28.
- de Groot JC, Storm H, Amelink M, et al. Clinical profile of patients with adult-onset eosinophilic asthma. *ERJ Open Res* 2016;2:00100-2015.
- Denton E, Price DB, Tran TN, et al. Cluster analysis of inflammatory biomarker expression in the international severe asthma registry. *J Allergy Clin Immunol Pract* 2021;9:2680–8.
- Wu W, Bleeker E, Moore W, et al. Unsupervised phenotyping of severe asthma research program participants using expanded lung data. *J Allergy Clin Immunol* 2014;133:1280–8.
- Pavord ID, Afzalina S, Menzies-Gow A, et al. The current and future role of biomarkers in type 2 cytokine-mediated asthma management. *Clin Exp Allergy* 2017;47:148–60.
- Eastwood MC, Busby J, Jackson DJ, et al. Randomised trial of a T2-composite biomarker 1 strategy to adjust corticosteroid treatment in severe asthma: post-hoc analysis by sex. *J Allergy Clin Immunol Pract* 2023;11:1233–42.
- Jackson DJ, Busby J, Pfeffer PE, et al. Characterisation of patients with severe asthma in the UK severe asthma registry in the biologic era. *Thorax* 2021;76:220–7.
- Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343–73.
- Optimum Patient Care Research Database. OPCRd: our databases. 2020. Available: <https://opcrd.co.uk/our-database/>
- Di Martino M, Kirchmayer U, Agabiti N, et al. The impact of time-window bias on the assessment of the long-term effect of medication adherence: the case of secondary prevention after myocardial infarction. *BMJ Open* 2015;5:e007866.
- Global Initiative for Asthma. Global strategy for asthma management and prevention. 2018. Available: <https://ginasthma.org/reports/>
- Knudson RJ, Lebowitz MD, Holberg CJ, et al. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis* 1983;127:725–34.
- Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–43.
- Juniper EF, Bouquet J, Abetz L, et al. Identifying 'well-controlled' and 'not well-controlled' asthma using the asthma control questionnaire. *Respir Med* 2006;100:616–21.
- Thomas M, Gruffydd-Jones K, Stonham C, et al. Assessing asthma control in routine clinical practice: use of the Royal college of physicians' 3 questions Prim Care Respir J 2009;18:83–8.
- Khan NF, Perera R, Harper S, et al. Adaptation and validation of the Charlson index for read/OXMS coded databases. *BMC Fam Pract* 2010;11:1.
- Sweeney J, Patterson CC, Menzies-Gow A, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the optimum patient care research database and the British thoracic difficult asthma registry. *Thorax* 2016;71:339–46.
- Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology* 2009;20:488–95.
- Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986;51:1173–82.
- Zein JG, Udeh BL, Teague WG, et al. Impact of age and sex on outcomes and hospital cost of acute asthma in the United States, 2011–2012. *PLoS One* 2016;11:e0157301.
- Trawick DR, Holm C, Wirth J. Influence of gender on rates of hospitalization, hospital course, and hypercapnia in high-risk patients admitted for asthma: a 10-year retrospective study at Yale–new haven hospital. *Chest* 2001;119:115–9.
- Thompson AE, Anisimowicz Y, Miedema B, et al. The influence of gender and other patient characteristics on health care-seeking behaviour: a QUALICOPE study. *BMC Fam Pract* 2016;17:38.
- Morrison KE, Colón-González FJ, Morbey RA, et al. Demographic and socioeconomic patterns in health-care-seeking behaviour for respiratory symptoms in England: a comparison with non-respiratory symptoms between three healthcare services. *BMJ Open* 2020;10:e038356.
- Osborne ML, Vollmer WM, Linton KL, et al. Characteristics of patients with asthma within a large HMO: a comparison by age and gender. *Am J Respir Crit Care Med* 1998;157:123–8.
- Cydulka RK, Emerman CL, Rowe BH, et al. Differences between men and women in reporting of symptoms during an asthma exacerbation. *Ann Emerg Med* 2001;38:123–8.
- Morice AH, Jakes AD, Faruqi S, et al. A worldwide survey of chronic cough: a manifestation of enhanced somatosensory response. *Eur Respir J* 2014;44:1149–55.
- Dima AL, Hernandez G, Cunillera O, et al. Asthma Inhaler adherence determinants in adults: systematic review of observational data. *Eur Respir J* 2015;45:994–1018.
- Shore SA, Fredberg JJ. Obesity, smooth muscle, and airway hyperresponsiveness. *J Allergy Clin Immunol* 2005;115:925–7.
- Wang CJ, Noble PB, Elliot JG, et al. From beneath the skin to the airway wall: understanding the pathological role of adipose tissue in comorbid Asthma–obesity. *Compr Physiol* 2023;13:4321–53.
- Farah CS, Kermede JA, Downie SR, et al. Obesity is a determinant of asthma control independent of inflammation and lung mechanics. *Chest* 2011;140:659–66.
- Mosen DM, Schatz M, Magid DJ, et al. The relationship between obesity and asthma severity and control in adults. *J Allergy Clin Immunol* 2008;122:507–11.
- Akerman MJH, Calancanis CM, Madsen MK. Relationship between asthma severity and obesity. *J Asthma* 2004;41:521–6.
- Chen Y, Rennie D, Cormier Y, et al. Sex specificity of asthma associated with objectively measured body mass index and waist circumference: the humboldt study. *Chest* 2005;128:3048–54.
- Beckett WS, Jacobs DR, Yu X, et al. Asthma is associated with weight gain in females but not males, independent of physical activity. *Am J Respir Crit Care Med* 2001;164:2045–50.
- Hancox RJ, Milne BJ, Poulton R, et al. Sex differences in the relation between body mass index and asthma and atopy in a birth cohort. *Am J Respir Crit Care Med* 2005;171:440–5.
- Novelli F, Bacci E, Latorre M, et al. Comorbidities are associated with different features of severe asthma. *Clin Mol Allergy* 2018;16:25.
- Lugogo N, Green CL, Agada N, et al. Obesity's effect on asthma extends to diagnostic criteria. *J Allergy Clin Immunol* 2018;141:1096–104.
- Kapadia SG, Wei C, Bartlett SJ, et al. Obesity and symptoms of depression contribute independently to the poor asthma control of obesity. *Respir Med* 2014;108:1100–7.



ARTIGO ORIGINAL

Trajетórias distintas da função pulmonar desde a infância até meio da idade adulta

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RESUMO

Fundamentação As trajetórias de desenvolvimento e declínio da função pulmonar ao longo da vida influenciam o risco de doença pulmonar, mas estão pouco documentadas.

Objetivo Documentar as trajetórias da função pulmonar desde a infância até meio da vida adulta.

Métodos Modelamos o volume expiratório forçado em 1 segundo (FEV₁), a capacidade vital forçada (FVC) e FEV₁/FVC aos 9, 11, 13, 15, 18, 21, 26, 32, 38 e 45 anos de idade a partir de uma coorte de base populacional, utilizando a análise de perfil latente para identificar subgrupos distintos de participantes com trajetórias de função pulmonar semelhantes. Foram utilizadas análises de regressão para avaliar as associações entre as trajetórias, os fatores do início da vida e a obstrução ao fluxo aéreo após broncodilatador aos 45 anos.

Resultados Entre os 865 participantes com ≥6 medidas da função pulmonar, identificamos 10 trajetórias distintas de FEV₁. A maioria apresentou-se aproximadamente paralela, exceto uma trajetória persistentemente baixa relacionada com a hiper-responsividade das vias aéreas na infância (3% da população do estudo), duas trajetórias de declínio acelerado, uma das quais (8%) esteve associada ao tabagismo e a um índice de massa corporal (IMC) mais elevado na idade adulta, e uma trajetória de recuperação (8%). Os resultados relativos às trajetórias FEV₁/FVC foram semelhantes. Foram identificadas nove trajetórias para FVC: a maioria também se apresentou aproximadamente paralela, com a exceção de uma trajetória de declínio acelerado relacionada com IMC mais alto. As três trajetórias de FEV₁ que levaram aos valores mais baixos de FEV₁ corresponderam a 19% da coorte, mas contribuíram com 55% da obstrução do fluxo aéreo aos 45 anos.

Conclusões As trajetórias da função pulmonar até meio da idade adulta são em grande parte estabelecidas antes da adolescência, com algumas exceções: uma trajetória persistentemente baixa relacionada com a hiper-responsividade das vias aéreas na infância, que começa baixa e se agrava com a idade, e trajetórias de declínio acelerado na idade adulta associadas ao tabagismo e à obesidade. As trajetórias adversas estão associadas a um risco elevado de obstrução do fluxo aéreo a meio da vida adulta.

INTRODUCTION

Life course trajectories of lung function are related to health and longevity and influence the risk for chronic lung disease in older adulthood.¹ The main identified risk factor for chronic obstructive pulmonary disease (COPD) is accelerated forced expiratory volume in 1 s (FEV₁) decline due to smoking in adulthood,² but COPD can also follow failure to attain a normal peak lung function in early adulthood.³ Moreover, low lung function in early adulthood also predicts non-respiratory comorbidities and higher all-cause mortality.^{4,5}

Recent cohort studies suggest there are several distinct lung function trajectories in the general population.^{6–10} However, most of these only captured either lung function growth^{6,8,9} or decline phase.¹⁰ Only the Tasmanian Longitudinal Health Study (TAHS) reported data from both phases, us-

Key messages

What is the key question?

► Trajectories of lung function throughout life may influence the risk for lung disease in older adulthood. Failure to attain a normal peak lung function in early adult life may be as important as accelerated decline.

What is the bottom line?

► For most people, lung function trajectories are established early in childhood. Asthma and airways hyper-responsiveness are associated with life course-persistent adverse trajectories.

Why read on?

► Efforts to maximise lung function throughout life and prevent lung disease in older adulthood need to focus on early childhood.

ing up to six repeated assessments of lung function from ages 7 to 53 years, but did not measure lung function between ages 18 and 45.7 Including measurements from early adulthood when spirometry usually reaches a peak is important to provide insights into the natural history of lung function development. Furthermore, most studies only report trajectories for FEV₁; trajectories of other lung function parameters have received little attention.¹¹

We identified trajectories for FEV₁, forced vital capacity (FVC) and FEV₁/FVC in the Dunedin Multidisciplinary Health and Development Study (Dunedin Study), a population-based cohort with 10 lung function assessments from ages 9 to 45 years. We then investigated plausible predictors of these trajectories (online supplemental figure S1) and examined associations between lung function trajectories and airflow obstruction at age 45.

METHODS

Cohort

The Dunedin Study investigates health and behaviour in a population-based cohort born in Dunedin in 1972/1973.^{12,13} The cohort was formed at age 3 years when 1037 individuals (52% male; 91% of eligible births) attended the first follow-up. The cohort has been further assessed at ages 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, 38 and 45 years (see online supplement for additional methods).

Measurements

Height and weight were measured at each assessment. Spirometry was performed at each assessment since age 9.^{14,15} At age 45, spirometry was repeated after inhaling 200 µg salbutamol via a large-volume spacer.¹⁶ Predicted values for FEV₁, FVC and FEV₁/FVC at each age were generated using multiple linear regression models for non-

smoking, non-asthmatic, non-pregnant men and women adjusting for height and height squared. Airflow obstruction was defined as a postbronchodilator FEV₁/FVC ratio <0.7 at age 45.¹⁷

Definition of variables

Childhood asthma was defined as a parent/self-reported diagnosis with compatible symptoms or asthma medication use within the previous year at ages 9, 11 or 13 years.^{18,19} Childhood airway hyper-responsiveness (AHR) was defined as a positive response to methacholine/salbutamol challenge at ages 9, 11 or 13 years.²⁰

Participants were considered to be breastfed if breastfeeding continued for at least 4 weeks.²¹ Preschool attendance was reported at age 3. Household overcrowding at age 3 was defined as fewer than two rooms (excluding kitchen and bathroom) per child.²² Childhood cat and dog ownership was defined as having lived with cat and dog by age 9.²² Parental smoking was ascertained at ages 7, 9, 11 and 13 years.²² At 3 years, parents were asked about the number of coughs and colds the participant had had in the previous year.

Childhood socioeconomic status was assessed throughout childhood based on the education and income associated with their parents' occupation.¹⁸ Parental history of asthma or hay fever was ascertained when participants were aged 7 and 18.

Atopy was assessed at ages 13, 21 and 32 years by skin prick tests for common aeroallergens. Atopy was defined as a weal diameter 2 mm greater than the negative control to one or more allergens.²³

Cumulative smoking was calculated from the reported number of cigarettes smoked up to age 18 years and the number smoked between each subsequent assessment (one pack-year=20 cigarettes/ day for 1 year).¹⁶

Statistical analysis

We analysed FEV₁ at each age (from 9 to 45 years) using latent profile analysis (LPA) to identify distinct subgroups of study participants whose FEV₁ measurements followed a similar pattern over time. LPA is described extensively elsewhere.²⁴ Briefly, it identifies unobserved subgroups of individuals who share similar characteristics, based on a series of continuous variables. We used estimated posterior probabilities to assign individuals to the trajectory that they were most likely to belong to.

Based on previous studies,^{7,8} we hypothesised at least four FEV₁ trajectories. LPA models with 4–12 trajectories were fitted to the data. After excluding models with trajectories with <2% of the cohort, the model with the lowest Bayesian information criterion (BIC) value was selected.²⁵ Descriptive labels were assigned to the identified trajectories. The primary analysis included study members with at least six spirometry measures between ages 9 and 45, including at least one measure from each of childhood (ages 9–15), early adulthood (ages 18–32) and mid-adulthood (ages 38–45). Baseline/early childhood characteristics were compared between those included and not included in these models. Missing data were assumed to be mostly missing completely at random. A sensitivity analysis included those with at least two spirometry measures at any ages from 9 to 45 years.

Associations between childhood and adult factors (exposures) and trajectories were examined using multivariable binary logistic regression where the outcome belonged to that particular trajectory vs belonging to any other trajectory. Further analyses compared each trajectory with the 'average' trajectory. The choice of plausible exposures was informed by a directed acyclic graph (online supplemental figure S1). Initially, all exposures were included in each model, followed by univariable models for exploratory purposes. Firth logistic regression was used when the size of the trajectory of interest was below 50.²⁶ Statistical significance was determined using the Bonferroni-Holm method (per variable, separately for univariable and multivariable models). This controls the family-wise error rate without requiring assumptions about the (in)dependence of the hypotheses being tested.²⁷ This analysis was repeated for each identified FEV₁ trajectory.

The same approach was used for FVC and FEV₁/FVC. One participant with developmental abnormalities affecting lung function

Table 1 Characteristics of study population included in main analysis	
Characteristic	
Sex—male	442/865 (51%)
Birth weight (mean kg±SD)	3.4±0.5
Breastfed for ≥4 weeks	431/863 (50%)
Childhood asthma ages 9–13	124/807 (15%)
Childhood AHR ages 9–13	153/798 (19%)
BMI at age 9 (mean kg/m ² ±SD)	16.4±1.6
Childhood SES (mean±SD)*	3.2±1.1
Exposure to parental smoking	534/852 (63%)
Atopy at 21	520/796 (65%)
BMI at age 45 (mean kg/m ² ±SD)	28.5±5.8
Ever smokers by age 45	450/865 (52%)
Tobacco smoked by age 45 (mean pack years±SD)	7.1±10.4
865 study members with at least 6 spirometry measures between ages 9 and 45 were included in the main analysis. The numbers for each characteristic vary depending on the number providing data at that assessment.	
*Higher scores indicate lower socioeconomic status on a scale of 1–6. AHR, airway hyper-responsiveness; BMI, body mass index; SES, socioeconomic status.	

was excluded from all analyses. Measurements were excluded at ages when pregnancy was reported. Two-sided p values <0.05 were considered statistically significant. Analyses used Stata V.15.0 (StataCorp).

RESULTS

Trajectories of FEV₁

The primary analyses included 865 study members with at least six spirometry measures from ages 9 to 45 (table 1). Comparisons with those excluded from this analysis are shown in online supplemental table S1). The LPA model with the lowest BIC identified 10 distinct FEV₁ trajectories (online supplemental table S2). Most, but not all, trajectories were approximately parallel throughout follow-up (figure 1). Exceptions included two accelerated decline trajectories and a persistently low trajectory that started low and declined further over time.

Participant characteristics according to identified FEV₁ trajectories are shown in online supplemental table S3. The persistently low FEV₁ trajectory had the highest prevalence of childhood asthma and AHR and the highest prevalence of atopy. The accelerated-decline-II trajectory had the highest cumulative tobacco pack-years by age 45.

Pairwise comparisons showed that participants in the persistently low trajectory were more likely to have childhood AHR compared with all other trajectories combined (statistically significant associations are summarised in table 2: for full results, see online supplemental tables S4 and S5). Childhood AHR was also associated with the always-well-below-average trajectory. The accelerated-decline-II trajectory was associated with tobacco pack-years by age 45 and body mass index (BMI) at age 45. BMI at age 9 was positively associated with the persistently high trajectory. Overall, BMI at age 9 was also associated with lower odds of belonging to the always-below-average trajectory. However, there was evidence of a U-shaped association with higher odds of belonging to this trajectory among those with high BMI values (≥18.9 kg/m² (top 6.6%)) at age 9.

At age 45, participants in the persistently low FEV₁ trajectory had the highest prevalence of postbronchodilator airflow obstruction (59%), followed by accelerated-decline-II (23%) and always-well-below-average (16%) trajectories. By comparison, the overall prevalence of postbronchodilator airflow obstruction among the other 7 trajectories was 5%.

Trajectories of FVC

The LPA model with the lowest BIC identified 11 distinct FVC trajectories but one of these was very small (n=11, 1.3%). Therefore,

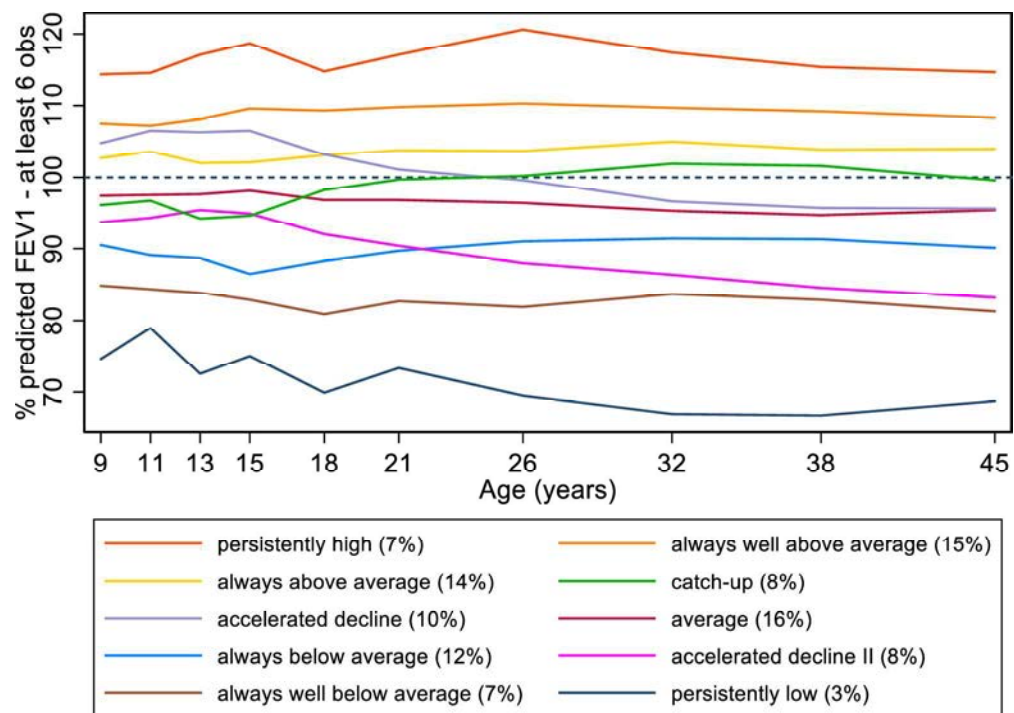


Figure 1 Distinct trajectories of FEV_1 from ages 9 to 45 years. FEV_1 , forced expiratory volume in 1 s.

the model with the second lowest BIC which had nine trajectories was selected (online supplemental table S2). Most of the identified FVC trajectories were approximately parallel during follow-up (figure 2).

The persistently low FVC trajectory had the highest prevalence of childhood AHR and atopy over the ages (online supplemental table S6). Pairwise comparisons showed that BMI at age 45 was positively associated with the accelerated-decline trajectory compared with all others and negatively associated with the catch-up trajectory (table 2, online supplemental tables S7 and S8).

Trajectories of FEV_1/FVC

The LPA model with the lowest BIC identified 10 distinct FEV_1/FVC trajectories (online supplemental table S2). Most were approximately parallel throughout follow-up (figure 3). Participants in the persistently low FEV_1/FVC trajectory had the highest prevalence of childhood asthma and AHR (online supplemental table S9). This trajectory also had the highest prevalence of atopy: all trajectory members were atopic at ages 21 and 32. The accelerated-decline trajectory had the highest tobacco pack-years by age 45.

Pairwise comparisons showed that participants in the persistently low trajectory were more likely to have childhood AHR compared with all others (table 2, online supplemental tables S10 and S11). Childhood AHR was also associated with the always-well-below-average trajectory and negatively associated with the always-well-above-average trajectory. Cumulative smoking was associated with accelerated-decline and above-average-but-with-decline trajectories, and negatively associated with the always-well-above-average trajectory. BMI at age 45 was negatively associated with the persistently high trajectory. Participants in the always-below-average trajectory were more likely to have attended preschool at age 3 years.

At age 45, participants in the persistently low FEV_1/FVC trajectory had the highest prevalence of postbronchodilator airflow obstruction (74%), followed by the always-well-below-average (43%) and accelerated-decline (37%) trajectories. The overall prevalence of postbronchodilator airflow obstruction among the other 7 trajectories was 2%.

The sensitivity analysis, including those with at least two spirometry measures from 9 to 45 years, is shown in online supplemental figure S2.

DISCUSSION

Using up to 10 assessments of spirometry in a large prospective population-based cohort followed from ages 9 to 45 years, we identified distinct trajectories of FEV_1 , FVC and FEV_1/FVC . A striking observation is that most, but not all, of the identified trajectories were approximately parallel, demonstrating that, for most people, their lung function trajectory into mid-adult life was already established before adolescence. Notable exceptions included childhood AHR-associated persistently low trajectories, which started low and diverged further from the others over time, and accelerated-decline trajectories associated with smoking and higher adult BMI. We also identified catch-up trajectories for FEV_1 and FVC, which, for FVC, were associated with lower adult BMI values. Importantly, we found that the three FEV_1 and three FEV_1/FVC trajectories leading to the lowest values at age 45 contributed most of the airflow obstruction at age 45 despite representing small proportions of the cohort.

The FEV_1 trajectories that we identified are broadly consistent with those reported in other cohorts. The only other study to cover a similar age range from childhood to mid-adulthood (ages 7–53), identified 6 distinct FEV_1 trajectories among 2438 Australian participants.⁷ Using a similar statistical approach to ours, a study of two British population-based cohorts identified four FEV_1 trajectories based on three or four spirometry measures from ages 5 to 24.⁸ Another British cohort observed high and low FEV_1 trajectories from ages 10 to 26.⁹ Among asthmatics, the Childhood Asthma Management Programme classified 684 participants into four FEV_1 trajectories based on spirometry measures from ages 7 to 26.²⁸ Looking at changes after peak adult lung function, an American study identified five FEV_1 trajectories from ages 25 to 55.¹⁰

We identified more distinct FEV_1 trajectories than all these studies.^{7–10,28} This is likely because we selected the model with the best empirical fit (lowest BIC), whereas other studies either limited the maximum number of trajectories or merged similar-looking trajectories. However, even if we were to merge similar trajectories, the combined evidence suggests that there are at least five FEV_1 trajectories in the general population: persistently high, average, below average, accelerated decline and persistently low. In addition, an early below average with catch-up during adolescence FEV_1 trajectory was observed in both our study (8%) and the TAHS (8%).⁷ None of the other cohorts had sufficient data to identify this. For comparison with earlier studies, graphs with fewer trajectory classes are shown in online supplemental figure S3.

Table 2 Summary of statistically significant predictors of lung function trajectories

Parameter	Predictor	Trajectory	OR (95% CI)
FEV ₁	Childhood AHR	Always above average	0.17 (0.06 to 0.49)
		Always well below average	3.57 (1.60 to 7.95)
		Persistently low	12.90 (3.45 to 47.9)
	Tobacco by age 45	Accelerated decline II	1.06 (1.03 to 1.08)
	BMI at age 9	Always below average	0.66 (0.54 to 0.81)
		Persistently high	1.31 (1.09 to 1.58)
BMI at age 45	Accelerated decline II	1.08 (1.03 to 1.13)	
	FVC	BMI at age 45	Catch-up
FEV ₁ /FVC	Childhood AHR	Accelerated decline	1.15 (1.10 to 1.20)
		Always well above average	0.23 (0.08 to 0.64)
		Always well below average	7.79 (3.61 to 16.9)
	Tobacco by age 45	Persistently low	12.40 (2.60 to 58.5)
		Always well above average	0.96 (0.93 to 0.99)
		Above average but with decline	1.04 (1.02 to 1.06)
	BMI at age 45	Accelerated decline	1.06 (1.03 to 1.09)
		Persistently high	0.89 (0.82 to 0.96)
	Preschool attendance	Always below average	2.78 (1.38 to 5.61)
	Summary of full results in online supplemental tables S4, S7 and S10. Statistical significance defined as p<0.05 after adjustment for multiple comparisons using Bonferroni-Holm method. ORs show the association of each unit of the predictor with membership of that trajectory compared with all other trajectories. Childhood AHR and preschool attendance are binary (yes/no). Units of tobacco smoked are pack-years. BMI units are kg/m ² .		
AHR, airway hyper-responsiveness; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.			

We also identified 10 distinct FEV₁/FVC trajectories. Two studies found normal/high and persistently low trajectories from ages 11 to 32 and 10 to 26 years.^{6,9} Only the recent TAHS study investigated FEV₁/FVC trajectories beyond early adulthood, reporting six trajectories.¹¹ Although they used a different statistical approach and had fewer ages of assessment with few lung function measurements in early adulthood, the patterns of trajectories were broadly consistent with our findings. In particular, the adverse trajectories leading to airflow obstruction in mid-adult life (‘early low-rapid decline’, ‘early normal-rapid decline’, ‘early low-normal decline’) were similar to the persistently low, accelerated-decline and always-well-below-average trajectories that we have identified. Graphs with fewer FEV₁/FVC classes are shown in online supplemental figure S4.

In our study FEV₁/FVC trajectories and FEV₁ trajectories had similar associations with AHR: for both parameters, persistently low (both 3% of the cohort) and always-well-below-average (7% and 8%, respectively) trajectories were associated with childhood AHR, whereas those in the always-well-above-average FEV₁/FVC trajectory (15%) and always-above-average FEV₁ (14%) trajectories were less likely to have childhood AHR. Other studies have found that asthma is associated with persistently low FEV₁ trajectories.^{7,8} AHR is a hallmark of asthma and these findings indicate that childhood asthma plays a key role in the impaired development of FEV₁ and airflow obstruction. Although parental asthma

has been reported to be associated with impaired lung function among offspring,^{6,29} we did not find any direct association between parental asthma and lung function trajectories, after accounting for the potential mediator of childhood asthma in the participants. The TAHS study found an association between parental asthma and low FEV₁/FVC (but not FEV₁) trajectories but did not report whether this association persisted after adjusting for childhood asthma.^{7,11} All participants in the persistently low FEV₁/FVC trajectory were atopic, although this was not a statistically significant independent predictor of this trajectory once adjusted for the other variables including AHR.

Unsurprisingly, accelerated-decline-II FEV₁ and accelerated-decline and above-average-but-with-decline FEV₁/FVC trajectories were all associated with cumulative smoking. Although smoking was not a statistically significant predictor of the accelerated decline FEV₁ trajectory in TAHS, this trajectory had the highest prevalence of smoking,⁷ and smoking was associated with the FEV₁/FVC trajectories leading to adult airflow obstruction.¹¹

We identified nine distinct trajectories for FVC. To our knowledge, only two previous studies have investigated FVC trajectories. A high and a low FVC trajectories were identified in the Isle of Wight cohort, based on three measures at ages 10, 18 and 26 years.⁹ The TAHS study identified five FVC trajectories.¹¹ Although fewer in number, several of these trajectories appear consistent with the trajectories that we identified, with persistently low, persistently high and catch-up trajectories. However, they did not identify an accelerated decline FVC trajectory. Graphs with fewer FVC classes are shown in online supplemental figure S5.

We found a high degree of overlap between identified FEV₁ and FVC trajectories (figure 4), for example, 68% of participants in the persistently low FEV₁ trajectory were assigned to either the persistently low or always-well-below-average FVC trajectory, and 87% of those in the persistently high FEV₁ trajectory were assigned to either the persistently high or always-well-above-average FVC trajectory. We also found considerable overlap between the FEV₁ and FEV₁/FVC ratio trajectories but there was less overlap between the FVC and FEV₁/FVC trajectories (online supplemental figures S6 and S7). The extent to which FVC and FEV₁/FVC trajectories provide additional health information to FEV₁ trajectories remains unclear and needs further investigation: although TAHS found that trajectories leading to obstructive, restrictive and mixed patterns of lung function disorder had different predictors and health associations, these classifications were based on the lung function outcomes at age 53 rather than the trajectories themselves.¹¹

We identified few associations between our potential exposures and the better than average lung function trajectories. BMI at age 9 was positively associated with the persistently high FEV₁ trajectory and negatively associated with the always-below-average trajectory, suggesting that early childhood growth may have a long-term protective effect on adult FEV₁, although there was also evidence that overweight children may be more likely to have always-below-average trajectories. By contrast, BMI at age 45 was associated with accelerated decline FEV₁ and FVC trajectories, and a lower likelihood of the catch-up FVC trajectory, confirming the detrimental impact of increasing body weight in adolescence and adulthood on lung function.

Collectively, the three trajectories leading to the lowest FEV₁ values (persistently low, always-well-below-average and accelerated-decline-II) represented 19% of the cohort and 55% of post-bronchodilator airflow obstruction (meeting GOLD spirometric criteria for COPD) at age 45. Moreover, the three FEV₁ trajectories that did not reach the normal peak in early adulthood (persistently low, always-well-below-average and always-below-average) represented 22% of the cohort and 44% of airflow obstruction at age 45. This is consistent with an analysis of three cohorts in which half of the participants with spirometric COPD had lower lung function in early adulthood, followed by a normal rate of lung function decline.³ It is also supported by our observations for the FEV₁/FVC trajectories: the persistently low and always-well-below-average-trajectories represented only 11% of study cohort, but contributed

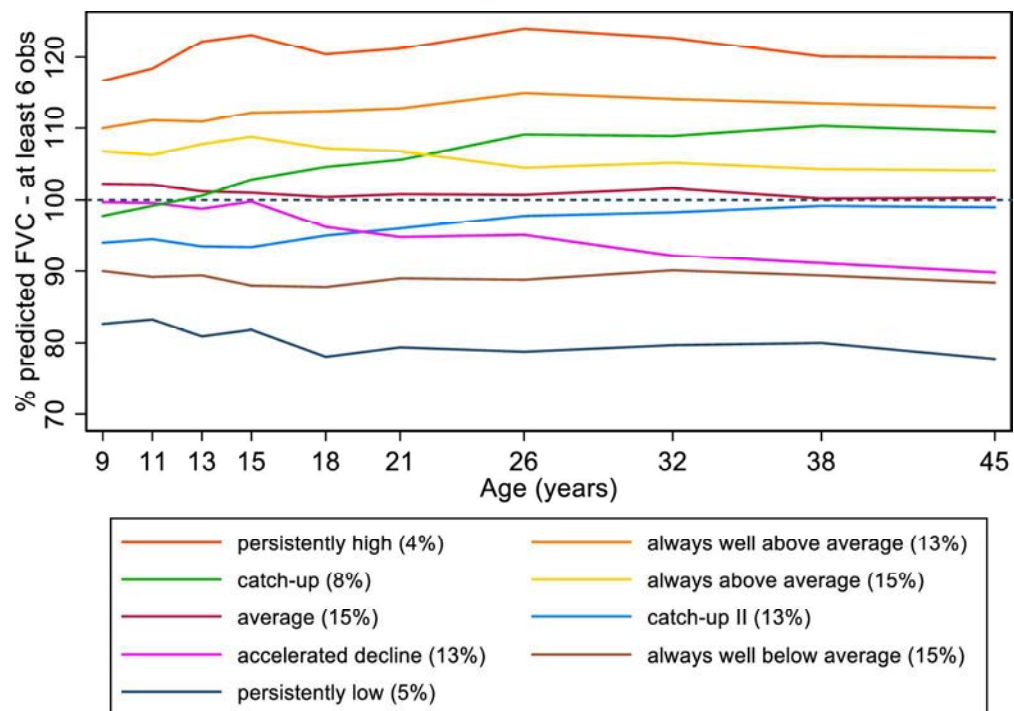


Figure 2 Distinct trajectories of FVC from ages 9 to 45 years. FVC, forced vital capacity.

60% of postbronchodilator airflow obstruction at age 45, indicating that over half of mid-adulthood spirometric COPD has childhood origins.

Our finding that most of the identified trajectories were approximately parallel suggests that, for most people, these trajectories are already established by adolescence. This raises important issues. First, it remains unclear how to maximise lung growth in early life to set people on beneficial trajectories. Second, it is unclear whether interventions involving better management of childhood asthma/AHR, avoiding smoking and maintaining healthy body weight could 'correct' the adverse lung function trajectories, or at what age(s) these interventions could be effective. Third, the underlying mechanisms of persistently high and catch-up lung function trajectories are unknown: understanding these would provide important insights into promotion of healthy lung function development

in the general population. Finally, the long-term consequences of different lung function trajectories for health and longevity are not yet established, for example, we do not know whether low lung function in late adulthood from persistently low trajectories has similar consequences to low lung function due to accelerated decline.

To our knowledge, these are the most complete longitudinal data on lung function from childhood to mid-adulthood currently available, and this is only the second study to characterise lung function trajectories in terms of all three main spirometric parameters. Strengths of the study include the prospective population-based design, large sample size, high retention rates during follow-up, assessments of lung function at up to 10 time points and an objective approach to model selection. Although 17% of the original cohort was excluded from the main analysis due to

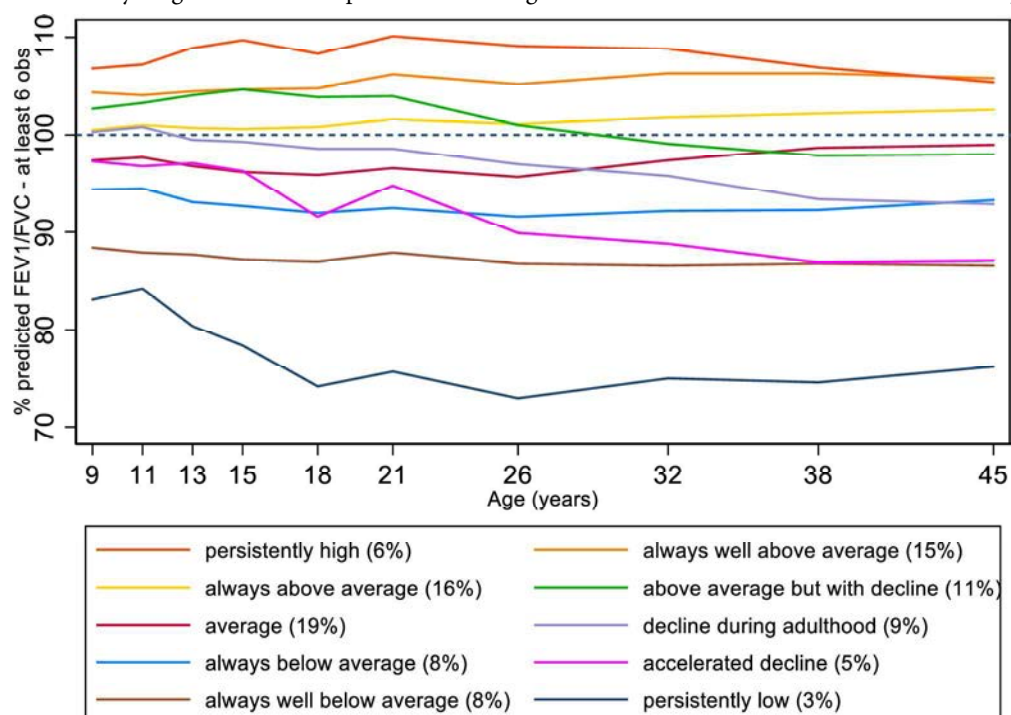


Figure 3 Distinct trajectories of FEV_1/FVC from ages 9 to 45 years. FEV_1/FVC , forced expiratory volume in 1 s/forced vital capacity.

FVC trajectories

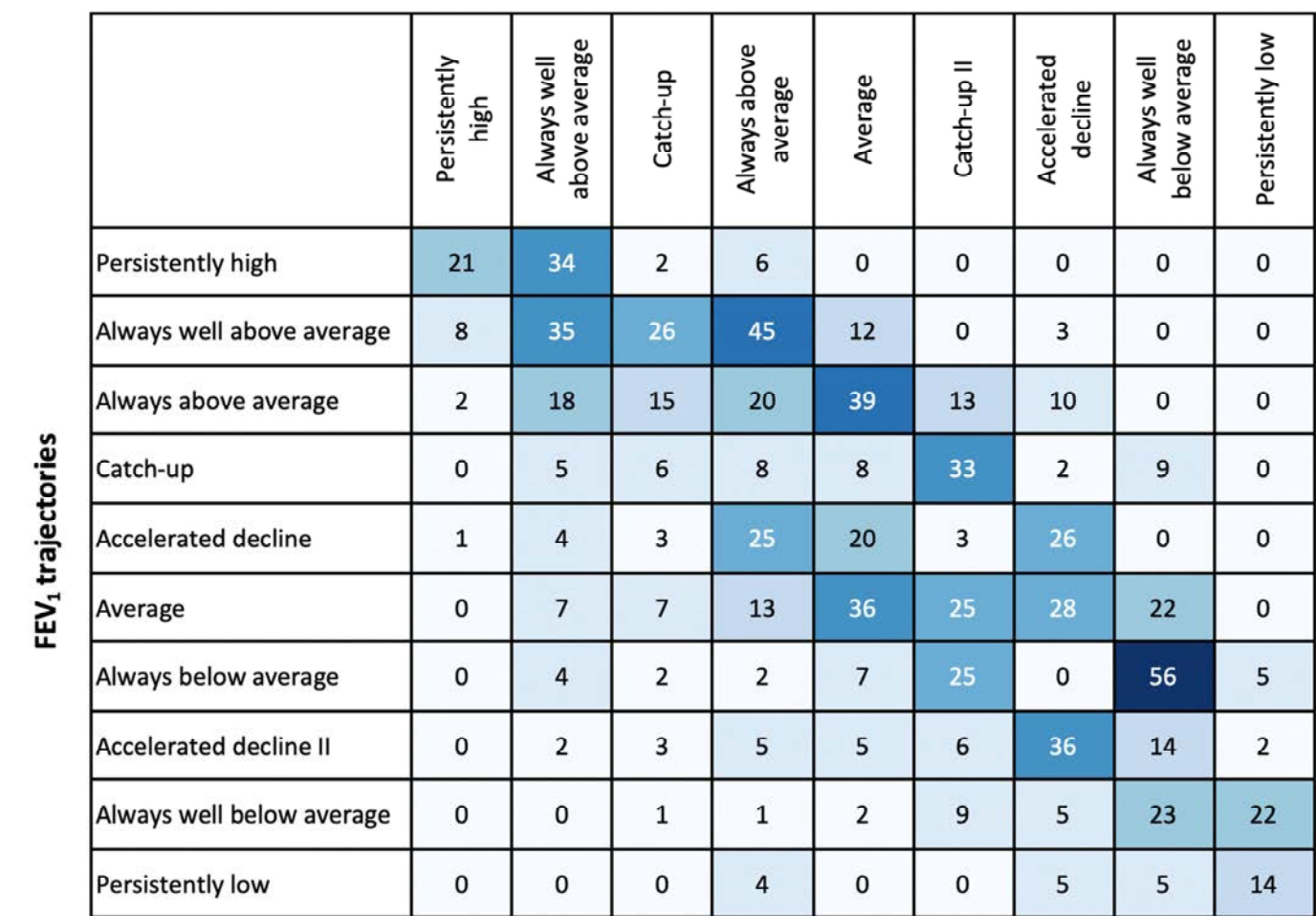


Figure 4 Heatmap showing overlap between trajectories of FEV₁ (rows) and FVC (columns) with darker shades for higher counts. Numbers indicate number of participants. FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

insufficient lung function measures, findings were very similar in the sensitivity analysis which included participants with at least two spirometry measures (n=1008; 97% of the original cohort; online supplemental figure S2). Furthermore, those included in and excluded from the main analysis had similar baseline characteristics (online supplemental table S1). We chose to analyse the data using LPA because this allows each individual to be assigned to the most likely trajectory. In our study, the posterior probabilities of belonging to the trajectories were very high (online supplemental table S12), indicating a good model fit. The trajectories for each individual participant associated with the identified FEV₁, FVC and FEV₁/FVC trajectory classes are shown in online supplemental figures S8–S10. The LPA approach has been used by several previous studies³⁰ and is conceptually similar, but mathematically different, to group-based trajectory modelling that has been used by some others.^{7,11}

Several limitations should be acknowledged. We do not have lung function data before age 9, when the trajectories of lung function may be largely determined,^{31,32} and we do not yet have lung function measures in later adulthood to complete the trajectories across the life course. Our definition of postbronchodilator airflow obstruction at age 45 does not necessarily indicate clinical COPD. However, in our cohort at this age, the lower limit of normal for FEV₁/FVC ratio (0.69) is very similar to the GOLD criterion of FEV₁/FVC ratio <0.7 that we used. Although we have reports of coughs and colds at age 3, we may have missed early life exposures such as severe lower respiratory tract infections.^{33,34} We also compared exposures for each trajectory to all other trajectories combined, whereas previous reports have tended to use the ‘average’ trajectory as the reference group. Our approach risks diluting risk factors that might

be shared by more than one trajectory. On the other hand, the ‘average’ group may simply have a mix of beneficial and adverse factors and may not necessarily represent ideal lung health. To facilitate comparisons with previous studies, multivariable analyses using the ‘average’ trajectories as the reference groups are shown in online supplemental tables S13–S15. Overall, there were few differences with the main analyses, although some of the associations changed statistical significance—mostly becoming non-significant, which is likely because of the lower power due to the smaller size of the reference category. Finally, the precision of our estimated associations for some exposure–trajectory combinations is limited by the size of the less common trajectories along with the collinearity between some exposures, such as AHR, asthma and atopy.

CONCLUSIONS

We identified distinct trajectories of lung function from childhood to age 45 years in a prospective population-based cohort. Most of these trajectories were approximately parallel, demonstrating that, for most people, their lung function trajectories appear to be established before adolescence. However, we observed a few exceptions: childhood asthma/AHR-associated persistently low trajectories, which started low and diverged further from the other trajectories over time, and accelerated decline trajectories associated with smoking and higher adult BMI.

Despite representing a minority of the cohort, the three trajectories leading to the lowest FEV₁ values contributed most of the post-bronchodilator airflow obstruction at age 45. To promote healthy adult lung function trajectories and reduce the risk of COPD, we need strategies to maximise lung growth in early life and minimise childhood asthma-related lung function impairment.

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REFERENCES

- Agusti A, Faner R. Lung function trajectories in health and disease. *Lancet Respir Med* 2019;7:358–64.
- Fletcher C, Peto R. The natural history of chronic airflow obstruction. *Br Med J* 1977;1:1645–8.
- Lange P, Celli B, Agustí A, et al. Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med* 2015;373:111–22.
- Agusti A, Noell G, Brugada J, et al. Lung function in early adulthood and health in later life: a transgenerational cohort analysis. *Lancet Respir Med* 2017;5:935–45.
- Vasquez MM, Zhou M, Hu C, et al. Low lung function in young adult life is associated with early mortality. *Am J Respir Crit Care Med* 2017;195:1399–401.
- Berry CE, Billheimer D, Jenkins IC, et al. A distinct low lung function trajectory from childhood to the fourth decade of life. *Am J Respir Crit Care Med* 2016;194:607–12.
- Bui DS, Lodge CJ, Burgess JA, et al. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018;6:535–44.
- Belgrave DCM, Granell R, Turner SW, et al. Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies. *Lancet Respir Med* 2018;6:526–34.
- Karmaus W, Mukherjee N, Janjanam VD, et al. Distinctive lung function Trajectories from age 10 to 26 years in men and women and associated early life risk factors - a birth cohort study. *Respir Res* 2019;20:98.
- Washko GR, Colangelo LA, Estépar RSJ, et al. Adult life-course trajectories of lung function and the development of emphysema: the CARDIA lung study. *Am J Med* 2020;133:222–30.
- Dharmage SC, Bui DS, Walters EH, et al. Lifetime spirometry patterns of obstruction and restriction, and their risk factors and outcomes: a prospective cohort study. *Lancet Respir Med* 2023;11:273–82.
- Poulton R, Moffitt TE, Silva PA. The Dunedin multidisciplinary health and development study: overview of the first 40 years, with an eye to the future. *Soc Psychiatry Psychiatr Epidemiol* 2015;50:679–93.
- Hancox RJ, Poulton R, Greene JM, et al. Associations between birth weight, early childhood weight gain, and adult lung function. *Thorax* 2009;64:228–32.
- American Thoracic Society. Standardization of spirometry. *Am J Respir Crit Care Med* 1995;152:1107–36.
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
- Hancox RJ, Gray AR, Zhang X, et al. Differential effects of cannabis and tobacco on lung function in mid-adult life. *Am J Respir Crit Care Med* 2022;205:1179–85.
- Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: 2022 report; 2022.
- Hancox RJ, Milne BJ, Taylor DR, et al. Relationship between socioeconomic status and asthma: a longitudinal cohort study. *Thorax* 2004;59:376–80.
- Hancox RJ, Gray AR, Poulton R, et al. The effect of cigarette smoking on lung function in young adults with asthma. *Am J Respir Crit Care Med* 2016;194:276–84.
- Sears MR, Jones DT, Holdaway MD, et al. Prevalence of bronchial reactivity to inhaled methacholine in New Zealand children. *Thorax* 1986;41:283–9.
- Sears MR, Greene JM, Willan AR, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. *Lancet* 2002;360:901–7.
- Shin HH, Lynch SJ, Gray AR, et al. How much atopy is attributable to common childhood environmental exposures? A population-based birth cohort study followed to adulthood. *Int J Epidemiol* 2017;46:2009–16.
- Mandhane PJ, Sears MR, Poulton R, et al. Cats and dogs and the risk of Atopy in childhood and adulthood. *J Allergy Clin Immunol* 2009;124:745–50.
- Vermunt JK, Magidson J. Applied latent class analysis. Cambridge: Cambridge University Press, 2002: 89–106.
- Schwarz G. Estimating the dimension of a model. *Ann Statist* 1978;6:461–4.
- Firth D. Bias reduction of maximum likelihood estimates. *Biometrika* 1993;80:27–38.
- Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat* 1979;6:65–70.
- McGeachie MJ, Yates KP, Zhou X, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med* 2016;374:1842–52.
- Svanes C, Sunyer J, Plana E, et al. Early life origins of chronic obstructive pulmonary disease. *Thorax* 2010;65:14–20.
- Okyere DO, Bui DS, Washko GR, et al. Predictors of lung function trajectories in population-based studies: a systematic review. *Respirology* 2021;26:938–59.
- Stern DA, Morgan WJ, Wright AL, et al. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* 2007;370:758–64.
- Martinez FD. Early-life origins of chronic obstructive pulmonary disease. *N Engl J Med* 2016;375:871–8.
- Johnston ID, Strachan DP, Anderson HR. Effect of pneumonia and whooping cough in childhood on adult lung function. *N Engl J Med* 1998;338:581–7.
- Dharmage SC, Erbas B, Jarvis D, et al. Do childhood respiratory infections continue to influence adult respiratory morbidity? *Eur Respir J* 2009;33:237–44.

ARTIGO ORIGINAL

Quantificar a sustentabilidade dos benefícios para o sistema de saúde de uma gestão da DPOC integrada nos cuidados de saúde primários: um estudo de séries temporais interrompidas de 6 anos

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RESUMO

Contexto A exacerbação grave da doença pulmonar obstrutiva crônica (DPOC) é um evento que altera a trajetória de vida dos doentes e que contribui em grande medida para os custos do sistema de saúde. Este estudo avalia o impacto no mundo real de um programa de cuidados primários com uma gestão integrada da doença (GID) na utilização aguda dos serviços de saúde (USS) no sistema de saúde canadense.

Métodos Análise de séries temporais interrompidas utilizando dados administrativos de saúde retrospectivos, comparando as taxas mensais de eventos de USS 3 anos antes e 3 anos após a implementação da GID da DPOC. Os resultados primários foram os internamentos hospitalares relacionados com a DPOC e as visitas ao serviço de urgência (SU). Os resultados secundários incluíram dias de hospitalização e todas as causas de USS.

Resultados O número de participantes foi de 2451. As taxas de USS relacionadas com a DPOC e com todas as causas aumentaram nos 3 anos anteriores à implementação da GID. Com a implementação, verificou-se uma diminuição imediata (mês 1) das taxas de hospitalização relacionadas com a DPOC e de visitas às urgências de -4,6 (IC 95%: -7,76 a -1,39) e -6,2 (IC 95%: -11,88, -0,48) por cada 1000 participantes por mês, respetivamente, em comparação com o grupo de controlo comparativo. Após 12 meses, as taxas de hospitalização relacionadas com a DPOC diminuíram: -9,1 eventos por cada 1000 participantes por mês (IC 95%: -12,72, -5,44) e as visitas às urgências diminuíram -19,0 (IC 95%: -25,50, -12,46). Esta diferença quase duplicou aos 36 meses. A USS por todas as causas também demonstrou reduções nas taxas aos 12 meses, a hospitalização situou-se em -10,2 eventos por cada 1000 participantes por mês (IC 95%: -15,79, -4,44) e as visitas às urgências situaram-se em -30,4 (IC 95%: -41,95, -18,78).

Conclusões A implementação de uma GID para a DPOC num contexto de cuidados primários foi associada a uma alteração da trajetória da USS relacionada com a DPOC e com todas as causas, passando de uma tendência crescente ano após ano para reduções sustentadas a longo prazo. Este facto realça uma oportunidade substancial no mundo real que poderá melhorar o desempenho do sistema de saúde e o prognóstico dos doentes.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung disease that causes persistent and often progressive airflow limitation.¹ It is characterised by chronic symptoms, notably dyspnoea, cough and sputum production.^{1,2} Globally, there were over 212 million people living with COPD in 2019, attributing 3.3 million deaths and accruing 74.4 million disability-adjusted life years.³ Exacerbation, characterised by moderate or severe symptom worsening, is a substantial burden to both patients

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Globally, the care of patients with chronic obstructive pulmonary disease (COPD) is characterised by low guideline concordance and high rates of acute health services use including hospitalisation and emergency department (ED) visits.
- Randomised controlled trials have confirmed the efficacy of integrated disease management (IDM), a cost-effective, team-based approach to improve concordance between clinical care and clinical practice guidelines, to reduce acute health service utilisation.
- Although a majority of patients with COPD are managed in the community in primary care, the effectiveness of COPD IDM has not been examined in a real-world primary care setting.

WHAT THIS STUDY ADDS

- Primary care-based COPD IDM is an effective intervention, and implementation was associated with a change in disease trajectory from increasing acute health service utilisation, to an immediate and sustained long-term reduction in hospitalisation and ED visits.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Strong supporting evidence for the real-world effectiveness of COPD IDM highlights that a substantial opportunity to improve health system performance and patient outcomes may exist, warranting IDM evaluation in different settings globally.

and health systems.^{1,2} Inpatient hospital admissions are responsible for the greatest proportion of direct economic costs and heighten the risk of subsequent severe exacerbation and mortality.^{1,2,4–8} In addition, people with COPD exhibit a higher prevalence of disease comorbidity than those without, further increasing health system utilisation and expenditure.^{1,9–11} These hospitalisation rates have persisted over time in multiple health jurisdictions globally and therefore, the



implementation of effective solutions is required to improve health system performance.^{7,12}

Integrated disease management (IDM) programmes provide an effective, proactive model of care—formally integrating current evidence-based COPD management guidelines using a multicomponent, multidisciplinary approach involving pharmacological therapies, pulmonary rehabilitation, case management, education and self-management strategies.^{1,2} The goal is to prevent and manage exacerbation effectively thereby improving COPD prognosis and avoiding costly acute care service utilisation.¹ Collectively, randomised controlled trials (RCTs) have demonstrated IDM can reduce respiratory-related hospital admissions and emergency department (ED) visits and improve health-related quality of life (HR-QoL).¹³ Pulmonary rehabilitation is highly effective, but its health system impacts are limited by access, high resource intensity and its waning effect over time.^{1,14,15} This highlights the need for more cost-effective, long-term interventions and continued surveillance to evaluate if health system impacts are sustained over time and across jurisdictions.¹⁶

Best Care COPD is a primary care-based, self-management IDM programme emanating from an RCT that confirmed programme efficacy, including reduced acute health service utilisation (HSU) and improved HR-QoL.¹⁷ Further evaluative studies of the Best Care COPD Programme supported real-world effectiveness, reporting that Best Care improved patient and provider experiences, and that it was cost-effective and dominant relative to the usual standard of care.^{18–23} As with the majority of studies forming a large body of published literature on IDM, the quantitative evaluations were limited to 1 year of locally collected follow-up data.¹³ Additionally, even for pulmonary rehabilitation, a gold-standard COPD IDM intervention, the long-term impacts are unproven.¹⁵ Considering the substantial multiyear impact that COPD has on health system utilisation, it is imperative to directly evaluate the effect of COPD IDM at the health system level and to extend the evaluation window. Accordingly, we used health administrative data from a publicly funded health system, the Ontario Health Insurance Plan (OHIP), to examine the impact of the Best Care COPD Programme on health system performance, including hospital admissions and ED visits, over a 6-year observation window.

METHODS

Study design

We quantified the impact of Best Care COPD using interrupted time series. HSU events between 13 January 2008 and 31 March 2020 were included. Data beyond 31 March 2020 were excluded to avoid potential bias from the COVID-19 pandemic period. HSU data were retrieved, from provincial health administrative databases, at monthly intervals for the 3 years prior to the initial Best Care appointment and for up to 3 years after or until the participant died. The observation periods for each participant were centred to the initial appointment (T0). Acute HSU was tracked from –36 months to T0 (pre-intervention period) and T0 to +36 months (intervention period). Date of initial appointment could therefore occur anytime between 13 January 2011 and 31 March 2019, so every participant had 36 months pre-intervention and a minimum of 12 months of intervention follow-up (figure 1).

Best Care COPD is a structured multidisciplinary IDM programme embedded in primary care across the province of Ontario, Canada. The programme creates a triad of collaborative care between a patient, their primary care provider and a certified respiratory educator-case manager. Best Care COPD is a complete knowledge translation module that delivers all elements of evidence-based care that are relevant to primary care including provincial quality standards, national and international COPD guideline recommendations related to diagnosis, comprehensive assessment, individualised care planning, education and self-management, smoking cessation, pharmacological management, vaccinations and referral for specialised respiratory care (figure 2).^{1,2,24} The Best Care Programme elements have been described in detail previously.^{17,20}

Data sources and measurement

Data were collected from two sources: the Best Care COPD IDM electronic health record and ICES (formerly known as the Institute for Clinical Evaluative Sciences).

Best Care COPD IDM

The Best Care COPD health record is an electronic point of service system used as an integrated technology solution that guides and standardises every patient encounter. The digital tool captures

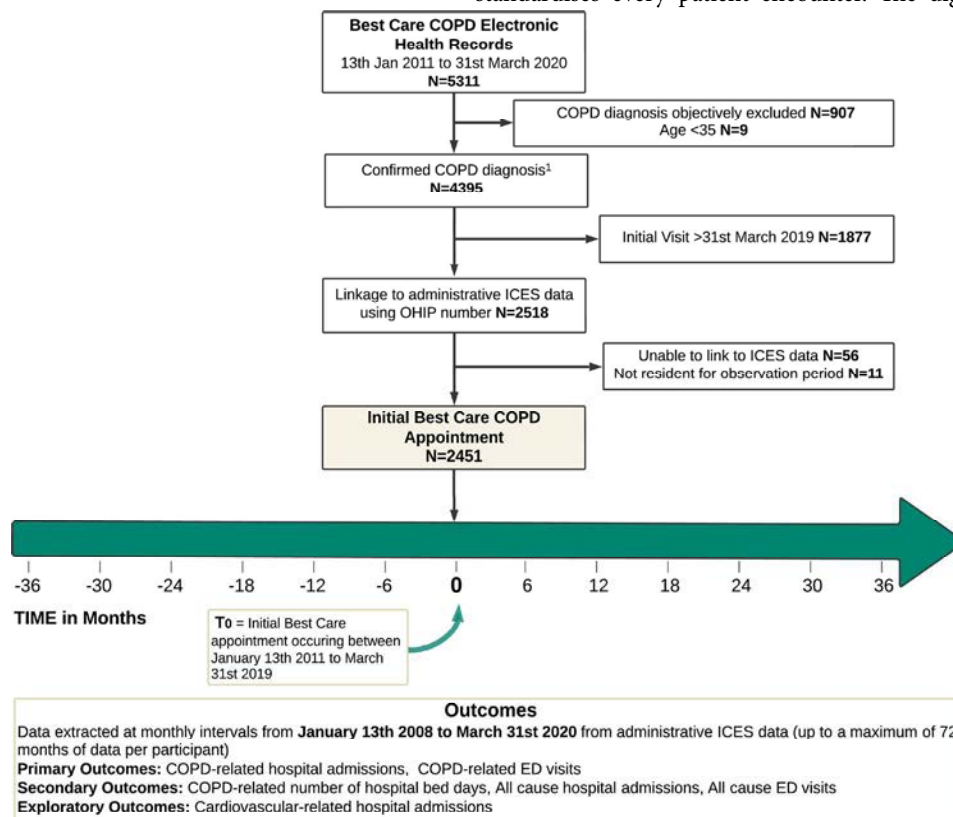


Figure 1 Flow diagram showing participant numbers, exclusion and inclusion, and study timeline. ¹COPD diagnosis at initial visit confirmed clinically or objectively. COPD, chronic obstructive pulmonary disease; ED, emergency department; OHIP, Ontario Health Insurance Plan.

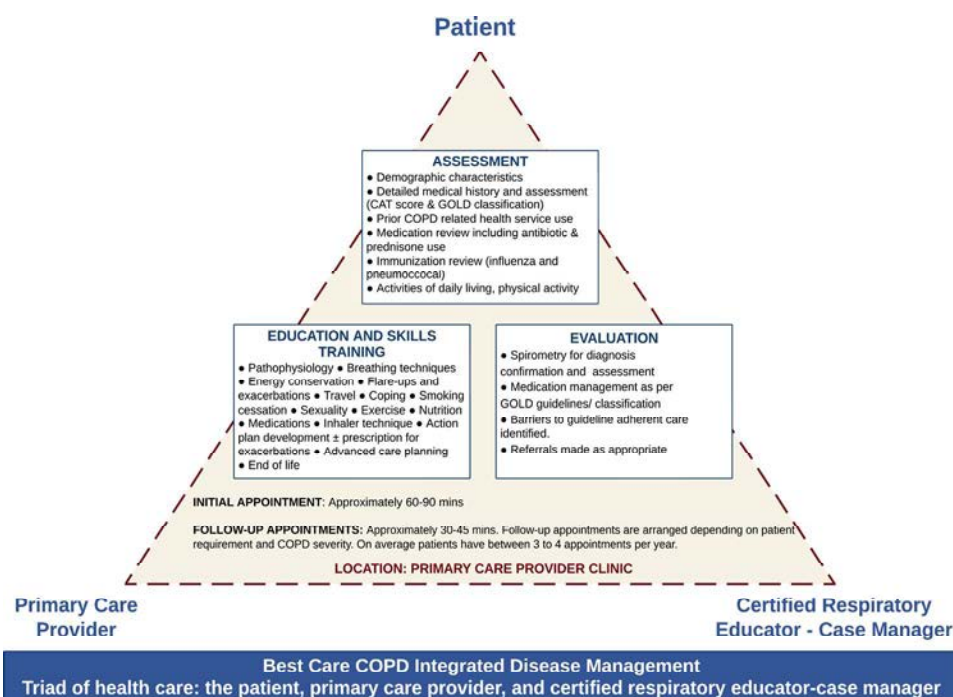


Figure 2 An overview of the Best Care integrated disease management programme. Adapted from Table 1: Ferrone *et al.*¹⁷ and Figure 1: Hussey *et al.*²⁰ CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; GOLD, Global initiative for Obstructive Lung Disease.

health outcomes and measures the achievement of guideline-based performance metrics. The baseline characteristics of all patients were extracted from this registry at T0 (initial visit). Baseline variables included age, sex, residence (rural vs urban), income (inferred from postal code), body mass index, race, smoking status, smoking pack years, self-reported comorbidities, vaccination status and prior year antibiotic and prednisone use.

COPD-specific baseline variables included: modified Medical Research Council (mMRC) score (0–4) which stratifies the severity of dyspnoea; COPD Assessment Test (CAT) score (0–40), a validated disease-specific quality of life tool that quantifies the impact of COPD symptoms on a patient's overall health; Global initiative for Obstructive Lung Disease (GOLD) (groups ABE) which categorises the severity of COPD using a combination of prior-year exacerbation history and COPD symptoms using mMRC or CAT; GOLD class (I–IV), a spirometric measure of airflow limitation, post-bronchodilator forced expiratory volume in 1 second.¹

ICES data

Ontario has a publicly funded health system administered under the OHIP. All essential medical services and claims are captured in health administrative databases. ICES houses Ontario health administrative databases, including the National Ambulatory Care Reporting System which captures ED visits, the Canadian Institute for Health Information Discharge Abstract which captures hospital admissions and the Registered Persons Database that records the date of death. Participants were linked by their unique OHIP number to the ICES database. Monthly HSU data were assembled. Primary reason for COPD-related hospital admission or ED visit was identified using the International Classification of Diseases, 10th revision codes. COPD-related HSU was defined as combined COPD-specific HSU and COPD-associated lower respiratory codes, for example 'influenza' or 'pneumonia' (online supplemental table 1E).

Participants

All Best Care Programme patients were included if they were: ≥35 years of age at the initial visit, residents in Ontario for the 3 years prior to commencing the Best Care COPD Programme, had a clinical or objective COPD diagnosis and had attended at least one Best Care appointment (figure 1). Participants were excluded if at any time during follow-up, a COPD diagnosis was objectively ruled out. Censoring occurred when a participant died.

Outcomes

Primary outcomes were COPD-related hospital admissions and COPD-related ED visits. Secondary outcomes included COPD-related hospital bed days, all-cause hospital admissions and all-cause ED visits. In a post-hoc exploratory analysis, we examined Best Care Programme impacts on cardiovascular (CV)-related hospitalisation.

Statistical analysis

Baseline characteristics of the study population were summarised as the mean and SD for continuous variables and frequency and percentage for categorical variables. In addition, we tabulated annual measures of observed HSU for the 6-year observation window, and mortality events were reported over the 3-year intervention period.

Interrupted time series analysis

Observed monthly HSU rates (events per 1000 participants per month) were calculated over the 6-year observation period. A 3-year pre-intervention and 3-year intervention trend were measured. A 'counterfactual control' was modelled by continuing the pre-intervention trend line through the intervention period, assuming the absence of any intervention (ie, a continuation of usual care). The counterfactual control trend line was compared with the observed intervention trend line. Differences between the counterfactual control and the observed intervention trends were considered as the 'difference-in-difference' in the interrupted time series analysis.

We used a segmented linear regression model to evaluate changes in HSU following the implementation of the IDM programme. Our model included a level change and slope change corresponding to the implementation of the IDM programme (T0), allowing for the estimation of immediate (level change: T0–month 1 of the intervention) and gradual changes (slope change: month 1–month 36) in HSU rates following the intervention. All observations were centred to the initial IDM appointment (T0) thereby eliminating the effect of seasonality. Estimated intervention effects are reported as absolute changes in HSU rates with 95% CIs.

Sensitivity analysis

We conducted two sensitivity analyses on the counterfactual control for the primary outcomes of COPD-related hospitalisation and ED visits. First, the data were modelled using a constant rate

Table 1 Baseline demographic and clinical characteristics of the overall study cohort at time of entry into COPD integrated disease management (time 0)

Baseline demographic and clinical characteristics		N=2451
Sex	Male	1266 (51.7%)
	Female	1185 (48.3%)
Age (years)	Mean (SD)	67.1 (10.6)
Residence	Urban	1994 (81.4%)
	Rural	457 (18.6%)
Neighbourhood income quintile*	1 (lowest)	592 (24.2%)
	2	501 (20.4%)
	3	550 (22.4%)
	4	459 (18.7%)
	5 (highest)	344–348†
	Missing	1–5†
Body mass index (kg/m ²)	Mean (SD)	29.4 (7.0)
Race	Caucasian	2408 (98.2%)
Smoking status	Current smoker	985 (40.2%)
	Prior smoker	1284 (52.4%)
	Never smoker	182 (7.4%)
	Pack-years <10	83 (3.4%)
	Pack-years >10	2186 (89.2%)
	Pack-years mean (SD)	42.0 (26.4)
COPD Assessment Test (CAT) (score 0–40)‡	Mean (SD)	15.9 (8.1)
	Missing	443 (18.1%)
Number of comorbidities	0	384 (15.7%)
	1–2	1124 (45.9%)
	>2	943 (38.4%)
mMRC dyspnoea score (0–4)§	Mean (SD)	1.4 (1.0)
GOLD group¶	A	403 (16.4%)
	B	1033 (42.2%)
	E	572 (23.3%)
	Missing	443 (18.1%)
GOLD class**	1 FEV ₁ ≥80%	357 (14.6%)
	2 50% ≤ FEV ₁ <80%	825 (33.7%)
	3 30% ≤ FEV ₁ <50%	323 (13.2%)
	4 FEV ₁ <30%	37 (1.5%)
	Missing	909 (37.1%)
Exacerbation-related medication	Prior-year antibiotics	1092 (44.6%)
	Prior-year prednisone	726 (29.6%)
Vaccinations	Influenza	1751 (71.4%)
	Pneumococcal	1531 (62.5%)

*Nearest census-based neighbourhood income quintile, based on postal code at initial visit.

†Small cells have been replaced by a range of values to ensure that data could not be used to reidentify participants. Due to rounding, categorical percentages may not total 100%.

‡A score of 0 indicates a good health-related quality of life, 40 indicates a very poor health-related quality of life.

§A score of 0 indicates little or no effect on breathlessness, 4 indicates a large effect on breathlessness.

¶GOLD A 0–1 exacerbation not leading to hospitalisation, mMRC 0–1 or CAT <10; GOLD B 0–1 exacerbation not leading to hospitalisation, mMRC ≥2 or CAT ≥10; GOLD E ≥2 exacerbation episodes or ≥1 exacerbation leading to hospitalisation.

**GOLD class based on post-bronchodilator FEV₁ (% predicted).

COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; GOLD, Global initiative for Obstructive Lung Disease; mMRC, modified Medical Research Council.

counterfactual control, assuming the rate remained constant from T₀ across the 36-month intervention period.^{25–26} Second, using a counterfactual control modelled from –36 to –13 months of pre-intervention outcome data, thereby eliminating any short-term steep rate elevations observed between –12 and T₀. An additional sensitivity analysis of the primary outcomes was performed exclu-

ding all participants who died, to investigate if a reduction in the most exacerbation-prone individuals due to mortality influenced the observed intervention trend by concentrating on the ‘healthier’ proportion of the study population.

All analyses were conducted using SAS Enterprise Guide V.8.3.

Patient and public involvement

Best Care has involved patients in programme design and measures patient experience.^{21–27–28} The Patient-Reported Experience Measure in COPD patient experience questionnaire is being implemented.²⁹ As this study is a retrospective administrative dataset evaluation of the Best Care COPD IDM Programme, no patients or members of the public were involved in the conduct of the study.

RESULTS

Participant characteristics

A total of 2518 participants met study entry criteria (figure 1). The mean number of Best Care appointments per participant was 3.4 (SD: ±2.5) over 12.1 months (±12.4) of follow-up. COPD pathophysiology, exercise and activity, and medication management are educational components of IDM received by 83.4–93.1% of the study cohort. Skills training in breathing techniques, flare-ups and exacerbation, and inhaler techniques were received by 93–96.5% and case management including action plan development, influenza vaccination and smoking cessation are elements of IDM received by 77.6–100% of the study cohort (online supplemental table 2E). Of the 2518 eligible participants, 2451 were linked to the administrative data and amounted over 13 000 person-years of follow-up (figure 1). The study cohort had a mean age of 67.1 years (±10.6), with 48.3% female, 98.2% Caucasian and 44.6% in the two lowest income quintiles. This cohort had a mean CAT score of 15.9 (±8.1), a mean mMRC of 1.4 (±1.0), 38.4% had two or more comorbidities, 42.2% were GOLD group B and 23.3% GOLD group E (table 1).

Observed HSU and mortality events

Table 2 shows the actual number of events and proportion of individuals experiencing a COPD-related or all-cause HSU in this study cohort. Over 6 years of study evaluation, 3 years pre-intervention and 3 years of intervention, COPD-related hospital admissions ranged from 78 to 283 events per year impacting between 62 (2.5%) and 225 (9.2%) individuals, and amounting to 483–1924 inpatient days. COPD-related ED visits ranged in number from 339 to 809 per year affecting between 205 (11.8%) and 499 (20.4%) individuals. During the intervention period, there were 328 deaths, representing 4.1–6.6% of the study population per year (table 2).

Interrupted time series analysis

COPD-related and all-cause

Figure 3 graphically represents the monthly rates of HSU based on the time series models. Both COPD-related and all-cause HSU demonstrated an increasing trend in the pre-intervention period. During the intervention period, the observed trend remained stable or decreased from T₀ to month 36. In the pre-intervention period, COPD-related hospital admission rates increased by 0.4 events per 1000 per month (95% CI: 0.24 to 0.46), inpatient bed days increased by 2.4 bed days per 1000 per month (95% CI: 1.72 to 3.12) and ED visits by 0.8 events per 1000 per month (95% CI: 0.56 to 0.95). From T₀ to the first month of the intervention period, there was an immediate drop in the event rate (level change) for hospital admissions of –4.6 events per 1000 per month (95% CI: –7.76 to –1.39), –32.7 inpatient bed days per 1000 per month (95% CI: –53.29 to –12.14) and –6.2 ED visits per 1000 per month (95% CI: –11.88 to –0.48). The reduction in rates remained over the 36-month intervention period for all COPD-related HSU events. Similarly, for all-cause HSU, there were increasing rates observed in the pre-intervention period and significant slope reductions in the intervention period, but there was no level change observed from T₀ to month 1 (figure 3 and online supplemental figure 1E for inpatient bed days).

Table 2 Observed health service utilisation events over the 6-year observation window

	Pre-intervention			Intervention period		
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
	N=2451*	N=2451	N=2451	N=2451	N=2350	N=1740
COPD-related hospital admissions						
Participants with event	62 (2.5%)	93 (3.8%)	225 (9.2%)	154 (6.3%)	138 (5.9%)	98 (5.6%)
Number of events	78	116	283	205	179	119
Mean events/participant (SD)	0.03 (0.24)	0.05 (0.28)	0.12 (0.41)	0.08 (0.37)	0.07 (0.37)	0.06 (0.29)
Number of bed days	483	768	1924	1387	1201	847
Mean bed days/participant	0.20 (1.66)	0.31 (1.96)	0.78 (3.48)	0.57 (2.94)	0.49 (2.52)	0.44 (2.44)
COPD-related ED visits						
Participants with event	213 (8.7%)	295 (12.0%)	499 (20.4%)	380 (15.5%)	314 (13.4%)	205 (11.8%)
Number of events	339	460	809	697	527	305
Mean events/participant (SD)	0.14 (0.66)	0.19 (0.69)	0.33 (0.88)	0.28 (0.93)	0.22 (0.77)	0.16 (0.57)
All-cause hospital admissions						
Participants with event	311 (12.7%)	337 (13.7%)	520 (21.2%)	501 (20.4%)	426 (18.1%)	319 (18.3%)
Number of events	410	466	743	752	641	470
Mean events/participant (SD)	0.17 (0.50)	0.19 (0.56)	0.30 (0.71)	0.31 (0.72)	0.26 (0.70)	0.25 (0.66)
All-cause ED visits						
Participants with event	876 (35.7%)	979 (39.9%)	1206 (49.2%)	1112 (45.4%)	932 (39.7%)	664 (38.2%)
Number of events	2070	2332	2941	2862	2406	1499
Mean events/participant (SD)	0.84 (2.07)	0.95 (1.96)	1.20 (2.04)	1.17 (2.19)	1.02 (2.33)	0.86 (1.74)
All-cause mortality				101 (4.1%)	113 (4.8%)	114 (6.6%)

See online supplemental table 1E for ICD-10 codes used for COPD-related disease classifications.
*N refers to the number of participants in the cohort at the beginning of the observation year.
COPD, chronic obstructive pulmonary disease; ED, emergency department; ICD-10, International Classification of Diseases, 10th revision; T₀, initial visit.

Differences between the counterfactual control and observed trends in the intervention period are quantified at 12, 24 and 36 months in figure 4. For all HSU outcomes, the difference between the counterfactual control and the observed trends increased through all three time periods. The difference for COPD-related hospital admissions was −9.1 events per 1000 per month (95% CI: −12.72 to −5.44) at month 12 and −18.1 events per 1000 per month (95% CI: −24.39 to −1.78) at month 36. There was a reduction of −61.9 inpatient bed days per 1000 per month (95% CI: −85.39 to −38.36) at 12 months and a further reduction of −120.2 events per 1000 per month (95% CI: −160.92 to −79.48) at 36 months. Likewise, for COPD-related ED visits, the rate difference was −19.0 events per 1000 per month (95% CI: −25.50 to −12.46) at 12 months and −44.6 events per 1000 per month (95% CI: −55.86 to −33.29) at 36 months. Similarly, all-cause HSU events showed significant differences at 12, 24 and 36 months (figure 4 and online supplemental table 3E for inpatient bed days). Estimated annual events avoided are presented in table 3; for COPD-related hospital admissions, the annual reduction ranged from 61 to 84 events per 1000 in year 1 and from 67 to 192 in year 3, and for COPD-related ED visits, there was a respective annual reduction ranging from 107 to 157 and 196 to 465 events per 1000 in year 1 and year 3.

CV-related hospitalisation

There were a total of 116 CV-related hospital admissions, affecting 94 (3.8%) individuals in the year prior to IDM. During the intervention period, there were 128 events in 104 (4.2%) individuals at 12 months and 73 events in 61 (3.5%) individuals at 36 months. At 12, 24 and 36 months, all event rates were significantly reduced compared with the counterfactual control rates: −1.8 per 1000 per month (95% CI: −3.20 to −0.43), −3.32 (95% CI: −5.15 to −1.49) and −4.8 (95% CI: −7.23 to −2.42), respectively (online supplemental tables 3E and 4E).

Sensitivity analyses

Three sensitivity analyses supported the main findings. A standard sensitivity analysis with the counterfactual HSU control held con-

stant from T₀ to 36 months demonstrated significant level and slope changes, and significant rate reductions at 12, 24 and 36 months when compared with the observed intervention trend for both primary outcomes.^{25 26} The counterfactual control modelled from −36 to −13 months of pre-intervention outcome data also demonstrated a significant slope change from a positive inclining slope pre-intervention to a negative declining slope during intervention. The rate reduction in COPD-related hospital admissions was of borderline significance at 12 months, reaching significance at 24 and 36 months. Lastly, when participants who died were removed from the models (N=328), the observed COPD-related hospital admission rate and ED visit rate remained significantly reduced in intervention period compared with the counterfactual control trend line at 12, 24 and 36 months (online supplemental tables 5E and 6E).

DISCUSSION

After 3 years of progressively increasing acute HSU, Best Care COPD, a primary care-based IDM programme, was associated with a significant and progressive reduction in COPD-related hospitalisation and ED visits over a 3-year interval. The observed impact was immediate and trajectory changing, a significant positive outcome for the COPD population and for the health system. Similarly, all-cause hospitalisation, ED visits and bed days exhibited significant and progressive reductions. To our knowledge, this is the first real-world interrupted time series analysis evaluating the beneficial long-term impact of IDM at the health system level.

The existence of an exacerbating phenotype, the ‘frequent exacerbator’, is codified in the GOLD guidelines.^{1 30 31} Best Care COPD sought to identify high-risk, exacerbation-prone individuals with COPD, as such, 23% were in the highest GOLD risk category group E (GOLD 2023 reclassified GOLD C and D). We observed increasing rates of COPD-related hospitalisation and ED visits over the 3 years before patients entered the programme. The observed pre-intervention increase in acute HSU aligns with the natural history of COPD where an increase in the frequency and severity of



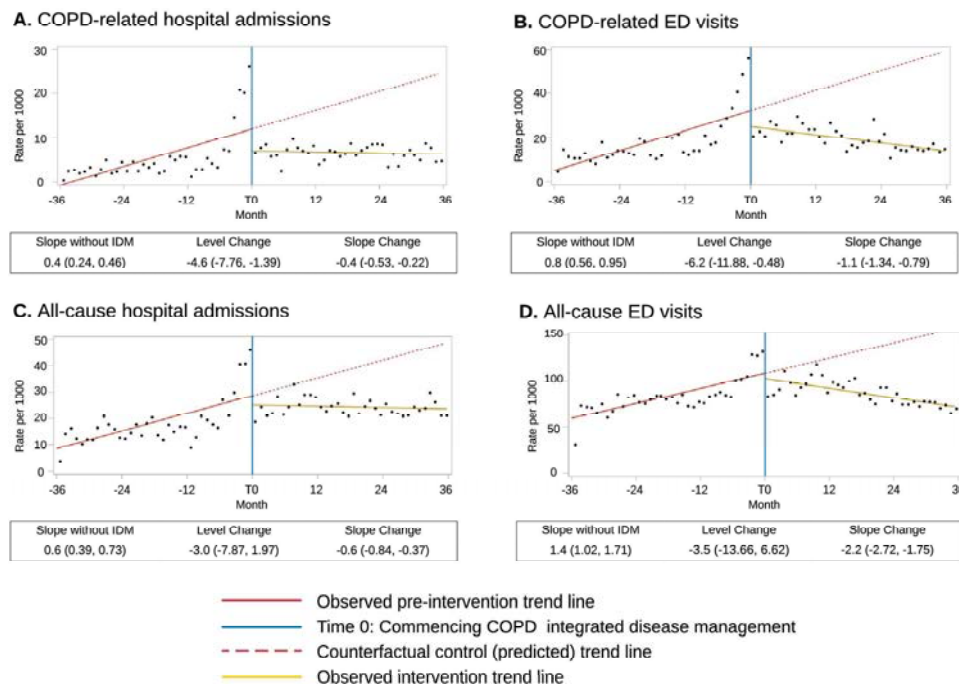


Figure 3 Time series graphs of health service events showing the observed pre-intervention monthly rate and trend line, the observed intervention monthly rate and trend line and the counterfactual control trend line for (A) COPD-related hospital admissions, (B) COPD-related ED visits, (C) all-cause hospital admissions, and (D) all-cause ED visits. Slope=the increase or decrease in event rate per 1000 individuals per month with (95% CI); level change=the increase or decrease in event rate per 1000 individuals from the observed pre-intervention trend line to the observed intervention trend line at time 0 with (95% CI); slope change=the difference between the slope without IDM and the slope with IDM in event rate per 1000 individuals per month (95% CI). Counterfactual control modelled from the observed pre-intervention trend line. COPD, chronic obstructive pulmonary disease; ED, emergency department; IDM, integrated disease management.

exacerbation has been documented in large observational cohort studies.^{6–8 30 32 33}

A majority of patients receive their COPD care in primary care.³⁴ Recently, the efficacy of COPD IDM has been confirmed in a high-quality meta-analysis with 52 RCTs and 21 086 patients including IDM administered in primary care.¹³ Importantly, efficacy in RCTs cannot be assumed, a priori, to translate into effectiveness in real-world clinical care.^{19 35} The effectiveness at 12 months after IDM

implementation in our real-world primary care clinical practice study is consistent with RCT efficacy data.¹³ In 4207 participants, from 15 RCTs, the authors found a difference in respiratory-related admissions between intervention and control of 89 hospital admissions per 1000 per year, with a median follow-up of 12 months. In our real-world primary care study, we observed a reduction of up to 84 hospital admissions per 1000 at 12 months (table 3). The relative reductions in hospitalisation and ED visits at 12 months in

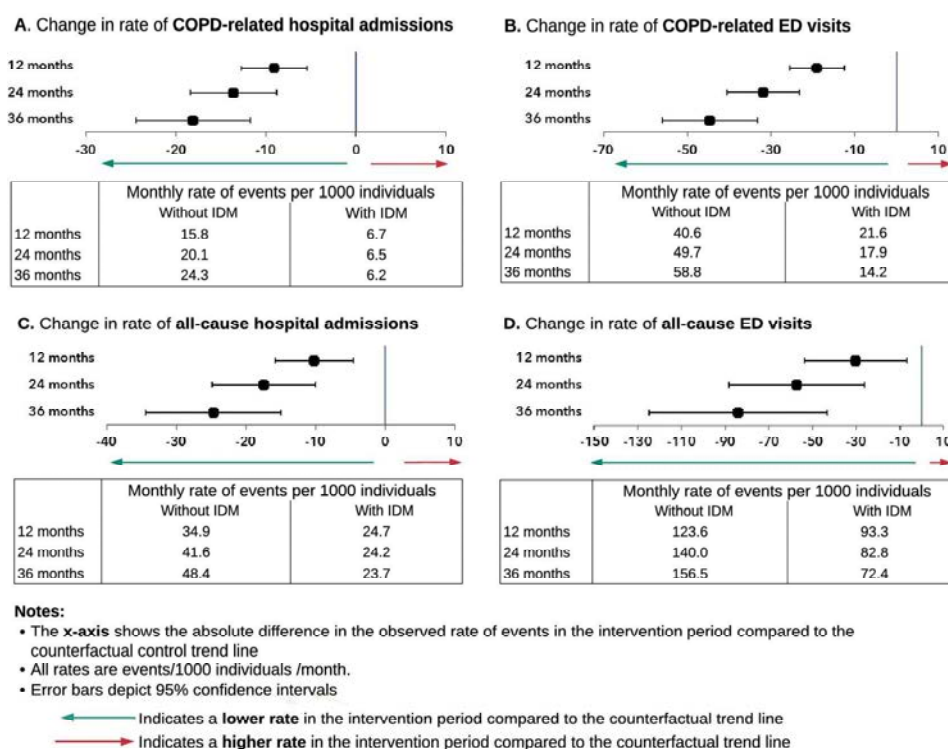


Figure 4 Change in the monthly rate of health service events comparing observed intervention trend line with the counterfactual control trend line at 12, 24 and 36 months for (A) COPD-related hospital admissions, (B) COPD-related ED visits, (C) all-cause hospital admissions, and (D) all-cause ED visits. COPD, chronic obstructive pulmonary disease; ED, emergency department; IDM integrated disease management.

Table 3 Estimated health service utilisation events avoided, per 1000 patients, with each year of integrated disease management (IDM) if the 3-year pre-intervention trend had continued along the same trajectory without intervention

	In year 1 of IDM		In year 2 of IDM		In year 3 of IDM	
	Events avoided/1000 participants/year*	Relative reduction in event rate/1000/year†	Events avoided/1000 participants/year*	Relative reduction in event rate/1000/year†	Events avoided/1000 participants/year*	Relative reduction in event rate/1000/year†
COPD-related hospital admissions	61–84	43–51%	64–138	45–64%	67–192	47–72%
COPD-related ED visits	107–157	28–36%	152–311	39–57%	196–465	51–71%
All-cause hospital admissions	45–82	13–22%	51–169	15–37%	57–256	17–47%
All-cause ED visits	126–217	10–16%	251–539	19–34%	376–861	29–48%

*Lower range: the rate of events per 1000 participants in a year if the pre-intervention rate had remained constant at T_0 minus the rate of events per 1000 participants under the observed trend during the intervention period. Upper range: the rate of events per 1000 participants in a year if the pre-intervention trend had continued along the same trajectory minus the rate of events per 1000 participants under the observed trend during the intervention period.

†Lower range: the events avoided per 1000 participants in a year as a percentage of the rate of events per 1000 participants in a year if the pre-intervention rate had remained constant from T_0 . Upper range: the events avoided per 1000 participants in a year as a percentage of the rate of events per 1000 participants in a year if the pre-intervention trend had continued along the same trajectory.

COPD, chronic obstructive pulmonary disease; ED, emergency department.

our study ranged up to 51% and 36%, respectively, vs 36% and 31% in the meta-analysis.

In parallel to the increase in COPD-related HSU, we also observed an increase in all-cause, ED visits and hospitalisation over the 3 years prior to the Best Care intervention. Disease comorbidity is common in patients who live with COPD and the general increase in acute HSU may be expected.¹⁰ In our COPD cohort, 84% had at least one comorbid disease and 38% had more than two (table 1). Gershon and colleagues observed that people with COPD had rates of all-cause hospital and ED visits that were substantially higher than a matched population without COPD.³⁶ We observed a marked reduction in all-cause hospitalisation and ED visits at 12, 24 and 36 months. Again, our observations aligned with the meta-analysis by Poot and colleagues. At 12 months, we demonstrated a relative reduction in all-cause hospitalisation of up to 22% vs a 25% reduction reported by Poot and colleagues.¹³ Although COPD IDM is targeted at management of COPD, the health system impact extends to all-cause HSU.

CV disease is one of the most prevalent comorbidities for individuals with COPD and contributed to all-cause hospitalisation in this study.^{10 37 38} Post-intervention, significant reductions in CV-related admissions were observed at 12, 24 and 36 months. Although this exploratory analysis requires confirmation, it raises interesting questions. For example, if a COPD IDM programme impacts CV outcomes, what is the mechanism, pharmacological, non-pharmacological or both? In the context of two large RCTs where the addition of inhaled corticosteroids generated a 0.8% and 1% reduction in all-cause mortality, a majority of which were CV-related deaths, it is interesting to consider that medication optimisation in COPD may have contributed to the reduction in all-cause and CV-related hospitalisation in our study.^{39 40}

To our knowledge, there were no other chronic disease management programmes introduced in Ontario that were consistently sustained in our study population. In addition, the 6-year chronological snapshot for each individual participant was centred around T_0 which includes dates from 2011 to 2019 mitigating any impact that a programme running concurrently would have. The quasi-experiment design used in this study is well suited to population health studies but inherent in the design is the lack of a physical control group. Rather, this methodology uses 36-month outcome measurements to establish a robust 3-year pre-intervention trend that when extended into the future, serves as a counterfactual control group.⁴¹ We observed a large increase in events in the year prior to commencing IDM, and while an increase in the frequency of COPD exacerbation is expected, we considered that referral bias may have contributed to this observation.^{6–8 30 32 33} To address this limitation, we conducted two sensitivity analyses with more conservative counterfactual controls and in each, confirmed our primary outcomes. Further to this limitation, we used both a clinical and objectively confirmed COPD diagnosis for study inclusion, introducing a potential for disease misclassification. Since the primary outcome data emanate from the provincial health system and

not from the primary care provider, the reported outcomes are not affected. The potential impact of misclassification will be a dilution of the reported health service rates. The inclusion of participants with a clinical diagnosis of COPD may strengthen external validity of the study.

While we acknowledge that a single interrupted time series analysis does not prove causation, there are several factors that support an inference of causation. In the case of an RCT, random allocation to group excludes the effect of confounding. In the single interrupted time series design, the control group has the same features as the intervention group (they are the same); thus, similar to the RCT, individual-level confounding is minimised. The interrupted time series design can be impacted by rapidly changing time-varying confounders such as seasonality; however, centring our data around the initial visit mitigated this effect.⁴¹ There is striking temporality in that the effect of IDM on COPD-related HSU in this study is immediate and sustained. Finally, our findings are aligned with experimental evidence from RCTs.⁴² In this study, we specifically sought to identify participants in primary care at risk of future exacerbation; thus, our study population was enriched by high-risk exacerbation-prone patients. We acknowledge therefore that the reported outcomes may not be generalisable across the full spectrum of disease severity in an unselected primary care population.

To our knowledge, this is the first health system study to associate a primary care-based COPD IDM programme with reduced hospitalisation and ED visits in a real-world setting. Further studies with other populations and in other jurisdictions are required to confirm the broader applicability of these findings. Future studies to identify the impact of COPD IDM in different patient subgroups considering disease severity, socioeconomic status, geography and comorbidity are needed. The health system impact of primary care-based IDM on other chronic diseases also deserves investigation.

CONCLUSION

In this large community-based, COPD population study including over 13 000 person-years of follow-up, we identified substantial and sustained long-term reductions in acute health services use after implementing primary care-based COPD IDM. Primary care IDM is an effective solution with the potential to improve international health systems where low guideline concordance and high rates of acute HSU are common. Our findings highlight how IDM, which implements a multiplicity of guideline-based care components, can deliver proactive upstream health system-level impacts.

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REFERENCES

- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive lung disease. 2023. Available: <https://goldcopd.org/2023-gold-report-2/> [Accessed 20 Sep 2023].
- Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of chronic obstructive pulmonary disease: American College of Chest Physicians and Canadian Thoracic Society guideline. *Chest* 2015;147:894–942.
- Safiri S, Carson-Chahhoud K, Noori M, et al. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990–2019: results from the Global Burden of Disease Study 2019. *BMJ* 2022;378:e069679.
- Kirsch F, Schramm A, Schwarzkopf L, et al. Direct and indirect costs of COPD progression and its comorbidities in a structured disease management program: results from the LQ-DMP study. *Respir Res* 2019;20:215.
- Rehman AU, Hassali MAA, Muhammad SA, et al. The economic burden of chronic obstructive pulmonary disease (COPD) in Europe: results from a systematic review of the literature. *Eur J Health Econ* 2020;21:181–94.
- Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax* 2012;67:957–63.
- Sánta B, Tomisa G, Horváth A, et al. Severe exacerbations and mortality in COPD patients: a retrospective analysis of the database of the Hungarian national health insurance fund. *Pulmonology* 2023;29:284–91.
- Rothnie KJ, Müllerová H, Smeeth L, et al. Natural history of chronic obstructive pulmonary disease exacerbations in a general practice-based population with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2018;198:464–71.
- Mannino DM, Higuichi K, Yu T-C, et al. Economic burden of COPD in the presence of comorbidities. *Chest* 2015;148:138–50.
- Divo M, Cote C, de Torres JP, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012;186:155–61.
- Gershon AS, Guan J, Victor JC, et al. Quantifying health services use for chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013;187:596–601.
- Gershon A, Thiruchelvam D, Moineddin R, et al. Forecasting hospitalization and emergency department visit rates for chronic obstructive pulmonary disease. A time-series analysis. *Ann Am Thorac Soc* 2017;14:867–73.
- Poot CC, Meijer E, Kruijs AL, et al. Integrated disease management interventions for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2021;9:CD009437.
- Alison JA, McKeough ZJ, Johnston K, et al. Australian and New Zealand pulmonary rehabilitation guidelines. *Respirology* 2017;22:800–19.
- Spencer LM, McKeough ZJ. Maintaining the benefits following pulmonary rehabilitation: achievable or not? *Respirology* 2019;24:909–15.
- Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ* 2008;337:a1655.
- Ferrone M, Masciantonio MG, Malus N, et al. The impact of integrated disease management in high-risk COPD patients in primary care. *NPJ Prim Care Respir Med* 2019;29:8.
- Scarffe AD, Licskai C, Ferrone M, et al. Cost-effectiveness of integrated disease management for high risk, exacerbation prone, patients with chronic obstructive pulmonary disease in a primary care setting. *Cost Eff Resour Alloc* 2022;20:39.
- Adams EJ, van Doornewaard A, Ma Y, et al. Estimating the health and economic impact of improved management in prevalent chronic obstructive pulmonary disease populations in England, Germany, Canada, and Japan: a modelling study. *Int J Chron Obstruct Pulmon Dis* 2023;18:2127–46.
- Hussey AJ, Wing K, Ferrone M, et al. Integrated disease management for chronic obstructive pulmonary disease in primary care, from the controlled trial to clinical program: a cohort study. *Int J Chron Obstruct Pulmon Dis* 2021;16:3449–64.
- Sibbald SL, Misra V, daSilva M, et al. A framework to support the progressive implementation of integrated team-based care for the management of COPD: a collective case study. *BMC Health Serv Res* 2022;22:420.
- Paciocco S, Kothari A, Licskai C, et al. Evaluating the implementation of a chronic obstructive pulmonary disease management program using the consolidated framework for implementation research: a case study. *BMC Health Serv Res* 2021;21:717.
- Sibbald SL, Paciocco S, Huizhu Chen L, et al. A peer-to-peer approach to implementation of a chronic disease management program. *JRIPE* 2023;12.
- Ontario Health. Quality standards: chronic obstructive pulmonary disease, care in the community for adults (2023 update). n.d. Available: <https://www.hqontario.ca/Portals/0/documents/evidence/quality-standards/qs-chronic-obstructive-pulmonary-diseasequality-standard-2023-en.pdf>
- Hawton K, Bergen H, Simkin S, et al. Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses. *BMJ* 2013;346:f403.
- Ansari F, Gray K, Nathwani D, et al. Outcomes of an intervention to improve hospital antibiotic prescribing: interrupted time series with segmented regression analysis. *J Antimicrob Chemother* 2003;52:842–8.
- Sibbald SL, Law B, Van Asseldonk R, et al. Using visual methods to capture patient perspectives in interprofessional team-based care for chronic disease management. *JRIPE* 2022;12.
- Law B, Chhatwal PK, Licskai C, et al. Patient engagement in Interprofessional team-based chronic disease management: a qualitative description of a Canadian program. *Patient Educ Couns* 2023;114:107836.
- Hodson M, Roberts CM, Andrew S, et al. Development and first validation of a patient-reported experience measure in chronic obstructive pulmonary disease (PREM-C9). *Thorax* 2019;74:600–3.
- Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010;363:1128–38.
- Pavord ID, Jones PW, Burge P-R, et al. Exacerbations of COPD. *Int J Chron Obstruct Pulmon Dis* 2016;11 Spec Iss:21–30.
- Whittaker H, Rubino A, Müllerová H, et al. Frequency and severity of exacerbations of COPD associated with future risk of exacerbations and mortality: a UK routine health care data study. *Int J Chron Obstruct Pulmon Dis* 2022;17:427–37.
- Hurst JR, Han MK, Singh B, et al. Prognostic risk factors for moderate-to-severe exacerbations in patients with chronic obstructive pulmonary disease: a systematic literature review. *Respir Res* 2022;23:1–23.
- Cho EE, McCreedy GC, Wong HH, et al. Which physicians are taking care of people with COPD? *Chest* 2019;155:771–7.
- Çolak Y, Nordestgaard BG, Lange P, et al. Prognosis of patients with chronic obstructive pulmonary disease not eligible for major clinical trials. *Am J Respir Crit Care Med* 2022;206:271–80.
- Gershon AS, McCreedy GC, Guan J, et al. Quantifying Comorbidity in individuals with COPD: a population study. *Eur Respir J* 2015;45:51–9.
- Chen W, Thomas J, Sadatsafavi M, et al. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med* 2015;3:631–9.
- Ellingsen J, Johansson G, Larsson K, et al. Impact of comorbidities and commonly used drugs on mortality in COPD – real-world data from a primary care setting. *Int J Chron Obstruct Pulmon Dis* 2020;15:235–45.
- Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med* 2018;378:1671–80.
- Rabe KF, Martinez FJ, Ferguson GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-severe COPD. *N Engl J Med* 2020;383:35–48.
- Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2017;46:348–55.
- HILL AB. The environment and disease: association or causation? *Proc R Soc Med* 1965;58:295–300.

ARTIGO ORIGINAL

Impacto da poluição do ar atmosférico na função pulmonar de crianças em idade escolar de nascimento prematuro

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RESUMO

Fundamentos O aumento da poluição do ar atmosférico exterior agrava a função pulmonar nas crianças. No entanto, estas associações foram menos estudadas em indivíduos de nascimento prematuro.

Objetivos Avaliámos as associações entre os poluentes do ar atmosférico e as medidas espirométricas em crianças de nascimento prematuro.

Métodos O estudo Respiratory Health Outcomes in Neonates recrutou crianças de nascimento prematuro com idades entre os 7 e os 12 anos que nasceram com ≤ 34 semanas de gestação. Associámos quatro poluentes do ar atmosférico (partículas com diâmetro aerodinâmico $\leq 2,5 \mu\text{m}$ ($\text{PM}_{2,5}$), PM_{10} , dióxido de azoto (NO_2) e dióxido de enxofre) no momento do nascimento e da avaliação espirométrica e a exposição média entre estes dois intervalos de tempo com medidas espirométricas, utilizando análises de regressão linear. A idade gestacional foi dividida em 23-28, 29-31 e 32-34 semanas. Os modelos de regressão estimaram os valores espirométricos em relação aos níveis de poluentes no nascimento e no momento da realização da espirometria.

Medições e principais resultados Das 565 crianças de nascimento prematuro, 542 (96%) apresentaram dados satisfatórios. Após ajustar para fatores de vida precoces e atuais, foram observadas associações nocivas significativas entre PM_{10} no nascimento e percentagem de capacidade vital forçada prevista (%FVC) para os grupos de gestação de 23-28 e 29-31 semanas e entre a exposição atual a $\text{PM}_{2,5}$ e NO_2 e %FVC para o grupo de gestação de 23-28 semanas. Não foram registadas associações com a espirometria para a média da exposição à poluição entre o nascimento e a espirometria. Os modelos preditivos mostraram diferenças de 5,9% e 7,4% na %FVC entre as exposições atuais mais elevadas e mais baixas à poluição para $\text{PM}_{2,5}$ e NO_2 , respetivamente, no grupo das 23-28 semanas.

Conclusões A exposição ao nascimento e a exposição atual a poluentes associados ao tráfego rodoviário afetaram negativamente a %FVC em crianças em idade escolar de nascimento prematuro, que já possuem uma função pulmonar comprometida.

INTRODUCTION

It is well established that both antenatal and postnatal exposures to increased levels of air pollution have significant associations with childhood morbidity and mortality: our previous UK-based study demonstrated that sulfur dioxide (SO_2), nitrogen dioxide (NO_2) and particulate matter with aerodynamic diameter $\leq 10 \mu\text{m}$ (PM_{10}) were differentially associated with all-cause neonatal and postneonatal mortality.¹ Increased postnatal PM_{10} exposure has also been linked to higher risk of death from respiratory causes in children and adolescents.² Aside from mortality, increased air pollution has also been linked to poorer respiratory health and lung function in childhood, although the relationships are not always clear. Antenatal exposure to PM_{10} ,

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Ambient air pollution from industry and road traffic sources has been linked to poorer respiratory health and reduced lung function. However, the impact on preterm born individuals, a significant proportion of who already have compromised lungs, has yet to be studied.

WHAT THIS STUDY ADDS

- We have studied the effect of ambient air pollution at the time of birth and in childhood on spirometry measures in one of the largest contemporary preterm-born cohorts, finding links between elevated PM_{10} , $\text{PM}_{2,5}$ and nitrogen dioxide exposure and reduced per cent predicted forced vital capacity but not on other spirometry measures.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Despite pollution levels being within recommended limits, this study highlights the need for further efforts to reduce ambient air pollution, as it has a significant impact on the respiratory function of the most preterm born individuals in later life.

especially that generated by road traffic, has been linked to decreased forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) in 8-year-old offspring in the UK-based Avon Longitudinal Study of Parents and Children (ALSPAC) cohort.³ Postnatal exposure to NO_2 , PM_{10} and $\text{PM}_{2,5}$ (PM with an aerodynamic diameter $\leq 2.5 \mu\text{m}$) has also been differentially linked to significantly reduced FEV_1 and FVC in childhood in several studies,⁴⁻⁷ with improvements in air quality over time associated with longitudinal increases in lung function.⁸ However, other studies have not demonstrated significant links between current air pollution and childhood lung function.^{9,10} Increased air pollution has been shown to be associated with worse lung function in individuals with underlying respiratory diseases. In children with asthma, exposure to SO_2 has been associated with reduced FEV_1 and FVC; and PM_{10} with reduced FEV_1/FVC ratio and peak expiratory flow.¹¹ In the large multicohort Evalu-



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ation Study of Congestive Heart Failure and Pulmonary Artery Catheterisation Effectiveness (ESCAPE) Study, long-term exposure to higher levels of NO_2 and PM_{10} was associated with significant decreases in FEV_1 and FVC in adults¹² with a trend towards development of adult-onset asthma.¹³

Maternal exposure to high levels of outdoor air pollution appears to be a risk factor for preterm birth, especially at extremely preterm gestations.¹⁴ We and others have consistently shown that preterm birth, both with and without a diagnosis of bronchopulmonary dysplasia in infancy (BPD, also called chronic lung disease of prematurity), is associated with decreased lung function in childhood and beyond.^{15–17} Second trimester PM_{10} exposure has been shown to impact lung function at 44 week's postconceptional age in preterm-born infants, especially in those born at 32–36 week's gestation.¹⁸ For preterm-born infants with established BPD, living closer to major roadways following discharge home, and therefore, higher exposure to traffic-related air pollution, has been associated with increased respiratory morbidity.¹⁹ However, the impact of perinatal and childhood exposure to air pollution on the lung function of preterm-born school-aged children has been less well studied. We hypothesised that children born preterm, who were born at an immature stage of lung development with subsequent altered postnatal lung development,²⁰ were at risk of decreased lung function when exposed to common ambient outdoor pollutants. We examined the relationships between SO_2 , NO_2 , $\text{PM}_{2.5}$ and PM_{10} (a) at the time of birth, (b) current exposure at assessment and (c) averaged pollution exposure between birth and spirometry assessment with spirometry measures in children aged 7–12 years who were born at ≤ 34 week's gestation.

METHODS

This study was conducted on the cohort of preterm-born children recruited to the Respiratory Health Outcomes in Neonates study (RHINO; EudraCT: 2015-003712-20), which has been previously described.^{16, 21} Briefly, children recruited as part of a previous questionnaire study²² were supplemented with additional preterm-born children, sourced from the National Health Service Wales Informatics Service, and sent a respiratory and neurodevelopmental questionnaire, if they were born ≤ 34 week's gestation and aged 7–12 years old. Children were recruited from South Wales between 2016 and 2019. Children with significant congenital malformations, cardiopulmonary or neuromuscular disease were excluded.

Responders were invited to take part in a home or hospital-based assessment by two trained research nurses. Neonatal history and current health status were ascertained from questionnaire responses and corroborated with medical records. BPD was defined as supplemental oxygen-dependency for 28 days of age or greater for those born < 32 week's gestation and at 56 days of age for those ≥ 32 week's gestation.²³ Intrauterine growth restriction (IUGR) was defined as a birth weight < 10 th centile adjusted for gestational age and sex (LMS Growth v2.77, Medical Research Council, UK²⁴). To evaluate contribution of non-respiratory neonatal illness, a severity score of zero or one, respectively, was created if none or one or more of the following diagnoses were present in the neonatal period: necrotising enterocolitis, intraventricular haemorrhage, retinopathy of prematurity and/or patent ductus arteriosus. Spirometry (Microloop, Care-Fusion, UK) was performed to American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines²⁵ and normalised using Global Lung Initiative references to give per cent predicted lung function measures.²⁶ Spirometry was performed at the time of recruitment. Averaged annual estimated measurements of four common air pollutants, $\text{PM}_{2.5}$, PM_{10} , NO_2 and SO_2 , were obtained from the UK Government's Department for Environment, Food and Rural Affairs (DEFRA) as previously reported,¹ for the respective calendar year in which the child was born and for when spirometry was performed. The UK Government collected this data as part of the European Union's Air Quality Directive from a network of monitoring stations throughout the UK, and verified by modelling to create pollutant levels for 1 km-by-1 km areas for each calendar year.²⁷ To assess socioeconomic

status, we used the most contemporaneous geographical assessed Welsh Index of Multiple Deprivation (WIMD) scores for 2014.²⁸ The scores are calculated from composite measures of eight domains of deprivation including wealth, school achievement and home ownership. WIMD scores are given for 1909 geographical areas of similar population size (termed lower layer super output areas (LSOA), containing an average of approximately 1500 residents or 650 households). The LSOAs were supplied with x-coordinates and y-coordinates, on the same scale as the DEFRA 1 km-by-1 km grid, for its centre of mass—based on population distribution within the LSOA. The pollutant level for each combination of LSOA and time point was allocated by determining the closest, that is, minimum Euclidean distance, of the DEFRA grid points to each LSOA's centre of mass to give pollutant exposure and WIMD scores for each participant at year of birth and at the time of spirometry.

Demographic variables were compared between groups using analysis of variance or χ^2 pairwise comparisons as appropriate, both with Benjamini-Hochberg post hoc correction. The differential associations of each pollutant at time of birth, age at spirometry and averaged pollutant exposure scored between birth and current age with per cent predicted lung function measures (including % FEV_1 , %FVC, FEV_1/FVC ratio and % $\text{FEF}_{25\%-75\%}$ (forced expiratory flow at 25%–75% of FVC)) were tested through univariable and multivariable linear regression models. Participants were grouped into three gestational age bands: 23–28, 29–31 and 32–34 weeks of gestation for analysis. The coefficients to be estimated were the estimands of main scientific interest, so gestation and pollution were included as an interaction term, whereby the beta values generated allowed direct comparison between the impact of pollution on lung function at the three gestation bands. Significant variables identified by univariable linear regression were visualised graphically in a directed acyclic graph. In the multivariable linear regression model, the continuous pollution-level variables and the categorical preterm group variable were included as interaction terms and in such a way as to cause the prematurity group variable to be treated like a dummy variable, consequently producing different pollution level coefficients for each prematurity group without requiring a reference category. This model was designed to include univariable linear regression results with $p < 0.1$ for any spirometry variable, or early life factor including sex, BPD, IUGR and maternal age at birth (banded into six 5-year groups) and assessed the effect of gestational age in bands as an interaction term with pollutant level.

To explore the relationship between how different levels of ambient air pollution exposure at birth and at the current time of assessment would affect lung function values, an additional regression model was created, based on the univariable and multivariable linear regression results, to give estimated spirometry values at minimum and maximum pollutant exposures within this cohort. Those variables with $p < 0.1$ for the univariable relationship with any of the lung function measures were combined into a multivariable linear model, including neonatal history of BPD, combined illness, IUGR and maternal age. Gestational band and raw pollutant level were included in a single interaction term to provide a simply interpretable beta coefficient for the effect of the pollutant at each gestation band. These models were used to calculate the predicted influence of the pollutant, at birth and at time of spirometry, over the full range of its measured values at these times on the lung function measures of % FEV_1 , %FVC, FEV_1/FVC ratio and % $\text{FEF}_{25\%-75\%}$ for each of the three gestational age bands. This included predicted spirometry values at minimum, mean and maximum pollutant exposure. All analyses were performed in SPSS V.25 (IBM) and R V.1.1.419.

RESULTS

From 565 preterm-born children taking part in the RHINO study, 544 (96.3%) had valid spirometry data available as previously described.¹⁶ Two additional children were excluded, one for incorrect birth weight and one for incomplete address data. Since pollution

Table 1 Participant demographics

Variable	Gestation group (weeks)			Total (n=542)
	23–28 (n=99)	29–31 (n=165)	32–34 (n=278)	
Sex (male), n (%)	49 (49.5)	93 (56.4)	137 (49.3)	279 (51.5)
Birth weight (kg), mean (SD)	0.94 (0.24)	1.52 (0.39)	2.07 (0.44)***	1.70 (0.58)
IUGR, n (%)	10 (10.1)	21 (12.7)	27 (9.4)	58 (10.7)
Maternal age (age in years banded), n (%)				
≤19	9 (9.1)	7 (4.2)	4 (1.4)	20 (3.9)
20–24	18 (18.2)	23 (13.9)	25 (9.0)	66 (12.2)
25–29	22 (22.2)	37 (22.4)	72 (25.9)	131 (24.2)
30–34	24 (24.2)	49 (29.7)	90 (32.4)	163 (30.1)
35–39	19 (19.2)	37 (22.4)	73 (26.3)	129 (23.8)
≥40	7 (7.1)	12 (7.3)	14 (5.0)	33 (6.1)
BPD, n (%)	80 (80.8)***\$\$\$	27 (16.4)***~	1 (0.4)\$\$\$~	108 (19.9)
Combined neonatal illness, n (%)	54 (54.6)***\$\$\$	34 (20.6)***~	6 (2.2)\$\$\$~	94 (17.3)
Antenatal smoking, n (%)	14 (14.6)	17 (10.4)	31 (11.4)	62 (11.7)
Postnatal smoking, n (%)	17 (17.3)	30 (18.3)~	27 (9.8)~	74 (13.8)
Wheeze ever, n (%)	62 (65.3)\$\$	93 (57.4)	124 (47.0)\$\$	279 (53.6)
Wheeze in last 12 months, (%)	24 (24.2)	51 (30.9)	76 (27.3)	151 (27.9)
WIMD 2014 rank, mean (SD)	1122 (587)	1047 (558)	1046 (572)	1060 (570)
WIMD 2019 rank, mean (SD)	1124 (579)	1038 (556)	1059 (573)	1065 (569)
Age at spirometry (years), mean (SD)	10.2 (1.5)	10.1 (1.3)	10.2 (1.34)	10.1 (1.35)
%FEV ₁ , mean (SD)	86.1 (12.2)*\$\$\$	89.9 (12.3)*~	93.6 (12.3)\$\$\$~	91.1 (12.6)
%FVC, mean (SD)	91.5 (10.6)\$\$	93.4 (10.1)	95.8 (12.2)\$\$	94.3 (11.4)
FEV ₁ /FVC, mean (SD)	0.83 (0.08)\$\$	0.84 (0.08)	0.86 (0.07)\$\$	0.85 (0.08)
%FEF _{25%–75%} , mean (SD)	69.1 (20.2)\$\$\$	74.9 (21.6)~	80.8 (19.2)\$\$\$~	76.9 (20.6)
Birth PM _{2.5} (µg/m ³), mean (SD)	9.87 (1.3)	9.6 (1.25)	9.74 (1.15)	9.72 (1.21)
Birth PM ₁₀ (µg/m ³), mean (SD)	15.54 (2.11)	15.13 (1.93)	15.37 (1.94)	15.33 (1.97)
Birth NO ₂ (µg/m ³), mean (SD)	15.95 (5.44)	15.1 (6.02)	15.67 (5.8)	15.55 (5.8)
Birth SO ₂ (µg/m ³), mean (SD)	3.08 (2.02)	2.8 (1.66)	3.05 (1.54)	2.98 (1.68)
Current PM _{2.5} (µg/m ³), mean (SD)	8.03 (0.96)	7.89 (1.04)	8.04 (0.95)	7.99 (0.98)
Current PM ₁₀ (µg/m ³), mean (SD)	12.49 (1.28)	12.39 (1.42)	12.57 (1.35)	12.5 (1.36)
Current NO ₂ (µg/m ³), mean (SD)	13.27 (4.59)	12.85 (5.34)	13.67 (5.04)	13.35 (5.06)
Current SO ₂ (µg/m ³), mean (SD)	1.98 (0.57)	2.06 (0.77)	2.1 (0.8)	(0.75)

Combined neonatal illness: at least one of Necrotising enterocolitis (NEC), Intraventricular haemorrhage (IVH), Retinopathy of prematurity (ROP), Patent ductus arteriosus (PDA).
 23–28 vs 29–31: *p<0.05, **p<0.01, ***p<0.001; 23–28 vs 32–34: \$p<0.05, \$\$p<0.01, \$\$\$p<0.001; 29–31 vs 32–34: ~p<0.05, ~~p<0.01, ~~~p<0.001 by ANOVA/χ² with post hoc Benjamini-Hochberg for multiple pairwise comparisons.
 ANOVA, analysis of variance; BPD, bronchopulmonary dysplasia; %FEF_{25%–75%}, forced expiratory flow at 25%–75% of forced vital capacity; %FEV₁, per cent predicted forced expiratory volume in 1 s; %FVC, per cent predicted forced vital capacity; IUGR, intrauterine growth restriction; NO₂, nitrogen dioxide; PM₁₀, particulate matter with aerodynamic diameter ≤10 µm; PM_{2.5}, particulate matter with aerodynamic diameter ≤2.5 µm; SO₂, sulfur dioxide; WIMD, Welsh Index of Multiple Deprivation.

data at time of birth was not available for six individuals due to changes in geographical boundaries, they were excluded from the 'pollution exposure at the time of birth' analyses only. The demographics for the included 542 children are shown in table 1. As expected, there was a significant difference between gestation groups for birth weight and rates of BPD, combined neonatal illness and wheeze-ever, with the most preterm-born group being affected the most. All lung function measures were significantly reduced in the

most preterm-born group compared with the least preterm-born. Measures of deprivation and pollutant levels were not significantly different between the groups at birth or at time of spirometry (online supplemental tables 1 and 2, respectively). Table 2 shows the range of air pollutant levels within the study compared with contemporary recommended limits.

Results of univariable regression analyses are shown in table 3. Significant negative associations were noted between spiro-

Table 2 Ambient air pollution levels in study and recommended annual exposure limits

	PM _{2.5}	PM ₁₀	SO ₂	NO ₂
Birth, mean (range), (µg/m ³)	9.72 (6.90–13.31)	15.33 (10.10–20.56)	2.98 (0.81–15.89)	15.55 (4.48–34.93)
Current, mean (range), (µg/m ³)	8.00 (5.58–10.58)	12.50 (8.83–16.31)	2.07 (0.55–8.82)	13.41 (3.80–29.24)
European Union limit value 2008, (µg/m ³)	25	40	20*	40
WHO guideline value 2005, (µg/m ³)	10	20	20†	40

*European Union directive gives an annual exposure limit for protection of vegetation, no annual exposure level recommended for protection of human health.
 †WHO average 24-hour limit.
 NO₂, nitrogen dioxide; PM₁₀, particulate matter with aerodynamic diameter ≤10 µm; PM_{2.5}, particulate matter with an aerodynamic diameter ≤2.5 µm; SO₂, sulfur dioxide.

Table 3 Univariable linear regression analyses of spirometry measures

Variable	%FEV ₁		%FVC		FEV ₁ /FVC ratio		%FEF _{25%-75%}	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
Sex (ref=female)	1.129 (−0.996 to 3.253)	0.296	1.127 (−0.794 to 3.048)	0.248	0.024 (0.011 to 0.037)	<0.001	−1.241 (−4.723 to 2.241)	0.483
IUGR (ref=no)	−4.842 (−8.256 to 1.428)	0.005	−2.767 (−5.867 to 0.334)	0.079	−0.016 (−0.037 to 0.005)	0.136	−8.741 (−14.325 to 3.157)	0.002
Gestational age group (weeks)								
23–28	−7.461 (−10.285 to 4.637)	<0.001	−4.253 (−6.847 to 1.66)	0.001	−0.032 (−0.049 to 0.014)	<0.001	−11.791 (−16.424 to 7.158)	<0.001
29–31	−3.645 (−6.016 to 1.274)	0.002	−2.324 (−4.502 to 0.146)	0.036	−0.017 (−0.032 to 0.003)	0.019	−5.957 (−9.847 to 2.067)	0.003
32–34 (ref)	ref		ref		ref		ref	
Mother age band (years)								
≤19	−9.751 (−15.553 to 3.949)	0.001	−4.071 (−9.36 to 1.217)	0.128	−0.053 (−0.089 to 0.017)	0.003	−16.291 (−25.822 to 6.761)	0.001
20–24	−4.316 (−7.889 to 0.743)	0.017	−3.446 (−6.702 to 0.189)	0.037	−0.007 (−0.029 to 0.015)	0.548	−3.776 (−9.645 to 2.092)	0.204
25–29	−1.972 (−4.846 to 0.901)	0.175	−0.873 (−3.492 to 1.747)	0.51	−0.007 (−0.025 to 0.01)	0.403	−2.7 (−7.42 to 2.02)	0.259
30–34 (ref)	ref		ref		ref		ref	
35–39	−2.386 (−5.272 to 0.5)	0.102	−1.211 (−3.842 to 1.419)	0.363	−0.005 (−0.022 to 0.013)	0.602	−4.039 (−8.78 to 0.701)	0.092
≥40	−4.452 (−9.127 to 0.222)	0.060	−3.097 (−7.358 to 1.164)	0.151	−0.014 (−0.042 to 0.015)	0.342	−3.973 (−11.652 to 3.705)	0.307
BPD (ref=no)	−6.08 (−8.691 to 3.469)	<0.001	−2.873 (−5.267 to 0.479)	0.018	−0.031 (−0.047 to 0.015)	<0.001	−10.227 (−14.5 to 5.955)	<0.001
Combined neonatal illness (ref=no)	−6.963 (−9.715 to 4.21)	<0.001	−3.861 (−6.385 to 1.338)	0.003	−0.031 (−0.048 to 0.014)	<0.001	−11.166 (−15.694 to 6.638)	<0.001
Antenatal smoking (ref=no)	−0.364 (−3.718 to 2.991)	0.831	−0.583 (−3.61 to 2.443)	0.704	0 (−0.021 to 0.02)	0.983	−0.01 (−5.505 to 5.485)	0.997
Postnatal smoking (ref=no)	−0.886 (−3.986 to 2.213)	0.574	−0.139 (−2.943 to 2.665)	0.922	−0.008 (−0.027 to 0.011)	0.402	−2.714 (−7.788 to 2.36)	0.292
NO ₂ (birth)	0.012 (−0.172 to 0.197)	0.896	−0.063 (−0.23 to 0.104)	0.455	0.001 (0 to 0.002)	0.184	0.094 (−0.205 to 0.393)	0.535
SO ₂ (birth)	0.095 (−0.544 to 0.734)	0.771	0.101 (−0.477 to 0.679)	0.731	0 (−0.004 to 0.004)	0.973	−0.015 (−1.049 to 1.02)	0.978
PM _{2.5} (birth)	−0.177 (−1.06 to 0.707)	0.694	−0.446 (−1.244 to 0.352)	0.272	0.003 (−0.003 to 0.008)	0.345	0.137 (−1.293 to 1.567)	0.85
PM ₁₀ (birth)	−0.267 (−0.81 to 0.276)	0.333	−0.522 (−1.011 to 0.032)	0.036	0.001 (−0.002 to 0.004)	0.579	0.192 (−0.687 to 1.071)	0.667
NO ₂ (current)	−0.064 (−0.275 to 0.146)	0.548	−0.17 (−0.36 to 0.019)	0.078	0.001 (0 to 0.002)	0.14	0.088 (−0.256 to 0.433)	0.615
SO ₂ (current)	0.064 (−1.349 to 1.476)	0.93	−0.486 (−1.763 to 0.79)	0.455	0.006 (−0.003 to 0.014)	0.206	1.092 (−1.221 to 3.404)	0.354
PM _{2.5} (current)	−0.454 (−1.539 to 0.631)	0.412	−0.907 (−1.886 to 0.072)	0.069	0.004 (−0.003 to 0.01)	0.257	0.331 (−1.448 to 2.11)	0.715
PM ₁₀ (current)	−0.098 (−0.882 to 0.685)	0.805	−0.508 (−1.216 to 0.199)	0.159	0.004 (−0.001 to 0.009)	0.108	0.516 (−0.767 to 1.798)	0.43
WIMD (birth)								
1 (most deprived)	1.157 (−2.12 to 4.434)	0.486	0.901 (−2.062 to 3.865)	0.548	0.003 (−0.017 to 0.023)	0.771	2.186 (−3.106 to 7.478)	0.415
2	0.865 (−2.256 to 3.985)	0.584	1.292 (−1.53 to 4.114)	0.366	−0.004 (−0.023 to 0.015)	0.689	0.959 (−4.08 to 5.998)	0.707
3	0.59 (−2.608 to 3.788)	0.716	1.768 (−1.124 to 4.659)	0.228	−0.012 (−0.032 to 0.007)	0.213	−0.796 (−5.96 to 4.368)	0.761
4	−0.718 (−4.139 to 2.702)	0.679	0.828 (−2.266 to 3.921)	0.597	−0.017 (−0.038 to 0.003)	0.098	−3.268 (−8.792 to 2.255)	0.243
5 (least deprived) (ref)	Ref		Ref		Ref		Ref	
WIMD (current)								
1 (most deprived)	0.483 (−2.817 to 3.783)	0.774	−0.791 (−3.774 to 2.192)	0.603	0.014 (−0.006 to 0.034)	0.172	3.306 (−2.088 to 8.699)	0.229

Continued

metry variables and demographic variables including gestational age band (%FEV₁, %FVC, FEV₁/FVC ratio and %FEF_{25%–75%}), BPD (%FEV₁, %FVC, FEV₁/FVC ratio and %FEF_{25%–75%}), combined neonatal illness (%FEV₁, %FVC, FEV₁/FVC ratio and %FEF_{25%–75%}), younger maternal age at birth (%FEV₁, %FVC, FEV₁/FVC ratio and %FEF_{25%–75%}) and history of IUGR (%FEV₁, %FEF_{25%–75%}). These are represented graphically in a directed acyclic graph in online supplemental figure 1. No associations were noted between lung function measures and antenatal/postnatal smoking or deprivation. A significant association was observed between PM₁₀ level at birth and %FVC ($\beta = -0.52$, $p = 0.036$).

Figure 1 and online supplemental table 3 show the results of the multivariable regressions. Significant negative associations were noted between %FVC for those born at 23–28 ($\beta = -0.66$, $p = 0.016$) and at 29–31 week's gestation (-0.58 , $p = 0.027$) and PM₁₀ exposure at birth. The %FVC results for those born at 32–34 week's gestation had β of -0.49 and p value of 0.058 for PM₁₀ exposure at birth. Current exposure to PM_{2.5} and NO₂ had a negative association for %FVC in the 23–28 week's gestation group (-1.19 , $p = 0.031$; -0.29 , $p = 0.05$, respectively). The associations for the 29–31 week's gestation group and PM_{2.5} and NO₂ were β of -0.92 and p value of 0.070 and β of -0.19 and p value of $p = 0.083$, respectively). No significant associations were noted between the pollutants and %FEV₁ or %FEF_{25%–75%}. The level of ambient air pollution decreased between the two time points measured. We did not observe any significant associations between the calculated mean pollutant exposure between these two time points (birth and current exposure levels) for PM_{2.5}, PM₁₀, NO₂ or SO₂ and any spirometry measure (online supplemental table 4).

As described in the methods, additional regression models were created based on the univariable and multivariable linear regression results for estimating spirometry values over the total range of pollutant exposures within this cohort. The results from these models for birth and current pollution exposure and %FVC are shown in table 4 and figures 2 and 3; and in online supplemental file 1 for %FEV₁, FEV₁/FVC ratio and %FEF_{25%–75%} (online supplemental tables 5–7 and figures 2–4, respectively). Online supplemental table 8 gives the decile measurement for each pollutant. PM₁₀ exposure at birth was associated with significant decrease in %FVC for those born 23–28 week's and 29–31 week's gestation, with 6.95% ($p = 0.02$) and 6.1% ($p = 0.03$) reduction in %FVC, respectively, between lowest and highest PM₁₀ exposures. No other significant associations were noted for %FVC and pollutant levels at time of birth. No significant differences were seen for %FEV₁, FEV₁/FVC and %FEF_{25%–75%}. There was a difference for %FVC of 5.94% ($p = 0.03$) for current PM_{2.5} and 7.44% ($p = 0.05$) for current NO₂ exposure for preterm-born children born at 23–28 week's gestation when the lowest and highest exposures were compared. The predictive models did not demonstrate any significant differences between %FVC and SO₂ at time of spirometry for any gestational group. No significant differences were noted for current exposure levels and predicted differences in %FEV₁, FEV₁/FVC and %FEF_{25%–75%} between the lowest and highest exposures.

DISCUSSION

In this study of preterm-born children, we have shown that current exposure to increasing levels of two major ambient air pollutants, PM_{2.5} and NO₂, was associated with significantly decreased %FVC in a graded manner with decreasing gestational age. We have also reported that increased PM₁₀ exposure at the time of birth was associated with reduced %FVC in the same gestationally graded manner as postnatal exposure. The averaged exposure between birth and spirometry assessment was not associated with any of the spirometry measures. However, we did not note any association between pollution levels at any time point with either %FEV₁ or %FEF_{25%–75%}. Furthermore, birth, current and averaged SO₂ exposures were not associated with any spirometry measures. We generated adjusted regression models which showed significant relationships between %FVC and PM₁₀ for exposures at birth; and between %FVC and PM_{2.5}/NO₂ for current pollution exposures. These effects occurred in a gestationally graded manner with the most prematurely born children affected the most.

Increased ambient outdoor air pollution has been strongly associated with increased respiratory morbidity and mortality in adult populations.²⁹ Our previous study suggested that both antenatal and postnatal exposure of the four pollutants studied here can affect both neonatal and postneonatal mortality possibly via antenatal maternal exposure and postnatal ex-

Table 3 Continued

Variable	%FEV ₁		%FVC		FEV ₁ /FVC ratio		%FEF _{25%–75%}	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
2	1.605 (–1.615 to 4.824)	0.328	2.153 (–0.757 to 5.063)	0.147	–0.004 (–0.023 to 0.016)	0.698	1.207 (–4.055 to 6.469)	0.653
3	–0.727 (–3.748 to 2.295)	0.637	–0.009 (–2.74 to 2.722)	0.995	–0.008 (–0.026 to 0.011)	0.423	–0.651 (–5.589 to 4.287)	0.796
4	1.903 (–1.41 to 5.215)	0.260	0.281 (–2.713 to 3.275)	0.854	0.011 (–0.01 to 0.031)	0.302	5.175 (–0.238 to 10.589)	0.061
5 (least deprived) (ref)	Ref		Ref		Ref		Ref	

Combined neonatal illness: History of any of the following neonatal diagnoses: necrotising enterocolitis, intraventricular haemorrhage, retinopathy of prematurity, patent ductus arteriosus. BPD, bronchopulmonary dysplasia; %FEF_{25%–75%}, forced expiratory flow at 25%–75% of forced vital capacity; %FEV₁, per cent predicted forced expiratory volume in 1 s; %FVC, per cent predicted forced vital capacity; IUGR, intrauterine growth restriction; NO₂, nitrogen dioxide; PM₁₀, particulate matter with aerodynamic diameter $\leq 10 \mu\text{m}$; PM_{2.5}, particulate matter with aerodynamic diameter $\leq 2.5 \mu\text{m}$; SO₂, sulfur dioxide; WMD, Welsh Index of Multiple Deprivation.

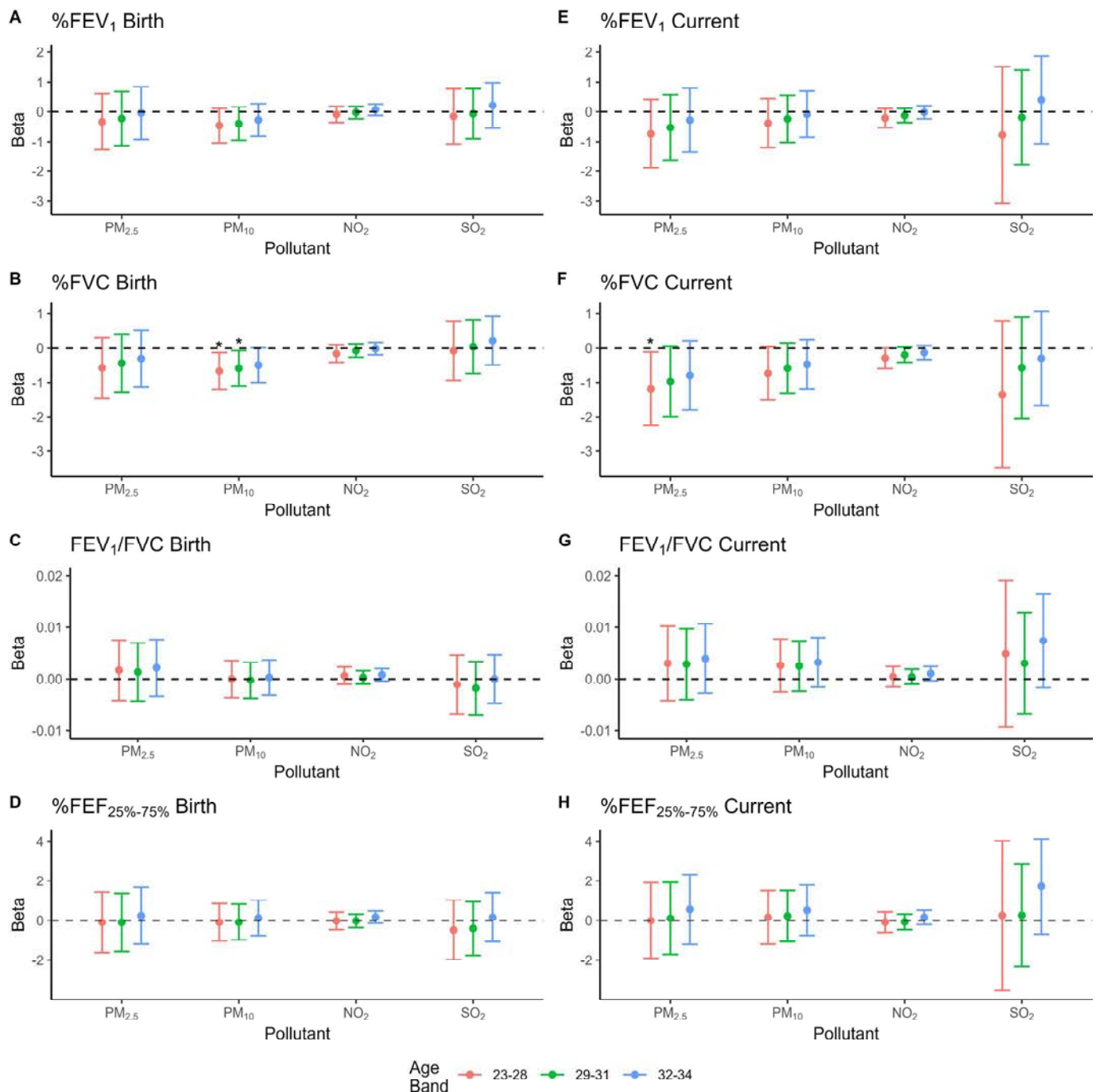


Figure 1 Plot of beta-values and 95% CIs from multivariable linear regression models of lung function parameters and pollutant exposures by each gestational age band (adjusted for sex, IUGR, BPD, combined neonatal illness and maternal age). Starred values represent betas with a $p < 0.05$. BPD, bronchopulmonary dysplasia; %FEV₁, per cent predicted forced expiratory volume in 1 s; %FVC, per cent predicted forced vital capacity; %FEF_{25-75%}, forced expiratory flow at 25%–75% of forced vital capacity; IUGR, intrauterine growth restriction; NO₂, nitrogen dioxide; PM_{2.5}, particulate matter with aerodynamic diameter $\leq 2.5 \mu\text{m}$; PM₁₀, particulate matter with aerodynamic diameter $\leq 10 \mu\text{m}$; SO₂, sulfur dioxide.

posure.¹ Preterm-born infants have previously been shown to be more susceptible to the detrimental effects of antenatal exposure than term-born infants, with increasing antenatal exposure to PM₁₀ associated with worse lung function and higher fractional exhaled nitric oxide at 44 weeks postmenstrual age.¹⁸ In addition, antenatal exposure to increased PM₁₀ has been demonstrated to have a detrimental impact on placental growth and function,³⁰ and on birth weight.^{31–32} Our current data have demonstrated that perinatal exposure to PM₁₀ could have lasting effects resulting in decreased %FVC in children who were born at <32 weeks gestation. These infants are likely to be at higher risk of airway epithelial injury which could potentially explain the detrimental effects we observed for pollutants on %FVC via the resultant injury on

the lung parenchyma. This association is in keeping with findings from the ALSPAC cohort³ which noted an association between antenatal PM₁₀ maternal exposure and reduced FVC in 8-year-old offspring who were, however, born at term. Unlike the ALSPAC study, we did not observe an association between pollutants and %FEV₁. The reasons for this are unclear. It is known that larger airways are compromised after preterm birth.¹⁷ Whether these airways are already so compromised in early infancy, especially in the lowest gestation group, such that additional epithelial injury from pollutant exposure has little further effect is very speculative and needs further study.

Several previous studies, largely of term-born children, have also reported that outdoor air pollution exposure has a negative impact

Table 4 Regression model for FVC values by gestational age band over minimum to maximum exposure to PM_{2.5}, PM₁₀, SO₂ and NO₂ at birth and current time points

Variable		For minimum	For mean	For maximum	Min–Max difference	Beta (95% CI)	P value
		Pollutant exposure	Pollutant exposure	Pollutant exposure	(% of mean)		
Birth PM _{2.5} (µg/m ³)		6.9	9.72	13.31	6.41 (65.94)		
%FVC by gestation (weeks)	23–28	93.11	91.49	89.44	3.68 (4.02)	–0.57 (–1.45 to 0.3)	0.2
	29–31	94.67	93.42	91.85	2.82 (3.02)	–0.44 (–1.28 to 0.4)	0.31
	32–34	96.62	95.75	94.64	1.98 (2.07)	–0.31 (–1.13 to 0.52)	0.46
Birth PM ₁₀ (µg/m ³)		10.1	15.33	20.56	10.46 (68.26)		
%FVC by gestation (weeks)	23–28	94.97	91.49	88.02	6.95 (7.6)	–0.66 (–1.2 to 0.13)	0.02
	29–31	96.47	93.42	90.37	6.1 (6.53)	–0.58 (–1.1 to 0.07)	0.03
	32–34	98.32	95.75	93.17	5.15 (5.37)	–0.49 (–1 to 0.02)	0.06
Birth SO ₂ (µg/m ³)		0.81	2.98	15.89	15.08 (505.82)		
%FVC by gestation (weeks)	23–28	91.66	91.49	90.51	1.15 (1.26)	–0.08 (–0.94 to 0.78)	0.86
	29–31	93.33	93.42	93.96	–0.62 (–0.67)	0.04 (–0.74 to 0.82)	0.92
	32–34	95.28	95.75	98.55	–3.27 (–3.42)	0.22 (–0.5 to 0.93)	0.55
Birth NO ₂ (µg/m ³)		4.48	15.55	34.93	30.45 (195.81)		
%FVC by gestation (weeks)	23–28	93.27	91.49	88.38	4.89 (5.35)	–0.16 (–0.42 to 0.09)	0.22
	29–31	94.23	93.42	92.01	2.23 (2.38)	–0.07 (–0.27 to 0.12)	0.46
	32–34	95.9	95.75	95.48	0.42 (0.44)	–0.01 (–0.19 to 0.17)	0.88
Current PM _{2.5} (µg/m ³)		5.58	7.99	10.58	5.01 (62.66)		
%FVC by gestation (weeks)	23–28	94.36	91.49	88.42	5.94 (6.49)	–1.19 (–2.26 to 0.11)	0.03
	29–31	95.76	93.42	90.92	4.84 (5.18)	–0.97 (–1.99 to 0.06)	0.06
	32–34	97.66	95.75	93.7	3.96 (4.13)	–0.79 (–1.79 to 0.21)	0.12
Current PM ₁₀ (µg/m ³)		8.83	12.5	16.31	7.48 (59.84)		
%FVC by gestation (weeks)	23–28	94.18	91.49	88.71	5.47 (5.98)	–0.73 (–1.5 to 0.04)	0.06
	29–31	95.56	93.42	91.21	4.35 (4.66)	–0.58 (–1.31 to 0.15)	0.12
	32–34	97.48	95.75	93.96	3.52 (3.68)	–0.47 (–1.19 to 0.25)	0.2
Current SO ₂ (µg/m ³)		0.55	2.07	8.82	8.27 (400.36)		
%FVC by gestation (weeks)	23–28	93.55	91.49	82.37	11.18 (12.22)	–1.35 (–3.49 to 0.79)	0.22
	29–31	94.29	93.42	89.58	4.7 (5.03)	–0.57 (–2.04 to 0.9)	0.45
	32–34	96.2	95.75	93.73	2.47 (2.58)	–0.3 (–1.67 to 1.07)	0.67
Current NO ₂ (µg/m ³)		3.8	13.35	29.24	25.44 (190.6)		
%FVC by gestation (weeks)	23–28	94.29	91.49	86.85	7.44 (8.13)	–0.29 (–0.59 to 0)	0.05
	29–31	95.28	93.42	90.33	4.95 (5.3)	–0.19 (–0.42 to 0.03)	0.08
	32–34	97	95.75	93.67	3.33 (3.48)	–0.13 (–0.34 to 0.07)	0.21

Regression model for %FVC values over range of current pollutant exposures measured. Beta and significance level for relationship between difference in lung function and pollutant levels for each gestational age band.

%FVC, per cent predicted forced vital capacity; NO₂, nitrogen dioxide; PM₁₀, particulate matter with aerodynamic diameter ≤10 µm; PM_{2.5}, particulate matter with aerodynamic diameter ≤2.5 µm; SO₂, sulfur dioxide.

on lung function in paediatric and adult populations, but whether such exposure affects preterm-born children is less known. A Swedish study reported that high exposure to traffic-related air pollution (nitrogen oxides (NO_x) and PM₁₀) in the first year of life was associated with decreased FEV₁ and FVC³³ and, although NO_x and PM₁₀ in the same cohort were associated with reduced FEV₁ at 8 years of age, no association was noted between pollutant exposure and FVC.³⁴ A Norwegian study examined NO₂, PM_{2.5} and PM₁₀ exposure in the first 2 years of life and in children up to 9–10 years noting a strong association between increasing air pollution exposure and reduced forced expiratory flows (peak expiratory flow, FEF_{25%} and FEF_{50%}) but no associations were noted for FVC. Longer-term exposure to high air pollution had a stronger association with reduced expiratory flows.³⁵ Another California-based study examined the effects of air pollution on changes of lung function over an 8-year period in children aged 10–18. They noted that exposure to higher levels of NO₂ and acid vapour (a

mixture of inorganic and organic acids, primarily produced by motor engines) resulted in slower growth of FVC over the study period, on average being 95 mL and 105 mL, respectively, lower than those exposed to low air pollution. Significant reduction in the growth of FEV₁ was also associated with higher exposure to NO₂, acid vapour and PM_{2.5}, with a near-significant association with PM₁₀.³⁶ A recent Chinese study demonstrated that long-term exposure to PM_{2.5} had a negative impact on lung function in children aged 7–12 years, with a one unit increase in the average daily dose exposure to PM_{2.5} resulting in 14.8 mL decrease in FVC and a 10 mL reduction in FEV₁.³⁷ Why there are differences between cohorts for spirometry measures for the common pollutants is unclear especially as the pollutants' exposures were similar between the cohorts. We did not see a significant relationship between FEV₁ and pollution exposure in our cohort and the reason for this is unclear from our data. We can hypothesise that the degree of FEV₁ impairment occurring solely as a consequence of preterm birth,

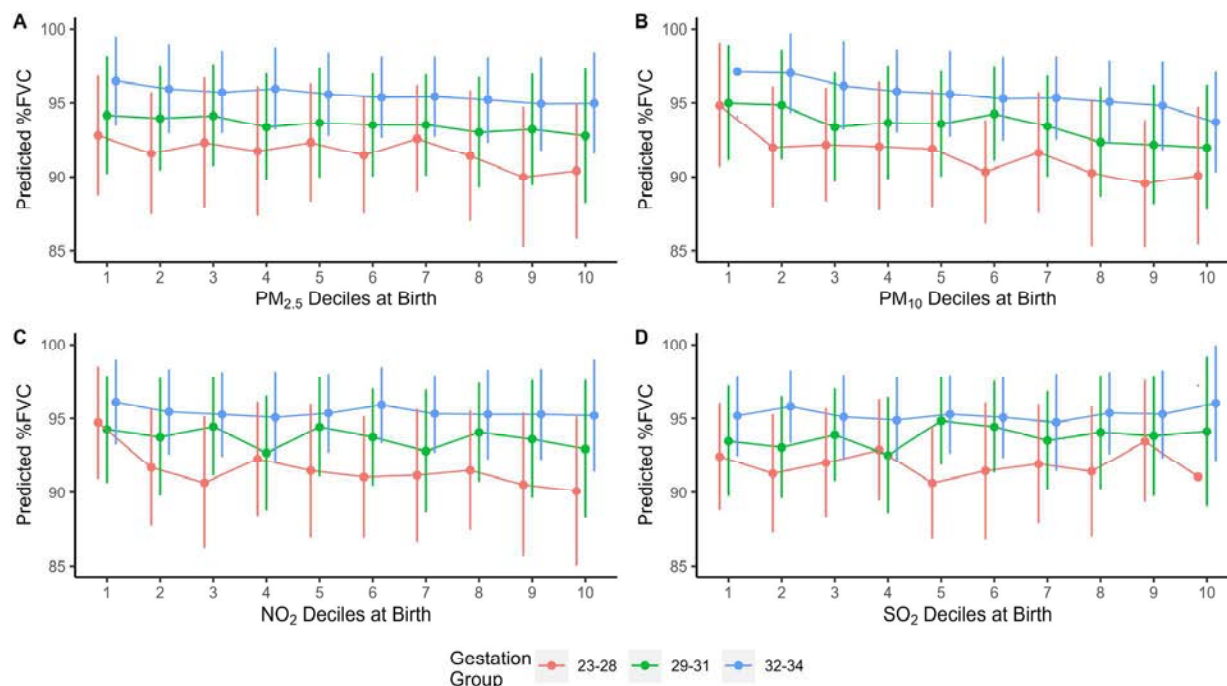


Figure 2 (A–D) Per cent predicted FVC values for each gestational age group from adjusted regression model by each pollutant decile at birth. Points represent mean value. Vertical bars represent 95% CI. FVC, forced vital capacity; NO₂, nitrogen dioxide; PM_{2.5}, particulate matter with aerodynamic diameter $\leq 2.5\mu\text{m}$; PM₁₀, particulate matter with aerodynamic diameter $\leq 10\mu\text{m}$; SO₂, sulfur dioxide.

which we have previously demonstrated,¹⁷ is so significant that the impact of ambient air pollution on FEV₁ in this population is masked. Additional studies, especially using personal exposure devices, are required to determine if FVC is commonly affected in all preterm-born cohorts.

Road traffic is the primary source of PM_{2.5}, PM₁₀ and NO₂ air pollution especially in urban areas, primarily from petrol-engine and diesel-engine exhaust fumes, and from vehicle tyre and brake wear. SO₂ is more associated with industrial activity and power station emissions.³⁸ We noted an improvement in air pollution levels between birth and time of spirometry, with the majority of pollution levels being below European Union legal limits and WHO guidelines.³⁸ However, even within these recommended limits, we have noted air pollution continues to have a detrimental associa-

tion with FVC. This highlights the paucity of evidence on what constitutes a 'safe' level of air pollution exposure. As many of the associations were seen between FVC and PM_{2.5}, PM₁₀ and NO₂, this highlights the importance of concerted efforts to reduce road traffic and fossil-fuel burning vehicle engines in urban areas to prevent further detrimental effects on preterm-born children's respiratory function. We did not see a significant association between deprivation and lung function in univariable modelling for our cohort, however, deprivation has been linked to higher air pollution exposure,³⁹ respiratory morbidity and decline in lung function^{40,41} in other studies.

Infants delivered at extremely preterm gestations (23–28 week's gestation) are born at an immature stage of lung development, at late canalicular and early sacular phases.⁴² Subsequent ex utero aber-

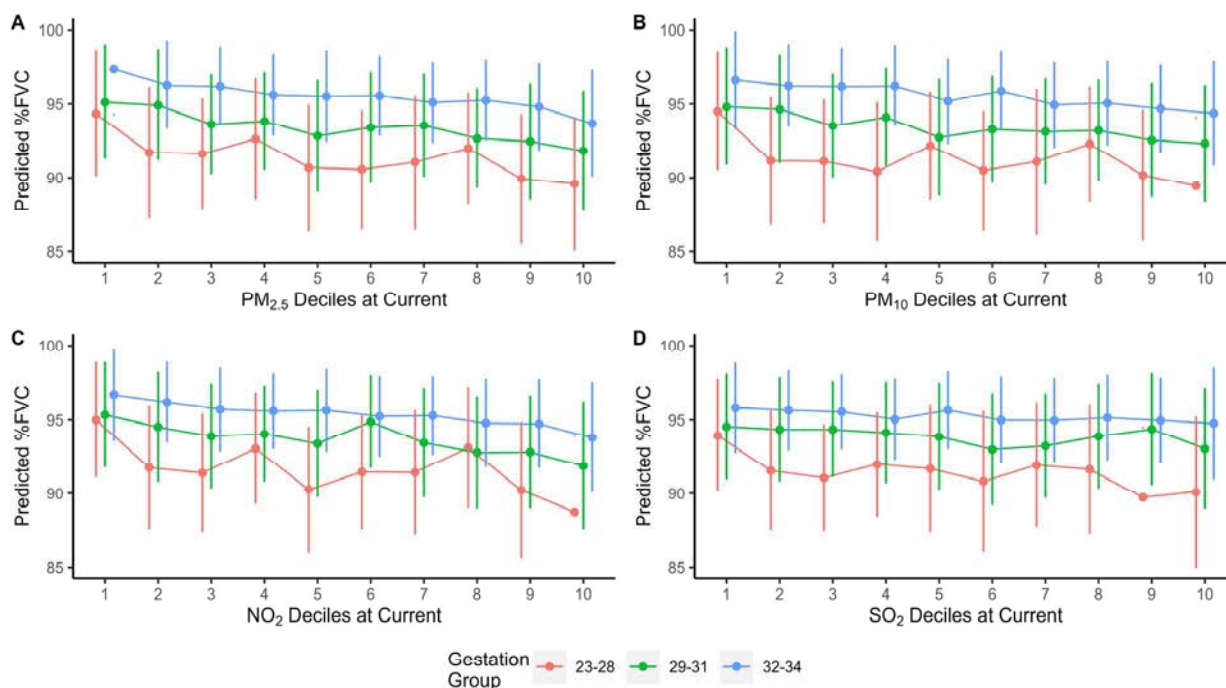


Figure 3 (A–D) Per cent predicted FVC values for each gestational age group from adjusted regression model by each pollutant decile at current exposure. Points represent mean value. Vertical bars represent 95% CI. FVC, forced vital capacity; NO₂, nitrogen dioxide; PM_{2.5}, particulate matter with aerodynamic diameter $\leq 2.5\mu\text{m}$; PM₁₀, particulate matter with aerodynamic diameter $\leq 10\mu\text{m}$; SO₂, sulfur dioxide.

rant lung development, partially due to postnatal interventions such as respiratory support and increased supplemental oxygen therapy, then results in structurally and functionally altered lungs for these infants in later life resulting in significant respiratory morbidity.¹⁷

²⁰ Our data showed that children born at extremes of gestational immaturity were most susceptible to the negative effects of several ambient outdoor air pollutants and may further impact lung growth as the primary effect we have observed was on FVC. Although the changes in lung function between lowest and highest pollution levels may seem small in childhood, these trajectories are likely to enhance with time given that lung function tracks over time⁴³ with consequent early development of chronic obstructive pulmonary disease as recently postulated.⁴⁴ Therefore, the negative effects on lung function of higher levels of ambient outdoor air pollution on this already vulnerable population cannot be ignored. Higher FVC, a proxy measure of lung size, has previously been shown to be positively associated with increased life expectancy in adults,⁴⁵ and therefore, this already vulnerable population may have increased early respiratory mortality if exposed to high levels of air pollution.

Strengths of this study include a large preterm-born cohort who represent a wide range of gestational ages at birth, with good representation of extremely preterm-born subjects, which permitted us to delineate the different associations of air pollution and lung function for individuals born at a range of different stages of lung development. We had comprehensive antenatal, neonatal and postnatal medical histories, which allowed us to model our results including important neonatal comorbidities such as BPD and IUGR. We used robustly modelled, publicly available pollution data, which allowed us to accurately ascertain individual participants exposures both at birth and at time of current assessment. Limitations include that we studied ambient outdoor air pollution but not indoor air pollution exposures, which may further adversely impact on lung function. Our measures of pollution exposures were based on small geographical area exposures and not on personal exposure thus may impact on our findings especially if localised exposures were either enhanced or reduced. Similarly, measures of deprivation, such as WIMD, are proxy measures of socioeconomic status based on geographical location. Even in small areas exposure may differ between close neighbourhoods, for instance, due to proximity to major roads or highways. Smoking status was self-reported by parents and may have been under-reported, explaining the lack of association seen in our study with spirometry values. Our prediction model has provided useful hypothesis generating results but requires validation in another similarly sized cohort which is difficult to source.

In conclusion, our study has demonstrated that exposure to traffic-related air pollutants, both perinatally and postnatally, have detrimental association with %FVC especially for those children born extremely preterm (<28 week's gestation). In our adjusted regression models based on current pollution exposure, we have shown that there may be up to 5.9% and 7.4% differences in %FVC between highest and lowest current pollution exposures for PM_{2.5} and NO₂, respectively. These data highlight the importance of air quality strategies to reduce any further detrimental impact on lung growth and function in this group of individuals with likely aberrant lung development, and who are already at heightened risk of long-term respiratory morbidity.¹⁷

Correction notice Since this paper first published, affiliations have been updated.

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Contributors SK conceived and designed the study. MC and KH were responsible for recruiting the children and for data collection. WJW, SJK, CWC and SK were involved in the data analysis and interpretation. CWC, WJW and SK drafted the manuscript. All authors were involved in revising the manuscript and approved the final submitted version. SK accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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collaborators subject to confidentiality and non-disclosure agreements. Contact Professor SK (kotch@cardiff.ac.uk) for any data requests.

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REFERENCES

- Kotecha SJ, Watkins WJ, Lowe J, et al. Differential association of air pollution exposure with neonatal and postneonatal mortality in England and Wales: a cohort study. *PLoS Med* 2020;17:e1003400.
- Gouveia N, Junger WL, Romieu I, et al. Effects of air pollution on infant and children respiratory mortality in four large Latin-American cities. *Environmental Pollution* 2018;232:385–91.
- Cai Y, Hansell AL, Granell R, et al. Prenatal, early-life, and childhood exposure to air pollution and lung function: the ALSPAC cohort. *Am J Respir Crit Care Med* 2020;202:112–23.
- Schultz ES, Hallberg J, Gustafsson PM, et al. Early life exposure to traffic-related air pollution and lung function in adolescence assessed with impulse oscillometry. *J Allergy Clin Immunol* 2016;138:930–2.
- Möller A, Agius RM, de Voigt F, et al. Long-term exposure to PM10 and NO2 in association with lung volume and airway resistance in the MAAS birth cohort. *Environ Health Perspect* 2013;121:1232–8.
- Lee YL, Wang WH, Lu CW, et al. Effects of ambient air pollution on pulmonary function among schoolchildren. *Int J Hyg Environ Health* 2011;214:369–75.
- Rice MB, Rifas-Shiman SL, Litonjua AA, et al. Lifetime exposure to ambient pollution and lung function in children. *Am J Respir Crit Care Med* 2016;193:881–8.
- Gauderman WJ, Urman R, Avol E, et al. Association of improved air quality with lung development in children. *N Engl J Med* 2015;372:905–13.
- Fuertes E, Bracher J, Flexeder C, et al. Long-term air pollution exposure and lung function in 15 year-old adolescents living in an urban and rural area in Germany: the GINIplus and LISAplus cohorts. *Int J Hyg Environ Health* 2015;218:656–65.
- Barone-Adesi F, Dent JE, Dajnak D, et al. Long-term exposure to primary traffic pollutants and lung function in children: cross-sectional study and meta-analysis. *PLoS One* 2015;10:e0142565.
- Tiotiu AI, Novakova P, Nedeva D, et al. Impact of air pollution on asthma outcomes. *Int J Environ Res Public Health* 2020;17:6212.
- Adam M, Schikowski T, Carsin AE, et al. Adult lung function and long-term air pollution exposure. ESCAPE: a multicentre cohort study and meta-analysis. *Eur Respir J* 2015;45:38–50.
- Jacquemin B, Siroux V, Sanchez M, et al. Ambient air pollution and adult asthma incidence in six European cohorts (ESCAPE). *Environ Health Perspect* 2015;123:613–21.
- Genin M, Lecoeuve A, Cuny D, et al. The association between the incidence of preterm birth and overall air pollution: a nationwide, fine-scale, spatial study in France from 2012 to 2018. *Environ Pollut* 2022;311:120013.
- Fawke J, Lum S, Kirby J, et al. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study. *Am J Respir Crit Care Med* 2010;182:237–45.
- Hart K, Cousins M, Watkins WJ, et al. Association of early-life factors with prematurity-associated lung disease: prospective cohort study. *Eur Respir J* 2022;59:2101766.
- Kotecha SJ, Gibbons JTD, Course CW, et al. Geographical differences and temporal improvements in forced expiratory volume in 1 second of preterm-born children: a systematic review and meta-analysis. *JAMA Pediatr* 2022;176:867–77.
- Decrue F, Goranova O, Salem Y, et al. Increased impact of air pollution on lung function in preterm versus term infants: the BILD study. *Am J Respir Crit Care Med* 2022;205:99–107.
- Collaco JM, Morrow M, Rice JL, et al. Impact of road proximity on infants and children with bronchopulmonary dysplasia. *Pediatr Pulmonol* 2020;55:369–75.
- Simpson SJ, Logie KM, O'Dea CA, et al. Altered lung structure and function in mid-childhood survivors of very preterm birth. *Thorax* 2017;72:702–11.
- Goulden N, Cousins M, Hart K, et al. Inhaled corticosteroids alone and in combination with long-acting β_2 receptor agonists to treat reduced lung function in preterm-born children: a randomized clinical trial. *JAMA Pediatr* 2022;176:133–41.
- Edwards MO, Kotecha SJ, Lowe J, et al. Management of prematurity-associated wheeze and its association with atopy. *PLoS One* 2016;11:e0155695.
- Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723–9.
- Pan H, Cole T. LMS growth, a Microsoft excel add-in to access growth references based on the LMS method; 2012. Available: <http://www.healthforallchildren.com>
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *European Respiratory Journal* 2005;26:319–38.
- Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–43.
- UKAir. Modelled background pollution data. London Department for Environment; 2022. Available: <https://uk-air.defra.gov.uk/data/pcm-data>
- StatsWales. Welsh index of multiple deprivation: [Welsh Government]. 2019. Available: <https://statswales.gov.wales/Catalogue/Community-Safety-and-Social-Inclusion/Welsh-Index-of-Multiple-Deprivation>
- Meng X, Liu C, Chen R, et al. Short term associations of ambient nitrogen dioxide with daily total, cardiovascular, and respiratory mortality: multilocation analysis in 398 cities. *BMJ* 2021;372:n534.
- van den Hooven EH, Pierik FH, de Kluizenaar Y, et al. Air pollution exposure and markers of placental growth and function: the generation R study. *Environ Health Perspect* 2012;120:1753–9.
- Giovannini N, Schwartz L, Cipriani S, et al. Particulate matter (PM10) exposure, birth and fetal-placental weight and umbilical arterial pH: results from a prospective study. *J Matern Fetal Neonatal Med* 2018;31:651–5.
- Niu Z, Habre R, Chavez TA, et al. Association between ambient air pollution and birth weight by maternal individual- and neighborhood-level stressors. *JAMA Netw Open* 2022;5:e2238174.
- Schultz ES, Hallberg J, Bellander T, et al. Early-life exposure to traffic-related air pollution and lung function in adolescence. *Am J Respir Crit Care Med* 2016;193:171–7.
- Schultz ES, Gruzdeva O, Bellander T, et al. Traffic-related air pollution and lung function in children at 8 years of age: a birth cohort study. *Am J Respir Crit Care Med* 2012;186:1286–91.
- Örtengren B, Brunekreef B, Nystad W, et al. Residential outdoor air pollution and lung function in schoolchildren. *Epidemiology* 2008;19:129–37.
- Gauderman WJ, Avol E, Gilliland F, et al. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004;351:1057–67.
- Li S, Cao S, Duan X, et al. Long-term exposure to PM2.5 and children's lung function: a dose-based association analysis. *J Thorac Dis* 2020;12:6379–95.
- Liu NM, Grigg J. Diesel, children and respiratory disease. *BMJ Paediatr Open* 2018;2:e000210.
- Horton A, Jones SJ, Brunt H. Air pollution and public health vulnerabilities, susceptibilities and inequalities in Wales, UK. *J Public Health (Oxf)* 2023;45:432–41.
- Thattipelli S, Kershaw KN, Colangelo LA, et al. Neighborhood socioeconomic deprivation in young adulthood and future respiratory health: the CARDIA lung study. *Am J Med* 2022;135:211–8.
- Edwards MO, Kotecha SJ, Lowe J, et al. Early-term birth is a risk factor for wheezing in childhood: a cross-sectional population study. *J Allergy Clin Immunol* 2015;136:581–7.
- Joshi S, Kotecha S. Lung growth and development. *Early Hum Dev* 2007;83:789–94.
- Agusti A, Faner R. Lung function trajectories in health and disease. *Lancet Respir Med* 2019;7:358–64.
- Hurst JR, Beckman J, Ni Y, et al. Respiratory and cardiovascular outcomes in survivors of extremely preterm birth at 19 years. *Am J Respir Crit Care Med* 2020;202:422–32.
- Goldberg RJ, Larson M, Levy D. Factors associated with survival to 75 years of age in middle-aged men and women. The Framingham study. *Arch Intern Med* 1996;156:505–9.

Impacto da condição pós-COVID-19 no estado de saúde e nas atividades da vida diária: o estudo PRIME pós-COVID

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RESUMO

Objetivo Avaliar a saúde e as atividades da vida diária (AVD) em adultos positivos para SARS-CoV-2 com e sem condição pós-COVID-19 (CPC) e compará-los com indivíduos com teste negativo. Adicionalmente, foram comparadas diferentes definições de casos de CPC com indivíduos negativos para SARS-CoV-2.

Métodos Foram convidados por e-mail todos os adultos com teste PCR positivo para SARS-CoV-2 no Serviço de Saúde Pública de Limburgo do Sul (Países Baixos) entre junho de 2020 e novembro de 2021 (n=41 780) e indivíduos com teste PCR negativo correspondentes (2:1, com base na idade, sexo, teste trimestral-anual, município; n=19 875). Foram avaliadas a saúde (índice de cinco níveis, cinco dimensões do EuroQol (EQ5D) e escala visual análoga do EuroQol (EQVAS)) e a incapacidade nas AVD. A classificação da CPC foi efetuada utilizando a definição de caso da OMS e cinco outras definições comuns.

Resultados No total, foram incluídos 8409 indivíduos (6381 SARS-CoV-2 positivos; 53±15 anos; 57% do sexo feminino; 9 (7–11) meses desde o teste). 39,4% dos positivos apresentaram CPC de acordo com a definição de caso da OMS (EQVAS: 71±20; índice EQ5D: 0,800±0,191; incapacidade nas AVD: 30 (10–70)%) e perceberam uma pior saúde e mais incapacidade nas AVD do que os negativos, ou seja, uma diferença de -8,50 pontos (IC 95% -9,71 a -7,29; p<0,001) para o EQVAS, que diminuiu 1,49 pontos (IC 95% 0,86 a 2,12; p<0,001) nos indivíduos com CPC por cada comorbidade presente, e diferenças de -0,065 pontos (IC 95% -0,074 a -0,056; p<0,001) para o índice EQ5D e de +16,72% (IC 95% 15,01 a 18,43; p<0,001) para a incapacidade nas AVD. A saúde e a incapacidade nas AVD foram semelhantes nos negativos e positivos sem CPC. A substituição da definição de caso da OMS por outras definições de CPC produziu resultados comparáveis.

Conclusões Os indivíduos com CPC apresentam uma saúde substancialmente pior e mais incapacidade nas AVD do que os controles negativos, independentemente da definição de caso. As autoridades deverão informar o público sobre o fardo associado à CPC e permitir um apoio adequado.

INTRODUCTION

A substantial proportion of SARS-CoV-2-infected people report lasting symptoms,^{1,2} initially referred to as 'long COVID'.³ This was later updated by the WHO to 'post-COVID-19 condition' (PCC) which is defined as 'a history of probable or confirmed SARS-CoV-2 infection usually 3 months from onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis'.⁴

Several studies have reported on the impact of PCC.^{5–6} Patients with PCC were found to have comparable health to that of people with chronic obstructive pulmonary disease and rheumatic arthritis.⁷ Furthermore, a negative impact of PCC on quality of life^{8,9} and activities of daily living

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- A substantial proportion of SARS-CoV-2-infected people develop the post-COVID-19 condition (PCC).
- PCC impacts health and activities of daily living (ADL).
- Published studies were prone to selection bias, lacked controls and used different criteria to define the same condition, hampering comparison between studies and undermining the validity of the evidence.

WHAT THIS STUDY ADDS

- PCC has a substantial impact on the health and performance of ADL compared with negative controls, irrespective of the case definition used.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Irrespective of the case definition, there is an associated burden of PCC, which requires an adequate response by authorities in terms of informing the public and enabling support.

(ADL) was found.^{10–11} However, the study populations in these studies were often recruited via online support groups and therefore prone to selection bias. Additionally, studies often lack controls.¹² Consequently, the true burden of PCC on health and ADL remains poorly reported in the general population at the time of writing. Moreover, the lack of clear diagnostic criteria for PCC⁴ and the use of different terminologies and criteria to define the same condition hamper comparison between studies and undermine the validity of the evidence.¹³ In addition, little is known about other factors (such as sex, age and comorbidities) that could potentially affect the impact of PCC on ADL and health.¹⁴

Therefore, the aims of the current study were (1) to assess experienced health and ADL in SARS-CoV-2-positive adults with and without PCC and compare this with SARS-CoV-2-negative individuals and (2) to compare these outcomes between SARS-CoV-2-negative individuals and various commonly used case definitions for PCC while accounting for potential confounding factors.

METHODS

Data from the first wave of a longitudinal open cohort study on the prevalence, risk factors, and impact evaluation of post-COVID-19 condition (PRIME post-COVID) was used. The protocol of the study was published elsewhere.¹⁵

Study design

In short, adults tested for SARS-CoV-2 at the Public Health Service (PHS) South Limburg in the Netherlands, with a valid PCR test result (positive or negative) between 1 June 2020 and 1 November 2021 and a valid email address were retrieved from test records in the registry. In November 2021, all PCR-positive individuals ($n=41\,780$) and a group of PCR-negative individuals (who only had negative test result(s); $n=19\,875$) matched (2:1 ratio) by age, sex, year-quarter of test and municipality of residence were invited for participation by email. Of note, when people tested negative multiple times, the last negative PCR test date was used. The online survey lasted 30–45 min and was available from 17 November 2021 to 9 January 2022. Digitally informed consent for the use and storage of data for research was asked prior to the start of the survey. The invitee could participate in the questionnaire after consent was provided on participation in the study and on the use of the data for research.¹⁵

Population in the current analysis

Individuals were excluded from the current study when they were tested less than 3 months prior to participation in the survey, sex was not reported, PCR-negative individuals in the registry self-reported seropositivity for SARS-CoV-2 before vaccination (because of missing relevant infection-related information) or if the health section of the survey was not completed. Furthermore, PCR-negative individuals (ie, SARS-CoV-2-negative individuals in the registry) were attributed to the SARS-CoV-2-positive group if they self-reported a positive test not in the registry (eg, tested in a hospital, outside a geographical service area and rapid antigen testing). This was the case for 87 individuals. Besides that, 166 individuals gave no consent to match registry data with their questionnaire data. For these individuals, we used self-reported data only.

Main outcome variables

Experienced health EQ5D index

Experienced health was assessed using the five-level EuroQol five-dimensions version (EQ5D), which includes five health dimensions (mobility, self-care, usual activities, pain or discomfort and anxiety or depression), each on a five-level scale ((1) no problems, (2) slight problems, (3) moderate problems, (4) severe problems and (5) extreme problems or unable to).¹⁶ An EQ5D index score was calculated by attaching weights to each level in each dimension. The attached weights were obtained by Versteegh and colleagues for the Dutch population via a standardised valuation study protocol by the EuroQol Group.¹⁷ Index scores could range between -0.446 (worst health) and 1.000 points (best health), whereas 0 is the value of a health state equivalent to dead.¹⁷

Experienced health EQVAS

Additionally, the EQ5D includes a vertical visual analogue scale (EQVAS) ranging from 0 (worst health you can imagine) to 100 points (best health you can imagine) to obtain the respondent's current perceived health.¹⁶

Impairment in ADL

Illness-related impairment in regular activities other than work (in the past 7 days) was assessed using a selected item of the Work Productivity and Activity Impairment questionnaire. Individuals were asked to indicate the degree to which their health affected productivity in regular unpaid activities using a 0 (no effect) to 10 (completely prevented me from doing my daily activities) scale. The degree of ADL impairment is expressed as a percentage, and a higher percentage indicates a higher overall impairment.¹⁸

Case definitions for PCC

SARS-CoV-2-positive individuals were grouped in the 'PCC' group (yes or no) based on the WHO case definition (here used as the main PCC definition) and five alternatives, commonly used definitions, including an adapted WHO case definition to take into account advances in scientific knowledge regarding the WHO case definition. All SARS-CoV-2-positive individuals included in the analyses were at least 3 months after their initial SARS-CoV-2 infection. All case definitions are listed below, a more detailed description of the definitions and questions used can be found in online supplemental eMethods 1.

1. WHO case definition for PCC: fulfilling the current WHO case definition referring to a condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.⁴ In concrete terms, this means experiencing ≥ 1 symptom; symptom(s) is/are present for ≥ 1 month; the time since the test is longer than or equal to the presence of symptom(s), and no new diagnoses have been confirmed since the test.
2. Adapted WHO case definition for PCC: fulfilling all criteria of the current WHO case definition,⁴ except for the criterion of an alternative diagnosis that could explain the symptoms, as recent studies showed associations between COVID-19 and new-onset illnesses.^{19–21}
3. Symptom present: having ≥ 1 symptom present.²²
4. Differentiating symptom present: having ≥ 1 symptom present that is observed to be significantly different between SARS-CoV-2 positives and negatives.^{1,23}
5. Differentiating symptom present with at least a moderate severity: having ≥ 1 symptom present that is observed to be significantly different between SARS-CoV-2 positives and negatives with a severity score of $\geq 5/10$.^{1,23}
6. Not recovered: Indicating not feeling (fully) recovered.²⁴

Of note, the following 44 prelisted symptoms (in alphabetical order) were considered: amnesia, brain fog, burning sensation in the trachea, chest tightness, cold, concentration difficulties, confusion, cough, coughing up mucus, diarrhoea, dizziness, dreariness or depression, earache, elevated body temperature, eye difficulties, fatigue, fear, fever, hair loss, headache, heat flushes, increased resting heart rate, irritability, joint pain, loss of appetite, loss or change of smell, loss or change of taste, muscle pain or weakness, nausea, nerve pain, pain between shoulder blades, pain or burning sensation in the lungs, palpitations, runny nose, shortness of breath, skin rashes or red spots on toes or feet, sleeping problems, sneezing, sore throat, stomach ache, sudden weight loss, tinnitus, voice difficulties and vomiting.²³

Statistical analysis

Descriptive statistics were presented for the three groups (ie, positives with PCC, positives without PCC and SARS-CoV-2 negatives). Categorical data were reported as numbers (frequencies) and ordinal data as medians (IQR). Continuous data were checked for normality using histograms and Q-Q plots and reported as mean (SD) or median (IQR) as appropriate. Univariable and multivariable regression models were performed for the main continuous outcomes (ie, EQVAS, EQ5D index and ADL impairment) with ordinary least squares linear regression to assess the main determinant (ie, PCC, no PPC and SARS-CoV-2 negatives). The multivariable analyses were adjusted for a minimally sufficient set of confounders identified in the literature: age, sex, pre-existing comorbidities when tested, time since the test and health the year prior to the test.^{2,22,23} The three groups were modelled as two dummy variables in this analysis, with the SARS-CoV-2 negatives as the reference group. The WHO case definition was used to classify SARS-CoV-2-positive individuals into the (no) PCC group. If multicollinearity was present (variance inflation factor >5), variables were identified and removed from the model. Interaction terms for sex, age, health the year prior to the test, pre-existing comorbidities when tested and time since the test on the one hand

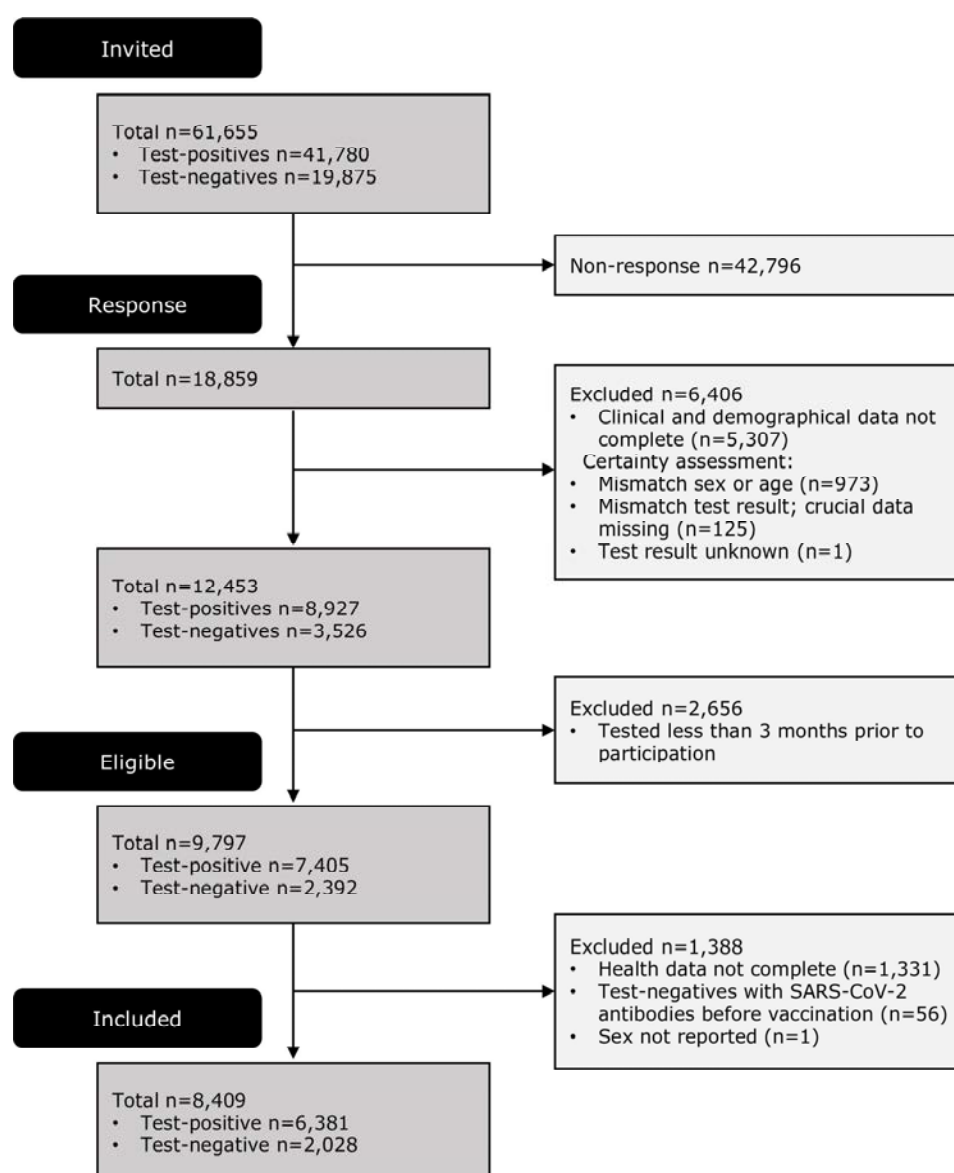


Figure 1 Flowchart of invitees, respondents, participants eligible for inclusion and study population included in the analysis.

and the two dummy variables (ie, group variables) on the other hand were explored, as a potential effect of the group variables on health and ADL might depend on these confounders included in the model.^{23 25} When found to be statistically significant, the interaction term was included in the final models.

Furthermore, analysis of covariance adjusting for time since the test and health the year prior to the test were performed for sub-groups by sex (male or female), age (18–40, 41–60 and 60+ years) and presence of pre-existing comorbidities at the test (yes or no). This was done for positives with and without PCC according to the WHO case definition and the SARS-CoV-2-negative group and for the various commonly used definitions for PCC.

A priori, the level of significance was set at 0.01 (two-tailed) to account for multiple testing in this study and the high sample size in the multivariable regression analyses. Model assumptions were checked when performing the analyses. Tables and figures include 95% CIs. Statistical analyses were performed using SPSS V.27.0 (IBM, Armonk, NY, USA). Visualisations were made using GraphPad Prism V.9.3.1 (GraphPad Software, La Jolla, CA, USA).

RESULTS

Adults (n=61 655) were invited by email to participate. Of the 18 859 respondents, 12 453 were eligible as they provided minimal data and showed sufficient certainty to be the intended invitee.²³ Individuals were excluded if they were tested less than 3 months prior to participation (n=2656), did not complete the health sec-

tion of the survey (n=1331), were PCR negative but reported to have SARS-CoV-2 antibodies before vaccination (n=56) or did not report sex (n=1). Consequently, 8409 individuals (6381 SARS-CoV-2 positive and 2028 negative) were included (figure 1). Age and sex data of all invitees and invitees (not) included in the analysis are reported in online supplemental eTable 1.

Description of the study population

In total, 39.4% of positive individuals (n=2513) had PCC, according to the WHO case definition. Demographical and clinical data of the SARS-CoV-2 positives with PCC, positives without PCC and negatives are shown in table 1. In short, the positives with and without PCC had a similar sex distribution (62% and 57% females, respectively), mean age (51±15 years) and median time since infection of 10 (7–11) months. Positives without PCC had, on average, better perceived health the year prior to the test and fewer comorbidities present when tested than positives with PCC and negatives. Furthermore, the negative group was, on average, 7 years older and had a lower proportion of females (49%) than both positive groups.

Differences in health and ADL

SARS-CoV-2 positives with PCC reported a higher median ADL impairment due to health (30% vs 0% and 0%) and a worse average perceived health at this moment (EQVAS: 70.8 vs 81.5 and 79.2; EQ5D index: 0.800 vs 0.896 and 0.878) compared with positives

Table 1 Characteristics of SARS-CoV-2 negatives and SARS-CoV-2 positives stratified for PCC according to the WHO case definition

	SARS-CoV-2 negatives (n=2028)	SARS-CoV-2 positives	
		No PCC (n=3868)	PCC (n=2513)
Female, No. (%)	991 (48.9)	2212 (57.2)	1564 (62.2)
Age, mean (SD), years	58.1 (14.7)	51.3 (15.2)	51.4 (14.7)
Body mass index, mean (SD), kg/m ²	26.3 (4.7)	26.6 (4.9)	27.2 (5.2)
Level of education, No. (%)			
Studying	22 (1.1)	102 (2.6)	62 (2.5)
Low	223 (11.0)	360 (9.3)	242 (9.6)
Medium	885 (43.6)	1801 (46.6)	1262 (50.2)
High	898 (44.3)	1605 (41.5)	947 (37.7)
Comorbidities reported at moment of test, No. (%)			
None	959 (47.3)	2306 (59.6)	1047 (41.7)
1	619 (30.5)	970 (25.1)	752 (29.9)
≥2	450 (22.2)	592 (15.3)	714 (28.4)
Time between survey and test, median (IQR), months	8 (6–11)	10 (7–11)	10 (7–11)
Hospital admission in acute phase of infection, No. (%)	NA	50 (1.5)*	47 (2.0)†
Experienced health			
Health the year prior to test (EQVAS), mean (SD), points	82.7 (15.8)	85.9 (14.3)	81.9 (16.0)
Health at the moment of survey (EQVAS), mean (SD), points	79.2 (20.7)	81.5 (19.0)	70.8 (19.8)
EQ5D index, mean (SD), points	0.878 (0.167)	0.896 (0.164)	0.800 (0.191)
Mobility (no problems), No. (%)	1547 (76.3)	3164 (81.8)	1619 (64.4)
Self-care (no problems), No. (%)	1919 (94.6)	3721 (96.2)	2294 (91.3)
Usual activities (no problems), No. (%)	1546 (76.2)	3064 (79.2)	1226 (48.8)
Pain or discomfort (no problems), No. (%)	1169 (57.6)	2527 (65.3)	870 (34.6)
Anxiety or depression (no problems), No. (%)	1562 (77.0)	3082 (79.7)	1599 (63.6)
Non-work related impairment due to health (WPAI)			
Overall activity impairment due to health, median (IQR), %	0 (0–30)	0 (0–30)	30 (10–70)

Data are presented as frequency and proportion, mean and SD or median and IQR.

*n=3399.

†n=2374, as only SARS-CoV-2 positives with symptoms at time of test were asked about hospital admission in the survey.

EQ5D, EuroQol five dimension; EQVAS, EuroQol visual analogue scale; NA, not applicable; PCC, post-COVID-19 condition; WPAI, work productivity and activity impairment.

without PCC and negatives, respectively. The greatest impairments in positives with PCC were observed for the domain's usual activities and pain/discomfort (table 1). A more detailed overview of the extent of impairment across the several health domains can be found in online supplemental eFigure 1.

The results of the univariable and multivariable regression models can be found in table 2. The adjusted EQ5D index was significantly lower in positives with PCC compared with negatives (−0.065 points, 95% CI −0.074 to −0.056; $p<0.001$). No significant difference between positives without PCC and negatives was observed (−0.003 points, 95% CI −0.011 to 0.005; $p=0.492$).

Also, the perceived health status measured using the EQVAS was 8.50 points (95% CI −9.71 to −7.29; $p<0.001$) lower in positives with PCC than in negatives. While the EQVAS was not statistically significantly higher in positives without PCC than in negatives (0.26 points, 95% CI −0.68 to 1.19; $p=0.593$). Our model indicated that the presence of PCC and comorbidities together has a smaller effect on EQVAS than the sum of each. Specifically, the associated burden of PCC on EQVAS decreases by 1.49 points (95% CI 0.86 to 2.12; $p<0.001$) for each comorbidity present. The specific models for EQVAS for people without comorbidities, with one comorbidity and with ≥2 comorbidities are reported in online supplemental eTable 2. The beta coefficients for PCC and no PCC (vs reference: negatives) in the abovementioned models are −9.00 points (95% CI −10.47 to −7.53; $p<0.001$) and −0.46 points (95% CI −1.72 to 0.80; $p=0.476$); −6.64 points (95% CI −8.54 to −4.74; $p<0.001$) and 0.99 points (95% CI −0.80 to 2.77; $p=0.278$) and −3.73 points

(95% CI −5.91 to −1.55; $p<0.001$) and 1.47 points (95% CI −0.80 to 3.73; $p=0.204$), respectively.

Furthermore, ADL impairment due to health problems was 16.72% (95% CI 15.01 to 18.43; $p<0.001$) higher in positives with PCC compared with negatives. The ADL impairment observed in positives without PCC was not significantly higher than that observed in negatives (1.97%, 95% CI 0.40 to 3.54; $p=0.014$).

A sensitivity analysis of 8156 individuals was performed for the abovementioned multivariable models (253 individuals with a self-reported test result were excluded from the analyses). The results can be found in online supplemental eTable 3. In short, a similar direction and extent of findings were observed as the analyses in 8409 individuals.

Differences in health and ADL stratified for sex, age and the presence of comorbidities

Results of analyses for EQVAS, EQ5D index and ADL impairment due to health after stratification on sex, age and the presence of pre-existing comorbidities and adjusted for health prior to the test and time since the test can be found in figure 2. Briefly, significantly worse health and larger ADL impairment were observed in the PCC group (by the WHO case definition) compared with the positive group without PCC and the negative group; this was observed in nearly all strata.

Health and ADL in different PCC definitions

Overall, similar (direction of) findings were observed when comparing different case definitions with the SARS-CoV-2-negative control group.

Table 2 Unadjusted and adjusted regression models for health and ADL impairment adjusted for age, sex, comorbidities at test, health status year prior to test and time since test, with SARS-CoV-2 negatives as reference group and PCC according to the WHO case definition

	Unadjusted unstandardised coefficient β (95% CI)	P value	Adjusted unstandardised coefficient β (95% CI)	P value
(1) Unadjusted and adjusted linear regression results for perceived health at the moment (EQVAS)				
Group (PCC by WHO)	−8.44 (−9.59 to −7.29)	<0.001	−8.50 (−9.71 to −7.29)	<0.001
Group (No PCC by WHO)	2.27 (1.21 to 3.33)	<0.001	0.26 (−0.68 to 1.19)	0.593
Interaction group (PCC by WHO)*comorbidities at test	NA	NA	1.49 (0.86 to 2.12)	<0.001
(2) Unadjusted and adjusted linear regression results for health at the moment (EQ5D index)				
Group (PCC by WHO)	−0.079 (−0.089 to −0.068)	<0.001	−0.065 (−0.074 to −0.056)	<0.001
Group (No PCC by WHO)	0.018 (0.009 to 0.028)	<0.001	−0.003 (−0.011 to 0.005)	0.492
(3) Unadjusted and adjusted linear regression results for ADL impairment due to health				
Group (PCC by WHO)	18.57 (16.78 to 20.37)	<0.001	16.72 (15.01 to 18.43)	<0.001
Group (No PCC by WHO)	−0.64 (−2.29 to 1.01)	0.448	1.97 (0.40 to 3.54)	0.014

ADL, activities of daily living; EQ5D, EuroQol five dimension; EQVAS, EuroQol visual analogue scale; PCC, post-COVID-19 condition.

In general, the participants meeting the criteria for the WHO case definition and the definition based on the presence of ≥ 1 symptom presented the best health and least ADL impairment of all definitions (ie, smallest differences with the SARS-CoV-2-negative group). Contrary, those meeting the criteria for the definition based on the presence of ≥ 1 differentiating symptom between SARS-CoV-2-positive and SARS-CoV-2-negative individuals with at least a moderate severity and the definition based on the feeling of not being recovered presented the worst health and highest ADL impairment of all definitions.

Results for EQVAS were comparable for all PCC definitions after stratification for age, sex and comorbidities, except for certain case definitions in the stratum of males aged 41–60 years without comorbidities (figure 3). Furthermore, slight differences between certain case definitions were found for the outcomes of the EQ5D index and ADL impairment. These differences (ie, absence of overlap of 95% CIs) were mainly located in the strata with men and women without comorbidities and between the above-mentioned PCC definitions.

DISCUSSION

In this population-based cohort study, the impact of PCC on health and impairment in ADL was studied in adults who tested positive for SARS-CoV-2 and controls. The associated burden of PCC on health and impairment in ADL is meaningful, irrespective of the case definition used, age, sex, presence of pre-existing comorbidities, time since the test or health status prior to the test.

Findings from the current study confirm previous reports that PCC affects health and ADL.^{6,8,9} Nevertheless, findings are difficult to compare, as most studies used other measures or reported the findings of all SARS-CoV-2-positive individuals without presenting results for PCC separately.^{6,25,26} Studies that specifically reported on PCC found values that were considerably worse in terms of health and ADL.^{6,10,11,27,28} Vaes et al, for example, used the same outcome measures and found a mean EQVAS of 56 points and ADL impairment of 60% around 6 months after infection.¹¹ A conceivable explanation for this is that previous studies mainly reported on individuals recruited via online support groups or clinics, describing a subgroup of the population with a possible bias resulting in an overestimation of the burden.^{10,11,28,29} Still, an associated burden of PCC is found when values are compared with Dutch population norms (EQVAS: 70.8 vs 81.4 and EQ5D index: 0.800 vs 0.869, respectively), while positives without PCC and negatives show similar values to the Dutch population norms.^{17,30} After controlling for possible confounders, the PCC group had on average 8.50 and 0.065 points lower EQVAS and EQ5D index scores, respectively, and 16.7% higher ADL impairment than the negative group. In the literature, a difference of 7 points for EQVAS (patients with cancer), 0.063 points for the EQ5D index (EQ5D value set for England) and 20% for ADL impairment (patients with psoriasis) is established as meaningful.^{31–33}

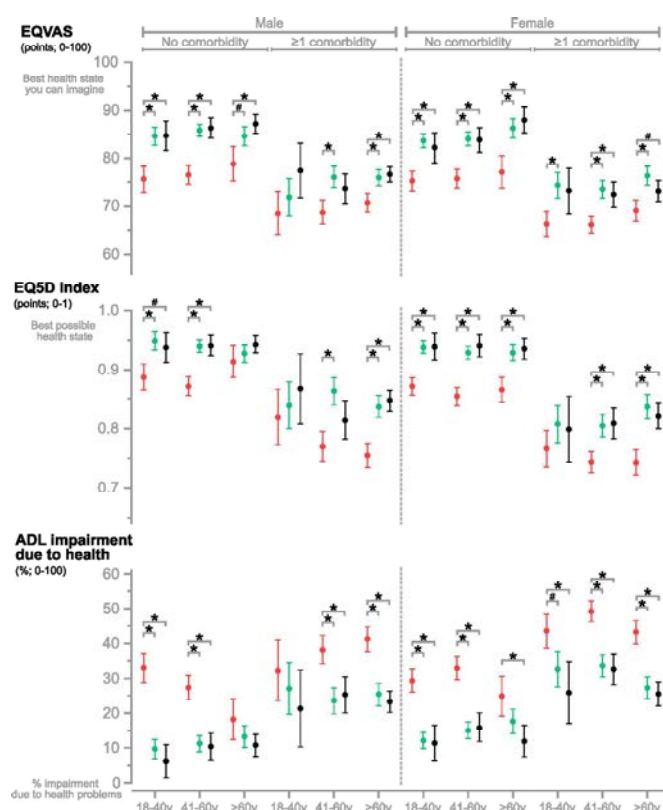


Figure 2 Health and ADL impairment for SARS-CoV-2 negatives and positives with and without post-COVID-19 condition according to the WHO case definition, stratified for sex, age and pre-existing comorbidities and adjusted for time since test and health prior to the test. From left to right: ●: SARS-CoV-2 positives with post-COVID-19 condition, ●: SARS-CoV-2 positives without post-COVID-19 condition; ●: SARS-CoV-2 negatives. Whiskers are 95% CI. #p<0.01 and *p<0.001. ADL, activities of daily living.

To date, the WHO case definition for PCC is considered the golden standard in the absence of a laboratory test to diagnose PCC.⁴ Though the different definitions for PCC found comparable results for health and ADL impairment, indicating that although there is heterogeneity in the case definitions, the same conclusion on the impact of PCC on health and ADL can be drawn. Slight differences observed between definitions can be due to misclassification, as evidence emerges that a SARS-CoV-2 infection and PCC are associated with new-onset illnesses in the case of the WHO case definition, for example,³⁴ or in the case of a definition using the presence of ≥ 1 symptom, as (generic) symptoms (eg, fatigue

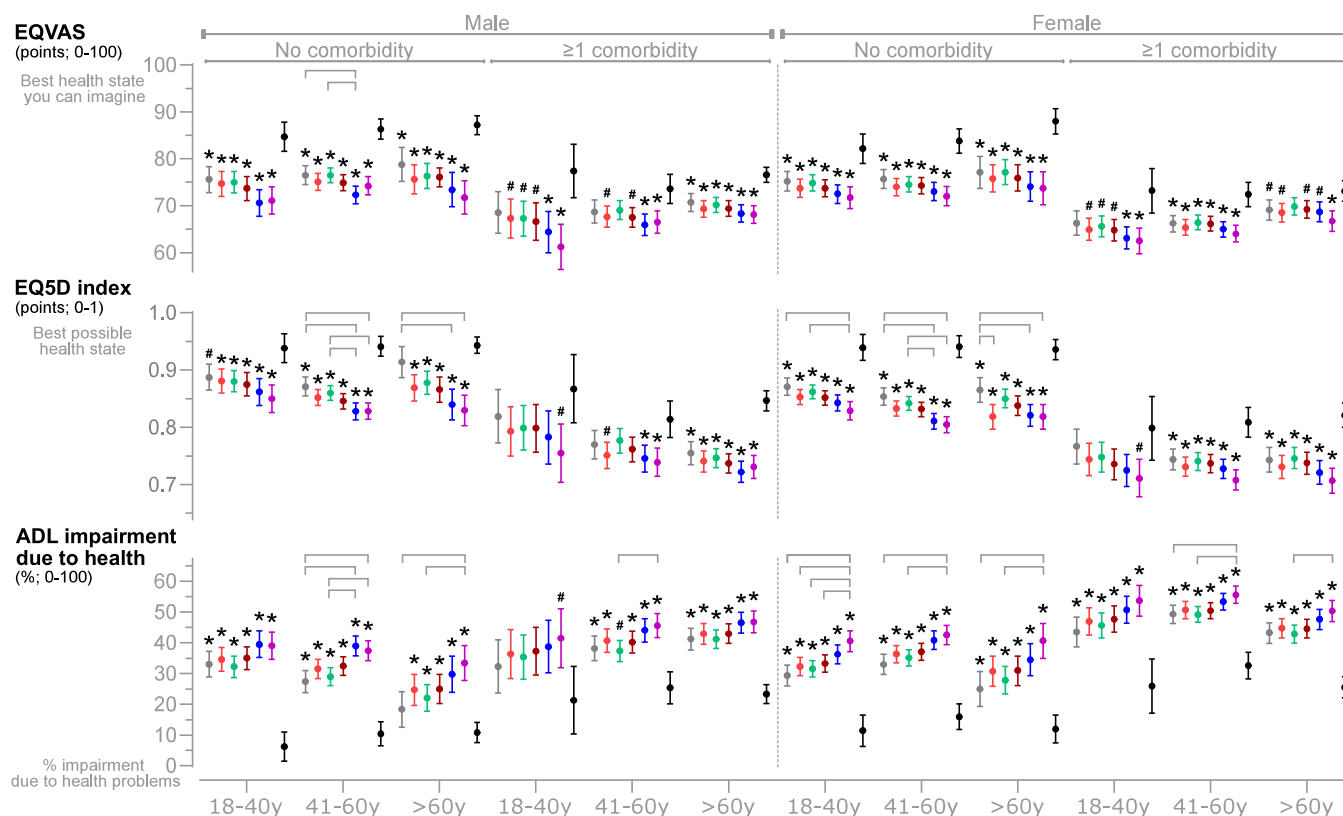


Figure 3 Health and ADL impairment for SARS-CoV-2 negatives and different PCC case definitions stratified for sex, age and pre-existing comorbidities. From left to right: ●: WHO case definition, ●: WHO case definition except for criterion of alternative diagnosis, ●: ≥ 1 symptom, ●: ≥ 1 symptom that differs between SARS-CoV-2 positives and negatives, ●: ≥ 1 symptom that differs between SARS-CoV-2 positives and negatives with a severity $\geq 5/10$, ●: feeling not recovered; ●: SARS-CoV-2 negatives. Whiskers are 95% CI, # $p < 0.01$ and * $p < 0.001$ from SARS-CoV-2 negatives. Horizontal brackets indicate the absence of overlap in 95% CI. ADL, activities of daily living; PCC, post-COVID-19 condition.

and pain) are also present in chronic diseases and the general population.^{1 35 36}

The associated burden on perceived health (ie, EQVAS) decreases with the presence of comorbidities, presumably because the room to deteriorate in terms of health is smaller when there are more comorbidities. In addition, no interactions between the presence of comorbidities and PCC were observed for the EQ5D index (and ADL impairment). This has to do with the nature of both health measures, as EQVAS assesses the perceived health of an individual, while the EQ5D index is a score based on limitations in five domains. Until today, it remains unknown whether PCC is a unique condition, an illness similar to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and other postinfectious illnesses or even a combination of conditions. To determine this, a comparison with ME/CFS and other postinfectious illnesses is needed.

The major strengths of this study are the large sample size and population-based study design, as the recruitment of individuals was done using the Dutch COVID-19 PCR test registry. By inviting all PCR-positive individuals and matched negative controls, we were able to compare results with a reference group and consider (non-) pandemic-related factors. Furthermore, various definitions for PCC were used and compared in the current study, as well as standardised and validated questionnaires.

This study has a number of limitations. Only individuals with a valid email address were invited for this online study. This may have resulted in a potential selection bias among digitally illiterate individuals, as they were not invited or did not complete the study. Likewise, this may have been the case for people with disabilities or severe diseases. In total, 14% of invitees are included in the current study, although this response rate would be higher if individuals were not excluded for several reasons.¹⁵ Similar rates were reported in other population-based studies regarding PCC with the same recruitment strategy (eg, Whitaker et al, 26%–29%, Hastie et al, 16%)^{2,25} and what is expected in email surveys in general.³⁷ Furthermore, an underrep-

resentation of invitees aged 18–40 years and an over-representation of invitees aged 50–80 years are observed in the current sample and were more pronounced in the negative invitees. In the current study, less than 2% of the population was hospitalised for COVID-19. It is possible that people went directly to the hospital instead of being tested at the PHS and are therefore underrepresented in our sample. Moreover, misclassification bias regarding the (confirmed) SARS-CoV-2 diagnosis is inevitable, as in the early phase of the pandemic, the availability and access to testing were limited.³⁸ As a consequence, individuals who had SARS-CoV-2 in the early phase of the pandemic (before 1 June 2020) or were asymptomatic could be included in the negative reference group. Nevertheless, the potential misclassification of SARS-CoV-2 positives in the negative group would not change the direction of the findings. Another potential limitation is that data gathering was done by self-report, leaving potentially relevant information missing (eg, comorbidities). To fulfil the WHO case definition, alternative diagnoses that could explain symptoms need to be excluded. Our study did not include clinician-reported information or information on alternative diagnoses based on medical records. The self-reported data regarding (pre-existing) comorbidities in our study may have a potential recall and misclassification bias. Furthermore, certain questions were prone to recall bias (eg, health the year prior to the test). The study includes test results until the last quarter of 2021 (ie, before the omicron wave). Therefore, results cannot be generalised to vaccinated individuals who developed PCC by a breakthrough infection, as the majority were unvaccinated when they were infected with SARS-CoV-2 or with PCC by the omicron variant. Hence, recent research suggests there is no difference in PCC sequela between SARS-CoV-2 variants.^{39 40} Of note, this study was limited to adults; however, PCC is also present in children and adolescents.³⁴

CONCLUSION

Individuals with PCC have substantial and clinically meaningful worse health and more impairment in ADL than negative controls,

irrespective of sex, age, pre-existing comorbidities, time since the test and health status prior to the test and regardless of the case definition used to define PCC.

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Patient consent for publication Not applicable.

Ethics approval The PRIME post-COVID study involves human participants.

The medical ethics committee of Maastricht University Medical Centre+ waived this study (Maastricht, the Netherlands; METC2021-2884), as the Medical Research Involving Human Subjects Act did not apply to this study. This study was registered at ClinicalTrials.gov Protocol Registration and Results System (NCT05128695). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. Data cannot be shared publicly because the data contains potentially identifying patient information. Data are available on request from the head of the data-archiving South Limburg Public Health Service (contact via Helen. Sijstermans@ggdzl.nl) for researchers who meet the criteria for access to confidential data.

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REFERENCES

1. Ballering AV, van Zon SKR, Olde Hartman TC, et al. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *Lancet* 2022;400:452–61.
2. Whitaker M, Elliott J, Chadeau-Hyam M, et al. Persistent COVID-19 symptoms in a community study of 606,434 people in England. *Nat Commun* 2022;13:1957.
3. Callard F, Perego E. How and why patients made long Covid. *Soc Sci Med* 2021;268:113426.
4. Soriano JB, Murthy S, Marshall JC, et al. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis* 2022;22:e102–7.
5. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* 2021;11:16144.
6. Malik P, Patel K, Pinto C, et al. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. *J Med Virol* 2022;94:253–62.

7. Twomey R, DeMars J, Franklin K, et al. Chronic fatigue and postexertional Malaise in people living with long COVID: an observational study. *Phys Ther* 2022;102:pzac005.
8. Meys R, Delbressine JM, Goërtz YMJ, et al. Generic and respiratory-specific quality of life in non-hospitalized patients with COVID-19. *JCM* 2020;9:3993.
9. Tarazona V, Kirouchena D, Clerc P, et al. Quality of life in COVID-19 outpatients: a long-term follow-up study. *J Clin Med* 2022;11:6478.
10. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine* 2021;38:101019.
11. Vaes AW, Goërtz YMJ, Van Herck M, et al. Recovery from COVID-19: a Sprint or Marathon? 6-month follow-up data from online long COVID-19 support group members. *ERJ Open Res* 2021;7:00141-2021.
12. Amin-Chowdhury Z, Ladhani SN. Causation or confounding: why controls are critical for characterizing long COVID. *Nat Med* 2021;27:1129–30.
13. Munblit D, O'Hara ME, Akrami A, et al. Long COVID: aiming for a consensus. *Lancet Respir Med* 2022;10:632–4.
14. Poudel AN, Zhu S, Cooper N, et al. Impact of COVID-19 on health-related quality of life of patients: a structured review. *PLoS One* 2021;16:e0259164.
15. Pagen DME, van Bilsen CJA, Brinkhues S, et al. Design and recruitment of a large-scale cohort study on prevalence, risk factors and impact evaluation of post-COVID-19 condition and its wider long-term social, mental, and physical health impact: the PRIME post-COVID study. *Front Public Health* 2022;10:1032955.
16. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727–36.
17. Versteegh MM, Vermeulen KM, Evers S, et al. Dutch tariff for the five-level version of EQ-5D. *Value Health* 2016;19:343–52.
18. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4:353–65.
19. Xie Y, Xu E, Bowe B, et al. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022;28:583–90.
20. Wrona M, Skrypnik D. New-onset diabetes mellitus, hypertension, dyslipidaemia as sequelae of COVID-19 infection-systematic review. *Int J Environ Res Public Health* 2022;19:13280.
21. Chang R, Yen-Ting Chen T, Wang S-I, et al. Risk of autoimmune diseases in patients with COVID-19: a retrospective cohort study. *EClinicalMedicine* 2023;56:101783.
22. Goërtz YMJ, Van Herck M, Delbressine JM, et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome. *ERJ Open Res* 2020;6:00542-2020.
23. Pagen DME, van Bilsen CJA, Brinkhues S, et al. Prevalence of long-term symptoms varies when using different post-COVID-19 definitions in positively and negatively tested adults: the PRIME post-COVID study. *Open Forum Infect Dis* 2023;10:ofad471.
24. Alwan NA, Johnson L. Defining long COVID: going back to the start. *Med* 2021;2:501–4.
25. Hastie CE, Lowe DJ, McAuley A, et al. Outcomes among confirmed cases and a matched comparison group in the long-COVID in Scotland study. *Nat Commun* 2022;13:5663.
26. Carfi A, Bernabei R, Landi F, et al. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020;324:603–5.
27. Tabacof L, Tosto-Mancuso J, Wood J, et al. Post-acute COVID-19 syndrome negatively impacts physical function, cognitive function, health-related quality of life, and participation. *Am J Phys Med Rehabil* 2022;101:48–52.
28. Daynes E, Gerlis C, Chaplin E, et al. Early experiences of rehabilitation for individuals post-COVID to improve fatigue, breathlessness exercise capacity and cognition - A cohort study. *Chron Respir Dis* 2021;18:14799731211015691.
29. van den Borst B, Peters JB, Brink M, et al. Comprehensive health assessment 3 months after recovery from acute Coronavirus disease 2019 (COVID-19). *Clin Infect Dis* 2021;73:e1089–98.
30. Janssen B, Szende A. Population norms for the EQ-5D. In: Szende A, Janssen B, Cabases J, eds. *Self-Reported Population Health: An International Perspective based on EQ-5D*. Dordrecht (NL): Springer Copyright 2014, The Author(s), 2014: 19–30.
31. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes* 2007;5:70.
32. McClure NS, Sayah FA, Xie F, et al. Instrument-defined estimates of the minimally important difference for EQ-5D-5L index scores. *Value Health* 2017;20:644–50.
33. Wu JJ, Lin C, Sun L, et al. Minimal clinically important difference (MCID) for work productivity and activity impairment (WPAI) questionnaire in psoriasis patients. *J Eur Acad Dermatol Venerol* 2019;33:318–24.
34. Davis HE, McCorkell L, Vogel JM, et al. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* 2023;21:133–46.
35. Goërtz YMJ, Braamse AMJ, Spruit MA, et al. Fatigue in patients with chronic disease: results from the population-based lifelines cohort study. *Sci Rep* 2021;11:20977.
36. Petrie KJ, Faasse K, Crichton F, et al. How common are symptoms? Evidence from a New Zealand national telephone survey. *BMJ Open* 2014;4:e005374.
37. Menon V, Muraleedharan A. Internet-based surveys: relevance, methodological considerations and troubleshooting strategies. *Gen Psychiatr* 2020;33:e100264.
38. Vos ERA, den Hartog G, Schepp RM, et al. Nationwide seroprevalence of SARS-CoV-2 and identification of risk factors in the general population of the Netherlands during the first epidemic wave. *J Epidemiol Community Health* 2020;75:489–95.
39. Mizrahi B, Sudry T, Flaks-Manov N, et al. Long Covid outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study. *BMJ* 2023;380:e072529.
40. Canas LS, Molteni E, Deng J, et al. Profiling post-COVID-19 condition across different variants of SARS-CoV-2: a prospective longitudinal study in unvaccinated wild-type, unvaccinated alpha-variant, and vaccinated Delta-variant populations. *Lancet Digit Health* 2023;5:e421–34.

Associação do tempo passado nas redes sociais com o consumo de cigarros e de cigarros eletrônicos por jovens no Reino Unido: um estudo longitudinal nacional

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RESUMO

Contexto As redes sociais podem influenciar o comportamento das crianças e dos jovens no que respeita à saúde, incluindo o consumo de cigarros de combustão e de cigarros eletrônicos.

Métodos Analisámos dados de participantes com idades entre os 10 e os 25 anos no UK Household Longitudinal Study 2015–2021 (Estudo Longitudinal das Famílias do Reino Unido). O volume de utilização de redes sociais reportado num dia de semana normal esteve relacionado com o consumo atual de cigarros de combustão e de cigarros eletrônicos. Os modelos de regressão logística de equação de estimativa generalizada (EEG) investigaram as associações entre a utilização de redes sociais e o consumo de cigarros de combustão e de cigarros eletrônicos. Os modelos controlaram possíveis fatores confundidores, incluindo a idade, o sexo, o país do Reino Unido, a etnia, o rendimento do agregado familiar e a utilização de cigarros de combustão /cigarros eletrônicos por outras pessoas no domicílio familiar.

Resultados Entre 10 808 participantes com 27 962 observações, o consumo atual de cigarros de combustão foi comunicado por 8,6% dos participantes em pelo menos um momento e a utilização atual de cigarros eletrônicos foi comunicada por 2,5% dos participantes. Nos modelos EEG ajustados, a utilização mais frequente de redes sociais esteve associada a uma maior probabilidade de consumo atual de cigarros de combustão. Isso foi particularmente aparente em níveis de utilização mais elevados (por exemplo, odds ratio ajustada (AOR) 3,60, IC 95% 2,61 a 4,96 para ≥ 7 horas/dia vs. nenhuma). As associações foram semelhantes para os cigarros eletrônicos (AOR 2,73, IC 95% 1,40 a 5,29 para ≥ 7 horas/dia de utilização de redes sociais vs. nenhuma). Observaram-se evidências de dose-resposta nas associações entre o tempo gasto nas redes sociais e a utilização de cigarros de combustão e cigarros eletrônicos (ambos $p < 0,001$). As análises estratificadas por sexo e rendimento familiar encontraram associações semelhantes para os cigarros de combustão. No entanto, para os cigarros eletrônicos, as associações concentraram-se nos homens e nos grupos de rendimento familiar mais elevado.

Conclusões A utilização de redes sociais está associada a um risco acrescido de consumo de cigarros de combustão e de cigarros eletrônicos, sendo necessária mais investigação sobre esta questão, bem como potenciais respostas políticas.

INTRODUCTION

Understanding the mechanisms that drive uptake and use of cigarettes and e-cigarettes is key to developing strategies to prevent harm. The use of social media has been identified as a novel potential vector, with substantial increases in time spent in this activity by young people.^{1–5} Social media use increases with age, and girls are more likely to spend longer periods of time on social media than boys.⁶ Social media may be driving cigarette smoking and e-cigarette use through both direct, targeted advertise-

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► There is substantial use of social media among children and young people, which has had debated impacts on health outcomes. There are studies examining social media use and associations with cigarette and e-cigarette use in the US but only two such studies in the UK. One study was cross-sectional, while one previous cohort study of data from 2014 to 2018 found that social media use at age 14 years was associated with a greater likelihood of cigarette smoking at age 17 years. This study did not, however, assess the use of e-cigarettes.

WHAT THIS STUDY ADDS

► This study examined daily use of social media among 10–25-year-olds from 2015 to 2021. It found that time spent on social media is associated, in a dose-dependent manner, with likelihood both of cigarette smoking and vaping. Those using social media for ≥ 7 hours/day were more than two and a half times more likely to use both cigarettes and e-cigarettes than those not using social media.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► This study highlights that more frequent social media use is associated with increased likelihood of using both cigarettes and e-cigarettes in the UK. This reinforces concerns that social media is a vector of direct and indirect marketing and promotion of these products and that policies to curtail this may be warranted.

ments and the use of paid influencers by the tobacco industry.⁷ To date, most evidence on the impact of social media on cigarette and e-cigarette use has focused on America.^{8–10} This has found associations with uptake, regular use and reduced perceptions of harm and has included assessment of engagement with different platforms.^{11–13} The only two previous UK studies include a cohort study which found that social media use at age 14 years was associated with greater likelihood of cigarette use at age 17 years.¹⁴ A second cross-national study from 42 countries including the UK concluded that there was a link between

social media use and substance use but did not examine cigarette use separately from other substances.¹⁵

Previous research has identified links between social media use and both cigarette and e-cigarette use. For example, analyses of Instagram have identified networks of influencers promoting e-cigarettes, often without disclosing financial relationships; while Juul has recently settled a lawsuit over marketing of e-cigarettes to teens, including on social media.^{16,17} Comparative analyses in the UK have found good compliance with advertising standards for e-cigarettes on traditional media, but high levels of breaches on social media.¹⁸ Analyses of 11 of the most popular social media platforms have highlighted high levels of tobacco promotion, with few platforms having policies to deal with novel forms of promotion such as sponsored or influencer content.¹⁹ A systematic review of exposure to tobacco promotion and use identified 29 studies (none from the UK) and concluded that there is a need for greater regulation.²⁰ Any proposal to regulate social media needs to be justified and based on evidence. To contribute to this, we examined the longitudinal relationship of social media use with cigarette smoking and e-cigarette use among children and young people in the UK.

METHODS

Data come from participants of the UK Household Longitudinal Study (UKHLS), also known as Understanding Society.²¹ This is a longitudinal household panel study with annual surveys starting in 2009. The original sample consisted of a clustered and stratified probability sample of approximately 28 000 households in the UK. Data are collected via face-to-face interviews carried out by a trained interviewer in the respondent's home and via online, self-completion questionnaires. Adults over the age of 16 years or above are asked to complete an individual questionnaire, including a self-completion questionnaire. Household members aged 10–15 years are asked to fill in a shorter self-completion questionnaire, with permission from their parent or carer.

We have focused on children and young adults aged 10–25 years using data from 2015/2016 to 2020/2021 (wave 7 to wave 12). Questions on e-cigarette use were added to UKHLS in 2015/2016. Participation in the panel is voluntary, with a gift voucher sent to encourage completion of questionnaires and a further gift voucher sent when these are completed. All participants provided consent to be interviewed. The University of Essex Ethics Committee approved all data collection.²²

Outcomes and exposure

We used three separate binary outcomes: current cigarette smoking, current e-cigarette use and current dual use of both products. Participants were classified as current cigarette smokers if they responded “I usually smoke between one and six cigarettes a week” or “I usually smoke more than six cigarettes a week”. All other responses were coded as non-users. The same question was used for all waves of data and for all ages.

Current e-cigarette use was first assessed in 2015/2016 with the question “Do you ever use electronic cigarettes (e-cigarettes)?” with response options “Yes” and “No”. From wave 8 (2016/2017) onwards participants were classified as current (weekly) e-cigarette users if they responded “I use e-cigarettes at least once a week”. All other responses were coded as non-users. Dual use was classified as participants currently using both products, with those using only one or no products classed as non-dual users.

The main exposure variable was social media use. Participants were first asked “Do you belong to any social networking websites?” (Yes/No), and if “Yes”, they were also asked how many hours they spend chatting or interacting with friends through a social website on a normal weekday, with the following response options: “None”, “<1 hour/day”, “1–3 hours”, “4–6 hours” and “≥7 hours”. We combined those reporting “None” along with those who were not a member of a social media website into a reference category of “Not a member or no use”.⁶

Covariates

We considered a range of potentially relevant sociodemographics: age, sex, country in UK, self-defined ethnic group (collapsed into White vs non-White due to low numbers in the non-White category), an indicator of living in an urban or rural areas (derived from Office for National Statistics Rural and Urban Classification of Output Areas) and equivalised household net income (based on the Organisation for Economic Co-operation and Development (OECD) equivalence scale, which was used to adjust household income by household composition²³).

Statistical analyses

We compared differences in sociodemographics between categories of social media use using ANOVA. We used binary generalised estimating equation (GEE) regression models (family: binomial; link: logit; correlation matrix: exchangeable) to assess relationships between social media use and product use, using separate models for each outcome: cigarette smoking, e-cigarette use and dual use. GEE models assess changes over time and account for the correlation caused by observations being from the same individuals.²⁴ We also present tests for trend based on frequency of social media use. Analyses were adjusted for time (categorical) as well as the sociodemographic variables listed above. Models of cigarette smoking were additionally adjusted for parental tobacco use, models of e-cigarette use were adjusted for parental e-cigarette use, and models of dual use were adjusted for both. Analyses used survey weights designed by the UKHLS survey team to account for clustered and stratified probability sampling and non-response bias.²⁵

We tested for interactions of social media use with age (split into above and below 18 years of age), sex and household income (in three groups). This was due to possible differences between those above and below the legal age of sale, greater social media use among women, and potentially differential effects by socioeco-

Table 1 Description of sample observations by social media use 2015–2021

Covariate	Weekday social media use					Total	P value for difference between groups
	None or not a member	<1 hour	1–3 hours	4–6 hours	≥7 hours		
Current cigarette smoking (%)	2.0	6.3	9.2	12.2	15.7	8.6	<0.001
Current e-cigarette use (%)	0.8	2.0	2.4	3.8	4.0	2.5	<0.001
Dual use (%)	0.3	0.9	1.1	1.7	2.0	1.1	<0.001
Male (%)	57.5	52.4	45.3	38.3	39.9	47.1	<0.001
Mean age (years) (SD)	12.0 (2.7)	15.22 (4.0)	16.49 (3.6)	16.95 (3.0)	17.7 (2.6)	15.74 (3.8)	<0.001
White ethnicity (%)	65.6	71.4	75.1	75.0	74.2	72.8	<0.001
Urban areas (%)	79.4	78.1	77.4	79.6	81.4	78.5	<0.001
Mean household income (£) (SD)	1679 (3485)	1709 (1290)	1689 (1055)	1622 (1066)	1551 (960)	1670 (1666)	<0.001
Parental cigarette smoking (%)	17.0	16.3	18.6	21.0	25.2	18.7	<0.001
Parental e-cigarette use (%)	7.3	7.5	8.3	9.4	10.5	8.3	<0.001
Overall N	4356	7808	11 739	5110	2715	31 728	

Results are collapsed across all survey years.

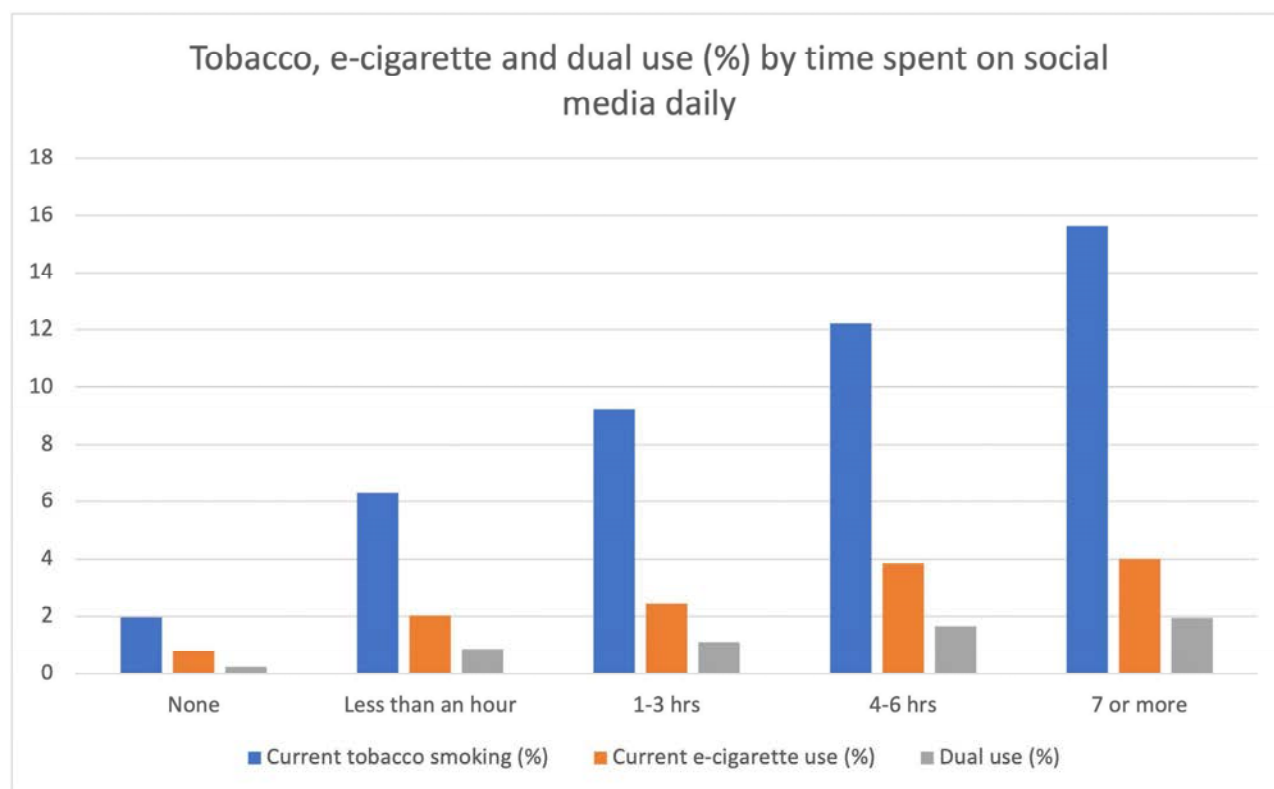


Figure 1 Cigarette smoking, e-cigarette use and dual use by social media use.

nomnic groups. All interactions were $p < 0.001$ and so we present stratified analyses. Due to the small numbers, we did not test interactions for dual use.

Table 2 Associations of social media use with current cigarette use from generalised estimating equation model

Weekday social media use (hours/day)	AOR	P value	Lower CI	Upper CI
None or not a member	Ref.	Ref.	Ref.	Ref.
<1 hour	1.92	<0.001	1.43	2.58
1–3 hours	2.56	<0.001	1.93	3.41
4–6 hours	2.87	<0.001	2.12	3.87
≥7 hours	3.60	<0.001	2.61	4.96
Year (2015/2016)	Ref.	Ref.	Ref.	Ref.
2016/2017	1.12	0.132	0.97	1.29
2017/2018	0.99	0.896	0.85	1.16
2018/2019	1.38	<0.001	1.17	1.62
2019/2020	1.24	0.019	1.04	1.48
2020/2021	1.01	0.925	0.82	1.25
Sex (male vs female)	1.15	0.084	0.98	1.34
Age (years)	1.20	<0.001	1.18	1.23
England	Ref.	Ref.	Ref.	Ref.
Wales	0.77	0.115	0.55	1.07
Scotland	0.86	0.290	0.65	1.14
Northern Ireland	1.07	0.608	0.82	1.41
White ethnicity	Ref.	Ref.	Ref.	Ref.
Non-White ethnicity	0.57	<0.001	0.43	0.76
Rural area vs urban	1.03	0.782	0.85	1.23
Lowest household income group	Ref.	Ref.	Ref.	Ref.
Middle household income group	0.84	0.011	0.74	0.96
Highest household income group	0.74	<0.001	0.63	0.86
Parental smoking yes vs no	2.91	<0.001	2.49	3.40

AOR, adjusted odds ratio; CI, confidence interval; Ref., reference.

Sensitivity analyses

We performed a range of sensitivity analyses to test the robustness of our findings. As it is possible that those not using social

Table 3 Associations of social media use and current e-cigarette use from generalised estimating equation model

Weekday social media use (hours/day)	AOR	P value	Lower CI	Upper CI
None or not a member	Ref.	Ref.	Ref.	Ref.
<1 hour	1.42	0.231	0.80	2.54
1–3 hours	1.92	0.030	1.07	3.46
4–6 hours	3.10	0.000	1.70	5.63
≥7 hours	2.73	0.003	1.40	5.29
Year (2015/2016)	Ref.	Ref.	Ref.	Ref.
2016/2017	0.21	<0.001	0.15	0.30
2017/2018	0.31	<0.001	0.24	0.41
2018/2019	0.41	<0.001	0.31	0.54
2019/2020	0.38	<0.001	0.27	0.54
2020/2021	0.43	<0.001	0.30	0.62
Sex (male vs female)	2.33	<0.001	1.81	3.00
Age (continuous)	1.20	<0.001	1.17	1.24
England	Ref.	Ref.	Ref.	Ref.
Wales	0.71	0.192	0.42	1.19
Scotland	0.73	0.130	0.48	1.10
Northern Ireland	0.82	0.398	0.53	1.29
White ethnicity	Ref.	Ref.	Ref.	Ref.
Non-White ethnicity	0.65	0.030	0.44	0.96
Rural area vs urban	1.08	0.582	0.82	1.43
Household income group lowest	Ref.	Ref.	Ref.	Ref.
Household income group middle	0.89	0.383	0.68	1.16
Household income group highest	0.78	0.085	0.59	1.03
Parental e-cigarette use yes vs no	2.97	<0.001	2.24	3.93

AOR, adjusted odds ratio; CI, confidence interval; Ref., reference.

Table 4 Associations of social media use with current e-cigarette and cigarette dual use from generalised estimating equation model

Weekday social media use (hours/day)	AOR	P value	Lower CI	Upper CI
None or not a member	Ref.	Ref.	Ref.	Ref.
<1 hour	2.33	0.095	0.86	6.27
1–3 hours	3.28	0.017	1.24	8.70
4–6 hours	4.26	0.005	1.55	11.72
≥7 hours	4.96	0.003	1.71	14.34
Year (2015/2016)	Ref.	Ref.	Ref.	Ref.
2016/2017	0.19	<0.001	0.11	0.31
2017/2018	0.26	<0.001	0.17	0.40
2018/2019	0.42	<0.001	0.28	0.63
2019/2020	0.30	<0.001	0.18	0.51
2020/2021	0.32	<0.001	0.17	0.59
Sex (male vs female)	2.16	<0.001	1.54	3.02
Age (continuous)	1.19	<0.001	1.13	1.25
England	Ref.	Ref.	Ref.	Ref.
Wales	0.96	0.903	0.52	1.77
Scotland	0.73	0.255	0.43	1.25
Northern Ireland	0.95	0.854	0.53	1.68
White ethnicity	Ref.	Ref.	Ref.	Ref.
Non-White ethnicity	0.72	0.282	0.39	1.32
Rural area vs urban	1.21	0.304	0.84	1.75
Household income group lowest	Ref.	Ref.	Ref.	Ref.
Household income group middle	0.89	0.526	0.63	1.27
Household income group highest	0.68	0.060	0.46	1.02
Parental smoking yes vs no	2.10	0.000	1.47	3.02
Parental e-cigarette use yes vs no	1.94	<0.001	1.29	2.91

AOR, adjusted odds ratio; CI, confidence interval; Ref., reference.

media at all are atypical, we repeated our analyses excluding these participants. Our main analyses used household income as a marker of socioeconomic status. We also performed our analyses using Index of Multiple Deprivation (IMD) (in five groups) as an alternative marker of socioeconomic status. We performed analyses categorising current e-cigarette use as participants who reported using e-cigarettes at least monthly. We also performed analyses controlling for a measure of mental health (the 12-item General Health Questionnaire (GHQ-12)) to consider whether this is a possible pathway, whereby social

media impacts mental health, which is then linked to cigarette and e-cigarette use.

Finally, we used fixed effects analyses to directly test if changes in social media use corresponded to uptake of cigarette smoking and e-cigarette use. These adjusted for the time-varying variables parental cigarette/e-cigarette use and household income. These models were on a smaller subset of individuals who were not product users when entering the study and who were found to change their social media use over time.

RESULTS

Outcomes and covariates across categories of social media use are shown in table 1. Overall, 8.6% of the sample reported current cigarette smoking at one or more data point, 2.5% reported current e-cigarette use, and 1.1% of participants were dual users at one or more data point. Social media use frequency broken down by covariates is shown in online supplemental appendix table 1.

Cigarette smoking, e-cigarette use and dual use were all more common among participants reporting greater social media use (all $p<0.001$) (figure 1). Some 2.0% of participants who used social media “None or not a member” reported being a current cigarette smoker compared with 15.7% among those using social media for ≥7 hours/day. Current e-cigarette use ranged from 0.8% among those not using social media to 2.5% among those using it for ≥7 hours/day.

Differences between categories of social media use were apparent for all variables studied (all $p<0.001$). Males were less likely to be in higher social media use groups than females (57.5% of the “None or not a member” social media group compared with 39.9% of the “≥7 hours/day” group). Social media use was more frequent at older ages (mean age of “None or not a member” social media group 12.0 years vs 17.7 years for the “≥7 hours/day” group). Parental cigarette smoking was more common among those using social media more frequently (17.0% for the “None or not a member” social media group vs 25.2% for the “≥7 hours/day” group) as was parental e-cigarette use (7.3% and 10.5%, respectively).

Table 2 shows results of our GEE models of social media use and cigarette smoking. Cigarette smoking was more common among those using social media more frequently (p for trend <0.001). Those using social media for “<1 hour/day” were more likely to be current cigarette smokers than those using social media “None or not a member” (adjusted odds ratio (AOR) 1.92, 95% CI 1.43 to 2.58) (table 2). Those using social media for “≥7 hours/day” were substantially more likely to be current cigarette smokers than those using social media “None or not a member” (AOR 3.60, 95% CI 2.61 to 4.96). Table 3 shows results for e-cigarette use. E-cigarette use was more common among those using social media more frequently (p for trend <0.001). E-cigarette use was more common

Table 5 Associations of social media use with current e-cigarette and cigarette use from gender stratified generalised estimating equation models

Weekday social media use (hours/day)	Males				Females			
	AOR	P value	Lower CI	Upper CI	AOR	P value	Lower CI	Upper CI
Current cigarette use								
None or not a member	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
<1 hour	1.83	0.003	1.23	2.74	2.01	0.002	1.30	3.10
1–3 hours	2.52	<0.001	1.70	3.75	2.59	<0.001	1.71	3.91
4–6 hours	2.81	<0.001	1.85	4.27	2.92	<0.001	1.90	4.49
≥7 hours	3.47	<0.001	2.22	5.44	3.72	<0.001	2.35	5.90
Current e-cigarette use								
None or not a member	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
<1 hour	1.85	0.068	0.95	3.59	0.89	0.811	0.34	2.35
1–3 hours	2.80	0.002	1.47	5.32	0.98	0.966	0.35	2.74
4–6 hours	4.97	<0.001	2.56	9.62	1.34	0.576	0.48	3.71
≥7 hours	4.10	<0.001	1.90	8.87	1.34	0.603	0.45	4.01

Results from models controlled for year, age, sex, country in UK, self-defined ethnic group (White vs non-White), an indicator of living in an urban or rural area, and equivalised household net income. Cigarette use models were adjusted for cigarette smoking by caregivers and e-cigarette models by use of e-cigarettes by caregivers.

AOR, adjusted odds ratio; CI, confidence interval; Ref., reference.

Table 6 Associations of social media use with current e-cigarette and cigarette use from household income stratified generalised estimating equation models

Weekday social media use (hours/day)	Lowest income group				Middle income group			
	AOR	P value	Lower CI	Upper CI	AOR	P value	Lower CI	Upper CI
Current cigarette use								
None or not a member	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
<1 hour	2.17	0.008	1.22	3.86	1.52	0.107	0.91	2.55
1–3 hours	3.06	<0.001	1.74	5.36	2.28	0.001	1.39	3.74
4–6 hours	3.69	<0.001	2.08	6.52	2.47	0.001	1.47	4.14
≥7 hours	4.17	<0.001	2.27	7.65	3	<0.001	1.74	5.17
–	–	–	–	–	Richest income group			
–	–	–	–	–	Ref.	Ref.	Ref.	Ref.
–	–	–	–	–	2.67	0.001	1.53	4.65
–	–	–	–	–	2.99	<0.001	1.73	5.18
–	–	–	–	–	3.41	<0.001	1.9	6.13
–	–	–	–	–	5.22	<0.001	2.82	9.67
Current e-cigarette use								
					AOR	P value	Lower CI	Upper CI
None or not a member	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
<1 hour	0.75	0.501	0.32	1.74	2.04	0.145	0.78	5.34
1–3 hours	0.87	0.735	0.39	1.94	2.61	0.069	0.93	7.34
4–6 hours	1.78	0.17	0.78	4.06	4.5	0.004	1.61	12.6
≥7 hours	1.65	0.301	0.64	4.23	4.51	0.008	1.49	13.69
–	–	–	–	–	Richest income group			
–	–	–	–	–	Ref.	Ref.	Ref.	Ref.
–	–	–	–	–	5.42	0.019	1.32	22.34
–	–	–	–	–	8.03	0.004	1.95	33.02
–	–	–	–	–	10.65	0.001	2.53	44.79
–	–	–	–	–	7.85	0.008	1.72	35.82

Results from models controlled for year, age, sex, country in UK, self-defined ethnic group (White vs non-White), an indicator of living in an urban or rural area, and equivalised household net income. Cigarette use models were adjusted for cigarette smoking by caregivers and e-cigarette models by use of e-cigarettes by caregivers. AOR, adjusted odds ratio; CI, confidence interval; Ref., reference.

among those using social media “1–3 hours per day” compared with those using it “None or not a member” (AOR 1.92, 95% CI 1.07 to 3.46). E-cigarette use was considerably more likely among participants using social media “≥7 hours/day” than those using social media “None or not a member” (AOR 2.73, CI 1.40 to 5.29).

Table 4 shows results for dual cigarette and e-cigarette use. Models have wide confidence intervals reflecting low levels of dual use. Those using social media more frequently were more likely to be dual users (p for trend <0.001). Those using social media “1–3 hours per day” were more likely to be dual users compared with those using it “None or not a member” (AOR 3.28, 95% CI 1.24 to 8.70). Dual use was more likely among participants using social media “≥7 hours/day” than among those using social media “None or not a member” (AOR 4.96, 95% CI 1.71 to 14.34).

Interactions of social media and sex were statistically significant for both cigarettes and e-cigarettes (both p <0.001). In stratified models (table 5) AORs were similar between the sexes for current cigarette smoking. For e-cigarettes, associations between social media use and e-cigarette use were statistically significant for males but not for females (AOR 4.10, 95% CI 1.90 to 8.87 for males for “≥7 hours/day” vs “None or not a member” social media use).

Interactions with household income categories were statistically significant (p <0.001 for both cigarettes and e-cigarettes) (table 6). In stratified analyses of cigarette smoking, point estimates for the richest income group were higher than for the lowest income group, although these overlapped (eg, AOR 5.22 for “≥7 hours/day”, 95% CI 2.82 to 9.67 for the richest income group vs AOR 4.17, 95% CI 2.27 to 7.65 for the lowest income group). For e-cigarette use, associations were statistically significant for the high-

est income groups (eg, AOR 7.85, 95% CI 1.72 to 35.82 for “≥7 hours/day” vs no social media use) but were not statistically significant for the lowest income group.

Analyses stratified by age found similar results to main analyses for cigarettes (online supplemental appendix table 2). Models for e-cigarette use were only statistically significant among those <18 years old.

Sensitivity analyses

GEE analyses excluding those not using any social media were similar to main analyses (online supplemental appendix table 3). Analyses using IMD as a marker of socioeconomic status rather than household income also gave similar results (online supplemental appendix table 4). Analyses classifying current e-cigarette use as participants using them at least monthly also gave similar results although with larger point estimates (online supplemental appendix table 5). Analyses controlling for GHQ-12 as a measure of mental health were similar for cigarettes but did not find statistically significant associations between social media and e-cigarette or dual use. This may indicate that social media use impacts mental health, which in turn impacts likelihood of using cigarettes or e-cigarettes, although this result should be treated with caution (online supplemental appendix table 6).

Fixed effect analyses gave similar results to main analyses for uptake of cigarette smoking (online supplemental appendix table 7). It should be noted that sample size was much reduced for this model ($n=864$). These analyses found some evidence that changes in social media use are linked to uptake of cigarette

smoking in a dose-response manner (p for trend=0.053). For example, changing to using social media for ≥ 7 hours/day was associated with more than double the odds of taking up cigarette smoking (AOR 2.33, 95% CI 1.28 to 4.24).

Associations between changes in social media use and uptake of e-cigarettes did not reveal associations between changes in social media use and uptake of e-cigarettes. These analysis models had even lower sample sizes ($n=564$). For example, AORs of e-cigarette uptake ranged from 0.71 (95% CI 0.34 to 1.48) for participants using social media " <1 hour/day" to AOR 0.84 (95% CI 0.38 to 1.85) for those using social media " ≥ 7 hours/day". The test for trend was not statistically significant ($p=0.584$).

DISCUSSION

The main finding of the present study is that in children and young adults more frequent social media use was associated with a higher likelihood of both current use of cigarettes and e-cigarettes. This association was independent of other factors associated with increasing smoking and vaping including age, gender, socioeconomic status and parental smoking and vaping. These findings were robust to sensitivity analyses, while in stratified analyses there were more consistent associations for e-cigarette use among those under the legal age of sale, males and those with higher household incomes.

While we were unable to assess use of specific social media platforms or what content was being accessed, we propose a number of possible, non-exclusive explanations for this relationship. First, and most straightforwardly, there is evidence that the corporations behind cigarette smoking and vaping make use of social media to advertise and promote their products.^{8–10,16} This includes direct advertising which is algorithmically targeted and the use of paid social media influencers who present smoking and vaping as a fashionable and desirable activity. Greater time spent on social media is likely to increase exposure to these forms of influence. While cigarettes and e-cigarettes are likely promoted differently, we found association with use of both products, highlighting the need for greater understanding of such corporate behaviours. Second, social media use has been shown to have features in common with reward-seeking addictive behaviour.²⁶

High social media use may increase susceptibility to other addictive behaviours like smoking. Alternatively, both behaviours may be driven by a common susceptibility. Third, as a space that is largely unsupervised by parents/caregivers, social media use may encourage behaviours that are transgressive, including cigarette smoking and vaping. There is evidence that peer smoking is a strong influence on child uptake of smoking²⁷ and social media is one of the ways in which peer smoking and vaping will be experienced, both by seeing others' behaviour and by sharing "influencer content" that promotes these behaviours. Stratified analyses revealed more consistent associations for cigarettes, while for e-cigarettes statistically significant associations were only found for those under the legal age of sale, among males, and those from richer households. Analyses of cigarette smoking did not identify changes over time, which fits with other evidence that smoking prevalence has been reasonably consistent over this time frame.²⁸ Analyses of e-cigarette use found reduced odds of these outcomes after 2015/2016, likely caused by changes in e-cigarette use ascertainment, although our main findings were robust to reclassification to examine monthly use. Our main analyses focused on weekly use of e-cigarettes; as any health impacts are probably related to amounts of vapour inhaled, this measure of regular use is more important for health than e-cigarette experimentation.

Strengths and limitations

This study uses a nationally representative cohort to examine social media use and use of cigarettes and e-cigarettes over time. UKHLS households are sampled based on geographical areas, population densities and ethnic composition, with survey weight adjusting for differential non-response across groups.²⁹ We conducted a range of sensitivity analyses, although other potential factors such as edu-

cation may also be important. All data are based on self-report, and specifically we do not have information about which social media platforms were being used or how individuals were using them, for example, the extent to which they are interacting socially with individuals they know or consuming content from influencers, personalities or media corporations, etc. Precise pathways remain to be fully elucidated: our sensitivity analyses point to a possible role for mental health, although it should be noted that a formal mediation analysis was outside the scope of this article. As cigarette smoking is linked to poorer mental health, these relationships could well be bidirectional.³⁰ This, as well as potential targeted advertising, are among pathways that should be investigated in both quantitative and qualitative research.

Policy implications

Although we do not have data on the specific platforms used or content used, there is compelling evidence that vape companies are using social media to market their products.^{2–5} The content that social media users are exposed to is to a substantial extent algorithmically controlled, both through targeted advertising and by the promotion of material that maximises engagement in order to increase revenue to the platform. This can be controlled. For example, far right imagery which is otherwise widely available is largely inaccessible in Germany, as a consequence of German law which social media platforms are bound to enforce. The companies that own social media platforms have substantial power to modify exposure to material that promotes smoking and vaping if they choose to or are compelled to. Voluntary codes seem unlikely to achieve this, and the introduction and enforcement on bans on material that promote this should be considered. In general, we think that algorithms should not be promoting products to individuals that they cannot legally buy. Legislation and enforcement around this and other corporate determinants of health concerns should be considered a core part of online safety and child protection.

CONCLUSION

This longitudinal analysis of children and young people in the UK found that more frequent social media use is associated with an increased risk of cigarette and e-cigarette use.

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REFERENCES

- 1 Royal Society for Public Health. Status of mind - social media and young people's mental health and wellbeing. London, 2018.
- 2 Kong G, LaVallee H, Rams A, et al. Promotion of vape tricks on YouTube: content analysis. *J Med Internet Res* 2019;21:e12709.
- 3 Phua J, Jin SV, Hahm JM. Celebrity-endorsed e-cigarette brand Instagram advertisements: effects on young adults' attitudes towards e-cigarettes and smoking intentions. *J Health Psychol* 2018;23:550–60.
- 4 O'Brien EK, Hoffman L, Navarro MA, et al. Social media use by leading US e-cigarette, cigarette, smokeless tobacco, cigar and hookah brands. *Tob Control* 2020;29:e87–97.
- 5 Smith MJ, Buckton C, Patterson C, et al. User-generated content and influencer marketing involving e-cigarettes on social media: a scoping review and content analysis of YouTube and Instagram. *BMC Public Health* 2023;23:530.
- 6 McNamee P, Mendolia S, Yerokhin O. Social media use and emotional and behavioural outcomes in adolescence: evidence from British longitudinal data. *Econ Hum Biol* 2021;41:100992.
- 7 Tobacco Tactics. Social media. Available: <https://tobaccotactics.org/wiki/social-media/> [Accessed 3 Jun 2023].

- 8 Huang GC, Unger JB, Soto D, et al. Peer influences: the impact of online and offline friendship networks on adolescent smoking and alcohol use. *J Adolesc Health* 2014;54:508–14.
- 9 Yoo W, Yang J, Cho E. How social media influence college students' smoking attitudes and intentions. *Comput Human Behav* 2016;64:173–82.
- 10 Vannucci A, Simpson EG, Gagnon S, et al. Social media use and risky behaviors in adolescents: a meta-analysis. *J Adolesc* 2020;79:258–74.
- 11 Shan L, Azagba S. Longitudinal associations of tobacco-related social media involvement with cigarette and e-cigarette initiation among US adolescents. *Eur J Pediatr* 2022;181:189–96.
- 12 Stanton CA, Pasch KE, Pericot-Valverde I, et al. Longitudinal associations between U.S. youth exposure to E-cigarette marketing and E-cigarette use harm perception and behavior change. *Prev Med* 2022;164:107266.
- 13 Vassey J, Galimov A, Kennedy CJ, et al. Frequency of social media use and exposure to tobacco or nicotine-related content in association with E-cigarette use among youth: a cross-sectional and longitudinal survey analysis. *Prev Med Rep* 2022;30:102055.
- 14 Vrinten C, Parnham JC, Filippidis FT, et al. Risk factors for adolescent smoking uptake: analysis of prospective data from the UK Millennium Cohort Study. *Tob Induc Dis* 2022;20:83.
- 15 Boniel-Nissim M, van den Eijnden RJJM, Furstova J, et al. International perspectives on social media use among adolescents: implications for mental and social well-being and substance use. *Comput Hum Behav* 2022;129:107144.
- 16 Vassey J, Valente T, Barker J, et al. E-cigarette brands and social media influencers on Instagram: a social network analysis. *Tob Control* 2023;32:e184–91.
- 17 Furlow B. Juul settles youth e-cigarette marketing lawsuits. *Lancet Respir Med* 2023;11.
- 18 Stead M, Ford A, Angus K, et al. E-cigarette advertising in the UK: a content analysis of traditional and social media advertising to observe compliance with current regulations. *Nicotine Tob Res* 2021;23:1839–47.
- 19 Kong G, Laestadius L, Vassey J, et al. Tobacco promotion restriction policies on social media. *Tob Control* 2022;tobaccocontrol-2022-057348.
- 20 Donaldson SI, Dormanesh A, Perez C, et al. Association between exposure to tobacco content on social media and tobacco use: a systematic review and meta-analysis. *JAMA Pediatr* 2022;176:878–85.
- 21 Institute for Social and Economic Research. Understanding society: waves 1-12, 2009-2021 and harmonised BHPS: waves 1-18, 1991-2009, user guide. Colchester: University of Essex, 2022.
- 22 Understanding Society: The UK Household Longitudinal Study. Consent information, Available: <https://www.understandingsociety.ac.uk/documentation/mainstage/consents> [Accessed 3 Jun 2023].
- 23 Anyaegbu G. Using the OECD equivalence scale in taxes and benefits analysis. *Econ Lab Market Rev* 2010;4:49–54.
- 24 Liang K-Y, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986;73:13–22.
- 25 Lynn P, Kaminska O. Weighting strategy for Understanding Society; 2010Nov, Understanding Society Working Paper Series-Number 2010-05. Available: <https://www.understandingsociety.ac.uk/wp-content/uploads/working-papers/2010-05.pdf>
- 26 Lindström B, Bellander M, Schultner DT, et al. A computational reward learning account of social media engagement. *Nat Commun* 2021;12:1802.
- 27 Lavery AA, Filippidis FT, Taylor-Robinson D, et al. Smoking uptake in UK children: analysis of the UK Millennium Cohort Study. *Thorax* 2019;74:607–10.
- 28 Office for National Statistics. Adult smoking habits in the UK. Available: <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2022#> [Accessed 21 Sep 2023].
- 29 Benzeval M, Bollinger CR, Burton J, et al. The representativeness of Understanding Society; 2020Mar, Understanding Society Working Paper Series-Number 2020-08. Available: <https://www.understandingsociety.ac.uk/wp-content/uploads/workingpapers/2020-08.pdf>
- 30 Taylor G, McNeill A, Girling A, et al. Change in mental health after smoking cessation: systematic review and meta-analysis. *BMJ* 2014;348:g1151.

Disponibilidade, custo e acessibilidade de medicamentos essenciais para doenças respiratórias crônicas em países de baixo e médio rendimento: um estudo transversal

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RESUMO

Faltam dados contemporâneos sobre a disponibilidade, custo e acessibilidade de medicamentos essenciais para doenças respiratórias crônicas (DRC) em países de baixo e médio rendimento (PBMR), apesar de a maioria das pessoas com DRC viverem em PBMR. Foram recolhidos dados transversais para sete medicamentos para DRC em farmácias, unidades de saúde e centros de distribuição de medicamentos de 60 PBMR em 2022-2023. Os medicamentos para alívio sintomático estavam amplamente disponíveis e acessíveis, enquanto os tratamentos preventivos variavam muito em termos de custo, estavam menos disponíveis e eram em grande parte inacessíveis. Há uma necessidade urgente de abordar estas questões se se quiser atingir o Objetivo de Desenvolvimento Sustentável 3 para as pessoas com asma até 2030.

INTRODUCTION

The forthcoming High-Level Meeting of the United Nations General Assembly on Non-Communicable Diseases (NCDs) will address the 15 million premature deaths from NCDs annually, most of which occur in low-income and middle-income countries (LMICs).¹ The United Nations Sustainable Development Goals (SDGs) demand 'safe, effective, quality and affordable essential medicines for all' by 2030.² Non-communicable chronic respiratory diseases (CRDs), for example, asthma and chronic obstructive pulmonary disease (COPD), cause substantial morbidity and mortality, disproportionately affecting those living in poverty in LMICs.³ Recommended medicines for CRDs include inhaled and oral drugs that are on the WHO Model List of Essential Medicines (EML), which defines safe, efficacious, cost-effective medicines that should be available everywhere.⁴ Access to essential, affordable CRD medicines is limited in LMICs.^{5,6} Up-to-date data on the availability, cost and affordability of WHO essential medicines for CRDs in LMICs are missing.

METHODS

This cross-sectional survey of medication availability and cost was completed by healthcare professionals working in LMICs (online supplemental appendix). Professionals collected standardised data from three facilities (pharmacy, healthcare facility (HCF) and central medicine store (CMS)) in each country. Prices (US\$) for 1-month treatment were compared. Affordability was defined by 1-month treatment costing the lowest paid government worker <1 day's wage, as per established methodology.⁷

RESULTS

Data from 60 LMICs were collected between June 2022 and April 2023 (online supplemental appen-

dix). 18 countries were low income, 24 lower middle income and 17 upper middle income. The sub-Saharan African region was best represented (27 countries). Information for all three facilities was submitted for 42/60 (70%) countries. Information for pharmacies, HCFs and CMS was provided by 57, 56 and 46 LMICs, respectively. Most pharmacies were private (89%), most HCFs were public institutions (80%).

Inhaled short-acting beta agonists

Inhaled short-acting beta agonist (SABA) was available in 93% of pharmacies, 79% of HCFs and 78% of CMS (table 1, figure 1, online supplemental appendix). The median cost of 1-month treatment in pharmacies was \$2.95 (IQR \$1.99–4.97), \$2.34 (IQR \$1.38–3.86) in HCFs and \$1.39 (IQR \$1.20–2.83) in CMS. SABAs were both available and affordable in 51% (29/57) of all pharmacies and 61% (31/56) of all HCFs that submitted data.

Inhaled corticosteroids

Beclomethasone 100 mcg/dose, or equivalent, was available in 54% of pharmacies, 55% of HCFs and 48% of CMS (table 1, figure 1, online supplemental appendix). The median costs were \$5.40 (IQR \$2.12–8.60) in pharmacies, \$3.01 (IQR \$1.21–5.89) in HCFs and \$1.16 (IQR \$0.11–3.24) in CMS. Inhaled corticosteroids (ICS) were both available and affordable in 30% (17/57) of pharmacies and 36% (20/56) of HCFs.

Combination inhaled corticosteroid–long-acting beta agonists

Budesonide-formoterol 200+6 mcg/dose, or equivalent, was available in 54% of pharmacies, 38% of HCFs and 20% of CMS (table 1, figure 1, online supplemental appendix). The median costs were \$19.20 (IQR \$9.73–27.43) in pharmacies, \$18.41 (IQR \$11.30–24.49) in HCFs and \$7.14 (IQR \$3.90–8.13) in CMS. Overall, it was both available and affordable in 11% (6/57) of pharmacies and 5% (3/56) of HCFs. Costs for budesonide-formoterol 100+6 mcg/dose were similar, but it was less available.

Long-acting anti-muscarinic antagonists

A standardised long-acting muscarinic antagonist (LAMA) formulation was available in 46% of pharmacies, 29% of HCFs and 24% of CMS (table 1, figure 1, online supplemental appendix). The median costs were \$30.53 (IQR \$9.45–47.29) in pharmacies, \$26.01 (IQR \$15.32–36.70) in HCFs and \$17.98 (IQR \$0.98–32.17) in CMS. LAMAs were available and affordable in 7% (4/57) of pharmacies and 4% (2/56) of HCFs.



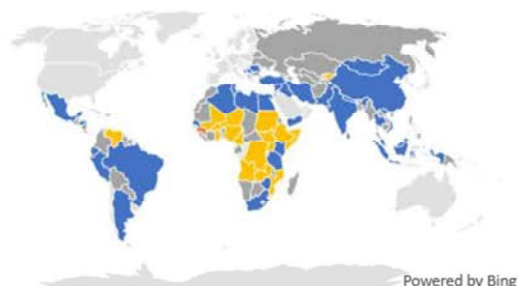
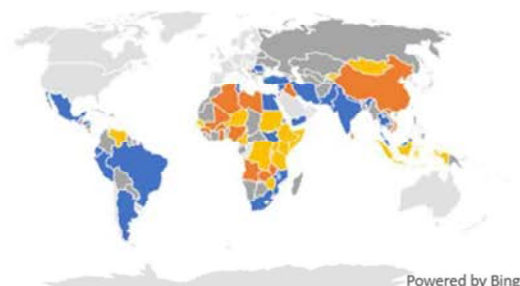
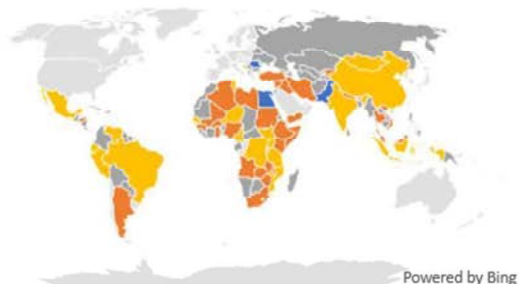
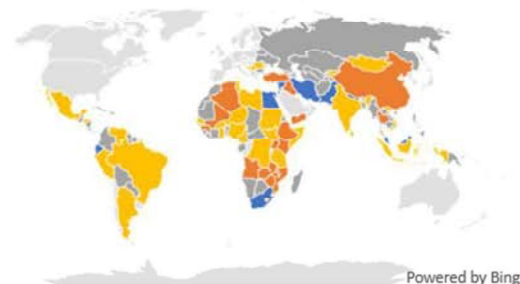
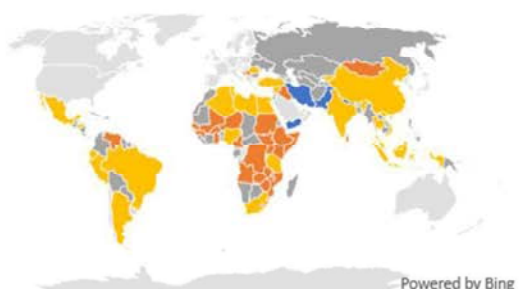
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Table 1 Comparisons of availability and costs for 1-month treatment for standardised SABA, ICS, ICS-LABA and LAMA formulations in pharmacy, HCF and CMS

Facility	Medicine					
	SABA	ICS	ICS-LABA (100+6 mcg/dose)	ICS-LABA (200+6 mcg/dose)	LAMA	5-day oral OCS*
Pharmacy						
Availability	53/57 (93%)	31/57 (54%)	22/57 (39%)	31/57 (54%)	26/57 (46%)	47/57 (82%)
Median cost (IQR, US\$)	2.95 (1.99–4.97)	5.40 (2.12–8.60)	19.71 (12.00–42.00)	19.20 (9.73–27.43)	30.53 (9.45–47.29)	1.65 (0.60–3.29)
Median DOW (IQR)	0.8 (0.2–1.8)	0.6 (0.3–3.5)	4.3 (2.6–8.3)	4.1 (1.9–6.9)	3.5 (1.4–5.8)	0.3 (0.1–1.0)
HCF						
Availability	44/56 (79%)	31/56 (55%)	10/56 (18%)	21/56 (38%)	16/56 (29%)	40/56 (71%)
Median cost (IQR, US\$)	2.34 (0.1–1.0)	3.01 (1.21–5.89)	16.49 (12.03–26.55)	18.41 (11.30–24.49)	26.01 (15.32–36.70)	0.02 (0.01–0.08)
Median DOW (IQR)	0.4 (0.1–1.9)	0.5 (0.1–1.8)	3.2 (2.2–4.4)	3.5 (1.5–6.1)	3.3 (1.4–5.6)	0.01 (0–0.03)
CMS						
Availability	36/46 (78%)	22/46 (48%)	7/46 (15%)	9/46 (20%)	11/46 (24%)	35/46 (76%)
Median cost (IQR, US\$)	1.39 (1.20–2.83)	1.16 (0.11–3.24)	26.48 (13.31–29.85)	7.14 (3.90–8.13)	17.98 (0.98–32.17)	0.02 (0.01–0.03)

Availability: number of facilities where medicine is available by total number of facilities that submitted data. See the online supplemental appendix for definitions of standardised formulations.
 *Standardised formulation for OCS is 5-day course of oral prednisolone, 40 mg once a day using 5 mg tablets. CMS costs are wholesale costs, unsuitable for affordability/days of work calculations.
 CMS, central medicine stores; DOW, days of work required to pay for 1-month treatment; HCF, healthcare facility; ICS, inhaled corticosteroid; ICS-LABA, inhaled corticosteroid–long-acting beta agonist (formoterol) combination; LAMA, long-acting muscarinic antagonist inhaler; OCS, oral corticosteroids; SABA, short-acting beta agonist inhaler.

A SABA availability and affordability**B** ICS availability and affordability**C** ICS-formoterol (100+6 mcg/dose) availability and affordability**D** ICS-formoterol (200+6 mcg/dose) availability and affordability**E** LAMA availability and affordability**Figure 1** Availability and affordability of standardised (A) SABA, (B) ICS, (C) ICS-LABA (100+6 mcg/dose), (D) ICS-LABA (200+6 mcg/dose) and (E) LAMA formulations in pharmacy or HCF. Blue: available and affordable. Yellow: available but not affordable. Orange: unavailable. Grey: low-income and middle-income country (LMIC), no information. HCF, healthcare facility; ICS, inhaled corticosteroid; ICS-LABA, inhaled corticosteroid–long-acting beta agonist (formoterol) combination; LAMA, long-acting muscarinic antagonist inhaler; SABA, short-acting beta agonist inhaler.

Other essential medicines, WHO regions and income groups

Oral prednisolone was affordable and available between 70% and 80% of facilities (table 1). Other medicines were less available (online supplemental appendix). There were variations which region and income groups had the cheapest and most affordable medicines across facilities.

DISCUSSION

This is the largest cross-sectional study of availability, cost and affordability of CRD medicines in LMICs to date. It included data from 60 LMICs, representing 84% of the global LMIC population, and 16 of the 20 most populous LMICs.

Inhaled SABA and prednisolone were almost universally available. There were large cost ranges, SABAs were the cheapest inhalers. Medicines were cheaper in HCFs than pharmacies and price typically increased between CMS and pharmacy/HCF. In some countries medicines were free or subsidised.

We identified improvement in inhaled corticosteroid–long-acting beta agonist (ICS-LABA) availability compared with the last decade, with ICS-LABA now being available in more than half of pharmacies, and one-third of HCFs, possibly because of inclusion in the WHO EML and international guidelines.⁶ SABA and ICS availability in HCFs and CMS also improved compared with previously.⁵

Acute, symptomatic treatments (SABA, prednisolone) for CRDs were more affordable than daily treatments needed to reduce morbidity and mortality (ICS, ICS-LABA, LAMA). Guidelines recommend that first-line asthma treatment should be ICS-LABA, or ICS whenever SABA is taken.⁸ However, our findings suggest that these recommendations are largely unaffordable, and economic realities may force patients to use cheaper, riskier approaches.⁸

The median daily wage was \$4.33 (IQR \$2.17–9.55) providing an indication of ‘affordability’ for a month’s treatment, but acknowledging that many earn less than the lowest paid government worker. Making ICS-formoterol (median cost at least \$16.49) affordable like this, or by benchmarking against SABA, could achieve a tipping point for the widespread adoption of anti-inflammatory reliever asthma therapy, especially considering the greater efficacy of ICS-formoterol.⁸ A similar approach to LAMA pricing could improve COPD management.⁹

Our study had several strengths. Data came from all income levels and regions and represented a large proportion of those living in LMICs. Comparisons were possible by using standardised data collection derived from established tools. Patient experience was reflected, as we presented a snapshot of the facility on the data collection day.

The study had some weaknesses. It was conducted over 11 months. Costs were compared using US\$, dependent on exchange rates. Median price ratios were previously used for benchmarking, but the reference prices are out of date and no longer recommended.⁷ Convenience sampling introduced possible selection bias towards better equipped facilities in urban areas. Mostly only one facility was sampled per country. We did not assess medicine quality, expiry date nor data from multiple time points.

Establishing national CRD strategies that include medicines, generating country-specific data, buy-in from global organisations and patient advocacy are key to improving medicine access by addressing in-country demand and political commitment.¹⁰ Cost-effectiveness data for inhaled medicines specific for LMICs are needed, given that they reduce exacerbations and hospitalisations, which substantially drive the costs of CRDs.⁹ There is an urgent need to address the availability and affordability of essential CRD medicines if SDGs are to be achieved for all by 2030.

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Contributors MS and KM devised the study. OBO, SJ, DMGH, RN, JM and CP provided input on the protocol. All Chronic Respiratory Diseases Medicines Survey Investigators contributed to data collection. MS completed the analysis with KM, and both assessed and verified the data. MS wrote a first draft, with input from KM, OBO, SJ, DMGH, RN, BWA, JM and CP. All investigators were invited to comment on a second draft. All had full access to all the data in the study and had final responsibility to submit for publication.

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REFERENCES

- 1 Bukhman G, Mocumbi AO, Atun R, et al. The lancet NCDI poverty commission: bridging a gap in universal health coverage for the poorest billion. *Lancet* 2020;396:991–1044.
- 2 United Nations. Sustainable development goals. Sustainable development goals publication. 2021. Available: <https://sdgs.un.org/goals> [Accessed 25 Sep 2021].
- 3 Meghji J, Mortimer K, Agusti A, et al. Improving lung health in low-income and middle-income countries: from challenges to solutions. *Lancet* 2021;397:928–40.
- 4 World Health Organization. World Health Organization model list of essential medicines - 22nd list. Geneva World Health Organization; 2021.
- 5 Babar Z-U-D, Lessing C, Mace C, et al. The availability, pricing and affordability of three essential asthma medicines in 52 low- and middle-income countries. *Pharmacoeconomics* 2013;31:1063–82.
- 6 Stolbrink M, Thomson H, Hadfield RM, et al. The availability, cost, and affordability of essential medicines for asthma and COPD in low-income and middle-income countries: a systematic review. *Lancet Glob Health* 2022;10:e1423–42.
- 7 Health Action International. Collecting evidence on medicine prices & availability [Health Action International]. 2020. Available: <https://haiweb.org/what-we-do/priceavailability-affordability/collecting-evidence-on-medicine-prices-availability/> [Accessed 13 Jul 2023].
- 8 Reddel HK, Bacharier LB, Bateman ED, et al. Global initiative for asthma (GINA) strategy 2021 - executive summary and rationale for key changes. *J Allergy Clin Immunol Pract* 2022;10:S1–18.
- 9 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease [Global Initiative for Chronic Obstructive Lung Disease]. 2023. Available: goldcopd.org
- 10 Stolbrink M, Chinouya MJ, Jayasooriya S, et al. Improving access to affordable quality-assured inhaled medicines in low- and middle-income countries. *Int J Tuberc Lung Dis* 2022;26:1023–32.