

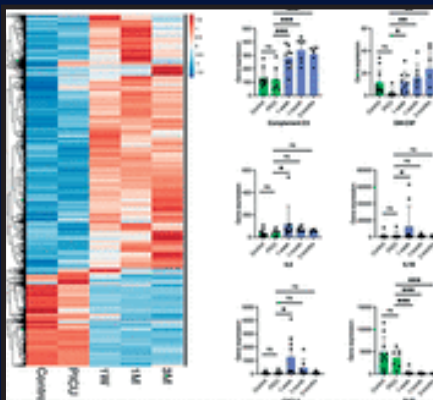
Thorax

ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

com artigos do

ARCHIVES OF
DISEASE IN
CHILDHOOD

Edição Portuguesa



Vacina
disponível na
época gripal
2023/24

PARA ADULTOS COM 60 OU MAIS ANOS DE IDADE

EFLUELDA®

AJUDA A QUEBRAR O CIRCUITO DA GRIPE

4x

MAIS ANTIGÉNIO
por estirpe vs. vacina
de dose padrão^{1,2}

+24,2%
(IC 95%; 9,7% - 36,5%)

EFICÁCIA RELATIVA SUPERIOR
vs. vacina de dose padrão em indivíduos
com 65 ou mais anos de idade^{1,3}

sanofi

Efluelda®
Vacina quadrivalente contra a gripe
(vírio fragmentado, inativado), 60 mcg HA/estirpe

REFERÊNCIAS:

1. DiazGranados CA, et al. (2014). Efficacy of High-Dose versus Standard-Dose influenza vaccine in older adults. New England Journal of Medicine, 371(7): 635-645. doi: 10.1056/NEJMoa1315727 2. CDC. Fluzone High-Dose Seasonal Influenza Vaccine. 2022. Disponível em: https://www.cdc.gov/flu/prevent/qa_fluzone.htm. Último acesso em Julho 2023. 3. RCM Efluelda® Agosto 2023.

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 4.8. do RCM completo. **Nome do medicamento:** EFLUELDA, suspensão injetável em seringa pré-cheia. Vacina quadrivalente contra a gripe (vírio fragmentado, inativado), 60 microgramas HA/estirpe. **Composição Qualitativa e Quantitativa:** Vírus da gripe (inativado, fragmentado) das seguintes estirpes*: A/Victoria/4897/2022 (H1N1) pdm09 - estirpe análoga (A/Victoria/4897/2022, IVR-238) 60 microgramas HA**, A/Darwin/9/2021 (H3N2) estirpe análoga (A/Darwin/9/2021, SAN-010) 60 microgramas HA**, B/Austria/1359417/2021 - estirpe análoga (B/Michigan/01/2021, tipo selvagem) 60 microgramas HA**, B/Phuket/3073/2013 - estirpe análoga (B/Phuket/3073/2013, tipo selvagem) 60 microgramas HA**. Por dose de 0,7 ml, * propagados em ovos de galinha embrionados ** hemaglutinina. Esta vacina está conforme as recomendações da OMS (Hemisfério Norte) e a decisão da UE para a época de 2023/2024. EFLUELDA pode conter vestígios de ovos, como ovalbumina, formaldeído que são utilizados durante o processo de fabrico (ver secção 4.3). Lista completa de excipientes, ver secção 6.1 do RCM Completo. **Forma Farmacéutica:** Suspensão injetável em seringa pré-cheia. Após agitação suave, EFLUELDA é um líquido incolor opalescente. **Indicações terapêuticas:** EFLUELDA está indicado para a prevenção da gripe, como imunização ativa dos adultos com 60 ou mais anos de idade. A utilização de EFLUELDA deve basear-se nas recomendações oficiais sobre a vacinação contra a gripe. **Posologia e modo de administração:** Posologia: Em adultos com 60 ou mais anos: uma dose de 0,7 ml. População pediátrica: A segurança e eficácia de EFLUELDA em crianças com menos de 18 anos de idade não foram estabelecidas. **Modo de administração:** A via de administração preferencial para esta vacina é a via intramuscular embora possa também ser administrada por via subcutânea. O local recomendado para a injeção intramuscular é a região deltoide. A vacina não deve ser injetada na região glútea ou em áreas onde possa existir um tronco nervoso principal. Para instruções acerca da preparação do medicamento antes da administração, ver secção 6.6. do RCM completo. **Contra-indicações:** Hipersensibilidade à substância ativa ou a qualquer um dos excipientes mencionados na secção 6.1 do RCM completo ou a qualquer componente que possa estar presente em quantidades vestigiais, como resíduos de ovo (ovalbumina, proteínas de galinha) e formaldeído. **Efeitos indesejáveis:** a. Resumo do perfil de segurança: A informação sobre reações adversas é baseada em dados provenientes de dois ensaios clínicos com EFLUELDA e na experiência clínica e de pós-comercialização com a vacina trivalente contra a gripe (vírio fragmentado, inativado) de dose elevada (TIV-HD). A segurança de EFLUELDA foi avaliada numa análise conjunta de dois ensaios clínicos (QHD00013 e QHD00011) em que 2549 adultos de 60 ou mais anos de idade (378 adultos de 60 a 64 anos de idade e 2171 adultos com 65 ou mais anos) receberam EFLUELDA. A reação adversa notificada com mais frequência após a vacinação foi dor no local da injeção relatada por 42,6% dos participantes do estudo, seguida por mialgia (23,8%), dor de cabeça (17,3%) e mal-estar (15,6%). A maioria destas reações ocorreu e resolveu-se dentro de três dias após a vacinação. A intensidade da maioria destas reações foi leve a moderada. No geral, as reações adversas foram geralmente menos frequentes em participantes com 65 ou mais anos do que em participantes com 60 a 64 anos. A reatogenicidade de EFLUELDA foi ligeiramente aumentada em comparação com a vacina de dose padrão, mas não foi observada nenhuma grande diferença na intensidade. A segurança de EFLUELDA (QIV-HD) foi avaliada num estudo descritivo (QHD00028) no qual os indivíduos receberam QIV-HD juntamente com uma dose de reforço experimental de 100 microgramas da vacina de mRNA COVID-19 (com nucleósido modificado) (n=100), indivíduos que apenas receberam QIV-HD ou uma dose de reforço experimental de 100 microgramas da vacina mRNA COVID-19 (com nucleósido modificado) (n=104). A frequência e gravidade das reações adversas locais e sistémicas foram semelhantes em indivíduos que foram coadministrados com QIV-HD e vacina mRNA COVID-19 e indivíduos administrados apenas com uma dose de reforço da vacina mRNA COVID-19. b. Resumo das reações adversas em forma tabelar: Os dados abaixo resumem a frequência de reações adversas que foram notificadas no seguimento da vacinação com EFLUELDA e as reações adversas notificadas durante o desenvolvimento clínico e a experiência pós-comercialização com a vacina TIV-HD (marcado com *). As reações adversas encontram-se listadas sob títulos de frequência utilizando a seguinte convenção: Muito frequentes (≥1/10); Frequentes (≥1/100 a <1/10); Pouco frequentes (≥1/1.000 a <1/100); Raros (≥1/10.000 a <1/1.000); Muito raros (<1/10.000); Desconhecido (não pode ser calculado a partir dos dados disponíveis). **REAÇÕES ADVERSAS - FREQUÊNCIA:** **Perturbações gerais e alterações no local de administração:** Dor no local de injeção, eritema no local da injeção, mal-estar - Muito frequentes; Tumorção no local de injeção, induração no local de injeção, contusão no local de injeção, febre (≥37,5°C), arrepios - Frequentes; Prurido no local de injeção, fadiga - Pouco frequentes; Astenia - Raros; Dor torácica - Desconhecido*. **Afeções musculoesqueléticas e dos tecidos conjuntivos:** Mialgia - Muito frequentes; Fraqueza muscular - Pouco frequentes; Artralgia, dor nas extremidades - Raros. **Doenças do sistema nervoso:** Cefaleia - Muito frequentes; Letargia - Pouco frequentes; Tontura, parestesia - Raros; Síndrome de Guillain-Barré (SGB), convulsões, convulsões febris, mielite (incluindo encefalomielite e mielite transversa), paralisia facial (paralisia de Bell), neurite ótica/neuropatia, neurite braquial, síncope (logo após a vacinação) - Desconhecido*. **Doenças do sangue e do sistema linfático:** Trombocitopenia, linfadenopatia - Desconhecido*. **Doenças respiratórias, torácicas e do mediastino:** Tosse, dor orofaríngea - Pouco frequentes; Rinorreia - Raros; Dispneia, sibilos, aperto da garganta - Desconhecido*. **Doenças gastrointestinais:** Náusea, vômitos, dispepsia*, diarreia - Pouco frequentes. **Doenças do sistema imunitário:** Prurido, urticária, suores noturnos, rash - Raros; Anafilaxia, outras reações alérgicas/hipersensibilidade (incluindo angioedema) - Desconhecido*. **Vasculopatias:** Rubor - Raros; Vasculite, vasodilatação - Desconhecido*. **Afeções do ouvido e do labirinto:** Vertigens - Raros. **Afeções oculares:** Hiperemia ocular - Raros. * Dispepsia, letargia e fraqueza muscular foram observadas com TIV-HD no ensaio QHD00013. 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/submissaoarar> (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 da revisão do texto: Agosto 2023 Medicamento Sujeito a Receita Médica. Não comparticipado. Para mais informações contactar o Representante Local do Titular da Autorização de Introdução no Mercado.

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Editorial

Chegou o outono, época do ano em que se intensifica a expressão das infeções respiratórias, das vias aéreas superiores e das inferiores. É tempo de prevenir, é tempo de vacinar. Reforço anual da vacinação anti-gripal, nova administração da vacina contra a COVID, revisão do estado individual da vacinação anti-pneumocócica, vacinação contra o VSR em adultos com mais de 60 anos,..., deve estar agora nas nossas prioridades clínicas.

Neste número da revista, que em breve completa 7 anos consecutivos de edição, encontramos importantes artigos que podem influenciar a nossa prática clínica.

Louise Kooiman e colaboradores, num ensaio aleatorizado controlado multicêntrico com 4 anos de duração, não encontrou qualquer benefício clinicamente mensurável na utilização da oxigenoterapia de alto fluxo (cada vez mais usada e com custos mais elevados), em comparação com a de baixo fluxo em crianças com hipoxemia decorrente de bronquiólite moderada a grave.

E, reforçando a importância da investigação sobre a segurança da vacinação anti-gripal em grávidas, chega-nos da Austrália o artigo original “Associação entre a vacinação materna contra a gripe e as perturbações do desenvolvimento neurológico na infância...”, que durante 5 anos incluiu 140514 crianças. Os autores concluem pela não existência do aumento do risco de perturbações do desenvolvimento neurológico após a exposição in utero à vacina inativada contra a gripe.

Ainda na idade pediátrica, num estudo de colaboração australiano liderado por Lex William Doyle, em crianças nascidas extremamente prematuras (<28 semanas), a displasia broncopulmonar (DBM) moderada a grave, mas não a ligeira, foi independentemente associada à redução do fluxo aéreo expiratório aos 8 anos de idade, o que reforça a importância da prevenção da DBM.

E se a Professora Paula Pinto nos alerta neste número que, globalmente, “a DPOC continua a ser uma doença desconhecida e subdiagnosticada” convidando à participação na 3ª edição do projeto COPD Future Leaders, isso mesmo é confirmado em África, por Chidiamara Maria Njokunum e colaboradores, numa interessante revisão sistemática com meta-análise, e ainda mais reforçado no artigo “Obstrução crónica ao fluxo de ar atribuível à pobreza no estudo multinacional *Burden of Obstructive Lung Disease (BOLD)*”.

Propomos finalmente artigos sobre investigação em asma, nomeadamente no uso de algoritmo terapêutico com corticóides em asmáticos graves e na definição de estratégias de mitigação para minimizar a prescrição de corticóides orais nos cuidados primários, terminando com uma reflexão sobre tabagismo em idade pediátrica, de Jonathan Coutts e Ross John, de leitura obrigatória e que nos deve incomodar. A todos...

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ARTIGO ORIGINAL

Oxigenoterapia de alto fluxo em bronquiolite moderada a grave: um ensaio aleatorizado controlado

Louise Kooiman,¹ Fenneke Blankespoor,¹ Roy Hofman,¹ Arvid Kamps,² Monique Gorissen,³ Anja Vaessen-Verberne,⁴ Ingrid Heuts,⁵ Jolita Bekhof¹

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RESUMO

Enquadramento e objetivo — A oxigenoterapia de alto fluxo (AF) tem sido cada vez mais utilizada em crianças com bronquiolite, apesar da ausência de evidências conclusivas da sua superioridade em relação ao baixo fluxo (BF). O nosso objetivo foi comparar o efeito do AF em relação ao BF em bronquiolite moderada a grave.

Métodos — Ensaio aleatorizado controlado multicêntrico durante quatro invernos (2016 — 2020), que incluiu 107 crianças com idade inferior a dois anos internadas com bronquiolite moderada a grave, saturação de oxigênio inferior a 92% e sinais vitais gravemente comprometidos. Não foram permitidos ensaios cruzados. O AF foi administrado a taxas de fluxo de 2 l/kg para os primeiros 10 kg, mais 0,5 l/kg por cada kg >10 kg, e o BF a uma taxa de fluxo máxima de 3 l/min. O principal resultado foi a melhoria dos sinais vitais e da gravidade da dispneia dentro das 24 horas, avaliada por um score composto. Os resultados secundários foram conforto, duração da oxigenoterapia, alimentação suplementar, duração da hospitalização e internamento em cuidados intensivos para ventilação invasiva.

Resultados — Ocorreu uma melhoria significativa no período de 24 horas em 73% dos 55 pacientes aleatorizados para AF e em 78% dos 52 pacientes para BF (diferença de 6%, 95% IC — 13% para 23%). A análise de intenção de tratamento revelou que não existem diferenças significativas em nenhum resultado secundário — duração da oxigenoterapia, alimentação suplementar, hospitalização e necessidade de ventilação invasiva ou internamento em cuidados intensivos —, excetuando o conforto (face, pernas, atividade, choro, consolabilidade), que registou mais um ponto (numa escala de 0 a 10) no grupo de BF. Não ocorreram efeitos adversos.

Conclusão — Não encontramos qualquer benefício relevante clinicamente mensurável na utilização do AF em comparação com o BF em crianças com hipoxemia decorrente de bronquiolite moderada a grave.

Número de registo do ensaio NCT02913040.

INTRODUCTION

Bronchiolitis is a common viral respiratory tract illness in young children, characterised by airway obstruction, resulting in many hospital admissions for supportive treatment of dyspnoea and feeding problems.¹ Since no pharmacological intervention has been proven effective, treatment is supportive, consisting of oxygen supplementation and fluid administration.² Traditionally, oxygen is given as dry gas through low-flow (LF) nasal prongs. In the last decade, high-flow nasal cannula (HFNC) has been introduced, delivering heated, humidified oxygen and facilitating higher flows. Meanwhile, high flow (HF) is being widely used, despite lack of solid evidence for its efficacy.^{3–6} Several systematic reviews have been published,^{7–10} basing conclusions on two randomised trials comparing HF to LF in infants with bronchiolitis in non-intensive care settings.^{11 12} In both studies, HF did not affect length of hospital stay, duration of supplemental oxygen or admission to the paediatric intensive

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► High flow (HF) is increasingly applied in bronchiolitis, despite earlier studies showing lack of effect on duration of supplemental oxygen, hospitalisation or intensive care admissions in mild to moderately affected patients. HF is assumed beneficial as rescue treatment in severe bronchiolitis.

WHAT THIS STUDY ADDS

► Also, in moderate to severe bronchiolitis, HF is not superior compared with low flow (LF) in improvement of vital signs, comfort, duration of supplementation of oxygen or feedings, hospitalisation or intensive care admissions.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► Since there is no measurable clinical benefit in the use of HF in infants with bronchiolitis and costs of HF are higher, HF should not be used preferentially over LF in this patient group.

care unit (PICU). Still, many authors conclude that HF may reduce treatment failure and may be used as rescue therapy. However, in both trials, crossover from LF to HF was applied in patients with treatment failure in the LF group, indicating that these studies actually evaluated early HF versus rescue HF.^{13 14} It has also been suggested that a large number of patients in the HF groups may not have required its use, implicating that the use of HF increases costs without a clear benefit.¹⁵ Recently, a third randomised trial that did not allow crossover showed no clinical benefit in HF over LF in young infants with moderate bronchiolitis.¹⁶

In this trial, we aim to compare HF with LF in children with moderate to severe bronchiolitis with vital parameters largely comparable to the criteria of treatment failure in earlier trials, in the setting of general paediatric wards without an in-building PICU, measuring the effect on vital signs, comfort, oxygen therapy, supplemental feedings, length of hospitalisation, and need for invasive ventilation or PICU admission.

PATIENTS AND METHODS

Study design

Five general paediatric departments across the Netherlands participated in this randomised controlled trial during four consecutive winter sea-

Table 1 VWS for evaluation of vital signs and severity of dyspnoea

VWS								
Component	Age group	Component subscore						
		4	2	1	0	1	2	4
Respiratory rate (breaths/min)	<3 months	<15	15–19	20–29	30–60	61–80	81–90	>90
	3–12 months	<15	15–19	20–24	25–50	51–70	71–80	>80
	1–4 years	<12	12–14	15–19	20–40	41–60	61–70	>70
Respiratory effort*	All ages				normal	mildly†	Moderate†	Severe† or apnoeic
Oxygen saturation (%)	All ages		<91	91–94	>94			
Oxygen therapy	All ages				Room air		LFNP/HFNC	NRB mask
Heart rate (beats/min)	< 3 months	<80	80–89	90–109	110–150	151–180	181–190	>190
	3–12 months	<70	70–79	80–99	100–150	151–170	171–180	>180
	1–4 years	<60	60–69	70–89	90–120	121–150	151–170	>170
Capillary refill (s)	All ages				<3			≥3
Temperature (°C)	All ages		<36	36–36.4	36.5–37.5	37.6–38.5	>38.5	

The score is calculated by summing the subscores of each component, resulting in a score 0–24. VWS of ≥8 warrants immediate attention of a physician.
Source: adapted from Fuijkschot *et al.*¹⁸
*Nasal flaring or retractions.
HFNC, high-flow nasal cannula; LFNP, low-flow nasal prong; NRB mask, non-rebreathing mask; VWS, Vital Warning Score.

sons (December 2016–March 2020). None of the hospitals had a PICU in place, with distances to the nearest PICU ranging from 5 km to 105 km. Children <24 months of age hospitalised with moderate to severe bronchiolitis were eligible. Bronchiolitis was defined as symptoms of upper and signs of lower airway disease (cough, tachypnoea or dyspnoea) and signs of airway obstruction during auscultation (wheeze or lengthened expirium, crackles or rhonchi). We defined the severity of bronchiolitis as moderate to severe in case of oxygen saturation below 92% and a Vital Warning Score (VWS) indicating significant respiratory or circulatory distress. Exclusion criteria were chronic lung disease requiring home oxygen, haemodynamic significant congenital heart disease, syndromal disease, congenital lung abnormalities, earlier PICU admission or facial deformities. After written informed consent was obtained from parents or caretakers, eligible

patients were randomised as soon as oxygen saturation fell below 92% without oxygen supplementation and vital signs were significantly impaired, depicted by a composite VWS indicating significant respiratory or circulatory distress (≥6). The VWS was adapted from a Paediatric Early Warning Score (PEWS), including respiratory rate and effort, oxygen supplementation and saturation, heart rate and capillary refill (table 1).^{17 18} The score may range from 0 to 24: scores of ≥6 indicate hourly monitoring of all vital signs and VWS of ≥8 indicates immediate warning of the attending physician. The VWS, Comfort Score (face, legs, activity, cry, consolability (FLACC); see online supplemental file 1), respiratory rate, retractions, heart rate, conscious state, oxygen saturation, FiO₂ and temperature were assessed by a nurse every hour in the first 3 hours after randomisation and at least 3 hours thereafter during the first 24 hours.¹⁹

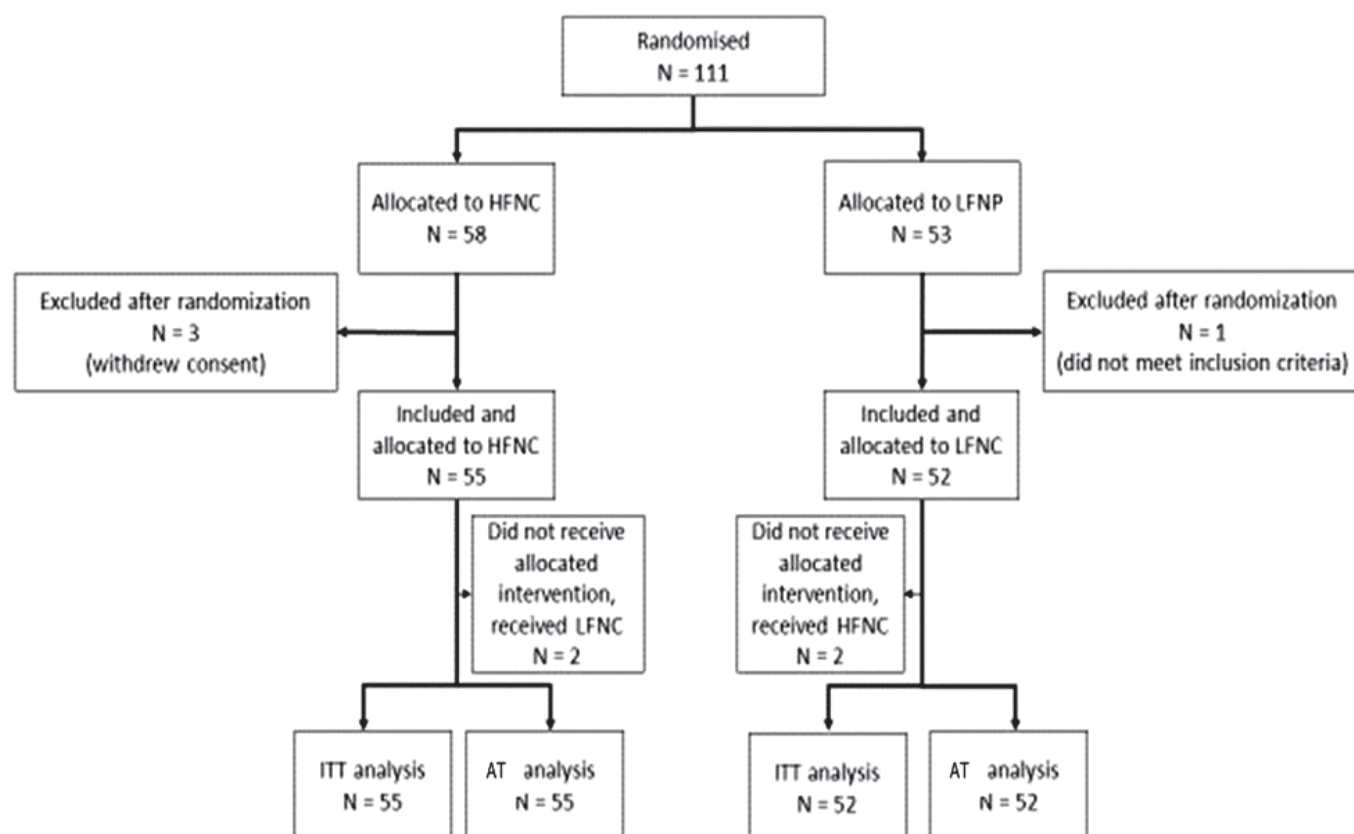


Figure 1 Participant flowchart. AT, as-treated, HFNC, high-flow nasal cannula; ITT, intention-to-treat; LFNC, low-flow nasal cannula; LFNP, low-flow nasal prong.

Table 2 Baseline patient characteristics of included patients (N=107)

	High flow (n=55)	Low flow (n=52)
Male sex	33 (60.0)	31 (59.6)
Age (months), median (IQR)	4.95 (2.0–10.0)	3.97 (1.9–10.7)
0–1	5 (9.1)	7 (13.5)
1–3	18 (32.7)	15 (28.8)
3–12	22 (40.0)	19 (36.5)
>12	10 (18.2)	11 (21.2)
Birth weight (kg), median (IQR)*	3.4 (3.1–3.8)	3.4 (2.9–3.8)
Gestational age (weeks ^{+days}), median (IQR)†	39 ⁺⁴ (38 ⁺² –40 ⁺³)	38 ⁺⁶ (37 ⁺⁴ –40 ⁺¹)
< 37 ⁺⁰ weeks	8 (15.7)	8 (17.4)
Clinical signs at the start of the intervention		
VWS, median (IQR)‡	6 (6–8)	7 (6–8)
Respiratory rate (breaths/min), mean (SD)§	53 (12)	53 (14)
Heart rate (beats/min), mean (SD)§	165 (17)	165 (19)
Retractions¶	48 (98)	50 (100)
Severe retractions	12 (25)	9 (18)
FLACC, median (IQR)**	3.5 (1.0–5.0)	4.0 (2.0–5.0)
Winter season		
2016–2017	11 (20.0)	12 (23.1)
2017–2018	19 (34.5)	21 (40.4)
2018–2019	12 (21.8)	8 (15.4)
2019–2020	13 (23.6)	11 (21.2)
Study site††		
1	5 (9.1)	4 (7.7)
2	7 (12.7)	7 (13.5)
3	2 (3.6)	2 (3.8)
4	31 (56.4)	31 (59.6)
5	10 (18.2)	8 (15.4)

N (%) unless stated otherwise.
VWS adapted from Fuijkschot *et al.*¹⁸
*Data missing in 15 patients.
†Data missing in 10 patients.
‡Data missing in 2 patients.
§Data missing in 5 patients.
¶Data missing in 8 patients.
**Data missing in 24 patients.
††1=Amphia, Breda; 2=Deventer Ziekenhuis; 3=Ikazia, Rotterdam; 4=Isala, Zwolle; 5=Martini, Groningen.
FLACC, face, legs, activity, cry, consolability; VWS, Vital Warning Score.

Randomisation

We performed computerised block randomisation with a block size of 4 in a 1:1 ratio, using the safe software tool Research-Manager. Block size was unknown to the treating physicians who asked for informed consent to guarantee concealment of allocation. Randomisation was stratified for participating centre and prematurity (<35⁺⁰ weeks).

Study intervention

Patients randomised to HF received 2 L/kg for the first 10 kg of bodyweight and an additional 0.5 L/kg for every kg bodyweight above 10 kg by Optiflow Junior (Fisher&Paykel) or Airvo2 (Fisher&Paykel). All patients started HF with FiO₂ of 1.0. We advised the staff to try and reduce the FiO₂ to 0.4–0.6 within 2 hours after starting HF while maintaining an oxygen saturation of >94% (weaning protocol; see online supplemental file 2). If reduction of the FiO₂ was not possible, patients were identified as non-responders, and referral to a PICU was considered. LF was administered with a maximum flow rate of 3 L/min.

Due to the visible differences in nasal cannulas and devices, care takers, nurses and physicians were not blinded for the intervention. We strongly advised against crossover to HF if therapy failed in patients randomised for LF.

Other treatments

For reasons of comfort and to lessen respiratory distress due to fever, all children with fever of >38.0° were given antipyretic therapy (acetaminophen 20 mg/kg three times a day). Since no effective interventions are proven effective in bronchiolitis, physicians were advised to withhold from other interventions than oxygen supplementation, administration of fluids and antipyretics. If other therapy was used, this was documented per patient.

Outcome measures

The primary outcome was a decrease in the severity of vital signs and dyspnoea depicted by the VWS (table 1).^{17 18} A decrease in VWS of two points in the first 24 hours was considered clinically relevant, based on the clinical experience of the research team, all using the VWS on a daily basis. Secondary outcome measures were comfort, measured by the FLACC (see online supplemental file 1), duration of oxygen supplementation, nasogastric tube feedings, referral to PICU for mechanical ventilation and length of hospitalisation. When a child needs a PICU admission, the child is transported by the paediatric intensivist of the nearest by PICU to one of the eight university hospitals in the Netherlands.

Sample size

To be able to find a clinical relevant difference in effect of 20% of patients showing a decrease in VWS of ≥2 points (numbers needed to treat 5), with a power of 80% (1-beta) and a two-sided significance level of 5% (alpha 0.05), the sample size was 118.

Statistical analysis

We performed intention-to-treat as well as as-treated analyses. For continuous data with normal distribution, an independent t-test was used, and for non-normal distributed data, a Mann-Whitney U test was used. For data with right skewness, a logarithmic transformation was performed, and differences were presented as geometric mean ratio. Proportions of categorical data were compared with the Pearson's χ^2 test, or Fisher's exact test as appropriate. A p value of <0.05 was considered statistically significant.

Data were analysed with SPSS V.28. The trial was registered at clinicaltrials.gov.

RESULTS

From 1 December 2016 to 31 March 2020, all patients with bronchiolitis were assessed for eligibility during the winter months (November–March). During this study period, 111 patients were randomised, of whom 107 were finally included and analysed using intention-to-treat analysis (figure 1). One child appeared not to meet the inclusion criteria after randomisation (VWS <6), and three parents withdrew consent after randomisation.

Registration of potential eligible patients was performed only at one site. At this site (Isala Zwolle), 386 patients with bronchiolitis were admitted during the four winter seasons, of whom 98 were eligible for randomisation at some point during the admission. Finally, 14.4% of all hospitalised patients with bronchiolitis during the study period were included (see online supplemental file 3).

Baseline characteristics of included patients can be found in table 2.

Primary and secondary outcomes are presented in table 3, showing no differences between the two treatment regimens, except for the VWS at 6 hours after randomisation, which was 0.9 point higher in the HF group, as well as a higher proportion in the HF group with VWS of ≥8 at 6 hours, and comfort depicted by the FLACC was one point higher in the LF group at 24. All patients transferred to the PICU underwent invasive mechanical ventilation. Unfortunately, we encountered some missing data on primary and secondary outcomes, as depicted in table 3.

Although we strongly advise against crossovers, this occurred in two patients: two patients randomised to LF were given HF because of increasing VWS of 8 and 11, respectively. The first patient was intubated and transferred to the PICU a few hours after the start of HF, and the other patient was weaned of HF back to LF within half a day. Both patients were analysed in the LF group in the

Table 3 Primary and secondary outcomes

	Intention-to-treat analysis					As-treated analysis			
	N*	HF (n=55)	LF (n=52)	Mean difference (95% CI)† or GMR (95% CI)¶	P value‡	HF (n=55)	LF (n=52)	Mean difference (95% CI)† or GMR (95% CI)¶	P value‡
Decrease in VWS ≥2 points (hours)									
2	94*	25/45 (55.6)	24/49 (49.0)	6.6 (−13.6 to 26.8)	0.52	26/46 (47.9)	23/48 (56.5)	−8.6 (−18.8 to 1.6)	0.40
6	95*	24/46 (52.2)	31/49 (63.3)	−11.1 (−30.9 to 8.7)	0.27	25/47 (53.2)	30/48 (62.5)	−9.3 (−29.1 to 10.5)	0.36
12	97*	35/47 (74.5)	31/50 (62.0)	12.5 (−1.5 to 26.5)	0.18	38/48 (75.0)	30/49 (61.2)	13.8 (−4.5 to 32.1)	0.15
24	99*	35/48 (72.9)	40/51 (78.4)	−5.5 (−23.5 to 12.6)‡	0.52	35/50 (70.0)	40/49 (81.6)	−11.6 (−29.0 to 6.7)‡	0.18
VWS (hours), mean (SD)									
2	94*	5.2 (2.3)	5.5 (2.1)	−0.3 (−1.2 to 0.6)	0.55	5.2 (2.3)	5.6 (2.0)	−0.4 (−1.3 to 0.5)	0.36
6	95*	5.6 (2.3)	4.7 (1.5)	−0.9 (−1.7 to −0.1)	0.03	5.5 (2.3)	4.8 (1.5)	−0.8 (−1.6 to 0.1)	0.06
12	97*	5.1 (2.3)	4.8 (1.7)	−0.3 (−1.1 to 0.6)	0.52	5.0 (2.3)	4.9 (1.7)	−0.1 (−1.0 to 0.6)	0.73
24	99*	4.0 (1.3)	4.2 (1.9)	−0.2 (−0.9 to 0.5)	0.53	3.9 (1.3)	4.2 (1.8)	−0.3 (−1.0 to 0.4)	0.37
VWS ≥8 (hours)									
2	94*	10/45 (22.2)	9/49 (18.4)	3.8 (−12.5 to 20.1)	0.64	10/46 (21.7)	9/48 (18.8)	−13.4 (−29.7 to 2.9)	0.72
6	95*	8/46 (17.4)	1/49 (2.0)	15.4 (5.6 to 25.2)	0.01	8/47 (17.0)	1/48 (2.1)	14.9 (3.4 to 26.4)	0.01
12	97*	8/47 (17.0)	5/50 (10.0)	7.0 (−6.6 to 20.6)	0.31	8/48 (16.7)	5/49 (10.2)	6.5 (−7.0 to 20.0)	0.35
24	99*	1/41 (2.4)	2/48 (4.2)	−1.8 (−9.2 to 5.6)	0.65	1/42 (2.4)	2/47 (4.3)	−1.9 (−9.3 to 5.5)	0.63
FLACC (hours), median (IQR)									
2	78*	1 (0–3)	1 (0–3)	Not applicable	0.50	1 (0–3)	1 (0–3)	Not applicable	0.36
6	73*	1 (0–3)	1 (0–3)	Not applicable	0.95	1 (0–3)	1 (0–3)	Not applicable	0.95
12	75*	0 (0–2)	1 (0–3)	Not applicable	0.17	0 (0–2)	1.5 (0–3)	Not applicable	0.11
24	73*	0 (0–0.5)	1 (0–2)	Not applicable	0.03	0 (0–1)	1 (0–2)	Not applicable	0.05
Length of stay (days), median (IQR)	107	4.2 (3.7–6.4)	4.8 (2.9–7.9)	0.96 (0.8 to 1.3)¶	0.78	4.7 (3.7–6.4)	4.3 (2.9–7.9)	1.0 (0.8 to 1.3)¶	0.98
Oxygen supplementation (days), median (IQR)	103*	3.3 (2.3–4.9)	2.9 (2.0–5.2)	1.9 (0.7 to 1.3)¶	0.72	2.9 (1.9–4.3)	2.6 (1.9–5.0)	1.1 (0.8 to 1.6)¶	0.43
Intensive care§	107	8/55 (14.5)	6/52 (11.5)	3.0 (−11.7 to 17.4)†	0.78	9/55 (16.4)	5/52 (9.6)	6.7 (−7.9 to 21.0)†	0.39
Tube feeding	105*	41/53 (77.4)	38/52 (73.1)	4.3 (−13.4 to 21.7)†	0.61	42/54 (77.8)	37/51 (72.5)	5.2 (−12.4 to 22.7)†	0.54

N (%) unless otherwise stated.
VWS 0–24.
FLACC non-normal distribution, 0–10.
*Lower than 107 due to missing data.
†95% CI.
‡Independent t-test for normally distributed variables, Mann-Whitney U test for non-normally distributed variables and χ^2 for dichotomous variables.
§All patients transferred to the paediatric intensive care unit underwent invasive mechanical ventilation.
¶GMR.
FLACC, face, legs, activity, cry, consolability; GMR, geometric mean ratio; HF, high flow; LF, low flow; VWS, Vital Warning Score.

intention-to-treat analysis and in the HF group in the as-treated analysis. At 24 hours, all patients received LF or HF as described in the as-treated analysis.

Table 4 shows additional interventions apart from HF or LF.

Since we encountered a substantial number of missing values for our primary outcome measure, we calculated ‘worst-case scenarios’: in case all seven patients in the HF group with missing outcome measures would have shown a clinically relevant positive effect (hypothetical effect in the HF group: 42/55, 76.4%) and the one patient in the LF group with missing outcome would have shown no effect (hypothetical effect in the LF group: 40/52, 76.9%), the difference would be −0.5% (95% CI −16.2% to 15.2%). In the opposite situation, when all seven patients in the HF group with missing outcome values would have shown no effect (hypothetical effect in

the HF group: 35/55, 63.6%) and the one patient in the LF group with missing values would have had a positive effect (hypothetical effect in the LF group: 41/52, 78.8%), the difference between the groups would have been −15.2% (95% CI −32.1% to 1.7%). Both scenarios showed no significant superiority of HF over LF.

No adverse events occurred; no barotrauma was found in both study groups; and no patient died.

DISCUSSION

In this randomised multicentre study, we found no measurable effect of HF compared with LF in infants under 2 years of age hospitalised with moderate to severe bronchiolitis. There was no evidence of clinically relevant between-group differences in short-term dyspnoea or vital signs, duration of oxygen delivery, hospital admission, comfort, tube feeding or PICU admission for invasive mechanical ventilation. We observed no adverse effects or air leak problems.

These results are in concordance with three earlier reports of RCTs comparing HF and LF in infants with bronchiolitis, not showing clear clinical effects on time of weaning of oxygen, duration of hospitalisation or PICU admissions.^{11 12 16}

Although the intention-to-treat analysis showed a statistically significant difference in comfort at the expense of LF, depicted by a one point difference in the FLACC score of 0–10 points, this difference was deemed not clinically relevant.

Authors of earlier trials argued that although HF showed no effect on clinical parameters, it might still be useful as a rescue

Table 4 Additional interventions

	High flow (n=53)*	Low flow (n=52)
Any extra treatment	17 (30.9)	22 (42.3)
Antibiotics	5 (14.5)	5 (9.6)
Bronchodilators	6 (10.9)	5 (9.6)
NSAIDs	9 (16.4)	16 (30.8)
Prednisolone	2 (3.6)	0 (0)

N (%).
*Data missing in two patients.
NSAID, non-steroidal anti-inflammatory drug.

treatment.^{11 12} Two of three earlier trials allowed crossover from LF to HF in case of treatment failure in the LF group.^{11 12} This conclusion, however, was questioned by others, stating that by allowing crossovers, the studies actually compared HF started early versus HF started late in the disease course.^{14 20} We assume that patients in our study might largely have been classified as qualifying for rescue treatment in earlier trials.^{11 12} A cohort study performed at one of our study sites showed that nearly 80% of hospitalised children with bronchiolitis received supplemental oxygen, while in the present study, only an estimated 25% of children had impairment of vital signs—apart from oxygenation problems—to such extent to fulfil our inclusion criteria.²¹ This, in our opinion, indicates that our results suggest that patients in our study had more severe bronchiolitis compared with earlier trials, suggesting that the usefulness of HF as a rescue treatment can be doubted.

Possibly, the flow rate might not have been optimal in our study; we used 2 L/kg/min for the first 10 kg bodyweight supplemented with 0.5 L/kg/min for every kg bodyweight of >10 kg, compared with 1 L/kg/min,¹¹ 2 L/kg/min¹² and 3 L/kg/min¹⁶ in other studies. Although physiology studies recommend higher flows to establish adequate Positive End Expiratory Pressure values,²² a recent trial comparing flow rates of 2 L/kg/min to 3 L/kg/min did not reduce treatment failure, at the cost of more discomfort at higher flow rates of 3 L/kg/min, suggesting that flow rates of 2 L/kg/min might be optimal.²³

The primary study outcome was a decrease in severity of dyspnoea depicted by improvement of the VWS. We were unable to compare this outcome measure to other studies, as the other trials used the Modified Wood Clinical Asthma Score (M-WCAS) to assess the severity of dyspnoea. We chose not to use the M-WCAS because a systematic review studying validity and reliability of dyspnoea scores showed large interobserver variation and insufficient validation of the M-WCAS.^{24 25} Since the VWS includes main objective vital parameters together with the criterion 'work of breathing', we reasoned this would be a more valid score to use. We used an adapted bedside PEWS, since this score was already in use at two of five participating sites and has acceptable inter-rater reliability and usability.^{18 26 27}

We purposely did not use treatment failure as outcome, as was used in earlier trials, since assessment of treatment failure is hampered by subjective judgement: interindividual variation between physicians in choosing the right moment for escalation in treatment, especially intubation and mechanical ventilation, is well known. Since in HF studies treatment blinding is not easily feasible, we wanted to avoid this potential bias. Although our study was not powered for PICU admissions as primary outcome, we found no statistically significant difference in PICU admissions between the two groups.

We acknowledge the following limitations of our study: we aimed to enrol 118 patients; unfortunately, despite extending our study period to four winter seasons, we were only able to enrol 107 patients. Due to lack of financial resources, we were not able to further extend our inclusion period. A second limitation is that although we strongly advised against crossovers, this occurred in two patients. However, we believe these two crossovers will not have significantly affected our results, which was confirmed by similar results of the as-treated analysis, where these two patients were analysed in the HF group. The third limitation was the missing values in outcome measurements. For data collection, often during night-times, we had to rely on busy nursing personnel, who sometimes did not manage to fill in the case report forms completely. We found that missing data were equal in both study groups, which makes bias less obvious.

CONCLUSION

We found no measurable relevant clinical benefit in the use of HF compared with LF in hypoxic children with moderate to severe bronchiolitis. Although we encountered no adverse effects, the cost of HF is much higher compared with LF, implicating that paediatricians should avoid the routine use of HF in children with bronchiolitis.

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Contributors UK carried out the data collection during the first two winter seasons and the initial analyses, drafted the initial manuscript and approved the final manuscript as submitted. FB performed data collection during the fourth winter season and the final data analysis and drafted several versions of the manuscript. Both FB as JB verified the data. RH performed data collection during the third winter season and performed interim analysis. AK, MG, AV-V and IH contributed to the design of the study and coordinated data collections at the specific study site. JB conceptualised and designed the study, coordinated and supervised the process, critically reviewed the manuscript, wrote the final draft as submitted and is guarantor.

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REFERENCES

- Florin TA, Plint AC, Zorc JJ. Viral bronchiolitis. *Lancet* 2017;389:211–24.
- Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics* 2014;134:e1474–502.
- Hutchings FA, Hilliard TN, Davis PJ. Heated humidified high-flow nasal cannula therapy in children. *Arch Dis Child* 2015;100:571–5.
- Jones AJ, Mathew S, Wong S-W, et al. A regional audit of high-flow nasal cannula therapy use for bronchiolitis in London district general hospitals. *Arch Dis Child* 2017;102:296–7.
- Panciatici M, Fabre C, Tardieu S, et al. Use of high-flow nasal cannula in infants with viral bronchiolitis outside pediatric intensive care units. *Eur J Pediatr* 2019;178:1479–84.
- Kalburgi S, Halley T. High-flow nasal cannula use outside of the ICU setting. *Pediatrics* 2020;146:e20190483.
- Beggs S, Wong ZH, Kaul S, et al. High-flow nasal cannula therapy for infants with bronchiolitis. *Cochrane Database Syst Rev* 2014;CD009609.
- Luo J, Duke T, Chisti MJ, et al. Efficacy of high-flow nasal cannula vs standard oxygen therapy or nasal continuous positive airway pressure in children with respiratory distress: a meta-analysis. *J Pediatr* 2019;215:199–208.
- Lin J, Zhang Y, Xiong L, et al. High-flow nasal cannula therapy for children with bronchiolitis: a systematic review and meta-analysis. *Arch Dis Child* 2019;104:564–76.
- Moreel L, Proesmans M. High flow nasal cannula as respiratory support in treating infant bronchiolitis: a systematic review. *Eur J Pediatr* 2020;179:711–8.
- Kepreotes E, Whitehead B, Attia J, et al. High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): an open, phase 4, randomised controlled trial. *Lancet* 2017;389:930–9.
- Franklin D, Bahl FE, Schlapbach LJ, et al. A randomized trial of high-flow oxygen therapy in infants with bronchiolitis. *N Engl J Med* 2018;378:1121–31.
- de Benedictis FM. The effectiveness of high-flow oxygen therapy and the fascinating song of the sirens. *JAMA Pediatr* 2019;173:125–6.
- Ralston SL. High-flow nasal cannula therapy for pediatric patients with bronchiolitis: time to put the horse back in the barn. *JAMA Pediatr* 2020;174:635–6.
- Linssen RS, van Woensel JB, Bont L. High-flow oxygen therapy in infants with bronchiolitis. *N Engl J Med* 2018;378:2445–6.
- Durand P, Guiddir T, Kyheng C, et al. A randomised trial of high-flow nasal cannula in infants with moderate bronchiolitis. *Eur Respir J* 2020;56:1901926.
- Seiger N, Maconochie I, Oostenbrink R, et al. Validity of different pediatric early warning scores in the emergency department. *Pediatrics* 2013;132:e841–50.
- Fuijkschoot J, Vernhout B, Lemson J, et al. Validation of a paediatric early warning score: first results and implications of usage. *Eur J Pediatr* 2015;174:15–21.
- Johansson M, Kokinsky E. The comfort behavioural scale and the modified FLACC scale in paediatric intensive care. *Nurs Crit Care* 2009;14:122–30.
- Leyenaar JK, Ralston SL. Widespread adoption of low-value therapy: the case of bronchiolitis and high-flow oxygen. *Pediatrics* 2020;146:e2020021188.
- Bekhof J, Wessels M, Ten Velde E, et al. Room sharing in hospitalized children with bronchiolitis and the occurrence of hospital-acquired infections: a prospective cohort study. *Hosp Pediatr* 2019;9:415–22.
- Milési C, Baleine J, Matecki S, et al. Is treatment with a high flow nasal cannula effective in acute viral bronchiolitis? A physiologic study. *Intensive Care Med* 2013;39:1088–94.
- for the GFRUP Respiratory Study Group, Milési C, Pierre A-F, et al. A multicenter randomized controlled trial of a 3-L/kg/min versus 2-L/kg/min high-flow nasal cannula flow rate in young infants with severe viral bronchiolitis (tramontane 2). *Intensive Care Med* 2018;44:1870–8.
- Bekhof J, Reimink R, Brand PLP. Systematic review: insufficient validation of clinical scores for the assessment of acute dyspnoea in wheezing children. *Paediatr Respir Rev* 2014;15:98–112.
- Fernandes RM, Plint AC, Terwee CB, et al. Validity of bronchiolitis outcome measures. *Pediatrics* 2015;135:e1399–408.
- Parshuram CS, Bayliss A, Reimer J, et al. Implementing the bedside paediatric early warning system in a community hospital: a prospective observational study. *Paediatr Child Health* 2011;16:e18–22.
- Langton L, Bonfield A, Roland D. Inter-rater reliability in the paediatric observation priority score (POPS). *Arch Dis Child* 2018;103:458–62.

ARTIGO ORIGINAL

Associação entre a vacinação materna contra a gripe e as perturbações do desenvolvimento neurológico na infância: um estudo de coorte longitudinal de base populacional

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RESUMO

Objetivo — Avaliar a associação entre a exposição in utero à vacina inativada contra a gripe sazonal (IIV) e o risco de diagnóstico de uma perturbação de desenvolvimento neurológico no início da infância.

Desenho Estudo de coorte retrospectivo.

Contexto Registo de nascimento de base populacional associado a bases de dados administrativas de saúde na Austrália Ocidental (WA).

Participantes Crianças únicas nadas-vivas, entre 1 de abril de 2012 e 1 de julho de 2016 na WA.

Exposição Receção de VII (vacina de influenza inativada) sazonal durante a gravidez obtida a partir de uma base de dados de vacinação pré-natal a nível estatal.

Principais medidas de resultados Foi registado o diagnóstico clínico de uma perturbação do desenvolvimento neurológico a partir dos registos de internamento hospitalar e dos serviços de urgência. Utilizámos a regressão de risco proporcional de Cox, ponderada pela probabilidade inversa de tratamento (vacinação), para estimar a probabilidade de risco (HR) de perturbações do desenvolvimento neurológico associadas à exposição in utero à vacina inativada contra a gripe sazonal.

Resultados O estudo incluiu 140 514 crianças, das quais 15 663 (11,2%) foram expostas a Vacina Inativada contra Gripe Sazonal in utero. A prevalência de perturbações do desenvolvimento neurológico foi de 5,4%, incluindo perturbações mentais ou comportamentais (0,4%), neurológicas (5,1%), convulsões (2,2%) e perturbações do sono (2,7%). A Vacina Inativada contra a Gripe Sazonal materna não foi associada a um risco acrescido de perturbações do desenvolvimento neurológico (HR 1,00; 95% IC 0,91 a 1,08). As crianças expostas no primeiro trimestre apresentaram um risco menor de convulsões (HR ajustado [aHR] 0,73; IC 95% 0,54 a 0,998) e as crianças pré-termo expostas em qualquer fase da gravidez apresentaram um risco menor de perturbações do sono (aHR 0,63; IC 95% 0,41 a 0,98).

Conclusões Não observámos um aumento do risco de perturbações do desenvolvimento neurológico após a exposição in utero a Vacina Inativada contra a Gripe Sazonal. Embora tenhamos observado algumas evidências de menor risco de convulsões e perturbações do sono, são necessários estudos adicionais para o confirmar.

INTRODUCTION

Influenza causes serious morbidity and mortality through seasonal epidemics each year. Although seasonal inactivated influenza vaccine (IIV) is the most effective preventative tool to protect against influenza illness,¹ there are no current vaccines licensed for use for infants aged <6 months.² To protect mothers and their infants from infection, prenatal administration of seasonal IIV is recommended for pregnant people in many countries, including Australia, any stage during pregnancy.²

Key messages

What is the key question?

- Vaccine safety is a commonly cited reason for vaccine hesitancy and low uptake of influenza vaccines among pregnant people.
- Few studies have evaluated the effect of maternal influenza vaccination on long-term paediatric health outcomes, including neurodevelopmental disorders in children exposed to influenza vaccines in utero.

What is the bottom line?

- Findings indicate no increase in the risk of neurodevelopmental disorders in early childhood associated with seasonal influenza vaccination during pregnancy.
- While we identified a lower risk of seizure disorders when the vaccine was administered early in pregnancy and a lower risk of sleep disorders among preterm children of vaccinated mothers, additional investigation is warranted.

Why read on?

- These results are supportive of the safety of prenatal administration of seasonal inactivated influenza vaccine and the continued provision of existing maternal vaccination programmes and policies.
- This study may be useful in health practice for healthcare providers when providing vaccine counselling to pregnant people and prospective parents.

Considerable evidence supports the safety of maternal influenza vaccination in regard to adverse health outcomes at birth, including preterm birth, small-for-gestational age, spontaneous abortion, stillbirth, low birth weight, congenital malformations, and fetal death.^{3–7} However, studies evaluating health outcomes following in utero exposure to seasonal IIV beyond early infancy are relatively scarce.⁸ The Developmental Origins of Health and

Disease hypothesis postulates that the prenatal period is a critical period of development and is susceptible to exposure to adverse agents, including infection, which can lead to long-term impacts on the health trajectory of children (ie, developmental programming).⁹ Studies evaluating childhood

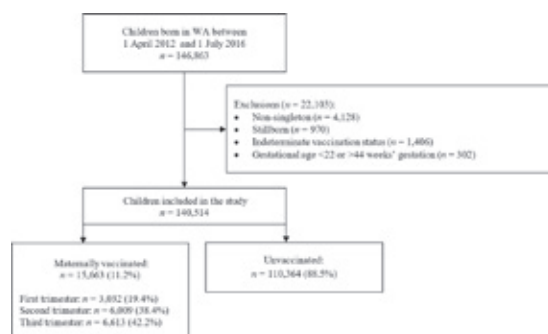


Figure 1 Flow diagram of study participants included in the cohort. WA, Western Australia.

health following in utero exposure to recommended vaccines are therefore needed.

We aimed to evaluate the association between seasonal IIV during pregnancy and paediatric neurodevelopmental health outcomes.

METHODS

Study cohort and design

This retrospective, population-based cohort study included all singleton, liveborn children born in Western Australia (WA) between 1 April 2012 and 1 July 2016 and their mothers (figure 1), identified using birth registrations. Mother-child pairs were probabilistically linked with other population-based administrative health datasets, including the Midwives Notification System (MNS), WA Antenatal Vaccination Database (WAAVD), Hospital Morbidity Data Collection, Emergency Department Data Collection, and death registrations (online supplemental table S1).¹⁰ This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (STROBE checklist).

Maternal influenza vaccination

Information on influenza vaccination during pregnancy and date of vaccination were obtained from the WAAVD, a state-wide antenatal vaccine database managed by the WA Department of Health. Children of mothers who had received seasonal IIV during pregnancy were considered 'maternally vaccinated'. We calculated gestational age at vaccination from estimated date of conception to date of vaccination, using the best clinical estimate of gestational age and date of birth from the MNS. We excluded children of mothers who received seasonal IIV <2 weeks prior to birth (ie, 'indeterminate' vaccination status).¹¹

Outcomes

Outcomes were identified from hospital inpatient and emergency department records.^{12,13} We assessed the diagnosis of any neurodevelopmental disorder. Within these, we evaluated the diagnosis of mental or behavioural disorders and neurological disorders, as identified by diagnostic codes (ie, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification) in primary or additional diagnosis fields (online supplemental table S2). Within neurological disorders, we had sufficient data to separately evaluate seizure disorders, including epilepsy, and sleep disorders as health outcomes. We included presentations for all-cause injuries as a negative control outcome, to identify potentially biased non-causal associations between prenatal exposure to seasonal IIV and the outcomes—typically the result of uncontrolled confounding.¹⁴

Covariates

Maternal characteristics included age at delivery (continuous), Aboriginal and/or Torres Strait Islander status (hereafter respectfully referred to as Aboriginal), socioeconomic status,¹⁵ body mass index (continuous), parity, pre-existing medical conditions, pregnancy complications, smoking during pregnancy, trimester at the first prenatal care visit and year and season of the pregnancy (measured from the date of delivery).

Missing data

For children with missing covariate information (n=16 652; 11.3%), we used multiple imputation by chained equations with 20 generated datasets to impute the missing data.

Statistical analyses

We compared the demographic and health characteristics between vaccinated and unvaccinated mothers and their children using univariate logistic regression models. Based on the predicted probability of vaccination from multivariate logistic regression, we estimated the inverse-probability of treatment (vaccination) weights (IPTW) to control for baseline probability of vaccination. To account for lack of independence for children with the same mother, we included the mother as a cluster variable. The final IPTW model included maternal age, body mass index, Aboriginal status, trimester of the first prenatal care visit, smoking during pregnancy, socioeconomic status, pre-existing medical conditions, pregnancy complications, and the year and season of birth. Because the pregnancy complications included in our study were predominantly diagnosed at 24 weeks of pregnancy,^{16,17} to appropriately account for temporality, pregnant people who were vaccinated before 24 weeks' gestation were considered to not have influenced a pregnant person's decision to vaccinate. We did not include pregnancy complications as a covariate in IPTW models for first trimester vaccination. IPTWs were trimmed at the 1st and 99th percentile. To assess the balance of maternal covariates included in the multivariate model, we examined the standardised mean differences of each covariate for maternally vaccinated and unvaccinated children. IPTWs were applied to trimmed and weighted Cox proportional hazards regression models to estimate HRs with 95% CIs for each study outcome.

Children were followed from the date of birth and were censored at the earliest of the: (a) date the child reached 5 years of age, (b) last date of available data (30 June 2017), (c) date the child died or (d) date of the event. To evaluate associations with more severe clinical outcomes, additional analyses defined outcomes based on hospital admission data only. To evaluate the importance of timing of maternal vaccination and duration of exposure to maternal antibodies, stratified analyses were planned a priori and performed by (1) trimester of vaccination, and by (2) preterm birth status, to determine whether results differed by length of gestation. All analyses were performed in Stata V.15.1 (StataCorp, USA). Post hoc power analysis was computed to determine the detectable difference in the risk of the outcome measures, with 90% and 80% power and alpha of 5%, between maternally vaccinated and unvaccinated children (online supplemental table S3).

RESULTS

A total of 146 863 children born in WA were identified; 6349 (4.3%) children were excluded because the child was a non-singleton (n=4128), stillborn (n=970), and/or had indeterminate vaccination status (n=1406); 140 514 singleton, liveborn children from 117 359 mothers were included in the study (figure 1).

Among the 140 514 children, 15 663 (11.2%) were maternally vaccinated: 3034 (19.4%) during the first trimester, 6014 (38.4%) during the second trimester, 6615 (42.2%) during the third trimester. Vaccination was more common among primiparous pregnant people and pregnant people with pre-existing medical conditions, and pregnant people who gave birth during winter compared with summer (table 1). Pregnant people who were of the lowest socioeconomic status, overweight, smoked during pregnancy, received no or later prenatal care and mothers of preterm infants were less likely to be vaccinated. After trimming and weighting, maternal characteristics were balanced (<10% difference) between maternally vaccinated and unvaccinated children (online supplemental figure S1) and the predicted probability of vaccination was similar with no extreme weights (online supplemental figure S2).

We identified 7436 (5.3%) children with a diagnosis of a neurodevelopmental disorder. We observed no association between risk of neurodevelopmental disorders and maternal influenza vaccination (adjusted HR [aHR] 1.00; 95% CI 0.91 to 1.08) (table 2) nor after stratifying by trimester of vaccination (table 2), preterm birth status (online supplemental tables S4 and S5) or when restricting to hospital admissions (online supplemental table S6).

There were 505 (0.4%) children with a diagnosis of a mental or behavioural disorder. The most common outcomes included

Table 1 Odds of seasonal influenza vaccination by maternal and child characteristics for children born in Western Australia between 1 April 2012 and 1 July 2016

Characteristic	Maternally unvaccinated (n=124 851) n (%)	Maternally vaccinated (n=15 663) n (%)	OR (95% CI)
<i>Maternal characteristics</i>			
Age (years)			1.01 (1.00 to 1.01)
≤19	3942 (3.2)	501 (3.2)	1.12 (1.01 to 1.25)
20–24	17 188 (13.8)	1947 (12.4)	Reference
25–29	35 774 (28.7)	4329 (27.6)	1.07 (1.01 to 1.13)
30–34	42 177 (33.8)	5573 (35.6)	1.17 (1.10 to 1.23)
≥35	25 770 (20.6)	3313 (21.2)	1.13 (1.07 to 1.20)
Aboriginal status			
Aboriginal	6503 (5.2)	832 (5.3)	1.02 (0.95 to 1.10)
Non-Aboriginal	118 348 (94.8)	14 831 (94.7)	Reference
Socioeconomic status*			
Quintile 1 (most disadvantaged)	24 965 (20.0)	2925 (18.7)	0.89 (0.85 to 0.94)
Quintile 2	25 681 (20.6)	3277 (20.9)	0.97 (0.92 to 1.03)
Quintile 3	26 558 (21.3)	3248 (20.7)	0.93 (0.89 to 0.98)
Quintile 4	24 787 (19.9)	3219 (20.6)	0.99 (0.94 to 1.05)
Quintile 5 (least disadvantaged)	22 860 (18.3)	2994 (19.1)	Reference
Body mass index			1.00 (1.00 to 1.00)
<18.5 (underweight)	4243 (3.4)	501 (3.2)	0.92 (0.84 to 1.01)
18.5 to <25 (normal)	59 174 (47.4)	7582 (48.4)	Reference
25 to <30 (overweight)	35 544 (28.5)	4302 (27.5)	0.94 (0.91 to 0.98)
≥30 (obese)	25 890 (20.7)	3278 (20.9)	0.99 (0.95 to 1.03)
Parity			
Primiparous	53 244 (42.7)	7335 (46.8)	Reference
1 prior birth	43 296 (34.7)	5405 (34.5)	0.91 (0.87 to 0.94)
≥2 prior births	28 311 (22.7)	2923 (18.7)	0.75 (0.72 to 0.78)
Pre-existing medical conditions			
Asthma†	12 859 (10.3)	1731 (11.1)	1.08 (1.03 to 1.14)
Essential hypertension†	1623 (1.3)	282 (1.8)	1.39 (1.23 to 1.58)
Pre-existing diabetes mellitus†	1044 (0.8)	202 (1.3)	1.55 (1.33 to 1.80)
Pregnancy complications			
Gestational diabetes‡	12 487 (10.0)	969 (6.2)	0.59 (0.55 to 0.63)
Gestational hypertension‡	5719 (4.6)	464 (3.0)	0.64 (0.58 to 0.70)
Pre-eclampsia‡	4107 (3.3)	319 (2.0)	0.61 (0.54 to 0.69)
Smoked during pregnancy	12 549 (10.1)	1403 (9.0)	0.88 (0.83 to 0.93)
Trimester at the first prenatal care visit			
First trimester	82 329 (65.9)	11 131 (71.1)	Reference
Second trimester	36 161 (29.0)	4075 (26.0)	0.83 (0.80 to 0.87)
Third trimester	6130 (4.9)	449 (2.9)	0.54 (0.49 to 0.60)
No prenatal care	231 (0.2)	8 (0.1)	0.26 (0.13 to 0.52)
Year of birth			
2012	22 844 (18.3)	1400 (8.9)	Reference
2013	29 458 (23.6)	3165 (20.2)	1.75 (1.64 to 1.87)
2014	29 827 (23.9)	3513 (22.4)	1.92 (1.80 to 2.05)
2015	27 444 (22.0)	5558 (35.5)	3.30 (3.11 to 3.51)

Continued

disorders of psychological development (n=206; 40.8%) and behavioural and emotional disorders (n=121; 24.0%). There was no association between risk of mental or behavioural disorders and maternal influenza vaccination (aHR 0.97; 95% CI 0.70 to

Table 1 Continued

Characteristic	Maternally unvaccinated (n=124 851) n (%)	Maternally vaccinated (n=15 663) n (%)	OR (95% CI)
2016	15 278 (12.2)	2027 (12.9)	2.16 (2.02 to 2.32)
<i>Season of birth</i>			
Summer (December–February)	30 700 (24.6)	2382 (15.2)	Reference
Autumn (March–May)	36 337 (29.1)	2524 (16.1)	0.90 (0.84 to 0.95)
Winter (June–August)	29 431 (23.6)	5893 (37.6)	2.58 (2.45 to 2.71)
Spring (September–November)	28 383 (22.7)	4864 (31.1)	2.21 (2.10 to 2.33)
<i>Child characteristics</i>			
Sex‡			
Male	64 244 (51.5)	8005 (51.1)	Reference
Female	60 604 (48.5)	7658 (48.9)	1.01 (0.98 to 1.05)
Aboriginal status			
Aboriginal	7043 (5.6)	915 (5.8)	1.04 (0.97 to 1.11)
Non-Aboriginal	117 808 (94.4)	14 748 (94.2)	Reference
Birth outcomes			
Preterm birth	8576 (6.9)	980 (6.3)	0.90 (0.85 to 0.97)
Moderate-to-late preterm	7572 (6.1)	908 (5.8)	0.95 (0.88 to 1.02)
Very preterm	644 (0.5)	54 (0.3)	0.66 (0.50 to 0.88)
Extremely preterm	360 (0.3)	18 (0.1)	0.40 (0.25 to 0.64)
Small-for-gestational age§	10 202 (8.2)	1304 (8.3)	1.02 (0.96 to 1.08)
Bold values indicate statistically significant associations.			
*Socioeconomic status was based on the Socioeconomic Index for Areas Index of Relative Socioeconomic Advantage and Disadvantage, an area-based index of relative access to resources for households within the same census collection district. ¹⁵			
†Comparisons were between the presence and absence of the condition by treatment groups.			
‡The sex of <5 maternally unvaccinated children was unknown.			
§Small-for-gestational age was based on the Australian national birth weight percentiles by sex and gestational age. ³¹			

1.35) (table 2) nor after stratifying by trimester of vaccination (table 2), preterm birth status (online supplemental tables S4 and S5) or when restricting to hospital admissions (online supplemental table S6).

In total, there were 7093 (5.0%) children diagnosed with a neurological disorder. The most common outcome included episodic and paroxysmal disorders (n=3880; 54.7%); 3055 (43.1%) episodes for a seizure disorder and 3696 (52.1%) for a sleep disorder. No associations were observed between risk of neurological disorders and maternal influenza vaccination (aHR 1.00; 95% CI 0.91 to 1.09) (table 2). Similarly, we observed no associations when stratifying by trimester of vaccination (table 2), preterm birth status (online supplemental tables S4 and S5) or when restricting to hospital admissions (online supplemental table S6).

Of children diagnosed with a seizure disorder, 354 (11.6%) diagnoses were epilepsy or status epilepticus and 2709 (88.7%) were convulsions. We observed no association between risk of seizure disorders and maternal influenza vaccination (aHR 0.99; 95% CI 0.87 to 1.14). When stratifying by trimester, we observed a lower risk of seizure disorders following vaccination during the first trimester (aHR 0.73; 95% CI 0.54 to 0.998) (table 2). This association was only observed among term children vaccinated during the first trimester (aHR 0.72; 95% CI 0.52 to 0.999) (online supplemental table S4). No other associations were observed following vaccination during later trimesters (table 2), when stratifying by preterm birth status (online supplemental tables S4 and S5) or

Table 2 Risk of neurodevelopmental disorders associated with prenatal exposure to seasonal inactivated influenza vaccine among children <5 years of age, by trimester of prenatal vaccination

	Unexposed to seasonal influenza vaccine during pregnancy (n=124 851) (n=122 385)*	Exposed to seasonal influenza vaccine during pregnancy (n=15 663) (n=15 272)*	Trimester of vaccine exposure		
			First trimester (n=3034) (n=2959)*	Second trimester (n=6014) (n=5896)*	Third trimester (n=6615) (n=6417)*
Neurodevelopmental disorder					
Cases, n (%)	6710 (5.4)	726 (4.6)	143 (4.7)	304 (5.1)	279 (4.2)
Unweighted HR (95% CI)	1 (reference)	1.01 (0.94 to 1.09)	1.02 (0.87 to 1.21)	1.03 (0.92 to 1.15)	0.99 (0.88 to 1.12)
Cases, n (%)	6594 (5.4)	713 (4.7)	140 (4.7)	299 (5.1)	274 (4.3)
Weighted HR (95% CI)†	1 (reference)	1.00 (0.91 to 1.08)	0.99 (0.82 to 1.18)	1.04 (0.91 to 1.18)	0.95 (0.83 to 1.09)
Mental or behavioural disorder					
Cases, n (%)	456 (0.4)	49 (0.3)	7 (0.2)	24 (0.4)	18 (0.3)
Unweighted HR (95% CI)	1 (reference)	1.02 (0.76 to 1.37)	0.75 (0.36 to 1.58)	1.21 (0.80 to 1.83)	0.95 (0.59 to 1.52)
Cases, n (%)	447 (0.4)	47 (0.3)	6 (0.2)	24 (0.4)	17 (0.3)
Weighted HR (95% CI)†	1 (reference)	0.97 (0.70 to 1.35)	0.69 (0.29 to 1.63)	1.19 (0.75 to 1.88)	0.91 (0.54 to 1.54)
Neurological disorder					
Cases, n (%)	6399 (5.1)	694 (4.4)	139 (4.6)	290 (4.8)	265 (4.0)
Unweighted HR (95% CI)	1 (reference)	1.02 (0.94 to 1.10)	1.04 (0.88 to 1.24)	1.03 (0.92 to 1.16)	0.99 (0.88 to 1.12)
Cases, n (%)	6291 (5.1)	683 (4.5)	137 (4.6)	285 (4.8)	261 (4.1)
Weighted HR (95% CI)†	1 (reference)	1.00 (0.91 to 1.09)	1.00 (0.83 to 1.20)	1.04 (0.91 to 1.19)	0.95 (0.83 to 1.10)
Seizure disorder					
Cases, n (%)	2744 (2.2)	311 (2.0)	52 (1.7)	132 (2.2)	127 (1.9)
Unweighted HR (95% CI)	1 (reference)	0.99 (0.88 to 1.11)	0.84 (0.64 to 1.11)	1.03 (0.87 to 1.23)	1.01 (0.85 to 1.21)
Cases, n (%)	2695 (2.2)	303 (2.0)	50 (1.7)	127 (2.2)	126 (2.0)
Weighted HR (95% CI)†	1 (reference)	0.99 (0.87 to 1.14)	0.73 (0.54 to 0.998)	1.10 (0.90 to 1.35)	1.00 (0.81 to 1.22)
Sleep disorder					
Cases, n (%)	3369 (2.7)	327 (2.1)	72 (2.4)	134 (2.2)	121 (1.8)
Unweighted HR (95% CI)	1 (reference)	0.98 (0.88 to 1.11)	1.12 (0.89 to 1.42)	0.96 (0.81 to 1.14)	0.96 (0.80 to 1.15)
Cases, n (%)	3317 (2.7)	325 (2.1)	72 (2.4)	134 (2.3)	119 (1.9)
Weighted HR (95% CI)	1 (reference)	0.97 (0.85 to 1.10)	1.11 (0.86 to 1.42)	0.96 (0.80 to 1.16)	0.91 (0.74 to 1.11)

Bold values indicate statistically significant associations.

All outcomes were identified from ICD-10-AM codes found in the principal and 20 additional diagnosis fields of hospital inpatient and emergency department presentation records, and from the presenting symptom code found in the emergency department presentation records (online supplemental table 2).

*Sample size after trimming the 1st and 99th percentile of the predicted probability of vaccination.

†HRs were weighted by trimmed inverse-probability of treatment weights factoring for maternal covariates including age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, trimester at the first prenatal care visit, year and season of birth.

ICD-10-AM, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification.

when restricting to hospital admissions (online supplemental table S6).

Among children diagnosed with a sleep disorder, 3557 (96.2%) diagnoses were sleep apnoea. There was no association between sleep disorders and maternal influenza vaccination (aHR 0.97; 95% CI 0.85 to 1.10) (table 2). When stratifying by preterm birth status, we observed a lower risk of sleep disorders among preterm children of vaccinated mothers (aHR 0.63; 95% CI 0.41 to 0.98) (online supplemental table S5). There were no other associations when stratifying by trimester of vaccination (table 2), preterm birth status (online supplemental tables S4 and S5) or when restricting to hospital admissions (online supplemental table S6). There was no association between risk of all-cause injuries and maternal influenza vaccination overall (aHR 1.04; 95% CI 0.99 to 1.09) (online supplemental table S7) or when stratifying by trimester of vaccination (online supplemental table S7).

DISCUSSION

In this large, population-based cohort study of 140 514 children, we found no evidence of an increased risk of neurodevelopmental disorders among children aged <5 years following prenatal exposure to seasonal IIV. However, we did observe an indication of a lower risk of seizure disorders following seasonal IIV administered during the first trimester and sleep disorders among preterm children of vaccinated mothers. These results support the safety of maternal influenza vaccination and continuance of existing maternal vaccination programmes and policies.

To date, most studies evaluating maternal influenza vaccination have focused on outcomes in the first 6 months of life.³ To our

knowledge, only three studies have assessed neurodevelopmental outcomes among children >6 months of age, two examining pandemic vaccines and one examining seasonal IIV.^{18–20} These studies identified no association between maternal influenza vaccination and paediatric neurodevelopmental disorder development. Zerbo et al²⁰ observed a suggestion of increased risk of autism spectrum disorder (ASD) following prenatal exposure to seasonal IIV in the first trimester (aHR 1.20; 95% CI 1.04 to 1.39). However, accounting for multiple comparisons using Bonferroni-corrected CIs, this association was no longer significant (p=0.1). We identified 22 children with a diagnosis for ASD; due to an insufficient number of cases among the vaccinated cohort (n<5), the analysis of ASD was not possible. Hviid et al¹⁹ reported no association between epilepsy among children exposed to pandemic influenza vaccine in the first trimester (adjusted risk ratio [aRR] 1.01; 95% CI 0.21 to 4.74) nor in the second or third trimester (aRR 1.22; 95% CI 0.79 to 1.86).

Our results examining composite outcomes and seizure disorders mostly align with previous studies examining individual outcomes. We observed a decreased risk of seizure disorders following first trimester influenza vaccination. To our knowledge, there have been no previous studies evaluating the association between maternal influenza vaccination and paediatric sleep disorders, and this novel finding requires additional investigation. While we cannot entirely rule out the possible influences of bias and type I error in the results from this observational study, several aspects of our study suggest a plausible protective relationship between maternal immunisation and the subsequent development of neurodevelopmental conditions in offspring.

Previous studies have observed adverse neurodevelopmental outcomes, including ASD, following prenatal exposure to viral or bacterial infections in offspring, including influenza infection.⁹ Influenza infection and subsequent maternal immune activation during pregnancy has been implicated in the development of seizure disorders in offspring.^{21–22} Using data from Norway, Canada and Australia, Oakley et al²³ identified a higher risk of seizure disorders (aHR 1.17; 95% CI 1.07 to 1.28) and febrile seizures (aHR 1.20; 95% CI 1.07 to 1.34) following maternal influenza infection. Vaccination during pregnancy is effective in preventing maternal influenza infection. A meta-analysis of 19 studies from 11 countries identified a lower incidence of laboratory-confirmed influenza among pregnant people following exposure to seasonal IIV during pregnancy (vaccine effectiveness, 63%).²⁴ Protection against influenza virus infection through maternal immunisation could therefore result in the reduced risk of influenza infection during pregnancy, and as a result prevent neurological harm to the fetal brain.

The strengths of our study include the use of a large, population-based mother-infant cohort with detailed information on maternal sociodemographic and health characteristics, receipt of prenatal vaccine, and record linkage to several administrative health datasets permitting follow-up of outcomes up to 5 years. The record linkage system in WA is long-standing, with expertise in linking large administrative health data since 1995.²⁵ With the exception of the antenatal vaccination database, these datasets are legally mandated, and have high data quality.²⁶ The MNS is estimated to capture 99% of all births in WA.²⁷ Because observational studies are subject to uncontrolled confounding, we assessed this using negative control analysis, which is increasingly used in observational studies to detect uncontrolled confounding between treatment groups. After adjusting for measured confounders, any observed association between the exposure and the negative control outcome would suggest residual confounding which we did not observe. However, it is possible that the negative control outcome in our study may not detect all possible residual confounding.²⁸

Despite these strengths, our study has limitations. First, these data are observational and we cannot rule out residual uncontrolled confounding and healthy vaccinee bias. Pregnant mothers with underlying chronic conditions are more likely to be vaccinated compared with their healthier counterparts.²⁹ However, we attempted to restrict the influence of health-seeking behaviour using IPTW. Second, maternal vaccination data linked from the WAAVD relied on immunisation reports from medical providers; although these records have high specificity, they are likely to be incomplete.³⁰ Third, outcomes were limited by diagnoses recorded in hospital inpatient and emergency department records, which do not capture outcomes diagnosed and treated in primary care. However, as severe medical events are unlikely to be managed entirely through primary care, especially in young children, we believe the majority of severe events are captured in our dataset. For this reason, our results may be more reflective of severe paediatric neurodevelopmental conditions. Finally, despite the large size of our cohort, small cell sizes (ie, <5) made it impractical to estimate effects by preterm birth status or when restricting to hospital admissions for all outcomes.

CONCLUSIONS

Our findings indicate seasonal IIV during pregnancy is not associated with adverse neurodevelopmental outcomes among children aged up to 5 years and support current global vaccine policies prioritising influenza immunisation for pregnant people. Our study detected a potential lower risk of seizure disorders following seasonal IIV administered in the first trimester and sleep disorders among preterm children of vaccinated mothers, these findings warrant further investigation. This information may be useful to reassure pregnant people and inform their healthcare providers when making vaccine decisions and providing vaccine counselling.

Correction notice This article has been amended since it was first published. Figure 1 has been replaced with the correct version.

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REFERENCES

- Kachikis A, Eckert LO, Englund J. Who's the target: mother or baby? *Viral Immunol* 2018;31:184–94.
- Vaccines against influenza WHO position paper – november 2012. *Wkly Epidemiol Rec* 2012;87:461–76.
- Giles ML, Krishnaswamy S, Macartney K, et al. The safety of inactivated influenza vaccines in pregnancy for birth outcomes: a systematic review. *Hum Vaccin Immunother* 2019;15:687–99.
- Nunes MC, Aqil AR, Omer SB, et al. The effects of influenza vaccination during pregnancy on birth outcomes: a systematic review and meta-analysis. *Am J Perinatol* 2016;33:1104–14.
- McMillan M, Porritt K, Kralik D, et al. Influenza vaccination during pregnancy: a systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes. *Vaccine* 2015;33:2108–17.
- Fell DB, Platt RW, Lanes A, et al. Fetal death and preterm birth associated with maternal influenza vaccination: systematic review. *BJOG* 2015;122:17–26.
- Bratton KN, Wardle MT, Orenstein WA, et al. Maternal influenza immunization and birth outcomes of stillbirth and spontaneous abortion: a systematic review and meta-analysis. *Clin Infect Dis* 2015;60:e11–9.
- Foo DYP, Sarna M, Pereira G, et al. Early childhood health outcomes following in utero exposure to influenza vaccines: a systematic review. *Pediatrics* 2020;146.
- Fitzgerald E, Hor K, Drake AJ. Maternal influences on fetal brain development: the role of nutrition, infection and stress, and the potential for intergenerational consequences. *Early Hum Dev* 2020;150:105190.
- Sarna M, Andrews R, Moore H, et al. "Links2HealthierBubs" cohort study: protocol for a record linkage study on the safety, uptake and effectiveness of influenza and pertussis vaccines among pregnant Australian women. *BMJ Open* 2019;9:e030277. 11 Blanchard-Rohner G, Meier S, Bel M, et al. Influenza vaccination given at least 2 weeks before delivery to pregnant women facilitates transmission of seroprotective influenza-specific antibodies to the newborn. *Pediatr Infect Dis J* 2013;32:1374–80.
- Government of Western Australia: Department of Health. Hospital morbidity data system. reference manual part A: contacts, hospital responsibilities, data element definitions. Department of Health, 2017.
- Government of Western Australia: Department of Health. Process for emergency department patient statistics – emergency department data collections. Department of Health. ed.: Data Collections Directorate, 2018.
- Lipsitch M, Jha A, Simonsen L. Observational studies and the difficult quest for causality: lessons from vaccine effectiveness and impact studies. *Int J Epidemiol* 2016;45:2060–74.
- Australian Bureau of Statistics. 0 - census of population and housing: reflecting australia - stories from the census. 2016. Available: <https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject%20701.0-2016-Main%20Features-Socio-Economic%20Advantage%20and%20Disadvantage-123>
- Poon LC, McIntyre HD, Hyett JA, et al. The first-trimester of pregnancy: a window of opportunity for prediction and prevention of pregnancy complications and future life. *Diabetes Res Clin Pract* 2018;145:20–30.
- Stepan H, Hund M, Andrzejek T. Combining biomarkers to predict pregnancy complications and redefine preeclampsia: the angiogenic-placental syndrome. *Hypertension* 2020;75:918–26.
- Ludvigsson JF, Winell H, Sandin S, et al. Maternal influenza A (H1N1) immunization during pregnancy and risk for autism spectrum disorder in offspring: a cohort study. *Ann Intern Med* 2020;173:597–604.
- Hvid A, Svanström H, Molgaard-Nielsen D, et al. Association between pandemic influenza A (H1N1) vaccination in pregnancy and early childhood morbidity in offspring. *JAMA Pediatr* 2017;171:239–48.
- Zerbo O, Qian Y, Yoshida C, et al. Association between influenza infection and vaccination during pregnancy and risk of autism spectrum disorder. *JAMA Pediatr* 2017;171:e163609.
- Bergdolt L, Dunaevsky A. Brain changes in a maternal immune activation model of neurodevelopmental brain disorders. *Prog Neurobiol* 2019;175:1–19.
- Meyer U. Neurodevelopmental resilience and susceptibility to maternal immune activation. *Trends Neurosci* 2019;42:793–806.
- Oakley LL, Regan AK, Fell DB, et al. Childhood seizures after prenatal exposure to maternal influenza infection: a population-based cohort study from Norway, Australia and Canada. *Arch Dis Child* 2022;107:153–9.
- Quach TH, Mallis NA, Cordero JF. Influenza vaccine efficacy and effectiveness in pregnant women: systematic review and meta-analysis. *Matern Child Health J* 2020;24:229–40.
- Western Australian Data Linkage Branch. About data linkage branch WA. n.d. Available: <https://www.data-linkage-wa.org.au/about>
- Australian Government: Australian Institute of Health and Welfare. Metadata standards. 2019. Available: <https://www.aihw.gov.au/about-our-data/metadatastandards>
- Gee V, Dawes V. Validation study of the western Australian midwives' notification system 1992. In: Health WADO. Perth, WA: Western Australian Department of Health, 1994.
- Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: A tool for detecting confounding and bias in observational studies. *Epidemiology* 2010;21:383–8.
- Okoli GN, Reddy VK, Al-Yousif Y, et al. Sociodemographic and health-related determinants of seasonal influenza vaccination in pregnancy: A systematic review and meta-analysis of the evidence since 2000. *Acta Obstet Gynecol Scand* 2021;100:997–1009.
- Regan AK, Mak DB, Moore HC, et al. Surveillance of antenatal influenza vaccination: validity of current systems and recommendations for improvement. *BMC Public Health* 2015;15:1155.
- Dobbins TA, Sullivan EA, Roberts CL, et al. Australian National birthweight percentiles by sex and gestational age, 1998–2007. *Med J Aust* 2012;197:291–4.



A DPOC continua a ser uma doença desconhecida e subdiagnosticada

A doença pulmonar obstrutiva crónica (DPOC) é, atualmente, a terceira principal causa de morte em todo o mundo e está associada a uma significativa perda da qualidade de vida e a uma elevada incapacidade. Contudo, continua a ser uma doença desconhecida da população, subdiagnosticada e, por conseguinte, apenas tratada nas suas fases mais avançadas.

Para o tratamento da DPOC é fundamental uma abordagem multidisciplinar que permita atuar ao nível da prevenção, diagnóstico e tratamento dos doentes. Neste contexto, o papel dos especialistas em Pneumologia, Medicina Interna e em Medicina Geral e Familiar bem como o de todos os profissionais de saúde, nomeadamente enfermeiros, técnicos de cardiopneumologia, fisioterapeutas, farmacêuticos, é essencial na prevenção, identificação, diagnóstico e acompanhamento destes doentes. Por isso, a terceira edição do projeto Future COPD Leaders chega agora a todos os profissionais de saúde, pois o contributo de todos é fundamental também na componente investigacional.

Com esta terceira edição, o programa pretende apoiar todos os profissionais que tenham interesse em DPOC e que pretendam desenvolver projetos de investigação científica. Este programa conta com o apoio de um reconhecido painel de peritos das várias especialidades (Pneumologia, Medicina Interna e Medicina Geral e Familiar) e a mentoria do chairman das recomendações GOLD o Professor Alvar Agustí que é também professor de Medicina na Universidade de Barcelona e cujo trabalho de pesquisa abrange diversos aspetos da DPOC, incluindo a identificação de biomarcadores, a compreensão dos mecanismos subjacentes a esta doença, a melhoria das estratégias de tratamento e a promoção de uma abordagem personalizada para o tratamento dos doentes com DPOC. Este programa que liga três sociedades médicas (SPP, NEDResp e GRESP) pretende apoiar o desenvolvimento contínuo das competências na abordagem ao tratamento do doente com DPOC, através de formação e programas educativos de excelência científica. Estamos certos, que representa uma enorme mais-valia para todos os colegas que tenham interesse e necessidade em aprofundar conhecimento sobre a Doença Pulmonar Obstrutiva Crónica e, dessa forma, proporcionar um melhor acompanhamento aos doentes pelos diferentes profissionais de saúde.

Além da transmissão de conhecimentos valiosos, queremos fomentar a inovação através do desenvolvimento de projetos que possam ajudar a diagnosticar mais e em fases mais precoces. Apenas desta forma conseguiremos inverter o caminho que tem sido traçado no que diz respeito a esta patologia.

A primeira fase do projeto arrancou sob o mote 'Learning to be an expert' com as sessões: 'Reunião de apresentação do Programa Future COPD Leaders a toda a comunidade médica', 'Reunião sobre desafios no tratamento da DPOC' e 'Reunião sobre Investigação em saúde respiratória', que podem assistir na plataforma do Future COPD Leaders em <https://futurecopdleaders.pt/>.

Apesar de a DPOC já ser a terceira causa de morte e estar associada a uma significativa perda de qualidade de vida continua a ser uma doença desconhecida e subdiagnosticada (cerca de 70% dos Portugueses nunca ouviu falar desta doença). A intervenção de todos os profissionais de saúde é importante para mudar este paradigma. Apelamos à participação de todos com as questões e dúvidas que possam ter. Juntos vamos fazer a diferença!

Prof.ª Paula Pinto,
Vice-Presidente da Sociedade Portuguesa de Pneumologia (SPP)

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

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RESUMO

Contexto Não está claro se a displasia broncopulmonar (DBP) está independentemente associada à redução do fluxo aéreo expiratório na idade escolar.

Objetivo Determinar as associações independentes de DBP moderada a grave, DBP leve, idade gestacional e score z de peso ao nascer com fluxo aéreo expiratório em crianças nascidas extremamente prematuras (PE; <28 semanas de gestação).

Métodos Todos os sobreviventes de PE nascidos em Victoria, Austrália, em três épocas (1991–1992, n=225; 1997, n=151; e 2005, n=170) foram recrutados ao nascer e 418/546 (77%) tinham dados espirométricos válidos aos 8 anos. A DBP foi classificada como moderada a grave (necessidade de oxigênio às 36 semanas de idade pós-menstrual) ou leve (oxigênio > 28 dias, mas não às 36 semanas de idade pós-menstrual). As variáveis do fluxo aéreo expiratório, incluindo o volume expirado forçado em 1 s (FEV₁), foram medidas e os valores convertidos para score z.

Resultados Em comparação com nenhuma DBP (n=94), a DBP moderada a grave (n=193) foi associada a uma redução substancial no fluxo aéreo expiratório (por exemplo, diferença média de zFEV₁ -0,69, IC 95% -0,97 a -0,41; p<0,001), mas DBP leve (n=131) não foi (diferença média de zFEV₁ 0,01, IC 95% -0,28 a 0,31; p=0,93). Na análise multivariada, a DBP moderada a grave permaneceu fortemente associada à redução do fluxo aéreo (diferença média do zFEV₁ -0,63, IC 95% -0,92 a -0,33; p<0,001), mas a DBP leve (diferença média do zFEV₁ 0,04, IC 95% -0,26 a 0,34; p=0,27), idade gestacional (zFEV₁ aumento médio de 0,06 por semana, IC 95% -0,05 a 0,17; p=0,29) e score z do peso ao nascer (zFEV₁ aumento médio de 0,07 por DP, IC 95% -0,06 a 0,20; p=0,28) não foram.

Conclusões Em crianças nascidas com PE, a DBP moderada a grave, mas não a DBP leve, foi independentemente associada à redução do fluxo aéreo expiratório aos 8 anos.

INTRODUCTION

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

Bronchopulmonary dysplasia (BPD) affects approximately 50% of survivors born EP,³ and is strongly associated with reduced expiratory airflow in later life in survivors born preterm.^{2–4–6} A recent report suggests that it is not BPD per se that is associated with reduced expiratory airflow, but it is increasing prematurity and fetal growth restriction that are more important in infants born <35 weeks' gestation.⁷ If that is so, efforts to reduce BPD alone

Key messages

What is the key question?

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

What is the bottom line?

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

Why read on?

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

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

The aim of this study was to determine the independent associations of BPD, including moderate–severe and mild BPD, gestational age and birth weight z-score with expiratory airflow in children born EP in Victoria, Australia, at 8 years of age in the years since exogenous surfactant has been

available to treat surfactant deficiency in newborn infants. We hypothesised that moderate-severe BPD would be independently associated with reduced expiratory airflow, but that mild BPD, gestational age and birth weight z-score would not.

METHODS

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

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

Respiratory function studies

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

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

Statistical analysis

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

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

All regression models were fitted using generalised estimating equations with robust error estimates to account for clustering within multiple births. Mean differences or ORs and 95% CIs were calculated, where appropriate. Data were interpreted based on magnitude of any differences and their 95% CIs, and not just on p values alone. We did not impute for missing data as it was unlikely that missing data occurred at random.

Informed consent was provided by parents for the 2005 cohort but was not required for the earlier cohorts where follow-up to school age was considered to comprise usual clinical care.

RESULTS

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

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

Associations of BPD with expiratory airflow

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

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

On univariable analysis there was evidence that increasing gestational age was associated with increases in z-scores for FEV₁ and FVC, and lower odds for clinically important airway obstruction, but there was little evidence that increasing birth weight z-score was associated with any expiratory flow variables, or clinically important airway obstruction (table 2; figures 1 and 2).

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

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

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

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

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

Data are mean (SD), unless otherwise specified.

*FEV₁ <5th centile.

FEF_{25%–75%} forced expiratory flow from 25%–75% of vital capacity; FEV₁, forced expired volume in 1 s; FVC, forced vital capacity.

analysis. The evidence for an increase in zFEV₁ with increasing gestational age diminished, but persisted for FVC on multivariable analysis. The lack of evidence for associations of airflows with increasing birth weight z-score persisted.

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

DISCUSSION

The major findings in the present study of school-age children born EP in the post-surfactant era are that moderate–severe BPD was associated with lower expiratory airflow and higher rates of poor expiratory airflow in the clinically important range. Importantly, adjustment for gestational age and birth weight z-scores had little effect on the strength of the evidence concerning the associations of moderate–severe BPD with poor expiratory airflow. Although there were some associations of better expiratory airflow with increasing gestational age, the strength of the evidence diminished on some multivariable analyses. The relationships with fetal growth were not straightforward; as a continuous variable there was little evidence that birth weight z-scores were associated with expiratory airflow,

but there was evidence that fetal growth restriction (birth weight <10th centile), as a dichotomous variable, was associated with reduced expiratory airflow. There was no evidence that mild BPD was associated with expiratory airflow on either univariable or multivariable analysis. These results were consistent with our hypotheses.

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

Our results with respect to the associations of expiratory airflow with the severity of BPD are similar to other studies of survivors born preterm in the surfactant era. Ronkainen et al¹⁷ reported the results of a systematic review of six studies with FEV₁ results published between 2000 and 2013; compared with term-born controls, survivors born preterm had an increasing reduction in FEV₁, from –7.4% predicted for no BPD, to –10.5% predicted for any BPD, to –17.8% for moderate–severe BPD. In a cohort of 35 survivors born EP in Norway in 1991–1992, Vollsæter et al¹⁸ reported that those who had moderate–severe BPD had worse expiratory airflow than those who had mild BPD, who in turn had worse expiratory airflow than those who had no BPD, at mean ages of 10.5 and 17.8 years. In a study of infants born <27 weeks' gestation in Sweden between 2004 and 2007, Thunqvist et al¹⁹ reported that expiratory airflow at 6½ years was lower in 17 children who had severe BPD compared with 65 children who had moderate BPD. They did not report results for children with mild or no BPD but there cannot have been many because overall 90% of their cohort had either moderate or severe BPD. Although they also reported that chil-

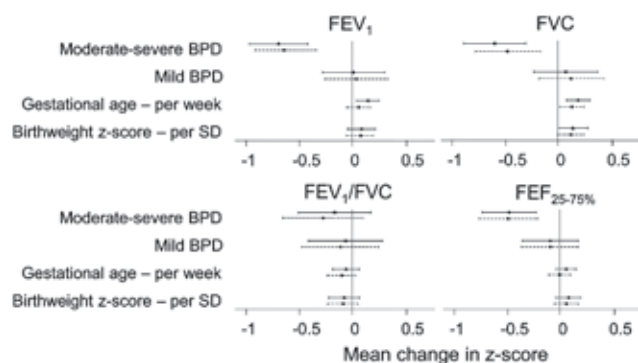


Figure 1 Mean differences and 95% CIs for associations of expiratory airflow with bronchopulmonary dysplasia (BPD), gestational age and birth weight z-score—univariable (solid line) and multivariable (dashed line) analyses. FEF, forced expiratory flow; FEV₁, forced expiratory volume in 1 s; FVC, forced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

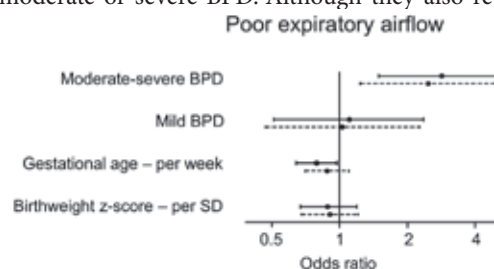


Figure 2 ORs and 95% CIs for poor expiratory airflow (forced expiratory volume in 1 s <5th centile) with bronchopulmonary dysplasia (BPD), gestational age and birth weight z-score—univariable (solid line) and multivariable (dashed line) analyses.

dren born 22–24 weeks' gestation had worse expiratory airflow than those born 25–26 weeks' gestation, there were no substantial differences in airflow between those with birth weight z-score ≤ -2 SD compared with those with birth weight z-score > -2 SD.

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

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

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

Limitations include that we were unable to obtain expiratory flow data on all participants; the high rate of major disability in those without valid expiratory flow data are one reason why such data were unavailable for some children who were assessed at 8 years; they were unable to complete satisfactory spirometry. Another limitation is that we did not record the precise inspired oxygen concentration or requirements for assisted ventilation at 36 weeks' postmenstrual age for all infants in all eras, and hence we could not classify moderate–severe BPD into categories of moderate and severe separately.

Of note the workshop report that proposed the categorisation of different levels of severity of BPD was published in 2001,¹⁰ after two of the three cohorts in the current study had been born and relevant data on respiratory and oxygen requirements in the newborn period had already been collected. A large study of expiratory flows across all grades of severity of BPD would be worthwhile. We corrected age for prematurity because children were assessed in multiple areas other than expiratory airflow, including IQ. Failure to correct IQ for prematurity results in a known bias in test scores at school age in children born EP.²⁰ Had we not corrected age for prematurity, our conclusions would have likely have been unaltered as correction for prematurity has little effect on expiratory airflow z-scores.²¹

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

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Contributors LWD and JC conceived and designed the study. LWD and JC were involved in identifying or assessing the children and in data collection. LWD, SR and JC were all involved in the data analysis or interpretation. LWD drafted the manuscript. All authors were involved in revising the manuscript and approved the final submitted version, and all agree to be accountable for all aspects of the work. LWD 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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REFERENCES

- Cheong JLY, Olsen JE, Huang L, et al. Changing consumption of resources for respiratory support and short-term outcomes in four consecutive geographical cohorts of infants born extremely preterm over 25 years since the early 1990s. *BMJ Open* 2020;10:e037507.
- Doyle LW, Andersson S, Bush A, et al. Expiratory airflow in late adolescence and early adulthood in individuals born very preterm or with very low birthweight compared with controls born at term or with normal birthweight: a meta-analysis of individual participant data. *Lancet Respir Med* 2019;7:677–86.
- Doyle LW, Carse E, Adams A-M, et al. Ventilation in extremely preterm infants and respiratory function at 8 years. *N Engl J Med* 2017;377:329–37.
- Doyle LW, Irving L, Haikerwal A, et al. Airway obstruction in young adults born extremely preterm or extremely low birth weight in the postsurfactant era. *Thorax* 2019;74:1147–53.
- Yang J, Kingsford RA, Horwood J, et al. Lung function of adults born at very low birth weight. *Pediatrics* 2020;145:e20192359.
- Hurst JR, Beckmann 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.
- Hart K, Cousins M, Watkins WJ, et al. Association of early life factors with Prematurity-Associated lung disease: prospective cohort study. *Eur Respir J* 2021. doi:10.1183/13993003.01766-2021. [Epub ahead of print: 08 Oct 2021].
- Doyle LW, Ford GW, Olinsky A, et al. Bronchopulmonary dysplasia and very low birthweight: lung function at 11 years of age. *J Paediatr Child Health* 1996;32:339–43.
- Doyle LW, Faber B, Callanan C, et al. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. *Pediatrics* 2006;118:108–13.
- Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163:1723–9.
- Cole TJ, Williams AF, Wright CM, et al. Revised birth centiles for weight, length and head circumference in the UK-WHO growth charts. *Ann Hum Biol* 2011;38:7–11.
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 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.
- Doyle LW, Victorian Infant Collaborative Study Group. Respiratory function at age 8–9 years in extremely low birthweight/very preterm children born in Victoria in 1991–1992. *Pediatr Pulmonol* 2006;41:570–6.
- Hacking DF, Gibson A-M, Robertson C, et al. Respiratory function at age 8–9 after extremely low birthweight or preterm birth in Victoria in 1997. *Pediatr Pulmonol* 2013;48:449–55.
- Kotecha SJ, Edwards MO, Watkins WJ, et al. Effect of preterm birth on later FEV1: a systematic review and meta-analysis. *Thorax* 2013;68:760–6.
- Ronkainen E, Dunder T, Peltoniemi O, et al. New BPD predicts lung function at school age: follow-up study and meta-analysis. *Pediatr Pulmonol* 2015;50:1090–8.
- Vollstaetter M, Roksund OD, Eide GE, et al. Lung function after preterm birth: development from mid-childhood to adulthood. *Thorax* 2013;68:767–76.
- Thunqvist P, Tufvesson E, Bjerner L, et al. Lung function after extremely preterm birth-A population-based cohort study (EXPRESS). *Pediatr Pulmonol* 2018;53:64–72.
- Wilson-Ching M, Pascoe L, Doyle LW, et al. Effects of correcting for prematurity on cognitive test scores in childhood. *J Paediatr Child Health* 2014;50:182–8.
- Doyle LW, Cheong JLY, Ranganathan S. Correcting standardized expiratory flows for prematurity in ex-preterm survivors—is it necessary? *Pediatr Pulmonol* 2019;54:205–11.

ARTIGO ORIGINAL

DPOC em África: fatores de risco, hospitalização, reinternamento e resultados associados — uma revisão sistemática e meta-análise

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RESUMO

Enquadramento — Esta revisão visa sintetizar as evidências disponíveis sobre a prevalência da doença pulmonar obstrutiva crônica (DPOC), os fatores de risco associados, as hospitalizações e os reinternamentos devido a DPOC em África.

Método — Utilizando as orientações dos estudos observacionais de revisão sistemática e meta-análise (Meta-Analyses and Systematic Reviews of Observational Studies), foram realizadas pesquisas em bases de dados eletrônicas, desde a criação até 1 de outubro de 2021. A qualidade dos estudos foi avaliada utilizando a escala Newcastle-Ottawa. As evidências existentes nos artigos consultados foram sintetizadas e foi realizada uma meta-análise utilizando o modelo de efeito aleatório. O protocolo foi registrado na PROSPERO.

Resultados — Trinta e nove estudos corresponderam aos critérios de inclusão, sendo 13 incluídos na meta-análise. A prevalência de DPOC variou entre os critérios da *Global Initiative for Chronic Obstructive Lung Disease* (2%–24%), da *American Thoracic Society/European Respiratory Society* (1%–17%) e do *Medical Research Council*, em relação à bronquite crônica (2% — 11%), respetivamente. O envelhecimento, a pieira e a asma foram fatores de risco constantes para DPOC nos estudos incluídos na síntese narrativa. A nossa meta-análise indicou que a tuberculose prévia (OR 5,98, 95% IC 4,18 para 8,56), o tabagismo (OR 2,80, 95% IC: 2,19 para 3,59) e a utilização de biocombustível (OR 1,52, 95% IC: 1,39 para 1,67) foram fatores de risco significativos para DPOC. A oxigenoterapia a longo prazo (HR 4,97, 95% IC (1,04 para 23,74)) e a hospitalização frequente (≥3 por ano) (HR 11,48, 95% IC (1,31 para 100,79)) foram fatores de risco associados ao reinternamento a 30 dias por DPOC.

Conclusão — Este estudo não só destaca fatores de risco específicos para o risco de DPOC em África, como também demonstra a escassez e ausência de investigação em vários países, num continente com mortalidade significativa associada a DPOC. As nossas conclusões contribuem para o desenvolvimento de orientações clínicas baseadas em evidências para a DPOC em África.

Número de registo na PROSPERO CRD42020210581.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by airflow limitation in the lungs and is associated with an abnormal inflammatory reaction of the lung to tobacco smoke, noxious particles or gases.¹ COPD was ranked the fourth (out of 369) condition with the highest disability-adjusted life years in the Global Burden of Disease report in 2019.² The Global Burden of Disease 2019 study estimated 212.3 million prevalent cases of COPD reported worldwide³ with 3.3 million deaths.⁴ Furthermore, COPD is one of the top three leading causes of death worldwide,¹ with 90% of COPD deaths occurring in low and middle-income countries (LMIC),⁴ mainly in South Asia and sub-Saharan Africa.⁵

Despite growing knowledge of the incidence and prevalence of COPD globally, there are scarce

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Chronic obstructive pulmonary disease (COPD) and COPD-related hospital admissions are prevalent in sub-Saharan Africa; yet the research on the risk factors for COPD and COPD hospital admission/readmission on the continent is sparse and diverse. There is a growing knowledge of the prevalence of, risk factors and predictors of COPD, COPD admission and readmission. Most of the published studies are from developed countries; hence, a systematic review is needed to identify predictors/risk factors of COPD, COPD admission and readmission in Africa.

WHAT THIS STUDY ADDS

► This study provides a comprehensive and up-to-date summary of the prevalence and risk factors of COPD in Africa. It also highlights the predictors of COPD admission and readmission that are unique to the continent.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► This study identified intervention opportunities that policymakers and healthcare professionals could target to reduce the burden of COPD in Africa.

data from many countries in Africa.^{5,6} In spite of the increasing burden of COPD in Africa being recognised as the second highest in the WHO regions category,⁶ there are no published reviews that systematically highlight the predictors and risk factors for COPD in Africa.⁷ It is, therefore, vital to understand these factors as COPD in Africa has been described as an ‘incoming storm’⁸ and ‘the silent epidemic’.⁹

There are several factors prevalent in Africa associated with COPD. Tobacco smoking is a major risk factor for the development and progression of COPD¹⁰ with its use in Africa on the increase.¹¹ There are 1.1 billion smokers in the world, of which 80% live in LMICs.¹² There is also an increase in the ‘non-smoking’ COPD population in Africa, which highlights the multifactorial pathogenesis of COPD.¹³ Other factors associated with COPD, especially in Africa, are environmental air pollution, exposure to combustion products of biomass fuel, occupational dusts/vapours/fumes, previous pulmonary tuberculosis (TB), HIV infection, poor



diet, malnutrition (including effects in utero), low socioeconomic status and childhood respiratory infections.^{14 15} Environmental pollution is a significant problem, with over 90% of households and individuals in rural Africa exposed to biomass fuel.^{16 17}

COPD is one of the leading causes of emergency hospitalisation and readmission in the world.^{18 19} Exacerbation of COPD has been reported to be one of the main reasons for admission and readmission of patients to hospital in high-income countries, with severe negative impacts on the patient and the healthcare system.²⁰ Prevention of exacerbation of COPD has been recognised as an international priority in improving the prognosis of COPD and reducing associated healthcare costs.^{19 21} Two recent systematic reviews on readmission for COPD focused on studies in developed countries with none from African countries to date,^{20 22} highlighting the need to gather and synthesise evidence from a continent with a high COPD burden to complement existing knowledge.

Although there has been a consensus on the importance of identifying risk factors for COPD and healthcare utilisation in Africa,^{15 23} there is no comprehensive review summarising these risk factors implicated in the development of, and hospitalisation for COPD in Africa. The available systematic reviews have focused on the prevalence, diagnosis and burden of COPD.^{6 24–27} The present systematic review aims to summarise identified predictors/risk factors of COPD and healthcare utilisation in Africa and review clinical characteristics and outcomes.

METHODS

This study was reported following the Meta-Analyses and Systematic Reviews of Observational Studies Guidelines²⁸ The protocol was registered on PROSPERO.

Data sources and search strategy

We searched four electronic databases (Medline, Scopus, Embase and Cumulative Index to the Nursing and Allied Literature (CINAHL) for relevant papers from the inception date to 1 October 2021. We used four main search keywords ('COPD', 'risk factors/consequences', 'admission/readmission' and 'Africa') as 'concepts' based on previous systematic reviews relevant to the topic.²⁰ Alternative terms and synonyms for each of the key concepts were identified as free-text terms and used to search in the databases as title and abstract. Database-specific controlled vocabulary/subject headings were also used in the search (online supplemental table S1). Detailed information on the search strategy is found in online supplemental table S2. Relevant studies identified through the reference list of eligible papers were also included.

Statistical analysis

Studies were included based on the following inclusion criteria:

- ▶ Studies included the numerical estimates of the prevalence of risk factors/predictors/causes for COPD or COPD admission or readmission; admission/readmission (s) of COPD clearly defined as one or more admission where COPD was the primary diagnosis for the admission/readmission (s)
- ▶ Studies undertaken in any of the 54 African countries. Studies were excluded based on these criteria:
- ▶ Studies were conference abstracts, editorial reports and letters, theses or reviews.
- ▶ Studies described the implementation of interventions or programmes beyond normal care.
- ▶ Studies were published in any language other than English.
- ▶ Studies undertaken in countries that are not in Africa.

Study definitions

COPD has been previously described based on both clinical and pathological presentations such as chronic bronchitis and emphysema.²⁹ These definitions do not explain the physiological impairment of the lungs that is manifest by reduced expiratory volume linked to the vital capacity of the lungs. A clear definition of COPD based on spirometry measures (a postbronchodilator ratio of forced expiratory volume in one second (FEV₁) to forced

vital capacity (FVC) of less than 70% (FEV₁/FVC<0.7)) has been provided by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)¹ and the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines³⁰ (online supplemental table S3). It has been acknowledged that the presence of mucus hypersecretion seen in chronic bronchitis can occur without airflow limitation in some patients. Hence, chronic bronchitis or the occurrence of cough and sputum production for at least 3 months in two consecutive years in a person in whom other causes of chronic productive cough have been excluded has been used in studies.¹ For the purpose of this review, COPD definition will be based on spirometry (1 and 2) and chronic bronchitis measurement will be termed the non-spirometry³ measure:

1. The GOLD criteria¹.
2. TheATS/ERS criteria,³⁰ (GOLD and ATS/ERS criteria both defined as a postbronchodilator ratio of FEV₁ to FVC of less than 70% (FEV₁/FVC<0.7)).
3. The British MRC definition of chronic bronchitis, defined as 'chronic productive cough on most days for 3 months in 2 consecutive years in a person in whom other causes of chronic productive cough have been excluded'.¹

Study selection and data extraction

Studies were exported into the Rayyan QCRI web app for systematic reviews following the removal of duplicates in EndNote X9 (Thomson Reuters, USA). Two authors (CMN and KO) independently screened titles and abstracts of potential studies. The full text of eligible articles following the initial screening was independently reviewed by two authors (CMN and KO) to ensure that included studies met the eligibility criteria. Disagreements on selected papers between independent reviewers were resolved by a third author (SB). Data were reviewed and extracted from eligible studies according to a standardised format based on variables of interest, such as study population, study design, age, gender, smoking status, the prevalence of COPD and readmission rates. The adjusted OR measurements of association were extracted from the included studies.

Risk-of-bias assessment

Two authors (CMN and KO) independently assessed the methodological quality of each included study using the Newcastle-Ottawa Scale³¹ for cohort studies and adapted form for cross-sectional studies.³² These tools are mainly employed for the appraisal of non-randomised studies. The scale evaluates the selection, comparability and outcome of the studies, using a 'star' system with a maximum of nine stars for each study.³¹ Two authors (CMN and KO) independently assessed the quality of the studies and discrepancies were resolved by consensus (CMN, KO and SB).

Data synthesis

The heterogeneity and inconsistencies in reporting risk factors across studies prevented the inclusion of all the results from the studies retrieved in the subsequent meta-analysis. The meta-analysis was conducted using summary data from 13 studies to synthesise adjusted ORs for risk factors where results were reported consistently. The pooled adjusted ORs and 95% CIs were estimated in a meta-analysis if at least five studies reported results that were sufficiently similar.³³ Only studies that used the same reference category for the smoking variable were included in the meta-analysis. Similar analyses were performed for risk factors of COPD admission/readmission. The heterogeneity of included studies was addressed by applying the random-effects model in Stata V.16.0, using the I² statistic to examine between-study heterogeneity. The heterogeneity was substantial if the value of I² was >50% and having a p value of >0.1 was considered an indicator of lack of heterogeneity.

RESULTS

The search identified 552 papers, of which 87 were duplicates and excluded. Following the initial screening of 465 titles and abstracts, 149 full-text articles were assessed for eligibility and 39 papers met

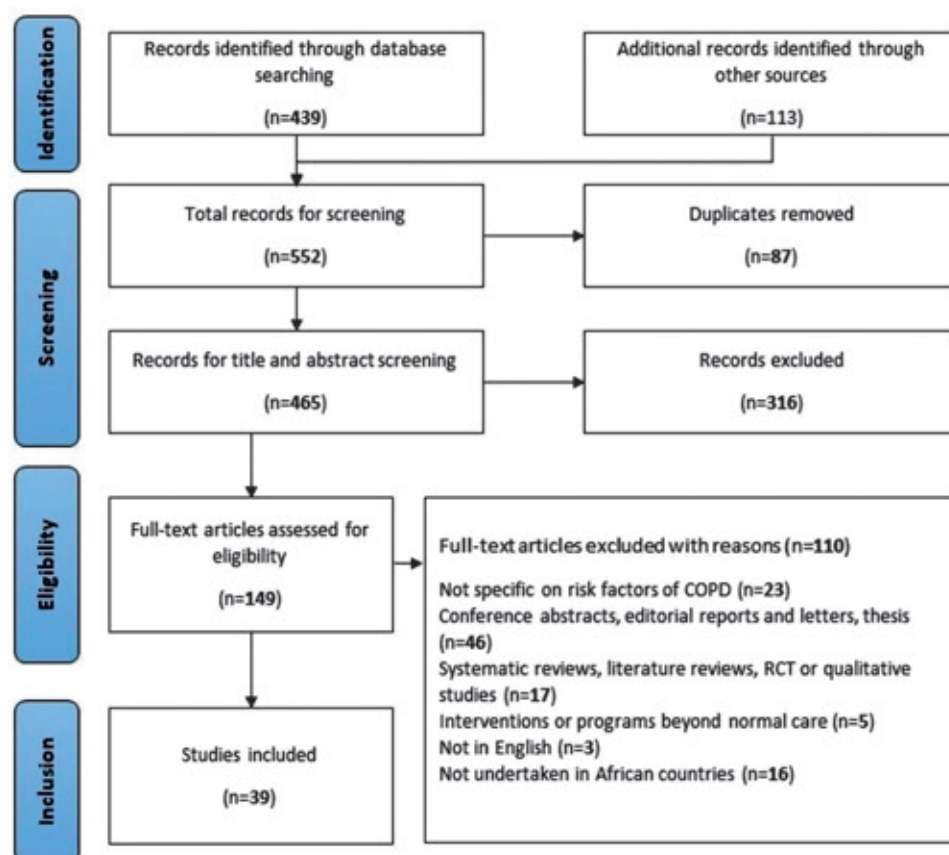


Figure 1 Study flowchart of included studies. COPD, chronic obstructive pulmonary disease.

the inclusion criteria. The detailed selection process is shown in figure 1. The result of the quality assessment showed that 38 studies (97.4%) had five or more stars with one study (2.6%) having three stars (online supplemental table S4).

Study characteristics

Table 1 shows the summary of relevant characteristics from 39 studies, which included 100 722 participants. Thirty-four of the studies (87%) were cross-sectional studies, with two studies (5%) conducted prospectively and another three (8%) conducted retrospectively. The studies were conducted across 14 of the 54 countries (26%) in the African continent. Five (out of 18) East African countries contributed the largest number of studies ($n=16$),^{15 17 34–47} followed by four (out of 6) North African countries with eight studies,^{48–55} two (out of 16) West African countries contributing seven studies^{56–61} and one (out of 5) Southern African countries^{62–65} and two (out of 9) Middle African countries^{66–69} both contributing four studies each. Seven studies were conducted in Uganda^{15 36 41–45}; six in Nigeria^{36–59 61 70}; four in South Africa^{62–65}; three each in Cameroon,^{67–69} Egypt,^{48 54 55} Morocco,^{51 52 54} Tanzania,^{17 40 47} and Tunisia^{49 50 54}; two each in Algeria,^{53 54} Ethiopia,^{34 46} Malawi,^{35,37} Rwanda^{38 39} and one each in Cape Verde⁶⁰ and Democratic Republic of Congo.⁶⁶ Thirty-five of the included studies (92%) were published within the last decade (2010–2020).

Prevalence of COPD, COPD admission and readmission

Fourteen studies described COPD prevalence based on GOLD spirometric criteria,^{17 36 37 39–41 46 48 50 52 59 62 64 67 10} on ATS/ERS spirometric criteria^{15 35 36 39 42 44 51 61 66 69} while 7 studies were on both GOLD and ATS/ERS criteria.^{45 47 49 51 55 57 69} Five studies utilised the MRC description of chronic bronchitis^{38 43 54 58 63} with one reporting both chronic bronchitis (MRC) and COPD (ATS/ERS) criteria.⁴³ Thirty-one studies reported a total of 41 rates of COPD prevalence based on spirometry while five studies reported nine rates of chronic bronchitis prevalence based on MRC criteria (table 1). The prevalence of COPD ranged from 2% to 24% (GOLD criteria) and 1% to 17% (ATS/ERS criteria). The prevalence of chronic bronchitis ranged from 2% to 11% (MRC criteria).

Eight studies from North African countries (4 out of 8) reported on the prevalence of COPD based on GOLD spirometry criteria ranging from 4.1% to 12.6%, ATS/ERS criteria from 5.3% to 17.4% and non-spirometry chronic bronchitis criteria from 2.2% to 3.7%. Twenty-eight studies from the sub-Saharan African countries reported the prevalence of COPD via GOLD criteria from 1.6% to 23.8%, ATS/ERS criteria from 1.4% to 17.4% and chronic bronchitis MRC criteria from 2.2% to 10.7%.

Two studies reported the rate of COPD admission as 56% over 12 months⁶⁵ and 8% over 5 years⁵⁶ of study period, respectively. Three studies reported the rate of COPD readmission as 6%³⁴ within 30 days postdischarge, 44% over 12 months⁶⁵ and 46% over 10 years of study period.⁵³

Risk factors for COPD, COPD admission and readmission

Twenty-one studies reported 12 possible risk factors for COPD.^{15 17 36–40 42 44–46 49 50 55 57 58 61 63 66 68 69} Of these, three factors (biomass fuel, TB, and smoking) were considered for pooled adjusted ORs as the remaining factors were examined in fewer than five studies.³³ No study reported on risk factors for COPD admission.

Long-term oxygen therapy (HR 4.97, 95% CI 1.04 to 23.74) and frequent hospitalisation (≥ 3 in a year) (HR 11.48, 95% CI 1.31 to 100.79) were found to be risk factors associated with 30 days COPD readmission.³⁴ Detailed summaries of the risk factors associated with COPD and COPD readmission are presented in online supplemental table S5 and S6.

Meta-analysis

Meta-analysis was not performed on all results because of the lack of data on admissions/readmissions and the heterogeneity of selected studies. We included 13 studies comprising 23 035 patients in the meta-analysis for the examination of COPD risk factors. Seven of the studies with 18 314 patients reported smoking as a risk factor, seven studies comprising 18 600 patients reported the use of biomass as fuel as a risk factor while five studies with 17 114 patients reported history of TB as a risk factor. The pooled adjusted OR indicates that previous pulmonary TB (OR 5.98, 95% CI 4.18 to 8.56), smoking (OR 2.80, 95% CI 2.19 to 3.59) and use of

Table 1 Characteristics of included studies

First author year	Region	Study design	Population studied	Number of patients	Mean age (years)	Gender (male %)	Current smoker (%)	Former smokers (%)	Biomass exposure (%)	COPD prevalence rate (%)			Rate of COPD admission/readmission
										Spirometric		Non spirometric	
										GOLD criteria	ATS/ERS criteria	MRC chronic bronchitis criteria	
Adeniji, 2017 ⁵⁶	Nigeria*	R		502		54.0						7.5 with 1 admission within 5 years	
Akanbi, 2015 ⁵⁷	Nigeria*	CS	Hospital based	356	44.5	41.0	3.7	17.1		15.4	12.1		
Anbesse, 2020 ³⁴	Ethiopia†	P		71	60.0	69.0	35.2	19.7				6.0 readmission with 30 days	
Badway, 2015 ⁴⁸	Egypt‡	CS	Mixed	2400		70.0	50.4	6.9	10.8	6.7			
Buist, 2007 ⁶²	South Africa§	CS	Mixed	847	53.6	37.0	48.8	21.3		23.8			
Daldoul, 2013 ⁴⁹	Tunisia‡	CS	Mixed	807	59.5	46.7	28.6	13.3		7.8	5.3		
Denguezli, 2016 ⁵⁰	Tunisia‡	CS	Mixed	807		46.2	27.3			7.8			
Desalu, 2011 ⁵⁸	Nigeria*	CS	Rural	391	55.5	34.5	2.6	9.2			5.6		
Desalu, 2010 ⁵⁹	Nigeria*	CS	Rural	269	55.5				59.9	7.4			
Ehrlich, 2004 ⁶³	South Africa§	CS	Mixed	13 826				3.6			2.6		
El Rhazi, 2016 ⁵¹	Morocco‡	CS	Mixed	966	56.1	43.0	8.0	17.0	38.6	12.6	8.9		
Fullerton, 2011 ³⁵	Malawi†	CS	Mixed	374	46.0	39.7	13.9	7.5			13.6		
Gathuru, 2002 ⁷⁰	Nigeria*	CS	Urban	270	47.6	57.6	10.8				9.3		
Iyaloo, 2020 ⁶⁴	South Africa§	CS	Occupational	149						12.8			
Kayongo, 2020 ³⁶	Uganda*	CS		722	48.0	40.3	5.4		88.5		6.22		
Laraqui, 2018 ⁵²	Morocco‡	CS	Occupational	924	40.8	100.0	46.6	23.3		4.1			
Magitta, 2018 ¹⁷	Tanzania†	CS	Rural	496	51.8	53.0	5.4	19.8	99.5	17.5			
Martins, 2009 ⁶⁰	Cape Verde*	CS	Urban	274	41.5	35.0	5.8	6.6	45.3	8.4			
Mbelambela, 2020 ⁶⁶	DR Congo¶	CS		235		0.0					12.3		
Meghji, 2016 ³⁷	Malawi†	CS	Urban	749	41.9	42.1				4.2			
Musafiri, 2018 ³⁸	Rwanda†	P		436	32.2				68.3		10.7		
Musafiri, 2011 ³⁹	Rwanda†	CS	Mixed	1824	38.3	48.1	16.7	15.8	60.3		4.5		
Mwaiselage, 2005 ⁴⁰	Tanzania†	CS	Occupational	222	40.0					12.2			
Ngahane, 2015 ⁶⁷	Cameroon¶	CS		300		0				1.6			
North, 2019 ⁴¹	Uganda†	CS		565	39.0	38.0	10.0	19.0		2.0			
Nuwagira, 2020 ⁴²	Uganda†	CS		95	39.0	60.0	1.0	24.0		23.0			
Obaseki, 2016 ⁶¹	Nigeria*	CS	Rural	1148		37	2.3	8.4			7.7		
Pefura-Yone, 2016 ⁶⁹	Cameroon¶	CS	Urban	1287	34.4	48.1	9.4	6.8	47.6		2.4		
Pefura-Yone, 2015 ⁶⁸	Cameroon¶	CS	Urban	922	42.6	32.3	7.0	8.1		5.1	1.4		

Continued

Table 1 Continued

First author year	Region	Study design	Population studied	Number of patients	Mean age (years)	Gender (male %)	Current smoker (%)	Former smokers (%)	Biomass exposure (%)	COPD prevalence rate (%)			Rate of COPD admission/readmission	
										Spirometric		Non spirometric		
										GOLD criteria	ATS/ERS criteria	MRC chronic bronchitis criteria		
Pienaar, 2015 ⁶⁵	South Africa§	R		178	63.0	57.9	34.0	65.7				56.2 with 1 admission, 24.7 with 2 admissions, 19.1 with ≥3 admissions, 43.8 with ≥2 readmissions within 12 months		
Ramdani, 2020 ⁵³	Algeria†	R		120	74.3	96.0						46.3 with 1 readmission, 19.5 with 2 readmissions, 34.1 3–12 readmissions within 10 years		
Said, 2015 ⁵⁵	Egypt‡	CS		363		78.0	73.8	5.5		9.6	17.4			
Siddharthan, 2018 ⁴⁴	Uganda: † Kampala	CS		596	44.2	48.7	8.7		93.5		1.7			
	Masindi	CS		414	49.7	50.0	36.2		92.8		15.5			
	Nakaseke	CS		721	49.1	45.9	6.9		99.6		7.4			
Siddharthan, 2019 ⁴³	Uganda†: Kampala	CS		665	44.1	47.8			93.6		1.5	2.2		
	Nakaseke	CS		837	49.1	45.4			99.6		6.1	3.5		
Tageldin, 2012 ⁵⁴	Algeria†, Egypt‡, Morocco‡, Tunisia‡	CS		62 086		51.0						3.7 3.5 2.2 3.7		
van Germert, 2015 ⁴⁵	Uganda†	CS	Rural	588	45.2	49.0	20.7	14.8	93.0	12.4	16.2			
van Germert, 2016 ¹⁵	Uganda†	CS	Rural	588	45.2	49.5	20.7	14.8	93.0		16.2			
Woldeamanuel, 2019 ⁴⁶	Ethiopia†	CS		734	39.2	57.4	9.0	2.7	82.0	17.8				
Zoller, 2018 ⁴⁷	Tanzania†	CS	Mixed	598	46	52.0	15.0	13.0	85.0	5.0	4.0			
*West Africa. †East Africa. ‡North Africa. §South Africa. ¶Middle Africa. ¶¶American Thoracic Society/European Respiratory Society; COPD, chronic obstructive pulmonary disease.; CS, cross-sectional study; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MRC, British Medical Research Council; P, prospective study; R, retrospective study.														

*West Africa.

†East Africa.

#North Africa.

§South Africa.

¶Middle Africa.

ATS/ERS, American Thoracic Society/European Respiratory Society; COPD, chronic obstructive pulmonary disease; CS, cross-sectional study; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MRC, British Medical Research Council; P, prospective study; R, retrospective study.

biomass as fuel (OR 1.52, 95% CI 1.39 to 1.67) are significant risk factors for COPD in Africa. These are presented using forest plots (figure 2A–C). The heterogeneity between studies was not significant with I^2 values of 0% (95% CI 0%, 61%, $p=0.84$), 15% (95% CI 0%, 61%, $p=0.31$) and 37% (95% CI 0%, 70%, $p=0.12$) for TB, smoking status and biomass as fuel, respectively (figure 2A–C).

Narrative synthesis for risk factors for COPD

Older age

Thirteen out of 19 studies that examined the relationship between age and COPD, associated older age across various age ranges (≥ 30 years to ≥ 74 years) with increased risk of COPD. Meghji et al reported that the odds of having COPD within the age range of 50–59 years compared with ≥ 60 varied significantly from OR of 4.66 to 10.12.³⁷ This was confirmed in research by Magitta et al where the risk of COPD significantly increased in patients aged between 51 and 60 (OR 9.66, 95% CI 4.79 to 18.25) compared with those between 41 and 50 (OR 4.02, 95% CI 1.10 to 14.66) in relation to those aged between 30 and 40.¹⁷ Desalu et al also reported a significant association between older age (65–74 and ≥ 74) and COPD compared with those < 35 years. However, ages between 55 and 64 had a significant protective effect with an OR of 0.20 in comparison to < 35 .⁵⁸

Other risk factors

Three studies reported patients with a wheeze to be more likely to develop COPD^{45 55 69} while no association was found in patients with chronic cough and sputum production.^{15 45 55 69} For example, Pefura-Yone et al found patients with lifetime wheeze to have almost threefold increased odds of developing COPD compared with those without lifetime wheeze.⁶⁹ Asthma was associated with increased risk for COPD in two studies^{50 61} while no association was found with other comorbidities (such as hypertension, heart failure, pneumonia and diabetes) and COPD. Several studies investigated sex ($n=13$), ethnicity ($n=2$), Body Mass Index ($n=8$), HIV ($n=6$), living in urban areas ($n=3$), educational level ($n=14$) and occupational exposure to dusts, gases or fumes ($n=6$) as risk factor for COPD, but the results were inconsistent. One study found men to have a 3.0 odds of COPD compared with being ³⁹women; however, another 10 studies found no association between sex and COPD.

DISCUSSION

This is the first systematic review to examine and summarise the risk factors for COPD and COPD admission in Africa. Our meta-analysis showed that history of TB, smoking and use of biomass fuel are associated with an increased risk of COPD. Increasing age, wheezing and comorbid asthma are also risk factors for COPD. We found that the prevalence of COPD ranged from 1% to 24% depending on the assessment criteria and setting. We estimated, for the first time, the prevalence of COPD in Africa and we also identified COPD risk factors that are of importance on the continent. Nevertheless, these estimates were from only 14 out of the 54 countries. This highlights the urgency and need for more research work to be conducted in COPD across Africa, considering that 90% of the COPD-related mortality rate occurs in Africa.

Our study reports the prevalence of COPD ranging from 1% to 24% is consistent with previous reviews that reported COPD prevalence in sub-Saharan African countries between 4% and 25%.^{24 25} Another review reported COPD prevalence in Africa in all spirometry-confirmed cases to be 13.4% and non-spirometry-confirmed cases to be 4.0%.²⁴ This was different to our result on spirometric confirmed cases and non-spirometric confirmed cases. The wide variation in the prevalence of COPD in Africa may be due to variations in the study population and setting, age of participants and criteria used for diagnosis.¹⁴ This is similar to the result of a recent systematic review that focused on developed countries.²⁰

The 12-month and 5-year admission rates for COPD were 56% and 8%, respectively, which are inconsistent with other studies in the literature. The rate of readmission ranged from 6% to 46%, depending on the follow-up period. Other reviews have only

considered readmission from COPD in developed countries.^{20 22} The COPD readmission rate reported in African populations is lower for 30 days of readmission (6.0%) compared with developed countries that varied from 8.8% to 26.0%;²² however, there was consistency in 1-year readmission. It is vital to highlight the lack of studies on readmissions in Africa and the challenges accessing affordable hospital care for those in need. Three studies reported COPD readmission (1=30 day, 1=1 year and 1=10 years). On the contrary,³² studies in developed countries reported 30 days, 90 days and 1-year all-cause COPD readmission²² and 54 studies reported 30 days, 90 days and 1-year COPD-related readmission.²⁰

Reasons for the differences in the figures observed between Africa and developed countries may include the economic burden of COPD due to poor access and affordability to hospital health-care for many populations from low socioeconomic areas. Another plausible reason could reflect the widespread under-recognition and underdiagnosis of COPD. There is also diversity both within and between African countries (eg, Northern African countries vs sub-Saharan African countries). Our study clearly highlights the importance of further research in this area with only 14 countries (out of 54) contributing to the studies.

Consistent with the literature, our results found previous TB infection to be independently associated with COPD.⁷¹ TB can result in airflow obstruction meeting the spirometric criteria for COPD. TB is known to trigger airway inflammatory response that consequently results in a decrease in lung volume.⁷¹ There is the inflammatory response of TB known by its increased oxidative stress in the airways and lung parenchyma which are vital pathological processes in the development and progression of COPD.⁷¹ The high prevalence of TB worldwide especially in many developing countries denotes a considerable public health significance both to epidemiologists and healthcare providers.

Asthma was found to be strongly associated with the development of COPD. Poorly controlled asthma, for example, in the absence of access to affordable therapy, can result in airflow obstruction that meets the spirometric criteria for COPD. This is in line with a report from the Tucson study that found patients with asthma to have a 12-fold higher risk of developing COPD compared with those without asthma.⁷² Although the reversibility of pulmonary obstruction in response to treatment is a hallmark of asthma, it has been shown to decrease over time in some asthmatic patients, to the point of irreversible or only partially reversible airway obstruction.⁷³ Systematic reviews have found an increased frequency of COPD exacerbation and hospitalisation in patients with asthma.^{74 75} This increases the disease burden for patients with COPD. Clinical respiratory guidelines that are tailored to the needs and demands of African countries by the global community may improve the diagnosis and management of COPD but are often lacking.⁷⁶ Accessibility, availability and affordability of COPD and respiratory medicines will go a long way in the management of COPD.

The use of biomass fuel for cooking and heating was found to be a significant risk factor for COPD. Globally almost three million people use biomass and coal as their essential source of energy for cooking, heating and other household requirements.⁷⁷ Over 90% of households in rural Africa are exposed to biomass fuel with women and young children, particularly at increased risk of exposure during food preparation.¹⁷ Exposure to solid fuels for cooking is associated with premature 3.8 million deaths a year.⁷⁸ Twenty-five per cent of deaths from COPD in adults in LMICs are due to exposure to household air pollution.⁷⁸ Cooking in poorly ventilated kitchens was associated with a fourfold increase in development of COPD.⁴⁶ In poorly ventilated dwellings, indoor smoke can be 100 times higher than appropriate levels for fine particles.⁷⁸ There is also the impact of pollution from industrialisation comprising of fossil fuel-driven machineries with limited implementation of safety and health standards in many settings. This highlights the potential for effective policies and strategies to reduce the exposure and impact of biomass fuels and the COPD burden of disease.

Seven studies found strong associations between smoking and COPD. Smoking is recognised to be the most important

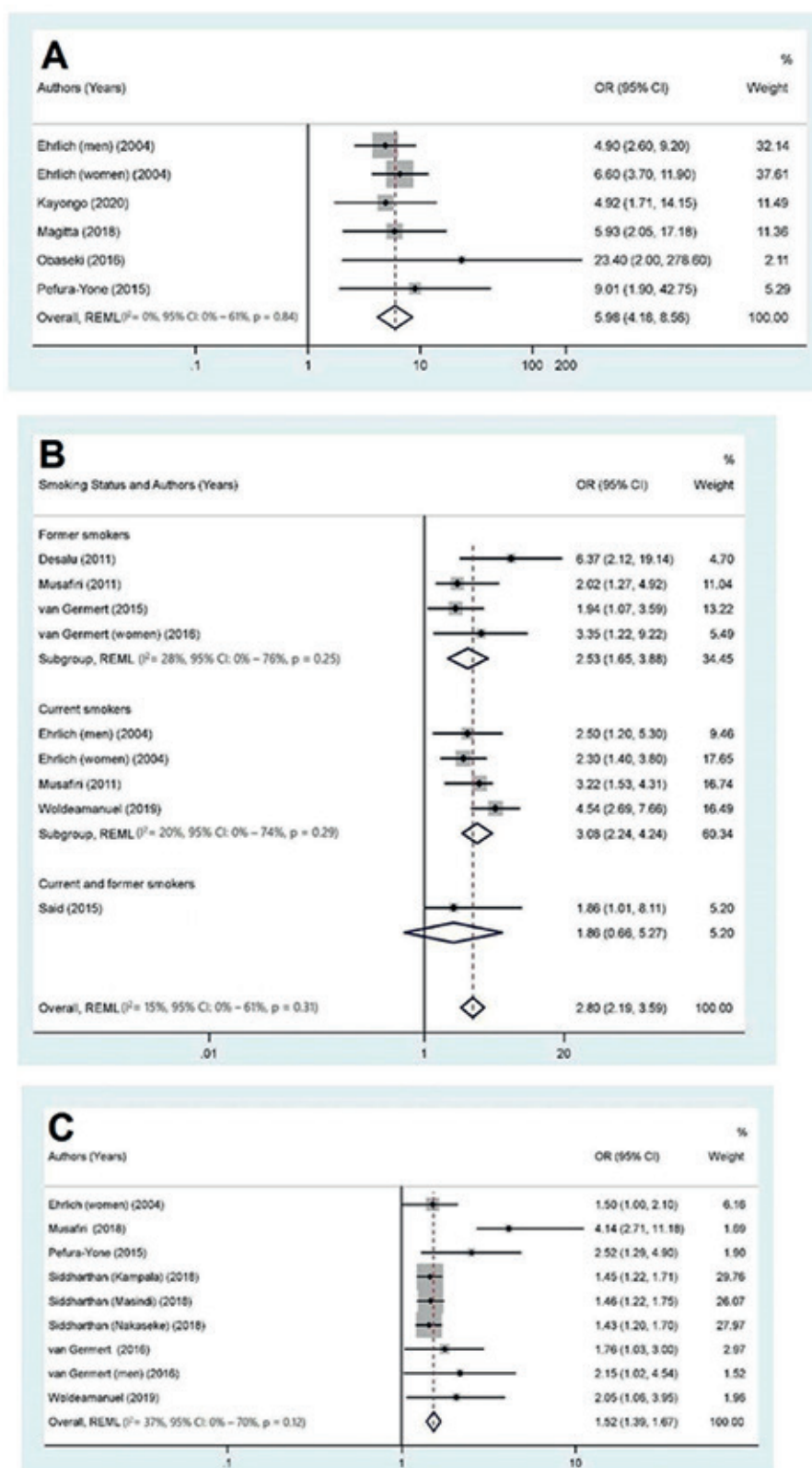


Figure 2 (A–C) The results of pooled adjusted ORs for tuberculosis, smoking status and biomass as fuel respectively. COPD, chronic obstructive pulmonary disease; REML, restricted maximum likelihood.

cause of COPD in high-income settings. This relationship was substantial in subgroups of current smokers, former smokers and combining current and former smokers. Forey et al in a meta-analysis comprising of 218 studies demonstrated a clear relationship between smoking (for ever, current and former smoking) and COPD.⁷⁹ Many of the African countries have lower tobacco taxation rates, weaker smoke-free policies with less stringent tobacco advertising restrictions in comparison to higher income

and developed countries. Hence, they are less likely to implement programmes aimed at prohibiting smoking in public places.¹¹ Urgent action is required by all stakeholders, including governments in implementing and advocating prohibition of smoking in public places.

The results of individual studies have demonstrated that the odds of having COPD are greater in older age groups compared with younger age groups. This finding is unsurprising and consistent

with previous reports.^{20–22} The average life expectancy in African countries has increased since 2000 from 50.8 years to 61.2 years in 2016.⁸⁰ This increase suggests that the burden of COPD will also be increasing and, therefore, requires urgent attention. The higher COPD risk among individuals in the older age category may be an indication of cumulative exposures during lifetime or ageing of the airways and parenchyma associated with structural changes in COPD.¹ Interestingly, the age range included in some studies was as low as 30 years suggesting early onset, with early and continuous exposure to biomass and noxious fumes. These in combination with poor lung growth and development associated with poverty and inadequately treated respiratory infections increased the burden of COPD disease. African governments need to implement urgent policies to reduce airborne exposures, tobacco smoke and indoor and outdoor pollution.

Two papers reported risk factors for readmission of COPD^{34,65} with one reporting only *p* values for the multivariate analysis. Anbesse et al found long-term use of oxygen therapy (a marker of respiratory failure, but a treatment not widely available in Africa) and frequent hospitalisation (≥ 3) in a year to be associated with an increased risk of COPD readmission.³⁴ This is consistent with a recent systematic review undertaken in developed countries.²⁰ Patients on long-term oxygen therapy are likely to have severe and advanced disease thereby increasing their risk of readmission. Similarly, frequent hospitalisation may indicate suboptimal management or disease severity.

There are limitations to this study. We limited our literature search to studies published in English; hence, it is possible that we might have missed studies published in other languages. In addition, Africa is geographically large and diverse with varying health determinants and socioeconomic factors. Diversity extends to differences within countries such that context varies greatly. The covariates reported in the studies included in the meta-analysis were not uniform, and the OR derived from various studies was adjusted for different covariates. There is also the variation in the method of diagnosing COPD, which reflects the diversity of formal and informal healthcare system found in most African countries. The diverse healthcare system is intertwined with social, cultural, and economic/affordability issues which are strong barriers to early assessing of appropriate healthcare services. Appropriate management of COPD will require appropriate diagnosis involving access to spirometry. A majority of healthcare facilities in Africa lack spirometry and must rely solely on clinical features for diagnosis, perhaps supported by case finding tools.⁸¹ There is also the issue of affordability of the life-long treatments for appropriate management of COPD. Adherence will continue to be severely affected by affordability of health cost imposed on poor income households. The availability of COPD therapy at an affordable price will be a starting point in the prevention and management of COPD, as will the effective implementation of guidelines.⁸² Further studies in partnership with international communities are urgently needed to tackle this global public health issue. We recognise that the causes of poorly reversible airflow obstruction in LMIC settings are diverse and that not everyone meeting spirometric criteria for COPD has an exposure-driven airway disease. In addition, respiratory exposures in LMIC may cause manifestations such as emphysema that are not necessarily associated with poorly reversible airflow obstruction despite being part of the COPD definition. These limitations are rarely adequately addressed in the individual studies we have summarised and are important areas for future research.

CONCLUSION

The prevalence of COPD is higher based on GOLD criteria (2%–24%) compared with ATS/ERS criteria (1%–17%) and MRC chronic bronchitis criteria (2%–11%). Comorbidity (TB and asthma), smoking and use of biomass as fuel are significant risk factors for COPD in Africa. Long-term use of oxygen therapy and frequent hospitalisation (≥ 3) in a year are associated with increased risk of COPD readmission. Further studies are needed for clearer reporting of the magnitude of the problem. These identified factors

potentially guide the development of evidence-based guidance and culturally acceptable local interventions tailored to the demands and needs of various regions on the African continent.

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REFERENCES

- Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2021. Available: https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf [Accessed cited Jan 10, 2021].
- GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet* 2020;396:1204–22.
- 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.
- World Health Organisation. Chronic obstructive pulmonary disease (COPD). fact sheet No. 315. Geneva: World Health Organisation, 2016. <http://www.who.int/mediacentre/factsheets/fs315/en/index.html>
- Burney P, Jarvis D, Perez-Padilla R. The global burden of chronic respiratory disease in adults. *Int J Tuberc Lung Dis* 2015;19:10–20.
- Adeloye D, Chua S, Lee C, et al. Global and regional estimates of COPD prevalence: systematic review and meta-analysis. *J Glob Health* 2015;5:020415.
- Halbert RJ, Natoli JL, Gano A, et al. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006;28:523–32.
- Mannino DM. Copd in Africa: the coming storm. *Int J Tuberc Lung Dis* 2013;17:572.
- Salvi S. The silent epidemic of COPD in Africa. *Lancet Glob Health* 2015;3:e6–7.
- Burney P, Jithoo A, Kato B, et al. Chronic obstructive pulmonary disease mortality and prevalence: the associations with smoking and poverty—a BOLD analysis. *Thorax* 2014;69:465–73.
- Brathwaite R, Addo J, Smeeth L, et al. A systematic review of tobacco smoking prevalence and description of tobacco control strategies in sub-Saharan African countries; 2007 to 2014. *PLoS One* 2015;10:e0132401.
- World Health Organization. Who report on the global tobacco epidemic, 2019. Geneva: World Health Organization, 2019. <https://apps.who.int/iris/bitstream/handle/10665/326043/9789241516204-eng.pdf?ua=1>
- Allwood B, Calligaro G. Pathogenesis of chronic obstructive pulmonary disease: an African perspective. *S Afr Med J* 2015;105:789.
- Magitta F. Epidemiology and challenges of managing COPD in sub-Saharan Africa. *Acta Sci Med* 2018;2:17–23.
- van Gemert F, Chavannes N, Kirenga B, et al. Socio-Economic factors, gender and smoking as determinants of COPD in a low-income country of sub-Saharan Africa: fresh air Uganda. *NPJ Prim Care Respir Med* 2016;26:1–6.
- Piddock KC, Gordon SB, Ngwira A, et al. A cross-sectional study of household biomass fuel use among a periurban population in Malawi. *Ann Am Thorac Soc* 2014;11:915–24.
- Magitta Ng'weina Francis, Walker RW, Apte KK, et al. Prevalence, risk factors and clinical correlates of COPD in a rural setting in Tanzania. *Eur Respir J* 2018;51:1700182.
- Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3:e442.
- 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.
- Njoku CM, Alqahtani JS, Wimmer BC, et al. Risk factors and associated outcomes of hospital readmission in COPD: a systematic review. *Respir Med* 2020;173:105988.
- Reducing COPD readmissions—a personal and political priority. *Lancet Respir Med* 2013;1:347.
- Alqahtani JS, Njoku CM, Bereznicki B, et al. Risk factors for all-cause Hospital readmission following exacerbation of COPD: a systematic review and meta-analysis. *Eur Respir J* 2020;29:190166.
- Jones R. The scale of the problem of obstructive lung disease in Africa becomes clearer, but where are the solutions? *Eur Respir J* 2018;51:1702562.
- Adeloye D, Basquill C, Papana A, et al. An estimate of the prevalence of COPD in Africa: a systematic analysis. *COPD* 2015;12:71–81.
- Finney LJ, Feary JR, Leonardi-Bee J, et al. Chronic obstructive pulmonary disease in sub-Saharan Africa: a systematic review. *Int J Tuberc Lung Dis* 2013;17:583–9.
- Varmaghani M, Dehghani M, Heidari E, et al. Global prevalence of chronic obstructive pulmonary disease: systematic review and meta-analysis. *East Mediterr Health J* 2019;25:47–57.
- 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.
- Stroup DF, Berlin JA, Morton SC, et al. Meta-Analysis of observational studies in epidemiology: a proposal for reporting, meta-analysis of observational studies in epidemiology (moose) group. *JAMA* 2000;283:2008–12.
- Viegi G, Pistelli F, Sherrill DL, et al. Definition, epidemiology and natural history of COPD. *Eur Respir J* 2007;30:993–1013.
- Celli BR, MacNee W, Agustí A, ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932–46.
- Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis, 2013. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 08 Jul 2018].

32. Modesti PA, Rebaldi G, Cappuccio FP, et al. Panethnic differences in blood pressure in Europe: a systematic review and meta-analysis. *PLoS One* 2016;11:e0147601.
33. Jackson D, Turner R. Power analysis for random-effects meta-analysis. *Res Synth Methods* 2017;8:290–302.
34. Anbesse ZK, Mega TA, Tesfaye BT, et al. Early readmission and its predictors among patients treated for acute exacerbations of chronic obstructive respiratory disease in Ethiopia: a prospective cohort study. *PLoS One* 2020;15:e0239665.
35. Fullerton DG, Suseno A, Semple S, et al. Wood smoke exposure, poverty and impaired lung function in Malawian adults. *Int J Tuberc Lung Dis* 2011;15:391–8.
36. Kayongo A, Wosu AC, Naz T, et al. Chronic obstructive pulmonary disease prevalence and associated factors in a setting of well-controlled HIV, a cross-sectional study. *COPD* 2020;17:297–305.
37. Meghji J, Nadeau G, Davis KJ, et al. Noncommunicable lung disease in sub-Saharan Africa. A community-based cross-sectional study of adults in urban Malawi. *Am J Respir Crit Care Med* 2016;194:67–76.
38. Musafiri S, Masaisa F, Bavuma MC, et al. Indoor air pollution from cooking with biomass fuels is a major cause of chronic bronchitis among women in a rural district of Rwanda. *African J. Respir. Med* 2018;14:16–19.
39. Musafiri S, van Meerbeeck J, Musango L, et al. Prevalence of atopy, asthma and COPD in an urban and a rural area of an African country. *Respir Med* 2011;105:1596–605.
40. Mwaiselage J, Bråtevit M, Moen BE, et al. Respiratory symptoms and chronic obstructive pulmonary disease among cement factory workers. *Scand J Work Environ Health* 2005;31:316–23.
41. North CM, Kakuhikire B, Vořechovská D, et al. Prevalence and correlates of chronic obstructive pulmonary disease and chronic respiratory symptoms in rural southwestern Uganda: a cross-sectional, population-based study. *J Glob Health* 2019;9:010434.
42. Nuwagira E, Stadelman A, Baluku JB, et al. Obstructive lung disease and quality of life after cure of multi-drug-resistant tuberculosis in Uganda: a cross-sectional study. *Trop Med Health* 2020;48:34.
43. Siddharthan T, Grigsby M, Morgan B, et al. Prevalence of chronic respiratory disease in urban and rural Uganda. *Bull World Health Organ* 2019;97:318–27.
44. Siddharthan T, Grigsby MR, Goodman D, et al. Association between household air pollution exposure and chronic obstructive pulmonary disease outcomes in 13 low and middle-income country settings. *Am J Respir Crit Care Med* 2018;197:611–20.
45. van Gemert F, Kirenga B, Chavannes N, et al. Prevalence of chronic obstructive pulmonary disease and associated risk factors in Uganda (fresh air Uganda): a prospective cross-sectional observational study. *Lancet Glob Health* 2015;3:e44–51.
46. Woldeamanuel GG, Mingude AB, Geta TG. Prevalence of chronic obstructive pulmonary disease (COPD) and its associated factors among adults in Abeshge district, Ethiopia: a cross sectional study. *BMC Pulm Med* 2019;19:181.
47. Zoller T, Mfinanga EH, Zumba TB, et al. Chronic airflow obstruction in Tanzania - a cross-sectional study. *BMC Pulm Med* 2018;18:11.
48. Badway MS, Hamed AF, Yousef FMA. Prevalence of chronic obstructive pulmonary disease (COPD) in Qena Governorate. *Egypt J Chest Dis Tuberc* 2016;65:29–34.
49. Daldoul H, Denguezli M, Jithoo A, et al. Prevalence of COPD and tobacco smoking in Tunisia--results from the BOLD study. *Int J Environ Res Public Health* 2013;10:7257–71.
50. Denguezli M, Daldoul H, Harrabi I, et al. Copd in nonsmokers: reports from the Tunisian population-based burden of obstructive lung disease study. *PLoS One* 2016;11:e0151981.
51. El Rhazi K, Nejari C, Benjelloun MC, et al. Prevalence of chronic obstructive pulmonary disease in Fez, Morocco: results from the BOLD study. *Int J Tuberc Lung Dis* 2016;20:136–41.
52. Laraqui O, Hammouda R, Laraqui S, et al. Prevalence of chronic obstructive respiratory diseases amongst fishermen. *Int Marit Health* 2018;69:13–21.
53. Ramdani I, Pescatore KA, Bouazza B. Causes of hospitalization and characteristics of Algerian chronic obstructive pulmonary disease patients in Tizi-Ouzou: a retrospective study. *Monaldi Arch Chest Dis* 2020;90:403–8.
54. Tageldin MA, Nafti S, Khan JA, et al. Distribution of COPD-related symptoms in the middle East and North Africa: results of the breathe study. *Respir Med* 2012;106 Suppl 2:S25–32.
55. Said AE, Eweis AA, Omran AA, et al. Prevalence and predictors of chronic obstructive pulmonary disease among high-risk Egyptians. *Egypt. J. Bronchol* 2015;9:27.
56. Adeniyi BO, Awokola BL, Irabor I, et al. Pattern of respiratory disease admissions among adults at federal medical centre, Owo, south-west, Nigeria: a 5-year review. *Ann Med Res* 2017;7:96–101.
57. Akanbi MO, Taiwo BO, Achenbach CJ, et al. HIV associated chronic obstructive pulmonary disease in Nigeria. *J AIDS Clin Res* 2015;6.
58. Desalu OO. Prevalence of chronic bronchitis and tobacco smoking in some rural communities in Ekiti state, Nigeria. *Niger Postgrad Med J* 2011;18:91–7.
59. Desalu OO, Adekoya AO, Ampitan BA. Increased risk of respiratory symptoms and chronic bronchitis in women using biomass fuels in Nigeria. *J Bras Pneumol* 2010;36:441–6.
60. Martins P, Rosado-Pinto J, do Céu Teixeira M, et al. Under-report and underdiagnosis of chronic respiratory diseases in an African country. *Allergy* 2009;64:1061–7.
61. Obaseki DO, Erhabor GE, Gnatiuc L, et al. Chronic airflow obstruction in a black African population: results of BOLD study, Ile-Ife, Nigeria. *COPD* 2016;13:42–9.
62. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD study): a population-based prevalence study. *Lancet* 2007;370:741–50.
63. Ehrlich RI, White N, Norman R, et al. Predictors of chronic bronchitis in South African adults. *Int J Tuberc Lung Dis* 2004;8:369–76.
64. Iyaloo S, Kootbodien T, Naicker N, et al. Respiratory health in a community living in close proximity to gold mine waste dumps, Johannesburg, South Africa. *Int J Environ Res Public Health* 2020;17:2240.
65. Pienaar L, Unger M, Hanekom S. A descriptive study of patients admitted with acute exacerbation of chronic obstructive pulmonary disease in three hospitals in Cape town, South Africa. *African J Respir Med* 2015;10:8–12.
66. Mbelambela EP, Muchanga SM, Villanueva AF, et al. Biomass energy, particulate matter (PM 2.5), and the prevalence of chronic obstructive pulmonary disease (COPD) among Congolese women living near of a cement plant, in Kongo central Province. *Environ Sci Pollut Res* 2020:1–9.
67. Mbathochu Ngahane BH, Afane Ze E, Chebu C, et al. Effects of cooking fuel smoke on respiratory symptoms and lung function in semi-rural women in Cameroon. *Int J Occup Environ Health* 2015;21:61–5.
68. Pefura-Yone EW, Fodjeu G, Kengne AP, et al. Prevalence and determinants of chronic obstructive pulmonary disease in HIV infected patients in an African country with low level of tobacco smoking. *Respir Med* 2015;109:247–54.
69. Pefura-Yone EW, Kengne AP, Balkissou AD, et al. Prevalence of obstructive lung disease in an African country using definitions from different international guidelines: a community based cross-sectional survey. *BMC Res Notes* 2016;9:124.
70. Gathuru IM, Bunker CH, Ukoli FA, et al. Differences in rates of obstructive lung disease between Africans and African Americans. *Ethn Dis* 2002;12:S3-107–13.
71. Allwood BW, Myer L, Bateman ED. A systematic review of the association between pulmonary tuberculosis and the development of chronic airflow obstruction in adults. *Respiration* 2013;86:76–85.
72. Silva GE, Sherrill DL, Guerra S, et al. Asthma as a risk factor for COPD in a longitudinal study. *Chest* 2004;126:59–65.
73. Vonk JM, Jongepier H, Panhuysen CIM, et al. Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. *Thorax* 2003;58:322–7.
74. Gibson PG, McDonald VM. Asthma-COPD overlap 2015: now we are six. *Thorax* 2015;70:683–91.
75. Nielsen M, Bärnes CB, Ulrik CS. Clinical characteristics of the asthma-COPD overlap syndrome--a systematic review. *Int J Chron Obstruct Pulmon Dis* 2015;10:1443–54.
76. Tabyshova A, Hurst JR, Soriano JB, et al. Gaps in COPD guidelines of low- and middle-income countries: a systematic scoping review. *Chest* 2021;159:575–84.
77. Assad NA, Balmes J, Mehta S, et al. Chronic obstructive pulmonary disease secondary to household air pollution. *Semin Respir Crit Care Med* 2015;36:408–21.
78. World Health Organization. Household air pollution and health. fact sheet NO: 292, 2018. Available: <http://www.who.int/mediacentre/factsheets/fs292/en/> [Accessed 29 Jan 2021].
79. Forey BA, Thornton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. *BMC Pulm Med* 2011;11:36.
80. World Health Organisation Regional Office For Africa. iAHO Integrated African Health Observatory: Displaying indicators for WHO Africa Region Life Expectancy. [Online]. Available: <https://aho.afro.who.int/ind/af?dim=62&dom=Life%20Expectancy&ccc=af&ci=1> [Accessed 01 Dec 2021].
81. Siddharthan T, Pollard SL, Quaderi SA, et al. Effectiveness-implementation of COPD case finding and self-management action plans in low- and middle-income countries: global excellence in COPD outcomes (GECO) study protocol. *Trials* 2018;19:571.
82. Hurst JR, Buist AS, Gaga M, et al. Challenges in the implementation of chronic obstructive pulmonary disease guidelines in low- and middle-income countries: an official American thoracic Society workshop report. *Ann Am Thorac Soc* 2021;18:1269–77.

Vacina da GSK para prevenção do Vírus Sincicial Respiratório (VSR) já está disponível em Portugal

Arexvy▼ (vacina contra o Vírus Sincicial Respiratório recombinante, com adjuvante) indicada para a imunização ativa na prevenção das doenças das vias respiratórias inferiores (DVRI), causadas pelo Vírus Sincicial Respiratório (VSR), em adultos com idade ≥ 60 anos^[1], já está disponível em Portugal. A GSK anuncia que esta é a primeira vacina do mundo aprovada para proteger adultos mais velhos contra o VSR^[2].

A vacina recebeu aprovação da Agência Europeia do Medicamento, em junho de 2023. A autorização de introdução no mercado baseia-se nos dados positivos do ensaio clínico de fase III AReSVi-006 da GSK. No ensaio clínico, a vacina demonstrou uma eficácia global, estatisticamente significativa e clinicamente relevante, de 82,6% (96,95% IC, 57,9-94,1, 7 de 12.466 vs 40 de 12.494) contra a DVRI-VSR, em adultos com ≥ 60 anos, cumprindo o objetivo primário. Além disso, a eficácia foi de 94,6% (IC 95%, 65,9-99,9, 1 de 4.937 vs 18 de 4.861) em adultos com ≥ 60 anos com, pelo menos, uma comorbilidade de interesse (asma, doença pulmonar obstrutiva crónica (DPOC) ou qualquer doença respiratória/pulmonar crónica, insuficiência cardíaca crónica, diabetes mellitus tipo 1 ou tipo 2, doença hepática avançada e doença renal avançada).^[2]

O VSR é um vírus que afeta todas as idades, mas os adultos com ≥ 60 anos e comorbilidades pré-existent apresentam um maior risco de complicações graves.^{[3] [4]} Anualmente, estima-se que cerca de 3 milhões de adultos nesta faixa etária sejam infetados pelo VSR, resultando em mais de 270.000 hospitalizações e 20.000 mortes, na Europa^[1].

Desde o início da pandemia da COVID-19, houve um aumento acentuado das infeções por VSR e uma alteração no padrão das infeções sazonais devido às medidas de proteção contra a COVID-19, aumentando a possibilidade de surtos fora da época onde é esperada uma maior incidência^[5].

Segundo Neuza Teixeira, Diretora Médica da GSK Portugal, “A vacina assume uma importância reforçada para pessoas com idade acima dos 60 anos, especialmente com condições médicas subjacentes, como a diabetes, doenças cardiovasculares tal como a insuficiência cardíaca e doenças pulmonares crónicas, as responsáveis pela maioria das hospitalizações por VSR^[6]”.

O Prof. Doutor António Morais, presidente da Sociedade Portuguesa de Pneumologia, afirma que “Todos os anos, os hospitais em Portugal verificam um aumento significativo nas admissões causadas por vírus respiratórios mais prevalentes no inverno, incluindo o VSR. Reduzir as consequências deste vírus debilitante é uma prioridade chave para os profissionais de saúde e, por isso, considero que a introdução desta vacina no mercado português é um avanço significativo uma vez que permite a proteção dos adultos com idade igual ou superior a 60 anos, muitos dos quais com outras doenças, o que os coloca numa situação de vulnerabilidade.”

O lançamento de Arexvy▼ no mercado privado português reflete o compromisso da GSK de continuar a investir no conhecimento científico do sistema imunitário, na genética humana e em tecnologia avançada, para disponibilizar inovação que permita prevenir e tratar doenças com Vacinas e Medicamentos e, dessa forma, ter um impacto na saúde pública em larga escala.



AREXVY, a única vacina com 94,6% de eficácia contra o VSR, em adultos com ≥ 60 anos e com comorbilidades.¹

VACINA JÁ DISPONÍVEL

SAIBA MAIS

Referências: 1. RCM Arexvy, junho 2023. VSR, vírus sincicial respiratório; IC, intervalo de confiança; DVRI, doença das vias respiratórias inferiores; DPOC, doença pulmonar obstrutiva crónica. AREXVY é um medicamento sujeito a receita médica, consulte o RCM. GlaxoSmithKline Biologicals SA, Rue de l'Institut 80, 1330 Rosensart, Bélgica é a detentora da AIM. O representante local do titular de AIM é: GlaxoSmithKline - Produtos Farmacêuticos, Lda. Para mais informações e em caso de suspeita de um acontecimento adverso ou de outra informação de segurança, contactar o Departamento Médico da GSK - +351 214128600 ou enviar um email para lis.nucleo-farmacovigilancia@gsk.com.
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GSK

Bibliografia

^[1] RCM Arexvy, junho 2023

^[2] EMA. First vaccine to protect older adults from respiratory syncytial virus (RSV) infection. Abril 2023. Disponível em: <https://www.ema.europa.eu/en/news/first-vaccine-protect-older-adults-respiratory-syncytial-virus-rsv-infection>. Acedido em setembro de 2023

^[3] Centers for Disease Control and Prevention (CDC), 2023. RSV in older adults and adults with chronic medical conditions. <https://www.cdc.gov/rsv/high-risk/older-adults.html> (acedido em agosto de 2023)

^[4] Nguyen-Van-Tam JS, O'Leary M, Martin ET, et al. Burden of respiratory syncytial virus infection in older and high-risk adults: a systematic review and meta-analysis of the evidence from developed countries. *Eur Respir Rev.* 2022;31(166):220105doi:10.1183/16000617.0105-2022

^[5] Moss crop L. et al. Respiratory syncytial virus after the SARS-CoV-2 pandemic — what next?. *Nature Reviews Immunology.* 22, 589–590 (2022)

^[6] CDC. RSV in Older Adults and Adults with Chronic Medical Conditions. Accessed March 2023. <https://www.cdc.gov/rsv/high-risk/older-adults.html>

ARTIGO ORIGINAL

Ensaio controlado aleatorizado para a titulação de corticosteroides orais utilizando marcadores de inflamação na asma grave

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RESUMO

Introdução Os biomarcadores são utilizados para selecionar terapêuticas biológicas para doentes com asma grave, mas não para ajustar regularmente a terapêutica, especialmente os corticosteroides orais (CO).

Objetivo O nosso objetivo foi testar a eficácia de um algoritmo para orientar a titulação de CO utilizando a contagem sanguínea de eosinófilos e a fração exalada de óxido nítrico (FeNO).

Desenho, participantes, intervenções e contexto Este ensaio prospetivo, aleatorizado e controlado, de prova de conceito, atribuiu aos participantes adultos com asma grave não controlada (n=32) uma gestão baseada em biomarcadores (BBM), em que a dose de CO foi ajustada com base numa pontuação combinada de biomarcadores, composta por uma contagem sanguínea de eosinófilos e a FeNO, ou um braço das melhores práticas padrão (SBP). O estudo foi realizado no Hunter Medical Research Institute, em Newcastle, Austrália. Os participantes foram recrutados na Clínica de Asma Grave local e não tinham conhecimento da sua inclusão no estudo.

Principal resultado Os resultados coprimários foram o número de exacerbações graves e o tempo até à primeira exacerbação grave avaliada ao longo de um período de 12 meses.

Resultados Registou-se um tempo médio mais longo para a primeira exacerbação grave com BBM, embora não significativo (295 vs 123 dias, Adj. HR: 0,714; 95% IC: 0,25 a 2,06; p=0,533). O risco relativo de uma exacerbação grave na BBM (n=17) vs SBP (n=15) foi de 0,88 (Adj.; IC 95%: 0,47 a 1,62; p=0,675) com uma taxa média de exacerbação por ano de 1,2 e 2,0, respetivamente. Registou-se uma redução significativa na proporção de doentes que necessitaram de uma visita ao serviço de urgência (SU) utilizando a BBM (OR 0,09, IC 95%: 0,01 a 0,91; p=0,041). Não houve diferença na dose cumulativa de CO utilizada entre os dois grupos.

Conclusão Um algoritmo de tratamento para ajustar os CO utilizando a contagem sanguínea de eosinófilos e a FeNO é viável num contexto clínico, resultando numa menor probabilidade de uma visita ao Serviço de Urgência. Isto justifica um estudo mais aprofundado para otimizar a utilização de CO no futuro.

Número de registo do ensaio Este ensaio foi registado no Registo de Ensaios Clínicos da Austrália e da Nova Zelândia (ACTRN12616001015437).

INTRODUCTION

Asthma affects approximately 340 million people worldwide, with an ever increasing prevalence, particularly in developed nations.¹ Recent estimates suggest approximately 4% of this population have severe refractory disease.² This population, although small, disproportionately accounts for up to half the healthcare resource use and direct and indirect costs to society due to asthma.³ Thus, optimisation of the management of asthma in this population represents an important opportunity for the improvement of asthma care. While there

Key messages

What is the key question?

► There have been multiple studies employing novel therapies and biomarker-based management (BBM) to improve outcomes in patients with severe asthma, with studies employing biologic medications demonstrating a significant reduction in the use of chronic systemic corticosteroid. Despite this, there remains a significant proportion of the population who continue to require treatment with oral corticosteroids (OCS) for various reasons and very little randomised controlled data to help guide management for these patients in an objective fashion using readily available biomarkers.

What is the bottom line?

► We sought to determine whether controlling airway inflammation by titrating OCS using a biomarker composite score made up of PBE and fraction of exhaled nitric oxide as a surrogate for sputum induction determined airway eosinophilia will reduce exacerbations in patients with severe asthma, compared with usual care alone, in a severe asthma clinic. This BBM approach proved feasible, although the primary endpoint of a reduction in severe exacerbation rate was not met, but a reduction in the proportion of patients who required an emergency department visit was observed, without a significant difference in the cumulative amount of OCS used.

Why read on?

► This furthers the concepts of precision medicine for the chronic management of severe asthma using objective biomarkers to improve outcomes for patients, reduce healthcare resource utilisation, and serve as a catalyst for future work in this field.

has been significant progress in the last 75 years in the availability of treatments for the asthma population, in general, it would appear that improvements in morbidity and mortality have plateaued over the last decade, with only small incremental gains.⁴ Biologic agents have been a significant advancement for the management of severe asthma for those patients with refractory type 2 airway inflammation demonstrating benefit in reducing the use of oral corticosteroids (OCS) for episodic



exacerbations and, in the case of mepolizumab, benralizumab, and dupilumab, reducing their use for regular maintenance treatment as well.^{5–10} Optimisation of the use of OCS in this population is important to ensure that risk is reduced and benefit maximised. Previous work has demonstrated the utility of titrating therapy based on sputum eosinophil counts and fraction of exhaled nitric oxide (FeNO).¹¹ Unfortunately, sputum cell count measures remain difficult to obtain at many centres.¹² Peripheral blood eosinophil (PBE) counts, however, are widely available and have been used as a surrogate for sputum cell counts.¹³ As a result, we sought to determine whether controlling airway inflammation by titrating OCS using biomarker-based management (BBM) via a composite score made up of PBE and FeNO, as a surrogate for sputum induction determined airway eosinophilia, will reduce exacerbations in patients with severe asthma, compared with standard best practice (SBP) alone, in a severe asthma clinic. Our hypothesis was that this would be feasible and effective for these outcomes, while resulting in a lower cumulative dose of OCS used.

METHODS

To explore this, we conducted a prospective randomised, single-blind, controlled proof-of-concept study comparing BBM with standard best practice clinical management (SBP) in participants with severe asthma. Potential participants were recruited from the Severe Asthma Clinic at the John Hunter Hospital, New Lambton, New South Wales, Australia. This is a tertiary referral specialist/multidisciplinary severe asthma clinic. All patients of the clinic had been assessed by the clinical team within a structured programme that confirms the diagnosis of asthma, assesses and controls factors that precipitate and trigger asthma, and assesses and treats the presence of comorbid conditions such as upper airway dysfunction, gastroesophageal reflux, rhinitis and obstructive sleep apnoea.¹⁴

Participants were recruited into the study if they were over 18 years of age, never or ex-smokers, and diagnosed with severe asthma. To be classified as severe, participants had to have been on Global Initiative for Asthma (GINA) Step 4/5 therapy¹⁵ and have had uncontrolled asthma despite this treatment, with either: a 6-point Asthma Control Questionnaire (ACQ)¹⁶ Score ≥ 1.5 , or a hospital admission for asthma in the last 12 months or at least two severe asthma exacerbations in the past 12 months requiring a burst of OCS (of at least 3 days). Mepolizumab was introduced into the severe asthma clinic after the initiation of the study protocol and participants taking any biological therapy available were included in the study, but randomisation was not adjusted for type of biological therapy. Participants did not have to be on OCS at baseline to be enrolled. Participants were excluded based on criteria in the online supplemental appendix.

Following a 4-week run-in period where participants remained on their usual asthma treatment, those who remained stable were

randomised to either BBM or SBP in a 1:1 ratio. Block randomisation was performed by an independent research associate using computer-generated randomisation tables with stratification based on the presence or absence of OCS maintenance dosing and blood eosinophil count at screening above or below 0.4×10^9 cells/L.

At baseline, inflammation was assessed with the following markers: exhaled nitric oxide, induced sputum analysis and peripheral full blood count. Participants were followed for a total 12-month period and assessed for outcomes on a monthly basis as per the study visit schedule (online supplemental table 1), with every second visit in the latter half of the study period being conducted by phone. At the end of each in-person visit, medication changes were made according to study arm allocation. Participants and clinicians were blinded to each participant's treatment group allocation as well as inflammatory marker results.

Study groups

In BBM, participants were assessed by a clinician at each visit and adjustment of OCS dose was performed using the algorithm in figure 1 as per the OCS adjustment table in online supplemental table 2 based on the results of their PBE count and FeNO. PBE count and FeNO were used to assign a participant an average biomarker score, which dictated the titration of their OCS dose.

Cut points for FeNO had been decided based on prior identification of the upper limit of FeNO at which people with asthma can undergo corticosteroid withdrawal, as well as that which is associated with control of eosinophilic inflammation.¹⁷ Cut points for PBE have been determined as those previously associated with increased airway eosinophilia in asthma and chronic obstructive pulmonary disease (COPD).^{13,18}

The participants in SBP had their asthma control assessed according to standard clinical parameters based on GINA treatment guidelines and treatment step or dose escalation or de-escalation.¹⁵ This was assessed every 4 months through the study, based on the recommendations of a consultation with a clinician (see online supplemental table 1). Standard care treatment decisions were made at these particular visits based on the result of clinician consultation without knowledge of biomarker results for that visit. This was based on the standard clinical care practice in the Severe Asthma Clinic at the John Hunter Hospital.

An additional analysis was performed on the subgroup of patients receiving mepolizumab, as it was expected their biomarkers may be affected by this treatment. PBE and FENO over the course of the study were measured in this cohort.

Outcomes

The coprimary outcomes were time to first and the number of severe exacerbations over 12 months. An asthma exacerbation was defined as a worsening of asthma control characterised by a progressive increase in symptoms requiring a change in treatment.

Biomarker Score (BS)	-1	0	1	2
FeNO (ppb)		<15	15 - <30	≥ 30
Blood eosinophil count (cells $\times 10^9$ /L)	<0.2		0.2-0.4	>0.4

In BBM, titration of oral corticosteroids was performed using a composite biomarker score (BS) comprised of FeNO and PBE. BS was assigned based on the measured biomarker values at each visit. Composite BS was calculated by taking the average of the FeNO and PBE BS scores and rounding up to the nearest whole number. Titration was then performed as follows:

- BS = 2: $\uparrow$ or (if treatment naïve) commence OCS at 7.5mg/day (or equivalent)
- BS = 1: no change to OCS
- BS = 0: reduce OCS. If off OCS, decrease ICS treatment.

The goal of this algorithm is to maintain a BS of 1 or lower using the lowest effective OCS dose.

Figure 1 Algorithm for biomarker-based management of oral corticosteroid dose. BBM, biomarker-based management; FeNO, fraction of exhaled nitric oxide; ICS, inhaled corticosteroid; OCS, oral corticosteroids.

Severe exacerbations were defined as those requiring systemic glucocorticoids or an increase in the dose of regular systemic glucocorticoids for at least 3 days.¹⁹ Secondary outcomes that were assessed were change in asthma symptom scores using the Asthma Control Questionnaire (ACQ),¹⁶ and Asthma Quality of Life Questionnaire (AQLQ),²⁰ total and maintenance dose of OCS, analysis of markers of inflammation at the final visit compared with entry (PBE, sputum eosinophil counts and FeNO), total dose of OCS used during the period of the study, and hospital admission or emergency room visit due to asthma.

Spirometry, FeNO and sputum and blood eosinophil measurements

FeNO measurements were performed using a NIOX VERO (Aerocrine, Sweden) device, as per the manufacturer's suggestions and prior to spirometry. Spirometry was performed as per American Thoracic Society (ATS) criteria²¹ using a MedGraphics CPFS/D USB-Ascensia spirometer and BreezeSuite software (Minneapolis, USA). Blood eosinophil counts were measured from samples obtained at each in-person visit through the study and processed at either Pathology North (New South Wales, Australia) laboratories or the Hunter Medical Research Institute. Sputum induction and processing were performed as previously described by Gibson et al.²²

Statistical considerations

All analyses were conducted using SAS V.9.4. An intention-to-treat analysis was performed for all randomised participants. Frequencies and percentages are provided for the categorical variables, while means, SD, median, first and third quartiles are provided for the continuous variables.

Time to first severe exacerbations was compared between treatment arms using a Kaplan-Meier plot, along with a log-rank test for the crude models and Cox regressions for both the crude and adjusted models. Negative binomial models were used to analyse the total number of severe exacerbations between treatment arms.

For the secondary outcomes that were recorded more than once, treatment arms were compared using linear mix modelling with random intercepts for within-subject correlation over time. Where the outcome was measured only once, treatments were compared using linear regression. Due to the low counts of hospital/emergency department (ED) visits and a small subgroup sample size for the participants on mepolizumab, the variables for the former were dichotomised to having had a hospital/ED visit versus not, logistic regression was used to compare the two treatment arms, and only crude models were used. Adjusted models are presented for each other outcome, which have been adjusted for age, sex, body mass index, education, smoking history, age at asthma diagnosis, baseline blood eosinophil count and baseline prednisolone dose.

Sample size was calculated based on uncontrolled prior data²³ demonstrating a reduction in exacerbations from a median of 5 (IQR 5–8) to 0 (IQR 0–1) with the use of a similar algorithm based on PBE for asthma management. Assuming $\alpha=0.05$, and allowing power to range from 0.8 to 0.95, yields a desired range of sample sizes for each of the two groups of 9–16. Thus, a conservative estimate of the necessary total sample size was 30.

RESULTS

Of the 41 patients screened, 32 were eligible for randomisation; 17 were randomised to BBM and 15 to SBP from 9 January 2017 to 23 May 2018, with 29 completing the study (online supplemental figure 1). The study was ended once the required sample size was reached and the last participant completed all required visits. A total of 32 patients were analysed in the intention-to-treat analysis. In BBM, one participant was lost to follow-up due to poor health and inability to attend study visits, and one was removed due to an adverse reaction to OCS. In SBP, one participant discontinued the study to undergo investigation for a newly discovered potential malignancy. Baseline measurements for participants are presented in table 1.

There were less ex-smokers in BBM versus SBP (29% vs 47%); however, the mean pack-year history was higher in BBM (17.9 vs 7.2 pack-years), both variations likely due to a small sample size. Mean baseline lung function was similar between the groups, as was mean sputum eosinophil count percentage (5.2% in BBM vs 6.0% in SBP) and exacerbation frequency in the last year (3.9 exacerbations/year vs 4.8) (table 1). With respect to the markers of inflammation that would form the basis for the composite biomarker score and adjustment of corticosteroid dose during the study, blood eosinophils were similar while FeNO was lower in BBM (24) vs SBP (43). The median baseline dose of oral prednisolone was the same between the groups at 5 mg/day.

Outcomes

Median time to first severe exacerbation was more than two times as long at 295 days with BBM vs 123 days with SBP, though this was not statistically different (Adj. HR: 0.714; 95% CI: 0.25 to 2.06; $p=0.533$) (table 2, figure 2). There was no significant difference in the number of severe exacerbations with BBM versus SBP (table 2, figure 2).

There was a significant difference in the proportion of participants who had at least one ED visit with a reduced OR with BBM versus SBP (OR: 0.09 95% CI: 0.01 to 0.91, $p=0.041$) (table 2). Similarly, the proportion of patients with at least one hospitalisation for asthma appeared to be reduced with BBM but this was not

Table 1 Baseline demographics of participants in standard best practice (SBP) and biomarker-based management (BBM) arms

Demographic	BBM, n=17	SBP, n=15
Age, mean (SD)	60.2 (13.6)	61.2 (10.5)
Sex (% male)	35%	47%
Highest level of education		
<Year 11	5 (36%)	8 (50%)
Year 12	3 (21%)	1 (6.3%)
Diploma	1 (7.1%)	2 (13%)
Certificate III/IV	3 (21%)	2 (13%)
Bachelors	2 (14%)	1 (6.3%)
Graduate/postgraduate degree	0 (0%)	2 (13%)
Ex-smoker	29%	47%
Pack-year history	17.9 (16.5)	7.2 (6.0)
Forced expiratory volume in one second (% predicted)	72.7 (18.9)	67.8 (17.8)
Peripheral blood eosinophil (cells $\times 10^9$ /L)	0.3 (0.3)	0.5 (0.5)
Fraction of exhaled nitric oxide (ppb)	24.3 (29.1)	42.7 (64.4)
Prednisolone dosage (mg/day)	4.7 (6.6)	5.4 (7.1)
Number with daily oral corticosteroids use (%)	9 (52.9%)	8 (53.3%)
Asthma Control Questionnaire-6 Score	2.2 (1.2)	1.8 (1.3)
Exacerbations in the last year	3.9 (2.9)	4.8 (3.6)
Sputum eosinophil count (%)	5.2 (7.2)	6.0 (8.7)
Presence of eosinophilic airway inflammation	7 (41.2)	8 (53.3)
Biologic treatment for asthma (n, %)		
Omalizumab	6 (35%)	9 (60%)
Mepolizumab	2 (11.8%)	1 (6.7%)
	4 (23.5%)	8 (53.3%)
Key comorbidities, (n, %)		
Gastroesophageal reflux disease (GORD)	12 (71%)	12 (80%)
Sinonasal disease	16 (94%)	8 (53%)
Cardiovascular disease	9 (52%)	8 (53%)
Anxiety/depression	8 (47%)	6 (40%)
Vocal cord dysfunction	1 (6%)	2 (13%)
Allergic bronchopulmonary aspergillosis (ABPA)/fungal disease	3 (18%)	5 (33%)
Data presented as number (proportion (%)) or mean (SD).		

Table 2 Primary outcomes of number of and time to first severe exacerbation and secondary outcomes of proportions of patients with at least one hospitalisation or emergency department (ED) visit in standard best practice (SBP) versus biomarker-based management (BBM)

Outcome	BBM	SBP	
Time to first severe exacerbation and HR (95% CI)	295 days	123 days	0.714 (0.248 to 2.057), p=0.533
Mean number of exacerbations (n, SD) and rate ratio (95% CI)	1.2 (1.6)	2.0 (1.9)	0.876 (0.472 to 1.624), p=0.675
Participants with at least one hospital admission (n, %) and OR (95% CI)	2 (12)	4 (27)	0.37 (0.06 to 2.37), p=0.292
Participants with at least one ED visit (n, %) and OR (95% CI)	1 (5.9)	6 (40)	0.09 (0.01 to 0.91), p=0.041

statistically significant (OR 0.37 95% CI 0.06 to 2.37, p=0.292). As there were only two participants in the BBM group, and six in SBP who required either a hospitalisation or ED visit for the exacerbation, numbers were considered too small to perform adjusted analyses. No reductions to inhaled corticosteroid (ICS) were undertaken during the study.

There was no difference between the two arms with respect to ACQ or AQLQ scores (figure 3). There was also no difference observed in blood or sputum eosinophil count, or FeNO levels when adjusted for outliers (online supplemental figure 2). The mean cumulative OCS dose between groups over the duration of the study was not significantly different (1655 mg (95% CI: 935 to 2374) of prednisolone with BBM vs 1544 mg (95% CI: 318 to 2770) with SBP, p=0.866).

Adherence to oral prednisolone was measured over the duration of the study via pill counts for those participants on OCS. There was no difference between the two groups in terms of mean adherence detected during the study for those on OCS (96.52% (95% CI: 94.5% to 98.5%) in BBM vs 96.4% (95% CI: 93.5% to 99.2%) in SBP, p=0.920). Dose adjustments were followed as per protocol at a similar frequency in either group. This was done correctly (47/51 times in BBM (92.2%, 95% CI: 84.8% to 99.5%) vs 11/12 times in SBP (91.7%, 95% CI: 76.0% to 107.3%), p=0.955).

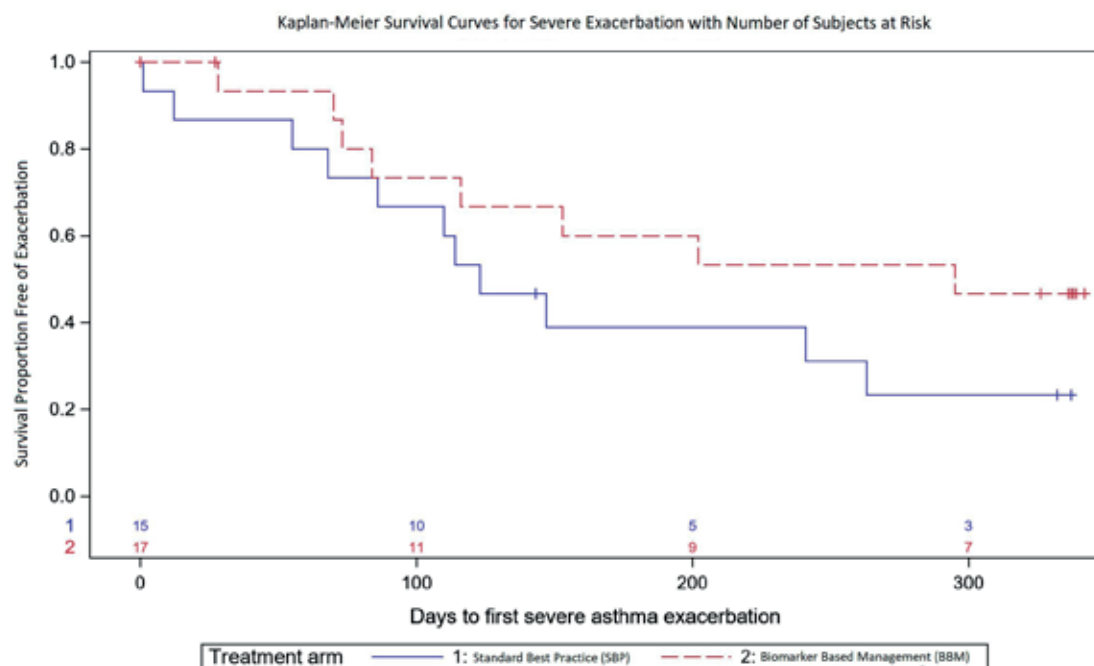
A subgroup analysis of PBE and FeNO levels for those participants on mepolizumab also did not demonstrate any significant difference over time, regardless of treatment arm (online supplemental figure 3). This may be related to the suppressive effect of this medication on eosinophils. In spite of this, in 18.2% (95% CI: 8.9% to 27.5%) of all visits among participants on a biologic in BBM vs 40.0% (95% CI: 29.9% to 50.1%, p=0.004) in SBP, biomarker measures were detectable and still elevated (FeNO>30 ppb or PBE>0.3×10⁹ cells/L).

Unfortunately, this study was underpowered to detect its primary outcomes due to an insufficient sample size. Post-hoc analysis revealed that 286 subjects would have been needed to provide a power of 80% to detect a difference at $\alpha=0.05$ for the HR and time to events observed in the study.

DISCUSSION

Our results demonstrate that a biomarker-based approach to the management of OCS in patients with severe asthma is feasible within a tertiary care severe asthma clinic. However, we were unable to demonstrate a significant difference in the coprimary outcomes of number of severe exacerbations and time to first exacerbation. While not significant, median time to first severe exacerbation in BBM was 295 days compared with only 123 days in SBP. The biomarker strategy may have had a greater impact on reducing more severe exacerbations as fewer participants in this arm experienced an exacerbation requiring an ED visit compared with the standard care arm and there was a trend towards a reduced proportion of participants requiring hospitalisation. Cumulatively, there was no statistical difference in the total dose of OCS used in the two treatment arms to achieve these outcomes. Unadjusted OCS trends over time were similar in both groups (online supplemental figure 4).

A reduction in ED visits is important since a large proportion of the costs attributable to the care of patients with severe asthma is associated with healthcare utilisation.³ In addition, recurrent emergency visits and hospitalisations are key components of severe asthma that affect quality of life for these patients.²⁴ The ability to influence the need for healthcare utilisation without increasing the cumulative dose of OCS administered would be beneficial to this patient group. However, this reduction in ED costs would need to be offset against the increased number of visits required

**Figure 2** Kaplan-Meier survival analysis of time to first severe exacerbation in the biomarker-based management versus standard best practice management groups.

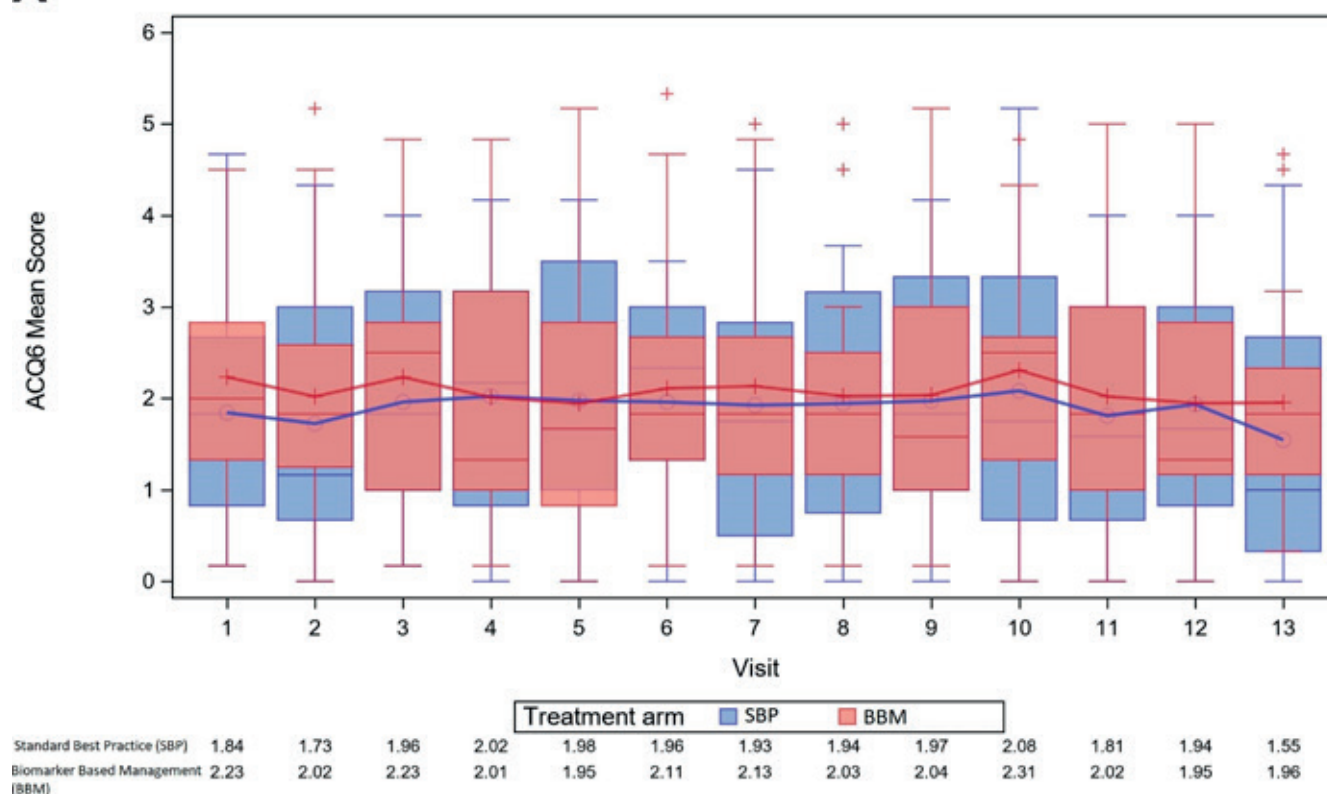
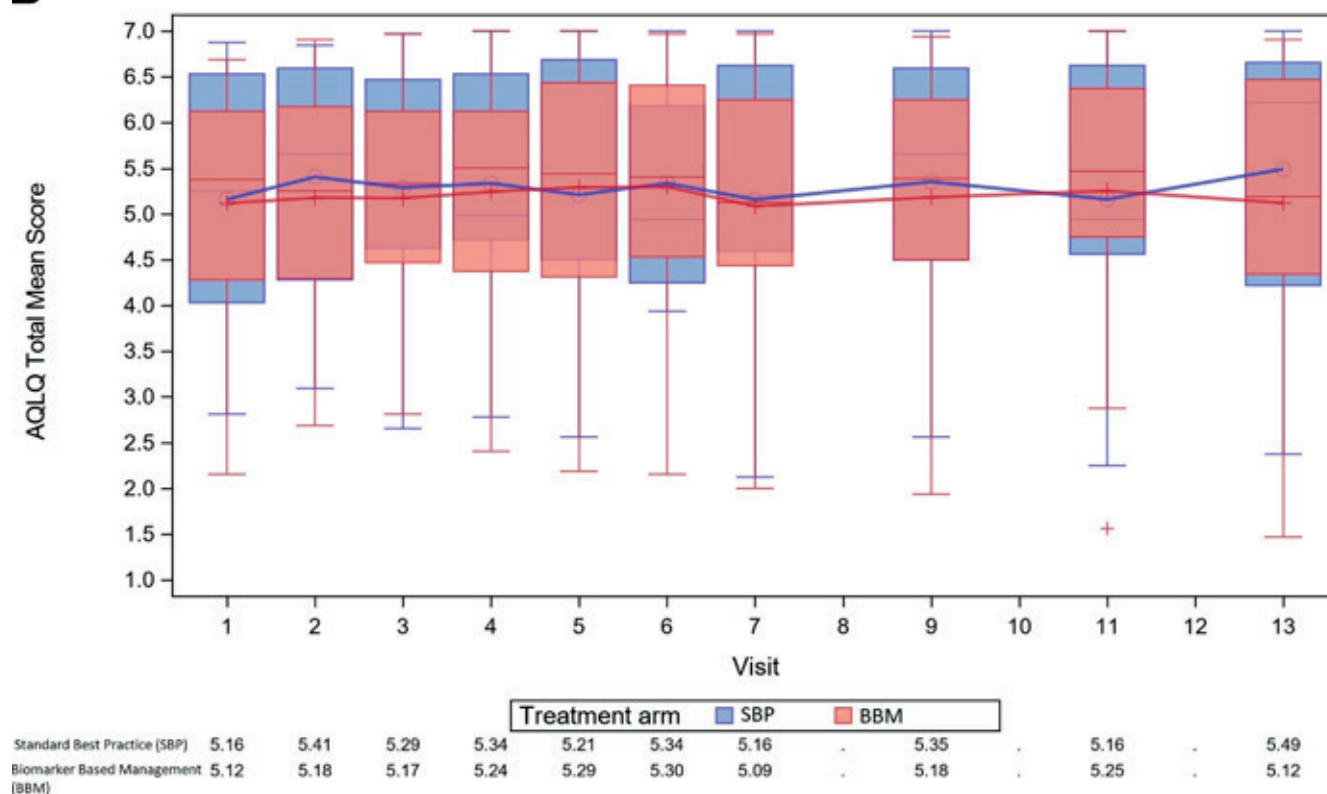
A**B**

Figure 3 Asthma Control Questionnaire-6 Score (ACQ6) (A) and Asthma Quality of Life Questionnaire (AQLQ) (B) mean scores over time in the biomarker-based management (BBM) and standard best practice (SBP) groups.

to achieve the adjustment of inflammation as participants in the biomarker arm attended monthly visits compared with 16-weekly visits in the standard care arm.

Interestingly, similar research conducted by Heaney et al has sought to use a composite biomarker-based approach incorporat-

ing FeNO, PBE and periostin. Participants in this study had their therapy adjusted based on their biomarkers every 8 weeks over a 48-week period, compared with usual care. Although failing their primary endpoint in the intention-to-treat analysis, a significant proportion of patients were able to reduce their corticosteroid

dose in the per-protocol analysis.²⁵ There was a similar, but not significant, trend towards reduced exacerbations rates. This difference in ability to reduce corticosteroids, but ultimate inefficacy, may be related to the different biomarkers used, for example, periostin was included in the work by Heaney et al compared with this study. Alternatively, the cut-offs chosen in the algorithm studied here may have limited the opportunity for reduction of corticosteroid, and conversely may have been too stringent with respect to restricting dose changes. In addition, while a lack of participants choosing to follow the treatment directives given at visits in the Heaney et al work was thought to affect the ability to demonstrate an effect,²⁵ this is not thought to be the case in this study cohort, as adherence was high, as monitored through the study based on pill counts, and treatment decisions were followed the vast majority of the time in both groups.

The authors postulate that, while titration of asthma therapy according to sputum eosinophilia has been successful in prior studies,^{11,26} peripheral blood eosinophilia and FeNO may not be direct enough measures of type 2 high inflammation or not sufficiently correlated with exacerbation risk, to be as useful for the adjustment of therapy longitudinally. Novel biomarkers may need to be considered in the future. Similarly, this strategy may not apply to patients without eosinophilic airway inflammation, and these participants comprised 53% of our population (table 1). Interestingly, in the studied population, among those participants on a biologic treatment, either FeNO or PBE remained detectable in upwards of 40% of participant visits, suggesting the composite biomarker score could still be considered a useful measure on which to base adjustments of medications in the biologic era (online supplemental figure 3). Direct conclusions on whether this weakened the effect of our intervention cannot be determined, however, due to the small numbers analysed. This likely affected the results with respect to time to first severe exacerbation (figure 2).

Further advances in artificial intelligence and machine learning may better allow for widespread utilisation of biomarkers as a guide, in this setting. Machine learning could allow for the exploration of which biomarkers, and at which levels, ideally predict good asthma control and improved outcomes, similar to what is being considered in other fields such as cardiology and oncology for their outcomes.^{27,28}

Benefits of the study and limitations

This study benefitted from its randomised and blinded design. Although participants were assessed equally as many times in both arms of the study, decisions were only made in SBP every 4 months, thus there were fewer opportunities to change the course of asthma control. Conversely, the small sample size may have limited the ability to identify a true effect. Unfortunately, although this was a pilot study with a sample size based on prior observed effects, it appears to have been underpowered to detect the primary outcome based on post-hoc calculations. A larger multicentre trial would allow for larger numbers as well as greater generalisability of the results. In addition, being a single-centre study based at a clinic specialised in the treatment of patients with severe asthma, the participants treated as per the clinical judgement of the study physicians would likely already reflect optimisation of the role of steroids in ongoing treatment. Clinicians were also not blinded to the fact that participants were enrolled in the study.

Further, the study was impacted by the introduction of mepolizumab as a treatment for severe asthma in our clinic after the study commenced. Due to the timing of availability of mepolizumab in Australia, the authors felt it would be unethical to disallow participants from accessing this novel therapeutic, but allowed for inclusion after 6 weeks of stability. Randomisation was not adjusted for this, and hence, our results may have been impacted by the differential effects of mepolizumab in our study population.

CONCLUSION

A treatment algorithm to adjust OCS using blood eosinophil count and FeNO is feasible in a clinical setting. There was a trend

towards a longer time to severe exacerbation and reduced odds of a hospital admission, although these results were not significant. The treatment algorithm did result in a reduced proportion of patients requiring an emergency visit for their asthma, without a significant difference in the cumulative amount of OCS used. This warrants further study in a larger sample to optimise the use of OCS with biomarkers in the future.

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Contributors JMR contributed to the conception and design of the work, data acquisition, analysis, interpretation, drafting, revision, and approval of the manuscript. JMR is the guarantor of the work. JLS contributed to the conception and design of the work, data analysis and interpretation, and revision, and approval of the manuscript. AC contributed to the design of the work, data acquisition, analysis, and interpretation, and revision and approval of the manuscript. PGG contributed to the conception and design of the work, data interpretation, and revision and approval of the manuscript. VM contributed to the conception and design of the work, data interpretation, and revision and approval of the manuscript. CG contributed to the conception and design of the work, data acquisition, analysis, and interpretation, and revision and approval of the manuscript. LGH contributed to the conception and design of the work, data interpretation, and revision and approval of the manuscript. PABW contributed to the conception and design of the work, data acquisition, analysis, and interpretation, drafting, revision, and approval of the manuscript. All authors agree to be accountable for the work.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Hunter New England Human Research Ethics (16/05/18/3.03) and University of Newcastle Human Research Ethics Committee (H-2016-0261; Safety approval number: 62/2016). 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. Please contact the corresponding author for details.

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REFERENCES

- Peters SP, Ferguson G, Deniz Y, et al. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. *Respir Med* 2006;100:1139–51.
- Hekking P-W, Wener RR, Amelink M, et al. The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015;135:896–902.
- Bahadori K, Doyle-Waters MM, Marra C, et al. Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009;9:24.
- Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. *Lancet* 2018;391:350–400.
- Ramsahai JM, Wark PA. Appropriate use of oral corticosteroids for severe asthma. *Med J Aust* 2018;209:S18–21.
- Farne HA, Wilson A, Powell C, et al. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev* 2017;9:CD010834.
- Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018;378:2475–85.
- Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017;376:2448–58.
- Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014;371:1189–97.
- Menzies-Gow A, Corren J, Bel EH, et al. Corticosteroid tapering with benralizumab treatment for eosinophilic asthma: PONENTE trial. *ERJ Open Res* 2019;5:00009–2019.
- Petsky HL, Li A, Chang AB. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. *Cochrane Database Syst Rev* 2017;8:CD005603.
- Cao WL, Sun YC, Yao WZ. A study on A therapeutic protocol to improve the control of persistent asthma by monitoring sputum eosinophil counts]. *zhonghua jie he hu xi za zhi = zhonghua jie he hu xi zazhi = Chinese Journal of Tuberculosis and Respiratory Diseases* 2007;30:334–8.
- Zhang X-Y, Simpson JL, Powell H, et al. Full blood count parameters for the detection of asthma inflammatory phenotypes. *Clin Exp Allergy* 2014;44:1137–45.
- McDonald VM, Vertigan AE, Gibson PG. How to set up a severe asthma service. *Respirology* 2011;16:900–11.
- GINA report, global strategy for asthma management and prevention (2020 update). 2020. Available: <https://ginasthma.org/2020>
- Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902–7.
- Berry MA, Shaw DE, Green RH, et al. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clin Exp Allergy* 2005;35:1175–9.
- Bafadhel M, McKenna S, Terry S, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2012;186:48–55.
- Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;371:1198–207.
- Juniper EF, Buist AS, Cox FM, et al. Validation of a standardized version of the asthma quality of life questionnaire. *Chest* 1999;115:1265–70.
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
- Gibson PG, Wlodarczyk JW, Hensley MJ, et al. Epidemiological association of airway inflammation with asthma symptoms and airway hyperresponsiveness in childhood. *Am J Respir Crit Care Med* 1998;158:36–41.
- Wark PA, McDonald VM, Gibson PG. Adjusting prednisone using blood eosinophils reduces exacerbations and improves asthma control in difficult patients with asthma. *Respirology* 2015;20:1282–4.
- Crossman-Barnes C-J, Sach T, Wilson A, et al. Estimating loss in quality of life associated with asthma-related crisis events (ESQUARE): a cohort, observational study. *Health Qual Life Outcomes* 2019;17:58.
- Heaney LG, Busby J, Hanratty CE, et al. Composite type-2 biomarker strategy versus a symptom-risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomised controlled trial. *Lancet Respir Med* 2021;9:S2213–2600 (20)30397-0: 57–68..
- Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715–21.
- Deo RC. Machine learning in medicine. *Circulation* 2015;132:1920–30.
- Ahmed Z, Mohamed K, Zeeshan S, et al. Artificial intelligence with multi-functional machine learning platform development for better healthcare and precision medicine. *Database (Oxford)* 2020;2020:baaa010.

ARTIGO ORIGINAL

Estudo de coorte observacional do Reino Unido que descreve os padrões de prescrição de corticosteroides orais intermitentes e a sua associação com resultados adversos na asma

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RESUMO

Introdução Os corticosteroides orais (CO) para a asma estão associados a riscos acrescidos de desenvolvimento de resultados adversos (resultados adversos); nenhum estudo anterior se centrou exclusivamente na utilização intermitente de CO.

Métodos Este estudo de coorte histórico (2008-2019) do Reino Unido usando registros médicos de cuidados primários de duas bases de dados anônimas e de vida real (OPCRD e CPRD) incluiu pacientes com idade ≥4 anos com asma recebendo apenas CO em regime intermitente. Os doentes foram indexados com base na primeira prescrição registrada de CO em regime intermitente para asma e categorizados de acordo com os padrões de prescrição de CO: pontual (única), menos frequente (≥90 dias de intervalo) e frequente (<90 dias de intervalo). Os doentes sem CO, emparelhados 1:1 em termos de sexo, idade e data de indexação, serviram de controle. Foi estudada a associação dos padrões de prescrição de CO com o risco de AO relacionada com CO, estratificada por idade, fase de tratamento da Global Initiative for Asthma (GINA) 2020 e prescrições de corticosteroides inalados (CI) e β²-agonista de ação curta (SABA) utilizando um modelo multivariável de risco proporcional de Cox.

Achados Dos 476 167 doentes elegíveis, 41,7%, 26,8% e 31,6% apresentaram padrões de prescrição de CO únicos, menos frequentes e frequentes e intermitentes, respectivamente. O risco de qualquer AO aumentou com os padrões cada vez mais frequentes de CO intermitente versus não CO (HR; IC 95%: one-off 1,19 (1,18 a 1,20), menos frequente 1,35 (1,34 a 1,36), frequente 1,42 (1,42 a 1,43)), e foi consistente com a idade, fase de tratamento GINA e subgrupos CI e SABA. Os riscos mais elevados de resultados adversos individuais relacionados com CO com uma utilização cada vez mais frequente de CO foram para a pneumonia e a apneia do sono.

Conclusão Uma proporção considerável de doentes com asma a receber CO em regime intermitente apresentou um padrão de prescrição frequente. Os padrões de prescrição de CO cada vez mais frequentes foram associados a um maior risco de resultados adversos relacionados com CO. São necessárias estratégias de mitigação para minimizar a prescrição de CO em regime intermitente nos cuidados primários.

INTRODUCTION

Despite the availability of novel and innovative treatments for asthma, oral corticosteroids (OCS) are still widely used.^{1,2} Both the British Thoracic Society/ Scottish Intercollegiate Guidelines Network³ and the Global Initiative for Asthma (GINA) report¹ recommend an intermittent OCS dose of 40–50 mg prednisolone daily for at least 5 days for the management of severe exacerbations, and in 2021, a Delphi study found consensus on a

Key messages

What is already known on this topic

► Although widely prescribed, particularly for acute exacerbations of asthma, both intermittent and long-term use of oral corticosteroids (OCS) are associated with an increased risk of developing acute and chronic adverse outcomes (adverse outcomes), and this risk increased with higher cumulative and mean daily systemic corticosteroid exposure. However, data on the adverse outcomes with patterns of intermittent OCS prescription are scarce.

What this study adds

► Using two large, well-established UK databases (OPCRD and CPRD) with high data quality and granularity enabled us to study the specific association between patterns of intermittent OCS prescriptions and risk of different OCS-related adverse outcomes in almost half a million patients with asthma.

How this study might affect research, practice or policy

► Increasingly frequent prescribing patterns of intermittent OCS were associated with a higher risk of individual OCS-related adverse outcomes, and this association remained consistent across levels of age, Global Initiative for Asthma treatment step and inhaled corticosteroid maintenance and short-acting β₂-agonist reliever use. Our results therefore suggest that the use of intermittent OCS in the management of asthma should be minimised whenever possible.

dose of 0.5 mg/kg/day for a short course of OCS.⁴ In a real-world study of OCS prescription patterns that included both intermittent and long-term OCS prescriptions in France, Germany, Italy and the UK from 2012 to 2017, 14%–44% of patients with asthma aged ≥12 years were prescribed OCS and 6%–9% had high OCS use (defined as ≥450 mg within 90 days, ie, corresponding to an average of ≥5 mg per day) at some point during follow-up (median range 33–55 months).⁵ In a systematic review of studies from Europe, North America



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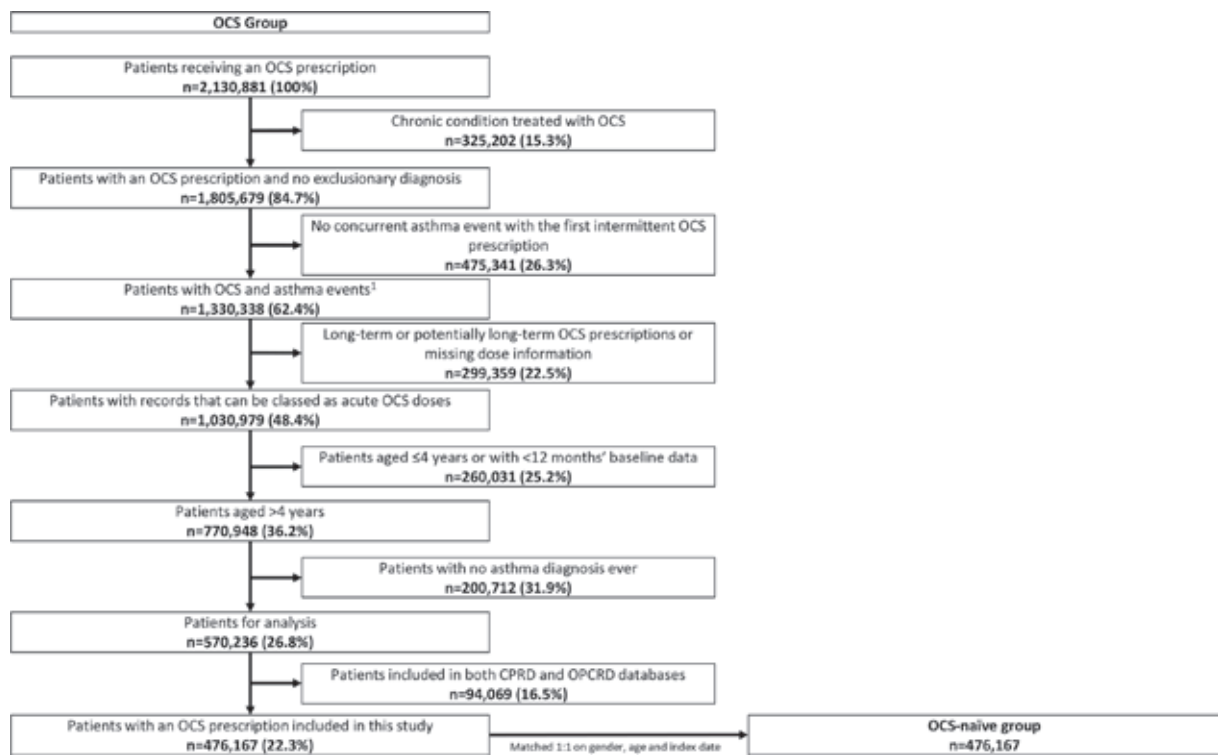


Figure 1 Flow chart of UK patients with asthma receiving intermittent OCS prescriptions in this study. ¹Asthma events include asthma medication, asthma review or asthma diagnosis. CPRD, Clinical Practice Research Datalink; OCS, oral corticosteroid; OPCR, Optimum Patient Care Research Database.

and Asia in patients with asthma aged >5 years, annual systemic corticosteroid (SCS) or OCS prescription was reported in ~50% of patients, with short-term use reported in up to 36% of patients; well above what might be expected for treatment according to guideline recommendations.⁶ Recent studies have shown a high prevalence of exacerbations treated with OCS across all severities of asthma,^{7,8} and exacerbations are increasingly being recognised as a major problem or as a risk factor for asthma death outside of severe asthma.

The use of SCS, even in the short-term, is associated with an increased risk of developing acute and chronic adverse outcomes (adverse outcomes).^{9–10} A study of both intermittent and long-term SCS prescriptions (parenteral or oral; median follow-up 7.4 years) showed that this risk increased with higher cumulative and mean daily SCS exposure.¹¹ This is supported by another study of intermittent and long-term SCS prescriptions (parenteral or oral; median follow-up 7.1 years) in which increases in cumulative incidences of steroid-related adverse outcomes were dose dependent.¹² Such OCS-related adverse outcomes can have a major impact on health-related quality of life^{13–16} and are associated with increased healthcare resource use.¹⁷

Prior research on OCS-related adverse outcomes has focused mostly on overall OCS exposure, on cumulative or average daily OCS exposure from both intermittent and long-term prescriptions. There have been no longitudinal studies that have focused exclusively on examining the association between patterns of intermittent-only OCS prescriptions and risk of adverse outcomes. Previous attempts to classify OCS use as intermittent or long-term use were varied and based on aggregate measures over a specific time period, such as continuous OCS prescription,¹⁸ continuous OCS use without a gap,¹⁹ average number of days on OCS,²⁰ titration patterns and cumulative daily dosage,^{17,21} none of which are perfect. As a result, it is challenging to separate out the adverse outcomes associated with intermittent use and long-term use given this absence of a clear definition of long-term use in secondary data. There is also a risk that, instead of identifying adverse outcomes related to intermittent OCS use, hidden historical cumulative OCS adverse outcomes are identified instead. Therefore, in this study, we specifically aimed to assess for the first time the association between longitudinal patterns of intermittent OCS prescriptions,

cumulative OCS dosages and OCS-related adverse outcomes in a large cohort of UK primary care patients with asthma identified as treated with intermittent-only OCS.

METHODS

Study design and data sources

This was a historical UK cohort study of patients ≥4 years with asthma using primary care medical records from 2008 to 2019, where adverse outcomes in a cohort of patients with intermittent-only OCS use were compared with a matched patient cohort of never users of OCS. Data were sourced from the Optimum Patient Care Research Database (OPCRD)²² and Clinical Practice Research Datalink (CPRD) GOLD,²³ two anonymised, real-life UK databases containing patient electronic medical records extracted from primary care and linked, in the case of CPRD, to a range of other health-related data to provide a longitudinal, representative UK population health dataset. CPRD contains data from primary care using Vision (Surgical Information Systems, Georgia, USA) software only; OPCR contains data from a range of software providers, including EMIS (EMIS Health, Leeds, UK), iSoft (DXD Technology, Sydney, Australia) and Vision. The OPCR contains data extracted through the optimum patient care (OPC) clinical service evaluation and contains research-quality data for ~17 million patients across the UK.²² At the time of study, the CPRD GOLD database had coverage of over 11 million current patients from 674 practices in the UK, with data linked to Hospital Episode Statistics up to March 2019, allowing for identification of any hospital admission, including admissions with asthma as the primary diagnosis, as well as outpatient visits and emergency department attendances. To avoid overlap of the same primary care data between CPRD and OPCR, Vision data were dropped from the OPCR database prior to commencing the study.

Patients

Patients aged ≥4 years with at least 12 months' clinical data prior to index date receiving only intermittent OCS (OCS cohort) were matched 1:1 on gender, age and index date with patients with or without asthma who had received no exposure to OCS ('never users' or 'non-OCS' cohort). Patients who were receiving or suspected of receiving long-term OCS prescriptions were excluded, as per a

Table 1 Baseline demographics and clinical characteristics of UK patients with asthma receiving intermittent OCS

	Non-OCS (never users) n=476 167*	Any OCS n=476 167 (100%)	One-off OCS n=198 422 (41.7%)	Less frequent OCS† n=127 419 (26.8%)	Frequent OCS‡ n=150 326 (31.6%)
Age, mean, years (SD)	38.1 (22.4)	38.1 (22.4)	35.6 (22.3)	36.9 (22.1)	42.4 (22.2)
Age category, n (%)					
4–<12 years	76 859 (16.1)	77 131 (16.2)	35 478 (17.9)	22 568 (17.7)	19 085 (12.7)
12–<18 years	36 329 (7.6)	36 262 (7.6)	19 336 (9.7)	9 518 (7.5)	7 408 (4.9)
18–<65 years	292 846 (61.5)	292 778 (61.5)	118 163 (59.6)	78 572 (61.7)	96 043 (63.9)
≥65 years	70 133 (14.7)	69 996 (14.7)	25 445 (12.8)	16 761 (13.2)	27 790 (18.5)
Female, %	55.7	55.7	51.8	56.3	60.2
Follow-up, median, years (IQR)	9.0 (4.7, 14.7)	8.3 (4.2, 13.7)	6.4 (3.1, 11.5)	9.8 (5.6, 14.9)	9.6 (5.1, 15.2)
Time in database pre index, median, years (IQR)	16.8 (7.8, 30.4)	17.0 (7.5, 31.1)	15.1 (6.9, 28.3)	16.2 (7.2, 30.1)	20.6 (9.1, 34.9)
BMI					
Underweight, n (%)	23 904 (5.0)	35 998 (7.6)	15 159 (7.6)	10 257 (8.0)	10 553 (7.0)
Normal, n (%)	144 517 (30.4)	138 469 (29.1)	56 728 (28.6)	37 665 (29.6)	44 061 (29.3)
Overweight, n (%)	102 328 (21.5)	109 042 (22.9)	42 521 (21.4)	28 899 (22.7)	37 612 (25.0)
Obese, n (%)	66 473 (14.0)	100 995 (21.2)	36 410 (18.3)	26 529 (20.8)	38 048 (25.3)
Unknown, n (%)	138 946 (29.2)	91 710 (19.3)	47 601 (24.0)	24 057 (18.9)	20 038 (13.3)
Mean (SD)	25.8 (5.9)	26.6 (7.0)	26.2 (6.8)	26.5 (6.9)	27.2 (7.1)
Smoking status, n (%§)					
Never	135 708 (28.5)	141 231 (29.7)	60 921 (30.7)	37 512 (29.4)	42 813 (28.5)
Current	117 089 (24.6)	131 851 (27.7)	53 508 (27.0)	34 951 (27.4)	43 384 (28.9)
Ex	67 711 (14.2)	84 377 (17.7)	33 951 (17.1)	21 075 (16.5)	29 375 (19.5)
Unknown	155 659 (32.7)	118 708 (24.9)	50 042 (25.2)	33 881 (26.6)	34 754 (23.1)
SABA prescriptions; n (%)					
0	470 929 (98.9)	113 262 (23.8)	44 766 (22.6)	30 987 (24.3)	37 507 (25.0)
1–2	3524 (0.7)	213 594 (44.9)	96 751 (48.8)	55 660 (43.7)	61 183 (40.7)
3–11	1476 (0.3)	133 255 (28.0)	51 519 (26.0)	36 602 (28.7)	45 134 (30.0)
≥12	238 (0.0)	16 056 (3.4)	5384 (2.7)	4170 (3.3)	6502 (4.3)
ICS prescriptions; n (%)					
0	472 462 (99.2)	191 141 (40.1)	80 403 (40.5)	50 177 (39.4)	60 560 (40.3)
1–3	2354 (0.5)	183 159 (38.5)	79 561 (40.1)	50 015 (39.2)	53 583 (35.6)
4–6	747 (0.2)	59 230 (12.4)	22 712 (11.4)	16 260 (12.8)	20 258 (13.5)
7–9	310 (0.1)	23 952 (5.0)	8874 (4.5)	6315 (4.9)	8763 (5.8)
10–12	179 (0.0)	11 968 (2.5)	4393 (2.2)	3043 (2.4)	4532 (3.0)
≥13	115 (0.0)	6718 (1.4)	2479 (1.2)	1609 (1.3)	2630 (1.7)

*Non-OCS patients were matched with all patients receiving OCS prescriptions according to 1:1 ratio.

†Patients who received all OCS prescriptions with a gap of ≥90 days.

‡Patients who received at least some OCS prescriptions with a gap of <90 days, allowing for other prescription gaps to be ≥90 days.

§Only the percentages of patient with known smoking status were calculated.

BMI, body mass index; ICS, inhaled corticosteroid; OCS, oral corticosteroid; SABA, short-acting β₂ agonist.

previously defined algorithm.²⁴ The index date for patients in the OCS cohort was the first intermittent OCS prescription within 3 months of an asthma event, which included asthma medication, consultation and/or diagnosis. Patients in the non-OCS cohort were indexed on the nearest general practitioner visit to the index date of the matched OCS patient.

OCS and non-OCS patients were also excluded if they had a diagnosis, ever, of one of the following chronic conditions commonly treated with OCS: ankylosing spondylitis, Sjögren's syndrome, systemic lupus erythematosus, ulcerative colitis, rheumatoid and psoriatic arthritis, multiple sclerosis, and Crohn's diseases. In order to ensure that the postindex adverse outcomes were incident events, patients with chronic adverse outcomes pre index were excluded, which led to different match sets for different individual adverse outcomes.

Study variables and outcomes

OCS exposures were converted into prednisolone equivalents using the defined daily dose (DDD) obtained from the Anatomical

Therapeutic Chemical/DDD classification system.²⁵ A patient's cumulative dose was calculated as the sum of all prednisolone, or equivalent, doses (g) prescribed from index date up until the outcome event.

The methodology for classification of intermittent OCS prescribing patterns has been described separately.²⁴ Briefly, OCS prescription patterns were evaluated across the entire follow-up period and classified as one-off, for patients with a single OCS prescription (as a proxy for OCS use), less frequent pattern, for patients with >1 prescription with any gaps >90 days but no gap <90 days, or frequent pattern, for patients with >1 prescription with <90 day gap(s).

Each patient was followed until first OCS-related AO and censored for that specific AO, or death or end of follow-up, but remained in the dataset for other conditions. The following adverse outcomes were recorded, defined according to International Classification of Diseases codes for diagnosis, and—for some adverse outcomes—other criteria, such as disease-specific medication prescription and/or physiological biomarkers:

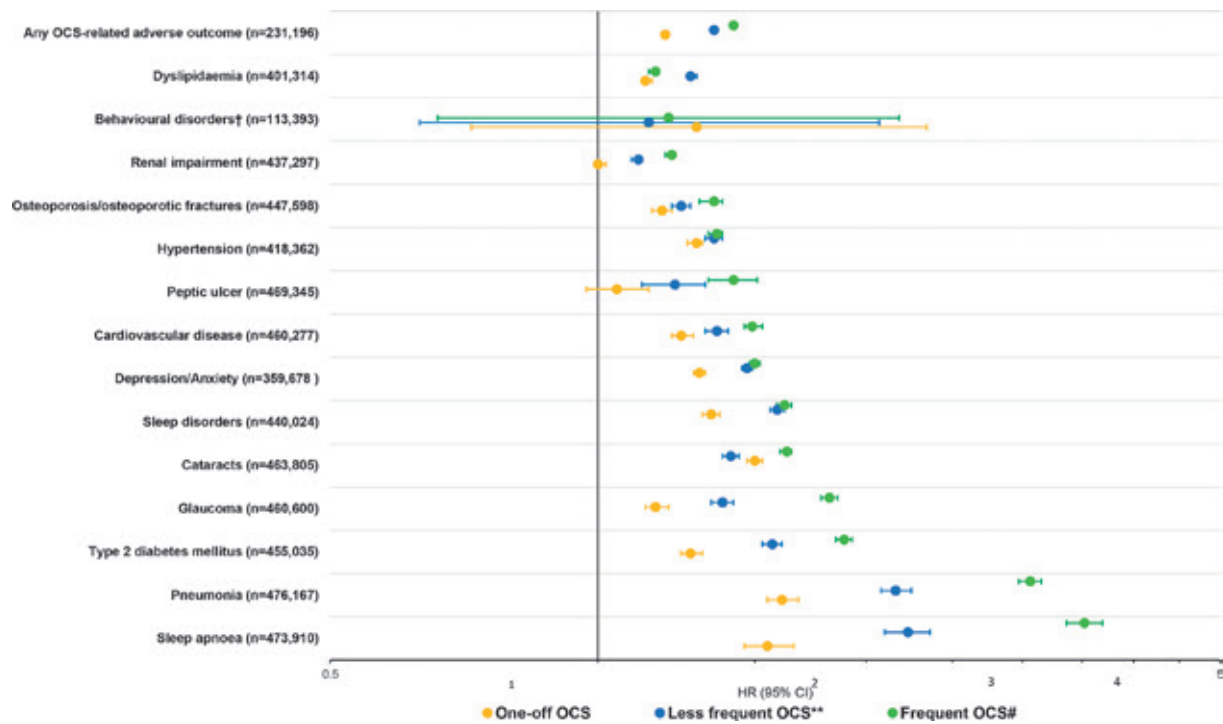


Figure 2 HRs[†] of adverse outcomes in UK patients with asthma receiving intermittent OCS prescriptions versus non-OCS patients. OCS, oral corticosteroid. Non-OCS patients were matched with all patients receiving OCS prescriptions according to a 1:1 ratio. **Patients with less frequent OCS use received all OCS prescriptions with a gap of ≥ 90 days. #Patients with frequent OCS use received at least some OCS prescriptions with a gap of < 90 days, allowing for other prescription gaps to be ≥ 90 day. [†]HRs were calculated using Cox regression analysis, adjusted for age, gender, body mass index, smoking and time-varying OCS prescriptions. *Behavioural disorders include diagnoses for distress, agitation, nervousness, emotional problems, irritable and abnormal behaviour among patients < 18 years.

dyslipidaemia, behavioural disorders (diagnoses of distress, agitation, nervousness, emotional problems and irritable and abnormal behaviour for patients < 18 years), renal impairment, osteoporosis/osteoporotic fractures, hypertension, peptic ulcer, cardiovascular disease, depression/anxiety, sleep disorders, cataracts, glaucoma, type 2 diabetes mellitus, pneumonia and sleep apnoea (online supplemental table S1).

Statistical analysis

Descriptive statistics were reported for the absolute and relative number of patients, mean, median, SD and IQR for continuous and categorical variables.

Patient demographic and clinical characteristics for the 12 months prior to index date (referred to as baseline) included age (4– < 12 , 12– < 18 , 18– < 65 and ≥ 65 years), sex, body mass index (BMI; underweight, normal, overweight, obese and unknown), smoking status (never, current, former and unknown), short-acting β_2 -agonist (SABA) prescriptions (0, 1–2, 3–11 and ≥ 12 fills) and inhaled corticosteroid (ICS) prescriptions (0, 1–3, 4–6, 7–9, 10–12 and ≥ 13 fills). The SABA and ICS prescription categories were based on the distribution of the study data in the OCS cohort (online supplemental figure S1).

The risk of developing an AO was analysed using survival analysis methods. Patients with prior diagnosis of an AO, and which was classed as chronic, were excluded from the corresponding analysis in order to specifically assess incident-only adverse outcomes, meaning that the sample size for analysis of individual adverse outcomes or a set of any adverse outcomes differed from one to another. Kaplan-Meier curves were used to describe the overall risk profile of each AO. To assess the association between intermittent OCS (vs non-OCS) prescription and risk of adverse outcomes, a multivariable Cox proportional hazard model was used to calculate HR and 95% CI for each AO. The Cox models were adjusted for age, sex, BMI, smoking status and time-varying OCS prescriptions, defined a priori. The multivariable analysis was further stratified by age, GINA 2020 treatment step and prescriptions for ICS and SABA in the 12 months pre index.

To assess the relation between cumulative OCS dose and each AO, adjusted incidence rate ratios and 95% CI were calculated for each AO, comparing the OCS categories (> 0 to < 0.5 g, 0.5 to < 1.0 g, 1.0 to < 2.5 g, 2.5 to < 5.0 g, 5.0 to < 10.0 g and ≥ 10.0 g) to the non-OCS group.

Analyses were conducted using Stata SE V.14.2 (StataCorp, College Station, Texas, USA) and statistical significance was defined at two-sided $p < 0.05$.

RESULTS

Patient characteristics

Of 2 130 881 patients receiving an OCS prescription for any condition (CPRD and OPCR) between 1985 and 2019, 476 167 met the eligibility criteria (figure 1); records from 476 167 matched non-OCS patients were included, 16 716 (3.5%) of whom had an asthma diagnosis or asthma treatment ever (0.8% and 1.1% of non-OCS patients had ≥ 1 ICS and ≥ 1 SABA prescription, respectively, in the 12 months before the index date). The median follow-up (IQR) duration was 8.3 (4.2–13.7) years for the OCS cohort and 9.0 (4.7–14.7) years for the non-OCS cohort; length of time in database preindex was 17.0 (7.5–31.1) and 16.8 (7.8–30.4) years, respectively. The mean (SD) age and sex distribution at index date for patients receiving OCS prescriptions and matched non-OCS was 38.1 (22.4) years and 55.7% were female in both cohorts. There were more obese patients in the OCS cohort than in the non-OCS cohort (table 1).

Of the study patients, 198 422 (41.7%), 127 419 (26.8%) and 150 326 (31.6%) had one-off, less frequent and frequent patterns of intermittent OCS prescription during the follow-up, respectively. The mean (median (IQR)) cumulative OCS dose was 176 (150 (150–200)) mg for one-off, 510 (420 (300–600)) mg for less frequent and 2357 (940 (540–1800)) mg for frequent patterns. Patients who had more frequent patterns of intermittent OCS prescriptions were older and more likely to be female. Those who had a frequent pattern of intermittent OCS prescriptions were more likely to be obese and to be current or ex-smokers compared with the one-off and less frequent OCS groups (table 1).

Table 2 HRs for any adverse outcomes in UK patients with asthma receiving intermittent OCS stratified by age, GINA treatment step, ICS and SABA prescriptions versus all non-OCS patients

HR (95% CI) by category	One-off OCS n=198 422 (41.7%)	Less frequent OCS* n=127 419 (26.8%)	Frequent OCS† n=150 326 (31.6%)
Age			
4–<12 years	1.11 (1.08, 1.14)	1.21 (1.17, 1.24)	1.32 (1.29, 1.36)
12–<18 years	1.17 (1.14, 1.20)	1.33 (1.29, 1.37)	1.45 (1.40, 1.50)
18–<65 years	1.24 (1.23, 1.26)	1.39 (1.38, 1.41)	1.48 (1.47, 1.50)
≥65 years	1.20 (1.18, 1.23)	1.35 (1.33, 1.38)	1.35 (1.33, 1.37)
GINA			
Step 0	1.25 (1.22, 1.28)	1.43 (1.40, 1.47)	1.46 (1.43, 1.49)
Step 1	1.21 (1.19, 1.23)	1.35 (1.33, 1.38)	1.40 (1.38, 1.43)
Step 2	1.16 (1.15, 1.18)	1.32 (1.30, 1.34)	1.38 (1.36, 1.41)
Step 3	1.19 (1.17, 1.21)	1.38 (1.35, 1.41)	1.46 (1.43, 1.49)
Step 4	1.28 (1.24, 1.32)	1.47 (1.43, 1.52)	1.58 (1.54, 1.63)
Step 5	1.33 (1.24, 1.43)	1.59 (1.49, 1.70)	1.89 (1.80, 1.99)
ICS prescriptions			
0	1.22 (1.20, 1.23)	1.38 (1.36, 1.40)	1.42 (1.40, 1.44)
1–3	1.18 (1.17, 1.20)	1.34 (1.32, 1.36)	1.45 (1.43, 1.47)
4–6	1.21 (1.17, 1.24)	1.41 (1.37, 1.46)	1.49 (1.45, 1.53)
7–9	1.20 (1.17, 1.20)	1.38 (1.35, 1.41)	1.44 (1.41, 1.47)
10–12	1.25 (1.18, 1.32)	1.44 (1.36, 1.52)	1.56 (1.49, 1.64)
≥13	1.26 (1.18, 1.36)	1.49 (1.38, 1.60)	1.65 (1.56, 1.76)
SABA prescriptions			
0	1.25 (1.23, 1.27)	1.42 (1.40, 1.45)	1.46 (1.44, 1.48)
1–2	1.21 (1.19, 1.23)	1.37 (1.34, 1.39)	1.43 (1.40, 1.45)
3–11	1.18 (1.17, 1.20)	1.34 (1.32, 1.36)	1.44 (1.42, 1.46)
≥12	1.08 (1.03, 1.13)	1.41 (1.35, 1.48)	1.45 (1.40, 1.51)

HR were calculated using Cox regression analysis, adjusted for age, gender, body mass index, smoking and time-varying OCS prescriptions; HR=1 for non-OCS patients.
 *Patients who received all OCS prescriptions with a gap of ≥90 days.
 †Patients who received at least some OCS prescriptions with a gap of <90 days, allowing for other prescription gaps to be ≥90 days.
 GINA, The Global Initiative for Asthma; ICS, inhaled corticosteroid; OCS, oral corticosteroid; SABA, short-acting β₂ agonist.

Across all patterns of intermittent OCS prescriptions, in the 12 months prior to initial OCS prescriptions, patients were most commonly receiving 1–2 SABA fills and ≤3 ICS fills. The proportion of patients receiving ≥3 SABA and ≥4 ICS fills at baseline increased with increasingly frequent patterns of OCS prescription (table 1).

Intermittent OCS prescribing patterns and risk of OCS-related adverse outcomes

The overall analysis of the association between patterns of intermittent OCS prescriptions and any OCS-related adverse outcomes included 231 196 patients, due to the exclusion of those with prevalent conditions. Compared with non-OCS patients, the risk of experiencing any adverse outcomes was elevated for one-off OCS and increased with increasing frequent pattern of intermittent OCS prescribing. The HR (95% CI) of experiencing any adverse outcomes versus non-OCS patients was 1.19 (1.18 to 1.20) for one-off OCS, 1.35 (1.34 to 1.36) for less frequent OCS and 1.42 (1.42 to 1.43) for frequent pattern of OCS prescriptions.

Similar to the risk of any OCS-related adverse outcomes, the risk of all individual OCS-related adverse outcomes except behavioural disorders, renal impairment and peptic ulcer was already detectable in one-off OCS, and increased with increasingly frequent patterns of intermittent OCS prescriptions (figure 2). The highest risk (HR>2) of OCS-related individual adverse outcomes with increasingly frequent OCS prescribing were for pneumonia and sleep apnoea (figure 2). Kaplan-Meier curves for the relation between patterns of intermittent OCS prescriptions and individual adverse outcomes are shown in online supplemental figure S2.

The association between patterns of intermittent OCS prescription and risk of OCS-related adverse outcomes remained consistent when stratified by age, GINA treatment step and ICS or SABA prescriptions (table 2).

When examining the dose-response relation between annual cumulative OCS exposure and risk of adverse outcomes, the risk increased in a dose-response fashion with greater annual cumulative OCS dose. Importantly, compared with the non-OCS group, risks started to increase at 0.5–1.0 g for all adverse outcomes except dyslipidaemia, with modest increases for hypertension and renal impairment (figure 3).

DISCUSSION

In this historical UK cohort study of patients with asthma, we found that almost a third of the patients with intermittent OCS use had a frequent pattern of use (ie, more than one prescription with less than 90-day gaps) at some point during the follow-up period. In those patients with intermittent-only OCS use, compared with matched individuals who were non-users of OCS, the risk of experiencing any OCS-related adverse outcomes increased with increasing frequent pattern of intermittent OCS prescriptions for most adverse outcomes studied, particularly pneumonia and sleep apnoea. The elevated risk of adverse outcomes was observed even for patients with one-off OCS prescriptions. The association between patterns of intermittent OCS prescriptions and risk of OCS-related adverse outcomes was relatively consistent across age categories, GINA treatment steps and prior asthma medication use.

To our knowledge, this study is the largest (with almost half a million patients), has the longest patient follow-up (34 years, with a median study period of over 25 years (pre-first and post-first OCS exposure)) and is the most definitive study yet to identify intermittent OCS use and assess the association of patterns of intermittent OCS use with risk of developing OCS-related adverse outcomes. Our study overcame the issues associated with mixed reporting of long-term and intermittent OCS prescriptions and related adverse outcomes by focusing exclusively on intermittent-only OCS prescriptions²⁴; it also fills a need for a longitudinal study using objective methods to collect data on intermittent OCS-related adverse outcomes, increasing the specificity of the findings by minimising the risk of bias.⁵

Despite the extensive research on adverse outcomes associated with OCS, the use of OCS remains widespread⁵ and recommended in certain instances.^{1–3} Our finding that increasingly frequent patterns of intermittent OCS prescription were associated with an increased risk for adverse outcomes is consistent with previous studies reporting a high risk of corticosteroid-related adverse outcomes with OCS prescriptions,^{1 12 26} and with studies in adult patients with severe asthma, showing that long-term high-dose use of OCS (defined as >10 mg/day) resulted in a higher risk of developing OCS-related complications than medium OCS use (defined as 5–10 mg/day), when both were compared with low OCS use (defined as <5 mg/day) and non-OCS patients.^{13 27} The fact that the risk of an OCS-related AO was highest for pneumonia in our study is not unexpected, as this is one of the most well-recognised adverse effects of even short-term OCS use.^{6 11 28} The elevated risk of sleep apnoea was more surprising, as this is not as commonly associated with OCS use. However, a link with sleep apnoea has previously been shown in patients with severe asthma receiving SCS²⁹ and in patients with difficult-to-control asthma receiving long-term or frequent bursts of OCS,³⁰ as well as in a broader population of patients with active asthma of all severities receiving SCS.¹¹ Furthermore, as our analysis was adjusted for BMI, our findings suggest that the association with OCS use may be independent of obesity—one of the best-known risk factors for sleep apnoea³¹ and also a common adverse effect of OCS use²—and is instead likely mediated by other mechanisms. Possible explanations include fat deposition in the upper airway or airway dilator muscle myopathy, as has been suggested for ICS,^{32 33} or an increase in airway collapsibility.³⁰

Our results demonstrating increased risks with even a one-off OCS prescription are also supported by previous research showing

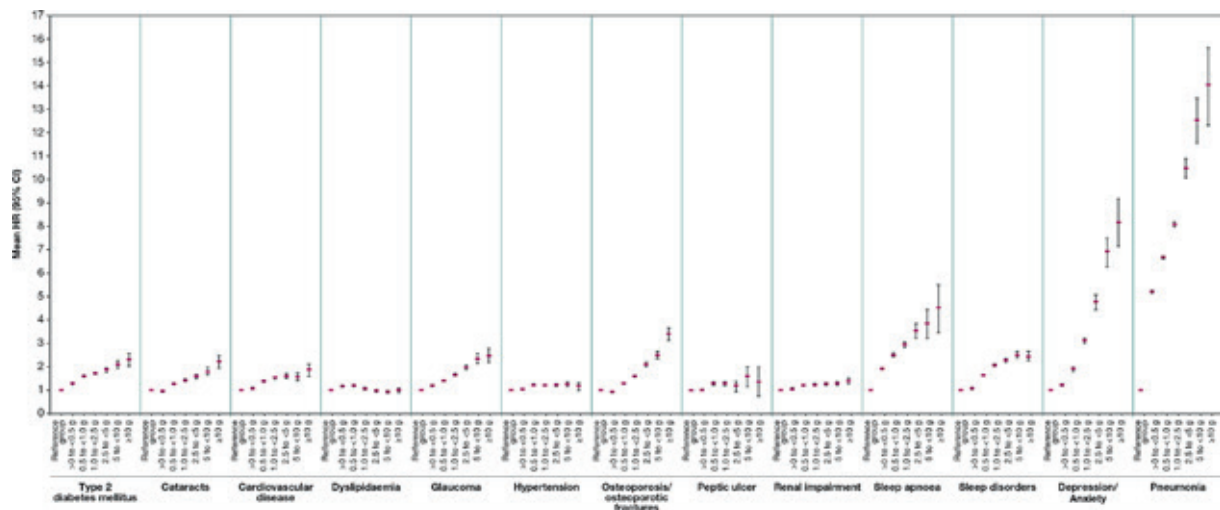


Figure 3 HR (95% CI) for each adverse outcome by overall, cumulative OCS exposures, compared with the reference category of non-OCS patients in UK patients with asthma. OCS, oral corticosteroid.

that short bursts of OCS can be associated with certain adverse outcomes and that each OCS prescription contributes to a cumulative burden, regardless of the dose and duration.⁹ Given that the median cumulative OCS dose is higher in this study in patients with a frequent pattern of prescription than the less frequent and one-off patterns, there may be correlation between frequent patterns of intermittent prescriptions and total exposure. This observation gives physicians another tool to gauge the risk of adverse outcomes in their patients, that is, future risk is higher if patients have received OCS with smaller gaps between prescriptions. Our finding that risks started to increase at dose levels of 0.5–1.0 g also confirms the importance of minimising total exposure, and the reasons behind persistent prescribing of OCS should be further investigated. Therefore, all patients, including those with mild disease and/or receiving regular ICS and SABA treatment, could potentially benefit from being monitored for frequent patterns of OCS prescription.

Our results also showed that over 30% of patients with intermittent-only OCS prescriptions had ≥ 3 SABA fills in the 12-month baseline period, and those with a more frequent pattern of intermittent OCS prescriptions had more prescriptions for SABA. It has been previously shown that increased SABA exposure is associated with severe exacerbation risk,³⁴ which is reflected in this study with more frequent pattern of intermittent OCS use among patients with a higher number of SABA prescriptions. This supports the move away from SABA-only treatment at GINA step 1. Similarly to the findings for SABA prescriptions, more ICS prescriptions were also observed in those with a more frequent pattern of OCS prescription, although the number of ICS prescriptions was low. On that note, the fact that 40% of the OCS cohort had no ICS prescriptions during the 12-month baseline period suggests that some patients might have received their first OCS prescriptions at the same time as their first attendance in primary care with asthma, and there might also be a population of patients with asthma who are underusing ICS. It is worth noting the population in this study generally had milder disease as a result of the exclusion of long-term OCS use.

This study had several strengths including the use of an algorithm that exclusively included patients on intermittent OCS and took a longitudinal view on the patterns of intermittent OCS use, resulting in a highly specific representation of patients receiving intermittent OCS only. Furthermore, the real-world design of this study allows for generalisation of the results to patients managed in all healthcare settings. Using two well-established databases (OPCRD and CPRD) with large size and high data quality and granularity allowed us to study the association between intermittent OCS prescriptions and associated risk of multiple different adverse outcomes.

Limitations of the study included the fact that, despite using a sophisticated algorithm that was reviewed by experts familiar with

the clinical implications of our study, some of the intermittent and long-term OCS prescriptions might have been misclassified, thereby underestimating the strengths of the effect estimates. The validity and completeness of individual patient records could not be assessed because the datasets represent information collected for clinical and routine use rather than specifically for research purposes. As a result, there were some missing data, especially for BMI and smoking status, which could potentially affect how confounding by these factors is adjusted for. Furthermore, since the multivariable Cox proportional hazard model was not adjusted for obesity but for BMI, with some missing values, there could have been some residual confounding. Although our study included patients of all ages, the only children-specific and adolescent-specific adverse outcomes to be analysed were behavioural disorders (including diagnoses of distress, agitation, nervousness, emotional problems, irritability and abnormal behaviour). Such diagnoses are difficult to capture and of varying origin, hence a possible reason for not detecting associations with this outcome. However, analysis of all adverse outcomes stratified by the different age categories also showed an increased risk with higher frequency of prescribing patterns of intermittent OCS for the youngest patients. In patients with one-off OCS use, there could be additional bursts that were not captured, which might explain the association detected between one-off OCS prescription and developing adverse outcomes. In the context of a chest infection, prescription of prednisolone alongside antibiotics in a patient with asthma, coupled with the potential for mislabelling of a chest infection as pneumonia, may have contributed to an association between the two. Lastly, OCS prescriptions may not be directly linked to OCS use, as there is no guarantee that patients used the prescriptions that they received.

CONCLUSIONS

In conclusion, our study found that a considerable proportion of patients with asthma who are prescribed OCS intermittently have a frequent pattern of use at some point. Increasingly frequent prescribing patterns of intermittent OCS were associated with a higher risk of individual OCS-related adverse outcomes, and this association remained consistent across levels of age, GINA treatment step and ICS maintenance and SABA reliever use. The increase in risk occurred early, even with one-off prescriptions and with doses as low as 0.5–1.0 g. Our results suggest that the use of OCS, even intermittently, in the management of asthma should be minimised whenever possible.

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Patient consent for publication Not applicable.

Ethics approval The study adhered to standards recommended for observational research.²⁴ The OPCRd is maintained by Optimum Patient Care and has ethical approval from the National Health Service Research Authority (Research Ethics Committee reference: 15/EM/0150). This study was approved by the Anonymised Data Ethics & Protocol Transparency (ADEPT) Committee²⁵ (OPCRd/ADEPT1120), and the Independent Scientific Advisory Committee (CPRD; ISAC 20_000071). The study is registered with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (registration number: EUPAS37065). No patient-identifying information was accessible during the study.

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REFERENCES

1 Global Initiative for Asthma. Global strategy for asthma management and prevention, 2022. Available: www.ginasthma.org

2 Sullivan PW, Ghushchyan VH, Globe G, et al. Oral corticosteroid exposure and adverse effects in asthmatic patients. *J Allergy Clin Immunol* 2018;141:110–6.

3 British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma, 2019. Available: <https://www.brit-thoracic.org.uk/document-library/guidelines/asthma/btssign-guideline-for-the-management-of-asthma-2019/>

4 Suehs CM, Menzies-Gow A, Price D, et al. Expert consensus on the tapering of oral corticosteroids for the treatment of asthma. A Delphi study. *Am J Respir Crit Care Med* 2021;203:871–81.

5 Tran TN, King E, Sarkar R, et al. Oral corticosteroid prescription patterns for asthma in France, Germany, Italy and the UK. *Eur Respir J* 2020;55:1902363.

6 Bleecker ER, Menzies-Gow AN, Price DB, et al. Systematic literature review of systemic corticosteroid use for asthma management. *Am J Respir Crit Care Med* 2020;201:276–93.

7 Ryan D, Heatley H, Heaney LG, et al. Potential severe asthma hidden in UK primary care. *J Allergy Clin Immunol Pract* 2021;9:1612–23.

8 Hancock KL, Bosnic-Anticevich S, Blakey JD, et al. Characterisation of the Australian adult population living with Asthma: severe - exacerbation frequency, long-term OCS use and adverse effects. *Pragmat Obs Res* 2022;13:43–58.

9 Ekström M, Nwaru BI, Hasvold P, et al. Oral corticosteroid use, morbidity and mortality in asthma: a nationwide prospective cohort study in Sweden. *Allergy* 2019;74:2181–90.

10 Waljee AK, Rogers MAM, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ* 2017;357:j1415.

11 Price DB, Trudo F, Voorham J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy* 2018;11:193–204.

12 Voorham J, Xu X, Price DB, et al. Healthcare resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma. *Allergy* 2019;74:273–83.

13 Chung LP, Upham JW, Bardin PG, et al. Rational oral corticosteroid use in adult severe asthma: a narrative review. *Respirology* 2020;25:161–72.

14 Hyland ME, Whalley B, Jones RC, et al. A qualitative study of the impact of severe asthma and its treatment showing that treatment burden is neglected in existing asthma assessment scales. *Qual Life Res* 2015;24:631–9.

15 Sweeney J, Brightling CE, Menzies-Gow A, et al. Clinical management and outcome of refractory asthma in the UK from the British Thoracic Society difficult asthma registry. *Thorax* 2012;67:754–6.

16 Thompson PJ, Salvi S, Lin J, et al. Insights, attitudes and perceptions about asthma and its treatment: findings from a multinational survey of patients from 8 Asia-Pacific countries and Hong Kong. *Respirology* 2013;18:957–67.

17 Zeiger RS, Schatz M, Li Q, et al. Burden of chronic oral corticosteroid use by adults with persistent asthma. *J Allergy Clin Immunol Pract* 2017;5:1050–60.

18 Bengtson LGS, Yu Y, Wang W, et al. Inhaled corticosteroid-containing treatment escalation and outcomes for patients with asthma in a U.S. health care organization. *J Manag Care Spec Pharm* 2017;23:1149–59.

19 Lefebvre P, Duh MS, Lefeuvre M-H, et al. Burden of systemic glucocorticoid-related complications in severe asthma. *Curr Med Res Opin* 2017;33:57–65.

20 Moore WC, Evans MD, Bleecker ER, et al. Safety of investigative bronchoscopy in the severe asthma research program. *J Allergy Clin Immunol* 2011;128:328–36.

21 Sá-Sousa A, Almeida R, Vicente R, et al. High oral corticosteroid exposure and overuse of short-acting beta-2-agonists were associated with insufficient prescribing of controller medication: a nationwide electronic prescribing and dispensing database analysis. *Clin Transl Allergy* 2019;9:47.

22 Optimum Patient Care. Optimum patient care UK, 2022. Available: <https://optimumpatientcare.org/>

23 Kousoulis AA, Rafi I, de Lusignan S. The CPRD and the RCGP: building on research success by enhancing benefits for patients and practices. *Br J Gen Pract* 2015;65:54–5.

24 Heatley H, Tran T, Bourdin A, et al. The burden of intermittent oral corticosteroid use in asthma. *Eur Respir J* 2021;58:OA1491.

25 World Health Organization. Atc/ddd index, 2022. Available: https://www.whocc.no/atc_ddd_index/

26 Rice JB, White AG, Scarpati LM, et al. Long-term systemic corticosteroid exposure: a systematic literature review. *Clin Ther* 2017;39:2216–29.

27 Volmer T, Effenberger T, Trautner C, et al. Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature. *Eur Respir J* 2018;52:1800703.

28 Yao T-C, Wang J-Y, Chang S-M, et al. Association of oral corticosteroid bursts with severe adverse events in children. *JAMA Pediatr* 2021;175:723–9.

29 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 Society Difficult Asthma Registry. *Thorax* 2016;71:339–46.

30 Yigla M, Tov N, Solomonov A, et al. Difficult-to-control asthma and obstructive sleep apnea. *J Asthma* 2003;40:865–71.

31 Jehan S, Zizi F, Pandi-Perumal SR, et al. Obstructive sleep apnea and obesity: implications for public health. *Sleep Med Disord* 2017;1. [Epub ahead of print: 12 12 2017].

32 Teodorescu M, Xie A, Sorkness CA, et al. Effects of inhaled fluticasone on upper airway during sleep and wakefulness in asthma: a pilot study. *J Clin Sleep Med* 2014;10:183–93.

33 Qiao Y-X, Xiao Y. Asthma and obstructive sleep apnea. *Chin Med J* 2015;128:2798–804.

34 Quint JK, Arnetorp S, Kocks JWH, et al. Short-acting beta-2-agonist exposure and severe asthma exacerbations: SABINA findings from Europe and North America. *J Allergy Clin Immunol Pract* 2022;10:2297–309.

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

**TRAVA
antes que
seja tarde**

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

*após alta hospitalar



**BEVESPI
AEROSPHERE®**

(glicopirrônio/fumarato de formoterol)
Suspensão Pressurizada para Inalação

DPOC, doença pulmonar obstrutiva crônica

Referências: 1. Riltrava Aerosphere 5 microgramas/7,2 microgramas/160 microgramas, suspensão pressurizada para inalação [Resumo das Características do Medicamento]. AstraZeneca AB, SE-151 85 Södertälje Suécia; abril 2022. Acedido em www.infarmed.pt em outubro 2022. 2. Bevespi Aerosphere 5 microgramas/7,2 microgramas, suspensão pressurizada para inalação [Resumo das Características do Medicamento]. AstraZeneca AB, SE-151 85 Södertälje Suécia; agosto 2022. Acedido em www.infarmed.pt em outubro 2022. 3. Ho T-W, Tsai Y-J, Ruan S-Y, et al. In-Hospital and One-Year Mortality and Their Predictors in Patients Hospitalized for First-Ever Chronic Obstructive Pulmonary Disease Exacerbations: A Nationwide Population-Based Study. *Bai C, editor. PLoS ONE*. 2014 Dec;9(12):e114866.

Informações essenciais compatíveis com o Resumo das Características do Medicamento

Bevespi Aerosphere 7,2 microgramas/5 microgramas, suspensão pressurizada para inalação. Cada dose única (dose libertada que sai do aplicador bucal) contém 9 microgramas de brometo de glicopirrônio, equivalente a 7,2 microgramas de glicopirrônio, e 5 microgramas de fumarato de formoterol di-hidratado. Isto corresponde a uma dose calibrada de 10,4 microgramas de brometo de glicopirrônio, equivalente a 8,3 microgramas de glicopirrônio, e 5,8 microgramas de fumarato de formoterol di-hidratado. **Indicações terapêuticas:** Bevespi Aerosphere é indicado como tratamento broncodilatador de manutenção para o alívio de sintomas em doentes adultos com doença pulmonar obstrutiva crônica (DPOC). **Posologia e modo de administração:** **Posologia:** A dose recomendada é duas inalações duas vezes por dia (duas inalações de manhã e duas inalações à noite). Os doentes devem ser aconselhados a não fazer mais de 2 inalações duas vezes por dia. Se for omitida uma dose, esta deve ser tomada assim que for possível e a dose seguinte deve ser tomada no horário habitual. Não deve tomar-se uma dose a dobrar para compensar uma dose esquecida. **Populações especiais:** **Idosos:** Não é necessário qualquer ajuste de dose em doentes idosos. **Compromisso renal:** Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, só deve ser utilizado se o benefício esperado for superior ao risco potencial. **Compromisso hepático:** Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Não existem dados relevantes sobre a utilização de Bevespi Aerosphere em doentes com compromisso hepático grave e o medicamento deve ser utilizado com precaução nestes doentes. **População pediátrica:** Não existe utilização relevante de Bevespi Aerosphere em crianças e adolescentes (com idade inferior a 18 anos) para a indicação de DPOC. **Modo de administração:** Utilização por via inalatória. **Instruções de utilização:** Ao acionar Bevespi Aerosphere, um volume de suspensão é expelido do recipiente pressurizado a alta velocidade. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes devem ser instruídos sobre a técnica de inalação correta. É importante instruir o doente para: Ler com atenção as instruções de utilização no folheto informativo, que se encontra dentro da embalagem de cada inalador. Não utilizar o inalador se o agente excicante, contido na bolsa de alumínio, tiver vazado da sua embalagem. Preparar o inalador agitando-o e acionando-o quatro vezes para o ar antes da primeira utilização ou duas vezes quando o inalador não tenha sido utilizado há mais de sete dias, tenha sido exposto a temperaturas baixas ou tenha caído. Para obter uma deposição pulmonar adequada das substâncias ativas, o carregamento da dose tem de ser coordenado com a inalação. Doentes com dificuldade em coordenar o carregamento da dose com a inspiração podem utilizar Bevespi Aerosphere com uma câmara expansora para garantir a administração adequada do produto. Foi demonstrada compatibilidade com a câmara expansora Aerochamber Plus Flow-Vu. **Contraindicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** **Asma:** Bevespi Aerosphere não deve ser utilizado no tratamento da asma. **Broncospasmo paradoxal:** Se ocorrer broncospasmo paradoxal, o tratamento com o medicamento deve ser interrompido e devem ser considerados outros tratamentos. **Não indicado para utilização em situações agudas:** Bevespi Aerosphere não é indicado para o tratamento de episódios agudos de broncospasmo, isto é, como terapêutica de alívio. **Efeitos cardiovasculares:** Podem ser observados efeitos cardiovasculares, após a administração de antagonistas dos recetores muscarínicos e simpaticomiméticos, incluindo glicopirrônio ou formoterol. Bevespi Aerosphere deve ser utilizado com precaução em doentes com doenças cardiovasculares graves, tais como cardiopatia isquémica, taquiarritmias ou insuficiência cardíaca grave. Recomenda-se também precaução em doentes com tirototoxicose ou com prolongamento do intervalo QTc conhecido ou suspeito. **Hipocaliemia:** Os agonistas β_2 -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_2 -adrenérgicos pode provocar o aumento da glucose plasmática. **Atividade anticolinérgica:** Devido à sua atividade anticolinérgica, Bevespi Aerosphere deve ser utilizado com precaução em doentes com hiperplasia da próstata sintomática, retenção urinária ou glaucoma de ângulo fechado. **Compromisso renal:** Como o glicopirrônio é excretado predominantemente por via renal, os doentes com compromisso renal grave (depuração de creatinina <30 ml/min), incluindo aqueles com doença renal em fase terminal com necessidade de diálise, apenas devem ser tratados com Bevespi Aerosphere se o benefício esperado superar o risco potencial. **Compromisso hepático:** Em doentes com compromisso hepático grave, Bevespi Aerosphere só deve ser utilizado se o benefício esperado superar o risco potencial. Estes doentes devem ser monitorizados para potenciais reações adversas. **Interações medicamentosas e outras formas de interação:** **Interações farmacocinéticas:** O potencial para interações metabólicas é considerado baixo. Como o glicopirrônio é eliminado principalmente por via renal, podem ocorrer potencialmente interações medicamentosas com medicamentos que afetam os mecanismos de excreção renal. **Interações farmacodinâmicas:** Outros antimuscarínicos e simpaticomiméticos: A coadministração de Bevespi Aerosphere com outros medicamentos contendo anticolinérgicos e/ou agonistas β_2 -adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas β_2 -adrenérgicos inalados. Não existe evidência clínica de interações quando utilizado concomitantemente com outros medicamentos para a DPOC, incluindo broncodilatadores β_2 -adrenérgicos de curta duração de ação, metilxantinas e esteróides orais e inalados. **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_2 -adrenérgicos, pelo que se recomenda precaução na sua utilização concomitante. **Bloqueadores β_2 -adrenérgicos:** Os bloqueadores β_2 -adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito dos agonistas β_2 -adrenérgicos, tal como o formoterol. O uso simultâneo de bloqueadores β_2 -adrenérgicos não seletivos ou seletivos deve ser evitado, a não ser que existam razões determinantes para a sua utilização. Se forem necessários bloqueadores β_2 -adrenérgicos (incluindo colírios), dá-se preferência a bloqueadores β_2 -adrenérgicos cardiosseletivos, embora também estes devam ser administrados com precaução. **Outras interações farmacodinâmicas:** Bevespi Aerosphere deve ser administrado com precaução em doentes que estejam a ser tratados com medicamentos conhecidos por prolongar o intervalo QTc. **Fertilidade, gravidez e aleitamento:** **Gravidez:** Não existem dados sobre a utilização de Bevespi Aerosphere em mulheres grávidas. Bevespi Aerosphere só deve ser utilizado durante a gravidez se os benefícios esperados superarem os potenciais riscos. **Amamentação:** Não é conhecido se o glicopirrônio ou o formoterol são excretados no leite humano. A administração de Bevespi Aerosphere a mulheres que estão a amamentar só deve ser considerada se o benefício esperado para a mãe for superior a qualquer possível risco para o bebé. **Fertilidade:** Considera-se pouco provável que Bevespi Aerosphere, administrado na dose recomendada, afete a fertilidade no ser humano. **Efeitos indesejáveis:** **Frequentes:** Ansiedade, Cefaleia, Tonturas, Boca seca, Náuseas, Espasmos musculares, Infecção do trato urinário, Dor torácica. **Pouco frequentes:** Reações de hipersensibilidade, incluindo erupção cutânea e prurido, Hiperglicemia, Agitação, Irrequietude, Insónia, Tremor, Taquicardia, Palpações, 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/submissao> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel.: +351217987373; Linha do Medicamento: 800222444 (gratuita); E-mail: farmacovigilancia@infarmed.pt). **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado:** Tecnimed - Sociedade Técnico-Medicinal, S.A., Rua da Tapada Grande, n.º 2, Abrunheira, 2710-089 Sintra. Informações revistas em agosto 2022. **Para mais informações deverá contactar o representante local do Titular da Autorização de Introdução no Mercado. Medicamento sujeito a receita médica. Medicamento compartilhado pelo Escalão B (69% de participação no regime geral e 84% de participação no regime especial). Versão 1.0 (agosto 2022).**

Informações essenciais compatíveis com o Resumo das Características do Medicamento

Riltrava Aerosphere 5 microgramas/7,2 microgramas/160 microgramas, suspensão pressurizada para inalação. Cada dose única (dose libertada que sai do aplicador bucal) contém 5 µg de fumarato de formoterol di-hidratado, 9 µg de brometo de glicopirrónio, equivalente a 7,2 µg de glicopirrónio e 160 µg de budesonida. Isto corresponde a uma dose calibrada de 5,3 µg de fumarato de formoterol di-hidratado, 9,6 µg de brometo de glicopirrónio, equivalente a 7,7 µg de glicopirrónio e 170 µg de budesonida. **Indicações terapêuticas:** Riltrava Aerosphere é indicado como tratamento de manutenção em doentes adultos com DPOC moderada a grave, que não estão adequadamente tratados com uma associação de um corticosteroide inalado e um agonista beta2 de longa duração de ação ou uma associação de um agonista beta2 de longa duração de ação e um antagonista muscarínico de longa duração de ação. **Posologia e modo de administração:** Posologia: A dose recomendada e máxima é de 2 inalações 2x/dia (2 inalações de manhã e 2 inalações à noite). Se for omitida uma dose, esta deve ser tomada assim que for possível e a dose seguinte deve ser tomada no horário habitual. Não se deve tomar uma dose a dobrar para compensar uma dose esquecida. Populações especiais: *Idosos:* Não é necessário qualquer ajuste de dose em doentes idosos. *Compromisso renal:* Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, apenas se o benefício esperado for superior ao risco potencial. *Compromisso hepático:* Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso hepático grave, o medicamento deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. *População pediátrica:* Não existe utilização relevante deste medicamento em crianças e adolescentes (com idade inferior a 18 anos) para a indicação da DPOC. Modo de administração: Para utilização por via inalatória. *Instruções de utilização:* De forma a assegurar uma administração correta do medicamento, o médico ou outro profissional de saúde deve demonstrar ao doente como utilizar corretamente o inalador, e deve monitorizar regularmente a técnica de inalação do doente. O doente deve ser aconselhado a ler com atenção o Folheto Informativo e seguir as instruções de utilização conforme indicado no mesmo. Ao acionar Riltrava Aerosphere, um volume de suspensão é expelido do recipiente pressurizado. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes que têm dificuldade em coordenar o acionamento com a inalação podem utilizar Riltrava Aerosphere com uma câmara expansora para garantir a administração adequada do medicamento. Pode ser utilizado com câmaras expansoras incluindo o Aerochamber Plus FlowVu. **Contra-indicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** Não indicado para utilização em situações agudas. Este medicamento não é indicado para o tratamento de episódios agudos de broncospasma, isto é, como terapêutica de alívio. Broncospasma paradoxal: A administração de formoterol/glicopirrónio/budesonida pode produzir broncospasma paradoxal com sibilos e dispnéia imediatamente após a administração e pode ser potencialmente fatal. O tratamento com este medicamento deve ser imediatamente interrompido se ocorrer broncospasma paradoxal. O doente deve ser avaliado e instituído tratamento alternativo, se necessário. Deterioração da doença: Recomenda-se que o tratamento com este medicamento não seja interrompido abruptamente. Se os doentes não considerarem o tratamento eficaz, devem manter o tratamento, mas tem de se procurar aconselhamento médico. O aumento da utilização de broncodilatadores de alívio indica um agravamento do quadro clínico subjacente e justifica uma reavaliação da terapêutica. A deterioração rápida e progressiva nos sintomas da DPOC é potencialmente fatal e o doente deve ser submetido a avaliação médica urgente. Efeitos cardiovasculares: Podem ser observados efeitos cardiovasculares, tais como arritmias cardíacas, p.ex. fibrilhação auricular e taquicardia, após a administração de antagonistas dos recetores muscarínicos e simpaticomiméticos, incluindo glicopirrónio e formoterol. Este medicamento deve ser utilizado com precaução em doentes com doença cardiovascular grave não controlada e clinicamente significativa, tal como cardiopatia isquémica instável, enfarte agudo do miocárdio, cardiomiopatia, arritmias cardíacas, e insuficiência cardíaca grave. Recomenda-se também precaução ao tratar doentes com prolongamento do intervalo QTc (QTc > 450 milissegundos para homens ou > 470 milissegundos para mulheres), conhecido ou suspeito, quer seja congénito ou induzido por medicamentos. Efeitos sistémicos com corticosteroides: Podem ocorrer efeitos sistémicos com qualquer corticosteroide inalado, particularmente em doses elevadas prescritas por longos períodos de tempo. Estes efeitos são muito menos prováveis de ocorrer com o tratamento por inalação do que com corticosteroides orais. Os efeitos sistémicos possíveis incluem síndrome de Cushing, manifestações Cushingoides, supressão suprarrenal, diminuição da densidade mineral óssea, cataratas e glaucoma. Devem ser considerados efeitos potenciais na densidade óssea especialmente com a administração de doses elevadas durante longo período de tempo em doentes com fatores de risco coexistentes para osteoporose. Perturbações visuais: Podem ser notificadas perturbações visuais com a utilização sistémica e tópica 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 β₂. 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 β₂-adrenérgicos pode provocar o aumento da glucose plasmática. A glicemia deve ser monitorizada durante o tratamento de acordo com as orientações estabelecidas para doentes com diabetes. **Condições coexistentes:** Este medicamento deve ser utilizado com precaução em doentes com tirototoxicose. **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 contactarem o seu médico imediatamente, caso algum destes sinais ou sintomas se desenvolvam. Não é recomendada a administração concomitante deste medicamento com outros medicamentos contendo anticolinérgicos. **Compromisso renal:** Como o glicopirrónio é excretado predominantemente por via renal, os doentes com compromisso renal grave (depuração de creatinina <30 ml/min), incluindo aqueles com doença renal em fase terminal com necessidade de diálise, apenas devem ser tratados com este medicamento se o benefício esperado superar o risco potencial. **Compromisso hepático:** Em doentes com compromisso hepático grave, este medicamento só deve ser utilizado se o benefício esperado superar o risco potencial. Estes doentes devem ser monitorizados para potenciais reações adversas. **Interações medicamentosas e outras formas de interação:** **Interações farmacocinéticas:** Prevê-se que o tratamento em associação com inibidores potentes do CYP3A, por exemplo itraconazol, cetoconazol, inibidores de protease do VIH e medicamentos que contêm cobicistate, aumente o risco de efeitos indesejáveis sistémicos, e deve ser evitado, a não ser que o benefício seja superior ao risco aumentado de reações adversas aos corticosteroides sistémicos, nesse caso os doentes devem ser monitorizados para reações adversas aos corticosteroides sistémicos. Este facto é de relevância clínica limitada em tratamentos de curta duração (1-2 semanas). Como o glicopirrónio é eliminado principalmente por via renal, podem ocorrer potencialmente interações medicamentosas com medicamentos que afetam os mecanismos de excreção renal. **Interações farmacodinâmicas:** *Outros antimuscarínicos e simpaticomiméticos:* A administração concomitante deste medicamento com outros medicamentos contendo anticolinérgicos e/ou agonistas β₂-adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas β₂-adrenérgicos inalados. A utilização concomitante de outros medicamentos beta-adrenérgicos pode ter efeitos potencialmente aditivos; portanto é necessário precaução quando outros medicamentos beta-adrenérgicos são prescritos concomitantemente com formoterol. *Hipocalcemia induzida por medicamentos:* A hipocalcemia pode aumentar a disposição para arritmias em doentes que são tratados com glicosídeos digitálicos. *Bloqueadores β-adrenérgicos:* Os bloqueadores β-adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito do formoterol. O uso simultâneo de bloqueadores β-adrenérgicos deve ser evitado, a não ser que o benefício esperado ultrapasse o risco potencial. Se forem necessários bloqueadores β-adrenérgicos, dá-se preferência a bloqueadores β-adrenérgicos cardioseletivos. *Outras interações farmacodinâmicas:* O tratamento concomitante com quinidina, disopiramida, procainamida, anti-histamínicos, inibidores da monoamina oxidase, antidepressivos tricíclicos e fenotiazinas pode prolongar o intervalo QT e aumentar o risco de arritmias ventriculares. Além disso, L-dopa, L-tirosina, oxitocina e álcool podem prejudicar a tolerância cardíaca aos beta2-simpaticomiméticos. O tratamento concomitante com inibidores da monoamina oxidase, incluindo medicamentos com propriedades semelhantes como furazolidona e procabazina, pode dar origem a reações hipertensivas. Existe um risco elevado de arritmias em doentes a receberem anestesia concomitante com hidrocarbonetos halogenados. **Fertilidade, gravidez e aleitamento:** A administração deste medicamento a mulheres grávidas só deve ser considerada se o benefício esperado para a mãe justificar o potencial risco para o feto. A administração deste medicamento a mulheres que estão a amamentar só deve ser considerada se o benefício esperado para a mãe for superior a qualquer possível risco para a criança. Considera-se pouco provável que este medicamento administrado na dose recomendada, afete a fertilidade no ser humano. **Efeitos indesejáveis:** *Frequentes:* Candidíase oral; Pneumonia; Hiperglicemia; Ansiedade; Insónia; Cefaleia; Palpitações; Disfonia; Tosse; Náuseas; Espasmos musculares; Infecção do trato urinário. *Pouco frequentes:* Hipersensibilidade; Depressão; Agitação; Irrequietude; Nervosismo; Tonturas; Tremor; Angina de peito; Taquicardia; Arritmias cardíacas (fibrilhação auricular, taquicardia supraventricular e extrasístoles); Irritação da garganta; Broncospasma; Boca seca; Equimose; Retenção urinária; Dor torácica. *Muito raros:* Sinais ou sintomas de efeitos sistémicos de glucocorticoides, por exemplo supressão suprarrenal; Comportamento anormal. *Desconhecido:* Angioedema; Visão turva; Cataratas; Glaucoma. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissao> (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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Obstrução crónica ao fluxo de ar atribuível à pobreza no estudo multinacional *Burden of Obstructive Lung Disease (BOLD)*

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RESUMO

A pobreza está fortemente associada à mortalidade por todas as causas e à doença pulmonar obstrutiva crónica (DPOC). Pouco se sabe sobre a contribuição da pobreza para a obstrução crónica ao fluxo de ar (CAO, do inglês *Chronic Airflow Obstruction*) - uma característica fundamental da DPOC. Utilizando dados transversais de um questionário baseado em bens para determinar a pobreza em 21 locais do estudo *Burden of Obstructive Lung Disease*, estimámos o risco de CAO atribuível à pobreza. Até 6% da população com mais de 40 anos apresentava CAO atribuível à pobreza. Compreender a relação entre pobreza e a CAO pode sugerir formas de melhorar a saúde pulmonar, especialmente em países de baixos e médios rendimentos.

INTRODUCTION

Poverty is an important risk factor for chronic obstructive pulmonary disease (COPD) prevalence and mortality, particularly in low-income and middle-income countries (LMICs).¹ In a previous report of 12 Burden of Obstructive Lung Disease (BOLD) study sites, we found that this association is also true between spirometrically defined post-bronchodilator chronic airflow obstruction (CAO) and individual wealth defined from household assets.² Here, we extend the investigation of the association between CAO and poverty to 21 BOLD sites and assess the population impact of poverty on CAO using site-specific population attributable risk (PAR) estimates.

METHODS

Data on ownership of household assets were collected from 14 611 adults (≥ 40 years) from 21 sites of the population-based BOLD study, between March 2010 and December 2016 (online supplemental table S1). We calculated a wealth score (0–10) based on household assets to estimate each participant's household wealth (online supplemental methods figure S1). We defined poverty as a wealth score ≤ 7 .³ We assessed the association of poverty with the forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio and with CAO (FEV_1/FVC < lower limit of normal (LLN)).⁴ We used a Bayesian hierarchical model to account for the multi-level structure of the data (online supplemental methods).⁵ Identification of potential confounders was based on previous findings and graphically represented in directed acyclic diagrams prior to analysis (online supplemental methods). We adjusted for age and sex in the analysis of FEV_1/FVC (model 1, online supplemental figure S2a), but not in the analysis of CAO,

as age and sex are already accounted for by the LLN. We did not adjust for other risk factors in the main analysis as these were most likely on the causal pathway between poverty and CAO. However, in secondary analyses, we further adjusted for education (model 2, online supplemental figure S2b), and for smoking pack-years, exposure to a dusty job, passive smoking, body mass index (BMI), childhood hospitalisation due to respiratory infection, family history of respiratory disease and history of tuberculosis (model 3, online supplemental figure S2c). These analyses were repeated using wealth score as a continuous measure.

We estimated the site-specific PAR of CAO attributable to poverty in all sites, except for Saudi Arabia (Riyadh), where the prevalence of poverty was 0. PAR estimates are reported with a 95% credible interval (95% CrI).

RESULTS

The pleural effusion segmentation model (M1) is a cascaded two-step deep-learning model (figure 1A). The initial input patterns was negligible.

DISCUSSION

CAO prevalence ranged from 3.1% in Saudi Arabia (Riyadh) to 16.4% in India (Kashmir) (online supplemental table S2). The mean wealth score was 6.3, ranging from just below 1 in Malawi (Chikwawa) to almost 10 in Saudi Arabia (Riyadh). The overall prevalence of poverty was 55%, with almost 100% in Malawi (Chikwawa). The prevalence of poverty was consistently high in LMICs (online supplemental table S2).

Per each unit increase in wealth score, the FEV_1/FVC increases by 0.30% (95% CrI 0.19% to 0.41%) and the risk of CAO is reduced by 11% (relative risk (RR)=0.89; 95% CrI 0.86 to 0.92) (table 1, main model). Using wealth score as a binary variable to define poverty, poorer individuals had on average 1.19% lower FEV_1/FVC (95% CrI –1.61% to –0.77%) and 57% greater risk of CAO (RR=1.57; 95% CrI 1.32 to 1.87), compared with wealthier individuals (table 1). In the secondary analysis, further adjusting for education (table 1, model 2) and for all other considered potential confounders (online supplemental table S3, model 3) did not change the association of wealth score or poverty with either FEV_1/FVC or CAO. There was no substantial heterogeneity across sites in the associations of wealth score or poverty with either FEV_1/FVC or CAO (online supplemental figures S3–S6).

The highest PAR for CAO due to poverty was in India (Kashmir) (PAR=6.1%; 95% CrI 3.65%



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Table 1 Association of wealth score and poverty with FEV₁/FVC (%) and chronic airflow obstruction (CAO)

Outcome variable	FEV ₁ /FVC (%)		CAO (FEV ₁ /FVC<LLN)	
	Model 1 (main model)	Model 2	Model 1 (main model)	Model 2
Variable	Coeff. (95% CrI)	Coeff. (95% CrI)	RR (95% CrI)	RR (95% CrI)
Wealth score	0.30 (0.19 to 0.41)	0.26 (0.16 to 0.36)	0.89 (0.86 to 0.92)	0.93 (0.89 to 0.96)
Poverty	−1.19 (−1.61 to −0.77)	−1.03 (−1.42 to −0.63)	1.57 (1.32 to 1.87)	1.34 (1.12 to 1.61)

Wealth score: calculated from ownership of a range of assets. Poverty: defined as a wealth score ≤7. Model 1 (main model) accounts for age and sex. Model 2 accounts for age, sex and education (education: the highest level of education completed). CAO, chronic airflow obstruction; 95% CrI, 95% credible interval; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; LLN, lower limit of normal.

to 8.59%) and the lowest in Malaysia (Penang) (PAR=0.16%, 95% CrI 0.03% to 0.41%) (model 1, online supplemental table S4). PAR estimates were inversely related to the wealth score (figure 1). The PAR results from models 2 and 3 are reported in online supplemental figure S7.

DISCUSSION

We have confirmed the association between poverty and CAO previously found in a subset of our BOLD study,² and we have shown that up to 6% of the population have CAO attributable to poverty.

Our results are consistent with findings reported by Grigsby et al using data from LMICs, where they used monthly household income as a proxy measure for poverty.⁶ Raju et al have also observed an association between self-reported COPD and household income in the USA.⁷ Previous findings of the BOLD study suggest that poor education, an indicator of socioeconomic deprivation, is the second most important risk factor for CAO after smoking.⁵ Using ecological data from the Global Burden of Disease study, we have previously reported a strong association between COPD mortality and poverty defined by Gross National Income per capita.⁸

The reduction in the RR observed in our secondary analyses adjusting for education and, subsequently, for other risk factors, including low BMI, is possibly due to the mediating effect of these factors, with adjustment for them leading to the underestimation of the impact of poverty on CAO.

The association between poverty and CAO could be due to limited access to healthcare services, poor nutrition, altered foetal programming during gestation, low birth weight, poor living conditions, overcrowding and water supply/sanitation for poorer people, particularly in LMICs.⁹

We did not adjust for solid fuel use because this was not associated with CAO in the BOLD study.¹⁰ Although meta-analyses have been interpreted as showing an association between airflow obstruction and solid fuel use, including for instance that of Smith et al,¹¹ they show very high heterogeneity across studies (I² between 67% and 98%) and strong evidence of publication bias, thus not supporting a causal association.

One of the strengths of BOLD is the use of a standardised protocol across study sites. Spirometry was performed post-bronchodilator, and its quality was assured with rigorous training and regular checks of all lung function curves.

Poverty is not a one-dimensional concept and understanding the nature of its relationship with CAO requires further investigation. The observed reduction of RR when adjusting for education suggests that education may partly mediate the effects of poverty on lung health. Nevertheless, the association with poverty is clear and suggests that poverty reduction itself is still important.

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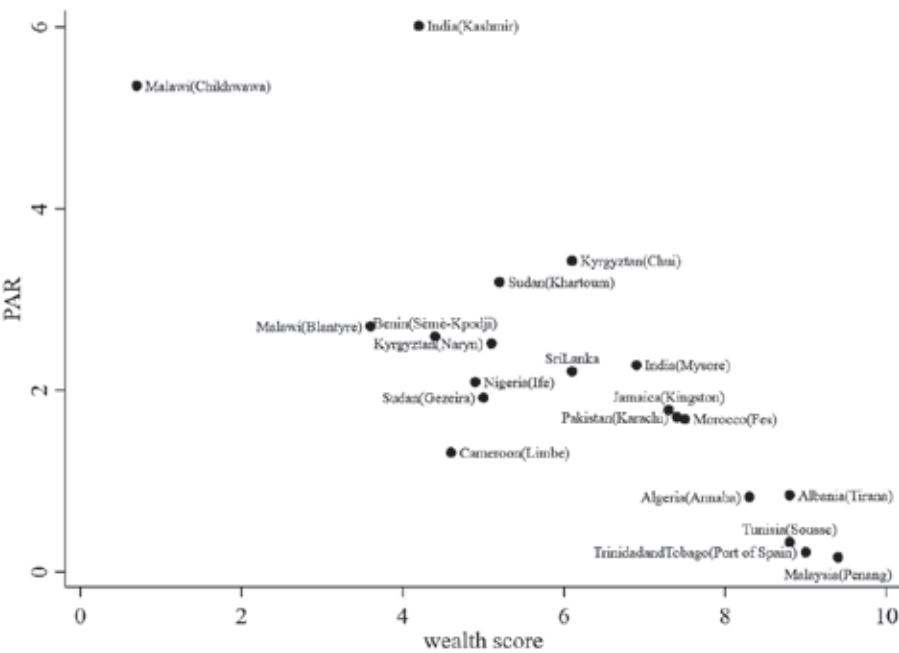


Figure 1 PAR for CAO due to poverty against wealth score. CAO, chronic airflow obstruction; PAR, population attributable risk.



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REFERENCES

1. Burney P, Kato B, Janson C, et al. Chronic obstructive pulmonary disease mortality and prevalence: the associations with smoking and poverty--a BOLD analysis. *Thorax* 2014;69:869–70.
2. Townend J, Minelli C, Mortimer K, et al. The association between chronic airflow obstruction and poverty in 12 sites of the multinational BOLD study. *Eur Respir J* 2017;49:1601880.
3. Townend J, Minelli C, Harrabi I, et al. Development of an international scale of socio-economic position based on household assets. *Emerg Themes Epidemiol* 2015;12:13.
4. Kiefer EM, Hankinson JL, Barr RG. Similar relation of age and height to lung function among whites, African Americans, and hispanics. *Am J Epidemiol* 2011;173:376–87.
5. Burney P, Patel J, Minelli C, et al. Prevalence and population-attributable risk for chronic airflow obstruction in a large multinational study. *Am J Respir Crit Care Med* 2021;203:1353–65.
6. Grigsby M, Siddharthan T, Chowdhury MA, et al. Socioeconomic status and COPD among Low- and middle-income countries. *Int J Chron Obstruct Pulmon Dis* 2016;11:2497–507.
7. Raju S, Keet CA, McCormack MC. Reply to: we are rural residence and poverty independent risk factors for chronic obstructive pulmonary disease in the United States? *Am J Respir Crit Care Med* 2019;200:520.
8. Burney PGJ, Patel J, Newson R, et al. Global and regional trends in COPD mortality, 1990–2010. *Eur Respir J* 2015;45:1239–47.
9. 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.
10. Amaral AFS, Patel J, Kato BS, et al. Airflow obstruction and use of solid fuels for cooking or heating: BOLD results. *Am J Respir Crit Care Med* 2018;197:595–610.
11. Smith KR, Bruce N, Balakrishnan K, et al. Millions dead: how do we know and what does it mean? methods used in the comparative risk assessment of household air pollution. *Annu Rev Public Health* 2014;35:185–206.

Efeitos tóxicos e de dependência da nicotina em crianças e adolescentes: estamos a caminhar inconscientemente para uma catástrofe de saúde pública?

Jonathan Coutts,¹ Ross John

Livingston FC, uma equipa do meio da tabela da primeira divisão escocesa, anunciou um novo acordo de patrocínio. Este facto pode parecer de pouco interesse para os pediatras do Reino Unido, mas trata-se da mais recente relação comercial entre o desporto e a indústria do vaping. O Reino Unido trabalhou arduamente para reduzir a exposição das crianças ao tabaco de combustão e aos seus subprodutos tóxicos, como a nicotina. Desde a década de 1960, o consumo de cigarros na adolescência tem vindo a diminuir constantemente através de uma campanha que chama a atenção para os efeitos negativos para a saúde, proibindo a publicidade, o consumo em espaços públicos, aumentando a idade legal e limitando o acesso às lojas. O aumento alarmante, de 3% para 43%, do número de adolescentes que usam cigarros eletrónicos/vaping (2011-2018) inverteu efetivamente grande parte deste trabalho para eliminar a exposição à nicotina e a dependência. No Reino Unido, a abordagem e a atual legislação relativas aos produtos de vaping baseiam-se no pressuposto de que são mais seguros do que o tabaco de combustão e oferecem redução de danos aos toxicodependentes. Neste artigo, defendemos a aplicação de uma legislação semelhante à que se aplica a outros dispositivos de libertação de nicotina aos produtos de vaping, devido às preocupações com o seu perfil de segurança e aos potenciais danos para as crianças antes e depois do nascimento.

TODA A GENTE SABE QUE O VAPING É SEGURO, CERTO?

Nutt *et al* referiram que os cigarros eletrónicos são “95% mais seguros” do que os cigarros normais, o que é frequentemente citado em documentos governamentais e nos principais meios de comunicação social.¹ Esta conclusão dramática não se baseou numa análise científica das evidências publicadas, mas na participação de 12 pessoas convidadas num processo Delphi. Duas delas tinham ligações financeiras com a indústria de vaping (não declarada por uma das pessoas) e, em vez de restringir o processo às preocupações com a saúde causadas pelos diferentes sistemas de nicotina, os “danos” comparados incluíam o contrabando, a desflorestação, a redução das terras aráveis e a perturbação da coesão social. A sua própria conclusão refere que “uma limitação deste estudo é a falta de dados concretos sobre os danos causados pela maioria dos produtos na

maioria dos critérios”. Apesar da falta de rigor científico e da possível contaminação das suas recomendações pelos interesses comerciais, a mensagem “95% mais seguro” continua a ser referenciada em documentos aprovados por organizações profissionais, como um relatório da *Public Health England* de 2015 e o documento do *Royal College of Physicians* (RCP) de 2016 “*Nicotine without smoke*”.²

Concordamos que os cigarros eletrónicos não contêm alguns produtos químicos tóxicos que são inalados com os cigarros tradicionais, mas a maioria dos produtos contém nicotina, muitas vezes em níveis alarmantemente elevados. A nicotina é altamente viciante e, apesar da opinião contrária partilhada por alguns profissionais de saúde, não é inofensiva.

OS EFEITOS NOCIVOS DA NICOTINA NO FETO

Os efeitos nocivos do tabagismo materno sobre o feto em desenvolvimento encontram-se bem descritos. Tornou-se claro que as consequências adversas do tabagismo materno devem-se, em parte, à toxicidade da nicotina.³ A investigação sobre fetos humanos expostos a produtos de nicotina do tabaco não combustível, como o rapé, animais expostos apenas à nicotina e a investigação biológica sobre os efeitos celulares da nicotina revelam resultados que vão desde uma diminuição de crescimento, um desenvolvimento pulmonar e cerebral fetal comprometido e um possível aumento da síndrome de morte súbita infantil. Os serviços de maternidade disponibilizam recursos anti-tabagismo para que as mães possam reduzir ou deixar de fumar, mas uma mãe preocupada pode ser influenciada pela mensagem “95% seguro” e mudar simplesmente para os cigarros eletrónicos durante a gravidez, não conseguindo reduzir os efeitos tóxicos para o feto decorrentes da exposição contínua à nicotina.

LESÕES PULMONARES AGUDAS E DE LONGA DURAÇÃO

A lesão pulmonar associada à utilização de cigarros eletrónicos ou vaping (do inglês: *EVALI: E-cigarette, or vaping, product use-associated lung injury*) é uma síndrome caracterizada por uma reação inflamatória intensa que resulta em insuficiência respiratória. Os estudos epidemiológicos e de toxicidade são claros quanto ao facto de os cigarros eletrónicos provocarem danos significativos para a saúde pulmonar a curto prazo. Os dados dos Centros de Controlo e Prevenção de Doenças revelam que, até à data, foram hospitalizados 2558 doentes com EVALI não fatal e 60 doentes com um desfecho fatal.⁴ Embora seja verdade que a maioria das fatalidades foi associada a líquidos com tetrahidrocanabinol, cerca de um terço eram produtos que continham apenas nicoti-

na. Estão a ser recolhidos cada vez mais dados longitudinais que demonstram consequências a longo prazo para a saúde. Foram necessários quase 50 anos para que o mundo da medicina se apercebesse, ou reconhecesse, a relação entre o tabagismo e a doença pulmonar obstrutiva crónica/câncer do pulmão, pelo que devemos proceder com cautela. Os estudos já demonstraram que o vaping pode causar inflamação pulmonar, stresse oxidativo que conduz a danos epiteliais e necrose, hiper-actividade das vias respiratórias e alteração das defesas do hospedeiro.

ADOLESCENTES E COMPORTAMENTO EM RELAÇÃO AO VAPING

O cérebro do adolescente é um órgão em desenvolvimento e, por conseguinte, vulnerável às toxinas.⁵ A exposição à nicotina pode ter consequências a longo prazo, incluindo um efeito inibitório sobre a conectividade neuronal (que ocorre rapidamente durante a adolescência), o que conduz a uma diminuição da memória e da atenção. Os adolescentes são mais vulneráveis ao desenvolvimento da dependência, especialmente da nicotina, e a abstinência pode aumentar a morbidade psicológica e psiquiátrica neste grupo vulnerável. A exposição à nicotina pode estar associada a taxas mais elevadas de consumo abusivo de outras substâncias, como o canábis e o álcool.

QUANTAS CRIANÇAS PRATICAM VAPING E QUAIS OS PRODUTOS QUE CONSOMEM?

Desde 2014, os cigarros eletrónicos têm sido o tipo de produto de nicotina mais popular utilizado pelos adolescentes nos EUA.⁶ Em 2018, 43% dos estudantes do ensino secundário tinham experimentado vaping, quase mais 20% comparativamente aos cigarros tradicionais. Embora a maioria afirme utilizar e-liquidos que contêm apenas aromas, 99% dos e-liquidos vendidos contêm nicotina. Cerca de um terço dos jovens utilizadores de cigarros eletrónicos modificaram os seus dispositivos para vaporizar óleos potentes à base de canábis. É também evidente que os vapores emitidos não são benignos, como muitos referem, uma vez que contêm metais pesados e substâncias cancerígenas, embora com um nível inferior ao dos produtos do tabaco de combustão.

CONSEQUÊNCIAS INDESEJADAS

O conceito inicial dos cigarros eletrónicos, como ajuda à cessação do tabagismo para adultos que consomem cigarros há muito tempo, evoluiu rapidamente para o mercado direcionado para os jovens, sendo o vaping atualmente três vezes mais comum nos adolescentes do que nos adultos mais velhos. A ideia de que estes produtos são atualmente comercializados como dispositivos médicos destinados a pôr termo à dependência da nicotina é completamente errada. Ao contrário dos produtos tradicionais do tabaco, cuja publicidade é proibida, há cada vez mais equipas desportivas e estádios a serem patrocinados por empresas de vaping. O atual design e marketing dos produtos vaping transformaram o consumo de nicotina pelos jovens. A publicidade agressiva nos meios de comunicação social, a

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baixa percepção de risco e os novos e apelativos designs ajudam a alimentar o desejo de fazer parte da “comunidade vaping”. Parece que todas as publicações sobre vaping, incluindo o documento do RCP de 2016, apresentam uma fotografia de uma pessoa jovem, muitas vezes vestida de forma elegante e profissional, que aprecia claramente o produto. Não há espaço para uma ilustração de um fumador compulsivo idoso com DPOC a tentar reduzir os danos causados por uma vida inteira a consumir tabaco. A imagem da vida no “Planet of the Vapes” é de tranquilidade e “cool”, mas ignora-se a realidade da toxicidade desconhecida e dos resultados a longo prazo.

QUAL O DEVER DOS PEDIATRAS?

As novas evidências de que o vaping é perigoso, de que os cigarros eletrônicos aumentaram o número de jovens viciados em nicotina e de que os jovens que utilizam cigarros eletrônicos têm maior probabilidade de fumar cigarros convencionais devem ser

motivo de grande alarme. Talvez o mais preocupante seja o facto de a dupla utilização ser comum, ainda mais prejudicial, e contrariar a finalidade destes dispositivos como “ajuda à cessação tabágica”. Atualmente, a comunidade médica está a fazer o trabalho dos departamentos de marketing das empresas de vaping, ao minimizar os riscos para a saúde e promover a sua aceitação como a nova forma de dispositivo de dependência da nicotina. Propomos uma regulamentação muito mais rigorosa em matéria de venda e comercialização de produtos de vaping, juntamente com o desenvolvimento de uma mensagem educativa, clínica e de saúde pública eficaz e clara que aborde esta nova epidemia de dependência da nicotina em crianças e jovens.

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REFERÊNCIAS

- 1 Nutt DJ, Phillips LD, Balfour D, et al. Estimating the harms of nicotine-containing products using the MCDA approach. Eur Addict Res 2014;20:218–25.
- 2 Royal College of Physicians. Nicotine without smoke: tobacco harm reduction. London RCP; 2016.
- 3 England LJ, Bunnell RE, Pechacek TF, et al. Nicotine and the developing human: a neglected element in the electronic cigarette debate. Am J Prev Med 2015;49:286–93.
- 4 Werner AK, Koumans EH, Chatham-Stephens K, et al. Hospitalizations and deaths associated with EVALI. N Engl J Med 2020;382:1589–98.
- 5 Chadi N, Hadland SE, Harris SK. Understanding the implications of the “vaping epidemic” among adolescents and young adults: A call for action. Subst Abuse 2019;40:7–10.
- 6 Farzal Z, Perry MF, Yarbrough WG, et al. The adolescent Vaping epidemic in the United States—How it happened and where we go from here. JAMA Otolaryngol Head Neck Surg 2019;145:885–6.

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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, controle de sintomas, qualidade de vida e redução de exacerbações vs terapêuticas padrão. 2. Gessner C, et al. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: A randomised, Phase IIIb, non-inferiority study (ARGON). Respir Med. 2020 Aug-Sep;170:106021. 3. Kerstjens HAM, et al. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. Lancet Respir Med. 2020 Oct;8(10):1000-1012. 4. EPAR: European public assessment report. https://www.ema.europa.eu/en/documents/assessment-report/zimbus-breezhaler-epar-public-assessment-report_en.pdf; consultado em 21/05/2021. LABA: Agonista Beta2 de longa duração de ação; LAMA: antagonista muscarínico de longa duração de ação; ICS: corticosteroides inalados.

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

NOTA: Antes de prescrever consulte o RCM do medicamento. APRESENTAÇÃO: Pó para inalação, cápsula (pó para inalação). Cada cápsula contém 150 microgramas de indacaterol, 50 microgramas de glicopirrônio e 160 microgramas de furoato de mometasona. Cada dose libertada (a dose libertada através do aplicador bucal do inalador) contém 114 microgramas de indacaterol (na forma de acetato), 8 microgramas de brometo de glicopirrônio equivalente a 46 microgramas de glicopirrônio e 136 microgramas de furoato de mometasona. **Excipiente(s) com efeito conhecido:** Cada cápsula contém 25 mg de lactose mono-hidratada. **INDICAÇÕES:** Zimbus Breezhaler está indicado como terapêutica de manutenção da asma em doentes adultos não controlados adequadamente com uma associação de um agonista beta₂ de ação prolongada e uma dose alta de corticosteroide inalado em regime de manutenção que experimentaram uma ou mais exacerbações da asma no ano anterior. **POSOLOGIA: Adultos:** A dose recomendada é uma cápsula inalada uma vez por dia. A dose máxima recomendada é de 114 µg/46 µg/136 µg uma vez por dia. **Doentes pediátricos (< 18 anos):** Não recomendado em doentes com menos de 18 anos de idade. **Populações especiais: População idosa:** Não é necessário ajuste de dose em doentes idosos (65 anos de idade ou mais). **Doentes com insuficiência renal:** Não é necessário ajuste de dose em doentes com compromisso renal ligeiro a moderado. Deve ter-se precaução em doentes com compromisso renal grave ou doença renal terminal que necessitem de diálise. **Compromisso hepático:** Não é necessário ajuste de dose em doentes com compromisso hepático ligeiro a moderado. Não existem dados disponíveis sobre a utilização deste medicamento em doentes com compromisso hepático grave, como tal deve ser utilizado nestes doentes apenas se o benefício esperado superar o risco potencial. **Modo de administração:** Apenas para utilização por via inalatória. As cápsulas não podem ser engolidas. Os doentes que não sintam melhorias na sua respiração devem ser questionados se estão a engolir o medicamento em vez de o inalar. As cápsulas têm de ser administradas usando apenas o inalador Zimbus Breezhaler. O tratamento deve ser administrado à mesma hora do dia todos os dias. Pode ser administrado independentemente da hora do dia. Após a inalação, os doentes devem lavar a boca com água sem engolir. Se for omitida uma dose, esta deve ser tomada assim que possível. Os doentes devem ser instruídos a não tomarem mais do que uma dose por dia. As cápsulas de Zimbus Breezhaler devem ser sempre conservadas no blister para proteger da luz e humidade, e só podem ser removidas do blister imediatamente antes da utilização. **CONTRAINDICAÇÕES:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **ADVERTÊNCIAS/PRECAUÇÕES:** ♦ **Asma Aguda:** não deve ser utilizado para tratar sintomas agudos de asma, incluindo episódios agudos de broncospasma, para os quais é necessário um broncodilatador de curta ação. ♦ **Hipersensibilidade:** Se ocorrer uma reação de hipersensibilidade, Zimbus Breezhaler deve ser descontinuado imediatamente e deverá ser instituída terapêutica alternativa. ♦ **Broncospasma paradoxal:** Tal como com outra terapêutica inalatória, a administração deste medicamento pode resultar em broncospasma paradoxal, o qual pode colocar a vida em risco. Se tal ocorrer, o tratamento deve ser interrompido imediatamente e deverá ser instituída terapêutica alternativa. ♦ **Efeitos cardiovasculares:** Tal como outros medicamentos contendo agonistas adrenérgicos beta₂, este medicamento pode produzir um efeito cardiovascular clinicamente significativo em alguns doentes conforme avaliado através de aumentos na frequência cardíaca, pressão arterial e/ou sintomas, alterações do electrocardiograma (ECG). Este medicamento deve ser usado com precaução em doentes com patologias cardiovasculares (doença arterial coronária, enfarte agudo do miocárdio, arritmias cardíacas, hipertensão, suspeita ou confirmação de prolongamento do intervalo QT, distúrbios convulsivos ou tirotóxicose) e em doentes com resposta aumentada aos agonistas adrenérgicos beta₂. ♦ **Hipocalcemia:** Os agonistas adrenérgicos beta₂ podem causar uma hipocalcemia significativa em alguns doentes, o que potencialmente pode levar a reações adversas cardiovasculares. Em doentes com asma grave, a hipocalcemia pode ser potenciada pela hipoxia e pela terapêutica concomitante, o que pode aumentar a suscetibilidade a arritmias cardíacas. ♦ **Hiperglicemia:** A inalação de doses elevadas de agonistas adrenérgicos beta₂ e corticosteroides pode produzir um aumento da glicose plasmática. Nos doentes diabéticos, ao iniciar o tratamento, a glicose plasmática deve ser monitorizada mais cuidadosamente. ♦ **Efeitos anticolinérgicos:** Tal como com outros medicamentos anticolinérgicos, este medicamento deve ser utilizado com precaução em doentes com glaucoma de ângulo fechado ou retenção urinária. ♦ **Doentes com compromisso renal grave:** Nos doentes com compromisso renal grave (taxa de filtração glomerular estimada inferior a 30 ml/min/1,73 m²), incluindo aqueles com doença renal terminal que necessitam de diálise, deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. ♦ **Prevenção de infeções orofaríngeas:** De modo a reduzir o risco de infeção orofaríngea por *Candida albicans*, os doentes devem ser aconselhados a lavar a boca ou a gargarejar com água, sem a engolir, ou a lavar os dentes após 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 psicótica, 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 intraoculares). Doentes que apresentem sintomas como visão turva ou outros distúrbios visuais, devem ser considerados para encaminhamento a um oftalmologista para avaliação de possíveis causas dessas perturbações visuais, as quais podem incluir cataratas, glaucoma ou doenças raras como a coriorretinopatia central serosa (CRCS), que foram notificadas após o uso de corticosteroides sistémicos ou tópicos. Este medicamento deve ser administrado com precaução em doentes com tuberculose pulmonar ou em doentes com infeções crónicas ou não tratadas. ♦ **Gravidez:** Este medicamento deve ser utilizado durante a gravidez apenas se o benefício esperado para o doente justificar o potencial risco para o feto. ♦ **Amamentação:** Tem que ser tomada uma decisão sobre a descontinuação da amamentação ou a descontinuação/abstenção da terapêutica, tendo em conta o benefício da amamentação para a criança e o benefício da terapêutica para a mulher. ♦ **Trabalho de parto:** Como outros medicamentos contendo agonistas adrenérgicos beta₂, o indacaterol pode inibir o trabalho de parto devido a um efeito relaxante no músculo liso uterino. **INTERAÇÕES:** ♦ **Bloqueadores adrenérgicos beta:** este medicamento não deve ser administrado com bloqueadores adrenérgicos beta (incluindo gotas para os olhos) a menos que existam razões importantes para a sua utilização. ♦ **Medicamentos conhecidos por prolongarem o intervalo QTc:** este medicamento deve ser administrado com precaução a doentes que estejam a ser tratados com inibidores da monoamina oxidase, antidepressivos tricíclicos ou medicamentos conhecidos por prolongar o intervalo QT. ♦ **Tratamento hipocalcémico:** O tratamento hipocalcémico concomitante com derivados da metilxantina, esteróides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocalcémico dos agonistas adrenérgicos beta₂. ♦ **Interação com inibidores do CYP3A4 e da glicoproteína P:** A inibição do CYP3A4 e da glicoproteína P (gp-P) não tem impacto na segurança de doses terapêuticas de Zimbus Breezhaler. ♦ **Outros antimuscarínicos de ação prolongada e agonistas adrenérgicos beta:** de ação prolongada não foi estudada e não é recomendada. ♦ **Cimetidina ou outros inibidores do transporte de cationes 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, parestesia. ♦ **Pouco frequentes (≥0,1% a <1%):** hiperglicemia, cataratas, boca seca, erupção cutânea, prurido, disúria. Para mais informações, consultar o titular de autorização de introdução no mercado ou o representante local do titular de autorização de introdução no mercado. Medicamento sujeito a receita médica. **Escalação de comparticipação:** Escalão B. **Titular da AIM:** Novartis Europharm Limited. **Representante local:** Laboratório Medinfar - Produtos Farmacêuticos, S.A. - Rua Henrique de Paiva Couceiro, Nº 29, Venda Nova, 2700-451 Amadora Informações Essenciais Compatíveis com o Resumo das Características do Medicamento (ZIM_RCM20210422_IEC_v2).