

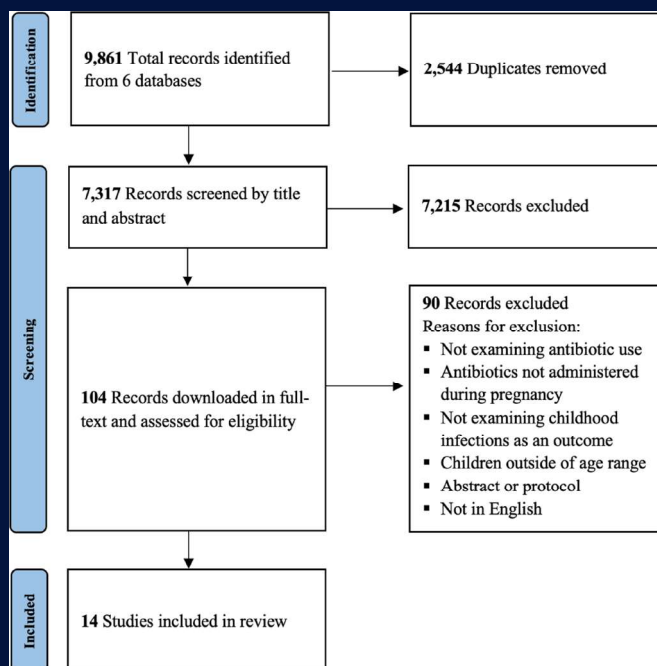
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Editorial

Com a aproximação do período estival, procedemos à apresentação de um novo número, contendo artigos selecionados das revistas *Thorax* e *Archives of Disease in Childhood*, com o objetivo de retomar o contacto com os nossos leitores.

Nesta edição da Revista, são apresentados vários artigos que poderão suscitar a atenção do leitor.

O primeiro, é um editorial que alerta para as lacunas no diagnóstico e desafios no tratamento da dispneia aguda em contextos com recursos limitados. Apesar dos esforços contínuos para melhorar a saúde em países com poucos recursos, persistem enormes desigualdades em termos de resultados de saúde e acesso aos cuidados de saúde. Os autores apelam à necessidade de se procurar compreender as diferenças nos percursos dos doentes em diferentes sistemas de saúde para se poder fornecer tratamentos de emergência adequados e cuidados de longo prazo.

O segundo artigo, é um estudo qualitativo que avalia a aceitabilidade e viabilidade de biomarcadores de inflamação eosinofílica das vias aéreas para a gestão da pieira em idade pré-escolar. A conclusão do estudo foi que os testes de picada no dedo, picada cutânea e FeNO são condicionalmente aceitáveis e viáveis na prática clínica para a avaliação da pieira em idade pré-escolar. No entanto, consideram ser necessária evidência da sua eficácia, comunicação empática entre pais e profissionais de saúde e demonstração de custo-efetividade para que o financiamento possa ser justificado.

No artigo seguinte, apresentamos uma revisão sistemática e meta-análise de ensaios clínicos aleatorizados sobre a utilização de brometo de ipratrópio inalado ou nebulizado em complemento ao tratamento de primeira linha com beta2 agonistas de curta duração inalados ou nebulizados e corticosteroides sistémicos na gestão das agudizações de asma. Esta revisão encontrou evidência de elevada certeza de que o BI nebulizado reduz a taxa de hospitalização. Dada a evidência atual e o perfil de segurança, o BI inalado ou nebulizado deverá eventualmente ser considerado como tratamento adicional na agudização de asma.

Por último, no artigo “O uso materno de antibióticos durante a gravidez aumenta o risco de infeções das vias aéreas na descendência: revisão sistemática e meta-análise” os autores concluem que a exposição pré-natal a antibióticos esteve associada a um aumento do risco de infeções na descendência, particularmente infeções das vias aéreas superiores. Estes resultados sugerem a necessidade de prescrição cautelosa de antibióticos durante a gravidez, embora não seja possível excluir totalmente fatores de confusão.

Com a aproximação do período de férias, desejamos a todos os nossos leitores que usufruam de um período de descanso reparador. Prometemos o regresso em breve com novas sugestões de artigos.

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Dispneia aguda em contextos com recursos limitados: lacunas no diagnóstico e desafios no tratamento

Van Le Hong,^{1,2} C Louise Thwaites^{1,2}

Apesar dos esforços contínuos para melhorar a saúde em países com poucos recursos, persistem enormes desigualdades em termos de resultados de saúde e acesso aos cuidados.¹⁻³ Um estudo recente de prevalência pontual, envolvendo doentes adultos internados em 180 hospitais de 22 países africanos, revelou que 1 em cada 8 preenchia critérios de doença crítica, sendo que aproximadamente metade apresentava insuficiência respiratória.⁴ Embora o oxigênio conste da lista de medicamentos essenciais da OMS há mais de 20 anos, cerca de metade dos doentes com insuficiência respiratória não estava a receber oxigenoterapia.⁵ Responder adequadamente a um fardo tão elevado constitui um enorme desafio, sobretudo porque os doentes críticos em contextos de baixos recursos são frequentemente tratados fora de unidades de cuidados intensivos.⁴

Melhorar os resultados globais em saúde exige simultaneamente melhor acesso e melhor qualidade dos cuidados. Cerca de 8 milhões de mortes ocorrem anualmente em países de baixo e médio rendimento devido a condições tratáveis.³ A melhoria da cobertura universal de saúde continua a ser uma ferramenta vital para aumentar o acesso, mas são necessárias medidas adicionais para enfrentar os 60% de mortes potencialmente evitáveis relacionadas com cuidados de má qualidade.⁶ Adaptar políticas de saúde, orientações terapêuticas e percursos do doente ao contexto local é essencial para alcançar resultados ótimos. Compreender esse contexto é, portanto, fundamental, mas frequentemente limitado pela escassez de dados.

Recentemente, Sulani e colaboradores rastream 24 724 doentes adultos em cinco unidades no Quênia, Malawi e Ruanda para hipoxemia (definida como saturação periférica de oxigênio (SpO₂) <90% ou administração de oxigênio suplementar).⁷ 7% dos doentes estavam hipoxêmicos à admissão. A causa mais comum atribuída à hipoxemia foi pneumonia aguda, seguida de insuficiência cardíaca e tuberculose (TB). Este estudo pragmático melhorou significativamente a compreensão da insuficiência respiratória na África subsaariana, destacando a importância da TB e da insuficiência cardíaca nesta população. Contudo, devido ao seu desenho pragmático, os investigadores dependeram dos diagnósticos registados nos

processos clínicos e não conseguiram incluir dados adicionais de comorbilidade, como o estado serológico para VIH.

Neste número da revista, Spencer aborda estas limitações e aprofunda a compreensão das causas de insuficiência respiratória na África subsaariana, através do rastreio sistemático de adultos com condições médicas agudas que se apresentavam com dispneia.⁸ Ao longo de três meses, 751 admissões adultas num hospital terciário e num hospital distrital no Malawi foram rastreadas prospectivamente para dispneia (definida como queixa de dispneia nos 7 dias anteriores, taquipneia, SpO₂ <94% ou administração de oxigênio suplementar). Foram incluídos 316 doentes que cumpriam a definição e submetidos a um conjunto padronizado de exames para identificar causas de dispneia e comorbilidades subjacentes. Esta abordagem permitiu combinar um método pragmático de inclusão com uma caracterização detalhada das causas subjacentes de dispneia.

A pneumonia foi a síndrome mais frequentemente identificada; contudo, menos de um terço dos casos teve confirmação microbiológica. Esta incapacidade de identificar rapidamente a etiologia da pneumonia é uma barreira comum ao tratamento adequado e atempado em países de baixo e médio rendimento, conduzindo ao uso inadequado de antimicrobianos e ao atraso na administração de antibióticos apropriados. As prioridades globais recentes da OMS para a investigação em resistência antimicrobiana incluem diagnósticos laboratoriais acessíveis, testes rápidos no ponto de cuidados e testes de suscetibilidade antimicrobiana à cabeceira do doente.⁹ Estas medidas representam um passo importante para melhorar a qualidade dos cuidados e os resultados da pneumonia em contextos com recursos limitados.

Entre os 36 casos de pneumonia com etiologia microbiológica confirmada, 58% (21/36) deviam-se a *Mycobacterium tuberculosis*, refletindo o elevado fardo da doença e a sua apresentação clínica heterogênea, tanto aguda como crónica. Embora um relatório recente indique uma diminuição da prevalência de TB pulmonar bacteriologicamente confirmada no Malawi,¹⁰ a TB continua a ser a principal causa infecciosa de admissões hospitalares de emergência. Mesmo com a implementação de rastreio direcionado em pessoas que vivem com VIH, a mortalidade intra-hospitalar permanece elevada.¹¹

Apesar da baixa prevalência estimada de TB multirresistente no Malawi — 2,27% (intervalo de incerteza (UI) 1,44–3,48%) em novos casos e 6,02% (UI 3,75–9,50%)

em casos previamente tratados — e de uma taxa global de sucesso terapêutico de 88% para TB suscetível,¹² a mortalidade associada à TB entre doentes que se apresentam com dispneia continua inaceitavelmente elevada. Para responder à necessidade crítica de diagnóstico precoce, a integração de tecnologias diagnósticas inovadoras e acessíveis demonstrou ser eficaz na deteção de casos, especialmente em contextos de poucos recursos e elevada carga de doença.¹³ Os resultados apresentados nesta revista reforçam a necessidade urgente de aplicar tecnologias que melhorem o diagnóstico preciso e atempado e reduzam atrasos no início do tratamento.

O estudo também destaca a importância da multimorbilidade e da coexistência de múltiplas patologias que podem contribuir para a hospitalização de emergência por dispneia. Estes dados são essenciais para orientar tanto a prática clínica como as políticas de saúde numa ampla variedade de condições. Os resultados respondem ao apelo recente da Federação Mundial do Coração para aumentar a disponibilidade de dados provenientes de países de baixo e médio rendimento, de forma a enfrentar a crescente desigualdade nos resultados das doenças cardiovasculares — apesar de estas serem a principal causa de morte global, os maiores avanços concentram-se em populações de alto rendimento.¹⁴

Compreender as diferenças nos percursos dos doentes em diferentes sistemas de saúde é essencial para fornecer tratamentos de emergência adequados e cuidados de longo prazo. Uma grande força deste estudo é a disponibilidade de resultados a longo prazo para quase todos os participantes. Os resultados mostram que a mortalidade ao fim de 1 ano é quase o dobro da mortalidade à alta hospitalar. Nos últimos anos, têm sido feitos esforços significativos para implementar tratamentos imediatos que salvam vidas ao nível hospitalar, com sucessos notáveis em áreas como a disponibilização de oxigênio e a administração atempada de antibióticos na sépsis.^{15,16}

Responder ao desafio das doenças crónicas e da multimorbilidade exigirá intervenções multidisciplinares complexas, mas surgem cada vez mais oportunidades para utilizar novas tecnologias, como inteligência artificial ou telemedicina, em abordagens inovadoras de cuidados. Uma melhor compreensão dos sintomas comuns e das apresentações de um vasto conjunto de condições subjacentes permite descobrir novas vias de prevenção ou intervenção e facilita cuidados de saúde centrados no doente.

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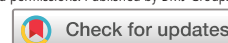
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Aceitabilidade e viabilidade de biomarcadores de inflamação eosinofílica das vias aéreas para a gestão da pieira em idade pré-escolar: um estudo qualitativo

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RESUMO

Objetivo Este estudo teve como objetivo analisar se os testes de biomarcadores — picada no dedo, prova de picada cutânea e FeNO offline (fração de óxido nítrico exalado) — são aceitáveis e viáveis como orientação para decisões terapêuticas, combinando de forma inédita as perspectivas de pais de crianças em idade pré-escolar com pieira e de profissionais de saúde (HCPs) a trabalhar em cuidados de saúde primários do National Health Service (NHS).

Desenho Estudo qualitativo baseado em entrevistas. Utilizou-se amostragem por critérios para recrutar 16 pais de 16 famílias e amostragem por conveniência para recrutar 16 profissionais de saúde (médicos e enfermeiros) de 14 unidades de cuidados primários do NHS. Os dados qualitativos foram recolhidos através de entrevistas individuais online e grupos focais (FGs), realizados via Microsoft Teams, transcritos e analisados tematicamente no software NVivo.

Resultados Os pais descreveram os testes de biomarcadores como aceitáveis quando acompanhados por evidência de eficácia e comunicação empática por parte dos profissionais de saúde. A prova de picada cutânea foi o teste preferido pelos pais, por ajudar a minimizar exposições a alergénios. Os profissionais de saúde preferiram a picada no dedo e o teste FeNO com respiração tidal, devido à maior familiaridade e viabilidade nos cuidados primários. Foram identificadas barreiras à implementação, incluindo limitações de tempo, custo dos dispositivos e necessidade de formação para realizar os testes. Ambos os grupos concordaram que a frequência dos testes deve depender da gravidade da pieira. Por fim, um futuro ensaio clínico aleatorizado que avalie se uma abordagem baseada em biomarcadores é superior à abordagem atual baseada em sintomas foi considerado aceitável e viável.

Conclusão Os testes de picada no dedo, picada cutânea e FeNO são condicionalmente aceitáveis e viáveis na prática clínica para a pieira em idade pré-escolar. No entanto, é necessária evidência da sua eficácia, comunicação empática entre pais e profissionais de saúde e demonstração de custo-efetividade para justificar financiamento pelo NHS.

INTRODUCTION

Wheeze in preschool children is common and distressing, leading to impaired quality of life, repeated hospital admissions and family stress.^{1,2} In the UK, its prevalence in 2017 was 7.7%. Although overall prevalence declined between 2008 and 2018, wheeze attack rates increased significantly, with preschoolers experiencing the highest attack rates compared with older children.^{3,4}

Currently, there are no clinical tests to guide treatment decisions in preschool wheeze; management relies on medical history and symptom reporting. Some children have underlying eosinophilic airway inflammation and respond well to inhaled corticosteroids (ICS), whereas others do not.⁵ Understanding the underlying airway pathology could enable better-targeted therapies and improve outcomes.⁵ The 2024 European Respiratory Society (ERS) Task Force suggested biomarkers like blood eosinophil

Key messages

What is known about this topic

- Preschool wheeze is common, yet its management is usually based on symptoms rather than biomarkers.
- While abnormal blood eosinophil count, atopic sensitisation and fractional exhaled nitric oxide (FeNO) tidal breathing may be associated with future wheeze attacks and act as a guide to inhaled corticosteroid treatment in preschool children, their use in primary care lacks evidence on feasibility and acceptability.

What this study adds

- This study found that parents and healthcare professionals consider these biomarker tests acceptable and feasible if supported by evidence of effectiveness, and clear communication between parents and healthcare professionals.

How this study might affect research practice or policy

- Findings indicate that biomarker-guided management could be implemented in a randomised controlled trial of preschool wheeze care, but challenges like time, cost and training must be addressed.

count (BEC) and allergic sensitisation could help identify children more likely to respond to ICS.⁶ However, before biomarker-based strategies can be implemented, their acceptability to parents and feasibility in clinical practice must be assessed.

Sekhon et al outlined that acceptability depends on perceived effectiveness, burden, ethics, understanding and practicality.⁷ Few studies have explored the acceptability and feasibility of finger-prick blood sampling, skin-prick testing (SPT) and fractional exhaled nitric oxide (FeNO) tidal breathing (offline) testing in preschool children with wheeze.

This study uniquely combined parent and HCP perspectives on the acceptability and feasibility of finger-prick, SPT and FeNO tidal breathing (offline) testing in NHS primary care settings, thereby supporting future personalised treatment approaches for preschool wheeze and informing the design of a planned randomised controlled trial of preschool wheeze biomarker-based treatment.

METHODS

Study design

The TAILOR study was a pragmatic, observational study on preschool wheeze (November 2021–



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December 2023). We examined whether BEC, allergic sensitisation and FeNO alone or in any combination were associated with future wheeze attacks and ICS treatment. Families were approached in NHS primary and secondary care settings and given 7 days to decide on participation after receiving study information. Informed consent was obtained before baseline testing, which included finger-prick BEC test, SPT for allergic sensitisation and FeNO offline testing. A second optional biomarker testing occurred 3–4 months following baseline. Children were followed up for 1 year to record wheeze attack occurrence. At the end of follow-up, a focus group (FG) or one-to-one interviews with one parent per family and HCPs was conducted to collect their views on the acceptability and feasibility of biomarker-guided ICS treatment.

Sampling and recruitment

Criterion sampling was used to recruit parents who had taken part in biomarker sampling within the TAILOR study. All parents were invited by AP via telephone to participate in FG or interviews. Convenience sampling was used to recruit HCPs (general practitioners (GPs) and nurses) working in NHS via email. Practices involved in identification and approach of eligible families in the main study were contacted by AP, while the Thames Valley and South Midlands National Institute for Health and Care Research (NIHR) network and the East Midlands Research Delivery Network (RDN) approached all practices in their network. Written informed consent was obtained from all participants.

Data collection

Topic guides for FG and interviews were developed based on a literature review^{7–12}; they were reviewed by the study team before use, but not formally piloted. Open-ended questions encouraged participants to share views freely. Topic guides' core structure remained consistent, but discussions were iteratively adapted using earlier FG insights to explore broader relevance with later participants. Interviews and FG were conducted online via MS Teams by AP (male pharmacist, PhD candidate), with a second researcher present for notetaking. Sessions were audio-recorded, transcribed and pseudonymised by AP. Transcripts were not returned to participants for comments/corrections. No remuneration/voucher was provided for their participation.

Qualitative data analysis

Thematic analysis was performed within the NVivo V.14 software. Coding was conducted by AP and GL (female postdoctoral researcher, qualitative experience) to explore differences or similarities and ensure preconceptions did not unduly affect analyses. Analysis followed Braun and Clarke's iterative process,¹³ actively seeking contrasting views to ensure a balanced interpretation. Themes were derived from the data. Pragmatism was used as the philosophical paradigm, while an inductive approach was used to develop inferences.¹⁴ Parent themes were derived from FG discussions, whereas HCP themes were drawn from one-to-one interviews and two FGs; individual interviews were often conducted to maximise participation given conflicting schedules.

RESULTS

Participants

Parents

Of the 95 families enrolled in the TAILOR study, 30 (31.6%) responded to telephone invitations to participate in qualitative interviews or FG discussions. Sixteen families (53.3%) attended FG, and five families (16.7%) would only accept participating in one-to-one interviews, but these were not invited as data saturation had already been reached from the focus groups. Nine families (30%) did not attend scheduled FG (figure 1). There were no differences in the clinical characteristics of children whose families did and did not participate in the FG discussions (table 1). Parents attending FG were all white, of whom 15 out of 16 (93.8%) were female, aged 32–53 years (children's age range: 20–63 months). There were three FGs with three parents and two with five and two parents, respectively, based on their availability.

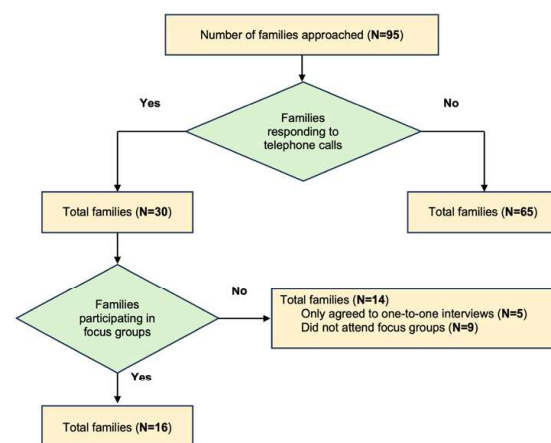


Figure 1 Recruitment and baseline testing flowchart.

Healthcare professionals

Sixteen HCPs (eight male) participated only in the qualitative component of the TAILOR study (table 2). The majority were GPs (n=14), while the remaining two participants were practice nurses. The sample included a broad range of professional experience (3–24 years) (table 2). HCPs were drawn from practices with varying number of patients registered, enabling capturing insights into the feasibility of biomarker testing across practices of differing sizes.

FG and one-to-one interviews lasted approximately 60 and 35 min, respectively, and there were no repeated interviews.

Thematic findings from parents' semistructured interviews

Analysis generated five themes, with illustrative quotations given in table 3.

Theme 1: providing evidence for usefulness of the biomarker tests

Parents expressed strong support for biomarker testing, conditional on evidence demonstrating its efficacy in guiding ICS treatment decisions. Objective data-based therapies would reassure them compared with the current symptom-based approach. Preferences for testing frequency varied; parents of poorly controlled children favoured frequent monitoring, while parents of stable children preferred testing only when needed. However, some parents would accept any frequency if supported by evidence and clinical rationale.

Theme 2: demonstrating regard for parent and child feelings; giving clear answers or reassurance

Parents felt that doctors often failed to address their concerns and worries, thus would prefer more communicative HCPs who clearly explain their child's condition and any explanation regarding their treatment decisions. This would provide reassurance and reduce their anxiety. Objective biomarker measurements would strengthen-

Table 1 Difference between those who did and did not participate in the focus group discussions

Factor	Participated (N=16)	Did not participate (N=79)	P value
Age (months), median (range)	33 (20–63)	36 (13–71)	0.73
Male sex, n (%)	13 (81.3)	45 (57)	0.07
Prescribed inhaled corticosteroid at baseline, n (%)	8 (50)	33 (41.8)	0.55
Allergic sensitisation, n (%)	5 (31.3)	40 (50.6)	0.16
Blood eosinophil count (cells/ μ L), median (range)	500 (0–900)	400 (0–1400)	0.34
Fractional exhaled nitric oxide (ppb), median (range)	12.5 (6.5–14.5), N=3	6 (0–18.5), N=34	0.25
Experienced a wheeze attack, n (%)	13 (81.3)	56 (70.9)	0.4
Number of wheeze attacks in the year following baseline, median (range)	2 (0–9)	1 (0–8)	0.17

Table 2 Semistructured interview and focus group healthcare professionals' demographics

HCP ID	Occupation	Gender	Experience (years)*	Patients registered in practice†	Data source
GP1	Doctor	Male	18	10 268 (0–9 years old: 1021)	Focus group 1
GP2	Doctor	Female	7	10 268 (0–9 years old: 1021)	Focus group 1
GP3	Doctor	Female	18	16 631 (0–9 years old: 1521)	One-to-one interview
GP4	Doctor	Male	5	58 389 (0–9 years old: 4719)	One-to-one interview
GP5	Doctor	Female	24	9365 (0–9 years old: 758)	One-to-one interview
GP6	Doctor	Female	8	24 639 (0–9 years old: 2098)	Focus group 2
N1	Nurse	Female	17	24 639 (0–9 years old: 2098)	Focus group 2
GP7	Doctor	Male	8	11 729 (0–9 years old: 947)	One-to-one interview
GP8	Doctor	Female	18	5 317 (0–9 years old: 336)	One-to-one interview
GP9	Doctor	Male	18	11 317 (0–9 years old: 1008)	One-to-one interview
GP10	Doctor	Female	18	8596 (0–9 years old: 1146)	One-to-one interview
GP11	Doctor	Male	3	12 521 (0–9 years old: 1015)	One-to-one interview
GP12	Doctor	Female	18	11 836 (0–9 years old: 1174)	One-to-one interview
GP13	Doctor	Male	18	10 350 (0–9 years old: 967)	One-to-one interview
GP14	Doctor	Male	13	23 816 (0–9 years old: 1806)	One-to-one interview
N2	Nurse	Male	22	4305 (0–9 years old: 475)	One-to-one interview

*Years after registration as GP, as per the General Medical Council register³⁴ and years after registration as per the Nursing and Midwifery Council register.³⁵

†Obtained from the NHS Digital General Practice Data Hub.³⁶

GP, general practitioner; HCP, healthcare professionals; NHS, National Health Service.

en parents' trust in doctors' decisions, rather than the latter relying solely on children's symptoms and medical history.

Theme 3: parents' preferences across the available tests

Parents were eager to improve their child's health and quality of life. In this study, 9 out of 14 parents (64.3%) preferred SPT due to familiarity from prior experiences and the belief it can help identify a potential cause of wheeze, thus offering relief and a sense of action. While most parents preferred SPT, some favoured finger-prick and FeNO tests, although they did not describe why they preferred the finger-prick test.

Theme 4: factors affecting children's willingness to undergo testing

Parents highlighted several factors influencing children's acceptance of the three biomarker tests: (1) age (younger children struggle with the FeNO testing as they may not understand instructions); (2) previous biomarker test experiences (positive experiences enhance cooperation); (3) empathetic interaction by HCPs; (4) use of diversionary techniques (ie, toys, cartoons, stickers); (5) biomarker testing order (in this study, performing the FeNO test last may have reduced its acceptability due to fatigue or stress from the previous tests); and (6) clear instructions before testing (using videos and information sheets to prepare children performing these tests).

Theme 5: factors affecting willingness to take part in a future intervention study

Parents reported that participation in a future intervention study, comparing a biomarker-based approach to current methods to guide ICS treatment decisions and whether it is associated with reduced wheeze attacks, depends on children's wheeze condition and concerns about health safety. They also emphasised the importance of receiving the biomarker test results and clear explanation of treatment decisions. Follow-up questionnaires should be brief, use lay language and focus on relevant periods.

Thematic findings from HCPs' semistructured interviews

Analysis generated four themes, with illustrative quotations given in table 4.

Theme 1: feasibility requires parents' acceptance and children's cooperation

Parents may express concern when their child becomes upset during testing and may ask HCPs to stop. This may affect feasibility, as they could stop testing and prevent HCPs from obtaining the necessary measurements. Additionally, children's coopera-

tion is unpredictable and influenced by age. Respondents noted that younger children may better tolerate finger prick tests due to limited awareness but struggle with FeNO tests because they cannot follow instructions. Conversely, older children may perform FeNO tests more successfully but resist finger pricks due to greater awareness and negative past experiences.

Theme 2: practical, evidence-based, financial and clinical considerations for implementing biomarkers

HCPs find finger-prick and FeNO testing more feasible as they are quick, simple and provide objective results. However, younger children may struggle with FeNO testing. SPT was seen as less practical due to its invasiveness, time-consuming nature, training needs, perceived anaphylaxis risk and limited clinical value, as some respondents thought that allergen avoidance may be challenging for many families. HCPs would adopt biomarker tests only if supported by evidence predicting future wheeze attacks and ICS treatment response, and if endorsed by guidelines as with FeNO testing.^{15–17}

High device and their consumable costs currently limit implementation. Demonstrating that these biomarkers predict ICS treatment response is crucial to secure funding from healthcare bodies, ultimately enabling NHS implementation. Testing frequency should reflect wheeze severity, with poorly controlled children requiring frequent assessments. Consumable costs and time demands influence testing frequency since time-consuming or expensive tests can increase workload and healthcare costs for practices, respectively.

Theme 3: maximising efficiency to incorporate testing into practice

The short duration of GP appointments (10–15 min) makes it impractical to incorporate biomarker testing. Rather than proposing double appointments, HCPs suggested delegating healthcare assistants (HCAs) or nurses before the GP consultation, ensuring time efficiency and cost-effectiveness due to their lower staffing costs.

Theme 4: perceived barriers and facilitators for trial feasibility

HCPs emphasise that realistic recruitment targets, child safety and strong supporting evidence are essential for a future intervention study. Financial incentives would be crucial for participation. Research-active practices may be better equipped to meet study demands. Clear communication will be necessary to prevent parental bias towards intervention groups, ensuring both study arms are seen as providing equally valid care without influencing decisions.

Table 3 Thematic analysis from parents' focus group discussions

Providing evidence for usefulness of the biomarker tests.	There needs to be evidence that the thresholds used are predictive of ICS treatment response to make parents feel reassured.	"We didn't know if the brown inhaler was just a precautionary or whether he would be receptive to it, so with the tests we would feel better knowing that there is something that can be done for this."—P1 "I think medicine is quite generalised and not all treatments work for everybody. So, if there is a way of testing individuals' responses and saying, oh well, that shows us exactly what we need to do, then I think that's a good thing."—P5
	There needs to be evidence for biomarker testing frequency	"I think if the research showed that having it quarterly was beneficial and that things could change, I think as a parent you do what you can. And if they want to test them more regularly because it would be beneficial, then that is fine."—P1 "I'd be amenable to coming back once more in the year or however many more times you thought appropriate based on your findings."—P7
	Biomarker testing frequency is affected by the children's wheeze severity	"I think it would depend on how ill the child was. If it was (child's name) when he was born until the age of two years old, where he was going into hospital every couple of weeks, I'd be happy to have a testing every couple of weeks. But now he is a bit older and it's not so much an infrequent review every three, six months, whenever they personally needed."—P5 "I don't feel she needs testing that often now, because we are able to manage any wheeze she does experience."—P11
Demonstrating regard for parent and child feelings; giving clear answers or reassurance.	Parents want doctors to show that they care more about their concerns and worries	"So, one time (child's name) was taken from home by ambulance because of struggling with breathing, which was the worst part for me, but later having no interest from our GP that was a very bad experience, because as a parent you feel that there is no one to support you."—P6 "The hospital just sorts of saw him and that was it. I feel like the information was quite minimal to the point I've had to chase up the respiratory team myself and just go directly to the consultant we saw to ask for more information."—P7
	Parents appreciate getting an explanation of what is happening with their child	"In the UK, they don't do tests on the child, so medication is just thrown out like wildfire, really, depending on the symptoms. But is that the right treatment for the child? That's currently what happens in a child because they don't know what's wrong with them. So, you've got no test, they don't do any tests. The doctor just prescribes it based on how they're breathing, how sick they get, how much time they have the wheeze etc. That is the current life with the NHS."—P12 "We've had a lot of people say to us 'he should be fine', 'he does not have any problems', 'does not have any allergies'. Many people keep repeating this 'he'll grow out of it' or 'oh, it's this and he is not growing out of it'. I think the lack of knowledge that we get as parents when they're little is quite hard."—P16
Parents' preferences across the available tests.	Parents are more familiar with the skin-prick testing and can understand it better, which increases its acceptability	"I would place the allergy test as number one because I probably understood it the best."—P3 "I would say the favourite is probably the allergy testing because obviously that's something that we're aware of and can take forward."—P9
	Skin-prick test results help parents take measures to help their child	"Being referred for an allergy test as a kind of first point of call would give parents some satisfaction that they were doing something for their children."—P1 "It has definitely helped us in certain ways that we've, you know, we've changed our carpet in our house to wooden flooring, we've got air purifiers in the house now, we change bedding more often. These things kind of gave us, you know, more options for how to help him"—P15
Factors affecting children's willingness to undergo testing.	Younger children find it difficult to understand and perform the FeNO tidal breathing test	"I would place the balloon test last, just because my child was not 100% sure what to do with that one. It was a bit harder for him to get his head in the mask."—P3 "He hadn't quite grasped the concept of being able to blow. So, we struggled, but he didn't... it didn't upset him, it didn't bother him, so I think it's more on the age of a child and their development and skills that they have."—P3
	A previous positive or negative experience with biomarker tests increases and reduces their acceptability by children, respectively	"I think partly he didn't understand what he had to do with the balloon test, and he's had experiences in the past with other things coming near his mouth that have been negative for him, so I think maybe there's a bit of correlation."—P3 "They were trying to do some blood test in the hospital shortly before came to you to do the tests. So, that's why it was very difficult to convince him that it was not as painful as it was in the hospital."—P6 "(Child's name) responds quite well in those situations, and you made him feel extremely relaxed. I don't know if it's because over the last few years he's been to the hospital many times, has been in ambulances, has been to the doctors."—P7
	Distracting children with toys and cartoons when performing the tests increases their acceptability as children associate it with fun	"When we came to the hospital, and you had the toy with the bubbles. During this, there was lots of bubbles. That was lots of fun, which probably wasn't relevant to you to what you were trying to get from the visit, but definitely the bubble gun was our highlight."—P5 "(Child's name) seemed to enjoy it. It was a good plan having the kind of toys and they laptop with Paw Patrol on, it kind of distracted him because otherwise it could have been a bit problematic."—P10
	HCPs need to be patient with children, supportive and engaging.	"Coming in with a 3-year-old can be quite chaotic, but you made it really simple and easy for us and you were very understanding."—P4 "We felt that when we first came to you, you were really interactive with (child's name) and he was really comfortable with the whole process and I think he had been in hospital quite a lot and was getting quite anxious about it, but actually the experience was great, and he loved the bubble machine."—P16
	FeNO testing was performed last, and children may have not liked it because they were disturbed or tired from the previous two tests.	"From our experience, it was the last test my child did, and I think he got quite stressed out from the previous tests. Potentially doing the FeNO test first just because my child had got a bit stressed out by this skin prick test and I think he wasn't in sort of the most compliant mindset for the last test."—P3 "I think he struggled with the balloon test. I think he possibly got a bit bored by that point or something. I think the FeNO test was the least favourite."—P8
	Younger children who struggled with FeNO test would benefit from having a preparation or an exercise prior to the meeting so that they know how to exhale in the gas collection bag.	"Maybe some pre-information about what's coming, so that we could practise, or something could help. So, a video or a leaflet or an e-mail, saying we're going to have to practise blowing up a balloon."—P1 "I know that in the preparation for the appointment, it said quite what was going to happen, but if there was a way to know in advance, a way that we could have to potentially practice at home, so it wasn't so alien and that could have been helpful before the appointment."—P3

Continued

Table 3 Continued

Factors affecting willingness to take part in a future intervention study.	Participation in a future intervention study may be affected by child's condition.	"From the perspective of my own child, every time he gets a virus, he's got chest problems, which is why he's part of this study."—P2 "My child's condition would affect my judgement on whether or not to participate."—P3
	Parents are concerned that participation in the intervention study may lead to wheeze attacks and hospitalisations.	"Through the current approach, my child's condition is managed, I guess through the test approach it's an unknown. I don't know if it is a better way of managing it or not. I'm personally nervous of the changes to medication that would then result in more hospital admissions."—P3 "For him to be completely just based on results...I'm 50–50 about it. The steroid inhaler has been a game changer for him, and we haven't been in hospital...it's been a huge improvement. But it took us a couple of years to finally get what he needed."—P16
	Parent would like to have the tests results, explanation of the treatments suggested and justification why the treatment was given.	"I think it's apparent just being given that information in advance like you've gone, you've put your children through this, and they don't particularly enjoy the prick test and the blood test, but being able to walk away knowing you did it and you've had those results and especially the allergy one, I think it's quite important that you are given that information."—P1 "I would like to know the test results. I think there should be a meeting for parents to tell them more about different type of treatments which would be prescribed to our children, what kind of side effects they would have."—P6
	Parents like quick and simple questionnaires.	"The monthly questionnaires coming through, I was able to answer them quite quickly. The questions weren't too long."—P1 "The questionnaires weren't a problem; they were quite short and easy to fill in."—P8 "The questionnaire had quite short simple questions which was not time consuming and were to the point."—P9 "The questionnaires haven't been an issue; they've been quick and convenient."—P11

FeNO, fractional exhaled nitric oxide; HCP, healthcare professional; ICS, inhaled corticosteroid.

Similarities and differences between parents' and HCPs' semistructured interviews

Both parents and HCPs agreed biomarker tests must be evidence-based to be accepted, with HCPs additionally seeking guideline support. Both groups mentioned testing frequency should reflect wheeze severity, though some parents would accept any frequency if evidence-based. Children's cooperation depends on age and prior experiences, affecting testing success. On the other hand, there were differences. Parents would like empathetic HCPs, detailed explanations of their child's condition and care for their worries and concerns. Thus, doctors could start expressing their thoughts and doubts regarding children's diagnosis because parents appreciate having a clear, transparent and honest discussion. Finally, parents preferred SPT, whereas HCPs found them less feasible due to time, training needs and rare anaphylaxis risks, making implementation dependent on HCPs' readiness.

DISCUSSION

To our knowledge, this is the first study to explore both parent and HCP perspectives on the acceptability and feasibility of finger-prick, skin-prick and FeNO tests. The findings showed these tests are acceptable and feasible under the following conditions: (1) there is evidence of their effectiveness, (2) empathetic interaction and clear communication between parents and HCPs is established and (3) there is evidence of their cost-effectiveness to support NHS funding.

Parents seek empathetic interactions, clear explanations and shared decision-making from HCPs, consistent with previous research highlighting the importance of reassurance and clearer communication.^{8 18–22}

Our findings align with those of Wajid et al,¹⁸ who found that parents were frustrated by diagnostic uncertainty and favoured investigative tests to guide treatment pathways. However, our study additionally included the views of HCPs, providing a broader, implementation-focused perspective.

Most parents preferred SPT because it gave them an active role in helping their child. This finding aligns with Clement et al, who reported that parents' interest in allergies is driven by their desire to improve their child's condition and exclude allergies as the causing factor for their symptoms.¹⁰ However, SPT detects allergic sensitisation, not allergy, leading to misconception regarding causality. In contrast to parents, HCPs regarded SPT as less feasible due to the training required, time demands and the risk of adverse reactions, despite the extremely low incidence of anaphylaxis (one in 55 000 patients) reported in large studies.²³

HCPs highlighted several practical considerations for implementation. Tight schedules and heavy workloads limit their ability to incorporate these tests into routine practice, making it essen-

tial to integrate testing into existing workflows without increasing burden. Successful implementation would require nurses or HCAs' training on both technical (ie, biomarker tests) and communication skills (incorporating distraction-based techniques (ie, toys and cartoons)) to facilitate children's cooperation. The success of these tests also depends on HCPs' skills.²⁴ Although not mentioned by HCPs, offering biomarker tests in community-based healthcare settings, such as community diagnostic centres (CDCs) or intermediate care clinics, could provide flexible appointment structures, relieve pressure on GP appointments and facilitate wider adoption.²⁵

Health economics also affects feasibility. The costs of biomarker devices and consumables are significant barriers unless centrally funded. Negotiations with clinical commissioning groups are therefore essential to make these tests available across GP practices. El-Osta et al reported that the lack of NHS reimbursement for point-of-care (POC) tests deters primary care adoption due to high initial and ongoing costs.²⁶ Comparable challenges were reported for the introduction of HbA1c POC tests in UK primary care, but funding routes were developed.^{27 28} Similar routes could support adoption of biomarker tests for preschool wheeze. Future cost-effectiveness analyses should consider device/consumables costs, staff training, workflow adjustments and long-term savings from reduced exacerbations and unscheduled healthcare visits. It should be noted that parents' out-of-pocket expenses (eg, travel and subsistence), as well as willingness or ability to pay for biomarker tests outside NHS (eg, private testing or co-payment) were not assessed as we focused on NHS primary care costs. Future work should explore this, as out-of-pocket costs may affect acceptability.

In this study, HCPs mentioned that biomarker test adoption depends on proven ability to predict outcomes and guide treatment decisions, aligning with Ciardiello et al.²⁹ They prefer quick, time-efficient tests, supported by guidelines and acceptable to patients.²⁹ High costs and lack of evidence or guideline support for the biomarker tests would prohibit clinical practice implementation.²⁹

Parents in this study emphasised transparency and children's safety to consider participation in a future intervention study. They expressed concern about randomisation in the control group, fearing it may deprive their child of potential benefits, as previously identified.³⁰ Building trust between parents and researchers, explaining randomisation, blinding and right to withdraw are critical to improve participation and prevent misconceptions and complaints during the study.^{31 32} Best practices, such as the use of multimedia consent tools, lay summaries and parent advisory groups could support informed decision-making and improve recruitment rates. Additionally, parents of children with poorly controlled wheeze are more likely to participate in studies, while those whose children's condition is stable are less inclined to do so.²¹ Fi-

Table 4 Thematic analysis from healthcare professionals' focus group and one-to-one discussions

Feasibility requires parents' acceptance and children's cooperation.	Doctors care for parents' opinions or reactions	"I think parents worry about their wheezing children. I imagine, they would be happy to have the testing done, but they may not be able to do the full testing because if they see their child stressed, they may not be willing to then let them have the other tests."—GP1 "In terms of the skin prick testing, I'm not sure how acceptable it would be to the parents if the child had finger prick testing first and they are already crying, then to go on further and have three skin prick tests, I think that would be quite distressing."—GP2
	Children's cooperation is unpredictable during biomarker testing	"I think it's just the unpredictability with that age group and it's like when giving childhood immunisation. Some children of that age are completely compliant and others, it takes you kind of four times as long as you hope."—GP6 "In my experience they're not necessarily the easiest ages to come on board. You know they've got minds of their own."—GP8
	Successful performance of tests in practice may depend on children's age	"Probably one to be finger-prick, second to be FeNO and skin-prick last in terms of tolerability I would say. The older the child then probably the FeNO first, finger prick second and skin prick testing last."—GP3 "I'd probably say FeNO, for maybe the four-and-five-year-old, finger-prick probably for the one-to-three, purely because you're not sure if they're going to reliably understand instructions to blow into the FeNO machine and I think that's possibly also part of the reason why we don't really tend to diagnose asthma in very young children, because if you give them a peak flow, they simply wouldn't follow the instructions very well. I think it would be a challenge for a 5-year-old to be re-pricked, especially if they had a bad experience in the past."—GP11
Practical, evidence-based, financial and clinical considerations for implementing biomarkers.	Finger prick test can be implemented in primary care because HCPs are competent in performing it, it is quick and easy to be performed and gives objective measurements	"I think the finger prick testing because it needs just one needle, probably seems like the easiest to do."—GP2 "The finger prick is something we do for a random blood glucose measurement or something like that and the nurses obviously give injections to kids all the time."—GP5
	FeNO test will be easy to be performed by the existing personnel and can be used in a wide age range of asthmatic patients	"I think the FeNO would be very straightforward because we use FeNO already for adults and I think we are using it for teenagers but not small children yet."—GP10 "The FeNO test would be the easiest one to do. I can't see that being a problem at all because we already use that as kind of part of standard care."—GP14
	It may be difficult to successfully perform the FeNO test in preschool children	"FeNO testing is actually very difficult for people to use. They take multiple times. I'd like to see how it is used on a child because I think that could be difficult for them to breathe out enough air."—GP1 "I suppose it could potentially be quite time consuming to engage children of that age and get the technique right. Probably getting reliable results in children of that age with FeNO testing is quite challenging."—GP4
	GP practices do not perform SPT, and its implementation in primary care will require training	"I mean from a clinician's perspective I suppose it's my unfamiliarity. Obviously, we have secondary care for that and the idea of me doing that, or one of our clinicians doing that, seems a little bit foreign."—GP10 "We've got no experience with using the skin prick. I don't think anybody does any skin prick test."—GP13
	Skin prick testing may cause anaphylaxis, and treatment is a time-consuming procedure	"There's risk of anaphylaxis and none of us would want to have anaphylaxis because number one, it's of course life threatening and secondly, it's incredibly time consuming."—GP1 "The other hesitation I can imagine that nurses could have if they were delivering the skin allergy test is worrying about anaphylaxis."—GP5
	HCPs think that SPT may not be a useful test as it cannot provide objective measures of helping children	"What is the benefit of knowing it? So, if your child is allergic to dust mite, What you're going to do? I mean it's good to know, but it's impossible to erase your house from dust mite. And then, if the family's got a beloved animal, a beloved dog, are you going to get rid of your dog? It's quite a difficult decision, isn't it? I think the skin-prick test results can be quite difficult to manage because a lot of people just want to do it for curiosity, but they're not willing to change their lifestyle."—GP2 "I wouldn't do the patch testing, because for example looking at tree pollen, there's nothing you can do about it. It's the same with people with hay fever. They want testing, but the only thing you can do is avoid the allergen, which is completely impossible. And so, you're treating the symptoms. And if you discover someone's allergic to pollen, then what? They're not going to live in a bubble at home. They're still going to go out, and you're just aware that they've got this allergy."—GP1
	Doctors want evidence that the tests can predict response to treatment	"It has to be justified. There has to be evidence that it works, so that we don't go into unnecessary cost when there is no evidence that it works."—GP10 "Everything is evidence-based medicine and if there's not good evidence to support its use then there is not really a point using it, because you're going to get unreliable results."—GP11
	Practices are keener to use the biomarker tests if they are supported by asthma guidelines	"It would need a bit like the BTS/SIGN and the NICE guidelines to have some trials saying that using these three tests will help to diagnose in this under five group with this degree of reliability."—GP9 "If there was evidence and it was incorporated into NICE guidelines, if all the national guidance was saying that this was best practise to check these things before making a diagnosis or changing treatments, then yeah, that would definitely make it more attractive."—GP13
	The inclusion of FeNO in guidelines facilitates its incorporation into daily routine practice	"Obviously the FeNO evidence is there, certainly in the older children and actually we are looking at BIONA FeNO machine currently within our practise...Realistically, we should be doing spirometry and FeNO."—GP12 "The guidelines basically could have an effect on doctor's decisions on taking the equipment because since the guidelines mentioned FeNO that made it more acceptable, buying the FeNO device."—GP13 "I mean FeNO is turning into sort of gold standard, it's what you must have, every surgery should consider having it. And it's something we've had for a couple of years now, so that would appear to be a push from the world of asthma that this is good practise and therefore you should kind of have it alongside spirometry."—GP14
	The cost of the devices and their consumables is an issue for implementation in primary care	"For a practise to spend £4000 on the machine and then for the tests, it's not going to happen, and I think there's no way a practice is going to spend £4000 on the device."—GP1 "That not something general practitioners are going to buy. I think it's quite unlikely that people will pay that kind of money per test."—GP3
	GP practices cannot afford buying the devices on their own	"If it was coming out of your wage how much would it make an impact, then? So, if I said I want you to do it in the hospital, but it's coming out of your monthly payment, would it make a difference?"—GP9 "Obviously the cost is a significant factor for the practise, especially at the moment when our expenses are shooting up and the money coming in is not."—GP12
	Funding is essential for the tests to be implemented in primary care	"If it works, the next day we would have to negotiate with the CCG or the ICB to make these available to all GP practices that they can each have one test or one offline kit which they can use."—GP1 "The key thing that we've got to be thinking about here is, how can we fund this to make it happen? Don't worry about the staff; that will occur if the healthcare provider, be that a hospital, a practice has appropriate funding to do it, they'll get it done."—GP9 "If there's no central funding to pay for the particular equipment it would be off putting."—GP13

Continued

Table 4 Continued

	If child's condition is poor, then biomarker testing should occur more frequently	"I imagine that the well-controlled ones, we'd probably be doing it annually, but for those who are struggling we would probably be doing it six monthly or quarterly." —GP10 "I don't know how frequently would be looking at testing them, it probably depends on their symptoms and how well controlled they are... If they're well controlled, you're not going to bring them back for repeated tests multiple times per year, it might be an annual asthma review." —GP13
	The frequency of tests per child, depends on the cost of the consumables and the time needed to perform the tests per child	"I think it depends how costly it is really and if you rolled it out into practice, how costly it would be well both financially and time wise." —GP12 "I think it's about ongoing cost. You can always make a case for a piece of equipment, but the fact is how much is going to cost per child." —GP3
Maximising efficiency to incorporate testing into practice.	Doctor appointments last 10 min and it may be difficult to do the tests in that meeting	"I get the feeling that probably a 10-to-15-minute appointment to do these three tests are not enough." —GP2 "General practice appointments tend to be 10 to 15 min and there's no way we could fit any of that in." —GP3 "I think, as (nurse's name) said, without having that time pressure of the GP time, I think I would definitely be having it as a separate appointment." —GP6
	The unpredictable nature of children during testing makes HCPs think that a separate appointment may be needed	"Say you have a 20 minute or half hour appointment, we are going to find we frequently waste appointments trying to engage children with those tests and if they can't engage properly, I presume it would affect the reliability of the results." —GP4 "If I'm going to collect the breath again and explaining that depending on the age of the child, that can be probably another 20 minutes. So, you're asking for a one hour appointment when I've got 10 minutes." —GP9
	Tests are more feasible to be done by nurses or healthcare assistants	"A test could be done on a different day a few days prior to the consultation with the nurse or perhaps by a technician, a suitably trained technician." —GP3 "Perhaps it should be a healthcare assistant if we can train them to do that and leave them." —GP9
	Testing performed by nurses may be a cost-effective route in GP practices	"I think ultimately if you could have a one of your respiratory nurses doing the tests prior to seeing a clinician ultimately that would be the most effective and probably cost-effective route." —GP4 "It feels like something that would sit better with a practise nurse activity and equally, if we had to look at it in terms of cost benefit type equation, having practice nurses is probably the right level of cost, in terms of staff costs." —N2
Perceived barriers and facilitators for trial feasibility.	Practices must be given a realistic and feasible number of participants to recruit and in a feasible time period	"The two big things that we found are a realistic number of recruits, so being realistic about the uptake of research within a population. You would probably get an uptake of somewhere between 10 and 15%. We might be able to find 40, but we're not going to find 400. And that puts us off going in, because we think we're not realistically going to be able to hit that number and if all of those children were half an hour appointment, 400 times, half an hour is a lot of days and weeks of nurses' kind of time to do that." —GP14 "I would make it a longitudinal study. It's good to have a roll out over several months because trying to recruit 60 in two months is sometimes logistically difficult. But if you have a target of how many per month that's a little easier." —GP3
	Practices want evidence prior to participating in a future RCT	"We want the evidence to give good care because there's a whole evidence-based medicine culture. We don't want to do things that are not safe, with no evidence. We want to do things that will improve care." —GP1 "It would have to be good quality, NIHR type level descriptors behind it, using a test that we don't quite know its accuracy yet." —GP9
	Practices would like a financial incentive to participate in the future intervention study, either to be paid for the time they provide to the study (based on their hourly payment) or keeping a device at the end of the study	"Remuneration that suitably covers nurse and doctor time for patients can make the randomised trial more acceptable to GP practices." —GP3 "I suppose the sort of first thing that everybody thinks of with these sorts of studies is free equipment. If you get to keep the FeNO equipment or the finger-prick equipment, then that's something that you might keep using after the end of the study." —GP13
	A future intervention study is more feasible in research-active practices as they have the capacity and capability to handle a RCT	"I think randomised control trials would be something that research active practises would be eager to take on." —GP4 "I think it would probably need practices that very much had a culture of research and had experience of research to be able to carry this out efficiently." —GP6 "Some research surgeries have a lot more resources and have dedicated nurses, they've got allocated nurses that do full time research. So, they definitely would have capacity for something like this." —GP11
	Parents seeing different treatment being given in the practice may make them intervene with treatment decisions	"If I'm told that my four-year-old kid might have a risk of wheezing because of the biomarker tests, but I'm told I'm in the control group, I'm going to be very worried as a parent as to whether I should be having the inhaler. And then the parents are going to come and see their GP and say I'm in the other group and I'd really like him to have an inhaler. Because parents, you know, if your kid is sick, you'll do anything for your kid." —GP1 "Similarly with all the all the studies we run that that people would think that the intervention is going to be beneficial, but you know that's what the trial's there for isn't it?" —GP4 "You have to be very clear to the parents that actually this is being done as part of a research study. We don't know whether using biomarkers is more superior to not using biomarkers." —GP6

FeNO, fractional exhaled nitric oxide; GP, general practitioner; HCP, healthcare professional; RCT, randomised controlled trial; SPT, skin-prick testing.

nally, HCPs highlighted the need for realistic recruitment targets and adequate funding for participating practices. These concerns should be explicitly addressed in trial design, by involving more practices with smaller recruitment targets and providing resources to offset additional workload.

Strengths and limitations

Strengths and limitations The key strength of this study is that it captured the perspectives of both parents and HCPs regarding the three biomarker tests, helping to identify important barriers to implementing them in NHS primary care. While this study offered valuable insights, several limitations should be acknowledged. Although data saturation (ie, the collection of qualitative data until the addition of new data does not yield new themes³³) was deemed achieved within parents' FG, not inviting families who agreed to one-to-one interviews may be a limitation. These parents might have felt uncomfortable sharing personal experiences in group settings. The inclusion

of parents with prior experience with biomarker tests enabled informed, pragmatic reflections on acceptability. However, this limits transferability to test-naïve populations. Participants also lacked ethnic diversity. Factors such as culture, health literacy and the presence or absence of previous biomarker testing could influence perspectives but were not explored. Future qualitative studies should consider deeper enquiry into these aspects of behaviour and belief, as well as broader recruitment strategies and purposive sampling strategies to support inclusion of children from diverse ethnic and demographic backgrounds to strengthen findings' transferability. Purposive sampling was not used to enable all parents from this study to participate, while convenience sampling for HCPs was used due to the study's time constraints, potentially leading to a less diverse sample. Additionally, HCPs lacked firsthand experience with the biomarker tests, making their feedback theoretical rather than practical. Although the sample was relatively homogeneous in professional roles, it was diverse in terms of gender, clinical experience and prac-

tice size, allowing collection of varied perspectives on biomarker testing implementation in primary care. Despite these limitations, the study provides important insights for future research and practice.

CONCLUSION

This study, by uniquely combining parents and HCPs' perspectives, showed that finger-prick and FeNO tests were the most acceptable and feasible, while SPT was the least feasible due to training, time and safety concerns. These tests may be best used in nurse-led or HCA-led clinics or CDCs, where sufficient time and child-friendly preparation can be provided. Implementation should be supported by clear communication, evidence of HCP and patient/parent perspectives, efficacy and cost-effectiveness data from future trials.

Contributors

AP, S-JB, IDP, LF, AB and CG were responsible for the planning of the work. AP collected and analysed the data. GL acted as a second independent coder to explore differences or similarities and ensure preconceptions did not unduly affect analyses of the manuscript. AP designed the open-ended questionnaires with the help of S-JB, IDP, LF, AB and CG. AP, GL, S-JB, IDP, LF, AB and CG helped revise the manuscript for corrections. AB acted as the guarantor.

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Competing interests LF reports receiving institutional payments for consulting fees from AstraZeneca, Sanofi, GSK and Regeneron, and for lectures or educational events from AstraZeneca and Sanofi. All payments have been made to her institution. She also serves as a chief investigator on an NIHR HTA grant and co-investigator on an NIHR EME grant. These activities are unrelated to the submitted work. IDP reports other from Sanofi, other from Regeneron Pharmaceuticals, Inc., non-financial support from Excerpta Medica, during the conduct of the study; other from Aerocrine AB, other from Almirall, other from AstraZeneca, other from Boehringer Ingelheim, grants and other from Chiesi, other from GSK, other from Novartis, other from Regeneron Pharmaceuticals, Inc., other from Sanofi, other from Teva, other from Circassia, other from Dey Pharma, other from Genentech, other from Knopp Biosciences, other from Merck, other from MSD, other from Napp Pharmaceuticals, other from RespiVert, other from Schering-Plough, outside the submitted work. CG is an investigator in the Genes and Health Programme. Genes & Health has recently been core-funded by Wellcome (WT102627, WT210561), the Medical Research Council (UK) (M009017, MR/X009777/1, MR/X009920/1), Higher Education Funding Council for England Catalyst, Barts Charity (845/1796), Health Data Research UK (for London substantive site), and research delivery support from the NHS National Institute for Health Research Clinical Research Network (North Thames). Genes & Health has recently been funded by Alnylam Pharmaceuticals, Genomics PLC; and a Life Sciences Industry Consortium of AstraZeneca PLC, Bristol-Myers Squibb Company, GlaxoSmithKline Research and Development Limited, Maze Therapeutics Inc, Merck Sharp & Dohme LLC, Novo Nordisk A/S, Pfizer Inc, Takeda Development Centre Americas Inc. AP, GL, S-JB and AB have no conflicts to disclose.

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Ethics Committee (REC reference: 21/PR/1195), and the study was registered at clinicaltrials.gov (NCT04942483). Participants gave informed consent to participate in the study before taking part.

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Utilização de brometo de ipratrópio inalado/nebulizado em complemento ao tratamento de primeira linha com beta 2-agonista de curta duração inalado/nebulizado e corticosteroide sistêmico na gestão das agudizações agudas de asma: uma revisão sistemática e meta-análise de ensaios clínicos aleatorizados

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RESUMO

Contexto O papel do brometo de ipratrópio (IB) inalado/nebulizado na asma permanece pouco claro.

Objetivos Avaliar a eficácia e segurança do IB inalado/nebulizado na gestão da asma em crianças.

Métodos Foram pesquisadas as bases de dados MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials e Web of Science até julho de 2024. Incluíram-se ensaios clínicos aleatorizados (RCTs) e seguiram-se as orientações internacionais para revisões sistemáticas. Os desfechos incluíram: morbidade, escalada de cuidados, duração do internamento, mortalidade, eventos adversos e função pulmonar.

Resultados Foram incluídos 24 estudos (total de participantes n=3238). A taxa de hospitalização foi semelhante entre grupos (RR 0.84, IC 95% 0.70–1.00, I² 30%), tal como a duração do internamento em horas (MD 1.75, IC 95% –0.87 a 4.36, I² 15%) e a admissão em cuidados intensivos pediátricos (PICU) (RR 0.91, IC 95% 0.35–2.32, I² 0%). A taxa de hospitalização foi inferior nos doentes que receberam IB por nebulização (RR 0.76, IC 95% 0.64–0.90, I² 0%). O resultado de gravidade da asma foi significativamente melhor no grupo IB (MD –0.38, IC 95% –0.63 a –0.12, I² 59%). Não foram reportados eventos adversos graves.

Conclusão Esta revisão encontrou evidência de elevada certeza de que o IB nebulizado reduz a taxa de hospitalização. Contudo, quando os IB inalados/nebulizados foram analisados em conjunto, a taxa de hospitalização foi semelhante, com evidência de certeza moderada. O IB melhorou os resultados clínicos de asma, com evidência de baixa certeza. Não foram observadas diferenças noutras desfechos pré-especificados. Dada a evidência atual e o perfil de segurança, o IB inalado/nebulizado deve ser considerado como tratamento adicional na agudização aguda de asma.

Registo PROSPERO: CRD42023405023.

INTRODUCTION

This is one of a series of systematic reviews commissioned by WHO to inform consolidated recommendations for managing common childhood illnesses. The recommendations will update the existing guidance in the pocketbook of hospital care for children and Integrated Management of Childhood Illness (IMCI) charts.^{1,2} Asthma is one of the most common chronic diseases, affecting an estimated 262 million people in 2019.³ It is a frequent cause of morbidity in children and adolescents⁴; thus, the

Key messages

What is known about this topic

- Simultaneous administration of inhaled/nebulised ipratropium bromide (IB) and a short-acting beta 2-agonist (SABA) may produce an additive bronchodilator effect, although the supporting evidence varies in strength.
- Inhaled/nebulised IB can be considered an adjunct to the treatment of severe asthma exacerbation.

What this study adds

- This review demonstrated a lower hospitalisation rate among patients who received IB nebulisation and a significant improvement in asthma clinical scores in children who received nebulised/inhaler IB.
- The use of inhaled/nebulised IB did not improve the length of hospital stay in hours, PICU admissions, additional treatments following interventions or lung function tests.

How this study might affect research practice or policy

- Further well-designed research would empower clinicians to draw a firm conclusion regarding the role of inhaled/nebulised IB in treating acute asthma exacerbations in children.

WHO has identified acute and long-term asthma management as a priority for evidence appraisal and guideline development.^{4,5} Initial management of an asthma exacerbation includes assessing severity, initiating supportive treatment, which may include oxygen as needed, administering a short-acting β 2-agonist (SABA) and considering ipratropium bromide (IB) and systemic steroids.^{6,7} Additional medications are added to this first-line treatment to manage more severe asthma exacerbations, supported by varying levels of evidence.⁸

Inhaled anticholinergic agents such as IB are believed to cause bronchodilation by alleviat-

ing cholinergic bronchoconstriction and decreasing mucosal oedema and airway secretions.⁹ It has been proposed that combining these medications may result in greater bronchodilation. The most recent Cochrane review (of Cochrane reviews), which, as part of the review, examined the role of IB in acute asthma in children, was based on one Cochrane review from 2013.¹⁰ It concluded that hospital admission is reduced when inhaled IB is added to inhaled SABA in moderate to severe exacerbations, in multiple, fixed doses in the first hour or two of treatment.¹¹ They recommended that further research was required to identify high-quality evidence regarding the efficacy of the inhaled/nebulised IB to determine which patients are most likely to benefit from IB therapy.¹¹ It has been 12 years since this last review, so we conducted the review to see if there was further evidence. We conducted this review to identify additional randomised controlled trials (RCTs) not included in the most recent systematic reviews.¹¹

This review aimed to assess the safety and efficacy of inhaled/nebulised IB, in addition to the standard first-line treatment with inhaled/nebulised SABA and systemic steroids, compared with the standard first-line treatment for acute asthma exacerbation in children and adolescents aged 18 years and under.

MATERIALS AND METHODS

This study adhered to the international recommendations for reporting systematic reviews and meta-analyses¹² and was registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42023405023.

Study selection and search strategy

The following databases were searched from 1966 to 7 April 2023 and updated on 9 July 2024: MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science. We inspected the reference lists of retrieved articles to identify any additional citations that the electronic searches might have missed. We also searched for unpublished ongoing clinical trials on the websites: www.clinicaltrials.gov and www.controlled-trials.com.

Terms for population, interventions and outcomes were included in our search strategy. Search terms are (attack, exacerbation, episode, or acute severe asthma) AND (ipratropium bromide or Atrovent). The whole search term used is shown in online supplemental appendix 1.

Eligibility criteria and outcomes

We included only RCTs that assessed the safety and efficacy of inhaled/nebulised IB alongside standard first-line treatment for bronchial asthma, compared with standard first-line treatment, with or without placebo, in children and adolescents aged 18 years and younger experiencing acute asthma exacerbations. The outcome measures to be assessed were as follows:

- ▶ Primary outcomes
 - ▶ Morbidity (symptoms, hospitalisation, school absence).
- ▶ Secondary outcomes
 - ▶ Escalation of care (ventilation/ paediatric intensive care admission).
 - ▶ Length of hospital stay.
 - ▶ Mortality due to exacerbation.
 - ▶ Adverse events
 - ▶ Lung functions (changes in forced expiratory volume (FEV₁) in litres or per cent of predicted, and peak expiratory flow rate (PEF) in litres/min).

We applied no language restriction and planned to translate relevant studies into English if needed.

Data collection and analysis

Selection of studies

Authors in pairs (SA, RS and AT, AZ) assessed the relevant manuscripts. They independently evaluated the eligibility of all identified trials. Discussions with a third author (ISA, CP) resolved disagreements among the authors.

Data extraction and management

Two authors (NA, AH) independently extracted data, including demographic information, methodology, intervention details and reported outcomes. They compared the extracted data, and any differences were resolved through consensus and discussion with a third author (AAH) if necessary. We analysed the extracted data using the Cochrane Collaboration's Review Manager.¹³

Assessment of risk of bias in included studies

Two authors (KM, AAH) used the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions to assess the risk of bias.¹⁴ They independently evaluated the risk of bias for each study, and any disagreement was resolved through mutual discussion or involving a third author (ISA, CP). We assessed the risk of bias according to the following domains:

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.

Each risk of bias was rated as either low, high or unclear.

Data collection and analysis

Selection of studies

Authors in pairs (SA, RS and AT, AZ) assessed relevant manuscripts. They independently evaluated the eligibility of all identified trials. Any disagreement among authors was resolved by discussions and consultation with a third author (ISA, CP).

Data management

The mean difference (MD) was calculated for continuous data where appropriate. For dichotomous data, we reported the risk ratio (RR). We highlighted all missing data in the Results section. Our analysis was based on intention-to-treat. Any dropout of included children was noted in the review. We planned to contact the authors of published primary studies for further clarification and to provide additional information as needed. The I² statistic was used to measure heterogeneity among the included trials.¹⁵

We considered an I² value of:

- ▶ 0% to 40% might not be as important.
- ▶ 30% to 60% represents moderate heterogeneity.
- ▶ 50% to 90% represents substantial heterogeneity.
- ▶ 75% to 100% represents significant heterogeneity.

When appropriate, we further explored the heterogeneity using sensitivity analyses. If there were 10 or more studies,¹⁶ we planned to investigate potential publication bias using funnel plots for each outcome.

Data synthesis

We synthesised and analysed data using the statistical package Review Manager V.5.4 provided by the Cochrane Collaboration.¹³ All measures were reported with 95% CIs. A random-effects model was employed for data synthesis. We used narrative descriptions when data could not be combined, or significant heterogeneity was found.

Sensitivity analysis

We planned to conduct a sensitivity analysis to examine the potential impact of missing data and any methodological heterogeneity. We intended to achieve this by excluding studies with a high risk of bias from the meta-analysis and analysing the data using random and fixed-effect models to assess their impact on the overall results.

Summary of findings

The principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system were applied to evaluate the quality of the evidence about specific outcomes.¹⁷ The grading was planned for the following outcomes: hospitalisation rate, asthma severity scores, PICU admission rate, the need for ad-

ditional treatment and length of hospital stay in hours. The quality level of the evidence was downgraded based on the following factors:

1. Methodological quality.
2. The directness of the evidence.
3. The heterogeneity of the data.
4. The precision of effect estimates.
5. The risk of publication bias.

RESULTS

Study selection

We identified 629 citations. After removing duplicates and evaluating titles and abstracts, we assessed the full texts of 26 citations that potentially met the inclusion criteria. Two studies were excluded: one included only adult subjects, and one compared IV aminophylline versus IB. We included 24 RCTs involving a total of 3238 participants. A flowchart detailing the selection process is illustrated in figure 1.

Study characteristics

We included only 24 studies (n=3238). The definition of bronchial asthma severity was based on the criteria used in the primary studies (online supplemental table 1).

Risk of bias

The risk of bias assessment is illustrated in figure 2 and online supplemental figure 1. Twelve of the included studies were categorised as having a low risk of bias concerning random sequence generation.^{18–29} Eleven studies were deemed to have an unclear risk due to insufficient details within the primary studies.^{21 30–39} One study was rated high risk because the authors employed a lottery method for random sequence generation.⁴⁰

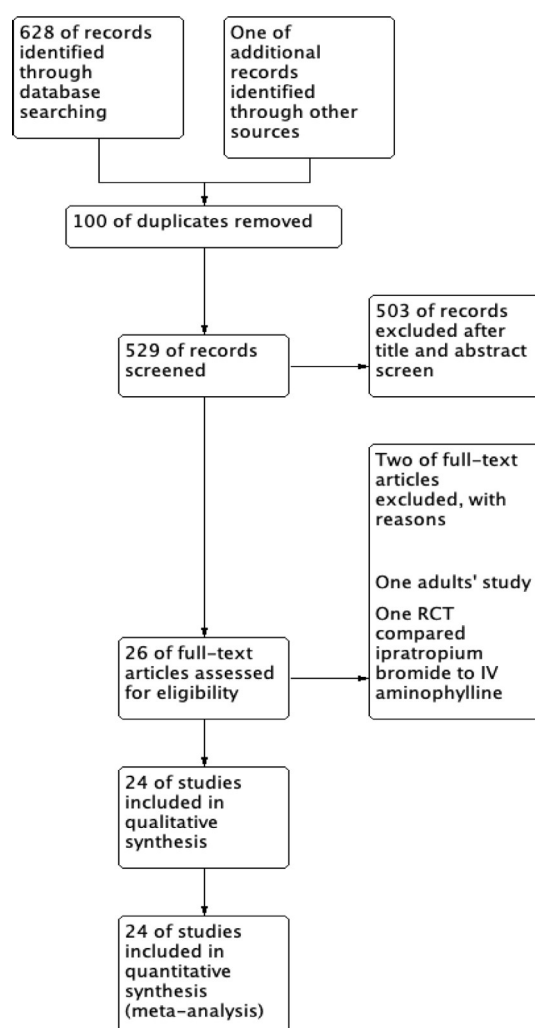


Figure 1 Study flow diagram.

Nine studies were assessed as having a low risk for allocation concealment.^{18 20 21 25 26 28–30 36} The remaining 15 studies were classified as having an unclear risk, as the authors did not provide further details.^{19 22–24 27 31–35 37–41}

Fourteen studies were classified as having a low risk of bias regarding blinding participants and personnel.^{18–20 22–30 33 36} Six studies were classified as having unclear bias due to the lack of further information.^{31 32 35 38 39 41} Four studies were classified as having a high risk because no placebo was used.^{21 34 37 40}

Fifteen studies were classified as low risk of bias regarding the blinding of outcome assessment^{3 18–30 33 36}; six studies were rated as

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Beck 1985	?	+	+	+	+	+	+
Butt 2022	+	?	+	+	+	+	+
Calvo 1998	?	?	?	?	+	+	+
Chakraborti 2006	+	+	+	+	+	+	+
Cook 1985	?	?	?	?	+	+	+
Craven 2001	+	?	+	+	+	+	+
Ducharme 1998	+	+	+	+	+	+	+
Fernandez 2000	+	?	+	+	+	+	+
Goggin 2001	+	?	+	+	+	+	+
Gokalp 2013	+	+	+	+	+	+	+
Iramain 2011	+	?	+	+	+	+	+
Memon 2016	?	?	?	?	+	+	+
Monge 2000	?	?	+	+	+	+	+
Murphy 2020	?	?	+	+	+	+	+
Qureshi 1997	+	+	+	+	?	?	?
Qureshi 1998	+	+	+	+	+	?	?
Rayner 1987	?	?	?	?	+	+	+
Reisman 1988	?	+	+	+	+	+	+
Schuh 1995	+	?	+	+	+	+	+
Sharma 2004	?	?	+	+	+	+	+
Storr 1986	?	?	?	?	+	+	+
Watanasomsiri 2006	?	?	?	?	+	+	+
Wyatt 2015	+	+	+	+	+	+	+
Zorc 1999	+	+	+	+	+	+	+

Figure 2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

having unclear bias due to a lack of additional information.^{31 32 35 38 39 41} In three studies, the outcome assessors were aware of the treatment group allocation, and thus these were scored as high risk.^{34 37 40} Twenty-one studies were rated as low risk for incomplete outcome data.^{18-24 26-31 33 35-41} One study was rated as unclear risk since no additional information was found,²⁵ and two studies were rated as high risk due to discrepancies in the number of participants in both studies.^{32 34} Twenty-two studies were classified as having a low risk of bias for selective reporting and other biases,^{18-24 27-41} while two studies reported unclear bias due to insufficient information.^{25 26}

Effect of intervention

Hospitalisation

Eleven studies reported this outcome.^{20 21 23 25-29 35-37} There was no difference in hospitalisation rates between the two groups (moderate certainty of evidence) (RR 0.84, 95% CI 0.70 to 1.00, I² 30%, n=2063) (figure 3). Ten studies compared nebulised IB to other treatments.^{19 20 23 25 27-29 36 37 39} The hospitalisation rate was significantly lower in patients who received an IB nebuliser (high certainty evidence) (RR 0.76, 95% CI 0.64 to 0.90, I² 0%, n=1716). One study compared the IB inhaler to other treatments and found no difference in hospitalisation rates (RR 1.09, 95% CI 0.94 to 1.27, p value 0.24, n=347).²¹ The funnel plot of the hospitalisation outcome showed no evidence of asymmetry (online supplemental figure 2).

Asthma clinical score

Eight studies reported this outcome.^{18 22-24 28 31 32 35} There was a significant improvement in the asthma clinical score in the IB group (low certainty) (MD -0.38, 95% CI -0.63 to -0.12, I² 59%, n=733), as shown in figure 4. Sensitivity analysis was conducted by omitting the studies with moderate to high risk of bias.^{31 32 35} No improvement in heterogeneity was noted (MD -0.44, 95% CI -0.9 to 0.01, I² 75%).

PICU admission

Two studies reported this outcome.^{26 29} No difference was found in the rate of PICU admission between the two groups (low certainty of evidence) (RR 0.91, 95% CI 0.35 to 2.32, I² 0%, n=861) (online supplemental figure 3).

The need for additional treatment

Three studies were included.^{19 35 37} The need for additional treatment was similar among the studied groups (moderate certainty of evidence) (RR0.70, 95% CI 0.39 to 1.26, I² 0%, n=297) (online supplemental figure 4).

Length of hospital stay in hours

Four studies reported this outcome.^{19 22 33 35} There was no significant difference in the length of hospital stay in hours (high certainty evidence) (MD1.75, 95% CI -0.87 to 4.36, I² 15%, n=357) (online supplemental figure 5).

Adverse events

Eight studies reported this outcome.^{21 25 27 30 33 36 37 39} The most common adverse events were tremor, vomiting, nausea, palpitations and headache. Tremor was reported in five studies, showing no difference between the two groups (RR 1.22, 95% CI 0.63 to 2.36, I² 42%, n=476).^{21 30 36 37} Four studies reported vomiting, with no observable difference between both groups (RR 2.45, 95% CI 0.67 to 8.98, I² 28% n=446).^{21 30 36 37} No difference was found regarding nausea, which was reported by four studies (RR 0.81, 95% CI 0.30 to 2.21, I² 0%, n=538).^{21 25 33 39} Three studies evaluated headache; no difference was recorded (RR 0.92, 95% CI 0.38 to 2.24, I² 0%, n=191).^{25 33 39} One study examined palpitation and found no difference (RR 1.20, 95% CI 0.9 to 3.65, p=0.75, n=90)²⁵ (online supplemental figure 6). No serious adverse events were reported.

PEF percentage measurements after interventions

Seven studies were included.^{18 23 24 28 31 35 40} Six studies showed no difference in the PEF measurement at 30–60 min when IB was compared with other treatments (MD 6.11, 95% CI -4.36 to 16.58, I² 96%, n=462)^{18 23 28 31 35 40} (online supplemental figure 7). Two studies showed no difference in PEF measurement at 120 min between both groups (MD 14.84, 95% CI -2.49 to 32.18, I² 96%, n=177)^{24 31} (online supplemental figure 7). When the fixed effect model was applied, there was a significant improvement in the PEF of the IB group at 30–60 min (MD 11.36, 95% CI 9.65 to 13.08, I² 96%, n=462) and at 120 min (MD 7.87, 95% CI 5.85 to 9.89, I² 96%, n=177).

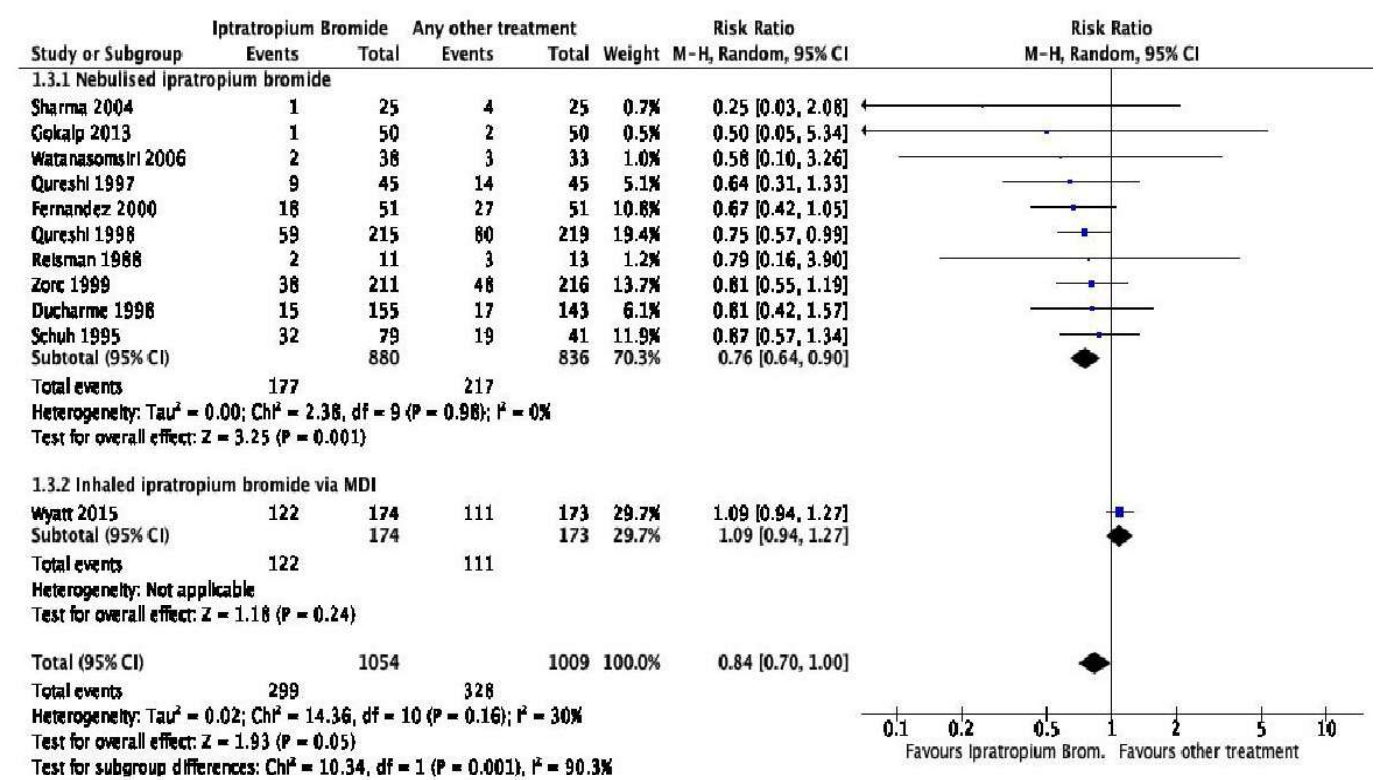


Figure 3 Forest plot of comparison: inhaled/nebulised ipratropium bromide vs other treatment, outcome: hospitalisation.

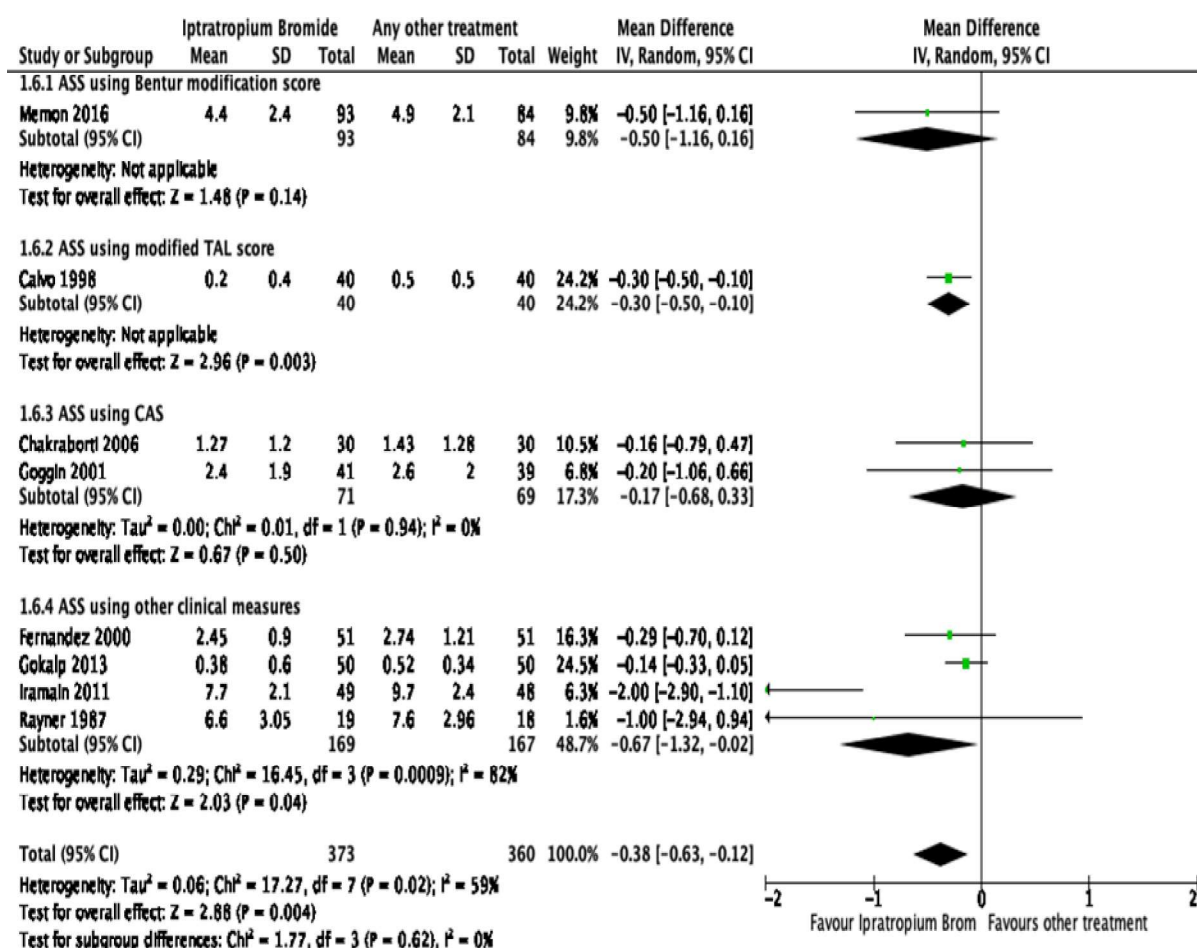


Figure 4 Forest plot of comparison: inhaled/nebulised ipratropium bromide compared with other treatment, outcome: asthma clinical scores after intervention.

Table 1 Summary of findings

Nebuliser/inhaled ipratropium bromide compared with placebo or any other treatment for acute asthma exacerbation in children and adolescents 18 years or younger

Patient or population: Acute asthma exacerbation in children and adolescents 18 years or younger

Setting: High and upper-middle income economy countries

Intervention: Nebuliser/inhaled ipratropium bromide

Comparison: Placebo or any other treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or any other treatment	Risk with nebuliser/inhaled ipratropium bromide				
Hospitalisation	325 per 1000	273 per 1000 (228 to 325)	RR 0.84 (0.70 to 1.00)	2063 (11 RCTs)	⊕⊕⊕○ Moderate ^a	
Asthma clinical score after intervention		MD 0.38 lower (0.63 lower to 0.12 lower)	—	733 (8 RCTs)	⊕⊕○○ Low ^{a,b}	
The need for PICU (Paediatric Intensive Care) admission	21 per 1000	19 per 1000 (7 to 48)	RR 0.91 (0.35 to 2.32)	861 (2 RCTs)	⊕⊕○○ Low ^c	
Needed additional treatment	154 per 1000	108 per 1000 (60 to 194)	RR 0.70 (0.39 to 1.26)	297 (3 RCTs)	⊕⊕⊕○ Moderate ^b	
Length of hospital stay in hours		MD 1.75 higher (0.87 lower to 4.36 higher)	—	357 (4 RCTs)	⊕⊕⊕⊕ High	

GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded to serious inconsistency due to moderate heterogeneity

b. Downgraded to serious risk of bias due to high/unclear risk of bias among included studies

c. Downgraded to very serious imprecision due to small sample size, low event rate and wide confidence interval (CI)

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

MD, mean difference; RCT, randomised controlled trial; RR, risk ratio.

Percentage change in PEF

Only one study was included. Measurements were taken at 60 and 120 min post-intervention.³⁷ The IB group showed a significant improvement in PEF percentage at both 60 min (MD 4.44, 95% CI 3.98 to 4.90, n=50) and 120 min (MD 5.24, 95% CI 4.80 to 5.68, n=50), as shown in online supplemental figure 8.

Forced expiratory volume in 1 second (FEV₁) (% predicted)

Three studies reported this outcome.^{18 24 30} There was no significant difference in FEV₁ (% predicted) between the two groups (very low certainty evidence) (MD 15.64, 95% CI -7.49 to 38.77, I² 96%, n=182) (online supplemental figure 9).

Other outcomes

The primary studies did not report data for the following outcomes: school absence and mortality due to exacerbation. No data was available for the following subgroup analysis.

1. Severity: mild-moderate, severe.
2. Timing of administration.

Quality of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) quality of evidence for the outcomes: the length of hospital stay in hours was graded as high certainty evidence. The hospitalisation rate and the need for additional treatment outcomes were graded as moderate certainty evidence. Paediatric Intensive Care (PICU) admission and asthma score were downgraded to low certainty evidence (table 1).

DISCUSSION

In this review, we evaluated the safety and efficacy of inhaled/nebulised IB alongside standard first-line treatment. Twenty-four studies involving 3238 participants were included. Since the last meta-analysis in 2013 by Griffiths et al, which included 20 studies,¹¹ there have been four additional studies involving a further 647 subjects.^{21 28 32 40} It is evident that nebulised IB has a role in children presenting with moderate to severe exacerbation, given in multiple doses at a fixed regimen during the first 2–3 hours after presentation, based on moderate to high-quality evidence. Our systematic review supports that conclusion. It is also clear that once admitted to the ward, there is no advantage to adding nebulised IB to the standard regimen with SABA in terms of length of hospital stay. No further studies have challenged these two conclusions. The recommendations from the Griffiths 2013 systematic review suggested that further research was needed to examine the impact of age, dose differences, method of delivery of IB, fixed or flexible regimens and severity. In the last 12 years since the last Cochrane reviews,¹¹ these areas of research have made little progress. There has been one study examining the delivery of IB via a spacer, which showed that using this mode of drug delivery did not influence hospital admission.²¹ Figure 3 illustrates the impact of this one study. So, until further spacer studies are published, the conclusion should be that the addition of IB to initial treatment should be via a nebuliser. No further studies have addressed fixed regimens versus flexible regimens, different dosing and the impact of age.

The meta-analysis of this review revealed no differences in length of hospital stay, need for additional treatment, PICU admission, FEV₁ after intervention and adverse events among the studied groups. One study showed a significant improvement in the percentage change in PEF in the IB group.³⁷ However, there was no significant improvement in forced expiratory volume in one second (FEV₁ % predicted) in the IB group. Inhaled anticholinergics appeared to have a beneficial effect on symptom scores in ED treatment, but not after children were admitted to the hospital.¹¹ The systematic review of children admitted to the ward also showed that no serious or non-serious adverse events were reported, and no differences were noted in the asthma clinical scores and lung function. There have been no further studies to refute these conclusions.

To our knowledge, we have identified all relevant studies in our search as of July 2024. This result pertains to participants who presented with acute asthma exacerbation and were treated with inhaled/nebulised IB in addition to the standard treatment. We assessed the certainty of evidence for each outcome using a 4-level rating scale based on the GRADE classification.

DISCUSSION

In this review, we assessed the safety and efficacy of intravenous magnesium sulfate as an adjunct to the first-line treatment of acute asthma exacerbation. Nine studies were included (n=473). Overall improvement in asthma severity scores, PICU admission rate and the length of hospital stay were similar among both groups. The hospitalisation rate and the need for non-invasive ventilation were

less in children who received intravenous magnesium sulfate. The requirement for oxygen supplements was similar in both groups. A study reported that the intravenous magnesium sulfate group improved the PEF from the baseline at 90 min.²²

Overall, there is limited evidence that hospitalisation rate, respiratory support and lung functions were better in the intravenous magnesium sulfate group.

Griffiths and Kew's comparable results revealed a reduction in hospital length of stay in children who received intravenous magnesium sulfate, with an unclear effect on ED treatment time.²⁸ However, a meta-analysis by Cheuk et al showed that intravenous magnesium sulfate probably provides an additional benefit in moderate to severe acute asthma in preventing hospital admission and significantly improving short-term pulmonary function tests and clinical symptom scores.²⁹

One study reported that the hospitalisation rate, length of hospital stay and hospital costs were lower in the group receiving a high intravenous magnesium infusion dose.

A previous systematic review, including adults and children, concluded that intravenous magnesium sulfate might be safe and beneficial in patients with severe acute asthma.³⁰ A recent systematic review of the adult population revealed that intravenous magnesium sulfate benefits FEV₁/PEF and hospital admission rate in treating asthma exacerbations.³¹

To our knowledge, we identified all relevant studies in our search up to May 2024. This result applies to the participants who presented with acute asthma exacerbation and were treated with intravenous magnesium sulfate in addition to the standard treatment. When available, we performed meta-analyses of the data studied. We graded the certainty of evidence for each outcome using the GRADE classification, a four-level rating scale (ie, high, moderate, low and very low).

Limitations

The limitations of this systematic review stem from the small sample size and thus the inability to complete subgroup analysis. The varied methodologies employed in some of the included studies lead to heterogeneity and low-grade evidence. The challenge continues to be developing large randomised controlled studies that will have the power to demonstrate the effect of different dosing, different regimens, different ways of administering the IB and the impact of age and severity on outcomes.

CONCLUSION

This review found that using the IB nebuliser in moderate to severe asthma reduces hospitalisation rates. However, adding IB via a spacer had no effect on hospitalisation rates. The length of hospital stay in hours, PICU admissions, additional treatment after interventions, adverse events and FEV₁ (% predicted) were similar in both groups. The asthma clinical score was significantly better in the group which received IB. The PEF measurement after the intervention was significantly better in the group that received IB. Considering the current evidence and safety profile, inhaled/nebulised IB needs to be considered as an additional treatment for acute asthma exacerbation. These data support recent guidelines recommendations for IB use.^{1 2 6 7}

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ARTIGO ORIGINAL

Duração de corticoterapia sistêmica guiada por eosinófilos sanguíneos em adultos hospitalizados por agudização de asma: ensaio clínico aleatorizado, controlado, aberto, de não-inferioridade

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RESUMO

Objetivo Os corticosteroides sistêmicos administrados durante 5–7 dias são o tratamento padrão para agudizações de asma, mas a duração ideal e o potencial para uma prescrição mais personalizada permanecem incertos. Abordagens guiadas por biomarcadores, como a contagem de eosinófilos no sangue, podem reduzir a exposição a corticosteroides sem comprometer os resultados clínicos. O objetivo deste estudo foi avaliar se a contagem de eosinófilos sanguíneos pode ser utilizada para reduzir de forma segura a exposição a corticosteroides sistêmicos em agudizações de asma que requerem hospitalização.

Métodos Neste ensaio aleatorizado, controlado, aberto e realizado em dois centros, adultos hospitalizados por agudização de asma foram distribuídos 1:1 para cuidados habituais (5 dias de prednisolona) ou para cuidados guiados por eosinófilos, utilizando a contagem de eosinófilos obtida antes da administração de corticosteroides (3 dias se <300 células/μL; 5 dias se ≥300 células/μL). O desfecho primário foi a não-inferioridade das taxas de falência terapêutica (compósito de extensão da corticoterapia, ventilação mecânica ou morte), com uma margem pré-definida de 20%.

Resultados Entre os 110 doentes aleatorizados (55 por grupo), 60% eram eosinofílicos e 40% não eosinofílicos. A falência terapêutica ocorreu em 6/55 (10,9%) no grupo guiado por eosinófilos versus 4/55 (7,3%) no grupo de cuidados habituais, uma diferença absoluta de 3,6% (IC 95% –8,9% a 16,2%), cumprindo o critério de não-inferioridade. A dose cumulativa de corticosteroides foi semelhante entre grupos, mas significativamente inferior nos doentes não eosinofílicos comparativamente aos eosinofílicos no grupo guiado por eosinófilos (136 vs 214 mg; $p=0,0004$). Esta diferença não foi observada nos cuidados habituais (186 vs 211 mg; $p=0,18$). Não houve diferenças significativas na duração do internamento, na alteração do Asthma Control Questionnaire-5, na necessidade de novos ciclos de corticosteroides aos 14 dias ou no tempo até à próxima agudização ao longo de 1 ano.

Conclusão A terapêutica guiada por eosinófilos reduziu de forma segura a exposição a corticosteroides sistêmicos em agudizações não eosinofílicas, mantendo resultados não-inferiores neste ensaio de prova de conceito.

Registo do ensaio: NCT05417906.

INTRODUCTION

Asthma is prevalent, affecting 262 million individuals worldwide.¹ It is a chronic inflammatory airways disease characterised by symptoms such as cough, sputum production, breathlessness, wheezing and chest tightness.² Symptoms may acutely worsen beyond the usual day-to-day variability, resulting in exacerbations.² Severe exacerbations may necessitate hospitalisation or even cause death.³ Asthma exacerbations are associated with significant mor-

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Current guidelines recommend 5–7 days of systemic corticosteroids for asthma exacerbations, but evidence supporting this duration is limited, and the optimal treatment length remains unclear. Biomarker-guided approaches could reduce unnecessary steroid exposure, particularly in non-eosinophilic exacerbations, which are less responsive to corticosteroids.

WHAT THIS STUDY ADDS

► This trial demonstrates that an eosinophil-guided strategy (3 days for non-eosinophilic exacerbations; 5 days for eosinophilic exacerbations) safely reduces corticosteroid exposure among non-eosinophilic patients without compromising outcomes, meeting non-inferiority for treatment failure compared with standard 5-day therapy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► The findings support further validation in larger, placebo-controlled trials and suggest that blood eosinophil counts could be used to personalise corticosteroid duration, promoting steroid stewardship and minimising adverse effects in asthma management.

bidity and mortality and account for the main share of healthcare costs.

Systemic corticosteroids are the mainstay of treatment for asthma exacerbations, but the optimal duration of treatment is not known.^{4 5} Clinical guidelines recommend giving 5–7 days. For example, the Global Initiative for Asthma strategy recommends 40–50 mg/day of prednisolone (or equivalent) for 5–7 days in adults.² Expert consensus from the USA similarly recommends 40–60 mg/day of prednisolone or equivalent for 5–7 days.⁶ UK guidelines suggest a minimum of 5 days.⁷

The evidence supporting these recommendations is limited. Systematic reviews (including a Cochrane review) identified only a few small, single-centre studies investigating different treatment durations.^{4 5} One early study randomised 35

patients hospitalised for exacerbation to a 1-week non-tapering course or to a 7-week tapering course and found no significant difference in re-exacerbation or readmission rates.⁸ Three randomised trials^{9–10} investigated hospitalised exacerbations, excluding life-threatening attacks requiring mechanical ventilation. The trials compared 5 versus 10 days,¹⁰ or 10 versus 17 days,^{9,11} and found no difference in peak flow, lung function or relapse rates beyond a 5–10-day course. In adults, the shortest duration ever investigated was 3 days, which was found to be inferior to 14 days in a small randomised trial of 20 patients, but 3 days was adequate for some patients.¹² The largest of these trials included just over 40 participants, and none of the trials were sufficiently powered to establish equivalence or non-inferiority.⁴ The Cochrane systematic review concluded that ‘evidence is not strong enough’ to compare the effectiveness of shorter versus longer regimens.⁵ Therefore, multicentre trials with adequate sample sizes are needed to investigate the efficacy of shorter treatment courses.

Treatment responses may vary due to heterogeneity of inflammatory mechanisms of exacerbations. Three subtypes of inflammation have been identified: eosinophilic with increased type 2 mediators, neutrophilic and bacteria-associated and predominantly type 1 inflammation associated with viral infections.¹³ The eosinophilic subtype is considered highly responsive to systemic corticosteroids,^{14–15} whereas non-eosinophilic subtypes are regarded as poorly corticosteroid responsive.¹⁶ This is supported by a recent observational study which found that patients with type 2 exacerbations experienced pronounced improvements in lung function and symptoms with oral steroid treatment, whereas those with non-type 2 exacerbations had minimal or no improvement.¹⁷ Thus, treatment duration could potentially be tailored to the inflammatory subtype.

A peripheral blood eosinophil count of ≥ 300 or 400 cells/ μL correlates strongly with eosinophilic airway inflammation.¹⁸ Conversely, counts below this threshold are indicative of non-eosinophilic airway inflammation. Compared with other biomarkers (exhaled nitric oxide, serum periostin and induced sputum cell counts), the peripheral blood eosinophil count is cheaper, easier to perform, widely available in clinical practice and offers the highest discriminative accuracy for eosinophilic vs non-eosinophilic airway inflammation.^{18–19} Thus, the peripheral blood eosinophil count could be used as a biomarker to identify patients having non-eosinophilic exacerbations, who may be effectively managed with shorter courses of systemic corticosteroids.

Even short courses of systemic corticosteroids carry risks, including sepsis, venous thromboembolism, fracture, peptic ulcer disease and cardiovascular events.²⁰ Because exacerbations recur throughout a patient's lifetime, repeated exposure further amplifies long term harms.^{20–21} Patients may even be willing to forego therapeutic benefits of corticosteroids to avoid adverse effects,²² underscoring the need for effective corticosteroid-stewardship strategies to minimise unnecessary exposure during exacerbations. To our knowledge, no prior trial has evaluated the use of blood eosinophils to guide precision prescribing of systemic corticosteroid in asthma exacerbations. Thus, the aim of this study was to investigate whether the blood eosinophil count can be used to safely reduce systemic corticosteroid exposure in hospitalised asthma exacerbations.

To that end, we conducted an open-label, randomised, controlled trial to evaluate the hypothesis that eosinophil-guided therapy to shorten systemic corticosteroid duration is non-inferior to usual care of uniformly prescribing a fixed duration in adults admitted for asthma exacerbation.

METHODS

Trial design

This was an investigator-initiated, randomised, controlled, open-label, parallel group, non-inferiority trial (ClinicalTrials.gov NCT05417906). There was no involvement of patients or the public in the design, conduct or reporting of this trial. The protocol was approved by the Singhealth Centralised Institutional Review

Board (CIRB no. 2022/2100) and Singapore Health Sciences Authority (Clinical Trials Notification no. CTN2200038). There were no changes to the original protocol after trial commencement.

Setting

General wards at two tertiary hospitals in Singapore (Singapore General Hospital and Changi General Hospital).

Inclusion and exclusion criteria

Subjects were eligible if aged ≥ 21 years old, admitted for acute exacerbation of physician-diagnosed asthma, and had not taken systemic corticosteroids within the 7 days of presentation. They were required to have a baseline blood eosinophil count taken as part of routine clinical care before administration of any systemic corticosteroids.

Exclusion criteria were: already received >3 days of systemic corticosteroids at the time of recruitment, concomitant pneumonia, admission to high-dependency or intensive care unit or requirement for invasive or non-invasive mechanical ventilation, conditions associated with secondary eosinophilia (eg, eosinophilic granulomatosis and polyangiitis, parasitic infections, malignancy), other concomitant respiratory conditions (eg, chronic obstructive pulmonary disease (COPD), bronchiectasis), on asthma biologic treatment (anti-IgE, anti-IL-5/5R, anti-IL-4R), life expectancy <12 months from any cause, prisoners or had participated in another clinical trial with investigation product within the last 6 months.

Randomisation, intervention and comparator groups

Individual participants were randomised 1:1 to eosinophil-guided or usual care. The random allocation sequence was generated using a computerised random number generator by a designated study team member who was not involved in enrolling and assigning participants. Randomisation was stratified by site and using permuted block randomisation with varying block sizes ranging from 2 to 6. Block size was not known by other study team members. Each allocation was placed inside a sealed, opaque envelope and numbered sequentially outside. Envelopes were opened by the research coordinator only after participants were confirmed eligible, had completed the informed consent form and been recruited into the trial.

The eosinophil-guided strategy involved the use of blood eosinophil as a biomarker to guide the duration of systemic corticosteroids prescribed. If the baseline blood eosinophil count was ≥ 300 cells/ μL , 5 days of one time per day, oral prednisolone at 0.5 mg/kg/day (limited to a range of 20–50 mg/day) was prescribed. If the eosinophil count was <300 cells/ μL , 3 days of prednisolone was prescribed. A shorter 3-day course was deemed to be safer than immediate discontinuation of steroids, given that this was a study of moderate-to-severe exacerbations leading to admission.

In the usual care group, all participants were prescribed 5 days of prednisolone regardless of the initial blood eosinophil count.

If subjects had received prednisolone during the hospitalisation but before recruitment into the trial, then only the doses for the remaining days were prescribed.

The study did not interfere with the initial decision to commence systemic steroids (ie, before recruitment into the trial, eg, intravenous hydrocortisone at the emergency department). Intravenous corticosteroids given prior to enrolment were included within the total cumulative dose of corticosteroids prescribed for the index admission, at a conversion ratio of prednisolone:hydrocortisone of 1:4. Decisions regarding extension of systemic corticosteroid duration, controller medications, rescue treatment, discharge and antimicrobial treatment were left to the discretion of the treating physicians based on routine clinical assessment (eg, improvement of symptoms, oxygen saturation levels, presence of wheeze).

Blinding

This was an open-label trial. Random allocation after recruitment was known to participants, care providers, data collectors, outcome assessors and data analysts. Placebo was not used.

Primary outcome

The primary outcome was 'treatment failure' during the index admission, a composite endpoint defined as death from any cause, need for invasive/non-invasive mechanical ventilation after recruitment or need to extend systemic corticosteroid treatment during the hospitalisation. Assessment for primary outcome was done by study physicians or clinical research coordinators at the time of discharge based on chart review.

Secondary outcomes

Length of stay at index admission and cumulative corticosteroid dose prescribed for the index exacerbation (including systemic

corticosteroid doses given at emergency department) were ascertained from chart review.

Post-discharge, subjects were contacted to ascertain the following secondary outcomes through questionnaires: additional systemic steroid bursts within 14 days; emergency department visits or admissions for asthma at 7, 14, 30 and 90 days; Asthma Control Questionnaire-5 (ACQ-5) at 7, 14, 30 and 90 days; and all-cause death, pneumonia, venous thromboembolism, sepsis, fractures, upper gastrointestinal bleeds/peptic or gastric ulcers at 30 and 90 days. A medical records review was also conducted to assess for emergency department visits or admissions for exacerbation up to 1 year.

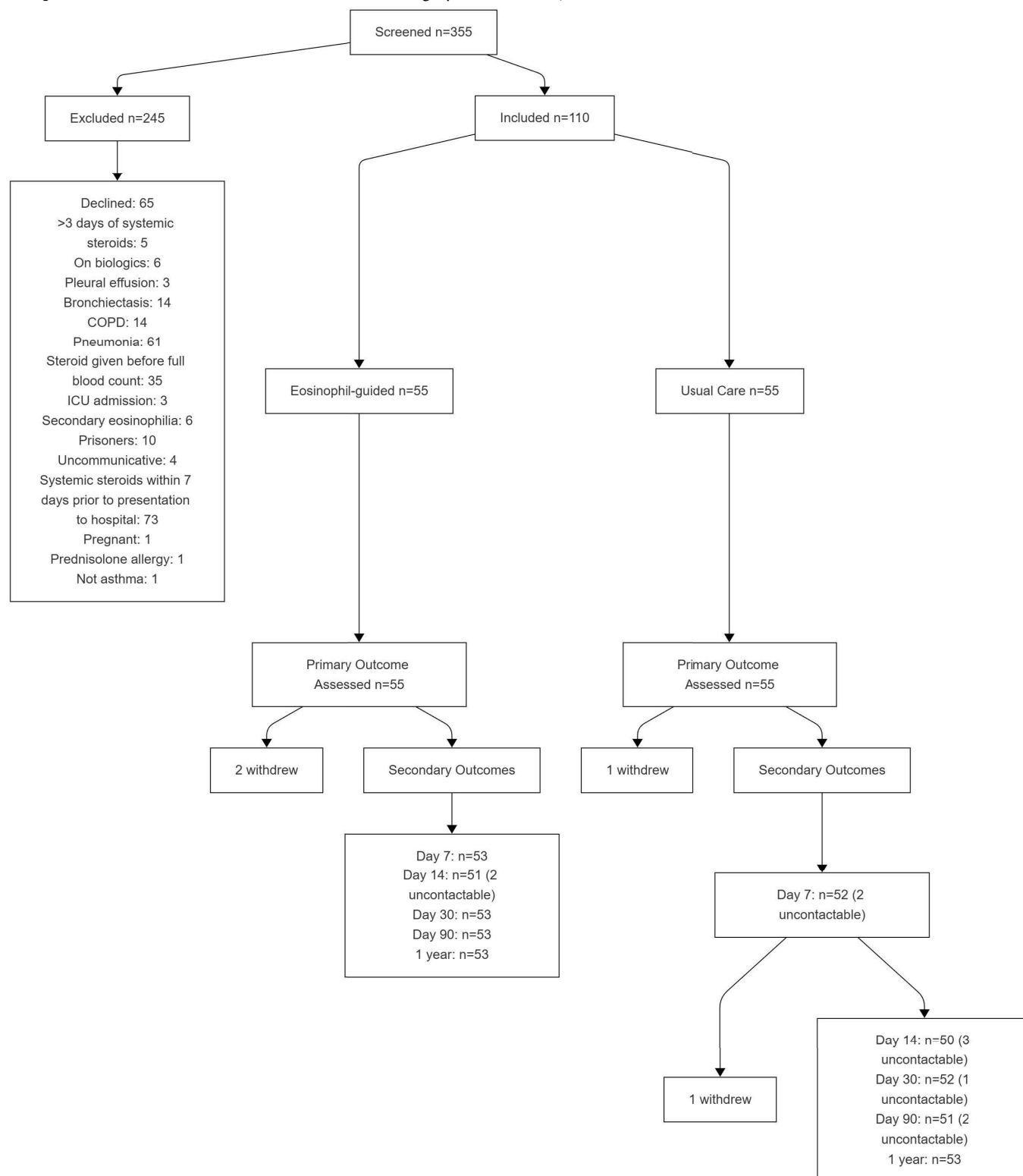


Figure 1 Enrolment, randomisation and follow-up. Patients may have more than 1 reason for exclusion. COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

Power calculation and statistical analysis

Sample size determination was based on the primary outcome of treatment failure. In a small historical study of hospitalised asthma exacerbations, the treatment failure rate was 11% for systemic steroid-treated and 56% for placebo-treated hospitalised, representing a 45% difference in absolute treatment failure rates favouring systemic corticosteroids.²³ We predetermined a non-inferiority margin of 20% absolute risk difference and considered this threshold clinically acceptable provided treatment failure is driven mainly by steroid extensions rather than life-threatening deteriorations (death or ventilatory support). Despite imprecision in the historical estimate, the 20% margin preserves >50% of the point estimate for the treatment effect of systemic steroids versus placebo. This non-inferiority margin led to an estimated sample size of $n=72$ based on 80% power and one-sided significance level of 0.025. Our final recruitment target was 110 or 55 in each group after accounting for potential dropouts.

Statistical analysis was done according to intention-to-treat. For the primary outcome of non-inferiority of treatment failure rates, we calculated the point estimate and 95% CI of the between-group difference in treatment failure rates, comparing usual and biomarker-directed care, and ascertained whether the 95% CI included the non-inferiority margin of 20%.

Secondary outcomes were compared between groups using the χ^2 test for categorical outcomes and the Student *t*-test for continuous outcomes. Participants with missing data on secondary outcomes were excluded. Time to next emergency department visit or admission for asthma was analysed using Cox proportional hazards regression, expressing the HR estimate with 95% CI. Change in ACQ-5 was modelled using linear mixed effects regression with multiple splines for each timepoint, assigned group as fixed effects and participants as random effects.

Statistical analyses were done using R.

RESULTS

Characteristics of participants

From May 2022 through April 2024, we screened 355 patients for potential enrolment. Of these, 65 declined to participate, and 180 had exclusions. The most common exclusions were exposure to systemic corticosteroids within 7 days before presentation to hospital ($n=73$), concomitant pneumonia ($n=61$), corticosteroid given before full blood count was drawn ($n=35$) and comorbid COPD ($n=14$) and bronchiectasis ($n=14$). In total, 110 patients were recruited, 55 to usual care and 55 to eosinophil-guided care (figure 1). The primary outcome was available for all 110 participants. Follow-up for secondary outcomes was high, with >90% of participants providing secondary outcome data in both groups.

Baseline characteristics are shown in table 1. Of the 110 participants, mean $\pm$ SD age was 48 $\pm$ 15 years, 68 (61.8%) were female and 31 (28.2%) were current smokers. 40 (36.4%) had at least one steroid burst in the past year, and 26 (23.6%) had at least one emergency department visit or hospitalisation for exacerbation in the past year. 66 (60%) were already on prior maintenance therapy with inhaled corticosteroid (ICS)-containing regimens. 66 (60%) of subjects were eosinophilic (≥ 300 cells/ μ L), and 44 (40%) were non-eosinophilic (<300 cells/ μ L). Mean blood eosinophils was 425 $\pm$ 429 cells/ μ L. Characteristics were broadly comparable between groups, although the mean blood eosinophil count and ACQ-5 at baseline was slightly higher in the eosinophil-guided group.

Primary outcome

Treatment failure occurred in six of 55 participants (10.9%) in the eosinophil-guided group, with four of these treatment failures occurring in subjects with eosinophils ≥ 300 cells/ μ L and two in subjects with eosinophils <300 cells/ μ L. In the usual care group, four of 55 (7.3%) experienced treatment failure, of which three treatment failures were in subjects with eosinophils ≥ 300 cells/ μ L and one in a subject with eosinophils <300 cells/ μ L. There was one treatment failure with eosinophils <150 cells/ μ L in each arm. All treatment failures were due to extension of treatment duration,

Table 1 Baseline characteristics

	Overall (n=110)	Usual care (n=55)	Eosinophil-guided (n=55)
Age (years)	48.4 $\pm$ 15.3	50.7 $\pm$ 15.4	46.2 $\pm$ 15.0
Female	68 (61.8%)	32 (58.2%)	36 (65.5%)
Race			
Chinese	42 (38.2%)	20 (36.4%)	22 (40.0%)
Indian	15 (13.6%)	7 (12.7%)	8 (14.5%)
Malay	40 (36.4%)	24 (43.6%)	16 (29.1%)
Others	13 (11.8%)	4 (7.3%)	9 (16.4%)
Current-smoker	31 (28.2%)	13 (23.6%)	18 (32.7%)
E-cigarettes or vaping	2 (1.8%)	1 (1.8%)	1 (1.8%)
No. of days unwell prior to admission	3 (2, 7)	3 (2, 7)	3 (1, 8)
No. of steroid courses in the previous 12 months			
0	70 (63.6%)	32 (58.2%)	38 (69.1%)
1	18 (16.4%)	8 (14.5%)	10 (18.2%)
≥ 2	22 (20.0%)	15 (27.3%)	7 (12.7%)
No. of ED visits/hospitalisations for asthma in the previous 12 months			
0	84 (76.4%)	38 (69.1%)	46 (83.6%)
1	18 (16.4%)	11 (20.0%)	7 (12.7%)
≥ 2	8 (7.2%)	6 (10.9%)	2 (3.6%)
Maintenance treatment prior to admission			
As-needed SABA or no anti-inflammatory treatment	44 (40.0%)	20 (36.4%)	24 (43.6%)
As-needed or regular low-dose ICS-formoterol	4 (3.6%)	2 (3.6%)	2 (3.6%)
Regular ICS	6 (5.5%)	2 (3.6%)	4 (7.3%)
Regular medium- or high-dose ICS+LABA	56 (50.9%)	31 (56.4%)	25 (45.5%)
History of life-threatening asthma	6 (5.5%)	5 (9.1%)	1 (1.8%)
Asthma Control Questionnaire-5	2.89 $\pm$ 1.69	2.73 $\pm$ 1.86	3.04 $\pm$ 1.50
Peripheral eosinophils			
Absolute ($\times 10^3$ / μ L)	0.425 $\pm$ 0.429	0.399 $\pm$ 0.485	0.451 $\pm$ 0.367
Relative (%)	4.0 $\pm$ 3.7	3.7 $\pm$ 3.9	4.3 $\pm$ 3.4
Comorbidities			
Cardiac	17 (15.5%)	8 (14.5%)	9 (16.4%)
Diabetes	28 (25.5%)	18 (32.7%)	10 (18.2%)
Aspirin exacerbated respiratory disease	1 (0.9%)	1 (1.8%)	0 (0%)
Obstructive sleep apnoea/obesity hypoventilation syndrome	12 (10.9%)	5 (9.1%)	7 (12.7%)
Gastro-oesophageal reflux disease	11 (10.0%)	3 (5.5%)	8 (14.5%)
Anxiety disorders	0 (0%)	0 (0%)	0 (0%)
Depression	1 (0.9%)	1 (1.8%)	0 (0%)
Venous thromboembolism	0 (0%)	0 (0%)	0 (0%)
Osteoporosis	2 (1.8%)	1 (1.8%)	1 (1.8%)
Upper gastrointestinal bleeding/peptic or gastric ulcers	0 (0%)	0 (0%)	0 (0%)

ED, emergency department; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist.

with no incident deaths or deterioration requiring invasive/non-invasive ventilation. The difference in treatment failure rate was 3.6%, favouring the usual care group, with a 95% CI of -8.9% to

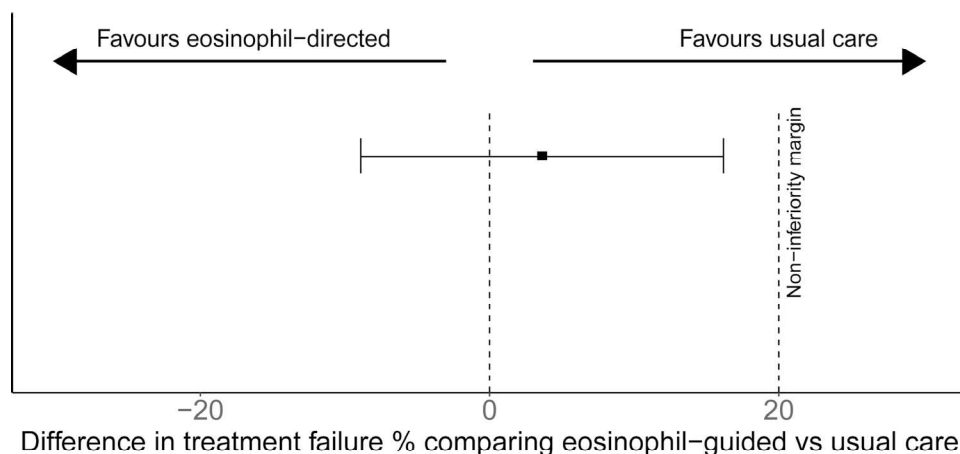


Figure 2 Difference in treatment failure rates.

16.2%. The upper limit of the CI was less than, and did not cross, the pre-specified 20% non-inferiority margin; hence, the primary outcome of non-inferiority was met (figure 2).

Secondary outcomes

Comparing eosinophil-guided to usual care, there were no significant differences in length of stay (2.5 ± 1.4 vs 2.7 ± 1.8 days, $p=0.68$) or additional systemic steroid bursts at 14 days (6/52 (11.5%) vs 4/50 (8.0%), $p=0.79$). There were no deaths at 30 and 90 days.

There was no statistically significant difference between eosinophil-guided versus usual care in ACQ-5 change (fixed effect coefficient: -0.20 , 95% CI -0.64 to 0.23 , $p=0.36$) at 7, 14, 30 and 90 days (figure 4).

The cumulative incidence of recurrent exacerbations is shown in figure 5. At 30 days, 1.9% (95% CI 0% to 5.5%) of participants in the eosinophil-guided group and 3.8% (95% CI 0% to 8.8%) in the usual care group had experienced a recurrent exacerbation. By 90 days, the cumulative incidence of recurrent exacerbation was 9.4% (95% CI 1.2% to 17.0%) in the eosinophil-guided group and 5.6% (95% CI 0% to 11.7%) in the usual care group. There was no statistically significant difference between the groups in recurrent exacerbations over 1 year (HR for eosinophil-guided vs usual care: 0.76, 95% CI 0.33 to 1.74, $p=0.52$).

Incidence of pneumonia at 30 days was similar between groups (eosinophil-guided vs usual care: 1/50 (2.0%) vs 1/48 (2.0%), $p=1.00$). No additional cases of pneumonia were observed at 90 days. There were no incident cases of sepsis, venous thromboembolism, gastrointestinal bleeds or peptic ulcers and fractures at 30 and 90 days.

DISCUSSION

This randomised, controlled, open-label trial investigated whether the blood eosinophil count can be used to safely reduce exposure

to systemic corticosteroid therapy in hospitalised asthma exacerbations. The eosinophil-guided strategy, consisting of prescribing a shorter duration of 3 days of prednisolone specifically for subjects with blood eosinophils <300 cells/ μ L or 5 days for ≥ 300 cells/ μ L, was found to be non-inferior for treatment failure compared with usual care of uniformly prescribing a fixed duration of 5 days of prednisolone for all patients irrespective of blood eosinophil count. No deaths were observed in this study. There were no significant differences in length of stay, change in asthma symptoms, additional systemic steroid use at 14 days and time to next emergency visit or admission for asthma exacerbation.

In chronic asthma, a wealth of evidence has established that disease characterised by type 2 inflammation is steroid-responsive, whereas non-type 2 inflammation is generally less responsive to systemic and inhaled steroids.^{24–28} Evidence regarding corticosteroid responsiveness of different inflammatory endotypes is more limited for acute exacerbations. Relapse rates are low among mepolizumab-treated severe asthmatics experiencing non-eosinophilic exacerbations and not given systemic corticosteroids.²⁹ A transcriptomic network analysis found that systemic corticosteroids selectively suppressed eosinophil activation pathways without affecting various other pathways associated with exacerbation.³⁰ Recently, lung function improvement was found to correlate with the degree of type 2 inflammation in systemic corticosteroid-treated exacerbations.¹⁷ A number of studies have evaluated the use of blood eosinophils to guide systemic steroid therapy in COPD exacerbations,^{31–33} but no studies have investigated the eosinophil-guided strategy in acute asthma. Our trial is the first to investigate the feasibility and safety of using the blood eosinophil count to reduce systemic steroid exposure in asthma exacerbations, and we were able to demonstrate that the eosinophil-guided strategy can be used to shorten the duration of systemic corticosteroid use without compromising safety.

5–7 days of systemic corticosteroids for all asthma exacerbations is an entrenched clinical practice but may undermine corticosteroid stewardship by missing opportunities for shorter courses in some patients, potentially resulting in unnecessary steroid exposure and increased risk of side effects. Population-based studies have linked the use of short-course systemic corticosteroid to increased risk of sepsis, venous thromboembolism, heart failure and fractures.^{20–34} In one such study, the median duration of systemic steroid use was only 6 days, and increased risk of steroid-related morbidities was evident even at low doses (prednisolone equivalent doses of <20 mg per day).²⁰ Among asthma patients, frequent corticosteroid courses are associated with increased risk of steroid-related adverse outcomes.²¹ The risk of steroid-related morbidities starts to increase when cumulative exposure exceeds prednisolone-equivalent doses of 500 to 1000 mg, which corresponds to two to four courses of treatment for asthma exacerbation.³⁵ Steroid-related morbidity accounts for significant additional costs of asthma, particularly among patients receiving multiple courses of systemic corticosteroids.³⁶ While optimising baseline inhaled maintenance

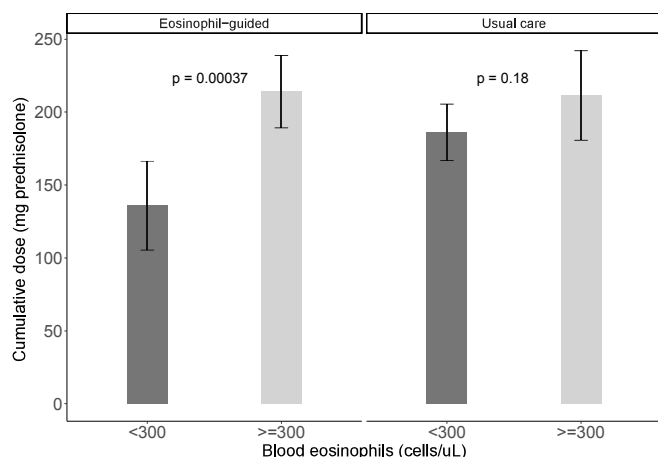


Figure 3 Cumulative systemic corticosteroid exposure, per patient, for the index exacerbation.

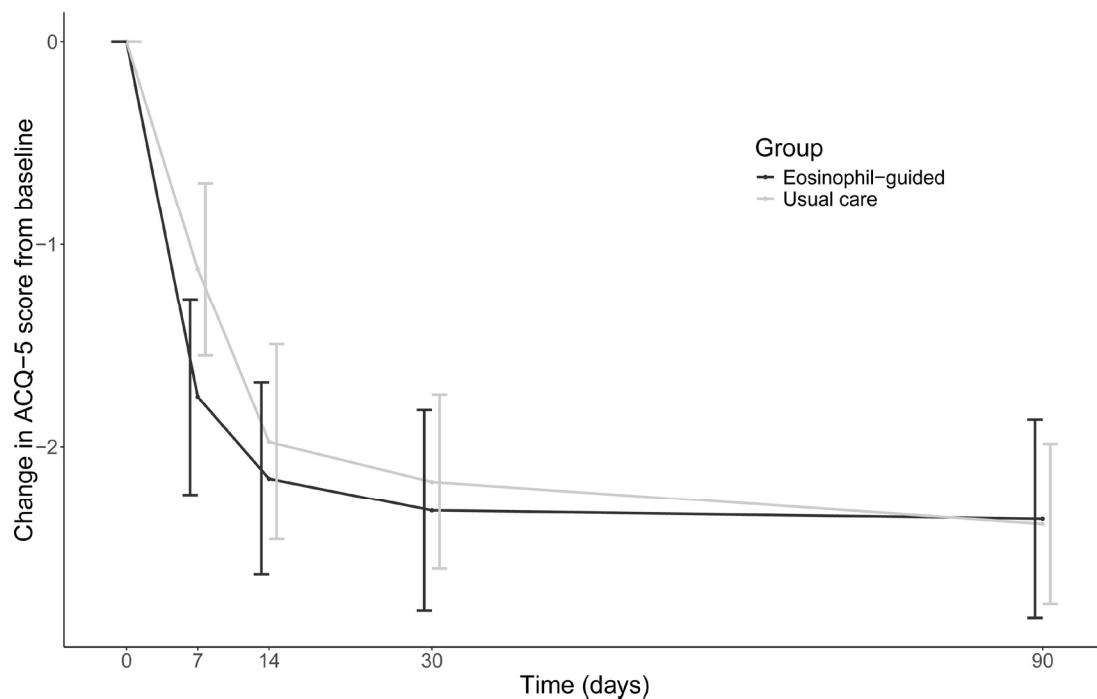


Figure 4 Change in Asthma Control Questionnaire-5 (ACQ-5).

therapy, inhaler technique, adherence, allergen avoidance and other preventive measures can reduce the frequency of exacerbations and thereby limit systemic corticosteroid exposure,^{37,38} exacerbations cannot be entirely prevented, underscoring the need for additional strategies to minimise corticosteroid use during these episodes of exacerbations.³⁹ Our results indicate that using the blood-eosinophil count to guide systemic corticosteroid therapy may provide a promising strategy for personalised corticosteroid stewardship in the setting of acute exacerbations. However, implementation requires validation in larger, more diverse cohorts.

In this study, 60% of patients were eosinophilic and 40% non-eosinophilic using a 300 cells/ μ L cut-point. The higher proportion of eosinophilic patients relative to non-eosinophilic patients may have diluted differences in mean cumulative steroid dose between usual care and eosinophil-guided groups. However, with the eosinophil-guided strategy, non-eosinophilic patients received significantly lower cumulative doses compared with eosinophilic patients, a difference that was not observed with usual care. Our study was not powered for non-eosinophilic subgroup analyses, and larger studies focusing solely on non-eosinophilic patients are needed to confirm safety of shorter steroid courses.

Although a <150 cells/ μ L threshold offers higher negative predictive value for type 2 inflammation, adopting this stricter cut-point would classify fewer patients as non-eosinophilic and reduce applicability to a narrower patient population in clinical

practice. Moreover, patients with counts between 150–300 cells/ μ L may still exhibit type 2 inflammation and corticosteroid responsiveness.¹⁷ For this reason, our intervention prescribed a shorter corticosteroid course for those with eosinophils <300 cells/ μ L, rather than omit treatment. Completely withholding treatment was deemed ethically and clinically challenging, given that systemic corticosteroids are current standard of care. We therefore adopted a pragmatic approach of reducing treatment duration in biomarker-low patients, while allowing clinicians to extend therapy based on clinical judgement.

This study has several limitations. First, the open-label design may have introduced bias in assessing treatment failure, which included subjective elements such as the decision to extend corticosteroid treatment. However, most extensions occurred in subjects with eosinophils $\geq$ 300 cells/ μ L (seven cases) versus <300 cells/ μ L (three cases), supporting feasibility and safety of dose reduction in the majority of non-eosinophilic exacerbations.

Second, the 20% non-inferiority margin may be considered generous. A fixed-margin approach using the lower 95% CI bound of the historical effect was impractical, requiring large sample sizes (eg, $\geq$ 15 327 per arm for a 1% margin). We therefore prespecified a 20% margin, deemed clinically acceptable provided that treatment failures are mainly driven by treatment extensions rather than serious clinical deteriorations resulting in ventilatory failure or death. Patient and provider preferences from a recent discrete choice experiment indicate tolerance for 26%–58% absolute increases in treatment failure risk,²² suggesting our margin is appropriate.

Other limitations include limited generalisability with the trial involving only two centres in Singapore, and the small number of events constrains meaningful subgroup analyses. Additionally, lung function data were unavailable, but clinical outcomes—including symptom improvement, length of stay and clinically meaningful deteriorations (need for ventilatory support or death)—are known to correlate with lung function recovery. Missing data could lead to bias in the secondary outcomes, but the risk of bias was low due to high rates of follow-up in both groups (>90%).

Addressing these limitations will require larger, double-blind, placebo-controlled trials, with a focus on non-eosinophilic exacerbations, and applying stricter but feasible non-inferiority margins (eg, 10%–15%), and use composite endpoints capturing meaningful clinical deterioration, re-treatment or healthcare utilisation over a longer follow-up period (eg, 30 days).

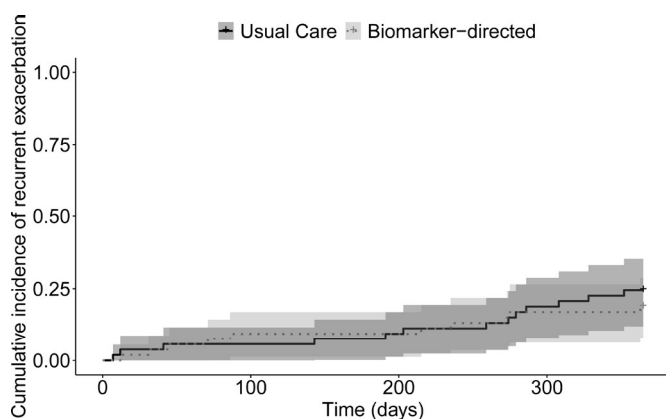


Figure 5 Cumulative incidence of recurrent exacerbation.

In conclusion, in this randomised trial of hospitalised patients with asthma exacerbation, using the blood eosinophil count to determine the duration of systemic corticosteroid therapy was non-inferior to usual care in preventing treatment failure, while reducing cumulative corticosteroid exposure for non-eosinophilic patients. These findings should be validated in a larger, randomised, double-blind and placebo-controlled trial.

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Contributors AY conceived and designed the study, obtained funding, performed statistical analyses and drafted the initial manuscript. All authors were responsible for patient recruitment, data collection and clinical oversight. All authors contributed to data interpretation, critically revised the manuscript for important intellectual content and approved the final version for submission. MSK is the guarantor and accepts full responsibility for the integrity of the work. The authors used artificial intelligence-based language models (ChatGPT and DeepSeek) to assist in improving the clarity, conciseness and structure of the manuscript text. The AI tool was not used for data analysis, interpretation or generation of scientific content. All revisions suggested by the AI were reviewed, verified and approved by the authors, who take full responsibility for the content of the manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involved human participants and was approved by the Singhealth Centralised Institutional Review Board (CIRB no. 2022/2100) and Singapore Health Sciences Authority (Clinical Trials Notification no. CTN2200038). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available from the corresponding author upon reasonable request. Individual participant data have been de-identified, and requests will be considered in line with institutional and ethics board policies.

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ARTIGO ORIGINAL

Fatores associados à medicação inalada de manutenção concordante com as guidelines na DPOC: um estudo de coorte longitudinal baseado na população

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RESUMO

Contexto Apesar das recomendações das guidelines, muitos doentes com doença pulmonar obstrutiva crônica (DPOC) não recebem, ou não mantêm, terapêutica inalada de manutenção concordante com as orientações clínicas. Avaliámos fatores do doente e do sistema de saúde associados à concordância com as guidelines e à persistência terapêutica.

Métodos Realizámos um estudo de coorte baseado na população, utilizando dados administrativos da Colúmbia Britânica, Canadá (2011–2022). Foram incluídos doentes ≥40 anos com diagnóstico recente de DPOC. Os doentes foram classificados como de alto risco (≥2 agudizações ambulatoriais ou ≥1 agudização com internamento no ano anterior) ou baixo risco (≤1 agudização ambulatorial). Esta classificação foi utilizada para determinar se a medicação dispensada era concordante com as guidelines. Modelos lineares generalizados independentes avaliaram a associação entre fatores do doente, clínicos e do sistema de saúde e: início de terapêutica concordante com as guidelines e persistência subsequente com essa terapêutica.

Resultados Foram incluídos 71 996 doentes, com um seguimento médio de 6,15 anos (DP 2,65). Apenas 30,42% iniciaram tratamento concordante com as guidelines. Entre estes, a proporção média de dias cobertos (PDC) por regimes concordantes foi de 31,93%. Os doentes de alto risco iniciaram terapêutica concordante com mais frequência do que os de baixo risco (70,4% vs 13,3%) e apresentaram maior PDC médio (57,33% vs 26,35% por doente-ano). O acompanhamento por pneumologista e o aumento das consultas ambulatoriais aumentaram tanto: o início (OR 5,14; IC 95% 4,88–5,41 e OR 1,25; IC 95% 1,24–1,26), como a persistência (OR 1,13; IC 95% 1,09–1,17 e OR 1,019; IC 95% 1,015–1,024) com terapêutica concordante com as guidelines.

Conclusão A utilização de medicação inalada de manutenção concordante com as guidelines é baixa. Um maior acesso a cuidados ambulatoriais e a acompanhamento especializado pode melhorar a gestão da DPOC.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive lung condition marked by persistent symptoms such as cough and dyspnoea, resulting from airflow obstruction.¹ Its global prevalence is projected to reach 600 million individuals by 2050.¹ Acute exacerbations of COPD (AECOPD), a major clinical event punctuating the course of COPD, accelerate lung function decline and double the risk of death within the following year, imposing a high burden on patients and healthcare systems.^{2,3} In Canada, AECOPD was the second leading cause of hospitalisation in 2022, following childbirth.⁴ Therefore, preventing AECOPD is a primary focus of COPD management.

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Preventing acute exacerbations of chronic obstructive pulmonary disease (AECOPD) through optimal use of guideline-concordant maintenance inhaled medication is a crucial component in the management of COPD. Previous studies have found that many patients do not receive guideline-concordant medications, and persistence with inhaled medications in general is poor. Our study examined prescriber and patient factors associated with guideline-concordant medication use, which provides a more complete understanding of medication persistence and strategies to improve guideline-concordant COPD management.

WHAT THIS STUDY ADDS

► Only one-third of patients in our study ever received guideline-concordant maintenance inhaled medications. Among these patients, guideline-concordant medication regimens persisted only one-third of the time. Rates of guideline-concordant medication use were especially low among patients with a low risk of AECOPD, suggesting that proactive management to reduce the future risk of AECOPD is rare. Receiving care from a pulmonologist and having more frequent outpatient visits are associated with increased initiation and persistence with guideline-concordant medications.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► Suboptimal use of maintenance inhaled medications recommended by evidence-based COPD management strategies is a large gap in COPD management. Improved access to outpatient and specialty care in patients at low risk of AECOPD, along with addressing missed opportunities to improve appropriate medication use to prevent future AECOPD, may improve long-term patient outcomes.

To prevent AECOPD, maintenance inhaled medications—including long-acting bronchodilators (LABDs) such as long-acting muscarinic antagonists (LAMA), long-acting beta agonists (LABA) and inhaled corticosteroids (ICS)—are mainstays of COPD management.¹ Since 2000, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has provided evidence-based management strategies to guide medication use in COPD, which have been shown to reduce AECOPD frequency and potential mortality.¹

Achieving guideline-concordant care depends on patients being prescribed appropriate medication regimens and taking them as prescribed. Previous research has shown that prescriber and patient concordance with COPD management strategy recommendations is suboptimal. In population-based studies in Canada and the USA, 40–50% of patients were not receiving adequate maintenance inhaled therapy.^{5,6} Similarly, only 10–50% of patients were persistent with any maintenance inhaled medications, regardless of guideline concordance.^{7–9} Strategies to improve uptake and persistence with guideline-concordant medications for treatment of COPD are needed.

Previous studies have explored patient and health system factors affecting guideline-concordant medication use within specific patient subgroups,⁶ for certain inhaled medications¹⁰ or over short time frames.⁵ Few studies have examined both the initiation of guideline-concordant regimens (reflecting prescriber behaviour) and patient persistence (reflecting medication-taking behaviour) across large COPD populations and over extended time periods.

Using a population-based incident cohort of patients newly diagnosed with COPD, our objectives were to: (1) quantify trends in the initiation of guideline-concordant maintenance inhaled medications and persistence of guideline-concordant medications after initiation, and (2) examine patient and health system factors associated with initiation and persistence of guideline-concordant medications, which may reflect distinct prescriber and patient behaviours. Our findings can inform targeted strategies and education to improve uptake of guideline-concordant management of COPD.

METHODS

Data sources

Our study used claims-based administrative health databases covering all legal residents of British Columbia (BC), a Canadian province with over 5 million people as of 2021.¹¹ We accessed the following deidentified, individually linked databases from 1 January 1997 to 31 March 2022, which included (1) PharmaNet (outpatient prescription drug claims), (2) Medical Services Plan (MSP) registration and income data (including socioeconomic status (SES) by neighbourhood income quintile), (3) MSP Payment File (fee-for-service outpatient visits), (4) demographics, (5) Discharge Abstract Database (hospital discharges) and (6) National Ambulatory Care Reporting System (ambulatory and emergency care visits). Access to data provided by the data steward(s) is subject to approval but can be requested for research projects through the data steward(s) or their designated service providers. Further information on the datasets used for this project is available at https://my.popdata.bc.ca/project_listings/21-070. All inferences, opinions and conclusions drawn in this material are those of the author(s) and do not reflect the opinions or policies of the data steward(s).

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Study population and study period

We created an incident cohort of individuals aged ≥ 40 years with physician-diagnosed COPD using a validated case definition that required ≥ 1 COPD-related hospitalisation or ≥ 3 outpatient visits within 24 months (International Classification of Diseases, Ninth Revision (ICD-9): 491, 492, 493.2, 496; Tenth Revision (ICD-10): J41–J44).¹² This definition demonstrated 57.5% sensitivity and 95.4% specificity in a previous study.¹² Patients were required to have their first COPD-related healthcare encounter (the index date) on or after 1 January 2011. This aligns with the significantly revised treatment algorithm first introduced in the 2011 version of the GOLD management strategy, which has largely been retained in subsequent versions. Patients were followed from the index date until death, end of registration, last recorded healthcare utilisation (including medication dispensing) or the end of data availability on 31 March 2022, whichever came first. Individuals needed to be registered in the database for at least 3 years prior to the index date and have a minimum of 2 years of follow-up after the index date to allow sufficient time for inhaled medication initiation (figure 1). We excluded patients who had any inpatient or outpatient visit with asthma as the primary diagnosis code (ICD-9: 493 or ICD-10: J45, J46) within 3 years prior to their COPD diagnosis date.

Guideline-concordant maintenance inhaled medication

The definition of guideline-concordant maintenance inhaled therapy was adapted from a systematic review of previous definitions used in administrative data studies to incorporate treatment recommendations for all GOLD versions from 2011 to 2024 regardless of symptom severity¹³ (table 1). Guideline-concordant medications were stratified by AECOPD risk, which has been consistently used to categorise patients in GOLD guidelines from 2011 to 2024. This approach also acknowledges potential variation in clinical practice, including both delays in guideline implementation and early adoption of emerging clinical trial evidence. Due to the absence of symptom scores and eosinophil counts in our data, further stratification could not be implemented (see online supplemental appendix 1 for a summary of GOLD treatment recommendations by AECOPD risk across major guideline versions). AECOPD risk was determined annually based on healthcare utilisation.¹ Patients were classified as low risk if they had ≤ 1 outpatient AECOPD in the previous year, and high risk if they had ≥ 2 outpatient AECOPDs or ≥ 1 AECOPD-related hospitalisation. Hospitalisations due to AECOPD had a primary discharge diagnosis of COPD.¹⁴ Outpatient AECOPD was defined as outpatient or emergency department (ED) visits with primary COPD diagnosis, not resulting in hospitalisation, but followed by a prescription for antibiotics and/or oral corticosteroids within 7 days (Drug Identification Numbers (DIN) are listed in online supplemental appendix 2). Patients diagnosed in hospital after AECOPD were considered high risk for the first year after diagnosis; all others were consi-

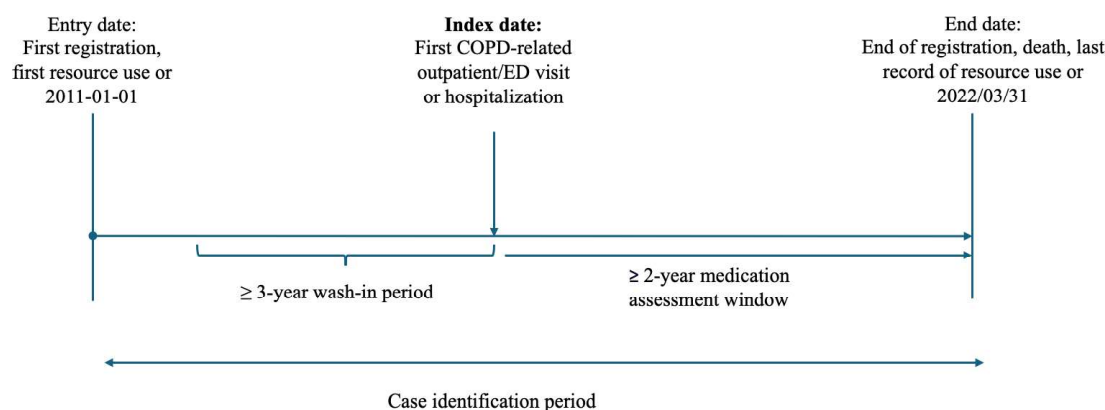


Figure 1 Schematic illustration of study design. COPD, chronic obstructive pulmonary disease; ED, emergency department.

Table 1 Guideline-concordant/discordant maintenance inhaled medication regimens for COPD

AECOPD risk*	Guideline-concordant regimens	Guideline-discordant regimens	
		Undertreatment	Overtreatment
Low risk of AECOPD	LAMA or LABA or LAMA plus LABA	No maintenance inhaled medication or ICS	ICS plus LAMA or ICS plus LABA or ICS plus LAMA plus LABA
High risk of AECOPD	LAMA or LAMA plus LABA or ICS plus LABA or ICS plus LAMA plus LABA	No maintenance inhaled medication or ICS or LABA	N/A

*AECOPD risk: Low risk is defined as having no more than one outpatient exacerbation in the previous year. High risk is defined as having two or more outpatient exacerbations or a COPD exacerbation requiring hospitalisation in the previous year. An outpatient exacerbation is defined as an outpatient or emergency department visit that does not lead to hospitalisation but is followed by the dispensing of antibiotics and/or oral corticosteroids within 7 days. AECOPD, acute exacerbation of COPD; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; N/A, not applicable.

dered low risk. Inhaled medications approved in Canada containing LAMA, LABA or ICS, either as single ingredients or in combination products, were identified using DINs (online supplemental appendix 2). Combination therapies were determined either by a single inhaler containing multiple drug classes or by overlapping days of supply from separate inhalers with different classes.

Outcomes

We evaluated two outcomes: (1) the initiation of guideline-concordant maintenance inhaled medication and (2) persistence with guideline-concordant medication after initiation. Outcomes were assessed per patient-year from the index date, excluding the final year if follow-up was incomplete. Only patient-years with a registration duration covering the majority of the year (≥ 220 days) were included.

Treatment initiation was defined as the first patient-year in which patients received guideline-concordant maintenance inhaled medication of any duration. Persistence was measured as the proportion of days covered (PDC) by a guideline-concordant inhaled medication, based on dispensed days supply, serving as a proxy for continued medication use.¹⁵ It was calculated as the number of days supplied with a medication divided by the total non-hospitalised days in that year, starting from the year of initiation, and expressed as a percentage. A PDC of 100% indicates that every day in that patient-year was covered by guideline-concordant medication, whereas a PDC of 0% indicates that no days in that patient-year were covered by guideline-concordant medication. Early refills were adjusted by adding overlapping days' supply from the previous fill to the start date of the next fill.

Outcomes

Informed by previous publications,^{5 16–19} clinical relevance, Andersen's framework of health service use²⁰ and data availability, we evaluated whether the initiation of a guideline-concordant regimen was associated with patient predisposing factors (sex, age), provider predisposing characteristics (pulmonologist vs general practitioner), enabling resources (health authority (HA), rurality, SES) and need characteristics (disease severity and comorbidities, total number of ED or outpatient visits in each patient-year). AECOPD risk and use of symptom-control medications served as proxies for disease severity. We evaluated the impact of these same factors on persistence, in addition to whether LAMA-based combination therapy was prescribed as a single inhaler.

Comorbidities were measured cumulatively in all years prior to the patient-year being analysed using the Charlson Comorbidity Index.²¹ Pulmonologist care was defined as ever having a pulmonologist visit before or during the analysed patient-year. AECOPD

risk in the analysed patient-year was based on AECOPD events from the previous year. All other variables, including age, HA, rurality, SES, medication use, ED visits and outpatient visits, were measured during the analysed patient-year. SES was defined as income-based neighbourhood quintiles, and rurality was defined by linking patients' forward sortation areas to regions identified in the 2024 BC Rural Practice Subsidiary Agreement.²²

Statistical analysis

We generated descriptive statistics on guideline-concordant medication use, including the proportion of patients on guideline-concordant therapy, by medication class and AECOPD risk, across years since COPD diagnosis. We also assessed the mean and SD of PDC by guideline-concordant medications in years since treatment initiation, stratified by AECOPD risk. Temporal trends in the proportion and PDC of guideline-concordant medication use were evaluated by calculating the mean annual change since diagnosis, with 95% CIs using Student's t-distribution (online supplemental appendix 3).

We conducted two separate regression analyses, logistic regression and binomial proportion regression with a logit link, to assess factors associated with the initiation and persistence of guideline-concordant inhaled medication, respectively. Generalised estimating equations with an exchangeable correlation matrix were used (see online supplemental appendix 4 for assumption checks). In the logistic regression, we estimated the probability of initiating guideline-concordant medication, adjusting for the previously described covariates. All patient-years up to and including the year of initiation (or end of follow-up) were included. In the binomial proportion regression, conducted within the subset of patients who initiated guideline-concordant medication, we examined factors associated with PDC after initiation. PDC was modelled by specifying the number of days covered (successes) as the numerator and total eligible days in the year (trials) as the denominator, while adjusting for the previously described covariates. This analysis included only patient-years following the initiation of guideline-concordant treatment, including the first year of initiation.

We assessed the significance of associations with SES and HA using joint Wald χ^2 tests within logistic regression and binomial proportion models adjusted for all covariates. As HA in BC is defined solely by geographical location, it encompasses a variety of factors related to SES and healthcare access. Because it has limited interpretability and generalisability beyond the BC healthcare context, HA was excluded from the final model. However, SES and rurality were included in the models, which include some of the underlying HA effects.

In sensitivity analysis, we repeated this analysis in all patients who met the diagnosis criteria for COPD, regardless of asthma history. A two-tailed p value < 0.05 was considered statistically significant. Analyses were conducted using R V.4.4.1²³ and SAS V.9.4.²⁴ The results of this study were reported in accordance with the Reporting of Studies Conducted Using Observational Routinely-Collected Health Data statement.²⁵

RESULTS

Study cohort

The final cohort included 71 996 patients with an average of 6.15 years (SD 2.65) of follow-up, resulting in 412 054 patient-years of observation (figure 2). At diagnosis, the mean patient age was 67.87 years; 45.17% were female, and 33.77% lived in rural areas. 30.42% (n=21 902) of patients initiated guideline-concordant maintenance inhaled medication during follow-up. Patients who initiated guideline-concordant medication were more likely to have received pulmonologist care within the first year of COPD diagnosis (13.41% vs 6.02%), have at least one high AECOPD risk patient-year during follow-up (48.48% vs 20.42%) and had more COPD-related outpatient visits (mean 2.07 vs 0.98 per patient-year) (table 2).

Trends in guideline-concordant maintenance inhaled medication use

In the first year after diagnosis, 63.84% of patients with COPD (n=46 268) were not receiving any maintenance inhaled medica-

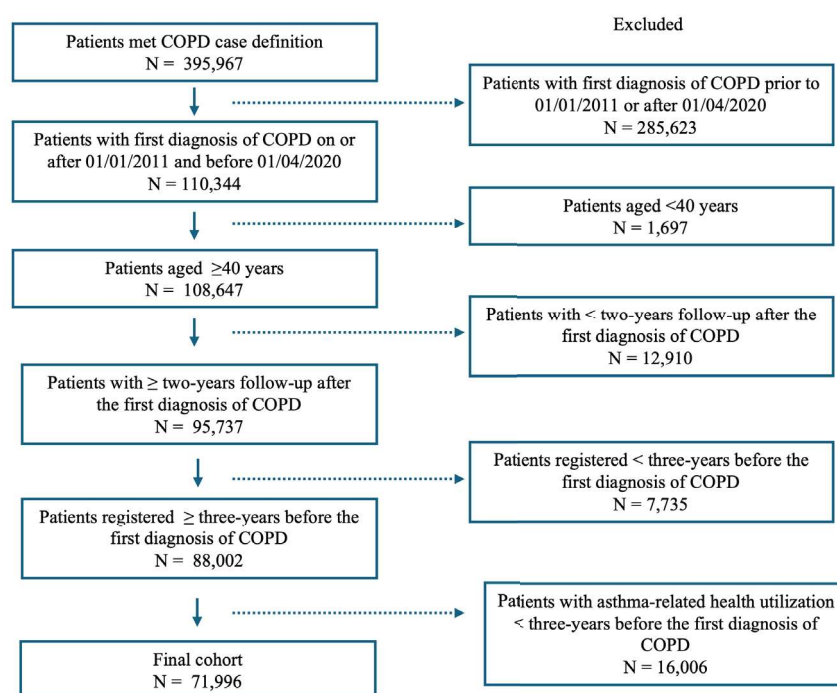


Figure 2 Flow diagram of building the study cohort. COPD, chronic obstructive pulmonary disease.

tions. The mean proportion did not change over years since diagnosis among all patients with COPD (95% CI -1.62% to 0.38%), despite decreasing in high AECOPD risk patients (-5.44% , 95% CI -10.75% to -0.12%), but not among low-risk patients (95% CI -1.93% to 1.29%).

Overall, 16.25% (median, IQR: 13.36–18.73%) of patients received guideline-concordant treatment per patient-year since diagnosis. Patients with low AECOPD risk were guideline concordant in a median of 13.24% (IQR: 11.30–14.71%) patient-years, compared with 70.41% (IQR: 62.44–75.57%) of patient-years among high-risk patients. The proportion of patients receiving guideline-concordant medications increased over time (0.94% per patient-year; 95% CI 0.49% to 1.38%) in the overall cohort, with a faster increase in high-risk patients (5.87% per patient-year; 95% CI 0.84% to 10.89%) compared with low-risk patients (0.74% per patient-year; 95% CI 0.38% to 1.10%). Figure 3 shows the proportion of patients receiving guideline-concordant maintenance inhaled medication by years since diagnosis, stratified by AECOPD risk.

Among the 21 902 patients who initiated guideline-concordant inhaled medications, the mean PDC per patient-year was 31.93% (95% CI 31.69% to 32.16%). 34.14% ($n=7477$) of all initiators had at least one patient-year with a PDC ≥ 0.8 , indicating high persistence.^{26,27} The PDC was higher among patients at high AECOPD risk (mean PDC 57.33%, 95% CI 56.77% to 57.90%, per year) than among those at low AECOPD risk (mean PDC 26.35%, 95% CI 26.10% to 26.59%, per year). As shown in figure 4, mean PDC did not significantly change over time in either group (high-risk 95% CI -2.10% to 5.52% ; low-risk 95% CI -2.34% to 0.91%).

Nearly half the cohort (42.44%; 30 557 patients, 87 332 patient-years) received exclusively guideline-discordant treatment for at least one patient-year of follow-up. Of these patient-years, 96.77% (84 508 patient-years) were classified as low AECOPD risk and 3.23% (2824 patient-years) as high risk. Patients could receive multiple different guideline-discordant regimens within the same patient-year. In low-risk patient-years, overtreatment, defined as ICS combined with LABDs (LAMA, LABA or both), occurred in 67.85% ($n=20\,734$) of patients receiving guideline-discordant medications, accounting for a mean of 75.12% (SD 6.54%) of all guideline-discordant patient-years (whether high risk or low risk). In contrast, undertreatment with ICS monotherapy accounted for 35.83% (SD 6.11%) of all guideline-discordant patient-years. In

high-risk patient-years, a mean of 95.29% (SD 2.77%) of guideline-discordant patient-years involved ICS monotherapy. The proportion of patients on ICS monotherapy remained stable over follow-up in high-risk guideline-discordant patient-years (95% CI -2.72% to 3.06%) but declined among low-risk guideline-discordant patient-years (-1.65% per patient-year, 95% CI -3.18% to -0.13%) (figure 5).

Factors associated with the initiation and persistence with guideline-concordant maintenance inhaled medication

Among all patients with COPD ($n=71\,996$), high AECOPD risk was strongly associated with initiating guideline-concordant regimens (OR 7.51, 95% CI 7.21 to 7.82). Other indicators of more severe or symptomatic disease, such as methylxanthine use (OR 1.60, 95% CI 1.12 to 2.29), short-acting bronchodilator use (OR 3.68, 95% CI 3.55 to 3.82) and PDE4 inhibitor use (OR 3.05, 95% CI 1.37 to 6.76), were also associated with higher odds of initiation (table 3). Health system factors, including pulmonologist care (OR 5.14, 95% CI 4.88 to 5.41), urban residence (OR 1.06, 95% CI 1.03 to 1.10) and more frequent COPD-related outpatient visits (OR 1.25, 95% CI 1.24 to 1.27) and ED visits (OR 1.34, 95% CI 1.30 to 1.39), were similarly associated with a greater likelihood of initiating guideline-concordant treatment. The initiation of guideline-concordant medication varied significantly across SES categories ($p<0.001$) and HAs ($p<0.001$).

Among the 21 902 patients who initiated guideline-concordant maintenance inhaled therapy, adjusted binomial proportion regression showed higher odds of a day being covered by guideline-concordant medication in patients with high AECOPD risk (OR 5.04; 95% CI 4.87 to 5.22), those receiving pulmonologist care (OR 1.13; 95% CI 1.09 to 1.17), with more frequent COPD-related outpatient visits (OR 1.019; 95% CI 1.015 to 1.024) and using LAMA-containing combination therapy in a single inhaler (OR 2.36; 95% CI 2.28 to 2.45, table 4). The odds of a day being covered by guideline-concordant medication were lower among those with COPD-related ED visits (OR 0.97; 95% CI 0.95 to 0.98). HA was associated with the odds of a day being covered by guideline-concordant medication ($p<0.001$), whereas SES was not ($p=0.528$). No significant associations were found with living in an urban area ($p=0.060$, reference: rural), use of PDE4 inhibitors ($p=0.486$), methylxanthines ($p=0.599$), mucolytics ($p=0.566$) and short-acting bronchodilators ($p=0.731$).

Table 2 Characteristics of study cohort, stratified by whether patients initiated guideline-concordant maintenance inhaled medication during follow-up

Characteristics	Total (n=71 996)	Initiated guideline-concordant maintenance inhaled medication (n=21 902)	Did not initiate guideline-concordant maintenance inhaled medication (n=50 094)
Female	32 521 (45.17%)	9544 (43.58%)	22 977 (45.87%)
Age at baseline*, mean±SD, year	67.87±11.63	68.18±10.77	67.74±11.99
Follow-up duration, mean±SD, year	6.15±2.65	6.46±2.62	6.02±2.65
Year of diagnosis			
2011–2013	27 523 (38.23%)	8836 (40.34%)	18 687 (37.30%)
2014–2017	30 018 (41.69%)	9236 (42.17%)	20 782 (41.49%)
2018–2020	14 455 (20.08%)	3830 (17.49%)	10 625 (21.21%)
Neighbourhood income quintile at baseline*			
5 (highest income quintile)	11 475 (15.94%)	3591 (16.40%)	7884 (15.74%)
4	13 023 (18.09%)	4063 (18.55%)	8960 (17.89%)
3	13 732 (19.07%)	4105 (18.74%)	9627 (19.22%)
2	15 202 (21.12%)	4662 (21.29%)	10 540 (21.04%)
1 (lowest income quintile)	17 665 (24.54%)	5260 (24.02%)	12 405 (24.76%)
Unknown	899 (1.25%)	221 (1.01%)	678 (1.35%)
History of PFT†	37 293 (51.80%)	14 063 (64.21%)	23 230 (46.37%)
Pulmonologist care at baseline*	5953 (8.27%)	2937 (13.41%)	3016 (6.02%)
≥1 Patient-year of high AECOPD risk over follow-up	20 846 (28.95%)	10 617 (48.48%)	10 229 (20.42%)
Mean COPD-related outpatient visits per year over follow-up, mean±SD	1.33±2.10	2.07±2.64	0.98±1.69
Location of residency at baseline*			
Urban	47 618 (66.14%)	14 720 (67.21%)	32 898 (65.67%)
Rural	24 310 (33.77%)	7165 (32.71%)	17 145 (34.23%)
Unknown	68 (0.09%)	17 (0.08%)	51 (0.10%)
Health authority at baseline*			
Interior	19 247 (26.73%)	5853 (26.72%)	13 394 (26.74%)
Fraser	19 909 (27.65%)	6229 (28.44%)	13 680 (27.31%)
Vancouver Coastal	12 166 (16.90%)	3635 (16.60%)	8531 (17.03%)
Vancouver Island	14 777 (20.52%)	4544 (20.75%)	10 233 (20.43%)
Northern	5859 (8.14%)	1629 (7.44%)	4230 (8.44%)
Unknown	38 (0.05%)	12 (0.05%)	26 (0.05%)
Charlson Comorbidity Index score at time of COPD diagnosis, mean±SD*	4.18±3.10	4.09±3.10	4.21±3.10
Comorbidities at time of COPD diagnosis‡			
Myocardial infarction	9168 (12.73%)	2771 (12.65%)	6397 (12.77%)
Congestive heart failure	14 894 (20.69%)	4591 (20.96%)	10 303 (20.57%)
Peripheral vascular disease	13 208 (18.35%)	4043 (18.46%)	9165 (18.30%)
Cerebrovascular disease	12 464 (17.31%)	3485 (15.91%)	8979 (17.92%)
Cancer	22 572 (31.35%)	6822 (31.15%)	15 750 (31.44%)
Dementia	5732 (7.96%)	1331 (6.08%)	4401 (8.79%)
Rheumatic disease	13 552 (18.82%)	3980 (18.17%)	9572 (19.11%)
Peptic ulcer disease	9798 (13.61%)	2821 (12.88%)	6977 (13.93%)
Paraplegia or hemiplegia	2010 (2.79%)	531 (2.42%)	1479 (2.95%)
Renal disease	10 801 (15.00%)	3032 (13.84%)	7769 (15.51%)
Liver disease	10 964 (15.23%)	3230 (14.75%)	7734 (15.44%)
Diabetes	24 564 (34.12%)	7110 (32.46%)	17 454 (34.84%)

Continued

Table 2 Continued

Characteristics	Total (n=71 996)	Initiated guideline-concordant maintenance inhaled medication (n=21 902)	Did not initiate guideline-concordant maintenance inhaled medication (n=50 094)
AIDS/HIV	692 (0.96%)	257 (1.17%)	435 (0.87%)

Data are presented as n (%) unless otherwise specified.
*Baseline parameters: assessed within the first year of COPD diagnosis date.
†History of PFT: PFT conducted within 1 year before or after the date of first COPD diagnosis.
‡Charlson Comorbidity Index at the time of COPD diagnosis (without age adjustment) was calculated cumulatively using all available data prior to the date of first COPD diagnosis.
AECOPD, acute exacerbation of COPD; COPD, chronic obstructive pulmonary disease; PFT, pulmonary function test; SD, standard deviation .

In the sensitivity analysis of 88 002 patients with COPD, including those with asthma history prior to COPD diagnosis, similar results were observed in both the regression and descriptive analyses (online supplemental appendix 5).

DISCUSSION

We evaluated guideline-concordant maintenance inhaled medication in a large, population-based cohort of patients with COPD from 2011 to 2022. Only one-third of patients ever initiated guideline-concordant treatment, and among those who initiated, they were persistent with guideline-concordant medications for only one-third of follow-up. COPD is an ambulatory care-sensitive condition, meaning exacerbations are preventable with effective

outpatient management, of which the daily use of guideline-concordant medication is a critical component.²⁸ We identified significant gaps in guideline-concordant medication use in our population-based study. Modifiable health system factors such as increased pulmonologist care and outpatient visits may support guideline-concordant medication use.

Our findings of low initiation of guideline-concordant therapy are consistent with other claims-based studies with shorter follow-up.^{5 29} Low persistence with inhaled medications, regardless of guideline concordance, is also commonly observed.^{7 26 30} This represents a significant gap in COPD care as patients with high persistence with inhaled therapy, regardless of guideline concordance, are up to 51% less likely to experience severe AE-

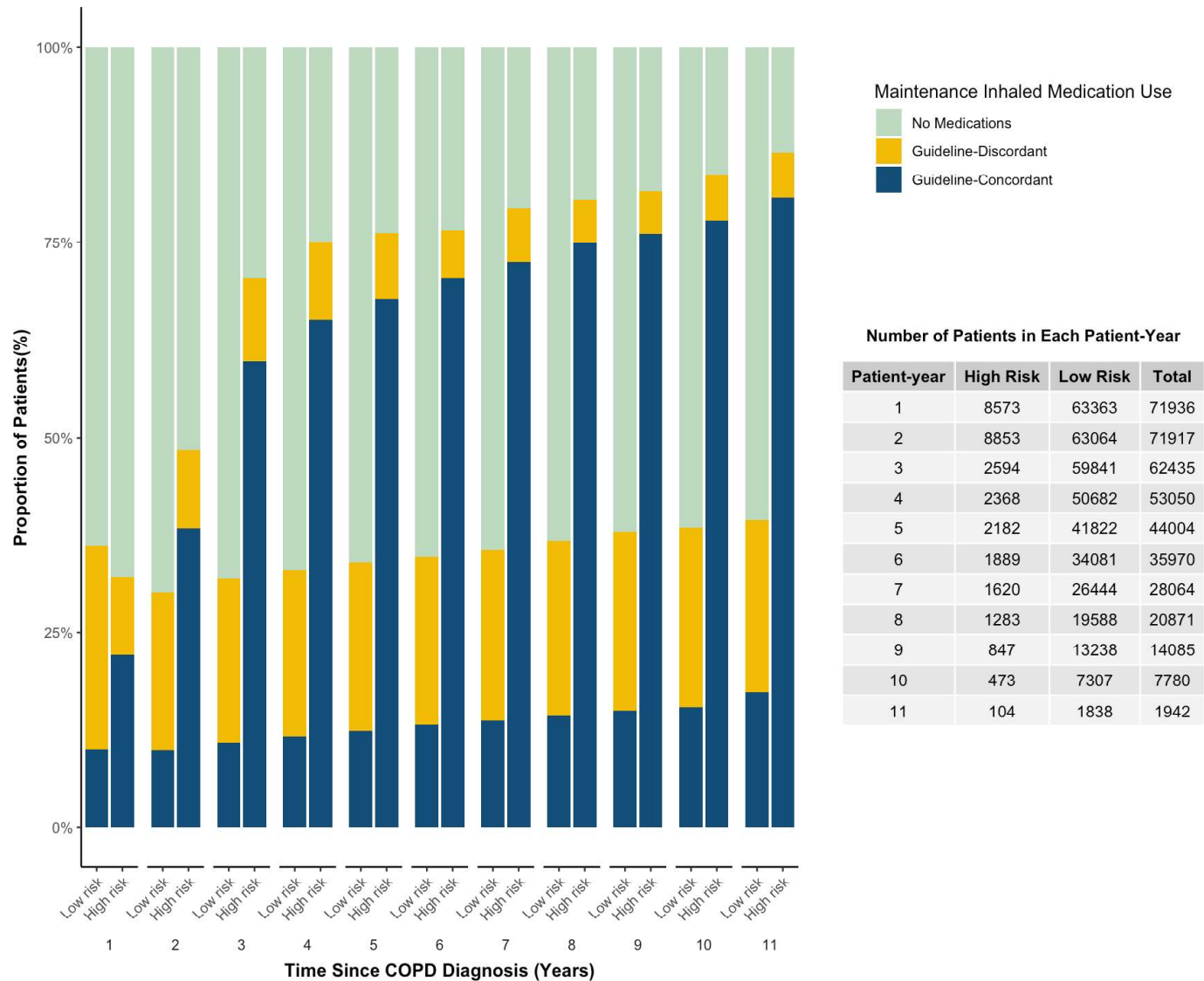


Figure 3 Guideline-concordant maintenance inhaled medication use by AECOPD risk and time since COPD diagnosis. AECOPD, acute exacerbation of COPD; COPD, chronic obstructive pulmonary disease.

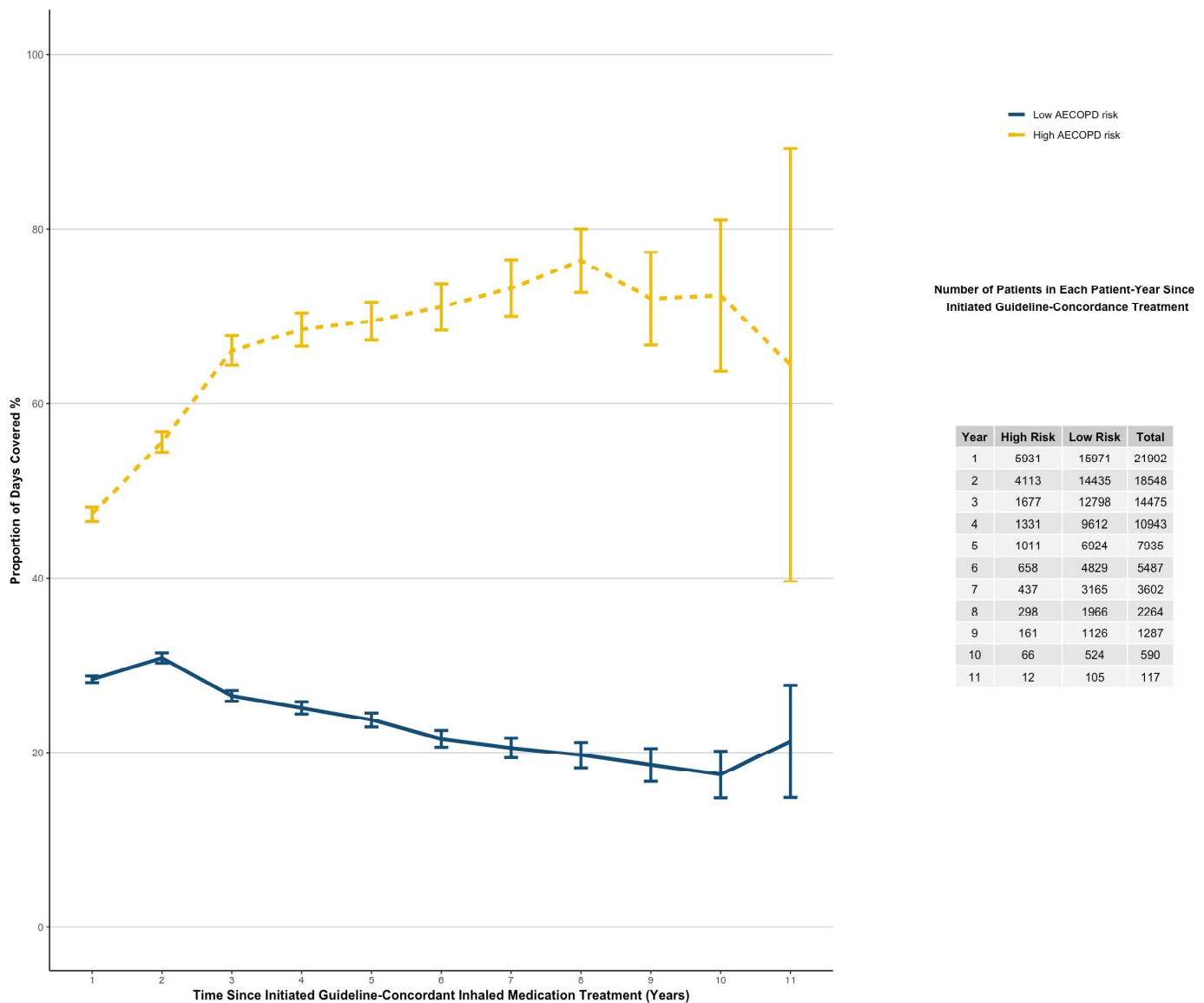


Figure 4 Mean PDC by guideline-concordant maintenance inhaled medications over time since initiation of guideline-concordant treatment, separated by AECOPD risk level (low vs high). Error bars represent the 95% CIs. AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

COPD compared with those with low persistence (PDC $\leq 20\%$).⁷ Given that guideline-concordant therapies provide even greater clinical benefits than discordant ones, it is reasonable to expect an even larger reduction in AECOPD risk among patients with high persistence with guideline-concordant medications. Our findings reaffirm that guideline discordance remains a persistent challenge in COPD management and likely contributes to adverse outcomes.

In our study, distinct patterns of guideline concordance emerged according to AECOPD risk level. High-risk patients were seven times more likely to initiate and five times more likely to persist with guideline-concordant medications compared with low-risk patients. This may be due to AECOPD being defined based on healthcare utilisation, high-risk patients had more health encounters, which may result in prescribers reinforcing guideline-concordant treatment. Additionally, patients with recent AECOPD events may perceive treatment as more necessary and thus improve persistence, while those with remote diagnoses and no exacerbations may see less value in maintenance therapy. Our findings may also suggest that healthcare resources are skewed towards high-risk individuals postexacerbation, potentially at the expense of low-risk patients.

Overtreatment by ICS alongside LABDs among patients at low risk of AECOPD was the primary driver of guideline-discordant medication use, even though our cohort excluded patients with a history of asthma. This may increase the risk of pneumonia, osteoporosis, oral thrush and major cardiovascular events, with no

evidence of clinical benefit in non-eosinophilic patients. Under-treatment with ICS monotherapy was also common, despite strong recommendations against its use since 2011 due to increased mortality risk. The reasons for inappropriate ICS use are unclear, but it may stem from a perceived similarity between COPD and asthma among providers, where low-dose ICS or ICS/LABA are the preferred treatment for asthma, leading to an assumed benefit for both conditions. It may also result from BC's more restrictive prior authorisation policy for public drug coverage for LAMA compared with ICS/LABA.

Despite the universal recommendation for early initiation of LABDs in all patients with COPD, over 40% of patients in our study did not receive any maintenance inhaled medications.^{5 12 31} While drug samples from physician offices (not captured in our dataset) may explain some cases, it is unlikely that patients relied exclusively on samples over our 2-year minimum follow-up period. Early use of LABDs in mild-to-moderate COPD has been shown to prevent AECOPD³² and possibly slow lung function decline.³³ The widespread underuse of LABDs represents a substantial missed opportunity to improve outcomes early in disease progression.

Patient access to care, particularly receiving pulmonologist care and increasing outpatient visits, is associated with both initiation and persistence with guideline-concordant medication. This finding aligns with previous studies, such as those by Gershon et al¹² and Case et al,¹⁶ who also found that pulmonologist involvement is associated with guideline-concordant treatment. Patients living in

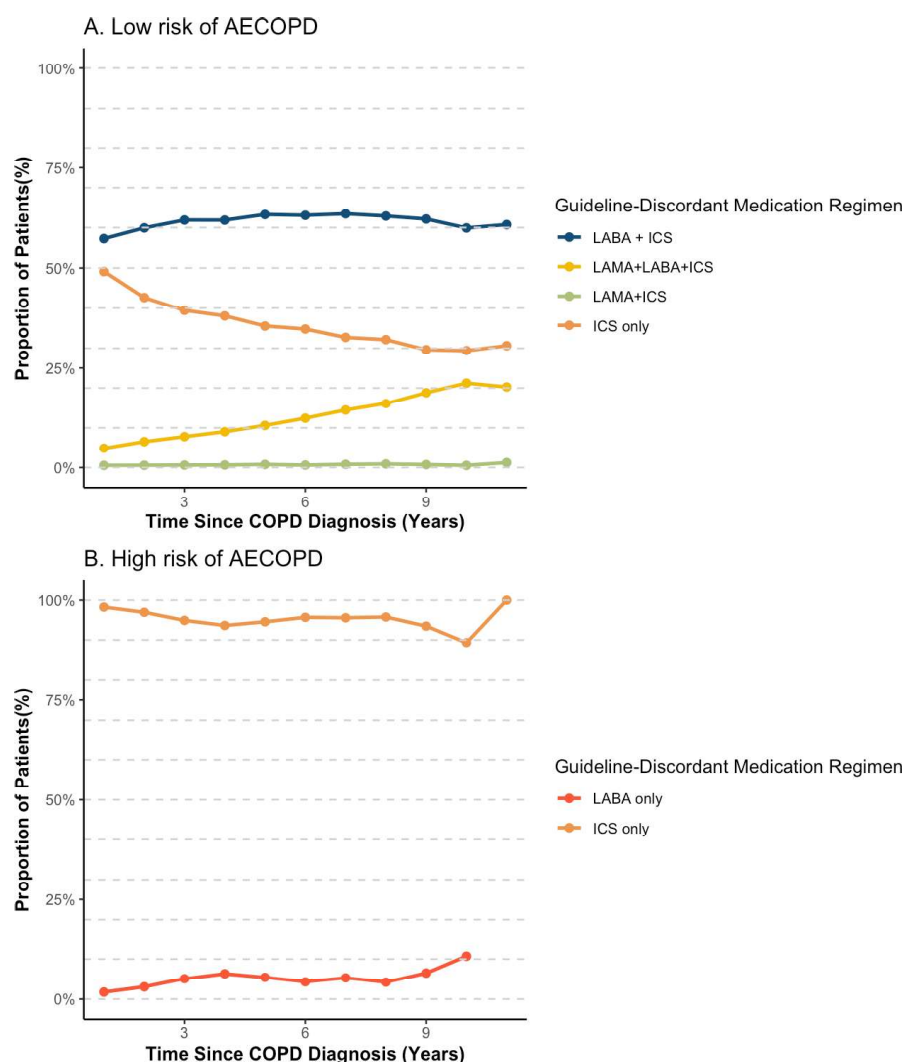


Figure 5 Longitudinal trends in the use of guideline-discordant medication regimens among patients with COPD, stratified by AECOPD risk and time since diagnosis, (A) Guideline-discordant medication regimen in patients with low risk of AECOPD; (B) Guideline-discordant medication regimen in patients with high risk of AECOPD. AECOPD, acute exacerbation of COPD; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist.

urban areas and those with higher SES were more likely to initiate guideline-concordant treatment, indicating potential disparities in access to appropriate medications.

Our cohort reflects the general COPD population in a large Canadian province, capturing long-term, real-world trends in medication use. To our knowledge, this is one of the first studies to evaluate both the initiation and persistence of guideline-concordant medication within a population-based cohort of patients with COPD. Although initiation and persistence with guideline-concordant treatment are closely linked, they highlight different components of concordance: prescriber concordance with management recommendations and patient persistence with the medications they are prescribed. Uniquely, in our study, we only considered patients to be persistent if they were receiving guideline-concordant medications, as these are the only evidence-based strategies for management of COPD. A second strength of our study is that we used pharmacy dispensing records rather than physician prescriptions or patient self-report, which minimises recall bias and accurately reflects the medications patients received. Our findings of poor guideline-concordant care among patients with low risk of AECOPD raise concerns about insufficient resource allocation in less severe COPD, where early intervention is crucial in preventing exacerbations. In clinical practice, early recognition of symptom worsening, timely risk assessments and early initiation of guideline-concordant care should occur among patients with less severe COPD. Future research should explore barriers to

delivering guideline-concordant care and evaluate the impact of early initiation on long-term outcomes.

Our study has several limitations. First, due to a lack of clinical data or symptom scores, we relied solely on AECOPD history to stratify guideline-concordant medications. Although we applied broad, inclusive definitions, they do not fully capture the differences in treatment recommendations based on symptom severity and biomarkers. Future research incorporating symptom scores or eosinophil counts could provide a more precise evaluation of guideline-concordant treatment. Nevertheless, since GOLD 2011 (the beginning of our follow-up period), categorising patients based on AECOPD history has been the primary method for stratifying medication recommendations. Other criteria such as symptom scores and biomarkers have varied across subsequent GOLD updates, which would have made finer classifications inconsistent over the duration of follow-up in our study. While our inclusive definition may have overestimated guideline-concordant care compared with year-specific definitions based on contemporary guidelines, the overall level of guideline concordance was suboptimal, highlighting room for improvement in guideline-concordant care. Second, our definition of guideline concordance was based only on the frequency of AECOPD in the last year and did not account for more remote AECOPD history. As a result, patients who initiated ICS-containing therapy following frequent or severe exacerbations but did not step down therapy after a year with no AECOPD or mild AECOPD would be classified as guideline discordant. Although this remains an area of clinical debate,

Table 3 Association of guideline-concordant maintenance inhaled medication initiation with patient, healthcare provider and disease characteristics (n=71 996)

Characteristic	OR (95% CI)	P value
Location of residency		
Urban	1.06 (1.03 to 1.10)	<0.001
Unknown	1.59 (1.34 to 1.88)	<0.001
Rural	Reference	–
Female	0.85 (0.83 to 0.88)	<0.001
Age	1.010 (1.008 to 1.011)	<0.001
Pulmonologist care	5.14 (4.88 to 5.41)	<0.001
Use of short-acting bronchodilators	3.68 (3.55 to 3.82)	<0.001
Neighbourhood income quintile		–
2	1.08 (1.03 to 1.13)	<0.001
3	1.10 (1.05 to 1.16)	<0.001
4	1.20 (1.14 to 1.26)	<0.001
5 (highest income quintile)	1.23 (1.17 to 1.30)	<0.001
Unknown	0.91 (0.78 to 1.06)	0.237
1 (lowest income quintile)	Reference	–
AECOPD risk (high)	7.51 (7.21 to 7.82)	<0.001
AECOPD risk (low)	Reference	–
Total annual COPD-related outpatient visits	1.25 (1.24 to 1.27)	<0.001
Charlson Comorbidity Index	0.997 (0.993 to 1.001)	0.274
Total annual COPD-related ED visits	1.34 (1.30 to 1.39)	<0.001
Use of PDE4 inhibitor	3.05 (1.37 to 6.76)	0.006
Use of mucolytic	1.17 (0.83 to 1.65)	0.376
Use of methylxanthines	1.60 (1.12 to 2.29)	0.010

Multivariable logistic regression was conducted using patient-year as the unit of analysis to examine the likelihood of initiating versus not initiating guideline-concordant therapy. The model was adjusted for the following time-dependent covariates, measured in the current patient-year: age, location of residency (urban/rural), neighbourhood income quintile, total COPD-related outpatient and emergency department visits, and (yes/no) use of short-acting bronchodilators, PDE4 inhibitors (can be prescribed by both generalists and specialists), mucolytics and methylxanthines. Time-independent covariates were sex (measured at COPD diagnosis), pulmonologist care (yes/no, defined as any visit prior to or during the current patient-year), AECOPD risk (high vs low, based on exacerbations in the prior year) and Charlson Comorbidity Index (cumulative up to the current patient-year). AECOPD, acute exacerbation of COPD; COPD, chronic obstructive pulmonary disease; ED, emergency department; PDE4, Phosphodiesterase 4.

the most recent 2024 GOLD guidelines emphasise that stepping down therapy should be considered.¹ Third, persistence was based on medication availability and does not capture whether the patient actually took the medication as instructed or used proper inhaler technique, and our dataset did not capture medications dispensed outside outpatient pharmacies, such as those from inpatient stays or physician office samples.

CONCLUSIONS

Initiation and persistence with guideline-concordant maintenance inhaled medications are unsatisfactory among patients with COPD. Guideline discordance primarily comprised overtreatment with ICS plus LABDs and underuse of LABDs. Improved access to pulmonologist care and more frequent outpatient visits may enhance guideline-concordant medication use and subsequently improve health outcomes in patients with COPD.

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Table 4 Association of PDC by guideline-concordant maintenance inhaled medication with patient, healthcare provider and disease characteristics in patients who initiated guideline-concordant regimens (n=21 902)

Characteristic	OR (95% CI)	P value
Location of residency		
Urban	1.04 (1.00 to 1.07)	0.060
Unknown	1.10 (0.97 to 1.26)	0.145
Rural	Reference	
Female	0.96 (0.91 to 1.00)	0.026
Age	1.007 (1.005 to 1.008)	<0.001
Pulmonologist care	1.13 (1.09 to 1.17)	<0.001
Use of short-acting bronchodilators	1.00 (0.97 to 1.02)	0.731
Neighbourhood income quintile		
2	1.02 (0.98 to 1.06)	0.440
3	0.99 (0.95 to 1.04)	0.747
4	1.02 (0.98 to 1.07)	0.264
5 (highest income quintile)	1.01 (0.97 to 1.06)	0.584
Unknown	0.95 (0.83 to 1.08)	0.425
1 (lowest income quintile)	Reference	
AECOPD risk (high)	5.04 (4.87 to 5.22)	<0.001
AECOPD risk (low)	Reference	
Total annual COPD-related outpatient visits	1.019 (1.015 to 1.024)	<0.001
Charlson Comorbidity Index	0.980 (0.975 to 0.984)	<0.001
Total annual COPD-related ED visits	0.97 (0.95 to 0.98)	<0.001
Use of PDE4 inhibitor	1.09 (0.86 to 1.38)	0.486
Use of mucolytic	1.06 (0.86 to 1.31)	0.566
Use of methylxanthines	1.05 (0.88 to 1.25)	0.599
Use of LAMA-containing combination therapy in a single inhaler	2.36 (2.28 to 2.45)	<0.001

Multivariable binomial proportion regression was conducted using patient-year as the unit of analysis to examine factors associated with the odds of a day being covered by guideline-concordant maintenance therapy. In this model, the number of days covered was specified as the numerator (successes) and the total eligible days in the year as the denominator (trials), allowing the PDC to be modelled directly. The model was adjusted for the following time-dependent covariates, measured in the current patient-year: age, sex, location of residency (urban/rural), neighbourhood income quintile, total COPD-related outpatient and emergency department visits, and (yes/no) use of short-acting bronchodilators, PDE4 inhibitors (can be prescribed by both generalists and specialists), mucolytics, methylxanthines and LAMA-containing combination inhalers. Time-independent covariates were sex (measured at COPD diagnosis), pulmonologist care (yes/no, defined as any visit prior to or during the current patient-year), AECOPD risk (high vs low, based on exacerbations in the prior year) and Charlson Comorbidity Index (cumulative up to the current patient-year). AECOPD, acute exacerbation of COPD; COPD, chronic obstructive pulmonary disease; ED, emergency department; LAMA, long-acting muscarinic antagonist; PDC, proportion of days covered; PDE4, Phosphodiesterase 4.

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ARTIGO ORIGINAL

O uso materno de antibióticos durante a gravidez aumenta o risco de infecções das vias aéreas na descendência: revisão sistemática e meta-análise

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RESUMO

Contexto Os antibióticos são amplamente prescritos durante a gravidez, mas o seu impacto no risco de infecções na descendência permanece incerto. Este estudo sintetiza todos os dados disponíveis e avalia a associação entre o uso materno de antibióticos durante a gravidez e o risco de infecções nas crianças ao longo da infância.

Métodos Realizamos uma revisão sistemática e meta-análise seguindo as orientações PRISMA, com registo no PROSPERO. Pesquisamos PubMed, Embase, Ovid, ISRCTN registry, ClinicalTrials.gov e Cochrane Library para estudos em inglês, sem restrições de data de publicação. Foram incluídos estudos que apresentavam dados quantitativos sobre exposição pré-natal a antibióticos e infecções na infância após o período neonatal. Dois autores procederam ao rastreio e extração dos dados. O risco de viés foi avaliado com a Newcastle–Ottawa Scale. O desfecho primário foi o risco de qualquer infecção na infância, analisado com meta-análises de efeitos aleatórios, incluindo análises de sensibilidade por tipo de infecção e qualidade dos estudos. A certeza da evidência foi avaliada com GRADE.

Resultados De 7317 registos, foram incluídos 14 estudos de coorte (n=5 011 183 crianças), dos quais 12 (n=4 995 449) forneceram dados para meta-análise. A exposição pré-natal a antibióticos associou-se a um aumento do risco de qualquer infecção na descendência (OR 1,33; IC 95% 1,01–1,76; p=0,04). Uma análise de sensibilidade (n=3 647 296) com seis estudos de elevada qualidade mostrou uma associação ainda mais forte (OR 1,48; IC 95% 1,13–1,95; p<0,01). Especificamente, as infecções otorrinolaringológicas (ouvido, nariz e garganta) estavam significativamente aumentadas (n=2 841 644 crianças) (OR 1,40; IC 95% 1,18–1,65; p<0,0001). A maioria dos estudos incluídos apresentou baixo risco de viés, e a certeza da evidência para o desfecho “qualquer infecção na infância” foi considerada elevada segundo GRADE.

Conclusões A exposição pré-natal a antibióticos esteve associada a um aumento do risco de infecções na descendência, particularmente infecções das vias aéreas superiores. Estes resultados sugerem a necessidade de prescrição cautelosa de antibióticos durante a gravidez, embora não seja possível excluir totalmente fatores de confusão. **Registo PROSPERO:** CRD42024599699.

INTRODUCTION

Antibiotics are among the most frequently prescribed medications during pregnancy. Global prevalence estimates indicate that around 23.6% of pregnant women receive antibiotic treatment, primarily for respiratory and urinary tract infections.¹ In Western countries specifically, prevalences are estimated to range from 20% to 40%.^{2–4} While essential for managing maternal infections, growing evidence suggests that prenatal antibiotic exposure may influence offspring risk of infections, possibly due to alterations in the microbiota and development of the fetal immune system.^{5,6}

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Prior evidence from individual cohort studies suggests an increased risk of offspring infections and in particular airway infections following prenatal antibiotic exposure, but no systematic reviews or meta-analyses have synthesised these findings.

WHAT THIS STUDY ADDS

► This is the first systematic review and meta-analysis to comprehensively assess the association between prenatal antibiotic exposure and childhood infection risk, encompassing over 5 million children from 14 cohort studies. Our meta-analysis found that prenatal antibiotic exposure significantly increased the risk of childhood infections, and in particular upper airway infections.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► These findings may indicate a need for cautious antibiotic prescribing during pregnancy, although large studies adjusting for potential confounding are warranted.

Recent studies have demonstrated associations between prenatal antibiotic exposure and increased childhood infection risk beyond the neonatal period. A large French cohort reported higher rates of serious infections among infants exposed in utero, particularly with three or more antibiotic courses.⁷ Similarly, a Swedish study showed elevated infant infection rates, consistent even in sibling comparisons,⁸ and a third Portuguese cohort study found that prenatal antibiotic exposure was associated with a higher risk of tonsillitis at 4 years of age.⁹

Childhood infections contribute significantly to global paediatric morbidity and mortality, as well as healthcare costs.^{10–12} Understanding the long-term associations between prenatal antibiotic exposures and childhood infection risk is therefore critical for clinical decision-making when prescribing maternal antibiotics as these may have lasting impacts on the unborn child.

Until now, no systematic reviews or meta-analyses have comprehensively assessed the potential impact of antibiotics during pregnancy on child infection risk by synthesising data from existing literature. Here, we conduct a systematic review to

summarise current evidence on the association between in utero antibiotic exposure and childhood infection risk supported by meta-analyses. In addition to the overall association, we explore variations by antibiotic timing, antibiotic type, dose, mode of delivery and infection subtype to inform evidence-based clinical strategies.

METHODS

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered with PROSPERO (CRD42024599699).

Search strategy

Relevant studies were identified through a systematic literature search across multiple databases: PubMed, Embase, Ovid MEDLINE, ISRCTN registry, ClinicalTrials.gov and the Cochrane Library. The search was limited to English language publications, with no restrictions on publication date to maximise the inclusion of potentially relevant studies. Search terms were categorised into four key themes: pregnancy, antibiotics, infection and child. Boolean operators were used to refine search combinations, incorporating both text-word terms and Medical Subject Headings when possible (online supplemental eFigure 1). The search strings used for each database are detailed in online supplemental eTable 1. Titles and abstracts were screened for eligibility by KA and MH, followed by a full-text reading to determine final selection of studies, and if in doubt all authors (KA, MH, BLKC and NB) were involved to discuss eligibility. Additionally, reference lists of included articles were manually reviewed to identify further relevant publications. An updated search was carried out prior to article submission to ensure inclusion of any new eligible literature (22 April 2025).

Study selection and data extraction

Studies were selected based on the following inclusion criteria: (1) peer-reviewed original research articles reporting quantitative data; (2) exposure defined as antibiotic use during pregnancy; and (3) outcome defined as any childhood infection beyond the neonatal period, that is, after the first 28 days of life. The following data were extracted from the included studies: first author, year of publication, country, study design, sample size, data source, time of antibiotic administration, type of antibiotic, maternal infection treated, percentage of exposed mothers during pregnancy, method of identification of antibiotic use, mode of delivery, child characteristics, child infection type, method of identification of infection in the child, covariates adjusted for in analyses and key results.

Quality assessment

Eligible studies were assessed for risk of bias using the Newcastle-Ottawa Scale for cohort studies.¹³ Studies were classified as high quality (low risk of bias) with a score of 7–9, moderate quality with a score of 4–6 and low quality (high risk of bias) with a score of <4 points according to recommendations. We assessed the certainty of evidence for each meta-analysed outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, starting at low certainty for observational studies, with downgrades or upgrades based on standard criteria.

Statistical analyses

The primary meta-analysis assessed the risk of any offspring infection from maternal antibiotic exposure reporting ORs. This was supported by a sensitivity analysis including studies with low risk of bias only. Additionally, a meta-analysis of studies reporting HRs was performed, including 1-year follow-up data from one study¹⁴ reporting incidence risk ratios (IRRs), which are suggested to closely align with HRs in short follow-up periods.¹⁵ One study was included in both primary meta-analyses as it reported data both as number of children infected and as HR.¹⁶ Subgroup analyses were performed where two or more studies provided comparable data,

with only infection types (ie, respiratory infections and ear, nose and throat (ENT) infections) having sufficient data for analysis. Statistical analyses were conducted using the meta package in the R Program for Statistical Computing V.4.4.3, and we fitted the random-effects model using the DerSimonian and Laird method for between-study variances. Infection in children was treated as the event of interest, and pooled ORs with 95% CIs were calculated using a random-effects model to account for heterogeneity between studies. For the meta-analysis using HRs, risk estimates were pooled with 95% CIs using a random-effects model. Heterogeneity was assessed using the I^2 statistic and χ^2 test. Results with a two-sided p value <0.05 were considered statistically significant. Publication bias was evaluated by visually inspecting funnel plots for asymmetry and performing Egger's test to quantify potential bias statistically; however, these assessments were applied cautiously in analyses with fewer studies (eg, as few as three studies in some subgroup analyses), where results may be less reliable due to limited statistical power.

RESULTS

Study selection

The systematic search identified 7317 potentially relevant records across databases after the removal of duplicates. Of these, 14 studies, encompassing 5 011 183 paediatric study participants, met the inclusion criteria and were included in the systematic review. 12 studies provided sufficient data for inclusion in the meta-analyses ($n=4\,995\,449$). The selection process is detailed in the PRISMA flow chart (figure 1).

Study characteristics

The included studies were all cohort studies, with eight retrospective^{8 14 16–21} and six prospective designs.^{9 22–26} Participants included children aged up to 14 years, with eight studies focusing solely on infants up to 1 year of age.^{8 17–19 21 22 24 26} Infections were identified primarily through hospital records, medical databases or parent-reported diagnoses. Maternal antibiotic exposure during pregnancy involved various classes and all studies examined exposure during any trimester. Studies were conducted across diverse regions, with three in Denmark,^{14 16 25} two in Sweden^{8 24} and one each in Australia,²³ the USA,²⁰ France,¹⁷ Portugal,⁹ the UK,²² Kenya,¹⁸ Norway,¹⁹ Taiwan²¹ and Poland.²⁶ Childhood infections studied varied widely, with respiratory, gastrointestinal, ear and urinary tract infections being the most frequently studied. See

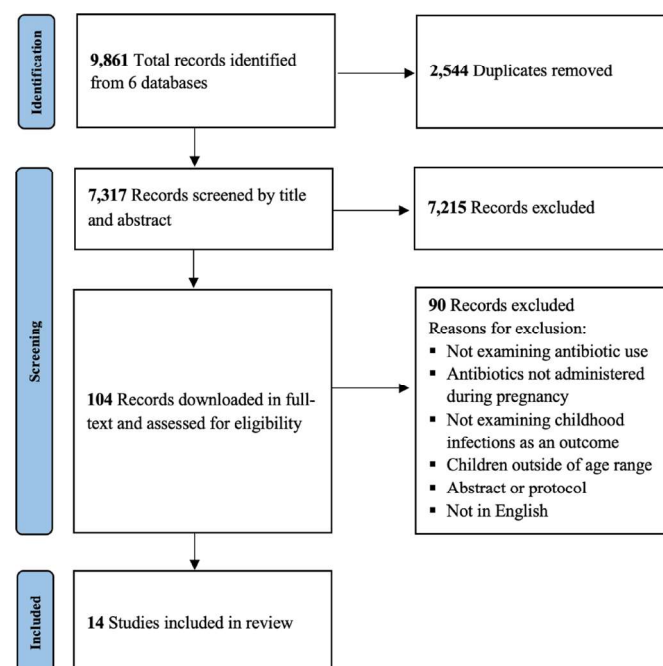


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

Table 1 Prenatal antibiotic exposure and childhood infection study characteristics

Reference	Country	Study design	Sample size	Data from	Exposed mothers (%)	Child characteristics	Child infection type	Covariates adjusted for	Key results
Kyvsgaard <i>et al</i> ^{14*}	Denmark	Prospective cohort study	662	COPSAC 2010 mother-child cohort	35.50	Children aged 0–3 years	Colds, pneumonia, gastroenteritis, AOM, acute tonsillitis, fever	Season, vitamin D and fish oil interventions, shared risk factors (maternal asthma, antibiotics, siblings, asthma exacerbation polygenic risk score, airway immune score)	Antibiotics during pregnancy were associated with increased infection burden, particularly colds, pneumonia, gastroenteritis and fever.
Tisseyre <i>et al</i> ¹⁷	France	Retrospective cohort study	2 836 630	French National Health Data System from 2012 to 2021	39.60	Full-term, singleton infants aged 3–12 months	Infection requiring hospitalisation, including respiratory, gastrointestinal, ENT, urinary tract and skin infections	Infant sex, mode of delivery, season of birth, maternal age, pregnancy year, medications, outpatient visits, hospitalisations, comorbidities (hypertension, epilepsy, diabetes, thyroid disorders, depression, asthma), prior antibiotic exposure, income status, socioeconomic deprivation index	Prenatal antibiotic exposure increased serious infection risk (aOR 1.12, 95% CI 1.11 to 1.13). Association was strongest for ≥3 courses of antibiotics (aOR 1.21, 95% CI 1.19 to 1.24).
Nakitanda <i>et al</i> ⁸	Sweden	Retrospective cohort study	1 347 018	Swedish population and health registers, hereunder Medical Birth Register, Prescribed Drug Register, National Patient Register, etc	21.90	Singleton infants aged 0–12 months born 2006–2018	Any infection (respiratory most common)	Birth year, birth season, maternal age, residence, parity, comorbidities (asthma, diabetes, renal disease, immunodeficiency), BMI, pre-pregnancy prescriptions, outpatient visits, hospitalisations, education, smoking, sibling analysis for familial factors	Infants exposed to in utero antibiotics had higher infection rates (aIRR for prescriptions: 1.34; infections diagnosed in care: aHR 1.28). Associations were attenuated in sibling analyses.
Cunha <i>et al</i> ⁹	Portugal	Prospective cohort study	7459	Generation XXI birth cohort from 2005 to 2006	14.70	Children aged 0–4 years	Tonsillitis, otitis, pneumonia, urinary tract infection, gastroenteritis, <i>Helicobacter</i>	Maternal education, mode of delivery, breastfeeding, child sex, day care attendance	Antibiotics during pregnancy increased tonsillitis risk at 4 years (aOR 1.19, 95% CI 1.03 to 1.38). There were no significant associations with other infection types.
Higgins <i>et al</i> ²²	UK	Prospective cohort study	412	Isle of Wight 3rd Generation Cohort from 2010 to 2016	24.20	Infants aged 0–12 months	Infectious wheezing	Maternal asthma, maternal age, smoking, maternal infection, infant sex, birth order, low birth weight	No significant association between prenatal antibiotics and infectious wheezing.
Hu <i>et al</i> ²³	Australia	Prospective cohort study	4500	LSAC from 2004 to 2014	10.40	Children aged 0–11 years	Ear infection	Child age, child sex, birth weight, mode of delivery, neighbourhood disadvantage, passive smoking	Antibiotics during pregnancy increased persistent/early ear infection risk (aOR for 'Moderate to Low' trajectory: 1.78; 'Consistently High' trajectory: 2.04).
Deichsel <i>et al</i> ¹⁸	Kenya	Retrospective cohort study	373	Kenyatta National Hospital cohort 1999–2001	20.10	Singleton or first-born twin, HEU infants aged 0–12 months	Diarrhoea	Household crowding, maternal CD4 per cent at 32-week gestation, maternal undernutrition	Prenatal antibiotic use was not significantly associated with infant diarrhoea (HR 1.06, 95% CI 0.84 to 1.33).
Fossum <i>et al</i> ¹⁹	Norway	Retrospective cohort study	7747	Medical Birth Registry of Norway and Norwegian Prescription Database 2004–2006	25.10	Children aged up to 1 year, a portion followed to 2 years	Antibiotic prescription, indicating infection	Child sex, prematurity, maternal smoking, maternal age	Prenatal antibiotic exposure increased antibiotic prescriptions in children (aOR 1.16, 95% CI 1.002 to 1.351). The effect was stronger when antibiotics were dispensed in the third trimester (aOR 1.27, 95% CI 1.06 to 1.53).

Continued

Table 1 Continued

Reference	Country	Study design	Sample size	Data from	Exposed mothers (%)	Child characteristics	Child infection type	Covariates adjusted for	Key results
Miller <i>et al</i> ¹⁶	Denmark	Retrospective cohort study	776 657	Danish National Health Registries 1995–2009	18.20	Live-born singletons followed from birth to 14 years	Infection requiring hospitalisation, including respiratory, gastrointestinal, invasive bacterial, soft tissue, viral, genitourinary	Maternal age, parents' educational level, smoking during pregnancy, child sex, number of siblings at birth, season of birth, population density, birth year	Maternal antibiotic use increased infection-related hospitalisation risk in children (aHR 1.18, 95% CI 1.17 to 1.19). The effect was stronger for vaginally born children compared with caesarean born. A dose-response effect was observed and the risk was highest when the last prescription was close to birth.
Poulsen <i>et al</i> ^{20*}	USA	Retrospective cohort study	8793	Geisinger Clinic electronic health records 2006–2012	60.40	Singleton children up to 3 years	Antibiotic prescription, indicating infection	Mode of delivery, birth weight, child's exact age, race/ethnicity, history of medical assistance, smoking during pregnancy, parity, pregravid BMI	Prenatal antibiotic orders were associated with increased antibiotic prescriptions in children. A dose-response relationship was observed.
Stecksén-Blicks <i>et al</i> ²⁴	Sweden	Prospective cohort study	100	Teg Child Health Centre 2011–2012	15	Infants aged 0–12 months	Oral <i>Candida</i> colonisation	Maternal fungal infection during pregnancy, lactoferrin in breast milk, antiseptatory factor in breast milk, furry pet at home, maternal serum ferritin level, siblings	No strong association was found between maternal antibiotic use and infant <i>Candida</i> colonisation.
Pedersen <i>et al</i> ²⁵	Denmark	Prospective cohort study	514	COPSAC 2010 mother-child cohort	37	Children aged 0–3 years	OM, VT insertion	Maternal age, maternal asthma, smoking in pregnancy, older siblings, maternal educational level, household income, family history of middle ear disease	Maternal antibiotic use increased OM risk (aHR 1.30, 95% CI 1.04 to 1.63). Those with third-trimester exposure and exposed mothers with vaginal deliveries had offspring with a greater increase in OM risk. The association was strongest for RTI antibiotics. A dose-response relationship was observed.
Chen <i>et al</i> ²¹	Taiwan	Prospective cohort study	21 248	Taiwan Birth Cohort Study 2005	2.45	Infants aged 0–6 months	Pneumonia requiring hospitalisation	Child sex, gestational age <37 weeks, congenital cardiopulmonary disease, maternal BMI >24 before pregnancy, tobacco exposure during pregnancy, parent's education ≤ senior high school, visible mould in the home	Prenatal antibiotic use increased infantile pneumonia risk (aOR 4.02, 95% CI 2.07 to 7.10).
Jedrychowski <i>et al</i> ^{26*}	Poland	Prospective cohort study	102	Krakow birth cohort study 2000–2002	30.40	Infants aged 0–12 months	Respiratory infections	Maternal educational level, child sex, maternal allergy, number of respiratory infections in the first year of life	No significant association between prenatal antibiotics and respiratory infections.

*Child infections were a secondary outcome in Kyvsgaard *et al*,¹⁴ Poulsen *et al*²⁰ and Jedrychowski *et al*.²⁶ aHR, adjusted HR; aIRR, adjusted incidence risk ratio; AOM, acute otitis media; aOR, adjusted OR; BMI, body mass index; COPSAC, Copenhagen Prospective Studies on Asthma in Childhood; ENT, ear, nose and throat; HEU, HIV-exposed uninfected; LSAC, Longitudinal Study of Australian Children; OM, otitis media; RTI, respiratory tract infection; VT, ventilation tube.

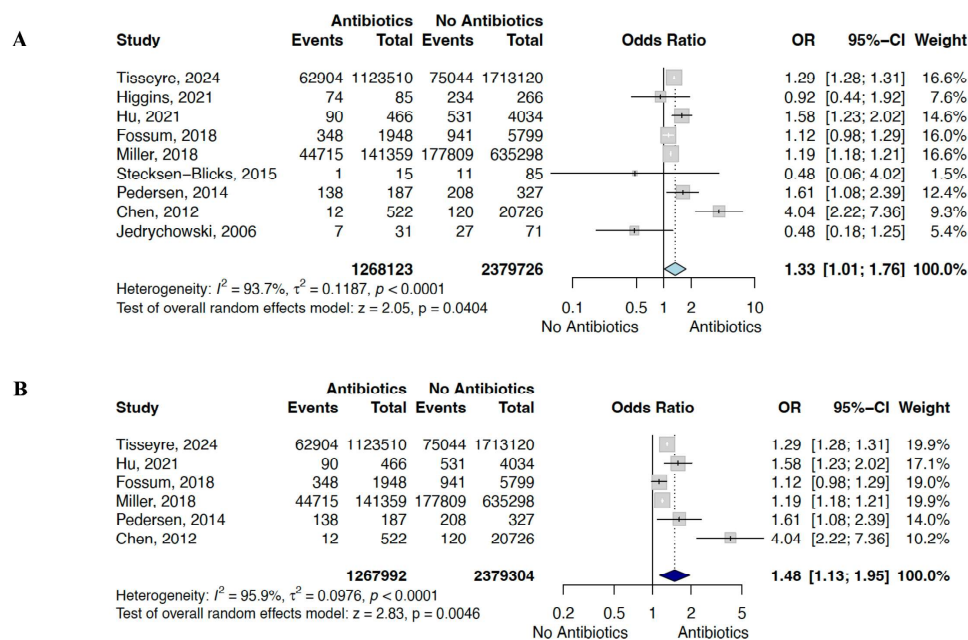


Figure 2 Forest plots showing the associations between prenatal antibiotic exposure and any childhood infection risk (A) and among studies with low risk of bias only (B). Estimates are ORs, with the sizes of markers illustrating the weights of studies; whiskers illustrate 95% CIs.

table 1 for a summary of study characteristics. Eight studies were of high quality with a low risk of bias, five were of moderate quality and one had a high risk of bias (online supplemental eFigure 2). We performed a directed acyclic graph showing the most common confounders adjusted for in the studies included (online supplemental eFigure 3).

Maternal antibiotic use in pregnancy and risk of any infection in offspring

Prenatal antibiotic exposure was associated with an increased risk of any childhood infection in the meta-analysis of nine studies encompassing 3 647 849 children (OR 1.33, 95% CI 1.01 to 1.76, $p=0.04$; $I^2=93.7\%$; figure 2A), with no indication of publication bias (Egger's test of asymmetry, $p=0.90$; see funnel plot in online supplemental eFigure 4). This was similar in a sensitivity meta-analysis ($n=3\ 647\ 296$) restricted to six studies of high quality (OR 1.48, 95% CI 1.13 to 1.95, $p<0.01$; $I^2=95.9\%$; figure 2B), with no indication of publication bias (Egger's test, $p=0.64$, online supplemental eFigure 4). Finally, the meta-analysis of four studies using reported HRs showed a significantly increased risk (HR 1.20, 95% CI 1.09 to 1.33, $p=0.0002$; $I^2=99.5\%$; figure 3), with no evidence of publication bias (Egger's test, $p=0.8050$, online supplemental eFigure 4).

Maternal antibiotic use in pregnancy and risk of specific infection types in offspring

We have used the GRADE framework for presenting the level of evidence for each of our clinical outcomes, which showed a high level of certainty of evidence for the analyses of any childhood infection risk. The detailed GRADE assessments for all outcomes are presented in online supplemental eTable 2.

GRADE assessment

The safety and potential efficacy of replacing chest physiotherapy with ExACT were assessed via adverse events and change from baseline to day 28 in spirometry (FEV_1), LCI2.5 by N2-MBW and rates of pulmonary exacerbations (defined as increased respiratory symptoms that required antibiotic treatment).

Trimester of antibiotic exposure

Trimester-specific effects of prenatal antibiotic exposure varied across four studies. A meta-analysis could not be conducted due to incomparable data. Fossum et al reported third-trimester exposure increased infant antibiotic prescriptions, unlike earlier trimesters.¹⁹ Similarly, Pedersen et al found third-trimester exposure

raised otitis media risk, with no significant earlier trimester effects.²⁵ Tisseyre et al noted weak associations across all trimesters for serious infections.¹⁷ Cunha et al⁹ found no significant third-trimester effect on tonsillitis, while there was a significant association for antibiotic use at any time during pregnancy. Although Miller et al did not examine antibiotic exposures by trimester, it was noted that the risk was highest when the last prescription was close to birth.¹⁶

Antibiotic type

Four studies reported effects of specific antibiotic classes used during pregnancy on childhood infections. Tisseyre et al found significant associations between prenatal exposure to all antibiotic classes and serious infant infections in unadjusted analyses, which were attenuated after adjustments but remained significant for most classes, except tetracyclines.¹⁷ Nakitanda et al reported similar increased risk of infant infections across frequently used antibiotic types, including penicillin, other beta-lactams, macrolides and nitrofurantoin derivatives.⁸ Miller et al noted increased infection-related hospitalisations for all classes, though the association was highest for non-penicillin beta-lactam antibiotics and lowest for quinolones.¹⁶ Pedersen et al found stronger associations between respiratory tract infection antibiotics and otitis media compared with urinary tract infection antibiotics.²⁵

Number of antibiotic courses

Four studies reported dose-response relationships between prenatal antibiotic exposure and childhood infections, and the remaining studies did not specify the number of antibiotic prescriptions during pregnancy. Tisseyre et al found the highest risk of serious infections with ≥ 3 antibiotic courses compared with none.¹⁷ Miller et al observed increased infection-related hospitalisation risk in offspring of mothers with multiple prescriptions during pregnancy, compared with those with one prescription.¹⁶ Pedersen et al noted a dose-response effect for otitis media with increasing treatments.²⁵ Poulsen et al provided data showing a similar trend, with a higher number of maternal prescriptions associated with their offspring having a greater number of antibiotic prescriptions.²⁰

Mode of delivery

One study, conducted by Miller et al, examined the effect of prenatal antibiotic exposure by mode of delivery, where antibiotic-exposed children had an increased risk of infection-related hospitalisation, with a stronger effect in vaginally born children compared with caesarean-born children.¹⁶

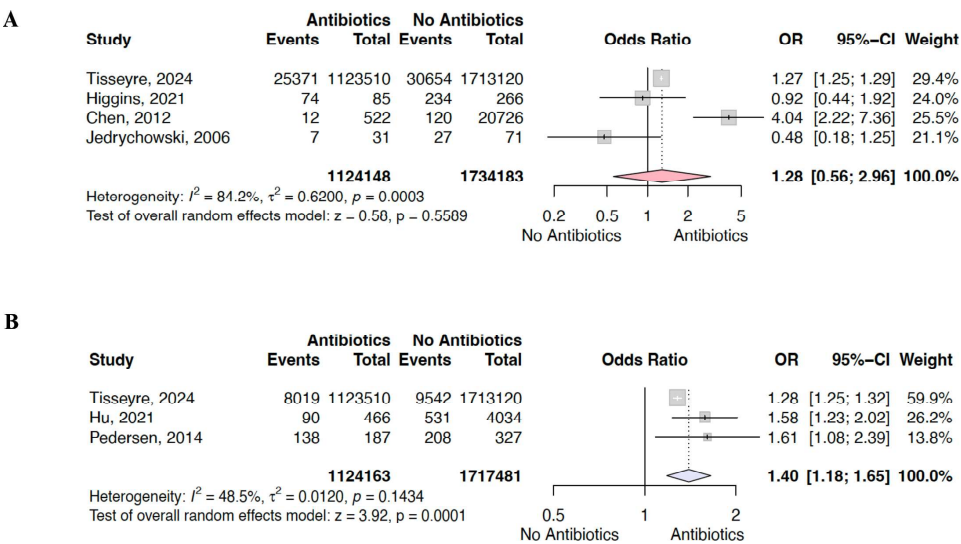


Figure 4 Forest plots showing the associations between prenatal antibiotic exposure and childhood respiratory infection risk (A) and ear, nose and throat (ENT) infection (B). Estimates are ORs, with the sizes of markers illustrating the weights of studies; whiskers illustrate 95% CIs.

DISCUSSION

In this comprehensive systematic review and meta-analysis, we examined the association between maternal antibiotic use and the risk of childhood infections. Of the 14 studies included, 12 studies comprising a total of more than 5 million mother-child pairs were available for meta-analysis. Our findings showed a significant association between maternal antibiotic use and increased offspring overall infection risk. This association was significant in subgroup analyses for ENT infections but not for any respiratory infections. Our systematic review indicated that the risk was most pronounced among children exposed to antibiotics during the third trimester and among children whose mothers received multiple courses of antibiotics. However, we were not able to conduct meta-analyses for these subgroups. No consistent patterns were observed for specific antibiotic types.

The observed association may be driven by disruption of the maternal microbiome, which shapes neonatal gut colonisation and immune maturation.^{27,28} Stockholm et al demonstrated that antibiotic use during pregnancy alters vaginal microbiota near birth, potentially reducing beneficial bacteria like *Bifidobacterium*, which play a significant role in immune regulation.²⁹ Miller et al’s finding of increased infection risk in vaginally born children exposed to prenatal antibiotics compared with caesarean-born children supports the dysbiosis theory, as it suggests that antibiotic-induced disruption of the maternal vaginal microbiota impairs the transfer of protective microbes during vaginal delivery.¹⁶ High certainty of evidence in the GRADE assessment for any childhood infection and ENT infections supports their clinical relevance, suggesting prenatal antibiotic exposure may warrant careful consideration in practice. On the other hand, the very low certainty of evidence for the analysis conducted for respiratory infection risk suggests the need for further studies to clarify this relationship, as the interpretation of the findings should be considered in relation to this gra-

ding. Further, the most contributing study (n=1 713 120 (99.7%)) of the total n=1 717 481 in the analysis for respiratory infection risk showed a significant increased risk (OR 1.27 (1.25–1.29)), indicating an increased risk from maternal antibiotic exposure here as well.

A systematic review and meta-analysis of studies covering 23 outcomes in nearly 22 million children found that exposure to antibiotics any time during pregnancy was associated with increased risk of various adverse health outcomes in children, including immune, metabolic and neurodevelopmental diseases such as food allergies, obesity, asthma, inflammatory bowel disease, cerebral palsy and cancer, but without investigating offspring infection risk.³⁰ These previously reported findings align with the hypothesis that a disturbed microbiota that may impair immune regulation thereby increases the risk of infection and other related immune disorders.^{31–37} The novelty of our findings supports previous evidence that maternal antibiotic use seems to have a lasting impact on the health of the unborn child many years after exposure. The prenatal period is known for its vulnerability and importance for fetal development and shaping of the immune system. Therefore, clinicians may consider antibiotics carefully when prescribing this for milder infections in pregnant women.

Several studies included in this systematic review highlight that the timing and cumulative exposure to antibiotics during pregnancy may play a role in shaping childhood infection risk. Notably, antibiotic use later in pregnancy was more often associated with childhood infection outcomes compared with earlier exposure, potentially due to proximity to delivery and disruption of the maternal microbiota at a crucial time for neonatal colonisation. Moreover, broad-spectrum antibiotics were consistently linked to increased infection risk, likely reflecting their impact on the maternal microbiome. These findings suggest that both the intensity and timing of antibiotic exposure are important determinants of postnatal immune health and warrant consideration in clinical decision-making, although we did not have sufficient data to conduct a meta-analysis of the specific antibiotic types.

Strengths of this review include its prospective and transparent approach, including PROSPERO registration before initiating the study and adherence to recommended PRISMA guidelines including risk of bias and GRADE assessments. The meta-analysis included a large proportion of children, enhancing statistical power, and the studies represented a broad range of geographical regions, improving generalisability. The risk of bias was low in most included studies.

Several limitations should be considered. All included studies were observational and could be subject to potential confounding. The studies differed in regard to population characteristics and infection types. Few studies adjusted for maternal propensity for in-

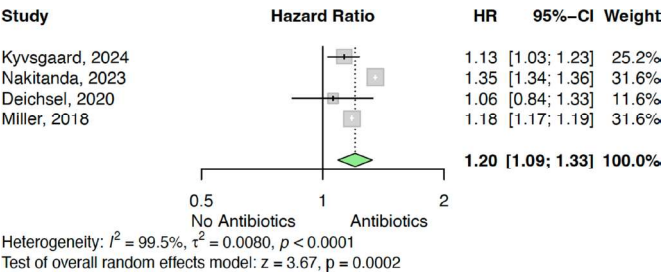


Figure 3 Forest plots showing the associations between prenatal antibiotic exposure and any childhood infection risk. Estimates are HRs, with the sizes of markers illustrating the weights of studies; whiskers illustrate 95% CIs.

fection, which may reflect shared genetic or environmental factors influencing both maternal and child infection risk. For example, one study found that maternal diarrhoea significantly increased the risk of infant diarrhoea, while antibiotics did not,¹⁸ suggesting maternal propensity to infections to be the driving factor. Additionally, both prematurity and mode of birth, which have been found to be risk factors for childhood infections,^{38–40} were rarely adjusted for in the included studies. Limited and inconsistent data precluded meta-analysis of antibiotic type, dose and trimester-specific effects. One study reported IRRs instead of HRs,¹⁴ and treating risk ratios as HRs assumed that infection rates were rare, which likely does not hold for the study, which includes common infections as an outcome (eg, colds), potentially biasing the pooled estimates. Finally, while no publication bias was detected, small subgroup sizes reduce confidence in these assessments.

CONCLUSION

Findings from this systematic review and meta-analysis suggest that maternal antibiotic use during pregnancy is associated with an increased risk of childhood infections. Current evidence proposes that the third trimester may be a period of heightened vulnerability, and that multiple courses may increase child infection risk further. The observed associations underscore the need for cautious antibiotic prescribing during pregnancy, particularly for milder maternal infections. Further research is needed to explore the biological mechanisms underlying this association and should also aim to clarify trimester-specific risks while accounting for key confounding factors such as prematurity, mode of delivery and maternal propensity for infection. Future large sibling studies are warranted to account for shared lifestyle and genetic factors, thereby mitigating the risk of confounding.

Contributors All authors contributed to the conception and design of the study. KA led the systematic search, data extraction, statistical analysis and drafting of the manuscript. MH assisted with article screening, data collection and statistical analysis. NB and BLKC reviewed and provided input on studies where inclusion was uncertain. All authors were involved in interpreting the findings and reviewing the manuscript. KA and MH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had final responsibility for the decision to submit the manuscript for publication. NB is the guarantor of the study. AI was not used for any of the work in this manuscript.

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ARTIGO ORIGINAL

Terapia posicional vibrotátil para o tratamento da apneia obstrutiva do sono posicional: ensaio multicêntrico, aleatorizado e controlado

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RESUMO

Contexto Os dispositivos de terapia posicional de nova geração fornecem feedback vibrotátil a doentes com apneia obstrutiva do sono posicional (POSA), reduzindo o tempo de sono em decúbito dorsal e a gravidade da apneia. No entanto, os efeitos a longo prazo na gravidade da POSA, na sonolência e na qualidade de vida (QoL) permanecem incertos.

Métodos Um ensaio aleatorizado, paralelo e duplamente cego comparou terapia posicional aplicada ao pescoço com terapia posicional simulada (sham) durante 3 meses (ClinicalTrials.gov: NCT04153240). Foram incluídos adultos com POSA (índice de apneia/hipopneia (AHI) >5 eventos/hora, com razão 2:1 entre posição supina e não supina), randomizados 1:1. O endpoint primário foi o AHI aos 3 meses, terapia posicional versus sham. As análises secundárias incluíram: interação entre efeito do tratamento e idade; qualidade de vida, incluindo Epworth Sleepiness Scale (ESS) e Pittsburgh Sleep Quality Index (PSQI).

Resultados Entre outubro de 2019 e agosto de 2022, foram randomizados 120 doentes com AHI basal mediano de 12,8 eventos/hora (IQR 9,2–18,5): 59 para terapia posicional e 61 para sham; 92 (77%) completaram o ensaio. A terapia posicional reduziu significativamente o AHI em –4,41 eventos/hora (IC 95% –7,77 a –1,06; p=0.011) comparativamente ao sham, correspondendo a uma melhoria de 34%. Observou-se uma melhoria significativa no PSQI: –1,0 (IC 95% –2,1 a 0,0; p=0.04), mas não na ESS: –0,6 (IC 95% –1,8 a 0,6; p=0.3), com terapia posicional versus sham (ESS basal 8,8). Resultados semelhantes foram observados nos grupos etários mais jovens (18–64 anos) e mais velhos (≥65 anos). Os parceiros de cama relataram melhorias no ronco e na qualidade do sono, tanto do doente como deles próprios. Mais de metade dos participantes que utilizaram o dispositivo ativo optaram por continuar a utilizá-lo.

Conclusão A terapia posicional aplicada ao pescoço reduziu a gravidade da OSA e melhorou a qualidade do sono, mas não a sonolência, ao longo de 3 meses. Os parceiros de cama relataram melhorias no ronco e na qualidade do sono.

Registro do ensaio: NCT04153240.

INTRODUCTION

Obstructive sleep apnoea (OSA) is a common disorder characterised by repetitive airway collapse during sleep. It has a prevalence of 5–10% across the global adult population,¹ rising to 30% in older patients² due to age-related changes in the pharyngeal airway.^{3–5}

Positional OSA (POSA) is a subset of OSA which either occurs exclusively, or is made worse by, the supine position. POSA is commonly defined as an apnoea–hypopnoea index (AHI) in the supine

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Vibrotactile positional therapy has been shown to reduce disease severity in the short term; there is little evidence over longer term, particularly controlled studies for neck-worn devices, which include quality-of-life outcomes.

WHAT THIS STUDY ADDS

► Longer term neck-worn vibrotactile positional therapy significantly reduced the severity of sleep apnoea and improved sleep quality, but not sleepiness in patients with predominately mild–moderate positional obstructive sleep apnoea (POSA). Additionally, patients' bed partners reported improvements in snoring and sleep quality for both the patient and themselves.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► The results of the POSA trial support the expert consensus reported in the National Institute for Health and Care Excellence NG202 recommendation: vibrotactile positional therapy should be considered for people with mild or moderate POSA.

position that is twice that of the non-supine AHI,⁶ and is present in between 50% and 75% of patients with OSA and in 53% of the general population.^{7,8}

Positional therapy aims to discourage sleeping in the supine position, and thereby reduce or eliminate airway collapse.⁹ UK guidelines recommend consideration of positional therapy for people with mild or moderate POSA if other treatments, such as continuous positive airway treatment (CPAP), are unsuitable or not tolerated.¹⁰ Positional therapy traditionally provided a physical barrier or deterrent to supine sleep. Although these interventions were effective at reducing AHI, poor comfort and intolerance combined with subsequent low long-term adherence rates meant that they were not adopted as standard practice.^{11–13}

New generation vibrotactile devices use position sensors to determine patient position and haptic motors to deter the supine position by vibratory



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feedback stimulation. These devices are worn either on the neck, the forehead or the chest.^{14–16} Systematic reviews and meta-analyses of the evidence for all vibrotactile positional therapy devices support reduction in supine sleep time and in AHI.^{17–19} Moreover, improved comfort and more promising adherence rates have been observed, compared with traditional methods.^{20,21}

The neck-worn vibrotactile positional therapy has been shown to reduce the severity of OSA in the short term.^{22–24} However, there are few data on the longer-term effects on sleep apnoea severity, limited information on the treatment effect on quality of life (QoL) and uncertainty on the effects in older individuals.^{10,19} The POSA trial aimed to investigate longer-term effects of neck-worn positional therapy on OSA compared with a sham-control. The POSA trial also sought to investigate the effect of age on the efficacy of positional therapy, given the high prevalence of OSA in older patients.

METHODS

Study design and participants

The POSA trial was a multicentre, double-blind, parallel group, randomised controlled trial (RCT) comparing positional therapy (NightShift; Advanced Brain Monitoring, USA) with sham-positional therapy (see below Intervention and control), for 3 months in older (≥ 65 years) and younger patients (18– <65 years). Recruitment was from six sleep centres by POSA trial investigators via the UK Respiratory Sleep Research Network (online supplemental tables s1 and s2). The trial was managed by the Trial Steering Committee and registered with ClinicalTrials.gov, NCT04153240.

Adult patients with suspected sleep apnoea were referred to their local sleep centre and assessed using local clinical management protocols. Patients with newly diagnosed POSA were invited to participate in the trial. Eligibility was confirmed by a home sleep test (respiratory polygraphy with automated scoring algorithm; Apnealink Air and Airview software, ResMed, Oxfordshire, UK) (see online supplemental section 2.2).

Inclusion criteria

Patients (≥ 18 years) were eligible to enter the trial if they had POSA, diagnosed as an overall AHI >5 events/hour (American Academy of Sleep Medicine (AASM) 2012 scoring criteria) with events occurring at a frequency of 2:1 when supine,⁶ compared with non-supine; a total percentage supine sleep time >10 and $<90\%$ of total sleep time; and if respiratory events were predominantly obstructive. Exclusion criteria in online supplemental section 2.3.

The full POSA protocol can be found on ClinicalTrials.gov: <https://www.clinicaltrials.gov/study/NCT04153240>.

Randomisation and masking

Eligible patients were randomly assigned (1:1) to positional therapy or sham-positional therapy using an online computer-generated randomisation schedule (registration/randomisation and manage-

ment of product), with minimisation based on age group (18– <65 : ≥ 65 years) and OSA severity (AHI <20 : ≥ 20 events/hour).

The positional therapy devices were preset by an unblinded researcher in the trial management team (ASA) who was not involved in outcome assessments or patient visits. Devices were preset to either 'TRIAL', which was the intervention—first night monitoring, vibration feedback from second night onwards, or 'MONITOR', which was the control—monitoring only, no vibration feedback. They were subsequently labelled with a trial asset number according to a random number sequence provided by Oxford Respiratory Trials Unit. Only the device numbers identified the allocation of each device. The participants, researchers, clinicians and trial statistician were blinded until after the data analysis was completed.

Procedures

Eligible patients attended two outpatient visits with their local sleep service, one at baseline and one at 3 months. At the baseline visit, patients provided demographic information, a medical history and completed baseline QoL questionnaires. Patients also reported the symptoms leading to their referral. At the end of the baseline visit, patients were randomised.

Intervention and control

The vibrotactile positional therapy was delivered by the NightShift Sleep Positioner (Advanced Brain Monitoring, Carlsbad, USA) worn on the back of the neck (figure 1). The active positional therapy vibrated when the supine position was detected and increased in intensity until the participant changed position. The sham-positional therapy device provided monitoring only with no vibration feedback.

Follow-up

After four nights, participants in both groups were contacted by the central research team (Royal Brompton Hospital), by either phone call or email, to determine early patient experience and troubleshoot any issues that had arisen.

After 3 months of treatment, participants had further follow-up, repeating the baseline QoL questionnaires and additionally completing questionnaires detailing their experience with the positional therapy device and, where applicable, their bed partner's experience (see online supplemental section 2.4). They also performed a follow-up home sleep test (Apnealink Air) with the positional therapy device in situ. Data from the positional therapy device, including adherence, was downloaded via an internet-based Report Portal (Advanced Brain Monitoring, Carlsbad, USA). Participants in the active treatment group were asked if they wished to continue positional therapy, and participants in the sham group were offered positional therapy treatment.

During the first wave of the COVID pandemic in March 2020, the trial was paused and the trial protocol, by necessity, was



Figure 1 NightShift Sleep Positioner (Advanced Brain Monitoring, Carlsbad, USA). In the POSA trial, the device was worn on the back of the neck. POSA, positional obstructive sleep apnoea.

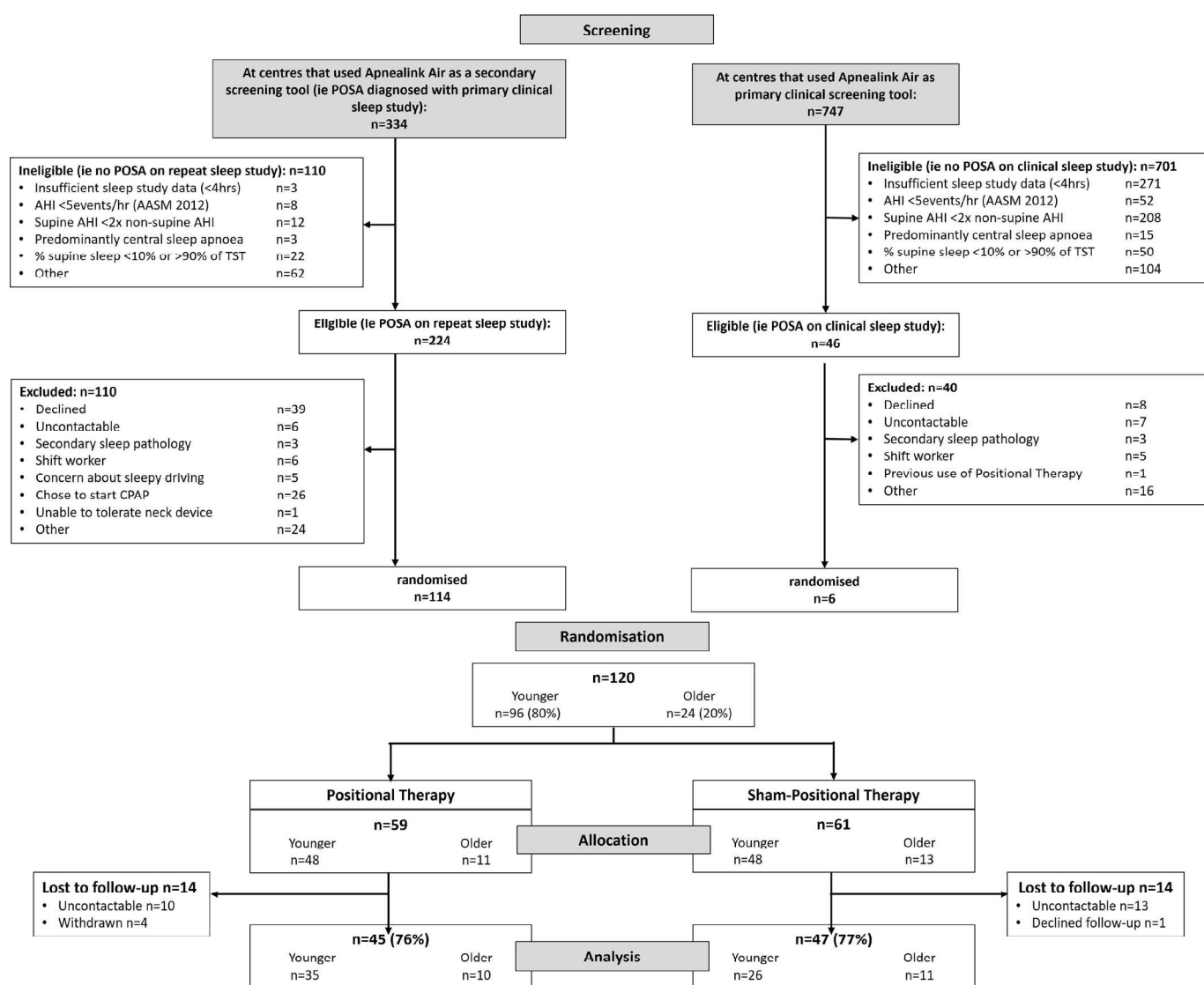


Figure 2 CONSORT diagram. AHI, apnoea/hypopnoea index; CONSORT, Consolidated Standards of Reporting Trials; CPAP, continuous positive airway treatment; POSA, positional obstructive sleep apnoea; TST, total sleep time.

amended to provide remote options for all patient interactions, that is, consent, trial visits and diagnostic sleep studies (see online supplemental section 2.5 and table s3).

Primary outcome

AHI at 3 months, measured by a repeat home sleep test (polygraphy) with the positional therapy device in situ, adjusted for baseline AHI and compared between positional therapy and sham-positional therapy.

Secondary outcomes

The comparison of the treatment effect between older and younger participants was a secondary outcome. Other secondary outcomes included the percentage supine sleep time and oxygen desaturation index (ODI), plus participants' subjective symptoms, well-being and QoL which were assessed by questionnaires: Epworth Sleepiness Scale (ESS),²⁵ Functional Outcomes of Sleep Questionnaire,²⁶ Hospital Anxiety and Depression Scale,²⁷ Independent Functioning (Townsend Disability Scale),²⁸ ShortForm-36 (eight scales),²⁹ a Healthcare Utilisation Questionnaire, EuroQol EQ-5D³⁰ and Pittsburgh Sleep Quality Index (PSQI).³¹ Partners' or carers' perspectives were also captured. Adherence to therapy was measured by the positional therapy device.

Sample size

A sample size of 138 participants (69 per group) was estimated to detect a clinically important treatment difference (AHI of 5 events/

hour at 3 months), powered to detect superiority of positional therapy compared with sham at 90% power and 5% significance level, assuming within-group SD of 9.05 events/ hour, based on systematic review data.¹⁷ Target recruitment was set at 155 patients to account for an assumed 10% drop-out rate.

Post COVID-19 pandemic, when recruitment rates were slower than expected (March 2022), the Trial Steering Committee decided to reduce the power of the study from 90% to 80% in line with previous UK sleep trials,^{32, 33} thus reducing the sample size from 138 to 104 participants (52 per group). A new target recruitment was set at 116 patients.

Statistical analysis

Data are presented according to CONSORT (Consolidated Standards of Reporting Trials) guidelines. All primary analyses were performed on an intention-to-treat principle. Statistical analysis was done by an independent statistician (blind to which group was which) in accordance with a predefined analysis plan. All data were imported into Stata V.17 for statistical analysis.

Analysis of the primary outcome was performed by linear regression of final AHI with respect to treatment, adjusting for baseline AHI and age group. All secondary data (objective sleep data and subjective QoL data) were analysed in the same way. No formal adjustments for multiple significance testing were made.

The trial was analysed as a 2x2 factorial design. The comparison of primary interest was between patients of all ages

Table 1 Baseline demographic and clinical characteristics of patients with positional obstructive sleep apnoea

	Positional therapy: (n=59)	Sham-positional therapy: (n=61)	Total: (N=120)
Age (years)	53.6 (11.8)	51.8 (12.8)	52.7 (12.3)
Gender: n(%)			
Male	42 (71.2)	52 (85.2)	94 (78.3)
Female	17 (28.8)	9 (14.8)	26 (21.7)
BMI (kg/m²)	28.3 (4.4)	28.4 (3.9)	28.4 (4.2)
Ethnicity: n(%)			
White	56 (94.9)	54 (88.5)	110 (91.7)
Hispanic/Latino	1 (1.7)	1 (1.6)	2 (1.7)
Asian (India/Pakistan/Bangladesh)	2 (3.4)	3 (4.9)	5 (4.2)
Mixed/Other	0 (0.0)	3 (4.9)	3 (2.5)
Neck circumference (cm)	40.0 (3.8)	40.9 (3.1)	40.5 (3.4)
Smoking status: n(%)			
Never smoked	30 (50.8)	40 (65.6)	70 (58.3)
People who quit smoking	25 (42.4)	18 (29.5)	43 (35.8)
People who currently smoke	4 (6.8)	2 (3.3)	6 (5.0)
Missing	0 (0.0)	1 (1.6)	1 (0.8)
Smoking (pack years)	12.8 (9.9)	8.7 (7.3)	11.2 (9.1)
Self-reported medical history: n(%)			
Coronary artery disease	5 (8.5)	1 (1.6)	6 (4.0)
Hypertension	11 (18.6)	18 (29.5)	29 (24.2)
Diabetes	4 (6.8)	3 (4.9)	7 (5.8)
Anxiety	21 (35.6)	12 (19.7)	33 (27.5)
Depression	18 (30.5)	13 (21.3)	31 (25.8)
Insomnia	11 (18.6)	13 (21.3)	24 (20.0)
Rhinitis/other nasal problem	18 (30.5)	12 (19.7)	30 (25.0)
Stroke/TIA	2 (3.4)	1 (1.6)	3 (2.5)
Sleep study results:			
AHI (events/hour)	12.5 (9.5–17.8)	13.1 (8.6–19.7)	12.8 (9.2–18.5)
Supine AHI (events/hour)	22.1 (16.7–32.0)	21.2 (13.9–35.6)	21.9 (15.1–34.2)
Non-supine AHI (events/hour)	3.8 (2.0–6.4)	4.6 (2.3–7.6)	4.4 (2.0–7.2)
AI (events/hour)	2.9 (1.1–5.5)	2.1 (0.7–6.2)	2.3 (0.8–6.0)
HI (events/hour)	9.6 (7.0–11.6)	8.9 (6.6–14.1)	9.3 (6.7–12.9)
ODI >3% (events/hour)	15.2 (10.7–20.1)	16.0 (9.8–21.5)	15.6 (10.1–20.9)
Supine %TST (%)	53.2 (33.9–62.2)	46.1 (36.7–69.4)	49.5 (34.9–65.8)
Randomisation OSA severity: n(%)			
AHI <20 (events/hour)	48 (81.4)	47 (77.0)	95 (79.2)
AHI ≥20 (events/hour)	11 (18.6)	14 (23.0)	25 (20.8)
Main reason for referral: n(%)			
Snoring	14 (23.7)	19 (31.1)	33 (27.5)
Witnessed apnoea	19 (32.2)	13 (21.3)	32 (26.7)
Unrefreshing Sleep	8 (13.6)	5 (8.2)	13 (10.8)
Fatigue	5 (8.5)	7 (11.5)	12 (10.0)
Excessive daytime sleepiness	2 (3.4)	7 (11.5)	9 (7.5)
Screening (preop or due to comorbidity, eg, resistant hypertension)	4 (6.8)	3 (4.9)	7 (5.8)
Poor memory/concentration	0 (0.0)	1 (1.6)	1 (0.8)
Other	7 (11.9)	6 (9.8)	13 (10.8)
Main driver for referral: n(%)			
Patient	24 (40.7)	24 (39.3)	47 (39.2)

Continued

Table 1 Continued

	Positional therapy: (n=59)	Sham-positional therapy: (n=61)	Total: (N=120)
Bed-partner	20 (33.9)	23 (37.7)	43 (35.8)
Respiratory physician	4 (6.8)	5 (8.2)	9 (7.5)
Cardiologist	5 (8.5)	3 (4.9)	8 (6.7)
GP	5 (8.5)	2 (3.3)	7 (5.8)
Other medical specialist	1 (1.7)	4 (6.4)	5 (4.0)
Missing	1 (1.7)	0 (0.0)	1 (0.8)
Quality of life: mean higher scores mean better status			
SF-36			
Physical functioning	78.6 (24.8)	78.3 (27.3)	78.5 (25.9)
Role limitations due to physical health	61.2 (38.4)	67.2 (40.1)	64.2 (39.2)
Role limitations due to emotional problems	66.7 (41.4)	69.0 (40.4)	67.8 (40.8)
Energy/fatigue	43.9 (23.6)	44.4 (20.4)	44.2 (21.9)
Emotional well-being	68.8 (21.5)	69.4 (18.1)	69.1 (19.8)
Social functioning	69.4 (29.2)	76.9 (26.5)	73.3 (28.0)
Pain	66.9 (26.0)	72.9 (25.3)	69.9 (25.7)
General health	52.5 (22.0)	56.6 (20.3)	54.5 (21.2)
FOSQ	16.8 (3.0)	16.7 (3.0)	16.7 (3.0)
General productivity	3.5 (0.6)	3.5 (0.6)	3.5 (0.6)
Social outcome	3.6 (0.7)	3.6 (0.7)	3.6 (0.7)
Activity level	3.1 (0.7)	3.1 (0.7)	3.1 (0.7)
Vigilance	3.4 (0.7)	3.3 (0.6)	3.3 (0.7)
Intimate activity	3.2 (0.9)	3.3 (0.8)	3.3 (0.9)
EQ-5D-5L (Index)	0.8 (0.2)	0.8 (0.2)	0.8 (0.2)
EQ-5D-5L (VAS)	72.4 (17.6)	72.6 (17.5)	72.5 (17.5)
Quality of Life: mean lower scores mean better status			
ESS	8.5 (4.4)	9.0 (5.0)	8.8 (4.7)
HADS (anxiety)	6.8 (4.8)	7.4 (4.7)	7.1 (4.7)
HADS (depression)	5.8 (4.4)	5.0 (4.3)	5.4 (4.3)
Townsend Disability Index	2.7 (4.6)	3.5 (6.1)	3.1 (5.4)
PSQI global score	8.5 (4.3)	9.4 (4.0)	9.0 (4.1)

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

AHI, apnoea–hypopnoea index; AI, apnoea index; BMI, body mass index; EQ-5D-5L, European quality of life five dimensions Questionnaire; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; GP, general practitioner; HADS, Hospital Anxiety and Depression Scale; HI, hypopnoea index; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; PSQI, Pittsburgh Sleep Quality Index; SF-36, Short Form-36; TIA, transient ischaemic attack; TST, total sleep time; VAS, Visual Analogue Scale.

randomised to the active treatment and patients of all ages allocated to the sham treatment, and the old–young comparison was a matter of secondary analysis. The final AHI was used as the primary outcome and included age as a blocking factor as well as including baseline AHI as a linear predictor which acted to slim the CIs and reduce bias caused by unfortunate randomisation. Age was used as a binary (older vs younger) variable rather than continuous as it was not certain that the effect of age was linear.

RESULTS

Between 30 October 2019 and 8 August 2022, 120 patients with POSA were recruited; 59 were randomised to positional therapy and 61 to sham-positional therapy. 96 participants (80%) were in the younger group (18–<65 years), and 24 participants (20%) were in the older group (≥65 years). 92 participants (77%) completed the trial (figure 2).

Baseline demographics and clinical characteristics are presented in table 1. The mean age was 52.7 (SD 12.3) years; (younger group: 49 (SD 10) vs older group: 70 (SD 3.8) years). The baseline sleep study showed that participants had, on average, mild OSA (AHI of 12.8 events/hour (IQR 9.2–18.5)). Participants were on average not sleepy (ESS 8.8 points (SD 4.7)); however, they were poor sleepers

as measured by the PSQI (9.0 points (SD 4.1)). Characteristics were similar between the groups.

Outcomes

Severity of OSA

Positional therapy significantly reduced the primary outcome of AHI by –4.4 events/hour (95% CI –7.8 to –1.1), $p=0.011$, a 34% improvement (figure 3). As expected, the reduction in AHI was matched by a reduction in the percentage supine sleep time of –14.5% (95% CI –23.8% to –5.2%), $p=0.003$. Other sleep study parameters are presented in table 2.

Quality of life and sleepiness

There was a significantly greater improvement in sleep quality (PSQI: mean treatment difference –1.05 points (95% CI –2.07 to –0.03), $p=0.04$), as well as the SF-36 emotional well-being score (mean treatment difference +7.01 points (95% CI +0.90 to +13.12), $p=0.03$) with positional therapy compared with sham-positional therapy at 3 months. There were no other significant differences in sleepiness or other QoL scores between positional therapy and sham-positional therapy (table 3).

Overall, when asked about their experience, 66% of participants in the positional therapy group reported a subjective improvement

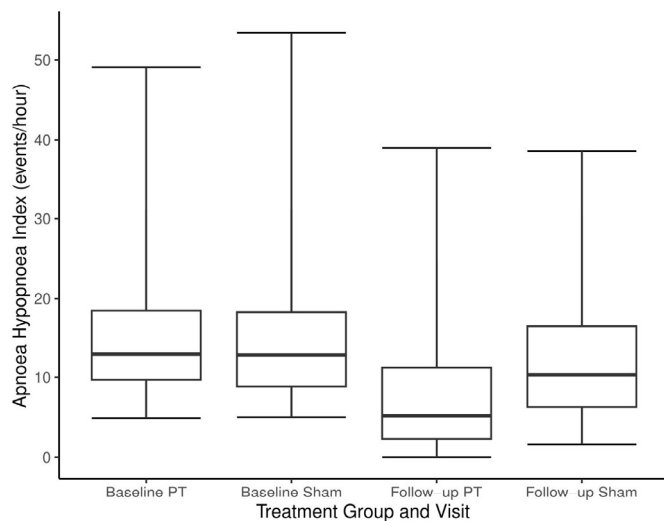


Figure 3 The apnoea–hypopnoea index at baseline and after 3 months of positional therapy and sham-positional therapy; Treatment difference=−4.414 events/hour (95% CI −7.768 to −1.059), $p=0.011$. Median change in AHI in positional therapy versus sham-positional therapy was −6.60 events/hour (IQR −9.70 to −3.90) vs −2.70 events/hour (IQR −7.60 to 3.00). AHI, apnoea–hypopnoea index; PT, positional therapy.

in their symptoms, compared with 22% in the sham group. 58% in the active group and 34% in the sham group wished to continue positional therapy (online supplemental table s4).

Effect of age on the efficacy of positional therapy

Analyses combining age groups and adjusted for age group were repeated separately for the two age groups (18–<65: ≥65 years) (online supplemental table s5 and s6). Beneficial effects of positional therapy were observed for both groups; however, it should be noted that a relatively small percentage (20%) of patient were aged 65+, and therefore the CIs for the treatment effects in age group 65+ were wider than in the main combined-age analyses.

Bed partners' perspectives

Approximately three quarters of the 92 completers (72%) had a bed partner during the study (online supplemental table s7). Bed partners of those participants receiving positional therapy were more likely to report an improvement in snoring compared with the bed partners of those receiving sham positional therapy (63% vs 24%). Likewise, the partners of those receiving positional therapy were also more likely to report improvements in sleep quality for both the participant (66% vs 9%) and themselves (50% vs 9%).

Adherence to positional therapy and side effects

Adherence data was available for 38 of 45 completers (84%) randomised to positional therapy, and 35 of 47 completers (74%) randomised to sham-positional therapy (online supplemental table

s8). The median nights used in the 90-day period were 66 nights (IQR 49–85) vs 68 nights (IQR 23–85) respectively. The median nightly use over 90 days was 5:00 hours (IQR 2:49–6:13) vs 5:26 hours (IQR 2:00–6:25).

Participants reported being aware of the vibrational feedback in 96% of those receiving positional therapy versus 3% of those receiving sham. Typically, those receiving positional therapy were aware of the feedback a median of 3 times (IQR 2–4) per night (online supplemental table s4).

Side effects were reported by 39 of 45 completers (87%) randomised to positional therapy, and 36 of 47 completers (77%) randomised to sham-positional therapy (online supplemental table s9). The main side effects were strap/device discomfort ($n=42$), waking due to vibrational feedback ($n=21$), continued snoring ($n=17$), position discomfort in non-supine positions ($n=17$) and continued symptoms ($n=10$). All reports of waking due to vibrational feedback were made by those receiving active positional therapy. Additionally, position discomfort due to sleeping in non-supine positions was reported more frequently by those receiving active positional therapy compared with sham-positional therapy ($n=13$ vs $n=4$ respectively). Continued symptoms were only reported in the sham group ($n=10$).

Post hoc analysis

Comparison of responders and non-responders

In a post hoc analysis, responders were defined as those whose AHI was reduced by ≥ 5 events/hour. There were 31 of 45 (69%) responders receiving positional therapy, compared with 16 of 47 (34%) of those receiving sham-positional therapy.

In the positional therapy group ($n=45$), the responders, when compared with the non-responders, tended to have a higher baseline median percentage supine sleep time (50% (IQR 36–62%) vs 33% (23–80%)), AHI (13 events/hour (IQR 11–22) vs 9 events/hour (IQR 6–18)) and ODI (16 events/hour (IQR 12–23) vs 11 events/hour (IQR 7–21)) at baseline (online supplemental table s10). Responders were also more likely to report snoring as their reason for referral, when compared with non-responders (32% vs 0%), while non-responders reported higher levels of witnessed apnoeas (43% vs 29%).

Sensitivity analysis

Of the 120 participants randomised, 92 (77%) had measurements in the primary outcome (AHI) both at baseline and at 3 months. Due to possible bias caused by more dropouts than anticipated, these compliant participants may possibly have been unrepresentative of the intended-to-treat population. Therefore, a post hoc sensitivity analysis was conducted using a completeness-propensity weighted analysis³⁴ for the treatment difference for AHI (online supplemental section 3.6). Baseline covariates of age, prerandomisation general practitioner visits and prerandomisation days off work predicted AHI completeness (online supplemental table s11 and figure s1). The sensitivity analysis provided similar estimates to our main analysis with a treatment difference for the AHI of −4.1 events/hour (95% CI −7.6 to −0.7, $p=0.02$) between the groups.

Table 2 Sleep study parameters in patients with positional obstructive sleep apnoea after 3 months of positional therapy versus sham-positional therapy

Outcome at 3 months	Positional therapy (n=45)	Sham-positional therapy (n=47)	Treatment difference (95% CI)	P value
AHI (events/hour)	5.2 (2.3–11.2)	10.3 (6.2–17.4)	−4.4 (−7.8 to 1.1)	0.011
Supine AHI (events/hour)	5.7 (1.6–13.5)	18.0 (10.2–27.8)	−8.6 (−14.2 to 2.9)	0.0034
Non-supine AHI (events/hour)	4.8 (2.3–9.6)	3.6 (1.3–5.7)	1.6 (−0.9 to 4.0)	0.2
AI (events/hour)	0.7 (0.2–2.2)	1.3 (0.4–3.2)	−1.5 (−3.3 to 0.2)	0.076
HI (events/hour)	4.6 (1.9–6.9)	7.9 (4.3–12.7)	−2.8 (−5.5 to 0.1)	0.039
ODI (events/hour)	8.5 (5.4–12.2)	13.9 (9.0–20.3)	−5.0 (−9.1 to 0.9)	0.017
Supine percentage TST(%)	21.6 (7.7–51.4)	41.4 (24.9–63.8)	−14.5 (−23.8 to −5.2)	0.0027

Data presented as median (IQR) and mean treatment difference (95% CI).
AHI, apnoea–hypopnoea index; AI, apnoea index; HI, hypopnoea index; ODI, oxygen desaturation index; TST, total sleep time.

DISCUSSION

The results of the POSA trial showed that neck-worn vibrotactile positional therapy significantly reduced sleep apnoea severity, compared with sham, over a 3-month period. This was accompanied by an improvement in subjective sleep quality, but not in sleepiness. Similar results were seen in both younger (18–<65) and older (≥65) age groups. Additionally, patients' bed partners reported improvements in snoring and sleep quality for the patient and themselves. Over half of participants using positional therapy opted to continue the therapy.

The reduction in AHI in the POSA trial is in keeping with previous data included in a recent meta-analysis of vibrotactile positional therapy.¹⁸ This analysis found a significant reduction in AHI at follow-up, compared with baseline (mean difference (95% CI) –5.09 events/hour (–7.37 to –2.81); $p < 0.00001$). However, the majority of the RCTs included in this analysis differed from the POSA study; they used chest or forehead-worn devices, did not use a sham control and had short follow-up periods (between one night and 8 weeks). One RCT has used a sham control device; this study tested a forehead-worn vibrotactile device over 12 weeks and found a significant reduction in AHI and supine sleep time in participants with on average severe OSA.³⁵ The study also reported on sleepiness, but only used a single QoL question (EuroQol Visual Analogue Scale).

The POSA trial showed a modest effect with neck-worn vibrotactile positional therapy, compared with the published results for forehead-worn positional therapy. This may have occurred because the participants in the POSA trial had mild OSA, which may have limited the treatment effect. The reduction in AHI in the POSA trial is less than the minimum important clinical difference (MICD) of 5 events/hour.³⁶ However, it is notable that the MICD for AHI was

determined across all OSA severities and may be less relevant to those with mild OSA. Moreover, in the POSA trial, over two thirds of participants responded to positional therapy based on achieving an AHI reduction ≥5 events/hour.

The prevalence of OSA is increased in older people² and the age-related increased collapsibility of the upper airway^{3–5} may be more, or less, amenable to positional changes. The effect of positional therapy has not been specifically investigated in older individuals. The results of the POSA trial showed that age did not influence the effect of neck-worn vibrotactile positional therapy, and therefore it should be considered as a treatment in this population, although the confidence limits for age group over 65 were wider due to a small number of participants. The POSA trial aimed to determine the effect of positional therapy on daytime sleepiness and QoL. Patient-reported outcomes for OSA frequently focus on sleepiness measured using the ESS. In the POSA trial, the ESS was reduced post-treatment in both groups, with a non-significant mean treatment difference of less than one point. Low levels of baseline sleepiness may have limited any treatment effect. In other studies, small but consistent reductions in daytime sleepiness have been reported in response to positional therapy.^{10 18 19} These reductions do not meet the MICD of between 2 and 3 points.³⁷ Taken together with the results of the POSA trial, there is no overall meaningful change in daytime sleepiness with vibrotactile positional therapy.

The SF-36 questionnaire, specifically the Energy and Vitality subscale, has previously been used to show treatment-related improvements in patients with OSA.^{32 33} Although Energy/Fatigue improved after 3 months in the POSA trial, there was no difference between the groups. Sleep quality improved in the POSA trial, when measured by the PSQI scores. However, the mean 3-month scores remained over 5 points, which is the threshold for poor sleepers.³¹

Table 3 Quality of life in patients with positional obstructive sleep apnoea after 3 months of positional therapy versus sham-positional therapy. N1 and N2 who completed each questionnaire in the positional therapy and sham-positional therapy groups respectively

Outcome at 3 months	N1, N2	Positional therapy	Sham- positional Therapy	Treatment difference (95% CI)	P value
Quality of life: higher scores mean better status					
SF-36					
Physical functioning	45, 44	75.4 (29.7)	75.1 (28.3)	–2.5 (–9.1 to 4.1)	0.45
Role limitations due to physical health	44, 43	69.3 (38.2)	62.5 (44.3)	3.4 (–9.4 to 16.2)	0.6
Role limitations due to emotional problems	44, 43	81.1 (34.0)	72.5 (41.2)	5.8 (–7.0 to 18.6)	0.37
Energy/fatigue	41, 40	50.2 (24.9)	47.3 (24.0)	2.34 (–4.5 to 9.2)	0.5
Emotional well-being	44, 43	71.6 (23.1)	66.4 (25.6)	7.0 (0.9 to 13.1)	0.025
Social functioning	41, 43	78.7 (27.7)	72.6 (28.0)	7.4 (–1.5 to 16.3)	0.1
Pain	44, 43	68.4 (25.8)	69.4 (26.3)	1.7 (–5.5 to 8.8)	0.65
General health	44, 41	52.8 (22.1)	52.4 (23.2)	0.2 (–5.9 to 6.3)	0.94
FOSQ	43, 46	17.1 (2.9)	16.3 (3.5)	0.6 (–0.3 to 1.4)	0.2
General productivity	43, 46	3.6 (0.5)	3.5 (0.6)	0.1 (–0.1 to 0.3)	0.18
Social outcome	42, 46	3.6 (0.6)	3.4 (0.8)	0.2 (–0.1 to 0.4)	0.15
Activity level	43, 46	3.3 (0.7)	3.0 (0.8)	0.2 (0.0 to 0.4)	0.11
Vigilance	43, 46	3.5 (0.6)	3.3 (0.7)	0.1 (–0.1 to 0.3)	0.31
Intimate activity	33, 38	3.2 (1.0)	3.2 (0.1)	0.0 (–0.3 to 0.3)	0.99
EQ-5D-5L - Your health today	45, 44	71.1 (19.8)	70.5 (20.9)	–2.2 (–7.6 to 3.2)	0.42
EQ-5D-5L (Index)	45, 43	0.8 (0.3)	0.8 (0.3)	0.0 (–0.0 to 0.1)	0.62
Quality of life: lower scores mean better status					
Epworth Sleepiness Scale	40, 44	7.8 (4.6)	9.0 (5.0)	–0.6 (–1.8 to 0.6)	0.3
HADS anxiety score	59, 61	4.6 (4.9)	5.2 (6.0)	–0.6 (–2.1 to 0.9)	0.44
HADS depression score	59, 61	3.9 (4.8)	3.8 (4.6)	–0.5 (–1.7 to 0.7)	0.42
Townsend Disability Index	41, 38	2.5 (4.7)	2.5 (4.9)	0.4 (–1.6 to 2.4)	0.68
PSQI global score	35, 35	7.5 (3.7)	9.1 (4.7)	–1.0 (–2.1 to 0.0)	0.044

Data presented as mean (SD) and mean treatment difference (95% CI).

EQ-5D-DL, European quality of life five dimensions Questionnaire; FOSQ, Functional Outcomes of Sleep Questionnaire; HADS, Hospital Anxiety and Depression Scale; PSQI, Pittsburgh Sleep Quality Index; SF-36, Short Form-36.

Sleep quality might have been affected by the use of vibrotactile stimuli which can cause arousal or awakening and thus lead to sleep fragmentation. However, participants reported being aware of the vibrations on average only three times a night. Side effects reported by those receiving active positional therapy included waking due to the vibrational feedback and positional discomfort due to sleeping in non-supine positions, whereas participants receiving sham-positional therapy were more likely to report ongoing symptoms. Despite these side effects, participants on active positional therapy were more likely to report improvement in their overall subjective symptoms (66% vs 22%) and were more likely to wish to continue the therapy (58% vs 34%) compared to those participants receiving sham. Overall, the neck-worn device was well tolerated without detriment to sleep quality, even leading to improved subjective sleep quality.

Bed partners of patients with OSA also experience benefits to their own sleep quality and daytime functioning following treatment.^{38,39} Improvements in relationships have also previously been reported with CPAP therapy.³⁹ In the POSA trial, the bed partners of those participants receiving neck-worn vibrotactile positional therapy were over twice as likely to report an improvement in the participant's snoring and were more likely to report improvements in sleep quality for both the participant and themselves.

Therapy adherence

In the POSA trial, adherence data was available in 84% of participants randomised to positional therapy and showed good overall levels of adherence. The median nightly use over 90 days was 5:00 hours (IQR 2:49–6:13), which is greater than the often quoted 4-hour recommended dose for CPAP treatment. Additionally, there were high levels of adherence to the sham-positional therapy, suggesting that even without therapeutic benefit, the device was well tolerated. Other studies have also suggested improved levels of adherence in vibrotactile positional therapy compared with traditional methods.^{20,21} Moreover, the adherence to vibrotactile positional therapy was greater than adherence to CPAP therapy, when directly compared.⁴⁰

Limitations

The generalisability of the POSA trial results may be limited due to several factors. A low symptom burden in the POSA trial cohort could reduce the application of the findings and may have represented referral bias, with those who were more symptomatic being referred straight for CPAP therapy. Participants reported on average normal daytime sleepiness and levels of anxiety and depression. There were also high numbers of Caucasian and male participants, limiting the generalisability of the findings across race and sex. Few female participants made any potential sex comparisons underpowered.

Importantly, unselected patients with POSA were recruited, without an upper limit AHI (ie, not only mild and moderate OSA) and there was no specific targeting of those with exclusive positional dependence (ie, those whose AHI was <10 events/hour in non-supine).^{41,42} This is likely to have limited the response in AHI reduction. The modest reduction in supine sleep time of 14% may also have affected the reduction in AHI. However, care must be taken when comparing with other trials as there is no standardised measurement of supine, with position measurements arising from either sleep testing devices or indeed the positional therapy devices themselves. The method of measurement of sleep position may be a confounding factor because the head/neck position has been shown to influence the AHI, independently of trunk position.⁴³

Blinding patients in device trials is challenging, particularly when the device that is designed to provoke a response, that is, a change in body position in response to a vibration on the neck. We chose an objective primary outcome of the POSA trial, the AHI, to minimise any effect should participants become unblinded. The trial was conducted during the COVID-19 pandemic which affected both the recruitment rate and the need to deliver the protocol remotely. While some participants were grateful for the remote diagnosis and management options, there were several bar-

riers, for example, equipment and questionnaires needed posting during office hours. Ongoing staff redeployments also meant that research time was limited and led to frequent and multiple staffing changeovers, with unfortunate detrimental effects to follow-up and missing data. On the other hand, online information in the format of YouTube videos and online conversations was extremely useful, especially with respect to the use of a new treatment.

CONCLUSIONS

Neck-worn vibrotactile positional therapy reduces OSA severity in patients with POSA over 3 months. Taken together with the reports from bed partners, the vibrotactile positional therapy is also an effective treatment for sleep quality, despite only a small, non-significant improvement in some daytime symptoms in this minimally symptomatic group. Further research is now justified in a more symptomatic group with POSA.

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