

Thorax

ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

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ARCHIVES OF
DISEASE IN
CHILDHOOD

Edição Portuguesa

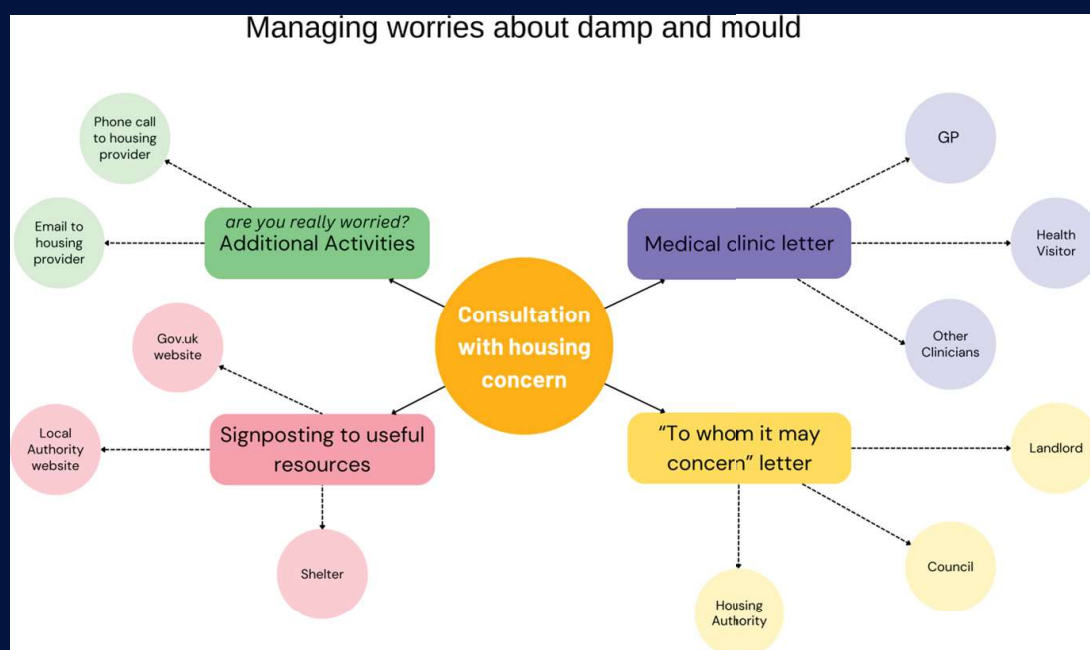


Figure 2 Potential interactions for a clinician supporting a child and family with substandard housing.



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

1 vez dia¹

**Zimbus®
breezhaler®**

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



**NOVA
ASSOCIAÇÃO
LABA/LAMA
/ICS¹**

Dá ritmo à vida^{2,3}

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

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

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

NOTA: Antes de prescrever consulte o RCM do medicamento. **APRESENTAÇÃO:** Pó para inalação, cápsula (pó para inalação). Cada cápsula contém 150 microgramas de indacaterol, 50 microgramas de glicopirrônio e 160 microgramas de furoato de mometasona. Cada dose libertada (a dose libertada através do aplicador bucal do inalador) contém 114 microgramas de indacaterol (na forma de acetato), 8 microgramas de brometo de glicopirrônio equivalente a 46 microgramas de glicopirrônio e 136 microgramas de furoato de mometasona. **Excipiente(s) com efeito conhecido:** Cada cápsula contém 25 mg de lactose mono-hidratada. **INDICAÇÕES:** Zimbus Breezhaler está indicado como terapêutica de manutenção da asma em doentes adultos não controlados adequadamente com uma associação de um agonista beta₂ de ação prolongada e uma dose alta de corticosteroide inalado em regime de manutenção que experimentaram uma ou mais exacerbações da asma no ano anterior. **POSOLOGIA: Adultos:** A dose recomendada é uma cápsula inalada uma vez por dia. A dose máxima recomendada é de 114 µg/46 µg/136 µg uma vez por dia. **Doentes pediátricos (< 18 anos):** Não recomendado em doentes com menos de 18 anos de idade. **Populações especiais: População idosa:** Não é necessário ajuste de dose em doentes idosos (65 anos de idade ou mais). **Compromisso renal:** Não é necessário ajuste de dose em doentes com compromisso renal ligeiro a moderado. Deve ter-se precaução em doentes com compromisso renal grave ou doença renal terminal que necessitem de diálise. **Compromisso hepático:** Não é necessário ajuste de dose em doentes com compromisso hepático ligeiro a moderado. Não existem dados disponíveis sobre a utilização deste medicamento em doentes com compromisso hepático grave, como tal deve ser utilizado nestes doentes apenas se o benefício esperado superar o risco potencial. **Modo de administração:** Apenas para utilização por via inalatória. As cápsulas não podem ser engolidas. Os doentes que não sintam melhorias na sua respiração devem ser questionados se estão a engolir o medicamento em vez de o inalar. As cápsulas têm de ser administradas usando apenas o inalador Zimbus Breezhaler. O tratamento deve ser administrado à mesma hora do dia todos os dias. Pode ser administrado independentemente da hora do dia. Após a inalação, os doentes devem lavar a boca com água sem engolir. Se for omitida uma dose, esta deve ser tomada assim que possível. Os doentes devem ser instruídos a não tomarem mais do que uma dose por dia. As cápsulas de Zimbus Breezhaler devem ser sempre conservadas no blister para proteger da luz e humidade, e só podem ser removidas do blister imediatamente antes da utilização. **CONTRAINDICAÇÕES:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **ADVERTÊNCIAS/PRECAUÇÕES:** ♦ **Asma Aguda:** não deve ser utilizado para tratar sintomas agudos de asma, incluindo episódios agudos de broncoespasmo, para os quais é necessário um broncodilatador de curta ação. ♦ **Hipersensibilidade:** Se ocorrer uma reação de hipersensibilidade, Zimbus Breezhaler deve ser descontinuado imediatamente e deverá ser instituída terapêutica alternativa. ♦ **Broncoespasmo paradoxal:** Tal como com outra terapêutica inalatória, a administração deste medicamento pode resultar em broncoespasmo paradoxal, o qual pode colocar a vida em risco. Se tal ocorrer, o tratamento deve ser interrompido imediatamente e deverá ser instituída terapêutica alternativa. ♦ **Efeitos cardiovasculares:** Tal como outros medicamentos contendo agonistas adrenérgicos beta₂, este medicamento pode produzir um efeito cardiovascular clinicamente significativo em alguns doentes conforme avaliado através de aumentos na frequência cardíaca, pressão arterial e/ou sintomas, alterações do electrocardiograma (ECG). Este medicamento deve ser usado com precaução em doentes com patologias cardiovasculares (doença arterial coronária, enfarte agudo do miocárdio, arritmias cardíacas, hipertensão, suspeita ou confirmação de prolongamento do intervalo QT, distúrbios convulsivos ou tirotóxicose e em doentes com resposta aumentada aos agonistas adrenérgicos beta₂). ♦ **Hipocalcemia:** Os agonistas adrenérgicos beta₂ podem causar uma hipocalcemia significativa em alguns doentes, o que potencialmente pode levar a reações adversas cardiovasculares. Em doentes com asma grave, a hipocalcemia pode ser potenciada pela hipoxia e pela terapêutica concomitante, o que pode aumentar a suscetibilidade a arritmias cardíacas. ♦ **Hiperglicemia:** A inalação de doses elevadas de agonistas adrenérgicos beta₂ e corticosteroides pode produzir um aumento da glicose plasmática. Nos doentes diabéticos, ao iniciar o tratamento, a glicose plasmática deve ser monitorizada mais cuidadosamente. ♦ **Efeitos anticolinérgicos:** Tal como com outros medicamentos anticolinérgicos, este medicamento deve ser utilizado com precaução em doentes com glaucoma de ângulo fechado ou retenção urinária. ♦ **Doentes com compromisso renal grave:** Nos doentes com compromisso renal grave (taxa de filtração glomerular estimada inferior a 30 ml/min/1,73 m²), incluindo aqueles com doença renal terminal que necessitam de diálise, deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. ♦ **Prevenção de infeções orofaríngeas:** De modo a reduzir o risco de infeção orofaríngea por *Candida albicans*, os doentes devem ser aconselhados a lavar a boca ou a gargarejar com água, sem a engolir, ou a lavar os dentes após inalarem a dose prescrita. ♦ **Efeitos sistémicos dos corticosteroides:** Podem ocorrer efeitos sistémicos dos corticosteroides inalados, principalmente no caso de doses elevadas prescritas por períodos prolongados. Os efeitos sistémicos possíveis podem incluir: síndrome de Cushing, manifestações Cushingóides, supressão adrenal, atraso do crescimento em crianças e adolescentes, diminuição da densidade mineral óssea, cataratas, glaucoma e, mais raramente, uma série de efeitos psicológicos ou comportamentais incluindo hiperatividade psicomotora, distúrbios do sono, ansiedade, depressão ou agressão (especialmente em crianças). Como tal, é importante que a dose de corticosteroide inalado seja titulada para a dose mais baixa na qual o controlo efetivo da asma é mantido. Podem ser notificados distúrbios visuais como o uso de corticosteroides sistémicos ou tópicos (incluindo intranasais, inalados ou intraculares). Doentes que apresentem sintomas como visão turva ou outros distúrbios visuais, devem ser considerados para encaminhamento a um oftalmologista para avaliação de possíveis causas dessas perturbações visuais, as quais podem incluir cataratas, glaucoma ou doenças raras como a coriorretinopatia central serosa (CRCS), que foram notificadas após o uso de corticosteroides sistémicos ou tópicos. Este medicamento deve ser administrado com precaução em doentes com tuberculose pulmonar ou em doentes com infeções crónicas ou não tratadas. ♦ **Gravidez:** Este medicamento deve ser utilizado durante a gravidez apenas se o benefício esperado para o doente justificar o potencial risco para o feto. ♦ **Amamentação:** Tem que ser tomada uma decisão sobre a descontinuação da amamentação ou a descontinuação/abstenção da terapêutica, tendo em conta o benefício da amamentação para a criança e o benefício da terapêutica para a mulher. ♦ **Trabalho de parto:** Como outros medicamentos contendo agonistas adrenérgicos beta₂, o indacaterol pode inibir o trabalho de parto devido a um efeito relaxante no músculo liso uterino. **INTERAÇÕES:** ♦ **Bloqueadores adrenérgicos beta:** este medicamento não deve ser administrado com bloqueadores adrenérgicos beta (incluindo gotas para os olhos) a menos que existam razões importantes para a sua utilização. ♦ **Medicamentos conhecidos por prolongarem o intervalo QTc:** este medicamento deve ser administrado com precaução a doentes que estejam a ser tratados com inibidores da monoamina oxidase, antidepressivos tricíclicos ou medicamentos conhecidos por prolongar o intervalo QT. ♦ **Tratamento hipocalcémico:** O tratamento hipocalcémico concomitante com derivados da metilxantina, esteróides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocalcémico dos agonistas adrenérgicos beta₂. ♦ **Interação com inibidores do CYP3A4 e da glicoproteína P:** A inibição do CYP3A4 e da glicoproteína P (gp-P) não tem impacto na segurança de doses terapêuticas de Zimbus Breezhaler. ♦ **Outros antimuscarínicos de ação prolongada e agonistas adrenérgicos beta de ação prolongada:** A coadministração deste medicamento com outros medicamentos contendo antagonistas muscarínicos de ação prolongada ou agonistas adrenérgicos beta₂ de ação prolongada não foi estudada e não é recomendada. ♦ **Cimetidina ou outros inibidores do transporte de catiões orgânicos:** Não é esperada qualquer interação medicamentosa clinicamente relevante. **EFEITOS INDESEJÁVEIS:** ♦ **Frequentes (≥1% a <10%) e potencialmente graves:** hipersensibilidade. ♦ **Muito frequentes:** asma (exacerbação), nasofaringite. ♦ **Frequentes (≥1% a <10%):** infeção do trato respiratório superior, candidíase, infeção do trato urinário, cefaleia, taquicardia, dor orofaríngea, tosse, disfonia, gastroenterite, dor musculoesquelética, espasmos musculares, piroxíria. ♦ **Pouco frequentes (≥0,1% a <1%):** hiperglicemia, cataratas, boca seca, erupção cutânea, prurido, disúria. Para mais informações, consultar o titular de autorização de introdução no mercado ou o representante local do titular de autorização de introdução no mercado. Medicamento sujeito a receita médica. **Escala de comparticipação:** Escalão B. **Titular da AIM:** Novartis Europharm Limited. **Representante local:** Laboratório Medinfar - Produtos Farmacêuticos, S.A. - Rua Henrique de Paiva Couceiro, N° 29, Venda Nova, 2700-451 Amadora. Informações Essenciais Compatíveis com o Resumo das Características do Medicamento (ZIM_RCM20210422_IEC_v2).



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ISSN: 0040-6376 (print)
ISSN: 1468-3296 (online)
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ISSN: 0003-9888 (print)

ISSN: 1468-2044 (online)

Impact factor: 4.4

Journal of the Royal College of

Paediatrics and Child Health

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ADC is published by BMJ Publishing Group

Ltd, typeset by Nova Techset Private Limited,

Bengaluru & Chennai, India and printed in the

UK on acid-free paper from sustainable forests.

ADC (ISSN No: 0003-9888) is published

monthly by BMJ Publishing Group Ltd and is

distributed in the USA by Air Business Ltd.

Periodicals postage paid at Jamaica NY 11431

and additional mailing offices. POSTMASTER:

send address changes to Thorax, Air Business Ltd,

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Jamaica, NY 11434, USA

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com artigos do
**Archives of
Disease in Childhood**

Edição bimestral em língua portuguesa

Editada por:

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Tiragem: 2000 exemplares

Tradução

Tradução de inglês para português,



Sea of Words - Traduções Técnicas, Lda

Rua Castilho nº23 5ºB

1250-067 Lisboa

Paginação e impressão

Ligação Visual

Quinta dos Estrangeiros - Zona Industrial Norte,

Pavilhão 63

2665-601 Venda do Pinheiro

Periodicidade: 6 números anuais

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£227
ISSN 0040-6376 (print)
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Editorial

Desta seleção de artigos das Revistas *Thorax* e *Archives of Disease in Childhood*, permito-me iniciar pelos temas pediátricos. A sibilância em idade pré-escolar mantém-se um tema de debate. É uma situação que, embora transitória, tem impacto significativo nas crianças e nas Famílias. É prognóstica para morbilidade em idade adulta jovem e para valores mais baixos de função pulmonar. Do ponto de vista clínico, os marcadores prognósticos são frágeis e as terapêuticas ambíguas. No entanto, a sibilância do pré-escolar é responsável por 1/3 dos custos com asma em idade pediátrica e apenas 30% das famílias adere a terapêutica com corticosteróides inalados. Mohammed Abdul Wajid L, et al. nos Arch Dis Child 2025 publicaram um estudo percepcional para avaliar as opiniões dos pais relativamente às orientações de acompanhamento destas crianças. No final, os Pais preferem uma abordagem consistente e estruturada nos vários níveis de cuidados e guiada por exames...

O artigo seguinte, um estudo do grupo PERN (Pediatric Emergency Research Networks) sublinha inconsistências relacionadas com a utilização de inúmeras escalas com utilização de indicadores diferentes na avaliação de crise aguda de asma na criança. Numa doença crónica frequente em idade pediátrica, as escalas de avaliação em urgência, ainda que incluídas em *guidelines*, falham na validação...

Mas o artigo cuja figura é capa deste número é “Casa húmida e com bolor: impacto na saúde pulmonar durante a infância”. Sublinha-se a responsabilidade que as más condições habitacionais têm na saúde respiratória da criança e que o médico deve ter uma intervenção. Este artigo decorre das conclusões e Resultados do Médico Legista no caso da morte do menino de 2 anos, Awaab Ishak.

Um estudo retrospectivo Coreano descreve a relevância de atingir precocemente o controlo de asma, definido como remissão clínica baseada em indicadores específicos, com impacto na redução das agudizações e na melhoria da função pulmonar.

Ainda no adulto destaca-se vai para um estudo efetuado no Canadá que incluiu quase 500.000 doentes e que descreve como a associação entre doença pulmonar obstrutiva crónica (DPOC) e doença cardiovascular, reduz a probabilidade de práticas terapêuticas adequadas que resultam em desfechos menos favoráveis do ponto de vista cardiovascular (CV), pelo que os autores recomendam que a DPOC seja adicionada à diabetes e à doença renal crónica na lista de doenças que aumentam a probabilidade de um evento CV adverso.

Outro destaque é para o estudo de base populacional que decorreu na Suécia e que determinou a associação positiva entre asma e diabetes tipo 2, mesmo depois de correção para os fatores de risco do costume, apresentados num diagrama muito elegante na página 234.

Três artigos completam este número: os resultados do estudo DISCOVERY sobre o impacto da LTOT nos doentes pulmonares crónicos, a redução dos internamentos por asma no adulto, na Finlândia e na Suécia e o Efeito da hora do dia e da variação sazonal na resposta ao broncodilatador: o estudo SPIRO-TIMETRY...

Desejamos boas leituras para o Verão, antes, durante ou depois de férias!

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Print (includes online access at no additional cost)
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£240

ISSN 0003-9888 (print); 1468-2044 (online)

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Informações essenciais compatíveis com o Resumo das Características do Medicamento

Bevespi Aerosphere 7,2 microgramas/5 microgramas, suspensão pressurizada para inalação. Cada dose única (dose libertada, a dose que sai do aplicador bucal) contém 9 microgramas de brometo de glicopirrónio, equivalente a 7,2 microgramas de glicopirrónio, e 5 microgramas de fumarato de formoterol di-hidratado. Isto corresponde a uma dose calibrada (isto é, a dose que sai da válvula) de 10,4 microgramas de brometo de glicopirrónio, equivalente a 8,3 microgramas de glicopirrónio, e 5,8 microgramas de fumarato de formoterol di-hidratado. **Indicações terapêuticas:** Bevespi Aerosphere é indicado como tratamento broncodilatador de manutenção para o alívio de sintomas em doentes adultos com doença pulmonar obstrutiva crónica (DPOC). Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, só deve ser utilizado se o benefício esperado for superior ao risco potencial. **Compromisso hepático:** Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Não existem dados relevantes sobre a utilização de Bevespi Aerosphere em doentes com compromisso hepático grave e o medicamento deve ser utilizado com precaução nestes doentes. **População pediátrica:** Não existe utilização relevante de Bevespi Aerosphere em crianças e adolescentes (com idade inferior a 18 anos) para a indicação de DPOC. **Modo de administração:** Utilização por via inalatória. **Instruções de utilização:** Ao acionar Bevespi Aerosphere, um volume de suspensão é expelido do recipiente pressurizado a alta velocidade. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes devem ser instruídos sobre a técnica de inalação correta. É importante instruir o doente para: Ler com atenção as instruções de utilização no folheto informativo, que se encontra dentro da embalagem de cada inalador. Não utilizar o inalador se o agente excicante, contido na bolsa de alumínio, tiver vazado da sua embalagem. Preparar o inalador agitando-o e acionando-o quatro vezes para o ar antes da primeira utilização ou duas vezes quando o inalador não tenha sido utilizado há mais de sete dias, tenha sido exposto a temperaturas baixas ou tenha caído. Para obter uma deposição pulmonar adequada das substâncias ativas, o carregamento da dose tem de ser coordenado com a inalação. Doentes com dificuldade em coordenar o carregamento da dose com a inspiração podem utilizar Bevespi Aerosphere com uma câmara expansora para garantir a administração adequada do produto. Foi demonstrada compatibilidade com a câmara expansora Aerochamber Plus Flow-Vu. **Contraindicações:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **Advertências e precauções especiais de utilização:** Não indicado para utilização em situações agudas. Bevespi Aerosphere não é indicado para o tratamento de episódios agudos de broncospasma, isto é, como terapêutica de alívio. **Asma:** Bevespi Aerosphere não deve ser utilizado no tratamento da asma. **Broncospasma paradoxal:** Tal como com outra terapêutica inalatória, a administração deste medicamento pode resultar em broncospasma paradoxal, o qual pode colocar a vida em risco. Se ocorrer broncospasma paradoxal, o tratamento com o medicamento deve ser interrompido e devem ser considerados outros tratamentos. **Efeitos cardiovasculares:** Podem ser observados efeitos cardiovasculares, após a administração de antagonistas dos receptores muscarínicos e simpaticomiméticos, incluindo glicopirrónio ou formoterol. Bevespi Aerosphere deve ser utilizado com precaução em doentes com doenças cardiovasculares graves, tais como cardiopatia isquémica, taquiarritmias ou insuficiência cardíaca grave. Recomenda-se também precaução em doentes com tirotoxicose ou com prolongamento do intervalo QTc conhecido ou suspeito. **Hipocalcemia:** Os agonistas β_2 -adrenérgicos podem causar hipocalcemia significativa, o que pode aumentar a suscetibilidade para arritmias cardíacas. A diminuição do potássio sérico é normalmente transitória, não necessitando de suplementação. Em doentes com DPOC grave, a hipocalcemia pode ser potenciada por hipoxia e tratamento concomitante. **Hiperglicemia:** A inalação de doses elevadas de agonistas β_2 -adrenérgicos pode provocar o aumento da glucose plasmática. **Atividade anticolinérgica:** Devido à sua atividade anticolinérgica, Bevespi Aerosphere deve ser utilizado com precaução em doentes com hiperplasia da próstata sintomática, retenção urinária ou glaucoma de ângulo fechado. **Doentes com compromisso renal grave:** Como o glicopirrónio é excretado predominantemente por via renal, os doentes com compromisso renal grave (depuração de creatinina <30 ml/min), incluindo aqueles com doença renal em fase terminal com necessidade de diálise, apenas devem ser tratados com Bevespi Aerosphere se o benefício esperado superar o risco potencial. Doentes com compromisso hepático grave: Em doentes com compromisso hepático grave, Bevespi Aerosphere só deve ser utilizado se o benefício esperado superar o risco potencial. Estes doentes devem ser monitorizados para potenciais reações adversas. **Interações medicamentosas e outras formas de interação:** **Interações farmacocinéticas:** O potencial para interações metabólicas é considerado baixo. Como o glicopirrónio é eliminado principalmente por via renal, podem ocorrer potencialmente interações com medicamentos que afetam os mecanismos de excreção renal. **Interações farmacodinâmicas:** **Outros antimuscarínicos e simpaticomiméticos:** A coadministração de Bevespi Aerosphere com outros medicamentos contendo anticolinérgicos e/ou agonistas β_2 -adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas β_2 -adrenérgicos inalados. Não existe evidência clínica de interações quando utilizado concomitantemente com outros medicamentos para a DPOC, incluindo broncodilatadores β_2 -adrenérgicos de curta duração de ação, metilxantinas e esteroides orais e inalados. **Hipocalcemia induzida por fármacos:** O tratamento concomitante com derivados da metilxantina, esteroides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocalcémico inicial dos agonistas β_2 -adrenérgicos, pelo que se recomenda precaução na sua utilização concomitante. **Bloqueadores β -adrenérgicos:** Os bloqueadores β -adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito dos agonistas β_2 -adrenérgicos, tal como o formoterol. O uso simultâneo de bloqueadores β -adrenérgicos não seletivos ou seletivos deve ser evitado, a não ser que existam razões determinantes para a sua utilização. Se forem necessários bloqueadores β -adrenérgicos (incluindo colírios), dá-se preferência a bloqueadores β -adrenérgicos cardiosseletivos, embora também estes devam ser administrados com precaução. **Outras interações farmacodinâmicas:** Bevespi Aerosphere deve ser administrado com precaução em doentes que estejam a ser tratados com medicamentos conhecidos por prolongar o intervalo QTc. **Fertilidade, gravidez e aleitamento:** **Gravidez:** Não existem dados sobre a utilização de Bevespi Aerosphere em mulheres grávidas. Bevespi Aerosphere só deve ser utilizado durante a gravidez se os benefícios esperados superarem os potenciais riscos. **Amamentação:**

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

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

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PT-M0331 aprovado em 12/2023, revalidado anualmente



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Complexa coexistência da DPOC e da doença cardiovascular

Rita Pavasini, Gianluca Campo

A doença cardiovascular (DCV) e a doença pulmonar obstrutiva crônica (DPOC) são duas das principais causas de morbidade e mortalidade a nível mundial, ocupando o primeiro e o terceiro lugar, respetivamente, entre as causas de morte. Estas duas doenças estão ligadas por um importante fator de risco modificável: o tabagismo.

Dados de estudos anteriores indicam que a prevalência de DPOC entre doentes com DCV varia entre 7% e 28%. É de notar que a DPOC em doentes com DCV tem sido historicamente subdiagnosticada. Em 2009, Soriano *et al.* demonstraram que a prevalência de limitação do fluxo aéreo variava entre 60% em doentes com DCV e 87% naqueles internados com doença coronária. Outro estudo revelou que, entre fumadores ou ex-fumadores hospitalizados por síndrome coronária aguda e submetidos a espirometria, o diagnóstico de DPOC atingia os 29%.

Cho *et al.* analisaram um grande estudo retrospectivo, baseado na população, envolvendo 496 056 doentes com historial de DCV (incluindo doença isquémica do coração, insuficiência cardíaca e AVC). Nesta população real, apenas 16% tinham diagnóstico de DPOC. Os autores observaram que os diagnósticos de DPOC foram determinados com base em internamentos relacionados com DPOC e/ou pelo menos três consultas externas por DPOC num período de dois anos. Embora esta definição não se baseie em espirometria — o padrão-ouro para o diagnóstico de DPOC — já foi utilizada anteriormente, demonstrando uma especificidade de 95% e uma sensibilidade de 58%. Estes dados reforçam fortemente a suspeita de que uma proporção substancial de casos de DPOC na população com DCV permanece por diagnosticar.

Além disso, Cho *et al.* verificaram que os doentes com DPOC e DCV recebiam menos terapêuticas específicas para o coração, incluindo betabloqueadores, inibidores da ECA e estatinas. A menor utilização de betabloqueadores é, em parte, compreensível, devido a preocupações históricas sobre a sua interação com agonistas beta-2 em doentes com DPOC. No entanto, evidências recentes demonstram que os betabloqueadores seletivos são seguros e eficazes em doentes com ambas as condições, sem efeitos adversos significativos.

Por outro lado, a menor prescrição de inibidores da ECA e estatinas é mais difícil de justificar. Embora os inibidores da ECA possam causar tosse — um sintoma comum na DPOC — existem alternativas, como os bloqueadores dos receptores da angiotensina II (ARAs), que poderiam ser utilizados. Além disso, os ARAs podem oferecer benefícios adicionais, como a preservação da massa muscular e da capacidade funcional em doentes com DPOC. As estatinas, por sua vez, têm mostrado resultados mistos em doentes com DPOC: alguns estudos sugerem um papel protetor contra exacerbações, além dos benefícios cardiovasculares, enquanto outros, como o estudo COSYCONET, não encontraram efeito nas exacerbações, embora tenham confirmado a sua segurança e eficácia cardiovascular.

Cho *et al.* também destacaram que os doentes com DCV, mas sem DPOC, têm maior probabilidade de consultar um cardiologista do que aqueles com ambas as condições. Isto sugere que a menor prescrição de terapêuticas cardiovasculares em doentes com DPOC-DCV pode estar relacionada com menos consultas de cardiologia, resultando em cuidados cardíacos subótimos.

As conclusões de Cho *et al.* traçam um cenário preocupante: a DPOC é provavelmente subdiagnosticada em doentes com DCV e, quando a comorbidade é reconhecida, estes doentes não só recebem menos terapêuticas específicas e menos acompanhamento especializado, como também apresentam piores desfechos cardiovasculares — incluindo taxas mais elevadas de eventos cardiovasculares adversos *major* (enfarte do miocárdio, AVC

e morte cardiovascular), bem como mais internamentos por insuficiência cardíaca.

Este estudo sublinha a necessidade de uma gestão partilhada entre cardiologistas e pneumologistas para doentes com comorbidade DPOC-DCV. É urgente melhorar os cuidados cardiológicos nestes doentes. Não está claro se a dependência exclusiva de especialistas em pneumologia contribui para a falta de atenção cardiológica. Os doentes já acompanhados por um especialista podem não sentir necessidade de consultar outro. Ao mesmo tempo, a gestão partilhada é essencial para doentes com DCV conhecida e fatores de risco para DPOC (por exemplo, tabagismo), que devem ser diagnosticados precocemente através de avaliação pneumológica especializada, espirometria e programas de apoio à cessação tabágica.

Reforçar a colaboração entre especialistas em campanhas de cessação tabágica pode ser fundamental para abordar este fator de risco modificável, com impacto prognóstico significativo. De facto, a DPOC não diagnosticada em doentes com DCV tem um impacto prognóstico grave, levando a maior mortalidade e maior incidência de eventos cardiovasculares.

Para enfrentar este problema, são cruciais campanhas de sensibilização que enfatizem a importância do acompanhamento conjunto cardiológico e pneumológico para doentes com doenças respiratórias concomitantes. Isto inclui doentes com DPOC e DCV conhecidas, doentes com DPOC com fatores de risco para DCV e doentes com DCV com fatores de risco para DPOC. Estudos futuros devem explorar se uma abordagem integrada cardiopulmonar — otimizando o tratamento de ambas as condições e promovendo intervenções físicas e comportamentais (como nutrição adequada e apoio à cessação tabágica) — poderá melhorar os desfechos nestes doentes.

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Contributors RP and GC: conception, design, drafting of the manuscript and revising it critically for important intellectual content, final approval of

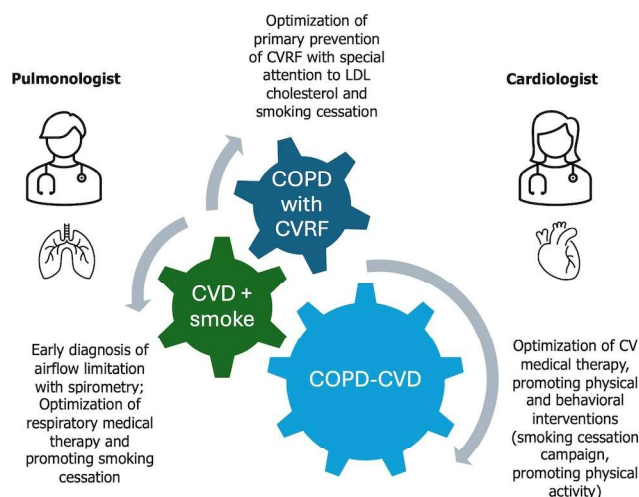


Figura 1 A abordagem combinada cardiológica e pneumológica para doentes com DPOC-DCV. **DPOC:** doença pulmonar obstrutiva crônica; **CV:** cardiovascular; **DCV:** doença cardiovascular; **FRCV:** fator de risco cardiovascular; **LDL:** lipoproteína de baixa densidade (colesterol LDL).

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the manuscript submitted. RP is the corresponding author and guarantor for the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed.

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To cite Pavasini R, Campo G. Thorax 2025;80:267–268.

Accepted 21 February 2025

Published Online First 18 March 2025



→ <https://doi.org/10.1136/thorax-2025-223054>

doi:10.1136/thorax-2025-223054

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ARTIGO ORIGINAL

Gestão da sibilância em idade pré-escolar: um estudo qualitativo sobre as opiniões e experiências dos pais

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/archdischild-2024-327781>).

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Received 2 August 2024

Accepted 27 November 2024

Published Online First 11 December 2024

RESUMO

Objetivo: O objetivo deste estudo foi explorar as opiniões e experiências dos pais na gestão da sibilância em crianças em idade pré-escolar, incluindo as suas perspectivas sobre a utilização de exames para orientar os planos de tratamento.

Desenho do estudo Foi utilizada uma amostragem intencional para recrutar 16 participantes de 14 famílias em Inglaterra e no País de Gales. Os dados qualitativos foram recolhidos através de entrevistas semiestruturadas com pais de crianças entre 1 e 5 anos com sibilância em idade pré-escolar, realizadas via Microsoft Teams. As entrevistas foram transcritas e analisadas por análise temática, com o apoio do software NVivo.

Resultados A análise gerou quatro temas principais: (1) Caminho até ao diagnóstico, (2) Gestão da medicação, (3) Viver com sibilância em idade pré-escolar, (4) Melhorar os cuidados de saúde para a sibilância em idade pré-escolar. Os resultados sugerem um impacto negativo da sibilância pré-escolar na vida das famílias, incluindo níveis elevados de preocupação e limitações na capacidade de trabalhar e viajar. Os obstáculos à gestão eficaz incluíram terminologias inconsistentes, incerteza diagnóstica, educação limitada e falta de apoio na gestão da condição. Outros entraves incluíram preocupações dos pais em relação à medicação, atrasos na realização de exames e dificuldades no acesso a cuidados especializados. Os pais mostraram-se favoráveis à realização de exames para orientar os tratamentos.

Conclusão As opiniões dos pais evidenciam os desafios no diagnóstico e tratamento da sibilância em idade pré-escolar a vários níveis do sistema de saúde. Para melhorar a gestão e garantir que os serviços prestados a estas crianças sejam eficazes, é urgente estabelecer uma terminologia consistente, uma abordagem unificada para orientar exames e tratamentos, e reforçar a formação dos profissionais de saúde nos cuidados primários e secundários.

INTRODUCTION

Preschool wheeze (PSW) is common. Approximately 30%–40% of all children will experience recurrent wheeze attacks in the first 6 years of life.¹ Seventy five per cent of all children with wheeze admitted to hospital are aged between 1 and 5 years.² The UK has the second highest prevalence of wheeze during the second year of life in Europe.³ PSW results in significant morbidity, healthcare costs and impaired quality of life for both the child and parent.⁴ Children with PSW account for a third of all healthcare costs for childhood asthma.⁴ Recurrent wheeze attacks predict long-term diminished lung function and increased all-cause morbidity and mortality in early adulthood.⁵

Optimal therapy for treating and preventing episodes of PSW is not well-defined and remains a matter of investigation and debate.⁶ Thus, in clinical practice, there are no diagnostic tests and no definitive pathways for treating PSW. Current management is based on expert consensus, history-taking and symptom patterns.⁶ Medications prescribed for PSW are often those used in school-age children and adults with asthma. Recommen-

Key messages

What is known about this topic

- Preschool wheeze results in significant morbidity, healthcare costs and impaired quality of life for child and parent.
- Currently, there is no diagnostic pathway or definitive guidelines to inform effective management of preschool wheeze.

What this study adds

- Parents' views highlight the problem of diagnosing and treating preschool wheeze at multiple system levels.
- Parents emphasise the need for consistent terminologies and integrated treatment pathways to improve management of preschool wheeze.
- Parents are in favour of using investigations to guide treatment for preschool wheeze.

How this study might affect research practice or policy

- There is a need for preschool wheeze management policies and treatment pathways, which are evidence-based and co-developed with parents.

dations for treatment by the British Thoracic Society⁷ and European Respiratory Society⁸ are based on parent-reported or child-reported symptoms. Inhaled steroids, salbutamol and montelukast are some of the medications recommended to prevent wheeze attacks, but acute presentations to healthcare continue.⁹

A recent review of literature by the European Respiratory Society taskforce⁸ indicates that diagnosis and management of PSW may be improved by identifying treatable traits, such as blood eosinophils and aeroallergen sensitisation, which could help to identify children who will have a differential response to inhaled corticosteroids (ICS). However, the taskforce notes that further prospective validation of using blood eosinophils as a biomarker in preschool children is needed before recommending it as an evidence-based clinical approach. A further gap in evidence relates to biomarkers that could identify children unlikely to respond to ICS.⁸

While the introduction of objective tests for identifying treatable traits (blood eosinophils and aeroallergen sensitisation) may present opportunities for more effective management of PSW (pending further validation), the acceptability to parents is unknown. Acceptability is a key consideration in the implementation of healthcare innovations; if new treatments or interventions are considered acceptable, patients are more likely to adhere to them and benefit.¹⁰ Parent acceptability of managing



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To cite: Mohammed Abdul Wajid L, Saglani S, Nagakumar P, et al. *Arch Dis Child* 2025;110:352–357.

PSW with steroids is also unclear, given that adherence to inhaled steroids, even in those with severe recurrent wheeze attacks, is only 30%.¹¹ An in-depth understanding of parents' perceptions of illness and treatment, including the acceptability of blood/allergy tests and steroid use, is therefore important for understanding current PSW management and determining the feasibility of implementing new approaches from a parental perspective. The aim of this study was to explore parents' views and experiences of managing children with PSW, including their perceived acceptability of steroids and blood/allergy tests to guide treatment pathways.

METHODS

Sampling and recruitment

Parents were purposefully recruited based on their child's age (1–5 years) and wheeze symptoms, as confirmed by a health professional, to include variation in demographics and a mix across primary, secondary and tertiary care. We excluded parent participants whose children were <1 year or >5 years of age, and those with co-existing comorbidities (congenital lung or heart disease, interstitial lung disease, cystic fibrosis, bronchiectasis, chronic lung disease of prematurity). Parents were recruited via adverts displayed in a hospital outpatient clinic and via social media. Potential participants who responded to study adverts received a study information pack via email, including an information sheet and consent form.

Data collection

A semi-structured interview guide was informed by existing literature,^{6–8} experiences of the clinical team and research objectives (see online supplemental file 1). Open questions covered parents' views and experiences of PSW, approaches to management, use of blood and allergy tests and barriers to accepting or performing such tests. LMAW conducted the interviews at a mutually convenient time via Microsoft Teams (April–August 2023). Interviews lasted 30–90 min and were recorded. Data collection continued until saturation was reached, that is, the point at which little new information was generated. This was established during the interviews, as well as by listening back to the interview recordings, conducting concurrent data analysis and discussing the data with the research team.¹²

Data analysis

Interview data were transcribed verbatim and analysed using Thematic Analysis.^{13 14} Transcripts were auto-generated by Microsoft Teams and manually checked by the first author. LMAW (female Clinical Research Fellow) led the data analysis, becoming familiar with the data through reading and re-reading transcripts. Codes were then generated inductively from the data, leading to the creation of an initial coding frame. Coding was carried out by LMAW, with a subsection double-coded by GH (female Health Psychologist) and discussed with PN (male Paediatric Respiratory Consultant). Following team discussion and iteration, an agreed-on coding frame was applied to all transcripts. Codes were then compared within and between participants and grouped into themes, which were further discussed by the team. Coding and data retrieval were supported via the qualitative data analysis software package NVivo V.12.¹⁵

RESULTS

Participants

A total of 22 expressions of interest were received from parent participants. Six did not respond to follow-up contact or were no longer interested in participating. Hence, there were 16 participants from 14 families in total. Families were recruited from a wide UK geographical area including Northwest England, West Midlands and Wales. The sample comprised those cared for in primary, secondary and tertiary care. 57% (8/14) of participants' children were on low-dose ICS and needed short-acting beta-agonist (SABA), corresponding to step 2 of Global Initiative for Asthma guidelines.¹⁶ 21% (3/14) were on SABA, ICS and montelukast,

14% (2/14) were on SABA, ICS and long-acting beta-agonist (LABA), 7% (1/14) was on SABA, ICS, LABA and montelukast. Further participant characteristics are presented in tables 1 and 2. The words most (>14), many (>10) and few (>5) are used to describe the strength with which parents supported the points made.

Thematic findings

Analysis generated four themes: (1) pathway to diagnosis, (2) medication management, (3) living with PSW and (4) improving PSW healthcare. Illustrative quotations are presented in table 3.

Pathway to diagnosis: "If it is not asthma, what is it?"

Many parents highlighted inconsistent terminologies and diagnostic uncertainty for their child's PSW (asthma, suspected asthma, viral wheeze, allergy) as confusing and problematic, with instances of receiving different views from different clinicians regarding symptoms and causes. For some parents, referring to wheeze as viral provided (potentially false) reassurance that their child was not being diagnosed as asthmatic. Others described frustration at not being provided with a definitive diagnosis, particularly where the child had experienced multiple wheeze attacks and hospital admissions.

Related to issues with diagnosis were parents' dissatisfaction with perceived delays in initiating investigations, particularly while being managed in primary care. Investigative tests were often described as only being initiated following extreme cases (multiple hospital admissions, severe wheeze attacks), and in all

Table 1 Participant demographics

Parent/Carer interviewees	
Mothers	14
Fathers	2
Current age of children of parents interviewed with PSW diagnosis	
Median	4 years
Range	2–5 years
IQR	1.25 years
Ethnicity of parents, n (%)	
White	
English, Welsh, Scottish, Northern Irish or British	10 (62.5%)
Asian or Asian British	
Indian	3 (19%)
Pakistani	1 (6.25%)
Southeast Asian	1 (6.25%)
Other ethnic group	
Arab	1 (6.25%)
Geographical area	
West Midlands	12
Northwest England	2
Wales	2
Clinical history	
Children in education placement, n (%)	12 (86%)
Children with allergy to food/aero-allergens, n (%)	7 (50%)
Atopy, n (%)	10 (71%)
Family history of asthma, n (%)	8 (57%)
Parent smokers (n)	1
Number of GP visits for PSW in 1 year (median)	1
Number of hospital visits for PSW in 1 year (median)	3.5
Number of children with courses of oral steroids in last 1 year	11/14
Current medications, n (%)	
SABA+ICS	8/14 (57%)
SABA+ICS+montelukast	3/14 (21%)
SABA+ICS+LABA	2/14 (14%)
SABA+ICS+LABA+montelukast	1/14 (7%)
GP, general practitioner; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; PSW, preschool wheeze; SABA, short-acting beta-agonist.	

Table 2 Age and employment status of participants, age of children and setting of care at the time of the interview

Parent	Parental age (years)	Employment	Age of child at the time of the interview	Setting of care for PSW
P1 (mother)	35–40	HR manager	Son, 3 years	Secondary care
P2 (mother and father)	35–40	Mother nurse	Son, 4 years	Secondary care
P3 (mother)	30–35	Housewife	Daughter, 3 years	Secondary care
P4 (mother)	30–35	Housewife	Son, 2 years	Secondary care
P5 (mother)	35–40	Self-employed	Daughter, 4 years	Secondary care
P6 (mother)	40–45	Housewife	Son, 2 years	Secondary care
P7 (mother and father)	40–45	Nurses	Son, 4 years	Secondary care
P8 (mother)	30–35	Housewife	Daughter, 4 years	Secondary care
P9 (mother)	35–40	Clinical scientist	Son, 2 years	Secondary care
P10 (mother)	30–35	Self-employed	Son, 4 years	Primary care
P11 (mother)	30–35	School teacher	Son, 4 years	Primary care
P12 (mother)	30–35	Customer care services	Son, 4 years	Secondary care
P13 (mother)	30–35	Self-employed	Son, 4 years	Secondary care
P14 (mother)	30–35	Survey office manager	Son, 4 years	Secondary care

PSW, preschool wheeze.

instances were initiated by specialist (tertiary care) health professionals. Many parents expressed relief once tests were initiated, constructing them as vital for treatment decision-making. Parents were keen to identify a cause for their child's wheeze that could inform management options, rather than starting inhalers and only initiating tests following poor wheeze control. Most parents were united in their view that investigations formed a key component in informing the management of their child's condition, echoing frustration with a 'wait and watch' approach.

Despite parental preference for timely tests, the importance of a sound rationale for child testing was emphasised by parents, for example, explaining why the investigations were being undertaken, differences between the types of tests and how each test would inform their child's wheeze management. Many parents further highlighted that to be acceptable, more invasive tests (eg, blood tests) needed to be performed in a considered and personalised way to minimise child distress, ensuring that the child was not subject to repeated tests unnecessarily.

Medication management: "an acceptable cost"

In all cases, wheeze was managed using a combination of steroid and salbutamol inhalers. While acceptable to parents and described as helpful in reducing exacerbations, a few parents described limited education and support in administering inhalers and using spacers. Specifically, parents perceived a lack of knowledge at District General Hospitals and in primary care, describing inconsistent instruction from different professionals, leading to them seeking alternative advice (eg, from other family members, internet).

Many parents also expressed concerns regarding the side effects of steroid inhalers for young children, including long-term dependence, reliance on relievers for physical exertion and tooth decay. The risks, however, were weighed by parents, and generally, it was felt that the benefits of using inhalers in terms of reducing wheeze attacks and hospital admissions outweighed the risks associated with side effects, deeming the medication an 'acceptable cost'.

Management was also discussed in relation to childcare providers, with a few parents expressing concerns about preschool nursery staff administering inhalers incorrectly or not in a timely manner, despite providing a wheeze plan. These anxieties extended to worries about how the child would cope once attending school. Many parents also described feeling reassured by regular follow-up checks after a PSW attack and the ability to access specialist care when required.

Living with PSW: "We are terrified"

Witnessing a severe attack of PSW was frequently described as 'traumatic' and had a significant psychological impact on some

parents, particularly in cases where the child was admitted to a high-dependency or intensive care unit because of their wheeze. In some families, parents had decided to reduce or stop working to manage the child's recurrent wheeze, while others described high levels of anxiety and vigilance due to the unpredictability of their child's condition. Many parents also described missing work to attend appointments and accompany their child to hospital, which presented a financial burden.

In addition to the impact on work, some families felt unable to go on holiday for fear of a wheeze attack and worry about accessing healthcare abroad. A few families expressed a desire for social support from a peer network so they could meet other parents and share experiences of PSW.

Improving PSW healthcare: "The problem is accessibility"

While acknowledging the convenience of primary care (closer to home, less waiting time, less time away from work), most parents preferred secondary and tertiary care, where it was felt they could access specialist support. In hospital settings, parents felt that their concerns were validated, and that investigations and treatment could be initiated, whereas general practitioners were perceived as having little training in childhood wheeze, leading to a loss of confidence.

A few parents appreciated the opportunity for open access to local secondary care when their child experienced a wheeze exacerbation and emphasised the importance of wheeze management plans. However, there were barriers to attending secondary care, including the untimely availability of ambulances, arranging childcare, financial factors (such as car park fees, congestion charges) and some families suggested a need for virtual as well as face-to-face appointments.

Ultimately, most parents called for a more coordinated and integrated approach between primary, secondary and tertiary care providers, who would make use of shared care plans for PSW that can be accessed by primary and secondary care, as well as emergency services when required.

DISCUSSION

To our knowledge, this is the first study in the UK to explore parental views and experiences of managing PSW and the acceptability of steroids and blood/allergy tests to guide treatment pathways. We are unaware of other qualitative studies that have explored parents' perspectives on PSW. Findings suggest a negative impact of PSW on families' lives, including high levels of worry, and limiting capacity for work and travel. Barriers to effective management of PSW include inconsistent terminology and diagnostic uncertainty, limited education and management support, delayed investigations, concerns about medications and challenges accessing specialist care. Many parents favored performing blood and allergy investigations to guide treatment pathways.

Table 3 Illustrative quotations

Pathway to diagnosis	Inconsistent terminologies and diagnostic uncertainty	"Yeah, there's some that was saying it could be severe asthma. There's some that said it could just be normal asthma and he's having some attacks from that or it's this viral induced wheeze." (Parent 2, son 4 years) "I'm reading D's paperwork and it will say severe asthma, severe asthma attack and you know. It's got some pretty strong language in the discharge paperwork, but then on the other hand they'll say, but it's suspected asthma and you think. It's, there's a real grey area around it all and you know that could cloud judgement and so I think whilst if you're gonna categorise children like D in that grey area, then they need to back that up by saying, well, if it's not asthma, what is it?" (Parent 14, son 4 years)
	Delayed investigations	"The only one they did is when she was on her 7th one [hospital admission] I think. When I mentioned she's on her 7th one this year. And that's when they thought they will start investigating it, which I wasn't happy with, to be honest, because we were hospitalised so many times." (Parent 8, daughter 4 years) "I personally had a big problem with all the doctors telling me 'It's a mystery' because it didn't necessarily have to be a mystery if they did the tests that needed to be done, that could have, you know, helped them find out what's happening inside him to get that diagnosis. 'But it's a mystery'—was used for a long time before any blood tests were even taken. Yeah, you know, and that's not a diagnosis. That doesn't help a parent when you're so stressed and watching your child suffer for so long" (Parent 2, son 4 years)
	Guiding investigations	"I know what a blood test would entail, but obviously what could come out of it? What sort of benefits are there? So, knowing all right, this will give us a more specific idea of which thingy is allergic to, so we can avoid that and they reduce the use of medicine. And I would appreciate it, stuff like that. Yeah. I'm all for science, so I would be happy for them to be investigated." (Parent 11, son 4 years) "I think to actually explain to the two different types of allergy tests, because I know there's I think a prick test or something like that and a blood test. And do they write down what test they need? For example, they say blood test, do they kind of tell us we're going to do a blood test like for milk egg, or does that just all come up at once?" (Parent 8, daughter 4 years) "It's gotta be done, I think. But I think we were very much mindful that some children in my opinion have or what I would only explain is an astronomical amount of blood tests done and a lot of those tests are failed tests and so there repeat attempts to gain blood. Um and and I think sometimes as professionals they don't consider the impact on the child and their family and how traumatic that is." (Parent 7, son 4 years)
Medication management	Limited education and support	"I don't think there's a specialist respiratory team in in local hospital. This was a major flaw I think in local city. The nurses haven't got a clue how to give the inhaler themselves. So to educate somebody, one of the nurses was forcing it onto his face. R had a really deep mark on his face from the mask, being pushed on and being held there while he was struggling." (Parent 2, son 4 years) "We were sent home with Brown and Blue inhaler. So we're at that point where were given a brown inhaler and we weren't advised that that was something we should be doing daily. It was never discussed how often we were using the brown inhaler. So I feel like, If say, when D got wheezy and we went to either A&E or to the GP, depending on the time of day and felt to get some assistance for his chest and we were sent home being prescribed steroids. Nobody at that point said, 'What's your prevention like?'" (Parent 14, son 4 years)
	Medication concerns	"For me, like, inhalers was always something that meant "Ohh. My gosh. You're depending on something to sort of have to breathe", you know. He was always in a very intense form of medication, especially when the word steroid you always relate to something that's quite intense, so... Yeah. For me it was quite upsetting that he had to be on inhalers." (Parent 3, daughter, 3 years) "I think the medication overall was quite strong for him, I think because he was on oral steroids as well as inhaled steroids as well as a montelukast. I did feel a bit like this is a lot going into a little boy at such as, you know, without testing to see if one medication is working first." (Parent 2, son 4 years)
Living with PSW	Impact on families	"My wife's had to give up work just to kind of care for for him. Yeah. So because we don't know what's gonna happen to him. Right. We had to kind of sacrifice a few things just to make sure he's okay because that's priority for us." (Parent 2, son 4 years) "For the last 2 years it's had a significant impact on where I'm willing to travel with my family. So always looking at wherever we go, anywhere, where's the nearest paediatric A&E and how do I access emergency paediatric services, so we've never travelled abroad with [son]." (Parent 1, son 3 years)
Improving PSW healthcare	Accessing specialists	"I find people take me more seriously at the hospital, um, you know, being honest. But I would prefer to just be able to go to the GP and not have to trek all the way to the hospital and waste a lot of time. Not so much of the waiting time in the hospital, I feel like, It's just a distance, isn't it? It's just like it's not, it's not local." (Parent 11, son 4 years) "I think the GP needs more training with viral induced wheeze because their answer to J's wheeze is 'Ohh will give him antibiotics and steroids'." (Parent 6, son 2 years)

A&E, accident and emergency; GP, general practitioner; PSW, preschool wheeze.

Current management of PSW was perceived as unsatisfactory by parents, characterised by inconsistent diagnostic terminology, diagnostic uncertainty, delayed investigations and recurrent hospital presentations. Parents felt that obtaining a formal diagnosis of PSW, even as an umbrella term (from which other diagnoses, including asthma, might emerge), earlier in the care journey would help them manage their child's condition more effectively, improving both their and their child's quality of life, as well as improving access to specialist care. These findings resonate with other studies highlighting the uncertainty¹⁷ and frustration¹⁸ of the prediagnosis phase, as well as those describing the negative impact of childhood asthma on family well-being.¹⁹ The British Thoracic Society²⁰ and the Global Initiative for Asthma²¹ have published guidelines for the diagnosis and management of 'asthma' in children under 5 years. However, these guidelines do not describe 'PSW', and health professionals may find it difficult to label every child under 5 years with wheeze as having asthma.

Consistent with the 'Common-Sense Model' of managing health threats,²² parents in our study were keen to understand the causes of recurrent PSW in their children. Not feeling able to understand their child's symptom aetiology and frustrated with a lack of diagnostic labels or specified treatments, parents

supported investigations being performed earlier in the care pathway, conceiving investigations as a gateway to appropriate management based on objective results rather than (variations in) clinical experience. Domains of illness representations, including perceived timeline, consequences, cause and controllability of symptoms have previously been shown to impact treatment adherence in those with asthma.²³ To improve concordance, it is important that a child's treatment plan is coherent with parents' understanding of their child's condition. Good history-taking, which elicits parental concerns, establishes symptoms, identifies trigger factors and includes parent-reported outcomes, may reassure parents regarding diagnostic uncertainties, reducing their calls for objective investigations. Upskilling health professionals across healthcare settings and involving parents in PSW management could thus influence healthcare utilisation patterns, including emergency department visits, hospital admissions and primary care consultations.

While most parents in this study expressed concern about the long-term effects of ICS, they felt that dealing with side effects was better than frequent hospitalisation. Parents described a sense of reassurance when given instruction on the daily use and side effects of preventer inhalers. This was achieved through

signposting to National Health Service resources, as well as providing demonstrations and verbal and written instructions. In terms of service improvement, the current study aligns with others in demonstrating a need for coordinated and integrated care across the healthcare system.²⁴ In our study, education on PSW and management plans often differed between healthcare professionals, leading to inconsistent information being provided to parents. Managing PSW care via community-based diagnostic hubs may help meet the needs of parents requiring access to specialist care closer to home.

Strengths and limitations

A key strength of this study is the diverse representation of views from parents of children with varying degrees of PSW, sharing experiences from management at various levels of care. The parent participants were from across England and Wales. One of the limitations is that participants were mainly mothers, meaning fathers were under-represented. Mothers are often the primary caregivers of children with chronic health conditions and accompany their children to seek healthcare services.²⁵ A second (potential) limitation is that some members of the research team (SS, PN) are involved in the clinical management of children with severe wheeze in a tertiary care setting, which could have influenced the analysis. However, neither the first author (LMAW, Research Fellow) nor the lead author (GH, Health Psychologist) is involved in the clinical management of children with severe wheeze. Furthermore, the thematic analysis was based exclusively on data provided by parents who were not under the clinical care of the research team, which further reduces the potential for bias from clinical involvement. While a subsection of data were coded by two analysts, not all transcripts were. However, the final coding frame was reviewed by all authors, with team discussions used to develop and agree on salient themes.

RECOMMENDATIONS/CONCLUSION

Parents' views highlight the problem of diagnosing and treating PSW at multiple system levels. To improve the management of PSW, there is a need for consistent terminology, unified guidelines and a diagnostic pathway to guide investigations and commence treatment. To achieve this, there is a need for prospective clinical trials to determine the efficacy of treatment decisions made according to the results of investigations. To ensure services for children with PSW are effective and sustainable, there is a need to upskill health professionals in primary and secondary care and enable access to investigations in primary care. To be acceptable to parents, however, investigations need to have a sound rationale and be personalised to the child's need, ensuring children are not subjected to unnecessary diagnostic tests.

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Contributors LMAW: investigation, formal analysis, writing the original draft, review and editing; SS: conceptualisation, review and editing; PN: conceptualisation, methodology, formal analysis, writing the original draft, review and editing and supervision; GH: conceptualisation, methodology, formal analysis, writing the original draft, review and editing and supervision. PN is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the NHS Wales Research Ethics Committee 4 (REC reference: 23/WA/0109, IRAS project ID: 322156). Participants provided informed consent before taking part in the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed.

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ARTIGO ORIGINAL

Análise dos sistemas de pontuação para asma recomendados nas diretrizes para crianças que se apresentam no serviço de urgência: um estudo da Pediatric Emergency Research Networks

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► Additional supplemental material is published online only. To view, please visit the journal (<https://doi.org/10.1136/archdischild-2024-327635>).

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Received 5 July 2024

Accepted 17 March 2025

Published Online First 28 March 2025



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To cite: Gray C, Collings M, Benito J, et al. *Arch Dis Child* 2025;110:422–428.

RESUMO

Justificação Embora existam numerosos sistemas de pontuação pediátricos publicados para a asma, não se sabe com que frequência estes são recomendados nas diretrizes de asma em diferentes regiões geográficas a nível global, nem qual é o seu estado de validação.

Objetivos (1) Descrever quais diretrizes clínicas recomendam sistemas de pontuação para a asma em diferentes regiões geográficas. (2) Descrever a validação inicial e subsequente dos sistemas de pontuação para a asma mais frequentemente recomendados.

Métodos Estudo observacional dos sistemas de pontuação para a asma recomendados nas diretrizes para o tratamento da asma pediátrica aguda, provenientes de instituições da Pediatric Emergency Medicine Network — uma rede global de investigação em medicina de urgência pediátrica que inclui oito redes locais e regionais.

Principais resultados Foram identificadas 158 diretrizes. No total, 83 de 158 (53%) recomendam a utilização de um sistema de pontuação clínica à cabeceira do doente para avaliar a gravidade da asma. Enquanto um único sistema de pontuação específico por país foi recomendado em todas as diretrizes de Espanha e do Canadá, 27 de 28 (96%) das diretrizes dos EUA recomendam uma grande variedade de sistemas, sendo que raramente são recomendados nas diretrizes de outras redes de investigação (PERUKI — Paediatric Emergency Research in the UK and Ireland, e PREDICT — Paediatric Research in Emergency Departments International Collaborative na Austrália e Nova Zelândia) e de outros países (Costa Rica, África do Sul, Nigéria, Singapura, Índia). O Pediatric Respiratory Assessment Measure (PRAM) e o Pulmonary Score (PS) foram os instrumentos de pontuação mais frequentemente utilizados. Embora o PRAM tenha sido o mais amplamente validado, incluindo validade de construto, os estudos de validação do PS são limitados. A fiabilidade interobservador, bem como os aspetos de validade de critério, de resposta e discriminativa, representam as limitações mais comuns em muitos dos sistemas de pontuação. **Conclusões** Existem diferenças geográficas marcadas tanto na recomendação como no tipo de sistema de pontuação clínica para a asma incluído nas diretrizes clínicas. Embora muitos sistemas de pontuação sejam recomendados, a maioria apresenta validação insuficiente.

INTRODUCTION

Asthma is a frequent reason for presentation to an emergency department (ED), and one of the most common reasons for paediatric hospitalisation after an ED visit.^{1,2} Paediatric asthma carries a high burden of disease, with global estimates of an escalating rate of admission and increasing associated costs.^{3,4}

Key messages

What is known about this topic

► There is a plethora of paediatric asthma scores used both in research and clinical practice. However, we do not know which scores are recommended in clinical asthma guidelines in different geographical locations and what their validation status is.

What this study adds

► This observational study of 158 clinical guidelines from a global paediatric emergency research network found a marked geographical variation in the frequency and the type of score used, with scores frequently recommended in the USA, Canada and Spain, and infrequently elsewhere. The most common scores were the Paediatric Respiratory Assessment Measure (PRAM) and the pulmonary score.

How this study might affect research practice or policy

► This study highlights the need for future prospective validation studies of the commonly recommended asthma scores to establish their role. Overall, the PRAM score is the most extensively validated but would benefit from multisite validation studies. Further prospective studies are required to validate the remaining scores with a focus on their ability to discriminate differences in asthma severity and their responsiveness to changes in signs and symptoms for use in clinical practice guidelines.

Clinical practice guidelines are commonly recommended for use in the ED management of acute asthma,^{5–7} providing a background to the clinical condition, guiding the assessment of the asthma severity of an individual patient and recommending treatment based on this assessment. A recent qualitative study demonstrated that clinicians view clinical guidelines as a useful aid to

decision-making in children with acute asthma.⁸ Some of these guidelines may also make a reference to an asthma score.

An asthma score, in general, includes a combination of observations that a clinician can assign a numerical value to. These include oxygen saturation, heart rate, respiratory rate, accessory muscle use, wheezing and duration of the expiratory phase of the respiratory cycle. For each of these parameters, a child is assigned a score, usually between 0 and 3 points, with the sum of the points representing a total score. Clinical asthma scores are useful to guide severity-based treatment recommendations and to measure changes in a child's condition to determine response to treatment.¹⁹

The literature about the use of asthma scores in clinical practice, however, has been largely limited to surveys inquiring about clinicians' use of scores.^{13,18} In research, asthma scores are frequently employed as a clinical trial entry criterion to measure severity^{10–12} and as a measure of response to treatment.^{13,14} A lack of consistency in asthma score utilisation contributes to the challenge of a meaningful comparison of the outcomes between clinical trials.¹⁵ To our knowledge, the spectrum of the clinical asthma scores endorsed in guidelines for local hospitals and networks worldwide has not been documented. In this context and given our recent identification of the reliance the clinicians place on clinical guidelines,⁸ this paper addresses the above knowledge gap by investigating which paediatric asthma scores are recommended across a broad sample of healthcare institutions internationally.

Objective

The Pediatric Emergency Research Networks (PERN) asthma working group was formed in 2017, with the aims of developing consensus-based and evidence-based asthma outcome measures (with input from patients, families and clinicians), and international consensus guidelines for the conduct and reporting of clinical trials of therapies for acute asthma exacerbations. Currently, this group comprises members from seventeen countries; with most belonging to formal regional research networks.¹⁶

This study aims to assess current clinical asthma scores recommended in paediatric practice guidelines in the EDs associated with PERN.

Specifically, we aim to describe:

1. The proportion of guidelines which include a clinical asthma score from each country.
2. The distribution of various asthma scores across different PERN networks.
3. The validation spectrum of the commonly recommended asthma scores.

The recommendations for the management of acute exacerbations of asthma and the quality of these guidelines are reported elsewhere.¹⁷

Design

This is an observational study of the guidelines for the management of acute paediatric asthma from the institutions belonging to the global PERN network. The project is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.¹⁸

Setting and guideline collection

The hospitals and clinicians associated with the PERN asthma working group were invited to participate by email in October 2018 via the eight PERN partner networks. The PERN comprises the following networks: Research in European Paediatric Emergency Medicine (REPEM) in Europe; Pediatric Emergency Care Applied Research Network (PECARN) and Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics (PEM CRC) from the USA; Pediatric Emergency Research Canada (PERC); Paediatric Research in Emergency Departments International Collaborative (PREDICT) from Australia and New Zealand; Paediatric Emergency Research in the United Kingdom and Ireland (PERUKI); Red de Investigación de la Sociedad Española de Urgencias de Pediatría/Spanish Pediatric Emergency Research

Group (RISEUP/SPERG); and Red de Investigación y Desarrollo de la Emergencia Pediátrica Latinoamérica.¹⁹

The email recipients were then invited to forward the email to other ED physicians and hospitals where there existed formal and informal professional and academic relationships, aiming to allow sampling in countries without formal organised research networks. The request for participation was also shared on social media.

Each participating hospital was asked to provide a copy of its current guideline for the management of acute paediatric asthma. This could include local, regional or national guidelines, as well as any documents (such as order sets) providing recommendations on severity assessment and severity-based treatment of children presenting to the ED or hospital with acute onset of wheezing or asthma.

Data abstraction: guideline/order set content

To reduce the risk of bias, each clinical guideline was independently assessed by two trained reviewers, who were provided with clear definitions, rules for the interpretation of clinical guidelines and instructions for data extraction. Abstracted data were recorded on a paper-based form and then entered into a specifically designed Research Electronic Data Capture²⁰ database hosted at Monash University.

We originally planned for the guidelines written in languages other than English to be abstracted by two investigators fluent in both English and the language in which the guideline was written. While this was possible for guidelines written in Spanish and Catalan, we were unable to achieve this goal for those written in Dutch and French. An online translator (Google Translate) was therefore used to extract guideline content from Dutch and French guidelines.

Guideline content was extracted and analysed descriptively. Guidelines were collated into the following six groups, based on established PERN networks: UK and Ireland (PERUKI network); Spain (RISEUP-SPERG network); USA (PEM-CRC and PECARN networks); Australia and New Zealand (PREDICT network); Canada (PERC network) and 'Other' (single guidelines from Netherlands, Switzerland, France (REPEM network), Romania, Zimbabwe, Singapore, India, Costa Rica and two guidelines from South Africa).

Data abstraction: analysis of scoring systems

For each guideline, we determined and recorded whether a scoring system/s was reported within the guideline, the name of the scoring system/s and what the score was recommended for (ie, to assess severity, to measure change or to assist with disposition planning). The frequency of a particular scoring system recommended within each geographical region was presented as counts and percentages. If a scoring system was present in only one guideline, this score was included in the 'other scores' category. If a score was present in two or more guidelines, regardless of the geographical region, the name of that score was used.

Derivations of original scores and subsequent validation studies

The original studies outlining the development and purpose of scoring systems recommended in at least two clinical guidelines were sourced and categorised into the original validation measure by the lead author, CG. Bekhof et al in 2014⁹ conducted a systematic review of asthma scoring systems. We included in this review (online supplemental appendix 1) validation studies since this time, between November 2011 (the last date of the literature search in the original publication) and 20 April 2024. It was outside the scope of this study to assess the quality of the studies as was done by Bekhof. Data was extracted by the lead author, CG, on the nature and timing of the validation measures studied.

Patient and public involvement

Patients were not involved in the design of this study.

RESULTS

A total of 158 clinical guidelines were identified. The majority (95.6%) were obtained from hospitals participating in national

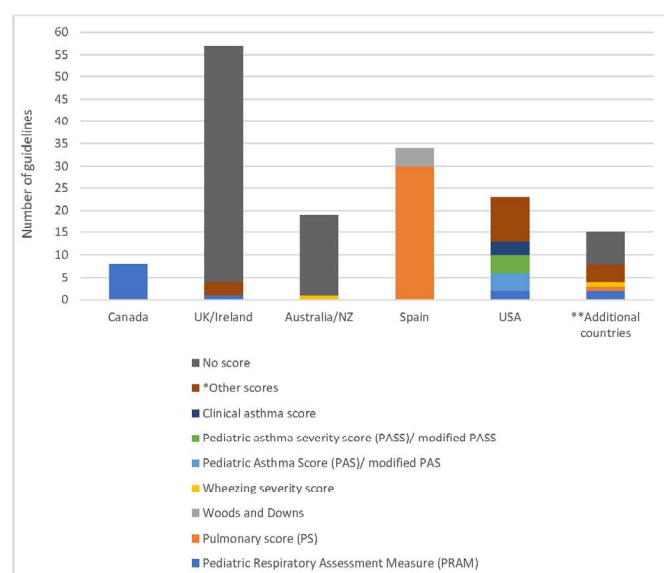


Figure 1 Geographical distribution of asthma score recommendation.

or regional paediatric emergency research networks; the greatest number (72%) of guidelines originated from the UK and Ireland (PERUKI network), Spain (RISEUP-SPERG network) and the USA (PECARN and PEM-CRC networks). All the guidelines represent a single institution; however, just over half, 88/158 (55%) of guidelines referenced a national or regional guideline. The most referenced national guideline was the British Thoracic Society (BTS) accounting for 27/57 (47%) of the total guidelines from this region.

Most guidelines were written in English; the most common non-English language was Spanish. A bedside clinical score was recommended in all guidelines from Spain 34/34 (100%) and Canada 8/8 (100%), and in 27/28 (96%) of guidelines from the USA (figure 1). In contrast, bedside clinical scores were recommended less commonly in guidelines from other research networks, UK and Ireland 4/57 (7%), Australia and New Zealand 1/17 (5%) or from other countries 8/15 (53%) (Costa Rica, South Africa, France, Nigeria, Singapore, India). Overall, 83/158 (53%) guidelines recommended the use of a bedside clinical score for assessment of asthma severity. The scores recommended in two or more guidelines and the components that they assess are outlined in table 1. Of the guidelines which recommend the use of an asthma score, 98% recommended the score be used to assess severity on initial assessment. Further recommendations for the use of an asthma score were to assist with reassessment after initial treatment (51%) and to guide disposition (48%). Timing of reassessment recommended varied from 15 min post initial treatment to every hour during the patient's ED stay.

The most frequently recommended scores included the pulmonary score (PS) 31/83 37% (all Spanish hospitals and one other hospital), the Pediatric Respiratory Assessment Measure (PRAM) score 13/83 16% (all Canadian hospitals and three other hospi-

tals) and the Pediatric Asthma Score 4/83 5% (PAS) as well as the Pediatric Asthma Severity Score 4/83 5% (PASS), in the USA.

The development and purpose of each of the scores present in two or more guidelines, as well as further validation studies (regardless of the network or country they were reported in), are presented in table 2.

Since the Bekhof paper in 2014, our literature review (detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram in online supplemental appendix 1) identified 10 further studies, with one further study by coauthor, SS, on initial review of the paper²¹ (total 11 studies). The most common validation measure of the scores was assessment of their predictive ability. The PRAM score has undergone the most extensive validation with five further trials, including one study which assessed responsiveness. Other validation works included the PAS in three studies, the PASS and the CAS in two studies, Wood and Downes score in one study. While the Wheezing Severity Score is cited in a paper by Foster et al, 2018 and described as a variation of the PS,²² we were unable to identify any validation of this instrument.

DISCUSSION

This study demonstrates there is considerable variation in the recommendation of asthma scores in guidelines around the world. Asthma scores are commonly recommended in Canada and Spain, with a near-universal recommendation of a single (but different) score in each country. In contrast, there is little consistency with respect to asthma score recommended in the USA, with a large variety of recommended scores. Additionally, many countries do not use an asthma score at all. This may be in part, as is the case in the UK/Ireland, where many of the guidelines are based on an overarching guideline, the BTS, which does not recommend an asthma score. An ideal score for use in a clinical practice guideline has not been established. The principal aim for scores in clinical guidelines is to assist in categorising an individual into a disease severity category, guide therapy and measure clinical change after therapy. Therefore, an ideal score would have good discriminative ability and responsiveness and have good construct validity. However, few of the current scores address this need. Only the PRAM, PASS and CAS assessed their responsiveness in the original validation studies, and the PRAM is the only score that has undergone further validation of responsiveness in a single centre of 503 patients.²³ In addition, the only two scores that have been assessed for their discriminative ability are the PAS¹² and the PRAM.²³ It is also common that most of the validation studies are conducted solely on the scores that were developed in their geographical region.²³

The PS was the instrument most often recommended overall, representing the sole score recommended in hospitals across Spain. The use of a single scoring system within a geographical region facilitates communication between healthcare providers about asthma severity and treatment decisions. The potential advantage of the PS is its requirement for the measurement of only three parameters: respiratory rate, wheeze and degree of accessory muscle use.²² A large single-centre retrospective study of the PS

Table 1 Overview of the scores and the components they measure

Component	Pediatric Asthma Severity Score (PASS)	Clinical Asthma score (CAS)	Pediatric Respiratory Assessment Measure (PRAM)	Wood and Downes score	Pulmonary score (PS)	Wheezing severity score (WSS)	Pediatric Asthma score (PAS)
Oxygen Saturation		✓	✓	✓			
Accessory muscle use	✓	✓	✓	✓	✓	✓	✓
Duration of expiratory phase	✓						
Absence/presence of inspiratory breath sounds				✓			
Wheezing	✓		✓	✓	✓	✓	✓
Heart rate							✓
Respiratory rate		✓			✓	✓	
Dyspnoea		✓					
Air entry			✓				
Cerebral function				✓			

Table 2 Original derivations and recent validation of asthma scores reported in two or more clinical guidelines

	Study design and number of patients	Derivation or validation	Construct validity	Predictive validity	Discriminative validity	Responsiveness	Statistics reported
Pediatric Respiratory Assessment Measure Chalut <i>et al</i> ²⁷	Prospective cohort study. Total n=217	Derivation	To correlate with mild, moderate and severe airway obstruction as measured by PEFR as the gold standard		Mild<5 Moderate>5	Measured as a change in PRAM score correlated to % change from baseline Rf08	Modest discriminative properties Responsiveness r=0.58, p<0.004
Study by Alnaji <i>et al</i> ³¹	Secondary analysis of prospective data set for children Total n=297	Validation		The ability of the score at 3 hours to predict the need for admission compared with the initial PRAM at triage			3-hour PRAM AUC 0.83
Arnold <i>et al</i> ³²	Single centre prospective study Total n=503	Validation				Comparison of change in PEFR compared with PRAM score at 2 and 4 hours.	The first 2 hours demonstrated change; 4 hours demonstrated ongoing change p<0.0001 compared with PEFR, which did not
Thaweerujirot and Daegsuwan ²⁹	Prospective study Total n=80	Validation		Admission versus discharge			ROC for PRAM 0.942
Eggink <i>et al</i> ²⁹	Prospective study Total n=50	Validation	Correlation with single clinical sign or oxygen saturation or airway obstruction	Admission versus discharge			No difference. Poor for most, slight correlation with O ₂ saturation.
Johnson <i>et al</i> ²¹	Prospective observational study Total n=48	Validation		Admission versus discharge			After treatment, AUC 0.8923
Pediatric Asthma Score Quereshi <i>et al</i> ¹²	Randomised, double-blind, placebo-controlled study Total n=434	Derivation			Mild 5–7 Moderate 8–11 Severe 12–15		No statistics provided
Study by Gardiner and Wilkinson ³³	Secondary analysis of prospective data Total n=101	Validation					IRR K=0.57 Triage PAS AUC of 0.62–0.65
Study by Jose and Namboodiripad ²⁵	Prospective study Total n=32	Validation	Ability of PAS to correlate with PEFR				p=0.004
Hulfish and Maloney ³⁴	Retrospective chart review Total n=44	Validation		Score PICU admission versus non-PICU admission			p<0.05
Pulmonary score Smith <i>et al</i> ²²	Convenience sample Total n=46	Derivation	The ability of the PS score to correlate with PEFR				R=0.57 p=0.0003
Paniagua <i>et al</i> ²⁴	Retrospective study n=14 953	Validation		Abnormal initial PS to predict children who would require hospitalisation			Initial PS>3 had a strong association with hospitalisation OR 8.1 and longer length of stay OR 6.2 and PICU admission OR 9.
Wood and Downes Wood <i>et al</i> ³⁵	Convenience sample Total n=18	Derivation	A score of 6 or more correlated with a PCO ₂ >65 mm Hg (this was the criteria for respiratory failure)				R=0.69, p<0.001
Thaweerujirot and Daegsuwan ³⁶	Prospective study Total n=80	Validation		Admission versus discharge			ROC=0.959
Pediatric Asthma Severity Score Gorelick <i>et al</i> ³⁷	Correlation between score and PEFR and oxygen saturations n=1224	Derivation		Admission versus discharge		Percentage change in score	AUC to predict hospitalisation 0.82 48% increase in score from start to finish of treatment, overall effect size 0.62
Ciftci <i>et al</i> ³⁸	Convenience sample Total n=70	Validation		Admission versus discharge Comparison for those who did and did not go on to get steroids			Sensitivity 95% for predicting need for admission
Eggnick <i>et al</i> ²⁹	Prospective study Total n=50	Validation	Correlation with single clinical sign or oxygen saturation or airway obstruction	Admission versus discharge			No difference. Poor correlation.
Clinical Asthma score Parkin <i>et al</i> ³⁹	Convenience sample Total n=58	Derivation	Correlation of score to three hypothetical constructs; hospital stay, amount of inhaled bronchodilator, pulse oximetry			Change in score from admission to discharge	Correlation with LOS=Spearman's correlation=0.47 Wilcoxon signed rank test p<0.01

Continued

Table 2 Continued

	Study design and number of patients	Derivation or validation	Construct validity	Predictive validity	Discriminative validity	Responsiveness	Statistics reported
Ahmareen <i>et al</i> ⁴⁰	Prospective study Total n=223	Validation		Admission versus discharge and duration of stay in ED			Diff in admission rates $p<0.001$. No correlation between CAS value and LOS in ED.
Ciftci <i>et al</i> ³⁸	Convenience sample Total n=70	Validation		Admission versus discharge			Sensitivity 95% for predicting need for admission.

AUC, area under the curve; CAS, Clinical Asthma score; ED, emergency department; LOS, Length of stay; PAS, Pediatric Asthma Score; PCO₂, partial pressure of carbon dioxide; PEFR, Peak Expiratory Flow Rate; PICU, Pediatric Intensive Care Unit; PRAM, Pediatric Respiratory Assessment Measure; PS, pulmonary score; R, Pearson's correlation coefficient; ROC, receiver operator curve.

suggested that initial assessment of PS>3 points is a good predictor of the need for hospitalisation.²⁴ However, this instrument had limited prospective validation because it was developed with the goal of comparing the score to an established 'gold standard' of asthma severity, that is, the pulmonary function tests (PFTs). PFT is rarely used in the ED setting because preschoolers who represent 60% of asthma visits to paediatric EDs cannot perform these tests, and 40% of the school-aged children are also unable to perform spirometry (PFTs).^{25 26}

The PRAM score was the second most recommended score in this study. In previous asthma research, it has been used as a threshold for study eligibility and to measure trial outcomes.^{13 14} Additionally, it has undergone the most extensive external validation, 27 including its ability to predict disposition and assessment of responsiveness.^{21 23 28} A recent study by Thaeweerujit et al (n=80) reported a PRAM score of greater than 5 at triage, prior to any treatment, strongly predicted the need for admission.

However, a similarly sized study by Eggnick and colleagues (n=50) found there was no statistical difference in the change in the score, from presentation to 30 min after treatment, between children that were hospitalised versus discharged.²⁹ Further, PRAM requires palpation of suprasternal and scalene muscle contraction not commonly used in the assessment of asthma in EDs.²⁷ Future multisite studies may be useful to further clarify the results of previous PRAM studies.

Limitations

This study was limited to reviewing clinical guidelines from hospitals recruited predominantly through the PERN network, which may limit generalisability. All the participants were from active research sites, which may have introduced some bias in the recommendation of asthma scores. In addition, there is under-representation in both guidelines from non-English speaking countries and both lower and lower-middle income countries.

Although we conducted a thorough search for derivation and validation papers relevant to each asthma score, we did not conduct a full systematic review. It is possible that some published information was not identified using our search strategy.

Guidelines were collated in 2018, and it is possible that some guidelines have changed since the study was conducted. Other scores with validation data may be less widely recommended in clinical practice guidelines, for example, the Acute Asthma Intensity Research Score which has been compared with the PRAM score.³⁰

CONCLUSION

This study demonstrates large international variation in the frequency of asthma scores as well as in the recommendation of specific scores in guidelines. While many asthma scores have been recommended in asthma clinical guidelines, the majority have insufficient validation. Further validation efforts at national and international levels may clarify their clinical utility for inclusion in clinical practice guidelines.

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Acknowledgements The authors would like to acknowledge Annie Rice, Anysha Walia, Caitlin Falloon, Claire Thomas, Emma Walker, Evita Lie, Jia Tan, Kang Hui Teow, Lauren Clementson, Lorna Pellegrino, Nam Gupta, Sarah Tan, Suma Sreedhar, Timothy Nguyen, Jessica Waghorn and Emma Ramage for assistance in data extraction, guideline assessment and data entry. We also thank members of all participating networks for contributing clinical guidelines for analysis. The authors wish to acknowledge the Pediatric Emergency Research Networks (PERN) executive committee at the time of study approval: Nathan Kupperman (Chair, PECARN), Stuart Dalziel (Vice Chair, PREDICT), Franz Bahl (PREDICT), Jim Chamberlain (PECARN), David Johnson (PERC), Mark Lyttle (PERUKI), Santiago Minteg (REPEM), Rakesh Mistry (PEMCR), Lise Nigrovic (PEMCR), Amy Plint (PERC), Damian Roland (PERUKI) and Patrick Van de Voorde (REPEM). On behalf of the Pediatric Emergency Research Networks (PERN). Participating networks include: the Paediatric Research in Emergency Departments International Collaborative (PREDICT), the Pediatric Emergency Care Applied Research Network (PECARN), the Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics (PEMCR), Pediatric Emergency Research Canada (PERC), Pediatric Emergency Research in the UK and Ireland (PERUKI), Research in European Pediatric Emergency Medicine (REPEM), the Red de Investigación SEUP (Sociedad Española de Urgencias Pediátricas—Spanish Pediatric Emergency Research Group (RISEUP SPERG) network and the Red de Investigación y Desarrollo de la Emergencia Pediátrica en Latino-americana (RIDEPLA) network.

Contributors SC and CG identified the research question. SC and CG were responsible for the study design and research protocol, with input from all authors. JB, RV, MC, SC and CG obtained data supervised data extraction and analysis. CG was responsible for statistical analysis. CG drafted the initial manuscript. All authors contributed equally to writing, reviewing and editing the manuscript. All authors provided comments on the drafts and have read and approved the final version of the article. All authors had full access to all of the data (including statistical reports and tables) at the conclusion of the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CG is the guarantor for the paper, accepts full responsibility for the work and/or the conduct of the study, had access to the data and controlled the decision to publish.

Funding This work is supported by the National Health and Medical Research Council (NHMRC) Centre of Research Excellence in Paediatric Emergency Medicine (GNT1171228), Canberra, Australia. SC's contribution was funded by the Thoracic Society of Australia and New Zealand and National Asthma Council Fellowship, 2020 and the Australasian College for Emergency Medicine 26 Foundation Al Spilman Early Career Research Grant 2017. SD's time was in part funded by Cure Kids New Zealand. FEB's time was funded by an NHMRC Investigator Leadership grant (GNT2017605) and the Royal Children's Hospital Foundation, Parkville, Australia.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Approval was provided by the Monash Health Human Research Ethics Committee (Melbourne, Australia) as a Quality Assurance project exempt from full ethical review (RES-18-0000-5252Q).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed.

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ARTIGO ORIGINAL

Efeitos da oxigenoterapia de longa duração nas exacerbações agudas e na carga hospitalar: o estudo nacional DISCOVERY

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► Additional supplemental material is published online only. To view, please visit the journal (<https://doi.org/10.1136/thorax-2023-221063>).

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Received 9 October 2023

Accepted 1 March 2025

Published Online First 20 March 2025

RESUMO

Contexto A oxigenoterapia de longa duração (LTOT) melhora a sobrevivência em doentes com hipoxemia grave em repouso, mas os seus efeitos sobre os internamentos hospitalares são desconhecidos. Este estudo avaliou o impacto potencial do início da LTOT nas exacerbações agudas e na carga hospitalar em doentes com doença pulmonar obstrutiva crônica (DPOC), doença pulmonar intersticial (ILD) e hipertensão pulmonar (HP).

Métodos Análise longitudinal de doentes consecutivos da coorte populacional sueca DISCOVERY que iniciaram LTOT entre 2000 e 2018, com um seguimento ≥ 3 meses. As exacerbações agudas totais e hospitalares da doença subjacente, os internamentos por todas as causas e as consultas externas por todas as causas foram anualizados e comparados entre o ano anterior e o ano posterior ao início da LTOT para cada grupo de doença, e também de acordo com o estado hipercápnico nos doentes com DPOC.

Resultados Os doentes com DPOC ($n = 10\,134$) apresentaram uma redução significativa nas taxas anualizadas de exacerbações agudas totais e hospitalares, bem como nos internamentos por todas as causas após o início da LTOT. Em contraste, observou-se um aumento dessas taxas nos doentes com ILD ($n = 2507$) e HP ($n = 850$). As consultas externas por todas as causas aumentaram em todos os grupos após o início da LTOT. Resultados semelhantes foram observados em doentes com DPOC hipercápnica e não hipercápnica. As análises de sensibilidade em doentes com 12 meses de seguimento mostraram uma redução das exacerbações agudas e dos internamentos por todas as causas nos grupos com ILD e HP.

Conclusão A LTOT está associada a uma redução das taxas de exacerbações agudas totais e hospitalares, bem como dos internamentos por todas as causas em doentes com DPOC, e também em doentes com ILD e HP com 12 meses de seguimento. No entanto, verificou-se um aumento das consultas externas por todas as causas em todos os grupos de doença após o início da LTOT.

INTRODUCTION

Chronic respiratory diseases are a major health burden worldwide, affecting over 7% of the global population with approximately three million deaths each year.^{1,2} Resting hypoxaemia is a key clinical manifestation of patients with advanced chronic respiratory diseases. The prevalence of chronic resting hypoxaemia varies across different disease groups, but is consistently associated with worse prognosis and increased symptom burden.^{3,4}

Long-term oxygen therapy (LTOT) is recommended for patients with chronic severe resting hypoxaemia, which is prescribed for home use of at

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Despite the widespread use of long-term oxygen therapy (LTOT), its impact on healthcare utilisation remains unknown.

WHAT THIS STUDY ADDS

► Using the Swedish nationwide, population-based DISCOVERY cohort, LTOT is associated with reduced rates of both total and hospitalised acute exacerbations and all-cause hospitalisations in patients with chronic obstructive pulmonary disease (COPD) with and without baseline hypercapnia. Similar observations were noted in patients with interstitial lung disease (ILD) and pulmonary hypertension (PH) who had over 12 months of follow-up.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► Our results provide supporting evidence on favourable impact of LTOT for treating resting hypoxaemia in COPD in reducing acute exacerbations and all-cause hospitalisations, which are important health outcomes in these populations. Furthermore, use of LTOT does not appear to adversely increase the risk of acute exacerbations or hospital burden in patients with hypercapnic COPD. In patients with ILD and PH, there may be beneficial effects in those with expected prognosis of ≥ 12 months.

least 15 hours per day.⁵ Two pivotal but small randomised controlled trials from the 1980s demonstrated survival benefits of LTOT in patients with chronic obstructive pulmonary disease (COPD) and severe resting hypoxaemia,^{6,7} which is now extrapolated to the management of people with other chronic diseases, including interstitial lung disease (ILD) and pulmonary hypertension (PH).^{8–12} Despite widespread use in these and other diseases, the effects of LTOT on acute exacerbation and healthcare utilisation remain uncertain.



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To cite: Khor YH, Palm A, Wong AW, et al. *Thorax* 2025;80:378–384.

The aim of this study was to evaluate the impact of LTOT initiation on acute exacerbations of the underlying chronic respiratory disease, hospitalisations and outpatient visits among patients with COPD, ILD, and PH. LTOT was hypothesised to be associated with reduced total and hospitalised acute exacerbations, annualised rates and cumulative lengths of stay of all-cause hospitalisations, and annualised rates of all-cause outpatient visits in patients with COPD, ILD and PH. We further hypothesised that among patients with COPD, there would be a similar reduction in acute exacerbations and hospital burden following the initiation of LTOT in both the presence and absence of hypercapnia.

METHODS

Study population

This longitudinal study was conducted using the nationwide, population-based DISCOVERY cohort consisting of the Swedish National Quality Registry of Respiratory Failure (Swedevox) with governmental and other Swedish national registries (online supplemental e-Methods 1).¹³ We included consecutive patients aged ≥ 18 years who were initiated on LTOT between 2000 and 2018 for physician-diagnosed COPD, ILD or PH with a follow-up duration of at least 3 months. There was no restriction on the underlying cause of COPD, ILD or PH. The guideline recommended prescribing criteria for LTOT included resting arterial blood gas (ABG) on room air showing partial pressure of oxygen ≤ 55 mm Hg or 56 to 59 mm Hg with evidence of polycythaemia, cor pulmonale, and/or PH.¹¹ The COPD cohort was further subdivided into hypercapnic (≥ 45 mm Hg) and non-hypercapnic (< 45 mm Hg) groups using baseline arterial partial pressure of carbon dioxide (breathing air). For patients with multiple episodes of LTOT initiation, data from the latest episode were used.

Outcome evaluation

Hospital burden was evaluated in the year prior to and up to 12 months following the initiation of LTOT. Outcomes included total and hospitalised acute exacerbations of the underlying disease responsible for LTOT initiation, all-cause hospitalisations and all-cause outpatient visits. Non-hospitalised acute exacerbations of the underlying disease were determined based on the medication prescription records on the National Prescribed Drugs Registry¹³ as follows for evaluation of total acute exacerbations:

- COPD and ILD: initiation of a prednisolone-equivalent dose of ≥ 20 mg/day or increased dose by ≥ 2 times compared with the preceding month for up to 2 weeks of use;
- PH: initiation or increased dose of furosemide for up to 2 weeks, with or without concurrent initiation of thiazide or potassium-sparing diuretics.

Medication prescriptions that were linked to hospitalisations were excluded in the definition of a non-hospitalised acute exacerbation. Of note, the evaluation of non-hospitalised acute exacerbations was from July 2005 onwards, when the National Prescribed Drugs Registry was commenced. Hospitalised acute exacerbations were identified using ICD codes from the Swedish National Patient Registry (online supplemental e-Table 1). For acute exacerbation-related and all-cause hospitalisations, the lengths of inpatient stay were also collected.

Additional data

Additional extracted data from the Swedevox Registry included patient demographics, smoking status, LTOT initiation date and indication, baseline ABG and lung function, disease stability status and WHO performance status at LTOT initiation, and concurrent use of ambulatory oxygen therapy and long-term mechanical ventilation. The disease stability status at LTOT initiation was classified as chronic stable disease or postacute illness. These data have previously been validated for accuracy.¹⁴

Statistical analysis

Statistical analyses were performed using Stata (V.17, StataCorp, USA). Summary statistics are presented as frequency (%) for categorical data and mean $\pm$ SD or median (IQR) for continuous data, depending on the distribution.

Primary analyses

To account for varying follow-up durations, events of acute exacerbations, hospitalisations and outpatient visits were annualised for comparison before and after LTOT initiation and then modelled using the multilevel negative binomial regression models with random intercept at individual level. This approach was chosen due to overdispersion of outcome variables (online supplemental e-Methods 2). Baseline assessments were evaluated at the time of LTOT initiation for the preceding 12 months. After the initiation of LTOT, outcomes were evaluated for up to 12 months of follow-up. For patients who ceased LTOT within 12 months, the outcomes were divided by the length of follow-up in days and multiplied by 365. The proportions of patients with ≥ 1 acute exacerbation, hospitalisation and outpatient visit before and after LTOT initiation were compared using the McNemar test. Adjusted analyses were performed by including prespecified covariates: age, sex, body mass index, WHO performance status, the year of LTOT initiation and length of follow-up, with the addition of the presence of hypercapnia for the COPD cohort. Concomitant use of non-invasive ventilation was also adjusted for in the models evaluating the COPD cohort with and without hypercapnia. Complete case analyses were performed with no imputation for missing data.

Subgroup and sensitivity analyses

Subgroup analyses were performed according to disease stability status at LTOT initiation (chronic stable disease vs postacute illness), adherence to LTOT eligibility (fulfilling and not fulfilling the prescribing criteria), and the year of LTOT initiation (2000 to 2009 vs 2010 to 2017). Sensitivity analyses were conducted for patients with 12 months of follow-up.

RESULTS

Patient characteristics

A total of 10 134 patients with COPD, 2507 with ILD, and 850 with PH were included (figure 1). Patients of different disease cohorts had comparable age, severity of hypoxaemia, disease stability status, and WHO performance status at LTOT initiation (table 1). The COPD cohort included a greater percentage of ever-smokers, had worse spirometric measurements and was more likely to have hypercapnia at LTOT initiation than the ILD and PH cohorts. The ILD cohort included a smaller percentage of females, compared with those with COPD and PH. Patients with less than 3 months of follow-up (online supplemental e-Table 2) and who had hypercapnic COPD (online supplemental e-Table 3) were more likely to have postacute illness at LTOT initiation, compared with the overall cohort and patients without hypercapnic COPD, respectively. Over the years, there was increasing proportion of LTOT initiation for ILD and PH over the years (online supplemental e-Figure 1). Between 2% and 6% of patients for different disease cohorts did not meet the prescribing eligibility criteria for LTOT (table 1). There were 7430 (73%), 1442 (58%) and 550 (65%) patients with COPD, ILD and PH, respectively, with 12 months of follow-up. The median follow-up durations were 1.8 years for patients with COPD, 1.1 years for patients with ILD and 1.3 years for patients

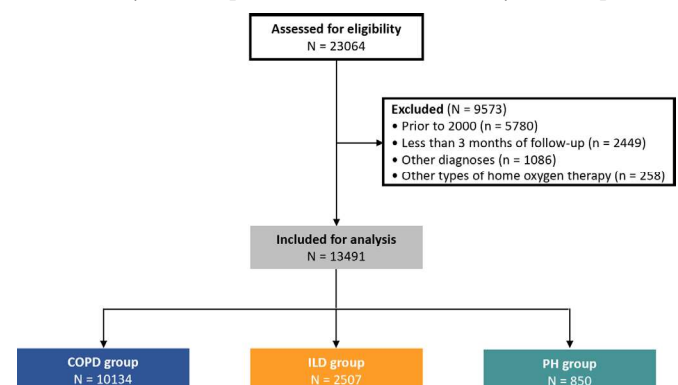


Figure 1 Study flow diagram. COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; PH, pulmonary hypertension.

with PH, with 1-year mortality rates post-LTOT initiation of 25%, 44% and 32%, respectively.

Acute exacerbation of underlying disease

Annualised rates of total and hospitalised acute exacerbations of the underlying disease in patients with COPD declined after LTOT initiation, with increment for those with ILD and PH (table 2 and online supplemental e-Table 4). There was a decline in annualised lengths of hospital stay for acute exacerbations following LTOT initiation in the COPD cohort only. However, the proportion of patients with ≥ 1 total and hospitalised acute exacerbations was reduced following LTOT initiation in all cohorts (online supplemental e-Table 5). Adjusted analyses of annualised rates of total and hospitalised acute exacerbations, as well as lengths of hospital stay for acute exacerbations, before and after LTOT initiation showed largely similar findings for the three disease cohorts (table 3 and online supplemental e-Table 6).

All-cause hospitalisation

Annualised rates of all-cause hospitalisations and lengths of stay decreased following LTOT initiation in patients with COPD, but increased in those with ILD (table 2 and online supplemental e-Table 4).

In patients with PH, there was increased annualised rates of all-cause hospitalisations but not the lengths of stay. The number of patients with ≥ 1 all-cause hospitalisation for all cohorts reduced during the year after the initiation of LTOT (online supplemental e-Table 5). In adjusted analyses, similar annualised rates and lengths of stay for all-cause hospitalisations before and after LTOT initiation for all cohorts were observed (table 3 and online supplemental e-Table 6).

All-cause outpatient visit

For all cohorts, annualised rates of all-cause outpatient visits increased after LTOT initiation (table 2 and online supplemental e-Table 4), although there were no differences in the number of patients with at least one all-cause outpatient visit (online supplemental e-Table 5). There were similar increments in annualised rates of all-cause outpatient visits following LTOT initiation for all cohorts in adjusted analyses (table 3 and online supplemental e-Table 6).

Hypercapnic and non-hypercapnic COPD groups

Among the COPD cohort, both hypercapnic and non-hypercapnic groups had a decline in annualised rates of total acute COPD exacerbations, as well as annualised rates of and lengths of stay for

Table 1 Baseline patient characteristics

	COPD (N=10 134)		ILD (N=2507)		PH (N=850)	
	N	Measurement	N	Measurement	N	Measurement
Age, years	10 134	75 (69, 80)	2507	76 (70, 82)	850	76 (69, 82)
Female	10 134	6113 (60)	2507	989 (39)	850	520 (61)
BMI	7748	23 (20, 27)	1981	25 (23, 29)	573	26 (23, 30)
Smoking history						
Ever-smoker	9619	9245 (96)	2198	1461 (66)	699	429 (61)
Never-smoker	9619	374 (4)	2198	737 (34)	699	270 (39)
Pulmonary function						
FEV ₁ , L	6504	0.7 (0.5, 1.0)	1676	1.6 (1.2, 2.1)	450	1.5 (1.1, 2.0)
VC, L	6345	1.8 (1.4, 2.4)	1659	2.0 (1.5, 2.6)	442	2.2 (1.7, 3.0)
Room air ABG						
PaO ₂ , mm Hg	8880	50 (45, 53)	2019	50 (45, 54)	671	49 (44, 53)
PaO ₂ , kPa	8880	6.6 (6.0, 7.1)	2019	6.6 (6.0, 7.2)	671	6.5 (5.8, 7.1)
PaCO ₂ , mm Hg	8841	46 (40, 53)	2009	38 (34, 43)	677	37 (32, 44)
PaCO ₂ , kPa	8841	6.1 (5.3, 7.0)	2009	5.0 (4.5, 5.7)	677	4.9 (4.2, 5.8)
Hypercapnia*	8841	4918 (56)	2009	368 (18)	677	144 (21)
Disease stability status at initiation						
Chronic stable disease	7191	5088 (71)	1832	1302 (71)	628	459 (73)
Postacute illness	7191	2103 (29)	1832	530 (29)	628	169 (27)
Performance status						
WHO 0	8935	617 (7)	2254	153 (7)	747	60 (8)
WHO 1	8935	4052 (45)	2254	1095 (49)	747	377 (50)
WHO 2	8935	2958 (33)	2254	698 (31)	747	203 (27)
WHO 3	8935	1206 (13)	2254	288 (13)	747	101 (14)
WHO 4	8935	102 (1)	2254	20 (1)	747	6 (1)
LTOT prescription						
Oxygen flow rate	10 134	1.5 (1, 2)	2507	2 (1, 3)	850	2 (1.5, 3)
Usage duration	10 134	16 (16, 22)	2507	18 (16, 24)	850	20 (16, 24)
Not meeting eligibility†	8880	213 (2)	2019	121 (6)	671	27 (4)
Ambulatory oxygen use						
Yes	9856	4984 (51)	2435	1591 (65)	828	501 (61)

Data are expressed as median (IQR), or n (%).

*Hypercapnia was defined as PaCO₂ of ≥ 45 mm Hg

†LTOT prescribing criteria: Resting ABG on room air showing partial pressure of oxygen ≤ 55 mm Hg or 56 to 59 mm Hg with evidence of polycythaemia, cor pulmonale, and/or PH ABG, arterial blood gas; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; ILD, interstitial lung disease; LTOT, long-term oxygen therapy; PaCO₂, partial arterial carbon dioxide tension; PaO₂, partial arterial oxygen tension; PH, pulmonary hypertension; VC, vital capacity.

Table 2 Incidence rate ratios of unadjusted annualised rates of acute exacerbation of underlying disease and all-cause hospital burden before and after the initiation of LTOT for patients with COPD, ILD and PH

	COPD		ILD		PH	
	IRR	P value	IRR	P value	IRR	P value
Acute exacerbation of underlying disease						
Total acute exacerbations	0.80	<0.001	1.31	<0.001	1.25	0.004
Hospitalised acute exacerbations	0.76	<0.001	1.27	<0.001	1.08	0.13
Length of stay for hospitalised acute exacerbations (days)	0.67	<0.001	1.19	0.001	0.87	0.07
All-cause hospital burden						
All-cause hospitalisations	0.86	<0.001	1.30	<0.001	1.10	0.03
Length of stay for all-cause hospitalisations (days)	0.73	<0.001	1.21	<0.001	0.96	0.47
Outpatient clinic visits	1.15	<0.001	1.16	<0.001	1.31	<0.001

Incidence rate ratios (IRR) refer to the ratio between the event rates before and after the initiation of LTOT.

COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IRR, incidence rate ratio; LTOT, long-term oxygen therapy; PH, pulmonary hypertension.

hospitalised acute exacerbations following LTOT initiation (online supplemental e-Table 7). The numbers of patients with ≥ 1 total and hospitalised acute exacerbation of COPD were reduced during the year following the initiation of LTOT for both groups (online supplemental e-Table 8). Following LTOT initiation, both groups also had a decline in annualised rates of and lengths of stay for all-cause hospitalisations, with increased annualised rates of all-cause outpatient visits (online supplemental e-Table 7). On adjusted analyses, similar observations of reduced acute exacerbations and all-cause hospitalisations with increased all-cause outpatient visits following LTOT initiation for both groups (online supplemental e-Table 9).

Subgroup and sensitivity analyses

Subgroup analyses according to the disease stability status at LTOT initiation, adherence to LTOT eligibility, the year of LTOT initiation and concurrent use of ambulatory oxygen therapy are presented in online supplemental e-Tables 10 and 11. Similar observations were seen for different subgroups analysed for all disease cohorts, with few exceptions primarily in those who did not meet LTOT eligibility criteria. Sensitivity analyses for patients with 12-month follow-up after LTOT initiation revealed similar results compared with the primary analyses for patients with COPD (online supplemental e-Tables 12 and 13). In patients with ILD and PH, there were reduced annualised rates of acute exacerbations and all-cause hospitalisations.

DISCUSSION

While LTOT has been used for treating severe resting hypoxaemia for decades, high-level evidence of its therapeutic effects from ran-

domised controlled trials remains sparse given the ethical implications of withholding treatment. Using nationwide, population-based data, the main finding of this study is that initiation of LTOT was associated with reduced disease-specific acute exacerbations and all-cause hospitalisations in patients with COPD who had severe resting hypoxaemia, as well as in those with ILD and PH who had follow-up of ≥ 12 months. Similar therapeutic benefits were observed in patients with hypercapnic and non-hypercapnic COPD. This was contrasted with an increase in all-cause outpatient visits across all cohorts following LTOT initiation. Reduced proportions of patients with ≥ 1 acute exacerbation and all-cause hospitalisation were consistently observed across the disease cohorts, which could be influenced by decreased follow-up durations due to the increased attrition rates in those with ILD and PH.

Over 540 million people are affected by chronic respiratory diseases, with COPD and ILD being among the most prevalent three diseases.¹ Up to 70 million people are estimated to have PH.^{15–16} Acute exacerbations are major events in COPD, ILD and PH with substantial risk of mortality, particularly in patients with greater disease severity.^{17–20} In-hospital mortality for hospitalised acute exacerbations is over 4% in COPD,¹⁷ over 50% in ILD,^{18,19} and between 14 and 100% in PH.²⁰ Acute exacerbations also cause substantial morbidity with worsened symptom burden and quality of life in patients with COPD, ILD and PH.^{17,18,20} Our study is the first to show that the use of LTOT is associated with a reduction in both total and hospitalised acute exacerbations in patients with COPD, as well as a subset of patients with ILD and PH with ≥ 12 months of follow-up. This suggests potential benefits of LTOT beyond

Table 3 Incidence rate ratios of adjusted annualised rates of acute exacerbation of underlying disease and all-cause hospital burden before and after the initiation of LTOT for patients with COPD, ILD and PH

	COPD		ILD		PH	
	IRR	P value	IRR	P value	IRR	P value
Acute exacerbation of underlying disease						
Total acute exacerbations	0.78	<0.001	1.25	<0.001	1.25	<0.001
Hospitalised acute exacerbations	0.75	<0.001	1.22	<0.001	1.21	0.003
Length of stay for hospitalised acute exacerbations (days)	0.63	<0.001	1.06	0.30	0.88	0.20
All-cause hospital burden						
All-cause hospitalisations	0.84	<0.001	1.26	<0.001	1.19	0.001
Length of stay for all-cause hospitalisations (days)	0.69	<0.001	1.10	0.03	0.99	0.94
Outpatient clinic visits	1.14	<0.001	1.13	<0.001	1.30	<0.001

Incidence rate ratios (IRR) refer to the ratio between the event rates before and after the initiation of LTOT.

Covariates for adjustment included age, sex, body mass index, WHO performance status, the year of LTOT initiation and length of follow-up, with the addition of the presence of hypercapnia for the COPD cohort.

COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IRR, incidence rate ratio; LTOT, long-term oxygen therapy; PH, pulmonary hypertension.

mortality, including significant cost savings from the reduction in hospital admissions and length of hospital stay, as well as likely improved symptoms and quality of life as a result of reduced total and severe acute exacerbations.

Healthcare utilisation is doubled in patients with COPD and ILD compared with age-matched and sex-matched controls.^{21–22} Pulmonary hypertension consists of five groups of different aetiology with varying healthcare utilisation that is directly associated with disease severity.^{23–24} Our findings confirm previous studies of reduced all-cause hospitalisations with LTOT in smaller COPD populations,^{25–27} with additional evidence of similar effects in selected patients with ILD and PH. Increments in all-cause outpatient visits were noted across different disease cohorts. This may reflect the need for additional support with LTOT and outpatient disease management in this population. In a previous survey of patients from the Swedevox Registry, over 70% experienced adverse events related to LTOT use, with common ones being reduced physical activity, dry mouth, nasal congestion or dryness, and increased fatigue.²⁸ Of note, there is no requirement for routine outpatient visits following LTOT initiation in Sweden. This may also indicate that LTOT allows managing acute exacerbation as outpatients in some patients, or opportunities to address different health issues during outpatient visits for LTOT management. LTOT has been reported to account for between 5% and 53% of total healthcare costs in patients with COPD.^{29–30} This variation is due to differences in COPD disease severity of the study populations, local healthcare costs and the cost categories included in the evaluation. Nevertheless, hospitalisations are the primary driver of healthcare costs,³¹ including in patients with COPD,²¹ ILD³² and PH.^{23–24} The shift in the use of healthcare utilisation from hospitalisation to LTOT use and outpatient visits is likely favourable for the total healthcare costs. In-depth evaluations of factors for increased all-cause outpatient visits and cost-effectiveness are needed to allow the delivery of optimal clinical care in patients using LTOT.

Chronic hypercapnia is present in up to 30% of patients with severe COPD.^{33–35} Oxygen-induced hypercapnia is a complex phenomenon that is caused by ventilation-perfusion mismatching, changes in minute ventilation, and the Halden effect with a rightward shift of the carbon dioxide dissociation curve.^{36–37} Uncontrolled supplemental oxygen therapy during COPD exacerbations is associated with increased mortality.^{38–39} After LTOT initiation, both hypercapnic and non-hypercapnic COPD cohorts had similar reduction in total and hospitalised acute exacerbations, as well as all-cause hospitalisations and outpatient visits. The benefits appear to be more pronounced in patients with hypercapnia on adjusted analyses. These findings support the safety of LTOT use in patients with mild-to-moderate hypercapnic COPD. Nevertheless, careful assessment and monitoring are encouraged to ensure the absence of worsening hypercapnia or development of respiratory acidosis with LTOT in this population.⁴⁰

Treatment effects of LTOT in patients who remain hypoxaemic postacute illness or without severe resting hypoxaemia are uncertain. Both groups had reduced acute exacerbation-related and all-cause hospitalisations following LTOT initiation in patients with COPD, but not in those with ILD and PH. Hypoxaemia following acute illness or hospitalisation is often limited to only a few days to a few weeks, resolving in up to 80% of patients at subsequent assessment between 30 and 90 days.^{41–42} In the LOTT trial of patients with COPD and moderate resting hypoxaemia, LTOT did not affect survival, hospitalisations and acute exacerbations.⁴³ Importantly, there are potential adverse effects with LTOT beyond the associated cost, including physical and psychological impacts and patient safety considerations such as falls and burn injuries.^{5–40} Hence, reassessments following LTOT initiation postacute illness are necessary, while prescribing LTOT in patients without severe resting hypoxaemia should generally be discouraged and carefully considered in individual cases.

A strength of this study is the use of national population data with a large number of patients for the three disease cohorts. There were no exclusion criteria related to health insurance status or

geographical location. There are some limitations. Definitions for non-hospitalised and hospitalised acute exacerbations were based on medication prescription records and ICD codes, respectively, which can cause diagnostic inaccuracy with either underestimation or overestimation due to misattribution of medication indication or hospital diagnosis. However, these biases should affect data for both before and after LTOT initiation equally, and should not affect the numbers of all-cause hospitalisations and outpatient visits. Annualised rates of events of interest were calculated and estimated for patients with a follow-up duration of less than 12 months. Of note, sensitivity analyses using patients with 12-month follow-up revealed similar findings. Patients with limited follow-up of less than 3 months were excluded, who may have different patterns of acute exacerbations and healthcare utilisation. Concomitant disease-specific treatments that may affect health outcomes could not be determined in this study. Subgroup analyses based on two separate enrolment periods with likely different contemporary treatments did not identify significant differences. Causes for outpatient visits, the number of general practitioner visits, and the cost for community or home care support could not be assessed, which warrants evaluation in future studies.

CONCLUSION

This large nationwide cohort study provides supporting evidence on favourable impact of LTOT for treatment of resting hypoxaemia in COPD, as well as selected cases of ILD and PH, in reducing acute exacerbations and all-cause hospitalisations, with an increase in outpatient visits that likely represents greater ability to manage acute exacerbations in an outpatient setting when patients are using LTOT. Use of LTOT does not appear to adversely increase the risk of acute exacerbations or hospital burden in patients with hypercapnic COPD. These findings suggest potential improvement in health outcomes and healthcare costs with LTOT in patients with advanced chronic respiratory diseases. Cost-benefit analysis is needed to fully elucidate the value of LTOT to inform clinical practice and guidelines.

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Acknowledgements YHK receives fellowship support from the National Health and Medical Research Council Investigator Grant (ID: 2008255). ZA was supported by the Swedish Heart-Lung Foundation (ID: 20200295). ME was supported by an unrestricted grant from the Swedish Research Council (ID: 2019-02081).

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Funding YHK receives fellowship support from the National Health and Medical Research Council Investigator Grant (ID: 2008255).

Competing interests YHK reports grants from NHMRC Investigator Grant during the conduct of the study, and non-financial support from Air Liquide Healthcare outside the submitted work. AP reports personal fees from ResMed, outside the submitted work. AWW reports personal fees from Boehringer Ingelheim and AstraZeneca, outside the submitted work. SAG reports funding and personal fees from Boehringer Ingelheim, Janssen, MSD and Gebro, outside the submitted work. CJR reports grants and personal fees from Boehringer Ingelheim, grants and personal fees from Hoffmann-La Roche, personal fees from Veracety, personal fees from Pliant Therapeutics, personal fees from AstraZeneca, personal fees from Cipla Ltd, grants from VIDA diagnostics and personal fees from Trevi Therapeutics, outside the submitted work. FB, ZA, JS and ME have nothing to disclose.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Swedish Ethical Review Board (DNR: 2018/51). 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.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed.

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ARTIGO ORIGINAL

Associação entre asma e diabetes tipo 2 numa população adulta sueca: um estudo transversal baseado em registos

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► Additional supplemental material is published online only. To view, please visit the journal (<https://doi.org/10.1136/thorax-2024-222819>).

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Received 5 December 2024

Accepted 6 March 2025

Published Online First 23 March 2025



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To cite: Mubanga M, Gong T, Smew AI, et al. *Thorax* 2025;80:385–391.

RESUMO

Objetivo A asma e a diabetes tipo 2 são duas causas importantes de morbilidade a nível global. Examinámos a associação entre a diabetes tipo 2 e a asma em adultos suecos, bem como a co-agregação familiar destas doenças.

Métodos Realizámos um estudo transversal com todos os adultos entre os 25 e os 85 anos na Suécia, entre 2009 e 2013. A presença de asma e diabetes tipo 2 foi determinada através dos registos de saúde. Os modelos foram ajustados para sexo, idade, nível de escolaridade, rendimento e país de nascimento e, numa subamostra, também para o índice de massa corporal (IMC). Realizámos ainda uma análise de co-agregação familiar para determinar se fatores familiares partilhados poderiam explicar os resultados observados.

Resultados O estudo incluiu 5 299 245 participantes, dos quais 25 292 (0,5%) tinham simultaneamente asma e diabetes tipo 2. Na população total, a razão de probabilidades (OR) para a associação entre diabetes tipo 2 e asma foi de 1,47 (IC 95%: 1,45 a 1,49); entre os homens foi de 1,30 (IC 95%: 1,27 a 1,32) e entre as mulheres 1,63 (IC 95%: 1,60 a 1,66). As ORs foram ligeiramente mais elevadas entre os homens (1,51) e mulheres (2,04) com medições de IMC disponíveis, mas atenuaram-se após o ajuste para o IMC: 1,45 (IC 95%: 1,40 a 1,51) nos homens e 1,76 (IC 95%: 1,68 a 1,84) nas mulheres. A diabetes foi mais provável em indivíduos cujo irmão de sangue tinha asma, em comparação com aqueles cujos irmãos não tinham (OR: 1,13, IC 95%: 1,10 a 1,15).

Conclusões Encontrámos uma associação entre asma e diabetes tipo 2 que se manteve mesmo após o ajuste para o IMC, o que indica que o IMC, por si só, não explica esta relação. Verificámos também que as duas condições co-ocorrem entre irmãos, sugerindo que a associação se deve, em parte, a fatores genéticos e ambientais familiares partilhados.

INTRODUCTION

Asthma and type 2 diabetes are two complex and prevalent diseases, each constituting a significant public health problem. Studies have shown that both may coexist in the same individual,^{1–3} and it is hypothesised that this may be due to several possible mechanisms. Both conditions share in common a sustained proinflammatory state,^{4,5} which may or may not be associated with obesity.^{2,6,7} Asthma is associated with the upregulation of multiple proinflammatory cytokines, possibly through the activation of nuclear factor (NF)-κB, such as interleukin (IL)-4, IL-5, IL-6, IL-13 and IL-17, tumour necrosis factor (TNF)-α and different adhesion molecules.^{8,9} It has been proposed that constantly raised levels of these cytokines may cause insulin resistance, drive systemic inflammation and consequently result in type 2 diabetes.^{2,5,10,11} There is also evidence that asthma is a systemic disorder with significant cross-commu-

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► There are conflicting findings regarding the within-person association between asthma and type 2 diabetes, but little is known about the possibility of familial coaggregation of both diseases.

WHAT THIS STUDY ADDS

► Shared familial risk factors explain some of the association between type 2 diabetes and asthma.
► BMI is an important confounder in the within-person association between asthma and type 2 diabetes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► This There needs to be an increased index of suspicion for asthma and type 2 diabetes in family members.

nification through inflammatory mediators to other distant organs.^{8,9} Further, hormone imbalances as observed in hyperleptinaemia, leptin resistance and hyperinsulinaemia are important in the development of both asthma and type 2 diabetes.^{3,12,13} Insulin plays an important role in physiological lung development, supporting alveolarisation. In hyperinsulinaemia, the levels interfere with lung development and maturation, while facilitating a proasthmatic immune environment.^{14,15}

The underlying factors associated with asthma, and independently with type 2 diabetes, are known to be dependent on several risk factors,^{8,10} with the phenotypic expression being modified by genetic and environmental factors.^{1,16} An important common risk factor for both diseases is obesity. Evidence exists for the shared genetics between asthma and obesity,¹⁷ and similarly, type 2 diabetes is a trait strongly correlated with obesity.¹⁶ While previous studies have shown conflicting findings regarding the within-person relationship between asthma and type 2 diabetes, to the best of our knowledge, there have been very few studies that have attempted to study the possibility of familial coaggregation of both diseases.

Familial coaggregation studies offer evidence for familial clustering of two diseases, allowing investigators to test for the presence of shared genetic and/or environmental factors that may contribute to this association.¹⁸ To further advance the understanding of the relationship between asthma and

type 2 diabetes in the Swedish population, we carried out a population-based cross-sectional study using the rich Swedish national registers, with the aim of examining both the association of type 2 diabetes with asthma in adults in this population regarding the familial coaggregation of the diseases.

METHODS

Study design

We conducted a register-based cross-sectional study with prospectively recorded data that included all Swedish singleton adults born between 1924 and 1984 ($n=8\,163\,216$). All participants had to be alive and residents of Sweden for the full duration of the study between January 2009 and December 2013.

Participants were identified using the Register of the Total Population with information on birth, migration and civil status of all Swedish residents.¹⁹ From the population of 8 163 216, we excluded people who died before 1 January 2014 ($n=1\,138\,473$), those who had not resided in Sweden during the full duration of the study ($n=432\,199$) to ensure complete coverage of diagnoses and medication in the registers and those who emigrated from Sweden ($1\,045\,242$). It was possible to extract information on physician-diagnosed asthma or type 2 diabetes from the National Patient Register²⁰ and the Swedish Prescribed Drug Register.²¹ The National Patient Register has had complete coverage for inpatient hospital diagnoses since 1987, and approximately 80% of outpatient specialist care visits since 2001. The Swedish Prescribed Drug Register has been available since July 2005 and contains information on drugs indicated for treatment which have been dispensed at pharmacies in Sweden.

Further, all participants who had a diagnosis of type 1 diabetes in the National Patient Register or were dispensed relevant medication from the Swedish Prescribed Register were also excluded. Type 1 diabetes was defined as the International Classification of Diseases (ICD)-10 E10 and/or insulin or insulin analogues (Anatomical Therapeutic Chemical (ATC) A10A), without any other blood glucose-lowering drugs ever²² ($n=85\,213$).

Due to the overlap in medication for asthma and chronic obstructive pulmonary disease (COPD), we additionally excluded 172 917 participants with COPD in either the National Patient Register (ICD-10 J44) or the Swedish Prescribed Drug Register (ATC codes R03AL (beta-2 agonists in combination with anticholinergics including triple combinations with corticosteroids) and R03BB (anticholinergics)). Finally, we also excluded everyone

missing socioeconomic information from the registers ($n=59\,927$).

We further distinguished between type 2 diabetes as defined by ICD-10 E11, and other forms of diabetes. These 'other' forms include malnutrition-related diabetes, gestational diabetes, unspecified diabetes or anyone on mixed insulin and oral hypoglycaemic medications. The other forms of diabetes were included under an extended diabetes definition. Of the 288 573 participants found with diabetes, 21 625 were identified with other forms of diabetes (extended diabetes). The exclusion left a final population of 5 229 245 (figure 1).

Information on family relations (full siblings) was further identified from the Multi-Generation Register.²³ First, both biological parents' personal identity numbers were used as the nuclear family ID to identify all sibling pairs. For families with more than two siblings, we have generated all possible sibling pairs for comparison (eg, six pairs for a three-sibling family who share the same family ID would be identified: sib1-sib2, sib1-sib3, sib2-sib3, sib3-sib2, sib3-sib1 and sib2-sib1). The pairs of full siblings within the study population who fell into the age category 45–78 in 2009 were then selected and included in the family coaggregation analyses ($n=3\,153\,219$), out of whom 750 153 were full brothers and 822 241 were full sisters.

Body mass index (BMI) was only available for a subset of the population. It was possible to retrieve information on BMI for a subset of men from the Swedish Conscription Register enlisted between 1967 and 2001 ($n=1\,535\,814$; 29.0% of the total population). This register includes information on all military conscripts around 18 years of age.²⁴ We then extracted information on BMI for pregnant women in the Medical Birth Register ($n=1\,223\,304$; 23.1% of the total population). The register reports >98% of all births in Sweden annually (established 1973) and includes maternal information such as BMI in early pregnancy at the first antenatal booking from 1982 and onwards²⁵ (figure 1).

The Longitudinal Integration Database for Health Insurance and Labor Market Studies includes microdata about highest attained education and income by calendar year.²⁶ We used it to extract information on socioeconomic status measured as education and household disposable income in 2011. Further information regarding the registers is included in the online supplemental material.

Dependent variable

Type 2 diabetes was defined as either physician-diagnosed in the National Patient Register²⁰ ICD-10 code E11 ($n=155\,396$) and/or as blood glucose-lowering drugs except insulin (ATC-code A10B) in the Swedish Prescribed Drug Register ($n=263\,686$). All cases

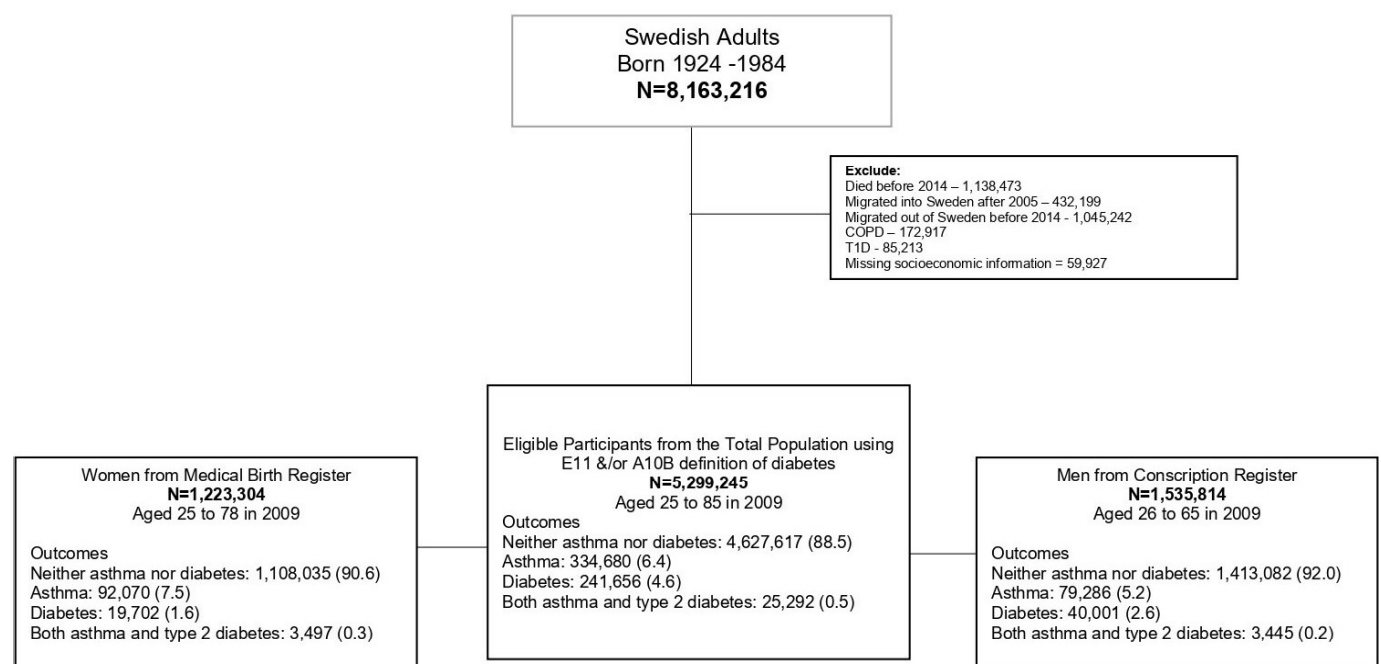


Figure 1 Eligibility flow chart. COPD, chronic obstructive pulmonary disease; T1D, type 1 diabetes.

had to fulfil the definition of current disease at any time between 2009 and 2013.

For additional analysis, we also identified all the other types of diabetes mellitus (extended diabetes definition) based on ICD-10 E11 in addition to the other non-insulin dependent definitions of diabetes including gestational diabetes O24 (3442), malnutrition-related diabetes mellitus ICD-10 E12 (n=126), other specified diabetes mellitus ICD-10 E13 (n=795) and unspecified diabetes mellitus ICD-10 E14 (n=17 424, online supplemental table 1).

To compare the association between asthma and diabetes using the different drug groups used to treat type 2 diabetes; we further identified biguanides (ATC A10BA; n=248 029), sulfonylureas (ATC A10BB; n=71 821), thiazolidinediones (ATC A10BG; n=7915) and combined oral hypoglycaemic use (ATC A10BD; n=6113).

Independent variable

Asthma was identified in the National Patient Register as ICD-10 J45 or J46 and/or identified in the Swedish Prescribed Drug Register as inhalations of selective β_2 -adrenoreceptor agonists (ATC R03AC), glucocorticoids (R03BA), fixed combinations of β_2 -agonists and glucocorticoids (R03AK) and leukotriene receptor antagonists (R03DC) according to a previously validated algorithm (n=359 972).²⁷ It was not possible to determine which individuals had previously been diagnosed with paediatric asthma as the Swedish Prescribed Drug Register has only been in existence since 2004 and would not cover childhood for all participants.

Covariates

Covariates were selected based on a directed acyclic graph (figure 2). Variables identified included age (continuous variable), sex (male/female), education level (primary ≤ 9 years, secondary 10–12 years, tertiary >12 years) and country of birth (Sweden, other Nordic country, non-Nordic country). Income was categorised into quintiles by birth year (1=lowest, 5=highest). This variable was created by dividing the annual household income into five groups, divided by quintiles, from lowest income to highest for each birth year. BMI was categorised as underweight (<18.5 kg/m²), healthy weight (18.5–24.9 kg/m²), overweight (25.0–29.9 kg/m²) and obesity (≥ 30 kg/m²).

Statistical analyses

Logistic regression was used to estimate ORs with 95% CIs examining the association between type 2 diabetes (dependent variable) and asthma (independent variable) with cluster-robust sandwich estimator to account for dependencies between siblings. In the first part of the study, this was done to measure within-person association in the total population, in only the men and then only in the women. Adjustment was made in three steps in the total population. First, we adjusted for age (continuous); then age and sex; then fully adjusted for age, sex, education level, income and birth country. We then repeated all three steps in a subset of the men only and women only populations, additionally adjusting for BMI.

In the second part of the study, we estimated the familial co-aggregation of type 2 diabetes (dependent) and asthma (independent). Using logistic regression with cluster-robust sandwich estimator to account for dependencies between sibling pairs, we estimated ORs and 95% CIs of type 2 diabetes in siblings of index persons with asthma compared with siblings of index persons without asthma. We adjusted for sex, age, siblings' asthma, income and education level. The analysis was done in the population of full siblings, among pairs of brothers, pairs of sisters and pairs of siblings of the opposite sex. If an index case had more than one eligible sibling, these were analysed as separate siblings' pairs.

In a sensitivity analysis, we repeated the analysis estimating the association between an extended definition of diabetes (dependent, see exclusion above) and asthma (independent). We also estimated the association between asthma and diabetes treated with oral hypoglycaemic drugs (biguanides, sulfonylureas, thiazolidinediones and mixed oral hypoglycaemic drug use).

All analyses were conducted using Stata V.16.

RESULTS

Out of 5 229 245 Swedish residents, 2 577 583 (49.3%) were male, 2 086 792 (39.9 %) were aged between 45 and 65, and 4 527 082 (86.6%) were born in Sweden. Additionally, 334 680 (6.4%) of the adults had asthma only, 241 656 (4.6%) had type 2 diabetes only and 25 292 (0.5%) had both asthma and type 2 diabetes. The baseline features of the study participants are detailed in table 1. We

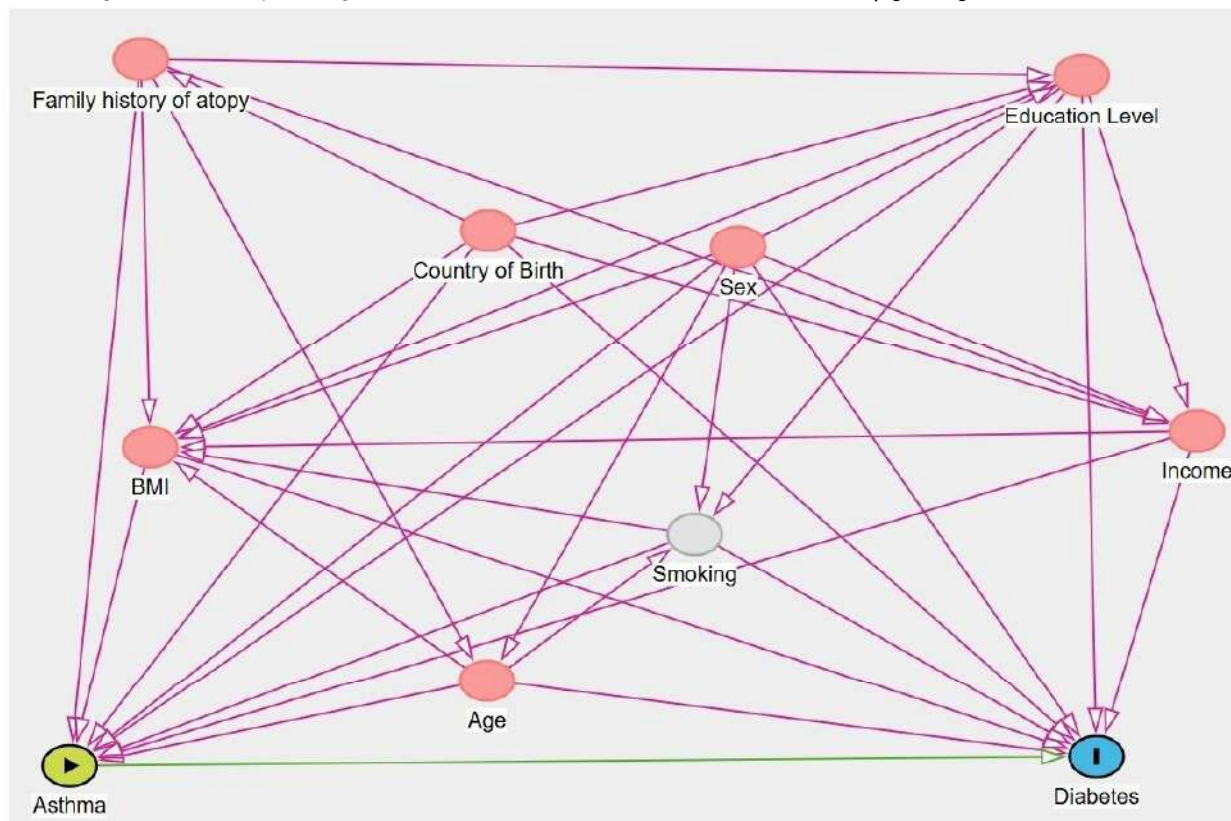


Figure 2 Directed acyclic graph. BMI, body mass index.

Table 1 Baseline characteristics*

	Total population	No asthma or diabetes	Asthma only	Diabetes only	Both asthma and diabetes
Characteristics					
Number (%)	5 229 245 (100)	4 627 617 (88.5)	334 680 (6.4)	241 656 (4.6)	25 292 (0.5)
Sex					
Male	2 577 583 (49.3)	2 293 656 (49.6)	130 918 (39.1)	142 226 (58.8)	10 783 (42.6)
Age category					
<45	2 140 963 (40.9)	1 986 918 (42.9)	130 987 (39.1)	20 332 (8.4)	2726 (10.8)
45–65	2 086 792 (39.9)	1 821 035 (39.4)	138 491 (41.4)	114 709 (47.5)	12 557 (49.6)
>65	1 001 490 (19.2)	819 664 (17.7)	65 202 (19.5)	106 615 (44.1)	10 009 (39.6)
Education level					
Compulsory	1 048 647 (20.1)	887 141 (19.2)	62 928 (18.8)	90 116 (37.3)	8462 (33.5)
Secondary	2 358 918 (45.1)	2 092 335 (45.2)	150 927 (45.1)	104 211 (43.1)	11 445 (45.2)
Tertiary	1 794 295 (34.3)	1 625 178 (35.1)	119 513 (35.7)	44 513 (18.4)	5091 (20.1)
Missing	27 385 (0.5)	22 963 (0.5)	1312 (0.4)	2816 (1.2)	294 (1.2)
Quantiles of income					
1 (lowest)	1 044 425 (20.0)	913 880 (19.8)	67 523 (20.2)	56 395 (23.2)	6627 (26.2)
2	1 045 588 (20.0)	918 353 (19.8)	70 433 (21.0)	50 948 (21.1)	5854 (23.1)
3	1 045 746 (20.0)	923 701 (20.0)	67 822 (20.3)	49 201 (20.4)	5022 (19.9)
4	1 046 396 (20.0)	931 525 (20.1)	64 108 (19.1)	46 479 (19.2)	4284 (16.9)
5 (highest)	1 047 090 (20.0)	940 158 (20.3)	64 794 (19.4)	38 633 (16.0)	3505 (13.9)
Country of birth					
Sweden	4 527 082 (86.6)	4 016 345 (86.8)	293 392 (87.7)	196 957 (81.5)	20 388 (80.6)
Other Nordic	161 453 (3.1)	137 249 (3.0)	11 973 (3.6)	10 911 (4.5)	1320 (5.2)
Other countries	540 562 (10.3)	473 887 (10.2)	29 308 (8.8)	33 784 (14.0)	3583 (14.2)
Missing	148 (<0.0)	136 (<0.0)	7 (<0.0)	4 (<0.0)	1 (<0.0)

*Describes the characteristics for the population of 5 229 245 between 2009 and 2013. Education level and quantiles of income are based on LISA data from 2011. Diabetes is defined as ICD-10 E11 and/or ATC code-A10B.

ATC, Anatomical Therapeutic Chemical; ICD-10, International Classification of Diseases, 10th Revision; LISA, Longitudinal Integration Database for Health Insurance and Labour Market Studies.

additionally show the baseline characteristics of the total population included as having the extended diabetes diagnosis in online supplemental table 2. Similar to the main study population, out of 5 250 870 Swedish residents, 2 588 027 (49.3%) were male, 2 094 413 (39.9 %) were aged between 45 and 65, and 4 544 298 (86.5%) were born in Sweden. In the characteristics of the men only and women only populations in online supplemental table 3; of 1 535 816 men, 1 128 077 (73.4%) had a BMI of 18.5–24.9 and most aged <45 years (n=950 827; 61.7%); while from the women only cohort, there were 1 222 304 women with 722 852 (59.1%) of these categorised with a BMI of 18.5–24.9 kg/m² and most aged <45 (n=708 446; 57.9%).

Asthma and type 2 diabetes (ICD-10 E11 and/or ATC code A10B)

In participants with asthma, there was an increased odds of type 2 diabetes observed in the total population on adjustment for age and sex (OR 1.44; 95% CI 1.42 to 1.46); and in the fully adjusted model (OR 1.47; 95% CI 1.45 to 1.49). In men among the total population, an association was observed after age-adjusted analyses (OR 1.28; 95% CI 1.25 to 1.30), which was sustained even after full adjustment (OR 1.30; 95% CI 1.27 to 1.32). Similarly, in the women-only population, an increased odds was observed in the age-adjusted analyses (OR 1.60; 95% CI 1.57 to 1.63), which remained even on full adjustment (OR 1.63; 95% CI 1.60 to 1.66).

In the Conscriptio Register (subgroup of men), we observed that, like men in the total population, there was an association observed between asthma and type 2 diabetes. However, on adjustment for BMI, there was an attenuation of the observed odds; (age-adjusted OR, 1.49; 95% CI 1.44 to 1.55 and fully adjusted OR 1.45; 95% CI 1.40 to 1.51). Similarly, in the Medical Birth Register (subgroup of

women), we observed that similar to the women in the total population, there was an association observed which attenuated after adjustment for BMI (age-adjusted OR 2.04; 95% CI 1.97 to 2.12 and fully adjusted OR 1.76; 95% CI 1.68 to 1.84) (table 2).

From the full siblings (same mother and father) identified in the Multi-Generational Register (n=3 153 219), 750 153 were brothers and 822 241 sisters. Among the full siblings of individuals with one disease, the prevalence of the other disease was higher. In index participants who had asthma, the adjusted OR of type 2 diabetes in their relatives was 1.13 (95% CI 1.10 to 1.15) compared with index persons without asthma (table 3). Furthermore, full brothers and full sisters with asthma were at increased odds of type 2 diabetes compared with the relatives of individuals without other disease seen in fully-adjusted models (OR 1.12; 95% CI 1.08 to 1.16 and OR 1.13; 95% CI 1.10 to 1.17, respectively).

Sensitivity analysis

Using the extended diabetes definition also including ICD-10 E12, E13, E14 and O24, online supplemental table 1; we observed, similar to the previous analysis, increased odds of type 2 diabetes in all five cohorts—general population, men among total population, women among total population, men in the Conscriptio Register and women in the Medical Birth Register respectively (fully adjusted OR 1.47; 95% CI 1.45 to 1.49, OR 1.30; 95% CI 1.27 to 1.32, OR 1.63; 95% CI 1.60 to 1.66, OR 1.51; 95% CI 1.45 to 1.56 and OR 2.04; 95% CI 1.96 to 2.11) (online supplemental table 4).

Regardless of whether only the ICD-10 E11 diagnosis or the drug ATC-A10B and all oral hypoglycaemic drug subgroups were considered, the odds of type 2 diabetes remained increased (fully adjusted ORs 1.30 to 1.67), online supplemental tables 5 and 6.

Table 2 ORs for the within-person association between asthma and type 2 diabetes using a type 2 diabetes definition of ICD-10 E11 and/or ATC code A10B

Population	N*	N†	Population included	Model 1 OR (95% CI)	Model 2‡ OR (95% CI)	Model 3‡ OR (95% CI)	Model 4‡ OR (95% CI)
Total population	5 229 245	5 201 728	Male and female	1.37 (1.36 to 1.39)	1.44 (1.42 to 1.46)	1.47 (1.45 to 1.49)	–
Total population (men only)	2 577 583	2 564 529	Male only	1.28 (1.25 to 1.30)	–	1.30 (1.27 to 1.32)	–
Total population (women only)	2 651 662	2 637 199	Female only	1.60 (1.57 to 1.63)	–	1.63 (1.60 to 1.66)	–
Men from Conscription Register	1 535 814	1 407 228	Male only	1.49 (1.44 to 1.55)	–	1.51 (1.45 to 1.56)	1.45 (1.40 to 1.51)
Women from Medical Birth Register	1 223 304	1 221 637	Female only	2.04 (1.97 to 2.12)	–	2.04 (1.96 to 2.11)	1.76 (1.68 to 1.84)

Model 1: age adjusted.
Model 2: adjusted for age, sex*.
Model 3: adjusted for age, sex*, education level, income, birth country.
Model 4: adjusted for age, sex*, education level, income, birth country, body mass index.
*Total number of people in the specified cohort.
†Number of participants in full model.
‡Sex*: This covariate is not included for the men only and female only cohorts.
ATC, Anatomical Therapeutic Chemical; ICD-10, International Classification of Diseases, 10 Revision.

DISCUSSION

In this population-based cross-sectional study, we found an association between current asthma and type 2 diabetes, with a 47% higher prevalence of asthma among those with type 2 diabetes. Although we could not directly account for smoking habits, this relationship sustained after adjusting for BMI, as well as other demographic and socioeconomic factors, as observed in both the male and female populations. The ORs for the female-only population were higher than those for the male-only population. Using different definitions of type 2 diabetes with an extended diabetes definition based on diagnoses from inpatient and outpatient specialist care and/or medication dispenses did not seem to change the observed associations. The familial coaggregation results suggested some shared familial risk factors explaining the association between asthma and type 2 diabetes.

Comparison with previous studies

The relationship between asthma and type 2 diabetes is considered bidirectional.²⁸

Previous studies have shown that there is an increased risk of type 2 diabetes in patients with asthma^{29–30} and of asthma in participants with type 2 diabetes.^{1–31} In the cross-sectional study by Black et al, those with asthma had a higher prevalence of type 2 diabetes.³² Although similar findings were observed in the longitudinal study by Mueller et al, the association between asthma and type 2 diabetes was attenuated after adjustment for BMI. The investigators thus concluded that obesity was an important confounder in this association.² In our study, we also found that obesity was a confounder in the relationship between asthma and type 2 diabetes; however, an association still remains.

In the reverse direction, an association has also been observed between diabetes and adult-onset asthma.³¹ According to Thomsen et al, this association remained even after adjusting for important risk factors like smoking, age and BMI.¹ According to Baek et al, despite similar findings, it was observed that only participants with severe or uncontrolled type 2 diabetes are at higher risk of developing asthma.³¹

Several mediators are possible for the association between asthma and type 2 diabetes. The regular use of oral corticosteroids is

associated with older age at asthma diagnosis.³³ Glucocorticoids are associated with a strong dose-dependent risk for obesity and type 2 diabetes³⁴ and tend to be prescribed in severe asthma. Further, asthma is associated with increased production of IL-6. High levels of chronic systemic IL-6 cause insulin resistance and general metabolic dysfunction. IL-6 impairs the phosphorylation of insulin receptor and insulin receptor substrate-1 by inducing the expression of suppressor of cytokine signalling-3, a potential inhibitor of insulin signalling.³⁵ This is important in the pathogenesis of type 2 diabetes.

Conversely, in the opposite direction, type 2 diabetes may also increase the likelihood of asthma. Hyperglycaemia leads to the production of advanced glycation end-products which induce oxidative stress; the resulting oxidative stress and pro-inflammatory responses cause microvascular damage and may induce dysfunction of the alveolar microvasculature.^{31–36} This may predispose patients with type 2 diabetes to asthma. In the Canadian National Population Health Survey, it was observed that obesity was related to the development of asthma in women but not in men.³⁷ Obesity is associated with more severe asthma and may lead to prescribing inhaled corticosteroids more frequently or at higher doses.³⁸ This may lead to a higher risk of type 2 diabetes,^{39–40} although this was disputed in a Swedish study by Hedberg and Rössner, who concluded that there was no strong evidence to suggest that modern pharmacological asthma treatment may contribute much to the development of obesity in either men or women taking asthma medication.⁴¹ They instead suggested that obesity was a modifiable risk factor for asthma.⁴¹

Furthermore, hyperinsulinaemia, associated with obesity, may inhibit surfactant A and D production by shifting T cells towards a Th2-type response, promote mast cell survival and proliferate and contract airway smooth muscle cells, all predisposing the individual to asthma.⁴² Additionally, obesity is characterised by a low-grade systemic inflammation with increased proinflammatory cytokines and adipokines.⁴⁰

We went further to expand our findings in the familial co-aggregation where even after controlling for co-occurrence of asthma and diabetes in full siblings, we found that there are shared familial factors in this relationship. These shared familial factors could

Table 3 ORs for type 2 diabetes in relatives of individuals with and without asthma

Type of relative	Unique index individuals	Model 1	Model 2	Model 3
Full siblings (total population)	3 153 219	1.20 (1.18 to 1.22)	1.15 (1.13 to 1.17)	1.13 (1.10 to 1.15)
Full siblings (brothers only)	750 153	1.16 (1.12 to 1.20)	1.13 (1.09 to 1.17)	1.12 (1.08 to 1.16)
Full siblings (sisters only)	822 241	1.23 (1.19 to 1.27)	1.18 (1.14 to 1.22)	1.13 (1.10 to –1.17)

1. Adjusted for asthma in relatives and diabetes in index person.
2. Adjusted for sex and age of both relative and index person and asthma in relative.
3. Adjusted for sex, age, income, education level and birth country of both relative and index person and asthma in relative.

be, for example, shared genetic components or lifestyle factors. A previous study on the association between asthma and type 1 diabetes also found familial coaggregation with estimates of (OR 1.27, 95% CI 1.13 to 1.42).⁴³ Although type 1 and type 2 diabetes have different aetiologies and manifestations, shared familial factors could still be similar. Future studies using other genetically informative designs will be able to elucidate how shared familial factors contribute to asthma and type 2 diabetes. For example, estimating shared heritability, linkage disequilibrium score regression, candidate genes or genome-wide cross-trait analyses will be instrumental in the understanding of the comorbidity.

Strengths and limitations

The strengths of our study include its large size, inclusion of the total population and several confounding variables. We also used BMI to account for some residual confounding. However, we acknowledge that BMI information was only available at antenatal booking in the Medical Birth Register (for women) and at call-up in the Conscription Register (for men); the measures were thus taken several years prior to the study period for many individuals. However, it has been shown that BMI tends to be consistent over the life course.

The unavailability of dispensed prescriptions before July 2005 made it impossible to conduct a prospective study, and there would have been no way of knowing which participants had asthma in childhood. Asthma is known to have its onset in childhood, with approximately two thirds of children experiencing remission in childhood. We could not account for this in our study.

Furthermore, we could not account for those who had diabetes but had not yet filled out a prescription or been given an in-patient diagnosis. We could not ascertain that other conditions such as autoimmune diseases may not also coaggregate with asthma and type 2 diabetes as we were unable to adjust for them. While we attempted to exclude all individuals with COPD, we did not conduct a separate analysis looking at this, as analysing individuals with COPD would have necessitated a re-evaluation of the study population and required adjustments to account for differences in disease onset, confounders and thus extended the scope of our analysis.

Our findings may certainly have a clinical application. Although they could be partly due to surveillance bias due to more frequent healthcare contacts in patients with chronic illnesses, as could be the case for other studies in the field. The association between asthma and type 2 diabetes underlines the importance of screening for diabetes.

CONCLUSIONS

We found an association between asthma and type 2 diabetes that remained significant also after adjusting for BMI. We also found that asthma and type 2 diabetes coaggregate in full siblings, indicating that the association is partly due to shared genetic and environmental risk factors. Thus, the family history of either disorder should indicate ascertainment of the other, and future studies should further investigate genetic variants underlying the co-occurrence.

Acknowledgements We wish to thank Aki Tuilainen for data management support, and Dr Samuel Rhedin for contributions to data collection.

Contributors Conception of the work: MM, CJ and CA. Design of the work: all authors. Acquisition of data: AIS, ECO, CL and CA. Analysis of data: MM and CL. Interpretation of analyses: all authors. Drafting the work: MM, CL and CA. Revising critically for important intellectual content: all authors. Guarantors: CL and CA. All authors have approved the final version of the work.

Funding Financial support was provided from the Swedish Research Council (grant no 2018-02640 and 2023-02327), the Swedish Heart-Lung Foundation (grant no 20210416 and 20240974), grants provided by Region Stockholm (ALF project RS2022-0674) and through the Stiftelsen Frimurare Barnhuset i Stockholm.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and ethical approval was obtained from the Regional Ethical Review Board in Stockholm, Sweden (diary number 2013/862-31/5 with amendment 2022-02904-02). No patients or the public were involved in the design, conduct, reporting or dissemination plans of our research. All data were anonymised prior to analyses. The Regional Ethical Review Board in Stockholm approved the study and waived the requirement for informed consent from study participants due to its register-based nature with data linked using individuals' unique personal identification numbers but pseudonymised for research purposes.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Original data are held by Swedish National Board of Health and Welfare and Statistics Sweden. Due to Swedish data storage laws, we cannot make the data publicly available. However, any researcher can access the data by obtaining an ethical approval from the Swedish

Ethical Review Authority and thereafter asking the registers for the original data. Pseudonymised data can also be provided from the principal investigator of this study on request after providing a reasonable proposal and if an appropriate data sharing agreement with Karolinska Institutet can be established.

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Remissão clínica precoce e o seu papel no declínio da função pulmonar e nas exacerbações em adultos coreanos com asma

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/thorax-2024-222679>).

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Received 1 November 2024
Accepted 17 February 2025
Published Online First 6 March 2025



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To cite: Bae E, Park H-J, Park H, et al. *Thorax* 2025;80:273–282.

RESUMO

Introdução Apesar dos avanços no tratamento da asma, muitos doentes continuam a apresentar um controlo deficiente da doença, declínio da função pulmonar e exacerbações frequentes. A remissão clínica (RC) tem sido proposta como um novo objetivo terapêutico e marcador substituto para resultados a longo prazo. Este estudo avalia se a RC precoce, um ano após o início dos corticosteroides inalados (CSI), influencia o declínio da função pulmonar e o risco de exacerbações na asma.

Métodos Este estudo de coorte retrospectivo avaliou 492 doentes com asma tratados com CSI em dois hospitais universitários. Os doentes foram classificados em dois grupos: RC precoce e não RC precoce. A RC precoce foi definida com base num conjunto de critérios compostos, incluindo ausência sustentada de exacerbações, não utilização de corticosteroides sistêmicos, controlo dos sintomas e função pulmonar estável ou melhorada no primeiro ano após o início dos CSI. Os resultados do estudo foram o declínio anual do volume expiratório forçado no primeiro segundo (FEV₁) e as exacerbações moderadas a graves. Resultados A RC precoce esteve significativamente associada a um declínio anual mais lento do FEV₁ (RC com 4 componentes, β ajustado = 31,6 mL/ano, $p = 0,001$; RC com 3 componentes, β ajustado = 15,7 mL/ano, $p = 0,043$). Os benefícios da RC precoce com 4 componentes na atenuação do declínio anual do FEV₁ foram mais evidentes em fenótipos específicos, incluindo asma tipo 2 elevada, limitação persistente do fluxo aéreo, asma grave e doentes que necessitam de antagonistas muscarínicos de longa duração como terapêutica adicional. A RC precoce com 4 componentes esteve associada a um risco reduzido de exacerbações moderadas a graves (HR ajustado = 0,591, $p = 0,011$) e de exacerbações graves (HR ajustado = 0,508, $p = 0,025$).

Conclusões Alcançar a RC no prazo de um ano após o início dos CSI esteve associado à preservação da função pulmonar e à redução do risco de exacerbações. Estes resultados sugerem a importância de alcançar a RC precoce como objetivo clínico na gestão da asma.

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways, characterised by variable and recurring symptoms, reversible airflow obstruction and bronchial hyper-responsiveness. Despite advances in therapeutic strategies, a considerable proportion of asthma patients continue to experience poor disease control, accelerated lung function decline and frequent exacerbations.^{1–3} Individual responses to inhaled corticosteroids (ICSs) vary considerably according to the underlying phenotypic heterogeneity of asthma.^{4,5} This phenotypic heterogeneity is associated with diverse inflammatory patterns and endotypes, among which eosinophilic and non-eosinophilic subtypes are particularly prominent.⁶ The patterns of

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Clinical remission (CR) has been proposed as a critical therapeutic goal in asthma management. However, evidence on the long-term influence of CR on attenuating lung function decline and reducing risk of exacerbations remains limited.

WHAT THIS STUDY ADDS

► Achieving early CR within 1 year of inhaled corticosteroid initiation is associated with slower lung function decline and a lower risk of exacerbations. The benefits of early CR on attenuating annual forced expiratory volume in 1 s decline were more pronounced in patients with type-2 high asthma, persistent airflow limitation, severe asthma and those on add-on long-acting muscarinic antagonists.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► This study underscores the importance of early CR as a clinical goal and highlights the need for personalised asthma management strategies. These findings can inform clinical guidelines and drive future research on improving long-term outcomes in asthma patients.

pathobiological inflammation in asthma patients are linked to disease severity, airway remodelling and comorbidities, all of which reportedly influence treatment outcomes.^{4,6,7}

Disease modification in asthma refers to strategies aimed at altering the natural trajectory of the disease by suppressing airway inflammation, mitigating structural changes and preserving lung function.⁸ In this context, clinical remission (CR) has been highlighted as a novel treatment goal for asthma management. Unlike traditional goals such as symptom control or exacerbation prevention, CR encapsulates sustained symptom resolution, stabilisation of lung function and minimal therapeutic burden.⁹ Given the phenotypic and endotypic heterogeneity in asthma, it is necessary to evaluate whether CR can be considered as a treatment goal to improve long-term outcomes in asthma patients treated with ICS.

Lung function decline and asthma exacerbations can serve as indicators of how effectively underlying pathological inflammation is being controlled. Lung function decline, particularly the annual rate of decline in forced expiratory volume in 1 s (FEV₁), is an indicator closely associated with airway remodelling and airway hyper-responsiveness in asthma.¹⁰ Asthma exacerbations reflect inadequate disease control and link to accelerated lung function decline.¹¹ These clinical outcomes are associated with the prognosis of asthma patients.^{12,13} However, the long-term influence of CR on attenuating lung function decline and reducing the risk of exacerbations has been insufficiently explored.

Therefore, this study aimed to evaluate the long-term clinical outcomes associated with achieving CR within 1 year after ICS initiation, with patients stratified into early and non-Early CR groups.

METHODS

Study design and participants

Our study adhered to the principles delineated in the Strengthening the Reporting of Observational Studies in Epidemiology) statement.¹⁴

Study design and participants

The present retrospective cohort study evaluated asthma patients at two teaching hospitals between January 2010 and December 2023. The inclusion criteria were as follows: (1) patients diagnosed with asthma aged 18 years or older, (2) treatment with ICS during the observation period, (3) annual laboratory tests and spirometry measurements performed using consistent methodologies and (4) a minimum follow-up duration of 2 years. Asthma diagnosis was confirmed based on the presence of variable respiratory symptoms and evidence of variable expiratory airflow limitation, as defined in the Global Initiative for Asthma (GINA) 2024 report¹⁵. Variable expiratory airflow limitation was confirmed by meeting one or more of the following criteria: (1) positive bronchodilator responsiveness (BDR), defined as an increase in FEV₁ of $\geq 12\%$ and ≥ 200 mL following the administration of 400 µg salbutamol; (2) improvement in lung function after treatment, defined as an increase in FEV₁ of $\geq 12\%$ and ≥ 200 mL following 4–8 weeks of controller therapy (eg, ICS or ICS-long-acting beta-agonist (LABA)) or (3) excessive variation in lung function between visits, characterised by documented variability in FEV₁ of $>12\%$ and >200 mL on at least two occasions over time. Outpatient visits for exacerbation monitoring and symptom control evaluation occurred at least three times per year for all patients.

Variables

Baseline characteristics were collected, including age, sex, body mass index, smoking status and cigarette pack-years in ever-smokers, and socioeconomic status. Underlying comorbidities such as chronic rhinosinusitis and nasal polyp were identified, and the Charlson comorbidity index was assessed. Emphysema, bronchiectasis and interstitial lung disease or interstitial lung abnormalities were evaluated based on radiologists' reports from chest CT scans. Laboratory data included blood eosinophil counts, total IgE levels, positivity for specific IgE and fractional exhaled nitric oxide (FeNO) levels. Spirometric assessments were performed including prebronchodilator and postbronchodilator FEV₁, forced vital capacity (FVC), FEV₁/FVC ratio and BDR.

Clinical features were assessed at 1 year after initiating ICS therapy to allow for an adequate observation period necessary to reliably determine asthma severity and the appropriateness of the treatment regimen.¹⁶ These assessments included clinical phenotypes of asthma, symptom control status—measured using the Asthma Control Test (ACT) score—and asthma severity. Type 2-high asthma was defined as the presence of blood eosinophils ≥ 150 cells/µL in conjunction with FeNO ≥ 25 ppb. Conversely, type 2-low asthma was defined as the presence of blood eosinophils <150 cells/µL and FeNO <25 ppb. Persistent airflow limitation (PAL) was defined as a postbronchodilator FEV₁/FVC ratio of <0.7 at the initiation of ICS therapy, measured during stable disease con-

ditions. Asthma severity was assessed 1 year after ICS initiation, following an adequate observation period to determine the treatment level required for disease control, ensuring it reflects both intrinsic disease burden and treatment response. Asthma severity was classified based on the GINA 2024 report.¹⁵ Mild asthma was defined as being well controlled with low-dose ICS, as-needed ICS/LABA or as-needed ICS with short-acting beta-agonist (SABA). Moderate asthma was defined as being well controlled with low-dose or medium-dose ICS/LABA. Severe asthma was defined as requiring high-dose ICS/LABA or remaining uncontrolled despite high-dose ICS/LABA. Low-dose, medium-dose and high-dose ICS were defined in accordance with the GINA 2024 report.¹⁵ For example, budesonide is categorised as low-dose at 200 to 400 µg/day, medium dose at >400 to 800 µg/day and high dose at >800 µg/day. Treatment regimens were meticulously documented, including the use of LABAs, ICS dosages, specific ICS drugs prescribed, reliever medications such as ICS-formoterol and SABA, and add-on therapies such as long-acting muscarinic antagonists (LAMAs), leukotriene receptor antagonists (LTRAs), theophylline and systemic corticosteroids.

Patient group definition

The index date was defined as the initiation of ICS therapy, and CR was evaluated over a 1-year exposure assessment window postindex. CR was assessed using two definitions: (1) 4-component CR, requiring the absence of asthma exacerbations, well-controlled asthma symptoms (ACT score ≥ 20), no need for systemic corticosteroids and stable or normal lung function (postbronchodilator FEV₁ decline $\leq 5\%$ predicted or postbronchodilator FEV₁ $\geq 80\%$ predicted) and (2) 3-component CR, defined similarly but excluding the lung function criterion.¹⁷ Patients were classified as either early CR or non-early CR based on whether CR was achieved at 1 year after ICS initiation.

Outcomes

The study outcomes were the annual rate of FEV₁ decline (mL/year) and acute exacerbation events. The evaluation of study outcomes commenced 1 year after the initiation of ICS treatment. The severity of asthma exacerbations was classified based on the previous guidance.¹⁸ Moderate asthma exacerbations were defined by at least one of the following: (1) deterioration in symptoms, (2) deterioration in lung function or (3) increased use of reliever medication. Severe asthma exacerbations were defined as either (1) the use of systemic corticosteroids or (2) hospitalisation or an emergency room visit. Moderate-to-severe exacerbations were defined as the occurrence of at least one moderate or severe asthma exacerbation.

Statistical analysis

Between-group comparisons were conducted using the χ^2 test or Fisher's exact test for categorical variables and Student's t-test or Wilcoxon rank-sum test for continuous variables.

The annual rate of FEV₁ decline was analysed using univariable and multivariable linear mixed-effects models. Subgroup analyses were performed to evaluate the impact of early CR on the annual FEV₁ decline rate across specific phenotypes, including type 2-high or type 2-low asthma, asthma with PAL, asthma severity, type of reliever medication (ICS-formoterol or SABA) and the use of add-on LAMA therapy.

The time to exacerbation event was analysed with Kaplan-Meier survival curves. Univariable and multivariable HRs for exacerbations were estimated using Cox proportional hazard models.

To identify confounding factors and ensure robust multivariable analyses, we constructed a directed acyclic graph to map the causal relationships between early CR achievement, study outcomes and other covariables (online supplemental information 1). We performed sensitivity analyses for unmeasured confounding using Oster's Delta Method for beta-coefficient and E-values for HR to estimate the robustness of our findings against potential unmeasured confounding.

Statistical significance was defined as a $p < 0.05$. Data analyses were performed using R statistical software (V.4.4.1).

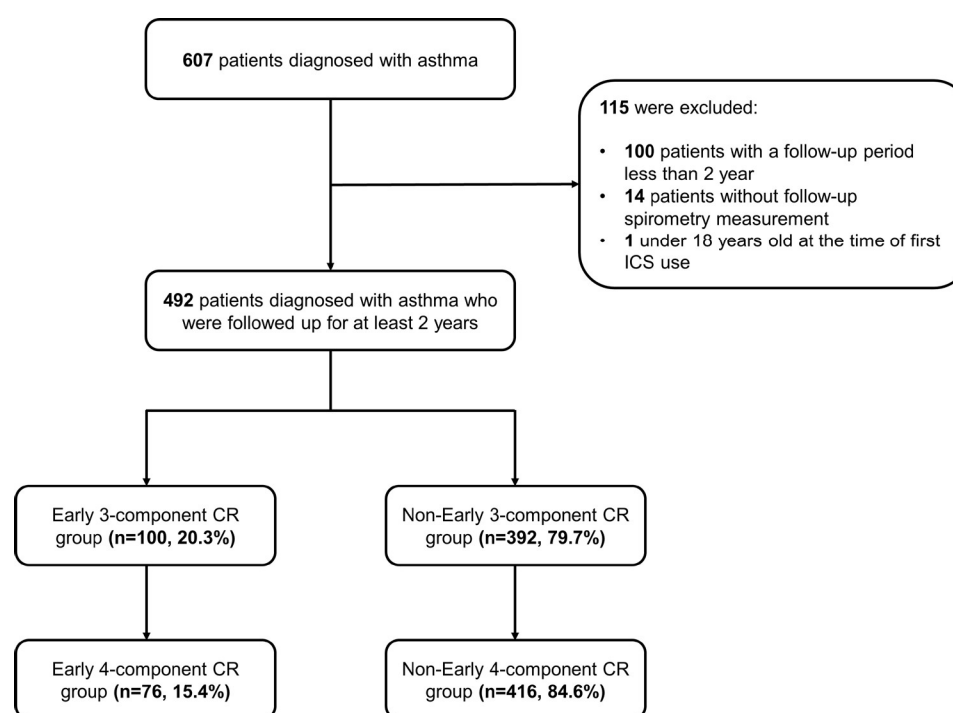


Figure 1 Flow diagram of patient inclusion. CR, clinical remission; ICS, inhaled corticosteroid.

RESULTS

Study population

A total of 607 patients with asthma were assessed for eligibility in this study (figure 1). Of these, 100 patients were excluded due to a follow-up period of less than 2 years, 14 patients did not undergo annual spirometric assessments during the observation period and 1 patient was diagnosed with asthma before the age of 18. This resulted in a final cohort of 492 patients who were eligible for the present study. These patients were stratified into two groups based on CR achievement at the 1-year follow-up time point: 100 patients (20.3%) were classified into the early 3-component CR group and 76 patients (15.4%) were classified into the early CR group. The median follow-up period was 89 (IQR=35–124) months for the early 4-component CR group, 95 (IQR=47–127) months for the non-early 4-component CR group. The percentages of patients meeting specific CR criteria are summarised in online supplemental information 2.

Baseline characteristics

The baseline characteristics of the early and non-early CR groups are summarised in table 1 and online supplemental information 3. The early 4-component CR group had a significantly higher proportion of ex-smokers. Among comorbidities, nasal polyps were significantly more prevalent in the early 4-component CR group. Radiological findings showed no significant differences between groups. In laboratory findings, the early 4-component CR group showed a slightly higher median blood eosinophil count and IgE level, although these differences were not statistically significant. FeNO levels were comparable between groups. Spirometric assessments showed no significant differences between the early and non-early 4-component CR groups in baseline prebronchodilator and postbronchodilator FEV₁, FVC, FEV₁/FVC ratio and BDR.

Clinical features 1 year after ICS therapy

One year after initiating ICS therapy, the early 4-component CR group demonstrated higher ACT scores (table 2). The early 4-component CR group showed a numerically higher proportion of type 2-high asthma and lower proportion of severe asthma without statistical significance. We found no significant differences in treatment patterns between the early and non-early 4-component CR groups. Similar results were found between the early and non-early 3-component CR groups (online supplemental information 4).

Annual FEV₁ decline rate

When examining the FEV₁ over time, the significant differences between the early CR and the non-early CR groups remained consistent throughout the observation period (all comparisons, $p < 0.001$, figure 2).

Specifically, the annual FEV₁ decline rate was significantly attenuated in the early 4-component CR group compared with the non-early 4-component CR group (adjusted $\beta = 31.6$ mL/year (95% CI=12.5 to 51.2, $p = 0.001$)) and in the early 3-component CR group compared with the non-early 3-component CR group (adjusted $\beta = 15.7$ mL/year (95% CI=0.5 to 30.8, $p = 0.043$)), table 3). These results remained robust even after accounting for potential unmeasured confounding factors (online supplemental information 5).

Significant interactions were observed in the effect of Early CR on the annual FEV₁ decline rate across specific subgroups (table 3). The early 4-component CR group was more associated with a reduced annual FEV₁ decline rate in subgroup population with type 2-high asthma ($\beta = 35.7$ mL/year (95% CI=2.0 to 69.4, $p = 0.038$), asthma with PAL ($\beta = 43.3$ mL/year (95% CI=23.6 to 63.5, $p = 0.023$)), severe asthma ($\beta = 31.4$ mL/year (95% CI=1.2 to 61.9, $p = 0.044$)) and those treated with add-on LAMA ($\beta = 15.5$ mL/year (95% CI=6.6 to 24.3, $p < 0.001$)). The early 3-component CR group was more associated with a reduced annual FEV₁ decline rate in subgroup population with asthma with PAL ($\beta = 41.5$ mL/year (95% CI=11.6 to 71.0, $p = 0.006$)), severe asthma ($\beta = 36.7$ mL/year (95% CI=2.5 to 71.6, $p = 0.039$)) and those treated with ICS-formoterol reliever ($\beta = 17.0$ mL/year (95% CI=3.2 to 30.3, $p = 0.014$)).

Acute exacerbations

In the Kaplan-Meier curves, the early CR groups had a significantly prolonged time to first moderate-to-severe exacerbation compared with the non-early CR groups (early 4-component CR, log-rank $p = 0.004$; early 3-component CR, log-rank $p = 0.045$; figure 3). Additionally, the time to severe exacerbation was significantly longer in the early CR groups compared with the non-early CR groups (early 4-component CR, log-rank $p = 0.032$; early 3-component CR, log-rank $p = 0.037$).

The early 4-component CR group showed a significantly reduced hazard for moderate-to-severe exacerbations (adjusted HR (aHR)=0.591 (95% CI=0.394 to 0.887), $p = 0.011$) in the multivariable Cox regression model (table 4). Similarly, the hazard for severe exacerbations was significantly lower in the early 4-component CR group (aHR=0.508 (95% CI=0.280 to 0.920), $p = 0.025$). In

Table 1 Baseline characteristics of asthma patients

	Early 4-component CR group (n=76)	Non-early 4-component CR group (n=416)	P value
Age, years, median (IQR)	64 (58–71)	65 (58–72)	0.711
Male sex, n (%)	60 (78.9)	284 (68.3)	0.084
BMI, kg/m ² , median (IQR)	24.4 (20.8–26.0)	23.7 (21.6–25.9)	0.660
Smoking history			
Never smoker, n (%)	19 (25.0)	151 (36.3)	0.076
Ex-smoker, n (%)	47 (61.8)	187 (45.0)	0.010
Current smoker, n (%)	10 (13.2)	78 (18.8)	0.314
Pack-years in ever-smokers, median (IQR)	30 (15–47)	30 (15–50)	0.789
Socioeconomic status			
Medicaid, n (%)	4 (5.3)	25 (6.0)	1.000
Underlying comorbidities			
Chronic rhinosinusitis, n (%)	20 (26.3)	87 (20.9)	0.369
Nasal polyp, n (%)	3 (3.9)	2 (0.5)	0.032
Charlson Comorbidity Index			
1, n (%)	24 (31.6)	121 (29.1)	0.763
2–3, n (%)	20 (26.3)	155 (37.3)	0.089
>3, n (%)	32 (42.1)	140 (33.7)	0.197
Radiologic findings			
Emphysema, n (%)	31 (40.8)	149 (35.8)	0.485
Bronchiectasis, n (%)	17 (22.4)	112 (26.9)	0.491
ILD or ILA, n (%)	6 (7.9)	14 (3.4)	0.128
Laboratory tests			
Blood eosinophil count, median (IQR)	249 (133–378)	188 (105–374)	0.144
≥300/μL, n (%)	30 (39.5)	139 (33.4)	0.373
Total IgE, median (IQR)	168 (28–683)	130 (33–596)	0.669
Positive for specific IgE, n (%)	39 (51.3)	200 (48.1)	0.693
FeNO, median (IQR)	26 (21–40)	27 (16–45)	0.668
≥50 ppb, n (%)	10 (13.2)	47 (11.3)	0.786
Spirometric assessments			
Pre-BDR FEV ₁ , L, median (IQR)	2.14 (1.78–2.38)	2.03 (1.76–2.30)	0.066
Pre-BDR FEV ₁ , %, median (IQR)	81 (80–84)	82 (80.5–84)	0.118
Pre-BDR FVC, L, median (IQR)	3.10 (2.69–4.00)	3.05 (2.05–3.78)	0.175
Pre-BDR FVC, %, median (IQR)	88 (75–103)	90 (79–103)	0.652
Pre-BDR FEV ₁ /FVC, %, median (IQR)	65 (57–76)	65 (56–75)	0.998
Post-BDR FEV ₁ , L, median (IQR)	2.41 (1.98–2.70)	2.28 (1.96–2.59)	0.056
Post-BDR FEV ₁ , %, median (IQR)	91 (90–94)	92 (90.5–94)	0.099
Post-BDR FVC, L, median (IQR)	3.20 (2.68–4.11)	3.19 (2.52–3.90)	0.294
Post-BDR FVC, %, median (IQR)	90 (81–105)	93 (81–105)	0.384
Post-BDR FEV ₁ /FVC, %, median (IQR)	71 (63–82)	71 (62–82)	0.616
Positive bronchodilator responsiveness, n (%)	45 (59.2)	211 (50.7)	0.216

BDR, bronchodilator responsiveness; BMI, body mass index; CR, clinical remission; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GERD, gastro-oesophageal reflux disease; ILA, interstitial lung abnormality; ILD, interstitial lung disease; ppb, parts per billion.

sensitivity analyses accounting for unmeasured confounding, the early 4-component CR group demonstrated robust associations with reduced risks of exacerbations (online supplemental information 6). While the early 3-component CR group also showed a significantly reduced hazard for moderate-to-severe and severe exacerbations in univariable analyses, this statistical significance was not retained in the multivariable analysis.

DISCUSSION

Our study evaluated the long-term clinical outcomes of asthma patients according to 4-component and 3-component CR achievement at 1 year after ICS initiation, focusing on its effects on lung function decline and exacerbation risk. Our results indicate that

early CR is associated with a significantly attenuated annual decline in FEV₁ compared with non-early CR, with a stronger effect size observed in the early 4-component CR group than in the early 3-component CR group. Notably, the benefits of early CR on FEV₁ decline were more evident in specific subgroups, including patients with type 2-high asthma, asthma with PAL, severe asthma or those receiving ICS-formoterol reliever or add-on LAMA therapy. These findings suggest that the effectiveness of achieving early CR may be modulated by underlying asthma phenotypes and treatment regimens. In terms of exacerbation outcomes, early CR was linked to a prolonged time to the first moderate-to-severe and severe exacerbation compared with non-CR. Especially, the early 4-component CR group demonstrated a significantly reduced hazard for both

Table 2 Clinical features at 1 year following ICS therapy

	Early 4-component CR group (n=76)	Non-early 4-component CR group (n=416)	P value
Asthma phenotypes			
Type 2-high asthma, n (%) [*]	37 (48.7)	156 (37.5)	0.088
Type 2-low asthma, n (%) [†]	11 (14.5)	87 (20.9)	0.256
Asthma with PAL, n (%) [‡]	36 (47.4)	204 (49.0)	0.886
Symptom control status			
ACT, median (IQR)	22 (21–24)	20 (20–22)	<0.001
Asthma severity			
Mild	8 (10.5)	39 (9.4)	0.919
Moderate	60 (78.9)	300 (72.1)	0.273
Severe	8 (10.5)	77 (18.5)	0.127
Treatment			
Controller			
ICS/LABA	70 (92.1)	370 (88.9)	0.534
ICS monotherapy	6 (7.9)	46 (11.1)	
ICS dose			
Low-dose ICS	37 (51.3)	173 (41.6)	0.147
Medium-dose ICS	29 (38.2)	182 (43.8)	0.436
High-dose ICS	8 (10.5)	61 (14.7)	0.438
Specific ICS drugs			
Beclomethasone dipropionate	2 (2.6)	26 (6.2)	0.326
Budesonide	33 (43.4)	156 (37.5)	0.397
Ciclesonide	3 (3.9)	23 (5.5)	0.774
Fluticasone furoate	12 (15.8)	66 (15.9)	1.000
Fluticasone propionate	26 (34.2)	145 (34.9)	1.000
Reliever			
ICS-formoterol	35 (46.1)	182 (43.8)	0.806
SABA	41 (53.9)	234 (56.2)	
Add-on LAMA, n (%)	37 (48.7)	202 (48.6)	1.000
Biologics, n (%)	1 (1.3)	4 (1.0)	1.000
Oral medication			
Xanthine, n (%)	24 (31.6)	162 (38.9)	0.276
LTRA, n (%)	32 (42.1)	186 (44.7)	0.768
Oral steroid, n (%)	0 (0.0)	13 (3.1)	0.241

^{*}Type 2-high asthma was defined as the presence of blood eosinophils ≥ 150 cells/ μ L along with FeNO ≥ 25 ppb.

[†]Type 2-low asthma was defined as the presence of blood eosinophils < 150 cells/ μ L along with FeNO < 25 ppb.

[‡]Asthma with PAL was defined as post-bronchodilator FEV₁/FVC < 0.7 at both the initiation of ICS therapy and 1 year after ICS therapy.

ACT, asthma control test; CR, clinical remission; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroids; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; PAL, persistent airflow limitation; SABA, short-acting beta-agonist.

moderate-to-severe exacerbations and severe exacerbations, underscoring its potential role in reducing future risk of exacerbations. In contrast, the early 3-component CR group did not show a significant reduction in hazard of acute exacerbations. These findings highlight the importance of incorporating stable lung function criteria in defining CR, as they may provide a more comprehensive reflection of underlying airway stability and disease control.

CR can be achieved in asthma patients treated with ICS, extending beyond the conventional concept of ‘good asthma control’. Generally, ‘good asthma control’ aims to minimise symptoms and manage exacerbation risk.¹⁹ When symptom control is maintained and no exacerbations occur for several months, asthma is considered well controlled, and ICS dose reduction is often initiated to minimise long-term adverse effects of ICS.¹⁵ In contrast, CR represents a more durable absence of symptoms, marked by the elimination of exacerbations requiring systemic corticosteroids and stabilisation of lung function for at least a year.¹⁹ CR differs fundamentally from ‘good asthma control’ by focusing on the elimination of airway inflammation as a central consideration.¹⁹ In our study,

early CR is speculated to contribute to reducing underlying pathological inflammation, as reflected by its association with attenuated FEV₁ decline and fewer exacerbations. Nonetheless, CR should not be conflated with concepts like complete remission, cure or disease modification, which imply the normalisation of underlying pathological states such as small airway remodelling and the absence of disease signs and symptoms without ongoing treatment.^{9, 20} Additionally, the challenge still remains that CR has been defined variably across countries and clinical studies, which limits its applicability in clinical practice.^{21, 22}

The prevalence of CR varies widely across studies, depending on the definitions and observation periods used. In the patients with severe eosinophilic asthma, biologics have been shown to induce CR in 14%–36%, while ICS with or without LABA therapy has reported CR rates ranging from 4% to 25%.^{23–28} A recent meta-analysis estimated a pooled CR rate of 30%–38% among patients with severe asthma treated with biologics.²⁹ In our study, approximately 15%–20% of patients met the criteria for early CR, a relatively lower rate compared with previous reports. This difference may be

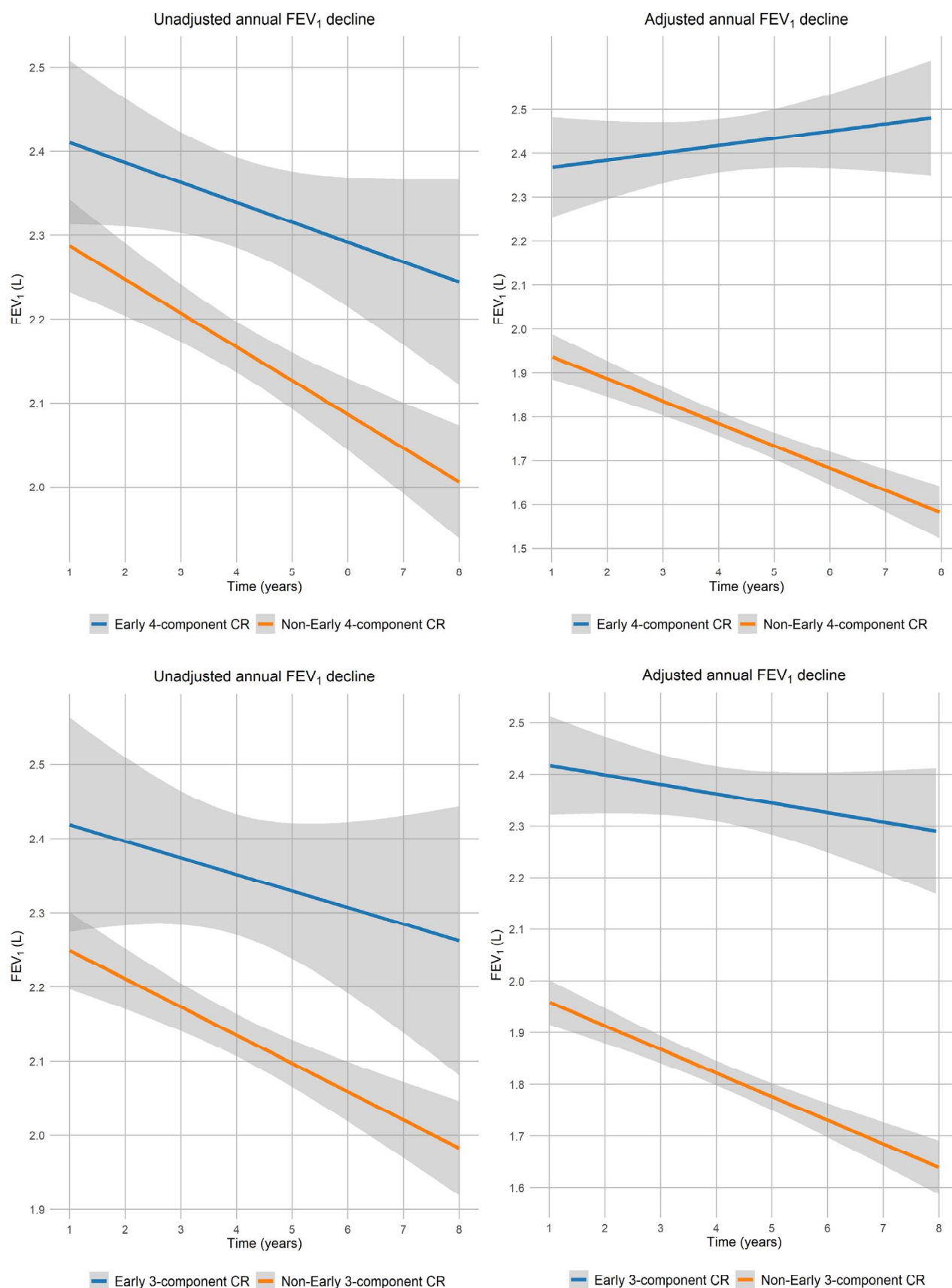


Figure 2 Annual FEV₁ change according to the CR status. The adjusted annual FEV₁ decline rate was estimated using covariables including age, sex, body mass index, smoking history, Medicaid status, chronic rhinosinusitis, emphysema, bronchiectasis, post-BDR FEV₁ (%), type 2-high or type 2-low phenotype, persistent airflow limitation, Asthma Control Test score, asthma severity, reliever, add-on LAMA, xanthine and LTRA. BDR, bronchodilator responsiveness; CR, clinical remission; FEV₁, forced expiratory volume in 1 s; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist.

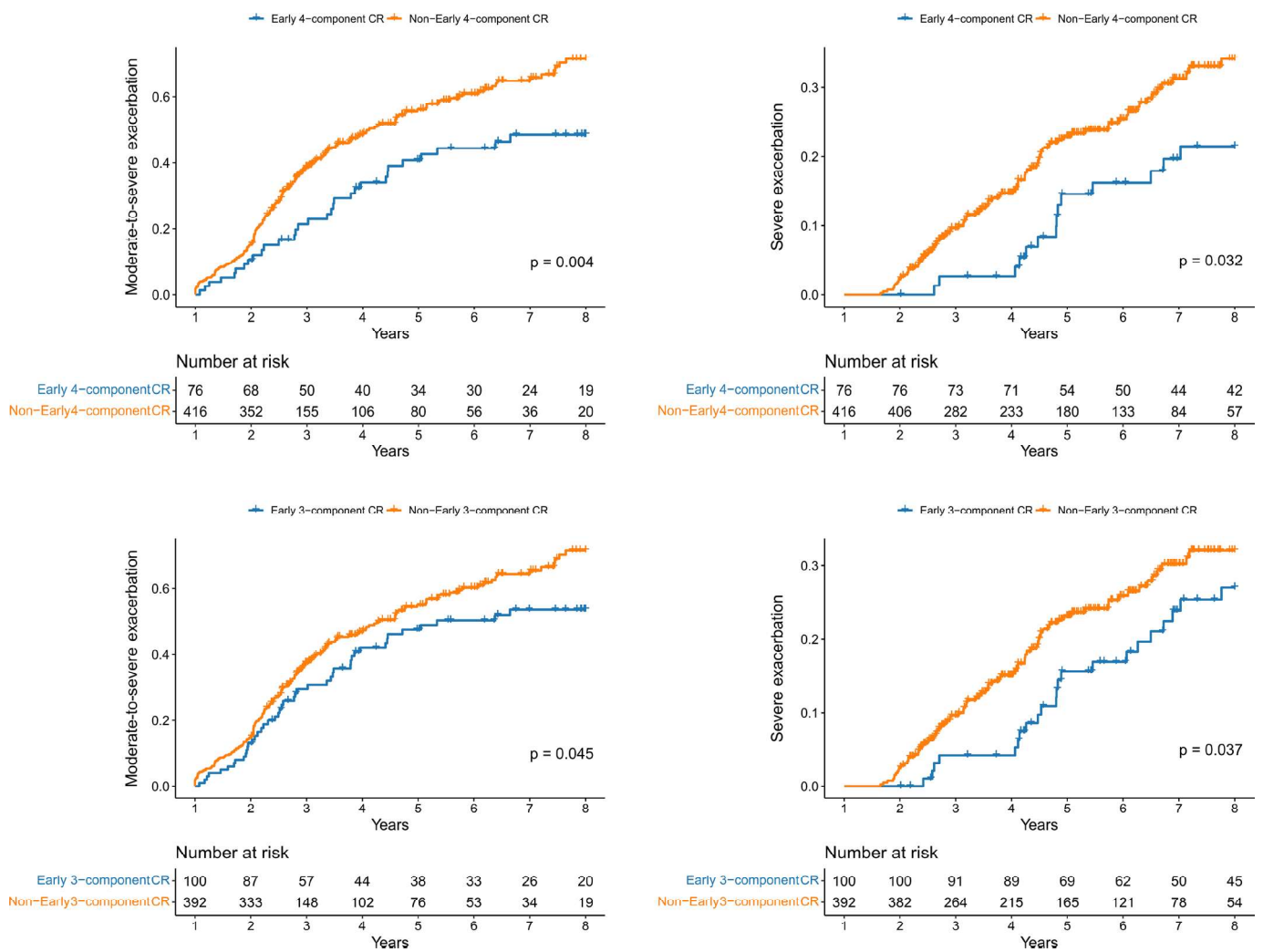


Figure 3 Time to exacerbation according to the CR status. CR, clinical remission.

explained by the limited use of biologics and the high prevalence of respiratory comorbidities in our cohort. Specifically, the use of biologics was rare, likely contributing to the lower CR rate. Indeed, the CR rates observed in our study are comparable to those reported for control groups receiving ICS without biologics in randomised controlled trials.^{24 27 28} Conversely, LTRA was used in approximately 44% of patients, reflecting the frequent use of LTRA in Korean clinical practice, as previous studies have shown usage rates nearing 50%.³⁰ The strict national insurance coverage criteria for biologics in Korea may explain the preference for LTRA as an alternative.

Additionally, our cohort included a significant proportion of asthma patients with PAL, reflecting the high prevalence of parenchymal destruction observed among asthma patients in Korea. Although the national smoking burden has been on a declining

trend, it remains substantial.³¹ Furthermore, the prevalence of mycobacterial infections in Korea is notably higher than in other developed countries.^{32,33} Notably, the prevalence of bronchiectasis among asthma patients in Korea was reported at approximately 17%, a rate significantly higher than that observed in other populations.³⁴

This study has several limitations. First, as a retrospective cohort study, it may be subject to bias from unmeasured confounding factors, despite efforts to adjust for known covariates. Potential confounders include socioeconomic or environmental factors, inspiratory flow, inhaler technique, the frequency of medication adjustments and the duration of treatment adherence assessment. Second, our study has a risk of selection bias given the predominance of moderate and severe asthma cases. This phenomenon likely reflects the patient population typically seen in teaching

Table 4 Cox regression analysis for acute exacerbation				
	Univariable Cox regression model		Multivariable Cox regression model*	
	HR (95% CI)	P value	HR (95% CI)	P value
Moderate-to-severe exacerbation				
Early 4-component CR (reference: non-early 4-component CR)	0.569 (0.388 to 0.836)	0.004	0.591 (0.394 to 0.887)	0.011
Early 3-component CR (reference: non-early 3-component CR)	0.714 (0.513 to 0.994)	0.046	0.786 (0.555 to 1.113)	0.175
Severe exacerbation				
Early 4-component CR (reference: non-early 4-component CR)	0.543 (0.308 to 0.957)	0.035	0.508 (0.280 to 0.920)	0.025
Early 3-component CR (reference: non-early 3-component CR)	0.701 (0.501 to 0.981)	0.038	0.709 (0.433 to 1.163)	0.173
*The adjusted annual FEV ₁ decline rate was estimated using covariables including age, sex, body mass index, smoking history, Medicaid status, chronic rhinosinusitis, emphysema, bronchiectasis, post-BDR FEV ₁ (%), type 2-high or type 2-low phenotype, persistent airflow limitation, Asthma Control Test score, asthma severity, reliever, add-on LAMA, xanthine and LTRA. BDR, bronchodilator responsiveness; CR, clinical remission; FEV ₁ , forced expiratory volume in 1 s; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist.				

hospitals. In addition, as the quality of inhaler technique remains unknown, it is possible that some cases of difficult-to-treat asthma were included among severe asthma patients, contributing to the high prevalence of severe asthma observed. Third, the study population was limited to patients from two teaching hospitals, which may restrict the generalisability of the findings to broader, more diverse asthma populations or to those managed in primary care settings. Fourth, although we stratified patients based on the timing of CR achievement, longitudinal assessments of airway inflammation markers, such as sputum eosinophil counts, were unavailable, limiting our ability to comprehensively evaluate the inflammatory control associated with CR. Fifth, due to the observational nature of this study, certain information could not be definitively obtained. Electronic medical records lacked details on the onset of asthma and associated symptoms. The prevalence of CRS and nasal polyps may have been underestimated, as not all patients with nasal symptoms underwent evaluation by an otolaryngologist. Additionally, causal relationships between CR timing and long-term outcomes, such as lung function decline and exacerbation risk, cannot be definitively established. Prospective studies are needed to validate these findings and further elucidate the mechanisms by which CR timing impacts asthma prognosis.

CONCLUSIONS

Our findings suggest that achieving early CR, particularly as defined by the 4-component criteria, may play an important role in improving long-term asthma outcomes. Early CR was associated with slower lung function decline and a lower risk of exacerbations, reflecting its potential as a comprehensive marker of airway stability. These effects were more evident in specific subgroups, such as patients with type 2-high asthma and PAL, highlighting the importance of considering individual phenotypes when evaluating CR. Incorporating early CR as a clinical target would help guide treatment strategies for asthma, though further studies are needed to validate its broader application.

Contributors Study concept and design: HWL. Acquisition of data: H-JP, HP, J-KL, EYH, CHL, DKK and HWL. Analysis and interpretation of data: EB, J-KL, CHL, DKK and HWL. Drafting the manuscript: EB and HWL. Critical revision of the manuscript and important intellectual content: J-KL, CHL, DKK and HWL. Study supervision: HWL. Guarantor: HWL.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study was conducted in accordance with the Declaration of Helsinki and received approval from the Institutional Review Board of the Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center (IRB no. 20-2024-10). The requirement for written informed consent was waived due to the retrospective nature of the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from IRB Committee of SNU-SMG Boramae Medical Center on reasonable request.

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ARTIGO ORIGINAL

Impacto da DPOC nos fatores de risco cardiovascular e nos desfechos em pessoas com doença cardiovascular estabelecida

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/thorax-2023-220991>).

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Received 19 September 2023
Accepted 11 February 2025
Published Online First 3 March 2025



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To cite: Cho EE, MacLagan LC, Chu A, et al. *Thorax* 2025;80:291–299.

RESUMO

Contexto Sabe-se pouco sobre a associação entre a doença pulmonar obstrutiva crônica (DPOC) e a doença cardiovascular (DCV) em pessoas com DCV já diagnosticada. Compreender se a DPOC está associada a um maior risco de eventos cardiovasculares pode orientar estratégias adequadas de prevenção secundária.

Objetivo Analisar o risco de eventos cardiovasculares adversos maior (MACE — enfarte agudo do miocárdio, AVC e morte cardiovascular) em pessoas com DCV conhecida, numa população real abrangente de uma grande província.

Métodos Estudo de coorte populacional retrospectivo, utilizando dados administrativos de saúde, medicação, análises laboratoriais, registros médicos eletrônicos e outras fontes da província de Ontário, Canadá. Foram incluídas todas as pessoas com histórico de DCV, com e sem diagnóstico médico de DPOC em 2008, acompanhadas até 2016. Foram comparados fatores de risco cardiovascular, fatores sociodemográficos, comorbidades e outros fatores. Modelos de risco específico por causa, ajustados para estes fatores, determinaram o risco de MACE em pessoas com DPOC.

Resultados Entre os 496 056 indivíduos com DCV em Ontário a 1 de janeiro de 2008, 69 161 (13,9%) tinham DPOC. Os MACE ocorreram com maior frequência entre os que tinham DCV e DPOC (45,3 por 1000 pessoas-ano) em comparação com os que tinham apenas DCV (28,6 por 1000 pessoas-ano), com um hazard ratio (HR) de 1,24 (IC 95%: 1,21–1,26), após ajuste para fatores de risco cardíaco, comorbidades, estatuto socioeconômico e outros fatores. As pessoas com DPOC tinham menor probabilidade de receber medicação preventiva para DCV ou de serem acompanhadas por um cardiologista.

Conclusão Numa grande população real com DCV estabelecida, a DPOC esteve associada a uma maior taxa de eventos cardiovasculares, mas a uma menor taxa de terapêutica preventiva. São necessárias estratégias para melhorar a prevenção secundária da DCV na população com DPOC.

INTRODUCTION

The prevalence of chronic obstructive pulmonary disease (COPD) has increased, and it is now the third leading cause of death worldwide.¹ Cardiovascular disease (CVD) is a leading cause of hospitalisation and death in the COPD population,^{2–4} with people with COPD being two times as likely to require healthcare services for (CVD) compared with people without COPD.⁵

Many studies have established the independent association between COPD and/or reduced lung function and CVD.^{6–10} Previous studies, however, have considered both people with and without previous CVD at baseline when determining the additional risk of COPD. These groups may differ. We demonstrated that people with COPD without a

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- We searched PubMed using the terms “COPD” and “cardiovascular disease”, “risk factors”, “prognosis” or “health outcomes” for articles published up until September 2023, with no publication date or language restrictions.
- We found no large, complete, longitudinal, population-based real-world studies that determined the impact of chronic obstructive pulmonary disease (COPD) on the development of cardiovascular disease in people with a history of cardiovascular disease.

WHAT THIS STUDY ADDS

- To our knowledge, this is the first study examining the association between COPD and the composite outcome of hospitalisation for acute myocardial infarction, stroke or cardiovascular death in a large, complete secondary prevention population-based cohort.
- After adjustment for demographics, cardiovascular risk factors, comorbidities, socioeconomic status, healthcare utilisation and smoking, the rate of major adverse cardiac event (MACE) was 24% higher in persons with compared with without COPD (HR 1.24, 95% CI 1.21–1.26).
- Despite a higher risk of MACE, we found people with COPD were less likely to receive secondary preventive cardiac care.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This study reveals that strategies are needed to improve secondary cardiovascular disease prevention among people with COPD and cardiovascular disease.

history of CVD had a 25% increased risk of CVD events.¹¹ To our knowledge, no studies have examined if the increased risk is also present in people with established CVD whose heightened CVD threat might diminish additional risk from COPD. Current guidelines on secondary CVD prevention recommend more aggressive management for

people with a higher risk of cardiovascular events, such as those with diabetes (DM) or chronic kidney disease (CKD).¹² Whether people with COPD should be included in this group has not been determined.

Knowing if people with COPD and CVD are at higher risk for future CVD events than those with CVD alone is particularly concerning because secondary prevention of cardiovascular events in people with COPD has been shown to be lacking. For example, beta-blockers have been shown to be under-prescribed in people with COPD, despite studies confirming their safety and benefit.^{13–15} People with COPD have also been shown to undergo coronary revascularisation less frequently than those without COPD.¹⁶ Establishing higher CVD risk in people with COPD and known CVD would shift the risk-benefit of interventions, justify more aggressive management and convince clinicians that these interventions are imperative.

The aim of the current study was to compare cardiovascular risk factors in individuals with versus those without COPD in a population with established CVD, and then to quantify the real-world impact of COPD on CVD outcomes by adjusting for these factors and other potential confounders. In further analysis, we sought to document gaps in preventive CVD care in the same population, to highlight opportunities to lessen this impact. Our ultimate goal was to provide a knowledge base to inform secondary CVD prevention in people with COPD.

MATERIAL AND METHODS

Study design and setting

We conducted a real-world cohort study of all community-dwelling adults residing in Ontario, Canada with established CVD using population health and other datasets. Ontario, the largest province of Canada, is home to a multiethnic population of over 15 million residents who have universal access to medically necessary hospital and physician care as well as medications for individuals aged 65 and older under publicly funded health insurance. The use of the data in this project is authorised under section 45 of Ontario's Personal Health Information Protection Act (PHIPA). The methods used in this study were very similar to those used in our previous study assessing the impact of COPD on CVD risk in people without known CVD.¹¹

Data sources

Ontario has a universal single-payer healthcare system that provides medically necessary services to its residents. Details of these are captured in large databases that can be linked to each other as well as to other complementary large population health data sources—including laboratory test result databases and health surveys providing comprehensive information on the population. These datasets were linked deterministically using unique encoded identifiers and analysed at ICES.¹⁷ ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyse healthcare and demographic data, without consent, for health system evaluation and improvement. ICES has numerous safeguards in place as well as regular audits to protect the sensitive data it holds. For this study, datasets previously linked to the Cardiovascular Health in Ambulatory Care Research Team¹⁸ database were used to obtain information on hospitalisations, emergency department visits, outpatient physician claims, drug prescriptions, electronic medical records, laboratory data and survey data (see online supplemental table S1 for a complete list of databases) since 2002. The cause of death was determined from the Office of the Registrar General of Ontario data which gets this information from death certificates. Immigrant status was obtained from the Immigration, Refugees and Citizenship Canada Permanent Resident Database. Laboratory test results were from the Ontario Laboratory Information System database which collects information from hospital and outpatient laboratories in Ontario.¹⁹ Survey data was obtained from the Canadian Community Health Survey (CCHS), an annual survey which is administered by Statistics Canada on a representa-

tive sample of the population and includes questions about health behaviours and health status. Details of these databases and examples of their use to study respiratory and CVD have been described elsewhere.^{20–22}

Study population

Using the linked databases aforementioned, we included all individuals aged 40+ years who lived in Ontario, Canada on 1 January 2008 (index date) with established CVD, defined as a prior history of acute myocardial infarction (AMI), ischaemic heart disease, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), heart failure (specifically left ventricular dysfunction) or stroke. The heart failure definition used included both heart failure with reduced ejection fraction and heart failure with preserved ejection fraction and has been validated against electronic medical records.²³ It was included because coronary atherosclerosis is the most common cause of heart failure. International Classification of Disease codes used to identify these and other conditions can be found in online supplemental table S2. Those with a previous lung transplant were excluded. Individuals were followed from the index date to 31 December 2016, an outcome of interest, loss of health insurance eligibility or until death, whichever occurred first.

Primary exposure

Our primary exposure was physician-diagnosed COPD determined using a previously validated case definition of one COPD-related hospital admission and/or at least three COPD ambulatory physician visits within 2 years, prior to the index date. This case definition has been shown to have a specificity of 95.4% and sensitivity of 57.5% when validated against a clinical reference standard.²⁴

Cardiovascular outcomes

The primary outcome was the composite of hospitalisation for AMI or stroke or death due to CVD. This outcome, referred to as major cardiovascular events, has been used in previous cardiovascular studies.^{25–26} Secondary outcomes included individual components of a major adverse cardiac event (MACE) as well as coronary revascularisation (ie, PCI and CABG surgery), heart failure, ischaemic heart disease and cause-specific mortality. The components of MACE have been validated through previous studies or the Office of the Registrar General of Ontario.^{20–23}

Baseline characteristics

Baseline characteristics, including sociodemographic factors, cardiac risk factors, comorbidities, health services utilisation and medications, were assessed using data on or before the index date. These were chosen based on literature and/or expert opinion because they potentially confound the association between COPD and CVD outcomes.

Cardiovascular risk factors

Traditional cardiac risk factors were obtained from several databases (online supplemental table S1). Hypertension, diabetes, dementia and other comorbidities were ascertained from health administrative data—using validated algorithms where available.^{27,28} Laboratory results, including total cholesterol, triglycerides and glycosylated haemoglobin were obtained from laboratory databases. Lifestyle behaviours, including smoking status and ideal physical activity, were collected from the CCHS. For those not included in the CCHS, smoking status was imputed using methods shown to provide accurate values even with a high prevalence of missing data.²⁹ Electronic medical records provided blood pressure measurements.

Cardiovascular and other care

Visits to physicians were captured from health administrative data and categorised by physician specialty (primary care physicians,

Table 1 Baseline demographics, cardiovascular risk factors, laboratory values, comorbidities, behavioural characteristics, types of physician visits and medication use for individuals with cardiovascular diseases and COPD (cardiovascular-COPD cohort) versus individuals with cardiovascular diseases without COPD (cardiovascular cohort)

Characteristic, % (unless otherwise noted)	Persons with cardiovascular diseases and COPD N=69 161*	Persons with cardiovascular diseases without COPD N=426 895†	Standardised difference
Sociodemographics			
Age, years			
40–49	1.4	6.7	0.27
50–59	8.1	16.4	0.26
60–69	20.8	25.1	0.10
70–79	35.0	28.5	0.14
80+	34.7	23.2	0.25
Female	41.1	37.9	0.06
Socioeconomic status as per income quintile			
1 (lowest)	25.9	19.5	0.15
2	22.5	20.5	0.05
3	19.0	19.7	0.02
4	17.2	19.8	0.07
5 (highest)	14.9	20.1	0.14
Rural residence	18.4	14.8	0.10
Immigrant	3.3	6.7	0.16
Cardiac risk factors and comorbidities			
Hypertension	83.5	77.0	0.17
Diabetes	39.2	33.0	0.13
Smoker‡	30.7	16.3	0.35
Peripheral arterial disease	9.6	3.7	0.24
Diastolic blood pressure‡, mean±SD	72.3±10.9	74.5±10.5	0.21
Systolic blood pressure‡, mean±SD	127.9±18.7	129.1±18.1	0.06
BMI, kg/m ² , mean±SD§	27.4±5.8	27.4±5.1	0.00
Moderate to active physical activity§	27.7	40.2	0.27
≥5 fruits and vegetables/day§	25.4	30.2	0.11
Heavy alcohol consumption§	6.8	7.5	0.03
Acute myocardial infarction	38.2	37.3	0.02
Heart failure	43.1	17.8	0.57
Atrial fibrillation	36.4	33.7	0.06
Stroke	14.3	15.4	0.03
Percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG)	32.5	40.8	0.17
Dementia	7.0	4.5	0.11
Cancer	4.7	2.6	0.11
Chronic kidney disease	9.3	4.1	0.21
Liver disease	0.7	0.3	0.05
HIV	0.1	0.1	0.02
Thyroid disease	10.5	8.7	0.06
Anaemia in previous 5 years	31.5	20.6	0.25
Surgical hospitalisation in the previous 2 years	21.6	19.3	0.15
Number of chronic conditions¶			
0–1	0.5	9.7	0.43
2	3.0	18.5	0.52
3	9.1	24.4	0.42
4	16.5	21.3	0.12
5 or more	71.0	26.0	10.01

Continued

Table 1 Continued

Characteristic, % (unless otherwise noted)	Persons with cardiovascular diseases and COPD N=69 161*	Persons with cardiovascular diseases without COPD N=426 895†	Standardised difference
Long-term oxygen therapy	11.0	0.6	0.46
Health service utilisation			
Cholesterol screening in previous 3 years	71.8	79.3	0.18
Non-pregnancy diabetes screening in previous 3 years	84.6	85.9	0.04
Influenza vaccination in previous season	46.8	55.5	0.17
Family physician visit in previous 2 years	96.3	95.7	0.03
Specialist visits in previous 2 years	89.0	86.5	0.08
Cardiologist visits	42.0	47.2	0.10
Respirologist visits	14.2	3.0	0.41
Medications (among persons aged 66 and older)**			
ACE inhibitor	45.3	47.5	0.04
Angiotensin II receptor blocker	18.6	19.0	0.01
Beta-blocker	40.1	52.6	0.25
Diuretic	48.7	36.7	0.24
Calcium channel blocker	35.7	32.0	0.08
Oral antihypertensive	17.6	17.8	0.00
Statin	55.1	60.4	0.11
Warfarin	24.4	23.3	0.03
Inhaled corticosteroids	34.8	4.4	0.83
Long-acting muscarinic antagonist	28.1	1.7	0.80
Long-acting beta agonist	25.8	2.3	0.72
Short-acting anticholinergic	7.6	0.6	0.36
Short-acting beta-agonist	27.2	3.4	0.70
Xanthine	2.0	0.4	0.19
Laboratory tests††			
Total cholesterol, mmol/L, median (IQR)	4.2±1.10	4.3±1.1	0.06
HDL cholesterol, mmol/L, median (IQR)	1.2±0.4	1.2±0.4	0.05
LDL cholesterol, mmol/L, median (IQR)	2.3±0.9	2.3±0.9	0.11
Triglycerides, mmol/L, median (IQR)	1.6±1.0	1.6±1.0	0.01
Total cholesterol to HDL ratio, median (IQR)	3.6±1.2	3.7±1.2	0.07
HbA1c, %, median (IQR)	4.69±3.03	4.80±2.9	0.04

*Not all variables were available for all individuals, see table footnotes for details.

†Values for some individuals imputed (see details in online supplemental materials).

‡Estimates are from a subpopulation of individuals linked to the electronic medical records. These variables were not used in any statistical models.

§Estimates from a subpopulation of 13 968 respondents of the Canadian Community Health Survey 2005–2014 (2061 with COPD; 11 907 without COPD).

¶Includes number of chronic conditions other than COPD, cardiovascular diseases and cardiovascular disease risk factors including asthma, arthritis (osteo-, rheumatoid and other), cancer, dementia, inflammatory bowel disease, mood/anxiety/depression and other nonpsychotic disorders, other mental illnesses, osteoporosis and renal failure.

**Estimates from a subpopulation of 319 889 individuals aged 65 years and above (54 973 with COPD; 264 916 without COPD).

††Laboratory test results were available for about 37% of the cohort who were tested for total cholesterol, 37% for HDL cholesterol, 37% of LDL cholesterol, 37% for triglycerides and 21% for HbA1c. Laboratory testing results were not available in some geographic regions.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

respirologists, cardiologists and all other specialists combined). Medication use was obtained for individuals 65 years and older through the drug database. To assess if subjects received quality CVD preventive care, we examined screening for cholesterol and diabetes in accordance with Canadian guidelines.^{30 31}

Analysis

Baseline cardiovascular risk factors, cardiovascular care, comorbidities and other factors were compared between people with established CVD with and without COPD using standardised differences. Researchers have proposed that a standardised difference of 0.1 or more denotes a potentially meaningful imbalance in the baseline covariate.³² These were used to avoid clinically unimportant differences being identified as statistically significant due to the large cohort size. Incidence rates for primary and secondary cardiovascular outcomes were calculated per 1000 person-years. Age- and sex-standardised rates and rate ratios for the primary

outcome were calculated using the entire secondary prevention cohort as the reference population.

To determine the impact of COPD on MACE in people with established CVD, individuals were followed until the first of three events: (1) experiencing any of the components of the composite outcome (MACE); (2) migration out of Ontario; (3) end of the study period or they left the province. Subjects for whom (2) or (3) were the first event experienced were censored at the time of migration or the end of the study period. We used sequential cause-specific Cox proportional hazard models accounting for the competing risk of death and sequentially adjusted for predefined sets of CVD risk factors, care and other potentially relevant confounders. All variables were included because of their clinical significance. All analyses were performed using SAS V.9.4 (SAS Institute).

Missing smoking data was addressed by using multiple imputations (see online supplemental methods for details).³³ Missing data for age, sex, income quintile or health services use (<1%) was

Table 2 Age- and sex-standardised rates of cardiovascular outcomes among individuals with cardiovascular diseases and COPD (cardiovascular-COPD cohort) versus individuals with cardiovascular diseases without COPD (cardiovascular cohort) in Ontario, Canada

Cardiovascular outcomes	Age-sex standardised rate per 1000 person-years (95% CI)		
	Persons with cardiovascular disease and COPD	Persons with cardiovascular disease without COPD	Rate ratio (95% CI)
Primary outcome			
Major cardiovascular event (composite of AMI, stroke or cardiovascular death)	45.3 (44.5–46.3)	28.6 (28.4–28.8)	1.6 (1.7–1.6)
Secondary Outcomes			
AMI	17.1 (16.5–17.7)	11.3 (11.2–11.4)	1.52 (1.5–1.6)
Stroke	9.5 (9.17–9.8)	7.8 (7.7–7.9)	1.2 (1.2–1.3)
Heart failure	17.1 (16.5–17.8)	11.3 (11.2–11.4)	1.5 (1.5–1.6)
Unstable angina	7.4 (7.0–7.8)	5.0 (5.0–5.1)	1.5 (1.4–1.6)
Coronary artery bypass graft surgery (CABG)	3.7 (3.5–3.9)	4.2 (4.1–4.3)	0.9 (0.8–0.9)
Percutaneous coronary intervention (PCI)	12.2 (11.7–12.6)	11.0 (10.9–11.2)	1.1 (1.0–1.1)
Revascularisation (PCI or CABG)	15.6 (14.9–16.0)	14.8 (14.7–15.0)	1.1 (1.0–1.1)
Cause specific death			
Death due to AMI	16.6 (16.1–16.9)	7.8 (7.7–7.9)	2.1 (2.1–2.2)
Death due to ischaemic heart disease	20.3 (19.8–20.7)	10.0 (9.9–10.2)	2.0 (2.0–2.1)
Death due to respiratory disease	20.3 (19.8–20.8)	10.0 (9.9–10.2)	2.02 (2.0–2.1)
Death due to stroke	2.2 (2.1–2.4)	1.7 (1.6–1.7)	1.3 (1.2–1.4)

Rates are standardised to the overall CVD population.

AMI, acute myocardial infarction; COPD, chronic obstructive pulmonary disease.

managed by excluding those people from the analysis. Laboratory missing data was managed by designing a 'not tested' category. This included people who were not tested because they lived in geographic areas not captured by the laboratory database or did not have testing indicated.

Stratified and subgroup analyses

Sex was specified a priori to be of interest because of previous research indicating that women with COPD and CVD may differ from men due to different smoking patterns, a higher likelihood of having small airway disease and female hormones modulating the inflammatory response.³⁴ Sex-stratified cardiovascular outcomes were calculated, and an interaction between COPD status and sex was considered for the hazard models.

A subgroup analysis adjusting for medication use was carried out in individuals aged 65 and older for whom medication information was available. Among respondents to the CCHS, a subgroup analysis adjusting for body mass index and health behaviours (physical activity, alcohol consumption, and fruit and vegetable consumption) was performed.

RESULTS

There were 496 056 individuals with established CVDs in Ontario on 1 January 2008 and they were followed for 8 years. Of those, 69 161 (13.9%) had physician-diagnosed COPD. The median age for the entire cohort was 71 (IQR 61–79 years) and 38.3% were women (table 1). About 201 806 had the primary outcome of MACE; 247 974 died of other causes not part of the primary outcome and 46 276 were censored at the end of the study period or because they left the province.

Cardiovascular risk factors and comorbidities

The prevalence of hypertension (standardised difference, SD=0.17), diabetes (SD=0.13), heart failure (SD=0.57) and peripheral artery disease (SD=0.24) were higher in those with CVD-COPD compared with CVD alone (table 1). Laboratory results were similar in the two groups. Additionally, the CVD-COPD cohort had higher rates of cancer (SD=0.11), CKD (SD=0.21) and anaemia (SD=0.25) than the CVD-only cohort at baseline. There were more active smokers in the CVD-COPD group than in the CVD-only group (30.7% vs 16.3%, SD=0.35). Among respondents

to the CCHS, the CVD-COPD cohort had lower rates of fruit and vegetable consumption and ideal physical activity levels.

Cardiovascular and other care

In the 2 years prior to 2008, there were no apparent differences between the two groups in visits to family physicians and specialists; however, people in the CVD-only cohort were more likely to have visited a cardiologist at least once (47.2% vs 42.0% in the CVD-COPD cohort).

Among individuals aged 65 and older, those in the CVD-COPD cohort were less likely to have filled a prescription for beta blockers, ACE inhibitors or statin. Use of oral anti-glycaemic medication and warfarin was comparable between the two cohorts.

Cardiovascular outcomes

Over the follow-up period, the incidence rate of the primary outcome—the composite of major adverse cardiovascular events, MACE—was 45.3 per 1000 person-years in the CVD-COPD compared with 28.6 in the CVD-only cohort (rate ratio 1.58 (95% CI 1.56–1.62)) (table 2).

In terms of the secondary outcomes, the individual components of the primary outcome showed similar trends in their differences, with higher rates of AMI, stroke and cardiovascular death in the CVD-COPD cohort than in the CVD cohort. The rate of heart failure was also higher in those with COPD (17.1 per 1000 person-years in CVD-COPD vs 11.3 in the CVD cohort) (table 2). Rates of coronary artery revascularisation (CABG surgery or PCI) were similar in the two groups (15.6 and 14.8 per 1000 person-years, respectively). The CVD-COPD group had lower rates of CABG but higher rates of PCI than the CVD group.

Younger age groups showed the largest rate ratios of MACE between those with CVD-COPD and CVD-only. Rate ratios were larger in females than in males (table 3).

Table 4 reports the HRs of MACE in people with COPD-CVD compared with CVD-only adjusting for, sequentially, age and sex; traditional risk factors and comorbidities; lab tests; income quintile, place of residence and immigration status; health services utilisation and finally, smoking. After adjustment for all factors, the rate of MACE remained higher in COPD-CVD patients than in those with CVD-only, with an HR 1.24, 95% CI 1.21–1.26 after full adjustment.

Table 3 Rates of major adverse cardiovascular events among persons with cardiovascular diseases and COPD (cardiovascular-COPD cohort) versus individuals with cardiovascular diseases without COPD (cardiovascular cohort) in Ontario, Canada, by sex and age*

Age group	Age-sex standardised* rate of MACE per 1000 person-years (95% CI)					
	Men			Women		
	Persons with cardiovascular diseases and COPD	Persons with cardiovascular diseases without COPD	Rate ratio (95% CI)	Persons with cardiovascular diseases and COPD	Persons with cardiovascular diseases without COPD	Rate ratio (95% CI)
40–49	25.3 (20.4–30.3)	14.8 (14.2–15.5)	1.7 (1.4–2.0)	26.3 (21.3–32.2)	9.5 (8.7–10.3)	2.8 (2.2–3.5)
50–59	32.6 (29.8–34.9)	17.8 (17.5–18.2)	1.8 (1.6–2.0)	27.6 (25.3–31.1)	12.3 (11.8–12.9)	2.2 (2.0–2.5)
60–69	39.1 (37.5–41.1)	20.6 (20.3–20.9)	1.9 (1.8–2.0)	35.8 (34.1–37.7)	17.3 (16.7–17.8)	2.1 (1.9–2.2)
70–79	50.8 (49.2–52.3)	31.9 (31.5–32.3)	1.6 (1.5–1.7)	44.0 (44.2–46.3)	28.8 (28.2–29.3)	1.5 (1.5–1.6)
80+	76.9 (74.8–79.2)	58.2 (57.2–59.1)	1.3 (1.3–1.4)	71.2 (68.3–73.0)	57.0 (56.2–58.0)	1.2 (1.2–1.3)

*Rates are age- and sex-standardised to the entire cardiovascular disease population, as appropriate.

COPD, chronic obstructive pulmonary disease; MACEs, major adverse cardiovascular events.

Stratified and subgroup analyses

Subgroup analysis in individuals aged 65 and above additionally adjusting for medication use showed the impact of COPD on MACE was consistent with the primary analysis (HR 1.19, 95% CI 1.16–1.22) (online supplemental file 1). Subgroup analysis among health survey respondents adjusting for additional health behaviours found a similar trend for the impact of COPD on MACE (HR 1.21, 95% CI 1.05–1.41) (online supplemental table S4). The interaction between COPD status and sex was not statistically significant ($p=0.15$).

DISCUSSION

We conducted a real-world population study of Ontario residents aged 40 and older with established CVD, with and without COPD at baseline. We found that after adjusting for CVD risk factors, care and other potential confounders such as socioeconomic status and healthcare use, people with COPD had 24% higher rates of hospitalisation for AMI or stroke or death due to CVDs than those without COPD. We also showed that they received fewer prescriptions for cardiac medications and had fewer cardiologist visits at baseline. This reveals the need for strategies to improve secondary CVD prevention in this population.

Our main finding of an association of COPD with MACE is likely related to the pathophysiology of COPD and its effects on the cardiovascular system. Systemic inflammation has been observed in a severity-dependent fashion in COPD.^{35–36} COPD has also been associated with increased oxidative stress and hypoxaemia, which likely contributes to increased risk of stroke and CVD.^{37–38} Furthermore, inflammatory markers that tend to be elevated in COPD, especially during exacerbations, are known to be pro-thrombotic, possibly also causing cardiovascular events.^{39,40} Smoking, a common risk factor of CVD and COPD, is also known to contribute to a high systemic inflammatory state.

Our findings are consistent with previous studies reporting higher risks of MACE in people with COPD compared with those without COPD.^{41–42} Cardiovascular events tend to be associated with COPD exacerbations.^{43–44} This is a particularly important concern in patients who, as our results show, may have existing cardiovascular conditions that are not adequately managed. Our findings extend those of previous studies by specifically studying the impact of COPD in those with established CVD in a large, complete real-world population.

Heart failure is a common chronic disease and a leading cause of hospital admission.⁴⁵ Previous studies have reported that about 20% of patients with COPD have concurrent heart failure, in which has been associated with early readmission rates.^{46–47} Our results are consistent with a previous study that described a heart failure risk ratio of 4.5 for people with, compared with those without COPD.⁴⁶

Despite worse CVD health outcomes and risk factors, we found that people with both CVD and COPD were receiving less secondary preventative cardiac care than those without COPD.

Use of evidence-based medications that are considered standard therapy for those with established CVD—such as statins and beta-blockers, and even ACE inhibitors and ARBs—was used less frequently in the CVD-COPD cohort. Additionally, people with COPD were found to have lower rates of visits to cardiologists; although higher rates than those seen in a previous study of all people with COPD in Ontario that revealed about 24% had seen a cardiologist.⁴⁸ Of note, we adjusted for these factors in the current analysis. Furthermore, although overall rates of revascularisation were similar, rates of CABG surgery were lower in people with CVD-COPD. This could have been because of concern about higher preoperative risks from COPD itself.⁴⁹ It is less clear, however, why cardiovascular medications would not be used or why referrals to cardiologists are made less often. Some practitioners may be mindful of drug–drug interactions between beta-blockers and inhaled beta-2 agonists despite studies showing that cardio-selective beta-blockers are safe in COPD patients.^{50–51}

A unique feature of our study was being able to study the behavioural aspects of cardiac risk stratification by individually linking to survey data for a subset of our cohort. Previous studies have shown that these factors are important in reducing the incidence of chronic conditions including CVDs.^{52–53} We found a trend of more physical activity and fruit and vegetable consumption in the CVD-only cohort than those with concomitant CVD and COPD (table 1).

The strengths of our study were its analysis of a large real-world population of hundreds of thousands of people with extensive, diverse population-based health information - including smoking, behavioural and lifestyle factors. We are also not aware of any previous studies that have examined the impact of COPD on a secondary CVD prevention cohort. Further, we were able to adjust for the effects of various factors in a stepwise fashion when studying the impact of COPD on MACE.

There were also limitations that merit discussion. We were only able to identify people with physician-diagnosed COPD, as we did not have pulmonary function testing for the whole COPD population. However, we chose a case definition with high specificity and people in our cohort reflect those with COPD in the real world, where a significant proportion are diagnosed without spirometry.⁵⁴ Second, our case definition lacked sensitivity and required up to three ambulatory care visits, meaning we likely missed some people with COPD. These people were more likely to have milder COPD. We were also not able to capture people with undiagnosed COPD.⁵⁵ However, as mild and undiagnosed COPD would also be associated with CVD, not capturing these individuals likely made our comparison cohorts (people with CVD with and without COPD) more similar than they actually were—attenuating the observed impact of COPD.

This suggests that the actual impact of COPD on cardiovascular events is even greater than we found. Third, we did not have lifestyle information or laboratory test values for all subjects. We did, however, have values for large representative subcohorts,

Table 4 HRs for a major adverse cardiovascular event (MACE: composite of hospitalisation for acute myocardial infarction or stroke or death due to cardiovascular disease) for individuals with cardiovascular diseases and COPD (CVD-COPD) compared with individuals with cardiovascular diseases without COPD (CVD)

Characteristic	Adjusted for age and sex (95% CI)	Add traditional cardiovascular risk factors and comorbidities (95% CI)	Add lab tests (95% CI)	Add income quintile, place of residence, immigration status (95% CI)	Add health services utilisation (95% CI)	Add smoking (95% CI)
COPD	1.50 (1.48 to 1.52)	1.42 (1.40 to 1.45)	1.35 (1.32 to 1.37)	1.32 (1.30 to 1.34)	1.31 (1.29 to 1.33)	1.24 (1.21 to 1.26)*
Female	0.89 (0.88 to 0.90)†	0.88 (0.87 to 0.89)	0.85 (0.84 to 0.86)	0.85 (0.84 to 0.86)	0.83 (0.82 to 0.84)	0.83 (0.82 to 0.84)
Age	1.05 (1.04 to 1.05)‡	1.04 (1.04 to 1.04)	1.04 (1.04 to 1.04)	1.04 (1.04 to 1.04)	1.04 (1.04 to 1.04)	1.04 (1.04 to 1.04)
Hypertension		1.25 (1.23 to 1.28)	1.31 (1.29 to 1.33)	1.31 (1.29 to 1.33)	1.26 (1.24 to 1.29)	1.28 (1.26 to 1.30)
Diabetes		1.42 (1.40 to 1.44)	1.45 (1.43 to 1.47)	1.44 (1.42 to 1.46)	1.44 (1.42 to 1.47)	1.46 (1.44 to 1.48)
Number of other chronic conditions (ref 0–1)§						
2		1.05 (1.03 to 1.06)	1.06 (1.05 to 1.08)	1.06 (1.05 to 1.08)	1.01 (0.99 to 1.02)	1.01 (0.99 to 1.03)
3		1.12 (1.10 to 1.14)	1.11 (1.09 to 1.13)	1.11 (1.09 to 1.13)	1.04 (1.03 to 1.06)	1.05 (1.03 to 1.06)
4		1.25 (1.22 to 1.27)	1.22 (1.19 to 1.24)	1.22 (1.19 to 1.24)	1.14 (1.12 to 1.17)	1.14 (1.12 to 1.17)
5+		1.35 (1.31 to 1.39)	1.29 (1.25 to 1.33)	1.29 (1.26 to 1.33)	1.22 (1.18 to 1.25)	1.22 (1.18 to 1.26)
HbA1c≥6.5% (ref=<6.5%)			1.10 (1.07 to 1.12)	1.09 (1.07 to 1.12)	1.08 (1.05 to 1.10)	1.08 (1.05 to 1.10)
Total cholesterol (ref=<2 mmol/L)						
5.2<6 mmol/L			1.20 (1.17 to 1.23)	1.20 (1.17 to 1.23)	1.20 (1.17 to 1.23)	1.20 (1.17 to 1.23)
≥6.2 mmol/L			1.50 (1.45 to 1.55)	1.50 (1.45 to 1.55)	1.50 (1.44 to 1.55)	1.49 (1.44 to 1.54)
HDL cholesterol≥0.9 mmol/L (ref= <0.9 mmol/L)			0.83 (0.81 to 0.85)	0.83 (0.81 to 0.85)	0.84 (0.82 to 0.86)	0.85 (0.83 to 0.87)
Income quintile (ref=1 lowest)						
2				0.92 (0.90 to 0.93)	0.91 (0.90 to 0.93)	0.92 (0.90 to 0.94)
3				0.90 (0.89 to 0.92)	0.90 (0.88 to 0.92)	0.91 (0.90 to 0.93)
4				0.86 (0.85 to 0.88)	0.86 (0.85 to 0.88)	0.88 (0.86 to 0.90)
5 (highest)				0.81 (0.80 to 0.83)	0.82 (0.80 to 0.84)	0.84 (0.82 to 0.86)
Rural residence (ref=urban)				1.07 (1.05 to 1.08)	1.04 (1.02 to 1.06)	1.05 (1.03 to 1.06)
Immigrant (ref=long term Ontario resident)				0.76 (0.73 to 0.78)	0.81 (0.79 to 0.83)	0.81 (0.79 to 0.84)
Family doctor visit in last 2 years					2.26 (2.17 to 2.36)	2.25 (2.16 to 2.35)
Specialist visit in last 2 years					1.04 (1.02 to 1.06)	1.05 (1.02 to 1.07)
Cholesterol screening in previous 3 years					0.91 (0.89 to 0.92)	0.91 (0.89 to 0.93)
Diabetes screening in previous 3 years					1.11 (1.08 to 1.14)	1.11 (1.08 to 1.14)
Health examination in previous 3 years					0.81 (0.80 to 0.82)	0.81 (0.80 to 0.82)
Smoker (imputed) (ref=non smoker)						1.39 (1.28 to 1.50)

HRs are sequentially adjusted for risk factors and other variables. (Includes 426 895 individuals without COPD and 69 161 people with COPD. People with missing residence type (rural vs urban) or income quintile were excluded from the analysis. This accounted for <0.5% of people for each.)

*When additionally adjusted for chronic kidney disease, this value did not significantly change.

†Only adjusted for age.

‡Only adjusted for sex.

§Includes number of chronic conditions other than COPD, cardiovascular diseases and cardiovascular disease risk factors including asthma, arthritis (osteo-, rheumatoid and other), cancer, dementia, inflammatory bowel disease, mood/anxiety/depression and other nonpsychotic disorders, other mental illnesses, osteoporosis and chronic kidney disease.

COPD, chronic obstructive pulmonary disease; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; ref, reference value.

preserving generalisability. We were also able to impute smoking for the whole population using methods that have been shown to provide accurate values even when there is a high prevalence of missing data.²⁹ Fourth, medication information was only available in individuals aged 65 and older. However, COPD is predominantly a disease of older individuals, as shown by the median age of 71 in our cohort, so this information is still very relevant. Fifth, these results might not be generalisable to other regions with different healthcare systems. Finally, the potential for unmeasured confounding is always a concern in observational studies. However, this is also the case for studies establishing the higher risk of cardiovascular events associated with DM or CKD that have guided care for these populations.^{56 57}

CONCLUSIONS

In conclusion, we examined the impact of COPD in a real-world population of hundreds of thousands of people with established CVD in Ontario, Canada and, after adjusting for demograph-

ics, cardiac comorbidities, lab results, healthcare utilisations and lifestyle characteristics, including smoking status, found that the rate of hospitalisation for AMI or stroke or death due to CVD was higher in people with COPD than those without. We also found people with COPD were less likely to receive secondary preventive cardiac care including evidence-based medications, referral to a cardiologist and coronary bypass graft surgery. CVD guidelines currently identify DM and CKD as associated with high risk of MACE among patients with established CVD.¹² This work not only calls for the increased use of proven treatments of CVD in COPD but also justifies including COPD on that list.

Acknowledgements This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). This document used data adapted from the Statistics Canada Postal CodeOM Conversion File, which is based on data licensed from Canada Post Corporation, and/or data adapted from the Ontario Ministry of Health Postal Code Conversion File, which contains data copied under license from Canada Post Corporation and Statistics Canada. Parts of this material are based on data and/or information compiled and provided by: MOH, CIHI, IRCC, Statistics Canada. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. Parts of this material are based on data and information compiled

and provided by the Ontario Ministry of Health. The analyses, conclusions, opinions and statements expressed here are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by CIHI and the Ontario Ministry of Health. The analyses, conclusions, opinions and statements expressed here are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. Parts of this report are based on Ontario Registrar General (ORG) information on deaths, the original source of which is ServiceOntario. The views expressed therein are those of the author and do not necessarily reflect those of ORG or the Ministry of Public and Business Service Delivery. Parts or whole of this material are based on data and/or information compiled and provided by Immigration, Refugees and Citizenship Canada (IRCC) current to 2017. However, the analyses, conclusions, opinions and statements expressed in the material are those of the author(s), and not necessarily those of IRCC. Adapted from Statistics Canada, CCHS, 2000 to 2012. This does not constitute an endorsement by Statistics Canada of this product. Parts of this material are based on data and information compiled and provided by the Ontario Ministry of Health. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. We thank IQVIA Solutions Canada for use of their Drug Information file.

Contributors ASG obtained funding and supervised the study. LM and RC had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ASG, LM and EEC were involved with the concept, design and drafting of the manuscript. LM and EEC were responsible for the administrative, technical and material support. EEC, LM, AC, RC, DDS, JU, DL, PA and ASG contributed to the acquisition, analysis or interpretation of data. EEC, LM, AC, RC, DDS, JU, DL, PA and ASG are accountable for the critical revision of the manuscript for important intellectual content. ASG, LM and RC are guarantors.

Funding This study was funded by a Canadian Institutes of Health Research (CIHR) Foundation Grant (Funding Reference Number 154319). Dr. DL is the Ted Rogers Chair in Heart Function Outcomes, University Health Network, University of Toronto. Dr. ASG was supported by a CIHR New Investigator Award while working on this study and is now supported by a PSI Foundation Translational Fellowship.

Competing interests DDS reports having received small honoraria from GSK, AstraZeneca and Boehringer Ingelheim. All other authors have no conflicts of interest to report.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. ICES is a prescribed entity under Ontario's Personal Health Information Protection Act (PHIPA). Section 45 of PHIPA authorizes ICES to collect personal health information, without consent, for the purpose of analysis or compiling statistical information with respect to the management, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects that use data collected by ICES under section 45 of PHIPA, and use no other data, are exempt from REB review. The use of the data in this project is authorised under section 45 and approved by ICES' Privacy and Legal Office. Obtaining informed consent from the participants would be impractical and introduce bias.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (eg, health-care organisations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

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Casa húmida e com bolor: impacto na saúde pulmonar durante a infância

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Received 29 October 2024

Accepted 28 December 2024

Published Online First 15 January 2025

RESUMO

Em todas as consultas de pneumologia pediátrica e pediatria geral, haverá sempre um número de crianças e famílias expostas a ambientes substandard nas suas habitações. Esta exposição pode estar a afetar a sua saúde, em particular a saúde respiratória. Enquanto clínicos, é fundamental estarmos conscientes dos riscos para a saúde, sabermos como abordá-los e atuarmos como defensores dos nossos doentes. Esta revisão percorre desde os impactos na saúde até às formas como podemos defender e apoiar os doentes e as suas famílias.

Mould and dampness are common in homes in the UK, especially over the winter months and in households whose residents cannot afford adequate heating and whose homes do not have adequate ventilation (figure 1). Mould is a collective term for various fungi formed into a spore-type structure, which grow in wet and humid environments. They can be known to cause harm in humans via direct irritation, type 1 hypersensitivity or the production of toxins.¹ There is a wide variety of moulds potentially within the home, which leaves it difficult to directly attribute blame from a health perspective on an individual health basis without the ability to professionally test all moulds in the home.

The environmental conditions that promote bacterial growth are often similar to those favouring fungal proliferation. Both bacteria and fungi can produce chemical compounds that may adversely affect human health. Consequently, when evaluating the risks associated with exposure to damp and mouldy environments, it is essential to consider the potential presence and health impacts of both fungi and bacteria.

Although exposure to mould and its associated produced substances is linked to health problems in multiple areas of the body, most individuals' contact is through breathing them in. This means they predominantly affect the airways and lungs. There is a large body of epidemiological evidence linking mould exposure to respiratory health effects, either directly or via the indirect marker of dampness. For example, associations are reported between exposure to dampness and/or mould and upper respiratory tract symptoms, cough, wheezing and, in asthmatic populations, increased exacerbations.² Although for individuals, it is often difficult to identify which specific moulds and components are driving symptoms, increased exacerbations of asthma are associated with increased concentrations of *Penicillium*, *Aspergillus*, *Cladosporium* and *Alternaria* species in the home measured via air or dust sampling.³ Children with chronic respiratory conditions are most susceptible to aerosolised bioagents, and mould exposure presents an increased risk of exacerbation.² While atopic children or those with allergic diseases are particularly susceptible to biological and chemical agents in damp indoor environments, adverse health effects have also been reported in non-atopic populations. For example, Ingham et al found a dose-response relationship between housing qual-

ity measures, particularly dampness-mould, and young children's hospitalisation rates with acute respiratory infections in New Zealand.⁴ Exposure to mould and other dampness-related microbial agents also increases the risks of rare conditions, such as hypersensitivity pneumonitis, allergic alveolitis, chronic rhinosinusitis and allergic fungal sinusitis.⁵ Indeed, the presence of dampness and/or mould is estimated by the UK Health and Security Agency to be associated with approximately 5000 new asthma cases and 8500 respiratory tract infections in 2019 in England. However, alternative data sources from self-reporting suggest estimates could be 3–8 times higher.⁶

Mould-associated respiratory symptoms are either due to exposure to the spores and hyphae of the mould themselves or due to chemical and organic compounds in the air as a result of microbial growth. Adverse health effects due to exposure to mould or mould-derived compounds are the result of three different mechanisms: generation of immune responses by both allergic and non-allergic pathways, exposure to mould byproducts such as mycotoxins and proteases causing toxicity or direct infection by the organism.⁷ Bioaerosols may either act as allergens or directly stimulate proinflammatory mediator release in the airway. Indeed, the higher the fraction of hyphae to spores in indoor air, the more proinflammatory potential of the aerosol.⁶ Given that exposure to inhaled mould in the indoor environment is associated with significant health impacts, the continued presence of mould and dampness in the home of any child with atopy or a respiratory disease must be considered a hazard to health.³ To date, there are no guidelines available for a safe threshold of mould or dampness within the home, and the presence of any mould or dampness should be minimised or remediated to reduce future growth and potential increases to airborne biological agents. Mould should be remediated using appropriate, specific products and recommended personal protective equipment and may require professional services to eradicate effectively. In addition to mould, dampness should be addressed by adequate ventilation since it not



Figure 1 Example of mould present in the home of a child with asthma (photo courtesy of Victoria Hadaway—(Community Matron for Asthma and Atopy)¹².



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To cite: Moorcroft C, et al. Arch Dis Child 2025;110:419–421.

Managing worries about damp and mould

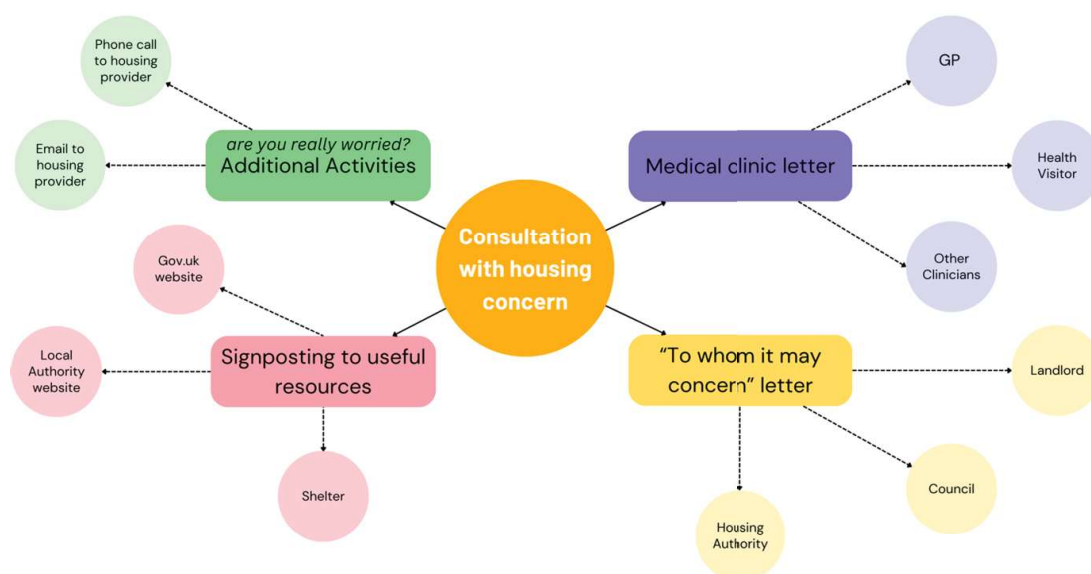


Figure 2 Potential interactions for a clinician supporting a child and family with substandard housing.

only supports mould growth but also initiates the degradation of materials in the home. Remediation to building structure may also be required depending on individual circumstances.

WHAT SHOULD CLINICIANS NOW DO WHEN PARENTS REPORT DAMPNES AND MOULD IN HOMES?

There is clearly an ongoing lack of clarity in the clinical obligations of clinicians when faced with a patient living in substandard housing. The health-related outcomes of exposure to mould and dampness are clearly found in the literature. However, the approach of the clinician will be very much patient dependent. Awaab's Law makes it very clear that no child or person should live in an environment that is toxic to their health. Families may not bring their housing concerns with them, so, all consultations should provide a time or ability to discuss concerns regarding a child's environment.

With the introduction of new local⁸ and national⁹ guidance as clinicians, we should be signposting patients to these documents as part of a consultation. Clinicians will need to take a proactive role in supporting the family to obtain remedial work or to move house, give appropriate advice and provide medical opinions on health effects where appropriate. This is likely to take the form of a medical letter that highlights the impacts on health (specific to the individual patient) and reiterates the landlord's responsibilities (examples are available on <https://www.rcpch.ac.uk/resources/health-inequalities-climate-change-tool-2-advocate-action>). In figure 2, we outline the possible interactions that a clinician may have when supporting a family living in substandard housing; of note, the majority are unlikely to be included as expected workload and will depend on the local networks available to the clinician. There is the possibility that the specific health impacts on an individual patient may be asked, 'is this mould actually causing this illness?'. In these cases, it should be reiterated that homes should be 'fit for habitation' as per the Housing Act and that landlords should take a zero-tolerance approach to dampness and mould as per the Housing Ombudsmen.¹⁰ Unlike the state of play in 1998,¹¹ it should be made clear that there is clear evidence that mould and dampness

are major risk factors for more severe respiratory symptoms, and reference should be made to the coroner's decision in the case of Awaab Ishak. However, more studies are still needed to define the extent of individual organisms' roles in causing pathology and to quantify individual exposure.

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Contributors Conception: AW, JG and CM; manuscript drafting and revising: AW, JG and CM. All authors contributed to writing the final manuscript. All authors have read and approved the final version of this manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests JG: support; NIHR Senior Investigator Award, Grants; OM Pharma, Marinomed; Advisory board; OM Pharma, Omron, Honoraria; AstraZeneca, equipment and materials donation; OM Pharma, Immunotek S.L., Omron, payment for medical evidence; Hogg Robertson solicitors. AW and CM: none declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Commissioned; internally peer reviewed.

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Internamentos hospitalares por asma em adultos diminuíram significativamente na Finlândia e na Suécia entre 2006 e 2022

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Published Online First 8 February 2025



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To cite: Kivistö JE, Protudjer JLP, Ekstrom S, et al. Thorax 2025;80:392–394.

RESUMO

Já foi reportada uma tendência decrescente nos internamentos hospitalares por asma entre crianças finlandesas e suecas. No entanto, as possíveis alterações nos internamentos por asma em adultos ainda não estão completamente caracterizadas. O nosso objetivo foi investigar a incidência de internamentos hospitalares por asma em adultos na Finlândia e na Suécia entre 2006 e 2022, utilizando o Registo Nacional de Altas Hospitalares da Finlândia e o Registo Nacional de Doentes da Suécia. Durante o período do estudo, a incidência de internamentos por asma diminuiu 65,8% na Finlândia (de 84,9 para 29,0 por 100 000 pessoas-ano) e 52,5% na Suécia (de 31,4 para 14,9 por 100 000 pessoas-ano). As incidências de internamentos por asma eram claramente mais elevadas na Finlândia em comparação com a Suécia no início do período de estudo, mas aproximaram-se da paridade entre ambos os sexos ao longo do tempo.

INTRODUCTION

Asthma remains a common chronic disease worldwide, although decreasing trends in asthma hospitalisations have been suggested, possibly due to improved medication and healthcare.¹ We previously reported decreasing a trend of asthma hospitalisations among Finnish and Swedish children during 2015–2020 and approaching parity. Comprehensive asthma care in Finland and Sweden may have contributed to the declining trend in paediatric asthma hospitalisations.² Previously, the increase of asthma prevalence has been reported.³ However, the trends in asthma hospitalisations among adults in Finland and Sweden are incompletely characterised. Thus, we aimed to investigate the incidence of adult asthma hospitalisations in Finland and Sweden from 2006 to 2022.

METHODS

This study is based on data from Finland's National Hospital Discharge Register and Sweden's National Patient Register. Both registers contain inpatient data including age, time of hospitalisation and diagnosis, from all hospitals in the respective countries.

Hospitalisations of adults aged at least 20 years with a primary diagnosis of asthma (International Classification of Diseases, 10th Revision (ICD-10) codes J45 (asthma) and J46 (status asthmaticus)) from 2006 to 2022 in secondary and tertiary care were identified from the registers. The primary outcome was the incidence (per 100 000 person-years) of hospitalisations for asthma and this was analysed according to gender in different age groups (20–29, 30–39, 40–49, 50–59, 60–69, 70–79 and over 80 years).

To compute the change in incidence of asthma hospitalisations over the study period, year 2022 was compared with year 2006. The annual age-specific mid-populations were obtained from Official Statistics of Finland and Statistics Sweden. The incidence of hospitalisation was based on the results

of the entire population of adults in Finland and Sweden.

Poisson regression was used to calculate incidence rate ratios (IRR) with 95% CI. Statistical analyses were performed with Stata 13.0 (Stata-Corp, College Station, TX, USA).

RESULTS

From 2006 to 2022, asthma hospitalisations among adults at least 20 years of age totalled 37 114 in Finland and 31 743 in Sweden. During the study period, the incidence of asthma hospitalisations decreased by 65.8% in Finland (from 84.9 to 29.0 per 100 000 person-years, IRR 0.34, 95% CI 0.32 to 0.36) and 52.5% in Sweden (from 31.4 to 14.9 per 100 000 person-years, IRR 0.48, 95% CI 0.44 to 0.51).

In both countries, the majority of the hospitalised adults were females (68.3% in Finland and 67.1% in Sweden). However, between 2006 and 2022, the incidence of asthma hospitalisations among females decreased by 62.0% in Finland (from 111.9 to 42.5 per 100 000 person-years, IRR 0.38, 95% CI 0.35 to 0.41) and by 50.2% in Sweden (from 41.0 to 20.4 per 100 000 person-years, IRR 0.49, 95% CI 0.45 to 0.54). Among males, the incidence of asthma hospitalisations decreased by 73.0% in Finland (from 56.0 to 15.1 per 100 000 person-years, IRR 0.27, 95% CI 0.24 to 0.31) and by 54.7% in Sweden (from 21.4 to 9.7 per 100 000 person-years, IRR 0.45, 95% CI 0.40 to 0.51) (figure 1).

In both countries, the incidence of asthma hospitalisations was higher in the older age groups throughout the study period (online supplemental table). Among females older than 80 years of age, the incidence of asthma hospitalisations decreased by 60.4% in Finland (from 265.9 to 105.1 per 100 000 person-years, IRR 0.40, 95% CI 0.34 to 0.47) and by 50.4% in Sweden (from 138.8 to 68.8 per 100 000 person-years, IRR 0.50, 95% CI 0.42 to 0.58). Similarly, among males older than 80 years of age, the incidence of asthma hospitalisations decreased by 62.7% in Finland (from 228.1 to 69.1 per 100 000 person-years, IRR 0.30, 95% CI 0.23 to 0.40) and by 66.0% in Sweden (from 84.6 to 28.8 per 100 000 person-years, IRR 0.34, 95% CI 0.26 to 0.47).

DISCUSSION

Based on national-level hospitalisation register data in Finland and Sweden, the incidence of asthma hospitalisations decreased by 65.8% in Finland and 52.5% in Sweden between 2006 and 2022. In both sexes, the incidences of asthma hospitalisations were distinctly higher in Finland compared with Sweden in the beginning of the study period but approached each other during the follow-up.

Our study has some limitations. As data were based on ICD-codes and hospitalisation statistics, consideration to treatments given in the emergency department (ED) or patient out-

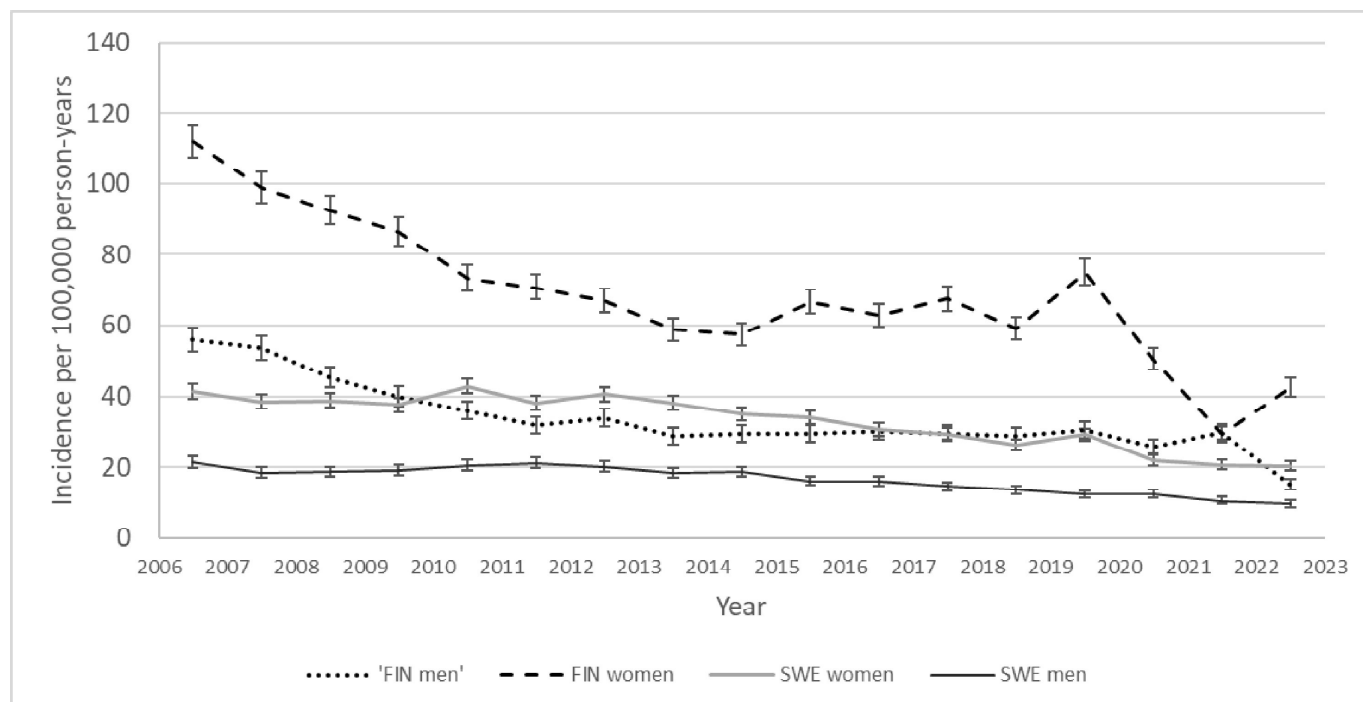


Figure 1 Incidence of hospitalisations for asthma per 100 000 person-years among Finnish and Swedish adults, by sex, between 2006 and 2022.

comes following discharge was not possible. Moreover, we cannot be certain if there were inter-country differences in diagnosing asthma, although asthma care in the two countries is regarded very similar.

Our study describes the national trends of asthma hospitalisations from 2006 to 2022 in two well-defined, neighbouring populations. The major strength of this study is the use of national level hospitalisation data from validated and well-established registers covering practically the whole countries.^{4–5} Moreover, the use of standardised ICD-10 diagnostic coding permitted estimations of incidence and an international comparison.

Asthma hospitalisations have decreased in many countries due to improved asthma care and updated guidelines.⁶ However, the decrease in asthma hospitalisations may not necessarily indicate a similar decrease in severe asthma exacerbations but rather a change in healthcare resources (eg, the number of hospital beds) and the possibility for ED physicians to take patients into ward care. This study examined hospitalisations in secondary and tertiary care. Thus, possible differences in primary healthcare resources between Finland and Sweden might also explain differences in secondary and tertiary level asthma hospitalisations between the countries.

In both countries, the incidence of asthma hospitalisations was higher in the older age groups throughout the study period but markedly higher in Finland compared with Sweden. In Finland, the diagnosis of asthma has been emphasised in the national asthma programme and most of the patients with both asthma and chronic obstructive pulmonary disease (COPD) have a diagnosis of asthma.⁷ It is possible that Swedish patients with comorbid asthma and COPD more commonly have the diagnosis of COPD which may explain differences between countries in hospitalisations labelled due to asthma.⁸ Smoking has been more common in Finland but has declined in both countries. The differences and changes in smoking habits may have had an effect on asthma hospitalisations and may explain some of the difference between the countries.⁹ The effect of COVID-19 pandemic on asthma hospitalisations is unclear since it is not known whether people with asthma hospitalised due to COVID-19 had a primary diagnosis of asthma or COVID-19.

In conclusion, the incidence of asthma hospitalisations decreased markedly in Finland and Sweden between 2006 and 2022. The incidence of asthma hospitalisation was distinctly higher in Finland compared with Sweden in the beginning of the study period but approached each other among both sexes. The differences in healthcare resources and practices may explain some of the differences between the countries.

Contributors JEK conceptualised and designed the study, designed the data collection instruments, carried out the analyses and drafted the initial manuscript, and approved the final manuscript as submitted. JLP and SE conceptualised the study, designed the data collection instruments, reviewed and revised the manuscript, and approved the final manuscript as submitted. JK conceptualised the study, reviewed and revised the manuscript, and approved the final manuscript as submitted. LL and IK conceptualised and designed the study, reviewed and revised the manuscript, and approved the final manuscript as submitted. HH conceptualised and designed the data collection instruments, carried out the analyses and approved the final manuscript as submitted.

Funding The project received funding from The Jalmari and Rauha Ahokas Foundation, Tampere Tuberculosis Foundation, Väinö and Laina Kivi Foundation, Foundation of the Finnish Anti-Tuberculosis Association and The Research Foundation of the Pulmonary Diseases.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable. Provenance and peer review Not commissioned; externally peer reviewed.

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Efeito da hora do dia e da variação sazonal na resposta ao broncodilatador: o estudo SPIRO-TIMETRY

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► Additional supplemental material is published online only. To view, please visit the journal online (<https://doi.org/10.1136/thorax-2024-222773>).

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Published Online First 11 March 2025

RESUMO

Investigámos a associação entre a hora do dia e a estação do ano em que é realizado o teste e o nível de resposta ao broncodilatador numa população hospitalar. Verificámos que, por cada incremento de 1 hora ao longo do dia de trabalho, a probabilidade de uma resposta positiva ao broncodilatador diminuía em 8%. Um efeito semelhante foi observado quando o dia foi dividido em dois períodos — manhã e tarde. Ao estratificar os dados consoante o motivo do encaminhamento, o impacto da hora do dia foi observado apenas nos casos referenciados por suspeita de asma ou diagnóstico de asma. Também constatámos que a resposta ao broncodilatador era mais comum nos meses de inverno em comparação com o resto do ano.

INTRODUCTION

A key diagnostic criterion of asthma is bronchodilator responsiveness, traditionally defined as an improvement in the forced expiratory volume in 1 s (FEV₁) or forced vital capacity (FVC) after bronchodilator administration.^{1,2}

Diurnal variability in symptom presentation is characteristic of asthma, with previous research suggesting that a biological clock mechanism is an important factor in asthma pathogenesis.³ With respect to bronchodilator responsiveness, it is unknown if the effect of diurnal variability is restricted to only patients with asthma. Furthermore, the role of seasonal variation on bronchial hyperreactivity is unknown. We investigated the association between time of day and season of testing on the level of bronchodilator responsiveness.

METHODS

We retrospectively analysed data from patients referred to Cambridge University Hospitals NHS Foundation Trust between 1 January 2016 and 31 December 2023. Data were included in this study for all patients who were 18 years or older at the time of testing, who had acceptable and reproducible prebronchodilator and postbronchodilator spirometry.⁴ Data were extracted directly from the testing software.

Spirometry was instructed by certified physiologists. Spirometry was performed on the MasterScreen-PFT-Pro from Vyair Medical before, and 20 min after inhalation of 400 µg of salbutamol delivered via a metered dose inhaler and spacer. Spirometers were calibrated daily and serviced according to manufacturer guidance. GLI race-neutral reference equations were used to calculate the lower limit of normal and percent predicted values.⁵ We defined bronchodilator responsiveness for both the American Thoracic Society/European Respiratory Society (ATS/ERS) 2005 (change in FEV₁ or FVC ≥ 12% and ≥ 200 mL of the initial value),¹ and ATS/ERS 2022 definitions (change of >10% relative to the predicted value for FEV₁ or FVC).²

We performed multivariable logistic regression analyses to investigate the influence of time of day

on the odds of having a positive bronchodilator response. We considered time of day in the context of the working hours of the lung function testing laboratory (08:30–16:30). We modelled time as a continuous (per 1-hour increment), binary (08:30–13:30 vs 13:30–16:30) and categorical predictor (08:30–11:00 vs 11:01–14:00 vs 14:00–16:30).

We adjusted regression models for age (years), sex (male/female), body mass index (BMI) (kg/m²), smoking history (ever/never) and prebronchodilator FEV₁/FVC. To check for effect modification, we performed stratified analyses on those referred for asthma/query asthma vs any other referral reason. We also investigated the significance of any interaction between referral reason and time of day on the odds of having a positive bronchodilator response. We compared the results from the model with the interaction term to a model with the individual predictors using the likelihood ratio test. Referral reason was based on clinical judgement and extracted from the consultant referral document. We repeated the above analyses to investigate the influence of seasonal variation on bronchodilator responsiveness. We considered results significant if the p value was less than 0.05. Analyses were performed using Stata V.18 (StataCorp).

RESULTS

Data from 1620 individual patients were included in our analyses (online supplemental efigure 1). 62% (1004 of 1620) were female, mean (SD) age was 53.2 (16.1) years and mean BMI was 29.4 kg/m² (7.1). 48% (722 of 1620) of patients reported having ever smoked, with 58% (944 of 1620) referred for asthma/query asthma. Other referral reasons are described in online supplemental efigure 1. 25% of patients (400 of 1620) had bronchodilator responsiveness according to the ATS/ERS 2005 definition, compared with 26% (416 of 1620) of patients when using the 2022 definition. A greater proportion of patients tested in the morning had bronchodilator responsiveness compared with those tested in the afternoon for both ATS/ERS 2005 (28% vs 22%) and ATS/ERS 2022 (28% vs 23%) definitions (table 1, figure 1a).

The results of the multivariable logistic regression showed that per 1-hour increment in the working day, the odds of having bronchodilator responsiveness declined by 8% (OR 0.92, 95% CI 0.88 to 0.97). When the time of day was dichotomised into morning and afternoon sessions, there was a similar association, with reduced odds of bronchodilator responsiveness in the afternoon (OR 0.68, 95% CI 0.54 to 0.85) (table 2). Patients referred for asthma/query asthma had a significant association with bronchodilator responsiveness, with the magnitude of the effect similar to that of the main analysis, while there was no association in those referred for other reasons (online supplemental efigures 2,3). There was also evidence of a



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To cite: Knox-Brown B, Kon FC, Sylvester KP, et al. Thorax 2025;80:395–397.

Table 1 Characteristics of study participants overall and by testing time

	Overall (n=1620)	Morning 08:30–12:30 (n=852)	Afternoon 13:30–16:30 (n=768)	P value
Demographics				
Age, years, mean (SD)	53.2 (16.1)	53.4 (15.9)	53.1 (16.5)	0.704
Female, n (%)	1004 (62%)	540 (63%)	464 (60%)	0.220
White, n (%)	1498 (92%)	784 (92%)	714 (93%)	0.469
BMI, kg/m ² , mean (SD)	29.4 (7.1)	29.8 (7.6)	28.9 (6.4)	0.006
Ever smoked, n (%)	772 (48%)	407 (48%)	365 (48%)	0.922
Referred for asthma/ query asthma, n (%)	944 (58%)	523 (61%)	421 (55%)	0.007
Baseline spirometry				
FEV ₁ , L, mean (SD)	2.5 (1.0)	2.4 (0.9)	2.6 (1.0)	0.001
FEV ₁ , pp, mean (SD)	86.5 (23.7)	84.3 (24.1)	88.9 (23.1)	<0.001
FVC, L, mean (SD)	3.7 (1.2)	3.6 (1.4)	3.7 (1.2)	0.017
FVC, pp, mean (SD)	101.0 (20.0)	99.5 (20.2)	102.7 (19.6)	0.001
FEV ₁ /FVC, %, mean (SD)	52.3 (23.4)	54.4 (22.8)	49.9 (23.9)	<0.001
FEV ₁ /FVC<LLN, n (%)	1047 (65%)	530 (62%)	517 (67%)	0.032
Postbronchodilator spirometry				
FEV ₁ , L, mean (SD)	2.7 (1.0)	2.6 (0.9)	2.8 (1.0)	0.006
FEV ₁ % change, median (IQR)	5.7 (1.9, 11.4)	6.5 (2.1, 12.6)	5.3 (1.9, 10.6)	0.010
FVC, L, mean (SD)	3.7 (1.2)	3.7 (1.1)	3.8 (1.2)	0.010
FVC % change, median (IQR)	1.0 (−1.7, 5.2)	1.4 (−1.6, 5.9)	0.5 (−2.0, 4.4)	0.002
FEV ₁ /FVC, %, mean (SD)	53.9 (25.4)	56.6 (24.2)	50.9 (26.0)	<0.001
FEV ₁ /FVC<LLN, n (%)	933 (58%)	467 (55%)	466 (61%)	0.017
BDR 2005 definition, n (%)	400 (25%)	234 (28%)	166 (22%)	0.006
BDR 2022 definition, n (%)	416 (26%)	242 (28%)	174 (23%)	0.008

Continuous variables are reported as mean with SD or median with IQR. Categorical variables are reported as number (n) with percentage (%). Independent t-test is used to compare differences in means, and Mann-Whitney U test is used to compare differences in medians between morning versus afternoon testing. χ^2 test is used to compare differences in the number and percentage in each category between morning versus afternoon testing. A $p < 0.05$ is considered significant. ATS/ERS 2005 definition: change in FEV₁ or FVC $\geq 12\%$ and ≥ 200 mL of the initial value.¹ Reversibility ATS/ERS 2022 definition: change of $>10\%$ relative to the predicted value for FEV₁ or FVC.² Predicted values for FEV₁ and FVC and the LLN for FEV₁/FVC calculated using race-neutral reference equations from the Global Lung Initiative.⁵ ATS/ERS, American Thoracic Society/European Respiratory Society; BDR, bronchodilator responsiveness; BMI, body mass index; % change, per cent change pre to post bronchodilator; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; LLN, lower limit of normal; pp, per cent predicted.

significant interaction between referral reason and time of day (per 1-hour increment) on the odds of having a positive bronchodilator response (p value for likelihood ratio test <0.001).

For the seasonal analysis, proportionally more patients tested in the winter had bronchodilator responsiveness compared with other seasons (figure 1b). Compared with those tested in winter, patients tested in autumn had significantly lower odds of having bronchodilator responsiveness but only for those with bronchodilator responsiveness according to the ATS/ERS 2005 definition (OR 0.67, 95% CI 0.48 to 0.92) (online supplemental tables 4,5).

DISCUSSION

We have found that in contrast to patients tested in the afternoon, patients tested for asthma/query asthma in the morning had low-

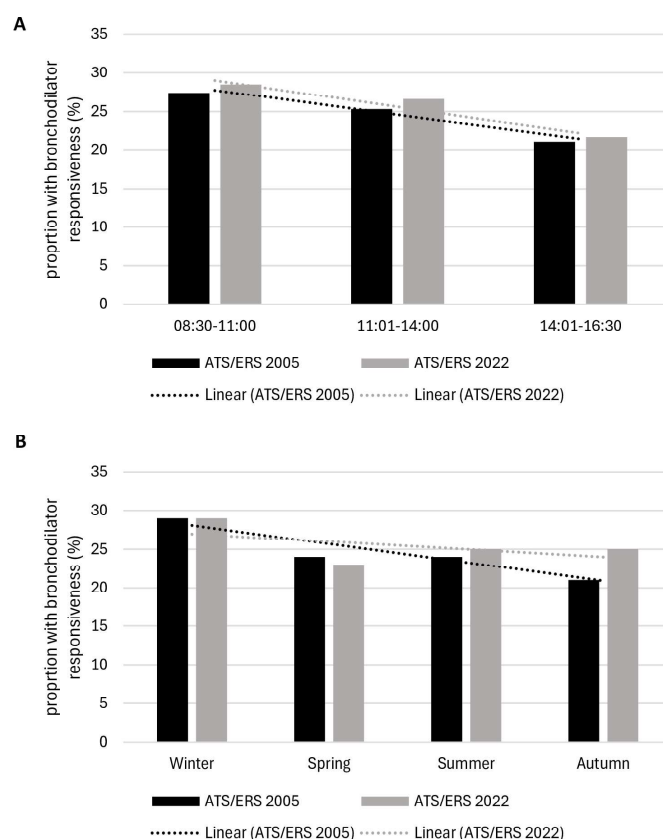


Figure 1 Graph showing (A) the association between time of test and bronchodilator responsiveness and (B) the association between season of test and bronchodilator responsiveness. ATS/ERS, American Thoracic Society/European Respiratory Society.

er lung function and were more likely to exhibit bronchodilator responsiveness. Studies have shown that the clock protein REV-ERBa controls airway hyperresponsiveness at different times of day, and that knocking down the Rev-erba gene abolishes the time-of-day effect.^{6,7} The results from our study are consistent with the recently published RADiCA study, which in a relatively small sample of patients with suspected asthma found that patients self-reported their worst symptoms in the morning and night, and that patients were more likely to demonstrate bronchodilator responsiveness in the morning compared with the afternoon.⁸ Taken together, these findings suggest that performing diagnostic testing when patients are most symptomatic, that is, in the morning, may improve diagnostic testing. This also reinforces the need to document the timing of spirometry testing whenever possible, and that repeat testing should be done at the same time of day.

Similarly, we also found seasonal variation in bronchodilator responsiveness, with bronchodilator responsiveness more likely to be seen in the winter months. Interestingly, previous groups found that adults or children with asthma or allergic rhinitis display greater FeNO and methacholine hyperresponsiveness during pollen season, characteristically seen during summer.^{9,10} We saw a slight increase in the proportion with bronchodilator responsiveness in the summer compared with the spring and autumn, but still to a lesser extent than seen in the winter. This could be because previous research has focused on a younger, more atopic population where an IgE response is more predominant, compared with older adults where asthma mortality and hospital admissions are higher during winter.

Although limited by cross-sectional study design and a lack of information regarding the formal diagnosis, we show that patients with asthma/query asthma are more likely to demonstrate bronchodilator responsiveness if spirometry testing is done in the morning compared with later in the working day. We also show that bronchodilator responsiveness is more likely in the winter months. This should be considered by clinicians when interpreting the results of bronchodilator responsiveness testing. It is im-

Table 2 Logistic regression analysis of the association between time of test and having bronchodilator responsiveness

	Total n	ATS/ERS BDR 2005			ATS/ERS BDR 2022		
		n (%)	OR (95%CI)	P value	n (%)	OR (95%CI)	P value
Time (per hour increment)	1620	400 (25%)	0.92 (0.88, 0.97)	0.001	416 (26%)	0.92 (0.88, 0.97)	0.001
Time (binary)							
08:30–12:30	852	234 (28%)	ref	ref	242 (28%)	ref	ref
13:30–16:30	768	166 (22%)	0.66 (0.52, 0.83)	0.001	174 (23%)	0.68 (0.54, 0.85)	0.001
Time (tertiles)							
08:30–11:00	547	150 (27%)	ref	ref	156 (29%)	ref	ref
11:01–14:00	552	140 (25%)	0.86 (0.66, 1.14)	0.316	147 (27%)	0.88 (0.67, 0.16)	0.373
14:01–16:30	521	110 (21%)	0.61 (0.45, 0.81)	0.001	113 (22%)	0.61 (0.46, 0.81)	0.001

Models adjusted for age, BMI, sex, baseline FEV₁/FVC and smoking status.
A p<0.05 is considered significant.
ATS/ERS 2005 definition: change in FEV₁ or FVC ≥12% and ≥200mL of the initial value.¹
Bronchodilator responsiveness ATS/ERS 2022 definition: change of >10% relative to the predicted value for FEV₁ or FVC.²
Predicted values for FEV₁ and FVC and the LLN for FEV₁/FVC are calculated using race-neutral reference equations from the Global Lung Initiative.⁵
ATS/ERS, American Thoracic Society/European Respiratory Society; BDR, bronchodilator responsiveness; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; LLN, lower limit of normal.

portant that prospective studies are conducted to confirm our findings, with particular focus on repeated measurements of the same individuals at different times of the day.

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Contributors AJ and BK-B conceived the study. BK-B performed the statistical analysis. FCK and BK-B drafted the manuscript with supervision from AJ. BK-B, FCK, KPS and AJ contributed to further drafting and approved the final version of the manuscript. BK-B and KPS had access to the raw data. BK-B is the guarantor.
Funding There is no specific funding attached to this project, however Dr Akhilesh Jha is funded by an MRC Clinician Scientist Fellowship; Reference MR/Y000935/1.
Competing interests KPS receives consultation fees from ndd Medical Technologies. All other authors declare no conflict of interest in relation to this study.
Patient consent for publication Not applicable.
Ethics approval This study involves human participants and approval to use the data was provided by the Electronic Healthcare Record Research and Innovation (ERIN) database data access committee (Reference A096990). This was a retrospective study of anonymised routinely collected healthcare data, therefore, individual participant consent was not required.
Provenance and peer review Not commissioned; externally peer reviewed. This study used data from patients seen in the National Health Service (NHS), therefore, data are not freely available.
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