

Thorax

ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

com artigos do

ARCHIVES OF
DISEASE IN
CHILDHOOD

Edição Portuguesa

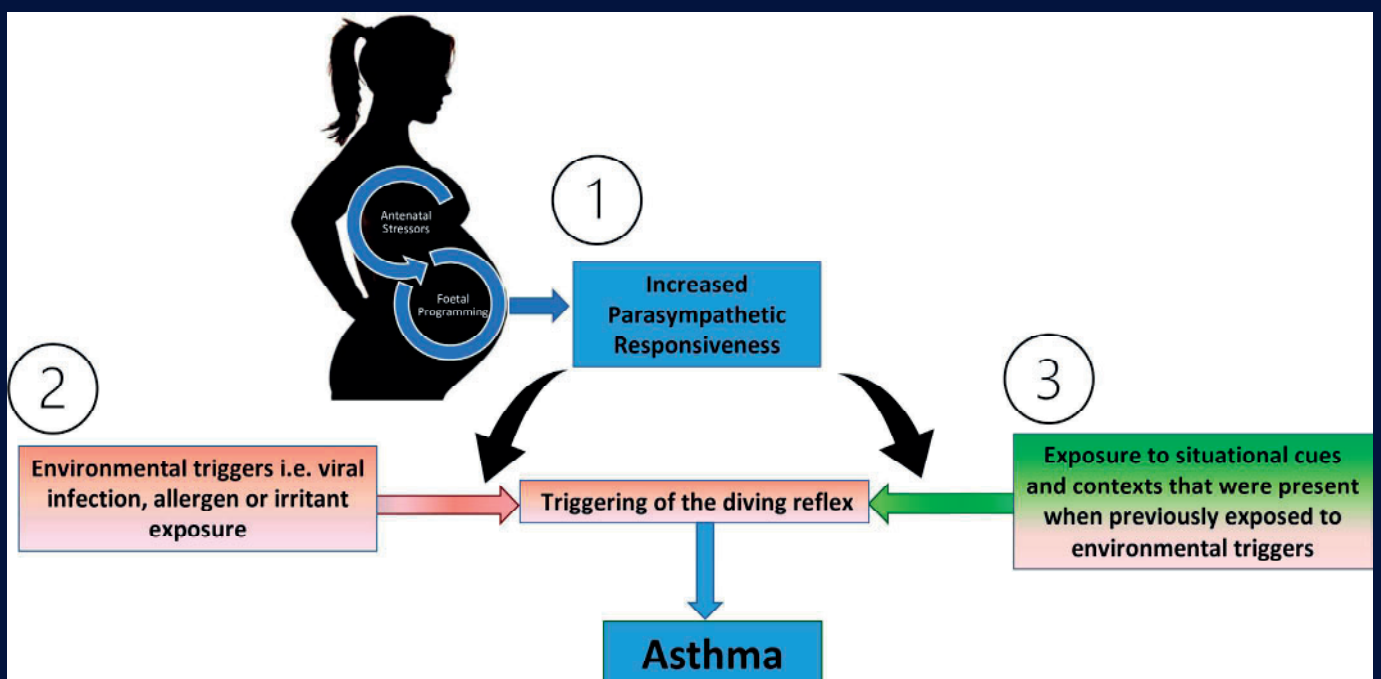


Figure 1 The autonomic basis for asthma. (1) Prenatal stressors alter autonomic development favouring parasympathetic pathways. (2) Increased vagal responsiveness after exposure to environmental triggers cause triggering of the diving reflex. (3) Situational cues and contexts cause reflex bronchoconstriction without the need for allergic sensitisation.



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

1 vez dia¹

**Zimbus[®]
breezhaler[®]**

Indacaterol, glicopirróio, 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 glicopirróio 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 glicopirróio 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 glicopirróio equivalente a 46 microgramas de glicopirróio 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 eletrocardiograma (ECG). Este medicamento deve ser usado com precaução em doentes com patologias cardiovasculares (doença arterial coronária, enfarte agudo do miocárdio, arritmias cardíacas, hipertensão, suspeita ou confirmação de prolongamento do intervalo QT, distúrbios convulsivos ou tirotóxicose e em doentes com resposta aumentada aos agonistas adrenérgicos beta₂). **Hipocalcemia:** Os agonistas adrenérgicos beta₂ podem causar uma hipocalcemia significativa em alguns doentes, o que potencialmente pode levar a reações adversas cardiovasculares. Em doentes com asma grave, a hipocalcemia pode ser potenciada pela hipoxia e pela terapêutica concomitante, o que pode aumentar a suscetibilidade a arritmias cardíacas. **Hiperglicemia:** A inalação de doses elevadas de agonistas adrenérgicos beta₂ e corticosteroides pode produzir um aumento da glicose plasmática. Nos doentes diabéticos, ao iniciar o tratamento, a glicose plasmática deve ser monitorizada mais cuidadosamente. **Efeitos anticolinérgicos:** Tal como com outros medicamentos anticolinérgicos, este medicamento deve ser utilizado com precaução em doentes com glaucoma de ângulo fechado ou retenção urinária. **Doentes com compromisso renal grave:** Nos doentes com compromisso renal grave (taxa de filtração glomerular estimada inferior a 30 ml/min/1,73 m²), incluindo aqueles com doença renal terminal que necessitam de diálise, deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. **Prevenção de infeções orofaríngeas:** De modo a reduzir o risco de infeção orofaríngea por *Candida albicans*, os doentes devem ser aconselhados a lavar a boca ou a gargarejar com água, sem a engolir, ou a lavar os dentes após inalarem a dose prescrita. **Efeitos sistémicos dos corticosteroides:** Podem ocorrer efeitos sistémicos dos corticosteroides inalados, principalmente no caso de doses elevadas prescritas por períodos prolongados. Os efeitos sistémicos possíveis podem incluir: síndrome de Cushing, manifestações Cushingoides, supressão adrenal, atraso do crescimento em crianças e adolescentes, diminuição da densidade mineral óssea, cataratas, glaucoma e, mais raramente, uma série de efeitos psicológicos ou comportamentais incluindo hiperatividade psicomotora, distúrbios do sono, ansiedade, depressão ou agressão (especialmente em crianças). Como tal, é importante que a dose de corticosteroide inalado seja titulada para a dose mais baixa na qual o controlo efetivo da asma é mantido. Podem ser notificados distúrbios visuais com o uso de corticosteroides sistémicos ou tópicos (incluindo intranasais, inalados ou intraoculares). Doentes que apresentem sintomas como visão turva ou outros distúrbios visuais, devem ser considerados para encaminhamento a um oftalmologista para avaliação de possíveis causas dessas perturbações visuais, as quais podem incluir cataratas, glaucoma ou doenças raras como a coriorretinopatia central serosa (CRCS), que foram notificadas após o uso de corticosteroides sistémicos ou tópicos. Este medicamento deve ser administrado com precaução em doentes com tuberculose pulmonar ou em doentes com infeções crónicas ou não tratadas. **Gravidez:** Este medicamento deve ser utilizado durante a gravidez apenas se o benefício esperado para o doente justificar o potencial risco para o feto. **Amamentação:** Tem que ser tomada uma decisão sobre a descontinuação da amamentação ou a descontinuação/abstenção da terapêutica, tendo em conta o benefício da amamentação para a criança e o benefício da terapêutica para a mulher. **Trabalho de parto:** Como outros medicamentos contendo agonistas adrenérgicos beta₂, o indacaterol pode inibir o trabalho de parto devido a um efeito relaxante no músculo liso uterino. **INTERAÇÕES:** **Bloqueadores adrenérgicos beta₂:** este medicamento não deve ser administrado com bloqueadores adrenérgicos beta₂ (incluindo gotas para os olhos) a menos que existam razões importantes para a sua utilização. **Medicamentos conhecidos por prolongarem o intervalo QT:** este medicamento deve ser administrado com precaução a doentes que estejam a ser tratados com inibidores da monoamina oxidase, antidepressivos tricíclicos ou medicamentos conhecidos por 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 beta₂ 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 catiónes orgânicos:** Não é esperada qualquer interação medicamentosa clinicamente relevante. **EFEITOS INDESEJÁVEIS:** **Frequentes (≥1% a <10%):** e potencialmente graves: hipersensibilidade, **Muito frequentes:** asma (exacerbação), nasofaringite. **Frequentes (≥1% a <10%):** infeção do trato respiratório superior, candidíase, infeção do trato urinário, cefaleia, taquicardia, dor orofaríngea, tosse, disfonía, gastroenterite, dor musculoesquelética, espasmos musculares, púrpura, **Pouco frequentes (≥0,1% a <1%):** hiperglicemia, cataratas, boca seca, erupção cutânea, prurido, disúria. Para mais informações, consultar o titular de autorização de introdução no mercado ou o representante local do titular de autorização de introdução no mercado. Medicamento sujeito a receita médica. **Escalação de participação:** Escalão B. **Titular da AIM:** Novartis Europharm Limited. **Representante local:** Laboratório Medinfar - Produtos Farmacêuticos, S.A. - Rua Henrique de Paiva Couceiro, N.º 29, Venda Nova, 2700-451 Amadora Informações Essenciais Compatíveis com o Resumo das Características do Medicamento (ZIM_RCM20210422_IEC_v2).



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Editorial

O direito das crianças ao ar puro como parte de um ambiente saudável está consagrado na Convenção das Nações Unidas sobre os Direitos da Criança.

As últimas Diretrizes Globais de Qualidade do Ar (AQG) da OMS, publicadas em 2021, estimaram que a poluição do ar é responsável por quase 7 milhões de mortes prematuras anualmente”.

A evidência dos mecanismos biológicos através dos quais os poluentes do ar atmosférico causam danos celulares e tecidulares têm evidência crescente. As crianças são particularmente suscetíveis pelas suas características fisiológicas e comportamentais.

Estes são aspetos introdutórios do artigo original publicado no ACD 2024;109:483–487, da autoria de um grupo do *King's College* de Londres.

Focam ainda que já existem recomendações para proteção da má qualidade de ar nas escolas e em casa, emitidas pelo *Royal College of Paediatrics and Child Health*, mas as ações devem ser tomadas antes e durante a construção das Escolas e não depois...

Quem está interessado nas origens e controlo das doenças respiratórias crónicas ler com prazer outros artigos deste número, nomeadamente na asma e na DPOC. Há ainda um importante artigo do grupo PERN (Pediatric Emergency Research Networks) sobre a heterogeneidade de práticas em urgência, desta vez nas crises de asma.

E talvez o mais curioso deste número “*Asthma, classical conditioning, and the autonomic nervous system – a hypothesis for why children wheeze*”, que desenvolve uma teoria interessante: “a asma pode ocorrer devido a alterações determinadas no desenvolvimento autonómico pré-natal, com aumento do desencadear das componentes parassimpáticas do reflexo de mergulho como gatilho para respostas reflexas condicionadas...”

Ambiente, heterogeneidade da prática clínica, reabilitação e contributos para a etiologia e trajetória das doenças respiratórias, da idade pediátrica ao adulto.

Tudo bons motivos para leituras de Verão!

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ARTIGO ORIGINAL

Investigação sobre a qualidade do ar nas imediações das novas escolas em Inglaterra: os parques infantis e os edifícios escolares poluídos constituem uma fonte de danos evitáveis

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RESUMO

Objetivo Avaliar os níveis de poluentes nos locais das novas escolas e se os alunos estão devidamente protegidos dos riscos associados.

Cenário A poluição atmosférica provoca danos na saúde das crianças, aumentando as taxas de infeções respiratórias, as agudizações de asma, as alergias e os cânceros na infância. Outros efeitos incluem resultados neurocognitivos mais fracos e doenças multissistémicas na idade adulta.

Desenho Obtivemos uma lista de todas as 187 novas escolas propostas em Inglaterra entre 2017 e 2025 e encontramos localizações para 147 das mesmas. Avaliámos a qualidade do ar em função dos objetivos de qualidade do ar da OMS e do percentil de qualidade do ar da localização em relação aos níveis de poluição em todo o Reino Unido. Analisámos a legislação e as orientações relevantes.

Resultados A nossa análise revelou que 86% das novas escolas (126/147) ultrapassaram os três objetivos da OMS e que todos os locais ultrapassaram pelo menos um objetivo. A nível nacional, 76% (112/147) dos locais situavam-se no percentil 60 ou superior de poluição. Em Londres, o percentil mediano de poluição era o 90, com um mínimo de 76 e um máximo de 99 (IQR=83 a 94).

Conclusão As orientações para as propostas de localização da escolas não incluem qualquer requisito de avaliação da qualidade do ar no local identificado. A regulamentação relativa à construção também não tem em conta a má qualidade geral do ar e subestima significativamente os níveis dos principais poluentes atmosféricos nas imediações das escolas. Defendemos que a avaliação da qualidade do ar deve ser obrigatória na fase de proposta e planeamento de qualquer novo edifício escolar e que as orientações e a legislação nacionais devem ser atualizadas com urgência.

INTRODUCTION

Children's right to clean air as part of a healthy environment is enshrined in the UN Convention on the Rights of the Child. The latest WHO Global Air Quality Guidelines (AQG) published in 2021 estimated that air pollution is responsible for nearly 7 million premature deaths annually.¹ The 2021 WHO Global AQG gives numerical targets for annual exposure to six pollutants: PM_{2.5}, PM₁₀, NO₂, O₃, SO₂ and CO₂, listed in table 1. These targets are defined as 'the lowest exposure level of an air pollutant above which ... there is an increase in adverse health effects'. The 2021 guideline significantly revised the 2005 standards, with annual PM_{2.5} reduced by 50%, PM₁₀ by 25%, NO₂ by 75% and introduced six new targets. These changes were informed by a meta-analysis of evidence regarding the adverse effects of air pollution.² An analysis by City Hall (The Mayor of London Assembly) in 2021 estimated that more than 3.1 million children in England

Key messages

What is the key question?

- Air pollution is detrimental to children's health and has long-term effects on adult health.
- Air pollution targets have been reduced as harm has been proven at lower levels than previously thought.
- It is already known that many areas of England have poor air quality.

What is the bottom line?

- This study contextualises and highlights alarmingly poor air quality surrounding new schools approved and proposed to open in England.
- This study provides descriptive data and visualisation of annual air quality breaches of WHO Air Quality Guidelines (AQG) targets surrounding new schools in England.
- This study analyses existing new school proposal and opening guidelines, including building regulations omitting statutory or mandatory recommendations to ameliorate poor air quality.

Why read on?

- In terms of the opening and planning of new schools this study could impact policy and guidelines to include monitoring and expert guidance if AQG targets are breached.

are attending schools in areas with unsafe levels of air pollution, exceeding WHO guideline targets for PM_{2.5}.³

Increased research has allowed a better understanding of the biological mechanisms by which inhaled air pollutants cause cellular and tissue damage. It is proposed that inhaled particulates enter the airway, accumulate in cells, and cause epigenetic changes, protein aggregation, mitochondrial impairment and arteriosclerosis.^{4,5}

Children are more susceptible to the harmful effects of pollutants as their developing tissues are undergoing rapid changes, paired with less developed anti-oxidant defence systems to respond to stress.^{6,7} This is exacerbated by a higher minute ventilation rate, and low stature, meaning they walk at the level of traffic fumes and higher concentrations of pollutants.⁸

The acute effects on children include higher incidence of asthma, worsening of symptoms and



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Table 1 WHO AQG targets for pollutants and data for new school sites

Pollutant (unit)	WHO AQG target for annual exposure	Median annual exposure at new school site (IQR)	Number of new school sites breaching target (%)
PM _{2.5} (mcg/m ³)	5	10.94 (9.95, 11.53)	147 (100)
PM ₁₀ (mcg/m ³)	15	17.40 (16.18, 18.16)	130 (88)
NO ₂ (mcg/m ³)	10	17.73 (14.27, 23.89)	137 (93)
Not included in our analysis	WHO ACG Target (duration)		
O ₃ (mcg/m ³)	100 (8 hour*)		
SO ₂ (mcg/m ²)	40 (24 hour*)		
CO (mg/m ³)	4 (24 hour*)		

* 99th percentile i.e. 3-4 exceedance days per year.

CO, carbon monoxide; NO₂, nitrogen dioxide; O₃, ozone; PM₁₀, particulate matter than is 10 micrometers or less in diameter; PM_{2.5}, particulate matter that is 2.5 micrometers or less in diameter.

frequency of asthma exacerbations in those already diagnosed, increased sensitivity to allergens, shortness of breath, nose and throat irritation, more frequent and severe respiratory tract infections, and pneumonia.^{5-9 10}

Long-term effects from air pollution include reduced lung function,⁶ intrauterine growth restriction (IUGR) and low birth weight,^{1 5 10} increased risk of chronic obstructive pulmonary disease (COPD), carcinoma and cerebrovascular and cardiovascular diseases including ischaemic heart disease and strokes.⁵⁻⁷

In addition to the physical health effects, adverse outcomes have been proven on cognition, behaviour, psychomotor development and academic performance in children in relation to air pollution exposure.¹¹ Positive associations have been found between long-term exposure to levels of PM_{2.5} and declines in cognition, symptoms of depression and mental health in adolescents and adults,^{12,13} with consistent patterns of white matter volume reduction demonstrated in multiple studies combining neuroimaging modalities.¹¹

The WHO stated: 'air pollution is now recognised as the single biggest environmental threat to human health'.¹ This study aims to visualise newly approved or proposed school locations in England in comparison to the WHO AQG targets. We provide an overview of the current status of new school locations and the extent they attain or surpass the WHO 2021 AQG targets. Our aim is to inform public policy and increase attention on this important issue.

METHODS

Data sources

We identified 187 newly approved, and pre-approved, school proposals in England between 2017-2025.¹⁴ Locations were acquired for 147 (79%) of these schools from their websites, proposals, consultation documents, local authority or multi-academy trust social media accounts, and contractor/architect project publications. For the seven greenfield sites that did not yet have postcodes, we identified the closest residential or business postcode using GPS coordinates, within 1-200 metres of the site. Proposals with no identifiable site at the time of our search were not included in the analysis (n=24), and an additional 16 proposals had been withdrawn.

We obtained air quality data from addresspollution.org for three WHO AQG pollutant metrics (PM_{2.5}, PM₁₀ and NO₂). This is a free public service from the Central Office of Public Interest (COPI) that utilises air pollution data for every UK address sourced from a national 20 m/sq resolution model developed by Imperial College London's Environmental Research Group (ERG). The pollution data are annual averages from a national model based on 2019 inputs. COPI calibrated this data with real-world pollution levels recorded at over 19 500 council monitors across the UK, resulting in a more accurate national model. The website also assigns percentile rankings to addresses, assigning colour-coded rankings

from 'low' to 'very high', based on the address's percentile relative to nationwide pollution levels. These are determined through standardising and calculating data for each pollutant at every address.¹⁵

PM_{2.5}, PM₁₀ and NO₂ levels were recorded for every school location, alongside the provided pollutant percentile. The number of WHO AQG targets breached was noted for each site (table 1, figure 1). We obtained longitude and latitude coordinates for each school location using a postcode conversion website.¹⁶

Statistical methods

The median (IQR) measures of PM_{2.5}, PM₁₀ and NO₂ were presented for all schools, alongside the total number and percentage breaching each target. The pollution percentiles, were categorised into five groups, represented by a colour gradient from light yellow (least polluted) to dark red (most polluted). Longitude and latitude coordinate information was then used to depict this geographically, superimposing colours onto road maps, with marker size proportional to the school population. The analysis provided in this study was conducted without adjustment for external factors and is intended solely for descriptive purposes. All analyses were conducted on R studio version 4.2.2. Maps were built using R-package leaflet.¹⁷

RESULTS

The schools proposed exhibited varying sizes, with a median capacity of 420 (IQR=142 to 630). Primary Schools made up 40.8% (n=60) of the data, 29.9% (n=44) were Secondary Schools, 25.2% (n=37) were All-Through schools and 4.1% (n=6) were ages 16-19 specifically.

The median (IQR) PM_{2.5} reading across all school sites was 10.94 µg/m³ (9.95 to 11.53 µg/m³), more than double the WHO AQG of 5 µg/m³. PM₁₀ showed a median (IQR) of 17.40 µg/m³ (16.18 to 18.16 µg/m³), with the lower quartile surpassing the WHO AQG of 15 µg/m³. The median (IQR) NO₂ level was 17.73 µg/m³ (14.27 to 23.89 µg/m³) with the lower quartile also surpassing the WHO AQG target of 10 µg/m³. NO₂ showed the most variability between locations of all three metrics. (table 1).

Every school location exceeded at least one of the WHO AQG targets, and 86% (126/147) exceeded all three (PM_{2.5}, PM₁₀ and NO₂). Only six locations breached only one WHO target, four in the South-West and one in the South-East and one in the West Midlands, the rest breached two or more targets (table 1, figure 1).

The median pollution percentile was 61 (IQR = 41 to 81), whereby 76% (112/147) were in the 60th or greater percentile compared with pollution levels across the UK. Schools with elevated pollution percentiles exhibited a clustering pattern in major UK cities including London, Birmingham, Manchester, and Leeds. Conversely, schools in other large English cities, including Liverpool, Bristol, and Newcastle, were found to have lower pollution percentiles (figure 2). Locations in Devon and Cornwall were seen to have the lowest pollution percentile.

The median pollution percentile for school locations in Central London was 90th (IQR = 83rd to 94th) with a minimum of 76th and maximum of 99th in comparison to the UK. School locations in the South-East of London appeared to have slightly lower pollution percentiles, however, this difference is minimal.

DISCUSSION

In England, children of mandatory school age spend around 7 hours a day, or 35 hours per week at school for more than half of the year. With wrap-around childcare, this can rise to as high as 55 hours a week for some children. Evidence suggests that although on average children spend around 30% of their time at school, this accounts for 44% of pollution exposure.¹⁸

Tackling this is complex and requires systemic national strategies to improve overall air quality as well as funding to identify high-risk schools and retrofit modern ventilation systems. Ensuring safe indoor air quality at newly built schools should be simpler, but only if the need for harm reduction is considered early in the process of selecting new school locations and designing sites.

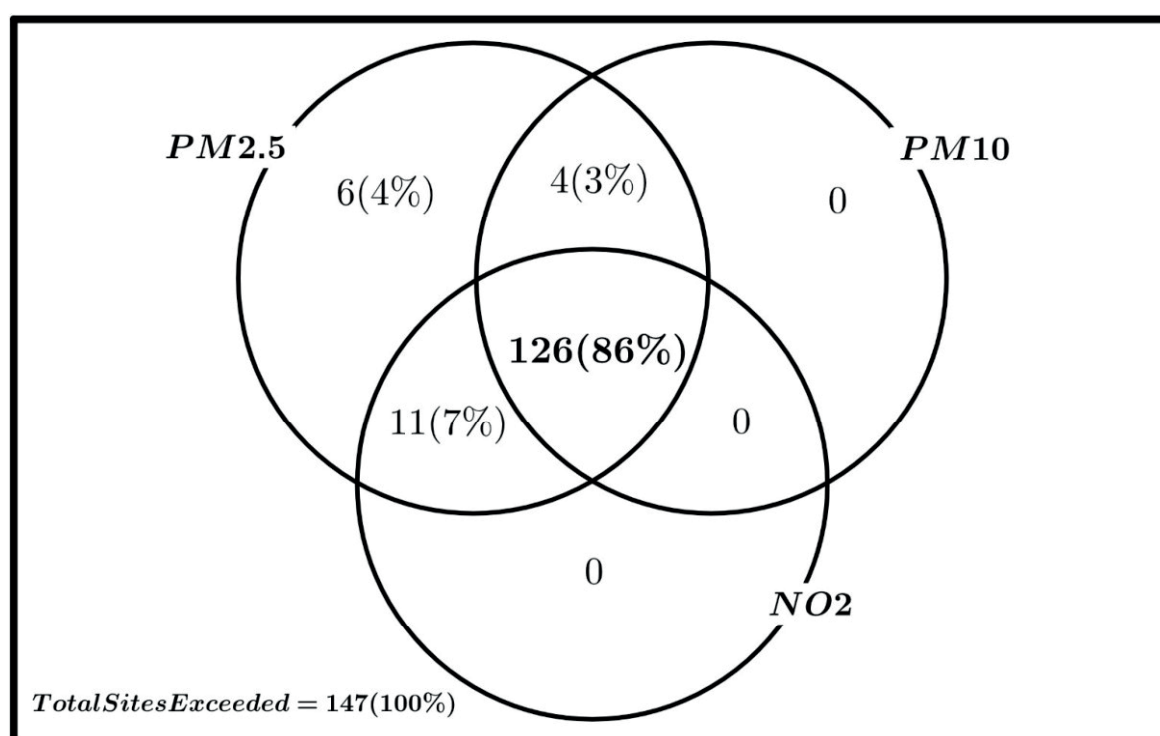


Figure 1 Venn Diagram of the number of school sites and percentage of total sites exceeding WHO AQG targets for PM2.5, PM10 and NO2.

In a previous publication, we showed that new school proposals do not consider air quality when assessing the suitability of a site. We obtained the proposal document for 36 (20%) of 180 of the same schools studied here (seven more proposals were approved subsequently), and searched each for the terms 'air quality' and 'pollution'. The return rate was zero.¹⁹ This is likely due to a lack of a mandatory requirement, although even a non-mandatory prompt to consider this issue when proposing new schools could be beneficial.

Our data shows that 86% of new school sites exceed three WHO AQG targets and this is not surprising given that schools are most needed in areas of higher population density, which are most likely to be affected by significant levels of pollution. Demographic changes across the UK mean the number of children enrolled in schools is projected to fall in the next 5 years²⁰ and beyond. This may result in a need for the closure of existing schools and building of new ones, making it even more important that new schools are designed with air pollution in mind.

Statutory and non-statutory national guidance for new school proposals^{21, 22} set out the standards against which each proposal is judged, including impact and equalities assessments, funding and financial viability, and public consultations. It is mandatory that each proposal includes evidence of 'suitable outdoor space in order to enable physical education ... and for pupils to play outside safely'. Proposals must also specify how children will be able to 'travel sustainably, where possible, e.g. by walking, cycling or using public transport'.^{21, 22} Travel and outdoor play result in peaks of exposure to pollutants¹⁸ and yet neither air quality, nor pollution is mentioned in the national guidance for new proposals.

We reviewed building regulations as we hoped once a new school was approved, poor air quality could be ameliorated by robust building design. The guidance states, 'Major UK cities now require measures to tackle the problem of exposure of staff and students to frequent high air pollution while working and studying' and 'The elevated air pollution levels close to some schools mean that designers must consider:

- ▶ ... location of air intakes in unpolluted zones
- ▶ closing windows when external pollutant levels are high
- ▶ ... effective air filtration in ventilation systems²³

Finally, a recommendation is made that 'Designers can find out about current air pollution levels in the area of a school using the 5 day air pollution forecasts provided by the Met Office'.²²

We believe this is inadequate as air quality can vary significantly according to seasonal weather and traffic.

The regulations fail to take into account how widespread poor air quality is, and place greater emphasis on ventilation and fresh air than filtration systems. However, unfiltered natural ventilation (windows and passive vents) brings polluted outdoor air inside and assumes that major pollutants are absent, which we have demonstrated is not the case.

The 2022 Department for Education Sustainability and Climate Change Strategy²⁴ sets out how schools can contribute to improving air quality by working towards carbon neutrality, but does not mention protecting children from the impact of the poor air quality that currently exists.

Comprehensive recommendations have already been made by the Royal College of Paediatrics and Child Health (RCPCH) regarding protection from poor air quality at home and school, with regards to construction and maintenance of buildings, and enforcement measures. These include:

- ▶ 'Legally enforceable standards for indoor and outdoor air quality
- ▶ Increased Local Authority powers and funding to enforce adherence to minimum safe standards
- ▶ Access to site-specific air quality monitoring
- ▶ Revision of Buildings Regulations to ensure air quality checks are done at completion of construction and meeting standards is required for building sign-off and continues to be monitored once buildings are in use'.²⁵

However, performing air quality monitoring only once construction is complete risks missing the opportunity to reduce exposure to pollution by better building design and other interventions.

Limitations

This study provides descriptive analysis using annual average air quality data derived from postcodes at new school locations, with figures serving as estimates of population exposure, thus limiting the depth of the analysis. Pollution levels are sensitive to factors such as time of day and seasonality, suggesting that a more detailed analysis could benefit from more granular pollution data. Furthermore, the data used in this analysis comes from a 2019 national model developed by Imperial College London. This data represents a snapshot from 5 years ago and current pollution levels will vary. However, given the disruptions caused by the COVID-19

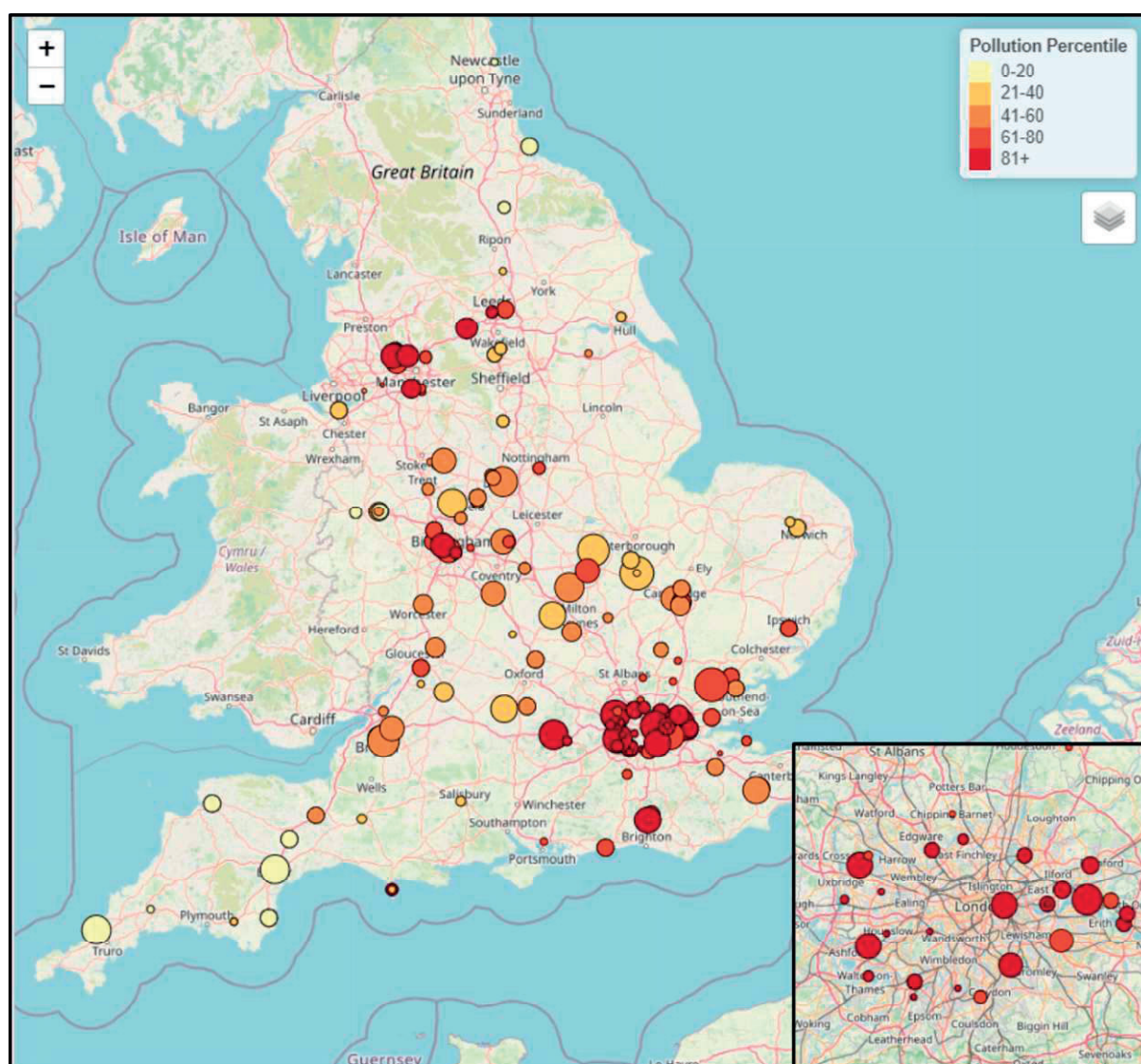


Figure 2 Pollution percentile mapped onto school sites in England, with inset of the City of London.

pandemic, using 2019 as a reference may be reasonable to assess 'normal' pre-pandemic pollution levels.

We did not analyse the reasons for identified poor air quality at individual sites, which may include proximity to roads and other transport routes, manufacturing sites etc. Dependent on the main cause different local interventions, such as traffic reduction strategies (congestion zones, low traffic neighbourhoods, 'School Streets' which involve temporary road closures at peak times of school drop-off and pick-up) may be fast and effective ways to improve air quality locally. We have therefore limited our recommendations to ways that indoor air quality can be improved, even if outdoor pollutants remain high, as we believe this could have significant health benefits and this aspect is not well considered in any existing literature or guidance.

RECOMMENDATIONS AND CONCLUSION

We believe that the Department for Education should update the guidance on new school proposals so that an air quality assessment is mandatory at the proposal stage. New buildings or campuses of existing schools should be given the same consideration and therefore planning regulations also need to be updated. These actions would ensure that:

1. Air quality dialogue is included in the public consultation stage.
2. Sites and buildings can be designed that minimise the impact of air pollution on children.

Building Regulations must also be updated to emphasise that poor air quality is widespread and significantly detrimental to health. The suggested voluntary use of 5 day Met Office air pollution

forecasts should be replaced. Both here and in the school proposal guidance, long-term exposure needs to be assessed according to the most up-to-date monitoring and modelled data. If two or more WHO AQG targets are breached we believe that on-site monitoring should be undertaken and expert advice should be sought.

Unless current recommendations are replaced with mandatory standards, it is unlikely that those proposing or designing new schools will make these assessments unless there is an individual already involved in the process who is both well-informed and passionate about reducing the impact of pollution.

We hope this study can influence school proposers, designers and national policy. The public health implications of avoidable childhood exposure to poor air quality could have significant effects on both the quality adjusted life years of the population and financial health expenditure in the United Kingdom. Children deserve protection from avoidable harm while at school.

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ARTIGO ORIGINAL

Análise das recomendações das linhas orientadoras para tratamento de agudizações da asma em crianças: um estudo da Pediatric Emergency Research Networks (PERN)

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RESUMO

Fundamentos Existe uma variação significativa na prática clínica da asma pediátrica aguda, particularmente nas agudizações graves. Não se sabe se esse facto se deve a diferenças nas linhas orientadoras clínicas.

Objetivos Descrever e comparar o conteúdo e a qualidade das linhas orientadoras clínicas para o tratamento de agudizações de asma agudas em crianças em diferentes regiões geográficas.

Métodos Estudo observacional das linhas orientadoras para o tratamento da asma pediátrica aguda das instituições no âmbito de uma colaboração global de seis redes regionais de investigação de urgências pediátricas.

Medições e principais resultados Foram identificadas 158 linhas orientadoras. Metade das linhas orientadoras apresentava recomendações para pelo menos dois grupos etários e a maioria das linhas orientadoras apresentava recomendações de tratamento de acordo com a gravidade da asma. A medicação anticolinérgica por inalação foi recomendada na maioria das linhas orientadoras para a asma grave e crítica, mas verificaram-se recomendações inconsistentes para a sua utilização em agudizações leves e moderadas. Outras terapêuticas inalatórias, como a mistura hélio-oxigénio (Heliox) e o magnésio nebulizado, foram recomendadas de forma inconsistente para a doença grave e crítica. A terapêutica broncodilatadora parentérica e a adrenalina foram maioritariamente reservadas para a asma grave e crítica, sendo o magnésio intravenoso o mais recomendado. Registaram-se diferenças regionais na utilização de outros broncodilatadores parentéricos, em particular a aminofilina.

A avaliação da qualidade das linhas orientadoras identificou classificações elevadas para clareza da apresentação, âmbito e objetivo, mas identificou classificações baixas para envolvimento das partes interessadas, rigor do desenvolvimento, aplicabilidade e independência editorial.

Conclusões As atuais linhas orientadoras para o tratamento de agudizações agudas da asma pediátrica apresentam défices substanciais em importantes domínios de qualidade e fornecem orientações limitadas e inconsistentes para agudizações graves.

INTRODUCTION

Clinical practice guidelines guide management of paediatric asthma exacerbations in hospital settings. These documents may have been developed by international asthma bodies,¹ by experts in individual countries or regions,^{2–9} or created at specific hospitals.¹⁰

Most children attending emergency departments (EDs) have mild or moderate exacerbations, and quickly respond to first-line therapy (usu-

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- There is significant practice variation in acute paediatric asthma, particularly regarding severe exacerbations where there is inconsistent selection and utilisation of parenteral bronchodilators.

WHAT THIS STUDY ADDS

- This observational study of 158 clinical guidelines from a global paediatric emergency research network found that current guidelines for the management of acute paediatric asthma exacerbations have substantial deficits in important quality domains and are limited and inconsistent due to different interpretations of weak evidence to inform the management of severe or critical asthma.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- The current development of hospital-specific, region-specific or even national guidance risks considerable duplication of effort, inefficiency and production of guidelines which are not of high quality.
- Large, well-designed, multicentre randomised controlled trials are needed to provide a solid foundation for future clinical practice guidelines, which should be developed through a rigorous global collaborative process to ensure high-quality robust guidance.

ally inhaled bronchodilators and oral steroids) for which there is general consensus and considerable research support.^{11–13} In contrast, the management of severe asthma exacerbations is less clear due to a lack of robust evidence.^{14 15}

Previous studies have documented significant practice variation in acute asthma, particularly for severe exacerbations.^{16–18} It has not been determined whether this is due to differences in clinical guidelines. Further, it is unknown whether there is variation in guidelines within or between geographic regions/ countries.

The Pediatric Emergency Research Networks (PERN) asthma working group was formed in 2017, with the aims of developing consensus evidence-based asthma outcome measures and international consensus guidelines for the conduct and reporting of clinical trials of therapies for acute asthma exacerbations. Currently, the group comprises members from 17 countries.¹⁹

The aims of this study were to assess current clinical practice guidelines used in EDs associated with PERN. We aimed to:

1. Describe and compare recommendations for the management of acute exacerbations of asthma in children between geographic regions.
2. Assess guideline quality.

METHODS

This was an observational study of acute paediatric asthma guidelines from institutions belonging to a global emergency research network. The project results are reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.²⁰

Setting and guideline collection

Physicians and hospitals were invited to participate in the study by email (October 2018) via the eight partner networks that belong to PERN, and to the members of the PERN asthma working group. The PERN comprises the following networks: Research in European Paediatric Emergency Medicine; 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 & 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 en Latinoamérica.²¹

The email recipients were invited to forward the email to other physicians and hospitals within their local geographical region and/or research network. The request for participation was also shared on social media. This snowball approach aimed to encourage sampling within countries without formal organised research networks.

Each participating hospital was asked to provide a copy of their current acute asthma guideline. This could include local, regional or national guidelines for management of acute onset of wheezing or asthma.

Data abstraction: guideline content

To reduce the risk of bias, each clinical guideline was independently abstracted by two trained reviewers, who were provided with clear definitions, rules for 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 Capture database hosted at Monash University.^{22,23}

Any discrepancies between reviewers resulted in a discussion; if the discrepancy remained unresolved, a senior author (SC) was consulted about a final decision.

We planned for guidelines written in languages other than English to be abstracted by two investigators fluent in both English and the non-English 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.

For each guideline, specific data were obtained on the definition of asthma (including age range); assessment of acute asthma severity (according to the criteria used within each guideline); and recommendations and severity thresholds for initiating various treatments, including: (1) inhaled beta-agonist therapy; (2) systemic corticosteroids; (3) adjunctive therapy, such as inhaled

Table 1 Overview of clinical guidelines for acute asthma management in children

Country/region (research network)	n (%)
UK and Ireland (PERUKI)	59 (37.3)
Spain (RISEUP-SPERG)	31 (19.6)
USA (PECARN, PEM-CRC)	27 (17.1)
Australia/New Zealand (PREDICT)	21 (13.3)
Canada (PERC)	9 (5.7)
Other (Singapore, India, Costa Rica, Africa and Europe)	11 (6.9)
Language	
English	122 (77.2)
Spanish	27 (17.1)
Catalan	5 (3.2)
Other (French=3, Dutch=1)	4 (2.5)
Minimum age	
<12 months	2 (1.3)
12 months	28 (17.7)
12 to <24 months	1 (0.6)
24 months	29 (18.4)
Not specified	98 (62)
Maximum age	
11 years	2 (1.3)
14 years	5 (3.2)
16 years	10 (6.3)
17 years	2 (1.3)
18 years	9 (5.7)
21 years	1 (0.6)
Not specified	129 (81.6)
Age groups	
Two age groups	62 (39.2)
Three age groups	17 (10.8)
Oldest age group >5 years	13 (8.2)
Oldest age group >11 years	4 (2.5)
Not specified	79 (50)
Lowest classification of severity described within guideline	
Mild	107 (67.7)
Mild/moderate	18 (11.4)
Moderate	28 (17.7)
Severe	5 (3.2)
Highest classification of severity described within guideline	
Critical/life-threatening	105 (66.5)
Severe	53 (33.5)
Number of guidelines which distinguish severe and critical/life-threatening	
Separate guidance for severe and critical/life-threatening	95 (60.1)
Guidance for severe, but <u>not</u> for critical/life-threatening	53 (33.5)
Guidance for critical/life-threatening but not severe	10 (6.3)

ipratropium and magnesium; (4) parenteral bronchodilator medications, including intravenous magnesium and epinephrine; (5) oxygen therapy (including devices and flow rates); (6) non-invasive and invasive ventilation; (7) Heliox; and (8) ketamine.

A copy of the data extraction sheet is provided in online supplemental appendix 1.

Guideline quality assessment

Each clinical practice guideline was assessed using the Appraisal of Guidelines for Research & Evaluation II (AGREE-II) instrument,

Table 2 Proportion (number and percentage) of guidelines providing treatment recommendations according to each severity of illness, by region

	Mild	Mild-moderate	Moderate	Moderate-severe	Severe	Critical
UK and Ireland	16 (27.1)	12 (20.3)	42 (71.2)	2 (3.4)	57 (96.6)	58 (98.3)
Spain	31 (100)	0 (0)	31 (100)	2 (6.5)	31 (100)	6 (19.4)
USA	26 (96.3)	3 (11.1)	24 (88.9)	2 (7.4)	22 (81.5)	12 (44.4)
Australia/New Zealand	20 (95.2)	2 (9.5)	18 (85.7)	1 (4.8)	18 (85.7)	21 (100)
Canada	9 (100)	0 (0)	9 (100)	1 (11.1)	9 (100)	2 (22.2)
Other	5 (45.5)	4 (36.4)	6 (54.5)	1 (9.1)	11 (100)	6 (54.5)

an international best-practice tool for the assessment of clinical practice guidelines.²⁴ Two raters were used, in accordance with recommendations from AGREE-II, to increase the reliability of the instrument.²⁴ All raters had specific training and were provided with an AGREE-II instruction manual. 23 items across six quality domains were assessed (scope and purpose; stakeholder involvement; rigour of development; clarity of presentation; applicability; and editorial independence), as well as overall quality, and whether each reviewer would (1) recommend the guideline, (2) recommend use of the guideline with modifications or (3) not recommend the guideline.

Quality domain scores were determined by summing up all scores of the individual items in a domain and scaling the total as a percentage of the maximum possible score.²⁵ The AGREE-II instrument does not provide specific advice on how to interpret domain scores and notes that ‘there are no empirical data to link specific quality scores with specific implementation outcomes’, but provides examples using a threshold of >70% as evidence of ‘high quality’.²⁵ We considered domain scores >70% as a high rating, while those <40% reflected a poor rating.

The process of online translation was deemed insufficient to assess guideline quality. Therefore, for the four guidelines written in Dutch or French, guideline content was extracted, but an assessment of guideline quality was not performed.

Statistical methods

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, Romania, Switzerland, France, Zimbabwe, Singapore, India, Costa Rica and two guidelines from South Africa). We did not pre-specify a sample size, as we aimed to obtain as many guidelines as possible throughout the participating networks.

Descriptive statistics were used to summarise guideline characteristics, treatment recommendations and guideline quality. Non-parametric data are reported using median and IQR, while

categorical data are presented as count and percentage. We did not impute any missing data. Differences in proportions of categorical and non-parametric data are compared using the χ^2 and Kruskal-Wallis test, respectively. All analyses were performed using SPSS for Windows (IBM Released 2021. IBM SPSS Statistics for Windows, V.28.0. Armonk, New York, USA: IBM Corp.).

Patient and public involvement

Patients were not involved in the design of this study.

RESULTS

There were 158 clinical guidelines identified. The majority (95.6%) were from hospitals participating in national or regional PERN-associated networks, with the greatest number submitted from the UK and Ireland (PERUKI network), Spain (RISEUP-SPERG network) and the USA (PECARN and PEM-CRC networks) (table 1).

Most guidelines were written in English; the most common non-English language used was Spanish. The majority did not provide a specific age range for inclusion; 60/158 (38%) provided a minimum age, and 29/158 (18%) provided a maximum age. Half of the guidelines provided separate management guidance for specific age groups. Of these, 62/79 (78%) had recommendations for two age groups, while 17/79 (22%) provided advice for three age groups.

Most guidelines provided distinct treatment recommendations according to asthma severity, although this varied by region (table 2). Mild asthma was addressed in over two-thirds, while 28 (18%) guidelines focused on asthma of moderate severity or worse, and 5 (3%) guidelines focused only on severe asthma. Recommendations on treatment for critical/life-threatening asthma were provided in 105 (66%), while 53 (34%) provided recommendations on severe (but not critical/life-threatening) asthma.

A summary of region-specific guidelines for each severity of asthma exacerbation is provided in online supplemental appendix 2. There were consistent recommendations for the use of inhaled short-acting beta-agonists at all levels of severity, and for systemic corticosteroids for moderate, severe and critical asthma (figure 1). Inhaled anticholinergic therapy was recommended in most guidelines for severe and critical asthma, with a few guidelines

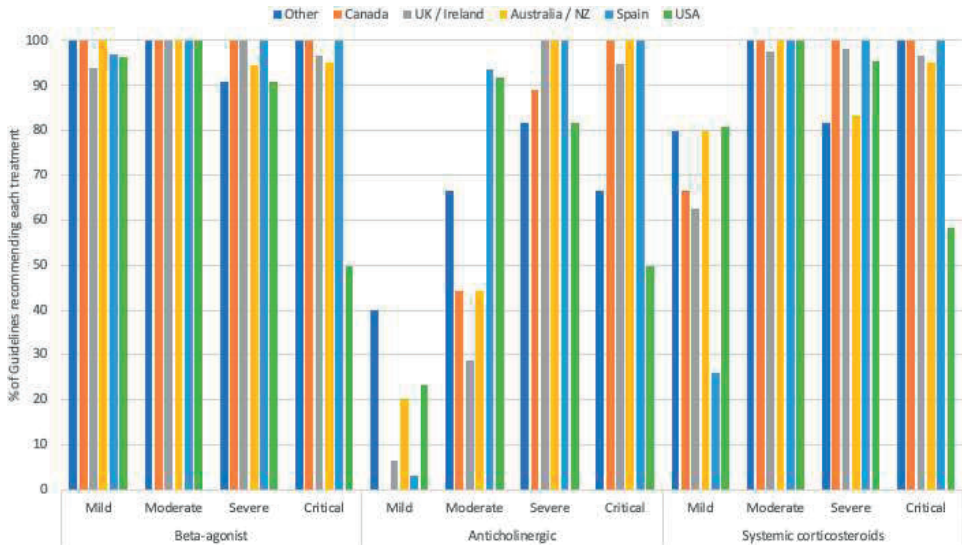


Figure 1 Guideline recommendations for inhaled bronchodilators and systemic corticosteroids, by region and exacerbation severity.

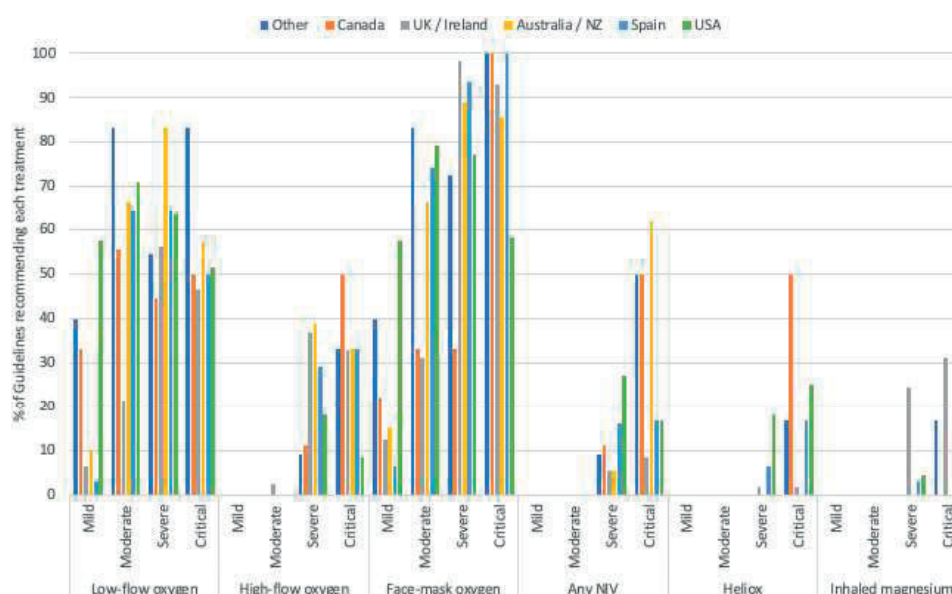


Figure 2 Guideline recommendations for respiratory support and additional inhaled therapy, by region and exacerbation severity. NIV, non-invasive ventilation (continuous positive airway pressure or bi-level positive airway pressure).

also recommending this therapy for mild and moderate asthma. There was considerable variation in inhaled anticholinergic recommendations for moderate asthma with over 90% of USA and Spanish guidelines recommending use compared with <30% of UK and Ireland. Some guidelines from the USA did not recommend inhaled beta-agonists or systemic corticosteroids for critical asthma; however, these guidelines focused on ventilatory support rather than pharmacological therapy.

Recommendations for oxygen therapy were less clearly articulated (figure 2). In general, supplemental oxygen delivered via low-flow nasal or face-mask route was the first-line treatment, while high-flow nasal cannulae and non-invasive ventilation were reserved for severe and critical illness. Other inhaled therapies such as helium-oxygen mixture (Heliox) and nebulised magnesium were inconsistently recommended for severe and critical illness.

Parenteral bronchodilator therapy (figure 3) and epinephrine (figure 4) were mostly reserved for severe and critical asthma. Intravenous magnesium was most recommended, however, there were some differences in the choice of specific therapies between regions. In nine guidelines, intramuscular epinephrine was also specifically advised in cases where anaphylaxis was suspected.

With respect to guideline quality (table 3), clarity of guideline presentation and scope and purpose of the guideline were rated highly. In contrast, stakeholder involvement, rigour of development, applicability and editorial independence received poor ratings. Only one guideline (the Global Strategy for Asthma

Management and Prevention,²⁶ provided as the guideline used in a Romanian hospital) was recommended for use without modification. Ninety-eight (63.6%) guidelines were recommended for use with modification, and 53 (34.4%) were not recommended.

DISCUSSION

Although clinical practice guidelines for the management of acute paediatric asthma provide consistent recommendations for management of mild and moderate exacerbations, there is considerable variation in treatment recommendations for severe and critical presentations. The guidelines have deficits in quality domains and are limited by a lack of robust evidence for the management of severe or critical asthma.

The use of inhaled bronchodilators and systemic corticosteroids for acute asthma exacerbations is supported by decades of practice and robust evidence.²⁶ This is reflected in consistent guideline recommendations. However, recommendations are inconsistent for children with severe or critical exacerbations, who require treatment beyond first-line therapies.

Cochrane reviews of escalated pharmacological treatment (beyond inhaled bronchodilators and systemic corticosteroids) of children with acute asthma exacerbations highlight a number of knowledge gaps.²⁷ The evidence supporting intravenous magnesium is extremely limited (including only five small randomised studies with disparate results from a total of 182 children),²⁸ while only one study (showing no significant benefit) was identified ad-

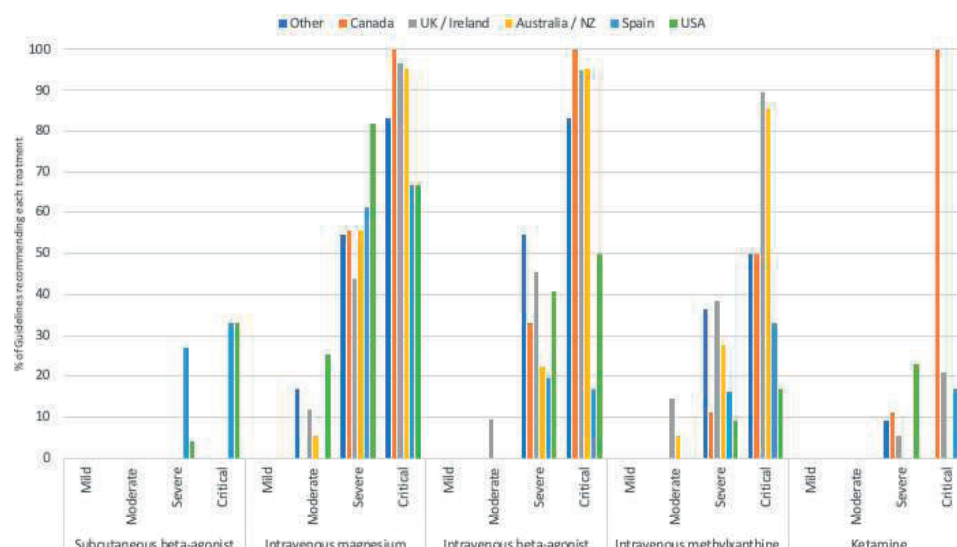


Figure 3 Guideline recommendations for parenteral bronchodilators, by region and exacerbation severity.

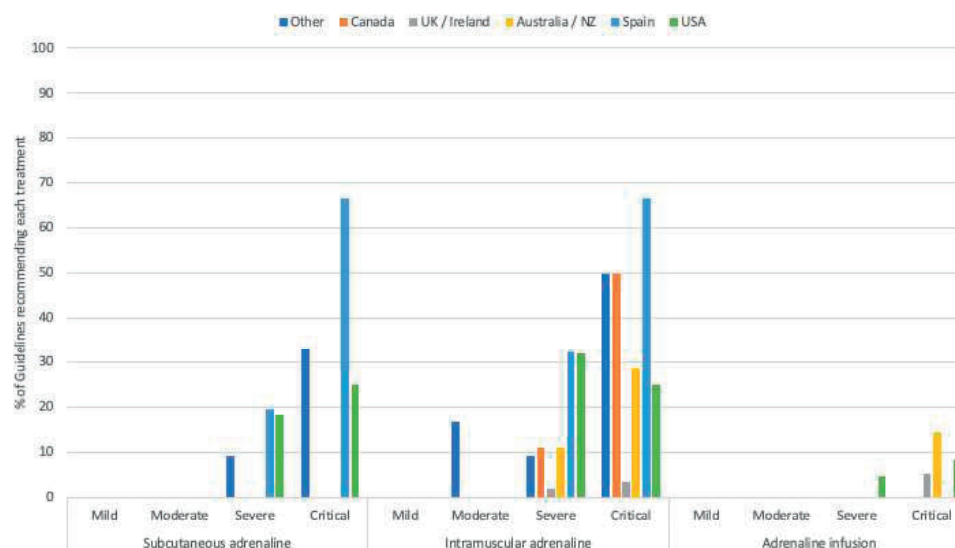


Figure 4 Guideline recommendations for epinephrine, by region and exacerbation severity.

dressings intravenous ketamine.²⁹ Despite a meta-analysis of nearly 3000 patients enrolled in trials of inhaled magnesium, review authors noted that large, well-conducted trials had not shown clinically meaningful benefits.³⁰ This finding has been reinforced by a recent Canada-wide randomised trial of over 800 children demonstrating no difference in hospitalisation when nebulised magnesium was added to nebulised albuterol.³¹

Meta-analyses of studies on intravenous beta2-agonists^{32,33} and/or intravenous aminophylline³⁴ have not demonstrated clinically significant benefit. There is no available Cochrane review on the utility of parenteral epinephrine for acute severe asthma in children.²⁷

A recent Overview of Cochrane reviews of clinical trials on escalated therapy for asthma²⁷ assessed the evidence for parenteral bronchodilators, Heliox, respiratory support and inhaled magnesium. The review found that the majority of comparisons involved between one and three trials and fewer than 100 participants, making it difficult to assess the balance between benefits and potential harms. The authors were unable to make firm practice recommendations.²⁷

A large multicentre study comparing high-flow nasal oxygen to low-flow oxygen for children aged 1–4 years with hypoxic respiratory failure (including a subgroup of children diagnosed with ‘obstructive’ lung disease, such as wheezing, asthma), did not find any overall benefits.³⁵ A Cochrane review of the use of non-invasive ventilation in paediatric asthma identified two trials, with a total of 40 children.³⁶ The authors concluded that current evidence did not permit confirmation or rejection of the effects of non-invasive

ventilation for acute asthma in children, and recommended large, well-designed randomised controlled trials.

It is therefore apparent, that existing recommendations for the best management of severe acute paediatric asthma are currently based on suboptimal evidence with inconsistent, inconclusive or absent results and a paucity of adequately powered randomised controlled trials. Large observational studies have identified that some outcomes (such as intubation) are likely too rare to be used as primary outcome measures, and practice-changing studies will require collaboration between a large number of centres.³⁷ There remains an urgent need for a global agreement regarding optimised trial designs with the most relevant core outcome measures to provide better evidence to inform future clinical practice.¹⁹

The overall guideline quality was moderate in our study, with high ratings for clarity of presentation, scope and purpose. A 2013 review of asthma guidelines providing recommendations for treatment of both children and adults identified significant deficits in guideline quality.³⁸ The proportion of guidelines rated as adequate was low for assessed categories including: scope and purpose, 44.1% (range: 10.0%–79.0%); stakeholder involvement, 33.8% (range: 4.0%–66.0%); rigour of development, 32.4% (range: 8.0%–64.0%); clarity and presentation, 52.1% (range: 17.0%–85.0%); applicability, 21.1% (range: 3%–55%); and editorial independence, 25% (range: 0%–58%).³⁸ Our study has demonstrated improvements in some areas (scope and purpose, clarity and presentation), but highlights ongoing deficits in other important domains such as stakeholder involvement, rigour of development, applicability and

Table 3 Guideline quality assessment (according to AGREE II domains). Results are expressed as the median (IQR) score from a maximum of 100. Each score represents the percentage of the maximum possible score for that domain

	Canada (n=9)	UK/Ireland (n=59)	Australia/New Zealand (n=21)	Spain (n=31)	USA (n=27)	Other (n=6)	Total (n=153)	P value
Scope and Purpose	56 (29–83.5)	97 (76.5–100)	86 (74.25–100)	14 (0–56)	98 (77.5–100)	91.5 (81.75–97.75)	83 (44–100)	0.04
Stakeholder involvement	14 (0.5–36.5)	17 (4.5–32)	40.5 (8–59)	6 (0–22)	29 (6–67)	0 (0–0)	17 (3–33)	0.08
Rigour of development	0 (0–0)	13 (1.5–27.5)	17.5 (3.5–24.5)	8 (3.5–13)	7 (1.5–31.5)	0 (0–0)	10 (1–23)	0.10
Clarity of presentation	94 (90.5–97)	92 (69.5–97)	89 (78.75–93.5)	75 (59.75–83)	86 (72–94)	82 (65.5–97.75)	87 (67–94)	0.36
Applicability	10 (0–32.5)	31 (20–51.5)	45 (17–57.5)	0 (0–4)	27 (7–43)	41 (18–49)	21 (4–44)	0.01
Editorial independence	0 (0–0)	0 (0–0)	0 (0–0)	33 (0–42)	0 (0–0)	0 (0–31.25)	0 (0–0)	0.37
Overall quality (rated from 0 to 7)	3 (2.5–4)	4 (3–5)	4 (3.25–5)	3 (2–4)	4 (3–5)	3 (2.75–3.25)	4 (3–5)	0.04
Reviewer recommends guideline for use?								
Yes	0	0	0	0	0	1	1	<0.001
Yes, with modifications	5	44	17	11	18	3	98	
No	4	15	3	20	9	2	53	

Green shading indicates a domain quality score of >70%; yellow shading indicates a domain quality score of 40–70%; red shading indicates a domain quality score of <40%.

editorial independence. Development of comprehensive, rigorous clinical guidance is a resource-intensive undertaking. The current development of hospital-specific, region-specific or even national guidance risks considerable duplication of effort and inefficiency. However, the current 246-page comprehensive Global Initiative for Asthma (GINA) Management and Prevention does not provide easily accessible, stand-alone guidance for acute severe exacerbations and provides little guidance beyond initial parenteral magnesium.²⁶

Collaboration between GINA and the PERN Asthma working group could enable development of a focused living guideline based on the best available evidence, updated with emerging research, and relevant to the emergency care of children globally. Such a guideline could then be readily adapted for local implementation.

The strengths of our study include solicitation of guidelines from a geographically wide representation by leveraging multiple research networks in paediatric emergency medicine and the appraisal of guidelines using a validated tool.²⁵

Despite this, there are limitations in our study. We did not extract data on methods of assessment of severity. Differences in severity assessment between countries/regions may explain differences in the use of inhaled anticholinergics for moderate exacerbations of asthma.

Although we attempted to obtain clinical guidelines from hospitals from many countries, a large proportion of the analysed guidelines were from the UK, Spain and the USA. Hospitals providing guidelines were members of active research networks, which may have introduced some bias. In addition, there were more guidelines from the UK than USA, despite a much larger number of hospitals and greater population size in the USA.

Although this may have introduced some bias, we made comparisons across geographical regions, thereby reducing the impact of different numbers of guidelines from each network. We had relatively few guidelines from Europe, Asia, South America or Africa, and did not have the capacity to fully translate guidelines from languages other than Spanish and Catalan.

Overall, around one-third of guidelines were not recommended by reviewers. The AGREE-II instrument requires appraisers to make an overall judgement as to whether or not they would recommend use of a particular guideline, however, does not require any explanation as to why this assessment was made.²⁵ We did not ask appraisers to provide specific reasons for their assessment, so are unable to comment on the main reasons why these guidelines were not recommended.

In conclusion, current guidelines for the management of acute paediatric asthma exacerbations have substantial deficits in important quality domains and are limited due to a lack of robust evidence for the management of severe or critical asthma. Large, well-designed, multicentre randomised controlled trials are needed to provide a solid foundation for future clinical practice guidelines.

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

**TRAVA
antes que
seja tarde**

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

*após alta hospitalar



BEVESPI
AEROSPHERE®

(glicopirrónio/fumarato de formoterol)
Suspensão Pressurizada para Inalação

DPOC, doença pulmonar obstrutiva crónica

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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). **Posologia e modo de administração:** **Posologia:** A dose recomendada é duas inalações duas vezes por dia (duas inalações de manhã e duas inalações à noite). Os doentes devem ser aconselhados a não fazer mais de 2 inalações duas vezes por dia. Se for omitida uma dose, esta deve ser tomada assim que for possível e a dose seguinte deve ser tomada no horário habitual. Não deve tomar-se uma dose a dobrar para compensar uma dose esquecida. **Populações especiais:** **Idosos:** Não é necessário qualquer ajuste de dose em doentes idosos. **Compromisso renal:** Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, só deve ser utilizado se o benefício esperado for superior ao risco potencial. **Compromisso hepático:** Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Não existem dados relevantes sobre a utilização de Bevespi Aerosphere em doentes com compromisso hepático grave e o medicamento deve ser utilizado com precaução nestes doentes. **População pediátrica:** Não existe utilização relevante de Bevespi Aerosphere em crianças e adolescentes (com idade inferior a 18 anos) para a indicação de DPOC. **Modo de administração:** Utilização por via inalatória. **Instruções de utilização:** Ao acionar Bevespi Aerosphere, um volume de suspensão é expelido do aplicador 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 broncospasmo, isto é, como terapêutica de alívio. **Asma:** Bevespi Aerosphere não deve ser utilizado no tratamento da asma. **Broncospasmo paradoxal:** Tal como com outra terapêutica inalatória, a administração deste medicamento pode resultar em broncospasmo paradoxal, o qual pode colocar a vida em risco. Se ocorrer broncospasmo paradoxal, o tratamento com o medicamento deve ser interrompido e devem ser considerados outros tratamentos. **Efeitos cardiovasculares:** Podem ser observados efeitos cardiovasculares, após a administração de antagonistas dos recetores 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 tireotoxicose ou com prolongamento do intervalo QTc conhecido ou suspeito. **Hipocaliemia:** Os agonistas β_2 -adrenérgicos podem causar hipocaliemia significativa, o que pode aumentar a suscetibilidade para arritmias cardíacas. A diminuição do potássio sérico é normalmente transitória, não necessitando de suplementação. Em doentes com DPOC grave, a hipocaliemia pode ser potenciada por hipoxia e tratamento concomitante. **Hiperglicémia:** 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. **Hipocaliemia induzida por fármacos:** O tratamento concomitante com derivados da metilxantina, esteroides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocaliémico inicial dos agonistas β_2 -adrenérgicos, pelo que se recomenda precaução na sua utilização concomitante. **Bloqueadores β -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 cardioseletivos, 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, Insónia, Tremor, Taquicardia, Palpitações, Arritmias cardíacas (fibrilhação auricular, taquicardia supraventricular e extra-sístoles), Retenção urinária. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaoam> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel.: +351217987373; Linha do Medicamento: 800222444 (gratuita); E-mail: farmacovigilancia@infarmed.pt). **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado:** Tecnimed - Sociedade Técnico-Medicinal, S.A., Rua da Tapada Grande, n.º 2, Abrunheira, 2710-089 Sintra. **Informações revistas em outubro 2023. Para mais informações deverá contactar o representante local do Titular da Autorização de Introdução no Mercado. Medicamento sujeito a receita médica. Medicamento compartilhado pelo Escalão B (69% de participação no regime geral e 84% de participação no regime especial). Versão 2.0 (outubro 2023).**

Informações essenciais compatíveis com o Resumo das Características do Medicamento

Riltrava Aerosphere 5 microgramas/7,2 microgramas/160 microgramas, suspensão pressurizada para inalação. Cada dose única (dose libertada que sai do aplicador bucal) contém 5 µg de fumarato de formoterol di-hidratado, 9 µg de brometo de glicopirronio, equivalente a 7,2 µg de glicopirronio e 160 µg de budesonida. Isto corresponde a uma dose calibrada de 5,3 µg de fumarato de formoterol di-hidratado, 9,6 µg de brometo de glicopirronio, equivalente a 7,7 µg de glicopirronio e 170 µg de budesonida. **Indicações terapêuticas:** Riltrava Aerosphere é indicado como tratamento de manutenção em doentes adultos com DPOC moderada a grave, que não estão adequadamente tratados com uma associação de um corticosteroide inalado e um agonista beta2 de longa duração de ação ou uma associação de um agonista beta2 de longa duração de ação e um antagonista muscarínico de longa duração de ação. **Posologia e modo de administração:** *Posologia:* A dose recomendada e máxima é de 2 inalações 2x/dia (2 inalações de manhã e 2 inalações à noite). Se for omitida uma dose, esta deve ser tomada assim que for possível e a dose seguinte deve ser tomada no horário habitual. Não se deve tomar uma dose a dobrar para compensar uma dose esquecida. *Populações especiais:* **Idosos:** Não é necessário qualquer ajuste de dose em doentes idosos. *Compromisso renal:* Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, apenas se o benefício esperado for superior ao risco potencial. *Compromisso hepático:* Este medicamento pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Pode também ser utilizado na dose recomendada em doentes com compromisso hepático grave, o medicamento deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. *População pediátrica:* Não existe utilização relevante deste medicamento em crianças e adolescentes (com idade inferior a 18 anos) para a indicação da DPOC. **Modo de administração:** Para utilização por via inalatória. *Instruções de utilização:* De forma a assegurar uma administração correta do medicamento, o médico ou outro profissional de saúde deve demonstrar ao doente como utilizar corretamente o inalador, e deve monitorizar regularmente a técnica de inalação do doente. O doente deve ser aconselhado a ler com atenção o Folheto Informativo e seguir as instruções de utilização conforme indicado no mesmo. Ao acionar Riltrava Aerosphere, um volume de suspensão é expelido do recipiente pressurizado. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes que têm dificuldade em coordenar o acionamento com a inalação podem utilizar Riltrava Aerosphere com uma câmara expansora para garantir a administração adequada do medicamento. Pode ser utilizado com câmaras expansoras incluindo o Aerochamber Plus FlowVu. **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 broncospasma, isto é, como terapêutica de alívio. **Broncospasma paradoxal:** A administração de formoterol/glicopirronio/budesonida pode produzir broncospasma paradoxal com sibilos e dispnéia imediatamente após a administração e pode ser potencialmente fatal. O tratamento com este medicamento deve ser imediatamente interrompido se ocorrer broncospasma paradoxal. O doente deve ser avaliado e instituído tratamento alternativo, se necessário. **Deterioração da doença:** Recomenda-se que o tratamento com este medicamento não seja interrompido abruptamente. Se os doentes não considerarem o tratamento eficaz, devem manter o tratamento, mas tem de se procurar aconselhamento médico. O aumento da utilização de broncodilatadores de alívio indica um agravamento do quadro clínico subjacente e justifica uma reavaliação da terapêutica. A deterioração rápida e progressiva nos sintomas da DPOC é potencialmente fatal e o doente deve ser submetido a avaliação médica urgente. **Efeitos cardiovasculares:** Podem ser observados efeitos cardiovasculares, tais como arritmias cardíacas, p.ex. fibrilhação auricular e taquicardia, após a administração de antagonistas dos 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 tópica de corticosteroides. Se um doente apresentar sintomas tais como visão turva ou outras perturbações visuais, o doente deve ser encaminhado para um oftalmologista para avaliação de possíveis causas que podem incluir cataratas, glaucoma ou doenças raras, tais como CRSC, que foram notificadas após a utilização de corticosteroides sistémicos e tópicos. **Transferência de terapêutica oral:** Recomenda-se atenção especial nos doentes que fazem a transição de esteroides orais, uma vez que podem continuar em risco de compromisso da função suprarrenal durante um período de tempo considerável. Os doentes que necessitam de terapêutica com doses elevadas de corticosteroides ou tratamento prolongado com a dose mais elevada recomendada de corticosteroides inalados, podem estar igualmente em risco. Estes doentes podem apresentar sinais e sintomas de insuficiência suprarrenal quando expostos a stress grave. Deve ser considerada cobertura adicional com corticosteroides sistémicos durante períodos de stress ou cirurgia eletiva. **Pneumonia em doentes com DPOC:** Tem sido observado um aumento na incidência de pneumonia, incluindo pneumonia que requer hospitalização, nos doentes com DPOC a receberem corticosteroides inalados. Existe alguma evidência de risco aumentado de pneumonia com o aumento da dose de esteroide, não tendo sido demonstrado de forma conclusiva nos diversos estudos. Não existe evidência clínica conclusiva para diferenças dentro da mesma classe na magnitude do risco de pneumonia entre os medicamentos contendo corticosteroides inalados. Os médicos devem continuar alerta para o possível desenvolvimento de pneumonia em doentes com DPOC pois as características clínicas de tais infeções sobrepõem-se aos sintomas das exacerbações da DPOC. Os fatores de risco para pneumonia em doentes com DPOC incluem tabagismo atual, idade avançada, IMC baixo e DPOC grave. **Hipocalcemia:** A hipocalcemia potencialmente grave pode resultar da terapêutica com agonistas-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 glucose plasmática. A glicemia deve ser monitorizada durante o tratamento de acordo com as orientações estabelecidas para doentes com diabetes. **Condições coexistentes:** Este medicamento deve ser utilizado com precaução em doentes com tiorixose. **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 cobicistate, aumente o risco de efeitos indesejáveis sistémicos, e deve ser evitado, a não ser que o benefício seja superior ao risco aumentado de reações adversas aos corticosteroides sistémicos, nesse caso os doentes devem ser monitorizados para reações adversas aos corticosteroides sistémicos. Este facto é de relevância clínica limitada em tratamentos de curta duração (1-2 semanas). Como o 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 digitais. **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, disopirramida, procainamida, anti-histaminicos, inibidores da monoamina oxidase, antidepressivos tricíclicos e fenotiazinas pode prolongar o intervalo QT e aumentar o risco de arritmias ventriculares. Além disso, L-dopa, L-tirosina, oxitocina e álcool podem prejudicar a tolerância cardíaca aos beta2-simpaticomiméticos. O tratamento concomitante com inibidores da monoamina oxidase, incluindo medicamentos com propriedades semelhantes como furazolidona e procarbazina, pode dar origem a reações hipertensivas. Existe um risco elevado de arritmias em doentes a receberem anestesia concomitante com hidrocarbonetos halogenados. **Fertilidade, gravidez e aleitamento:** A administração deste medicamento a mulheres grávidas só deve ser considerada se o benefício esperado para a mãe justificar o potencial risco para o feto. A administração deste medicamento a mulheres que estão a amamentar só deve ser considerada se o benefício esperado para a mãe for superior a qualquer possível risco para a criança. Considera-se pouco provável que este medicamento administrado na dose recomendada, afete a fertilidade no ser humano. **Efeitos indesejáveis:** *Frequentes:* Candidíase oral; Pneumonia; Hiperglicemia; Ansiedade; Insónia; Cefaleia; Palpitações; Disfonia; Tosse; Náuseas; Espasmos musculares; Infecção do trato urinário. *Pouco frequentes:* Hipersensibilidade; Depressão; Agitação; Irrequietude; Nervosismo; Tonturas; Tremor; Angina de peito; Taquicardia; Arritmias cardíacas (fibrilhação auricular, taquicardia supraventricular e extrassístoles); Irritação da garganta; Broncospasma; Boca seca; Equimose; Retenção urinária; Dor torácica. *Muito raros:* Sinais ou sintomas de efeitos sistémicos de glucocorticóides, por exemplo supressão suprarrenal; Comportamento anormal. **Desconhecido:** Angioedema; Visão turva; Cataratas; Glaucoma. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: <http://www.infarmed.pt/web/infarmed/submissaoam> (preferencialmente) ou através dos seguintes contactos: Direção de Gestão do Risco de Medicamentos: (Tel.: +351 21 798 73 73; Linha do medicamento: 800 222 444 (gratuita); E-mail: farmacovigilancia@infarmed.pt). **Titular da Autorização de Introdução no Mercado:** AstraZeneca AB, SE-151 85 Södertälje, Suécia. **Representante local do Titular da Autorização de Introdução no Mercado:** Tecnimed - Sociedade Técnico-Medicinal, S.A., Rua da Tapada Grande, n.º 2, Abrunheira, 2710-089 Sintra. **Informações revistas em abril 2022. Para mais informações deverá contactar o representante local do Titular da Autorização de Introdução no Mercado. Medicamento sujeito a receita médica. Medicamento compartilhado pelo Escalão B (69% de participação no regime geral e 84% de participação no regime especial). Versão 1.1 (abril 2022).**

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ARTIGO ORIGINAL

Utilização de corticosteroides inalados e o risco de hospitalização por pneumonia em crianças com asma: um estudo de coorte a nível nacional

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RESUMO

Contexto A potencial associação entre a utilização de corticosteroides inalados (CI) e o risco de pneumonia em adultos é controversa e as evidências pediátricas específicas são escassas.

Objetivo Avaliar a potencial associação entre a utilização de CI e o risco de hospitalização por pneumonia em crianças (2–17 anos) com asma.

Métodos Este foi um estudo de coorte baseado em dados de âmbito nacional provenientes da prática clínica habitual na Suécia (janeiro de 2007 a novembro de 2021). Entre 425 965 crianças com asma confirmada, foram identificados episódios de nova utilização e não utilização de CI através dos registos de medicamentos dispensados. Ajustamos para potenciais fatores confundidores com ponderação de sobreposição de pontuação de propensão e foi estimado o risco de uma hospitalização com pneumonia como diagnóstico primário. Também foram efetuadas múltiplas análises de subgrupos e de sensibilidade.

Resultados Identificamos 249 351 episódios de CI (seguimento médio de 0,9 anos) e 214 840 episódios de não utilização (seguimento médio de 0,7 anos). Durante o seguimento, foram observados 369 eventos de hospitalização por pneumonia nos episódios de uso de CI e 181 nos episódios de não uso de CI. A taxa de incidência ponderada de hospitalização por pneumonia foi de 14,5 por 10 000 doentes-ano para os episódios de utilização de CI e de 14,6 para os episódios de não utilização. A HR ponderada para hospitalização por pneumonia associada ao uso de CI foi de 1,06 (IC 95% 0,88 a 1,28) e a diferença de taxa absoluta foi de -0,06 (IC 95% -2,83 a 2,72) eventos por 10.000 doentes-ano, em comparação com a não utilização de CI.

Conclusões Neste estudo de coorte de âmbito nacional, não foram observadas evidências de uma associação entre a utilização de CI e o risco de hospitalização por pneumonia em crianças com asma em comparação com a não utilização de CI.

INTRODUCTION

Inhaled corticosteroids (ICS) are the cornerstone of asthma pharmacotherapy and a common first-line treatment.¹ Though considered generally safe, clinical studies suggest that ICS increase the risk of pneumonia in adults with COPD.² The safety evidence for children with asthma is limited.

ICS could increase the risk of pneumonia by immunosuppression and studies have shown increased carriage of *Streptococcus pneumoniae* in asthma patients using ICS in comparison with no ICS use.³ However, meta-analyses of randomised controlled trials (RCTs) show evidence of a protective or null effect of ICS on the risk of pneumonia in asthma patients.^{4–6} A meta-analysis of RCTs on children (31 trials; 11 615 patients; age<18 years) found no difference in the risk of pneumonia between the ICS and placebo group.⁴ A meta-analysis

Key messages

What is the key question?

► There is conflicting evidence regarding the potential association between inhaled corticosteroids (ICS) and risk of pneumonia in asthma patients, with limited data on children.

What is the bottom line?

► In our study, based on a large real-world sample of Swedish paediatric asthma patients (age 2–17 years), we found no association between ICS use and risk for hospitalisation due to pneumonia.

Why read on?

► Our findings support the safe use of ICS with regard to the risk of pneumonia and may be useful in the management of paediatric asthma.

lysis of 10 RCTs of mostly adults (19 098 patients; age>12 years) found that ICS use decreased the risk of pneumonia.⁵ Although patients in the RCTs were 12 years or older, no children-specific results were presented.⁵ Another meta-analysis (26 RCTs; 14 993 patients; age>4 years) also found that ICS use decreased the risk of pneumonia events.⁶ In contrast, two case-control studies in adults and patients aged 12–35 years with asthma, respectively, found that ICS use was associated with an increased risk of pneumonia.^{7,8} No paediatric-specific results based on real-world data have been presented to our knowledge.

Asthma is a chronic disease that requires long-term pharmacotherapy to prevent harmful inflammation, loss of lung function and long-term adverse effects. Most asthma patients develop symptoms and initiate ICS during childhood when the lungs and the immune system are still developing and the risk for respiratory infections is high.⁹ It is hence key to investigate potential adverse effects of ICS in children, such as the risk for pneumonia, and evidence from large real-world samples is needed.

In this study, we assessed the potential association between ICS use and the risk of hospitalisation for pneumonia in Swedish paediatric asthma patients (age 2–17 years), as compared with no ICS use.

METHODS

Source population and data sources

This was a Swedish nationwide cohort study using linked data from multiple Swedish national regis-

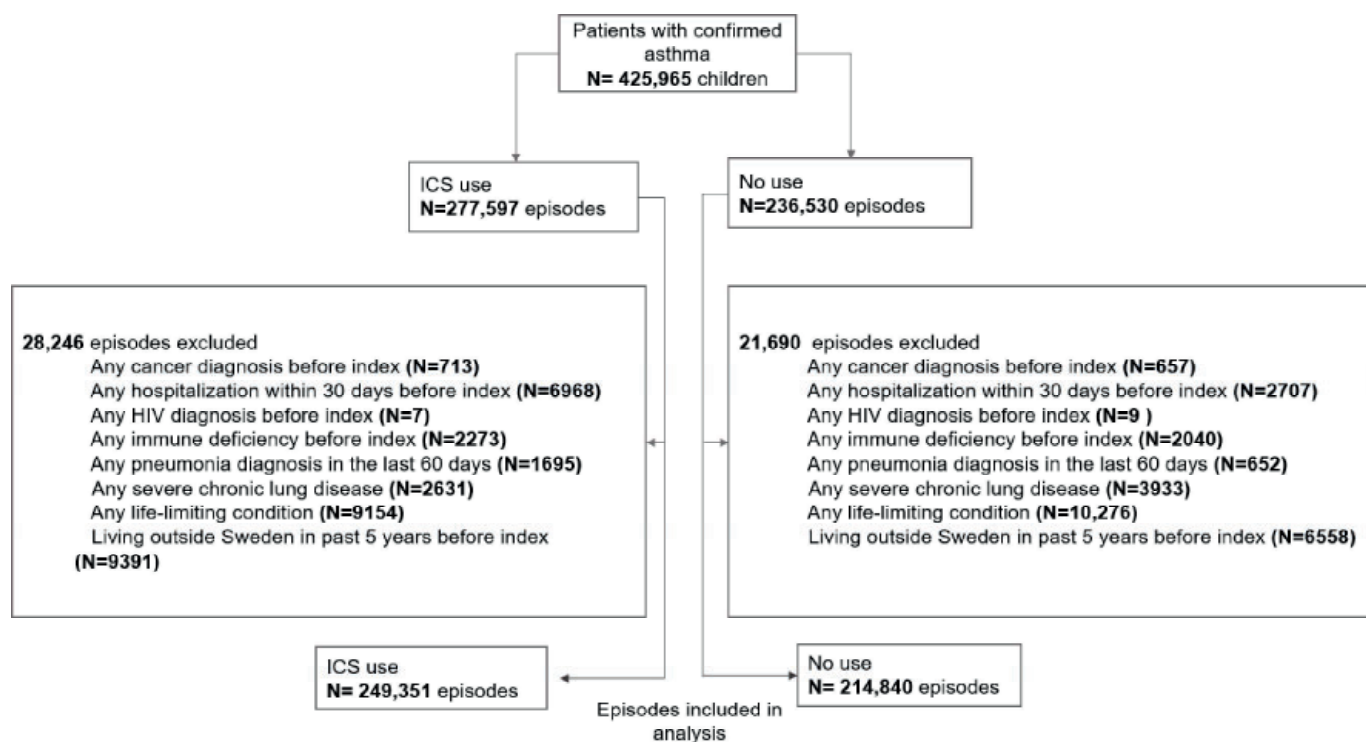


Figure 1 Selection flow of ICS and no-use episodes. Exclusion criteria are not mutually exclusive. *Episodes of patients with confirmed asthma at age 2–17 years, with recent respiratory pharmacotherapy (in last 12 months, including the index day) and with no recent ICS use (in last 18 months). ICS, inhaled corticosteroids.

ters. The data sources are further described in online supplemental appendix eTable 1. The study period was from 1 January 2007 to 30 November 2021. The source population consisted of children aged 2–17 years residing in Sweden and with a confirmed asthma diagnosis before or during the study period. Patients under the age of 2 years were not included in the primary analysis due to the difficulties in ascertaining both asthma and pneumonia in these patients.^{10–11} Confirmed asthma was defined based on a previously validated algorithm (online supplemental appendix eTable 2) using physician-assigned diagnosis records (international classification of diseases, 10th revision (ICD-10) codes) from the Swedish National Patient Register and records of asthma drug dispensing (anatomical therapeutic chemical (ATC) codes) from the Swedish Prescribed Drug Register.¹²

Procedures

The Swedish Prescribed Drug Register that contains details on dispensed prescription medication for all individuals residing in Sweden was used to identify exposure. From the children with confirmed asthma, mutually exclusive episodes of ICS use and no use during the study period were identified (see an overview of the design in online supplemental appendix eFigure 1).¹³ The index date for an ICS episode was the day of a new dispensing of an ICS drug. Potential index dates for no-use episodes were set with 12-month intervals during the study period. Eligible episodes, both ICS and no-use episodes, were preceded by an 18-month period of no ICS dispensing. No-use episodes were required to have at least one dispensing of another respiratory medication in the last 12 months to verify that patients during comparator episodes were currently or recently treated. Thus, one asthma patient could contribute with multiple ICS and no-use episodes during the study period. Episodes did not overlap, and each outcome event was only accounted for once.

The following exclusion criteria were applied to all episodes based on their status at the index date: previous hospitalisation within the last 30 days, previous pneumonia within the last 60 days, lived outside Sweden within the last 5 years, history of cancer, immune suppression including HIV, severe chronic lung disease or other life-limiting conditions.¹⁴ The exclusion criteria are further described in online supplemental appendix eTable 2.

Outcome

The primary outcome was hospitalisation for pneumonia, defined as an inpatient contact with a physician-assigned primary diagnosis of pneumonia (ICD-10 codes J12–18), based on data from the Swedish National Patient Register. The date of admission was used as the event date. The secondary outcome was hospitalisation or emergency outpatient contact for pneumonia, which was defined as the primary outcome but extended to also include pneumonia in the emergency outpatient setting.

Statistical analyses

We used propensity score overlap weighting to control for confounding.^{15–16} With this method, we accounted for confounding by balancing the distribution of covariates at baseline between the treatment groups (ICS use and no-use episodes).¹⁷ With overlap weights, we estimated the average treatment effect in the overlap population. The propensity scores were estimated with logistic regression. The potential confounders (baseline covariates) included in the propensity score were age, sex, season, socioeconomic status of parents (disposable income, education level), history of lower respiratory tract infections (LRTI), trisomy 21 and congenital heart disease, previous use of asthma medication, and asthma-related and general healthcare utilisation (online supplemental appendix eTable 3). Potential confounders were defined based on status at the index date of each episode and balance was assessed with standardised mean differences. Missing values (less than 0.1%) were observed for parental income and education. The missing values were imputed with median and mode, respectively. Episodes were censored at the first outcome event, maximum follow-up (12 months), end of study period (30 November 2021), age > 17 years, initiation of an ICS drug (for no-use episodes), death or emigration.

Cox proportional hazards regression was used to estimate the association between ICS use and the risk of the outcome, as compared with no use. The rates of outcome events during episodes of ICS use and no use were estimated. Cumulative incidence was estimated with the Kaplan–Meier function. Poisson regression was used to obtain absolute rate differences; events per 10 000 patient-years. The time scale was time since the index date. Robust sandwich estimators were used to estimate standard errors that account for the weighted nature of the cohort.

Table 1 Baseline characteristics of episodes included in the unweighted and weighted cohorts

	Unweighted, n (%)			Weighted, n (%)		
	ICS use (n=249 351)	No use (n=214 840)	Standardised difference (%)*	ICS use (n=247 815)	No use (n=214 838)	Standardised difference (%)*
Age, mean (SD)	10.0 (4.6)	11.1 (4.3)	24.9	10.5 (2.8)	10.5 (3.0)	0.2
Female	108 468 (43.5)	99 318 (46.2)	5.5	44 700 (45.6)	44 745 (45.6)	0
Calendar year						
2007–2009	33 987 (13.6)	32 063 (14.9)	3.7	14 044 (14.3)	14 053 (14.3)	0
2010–2012	49 323 (19.8)	42 223 (19.7)	0.3	19 515 (19.9)	19 548 (19.9)	0
2013–2015	52 299 (21.0)	46 527 (21.7)	1.7	20 988 (21.4)	21 015 (21.4)	0
2016–2018	58 582 (23.5)	49 639 (23.1)	0.9	22 903 (23.4)	22 924 (23.4)	0
2019–2021	55 160 (22.1)	44 388 (20.7)	3.6	20 494 (20.9)	20 528 (20.9)	0
Index season						
Winter	60 346 (24.2)	47 719 (22.2)	4.7	22 640 (23.1)	22 678 (23.1)	0
Spring	79 182 (31.8)	66 740 (31.1)	1.5	31 047 (31.7)	31 090 (31.7)	0
Summer	43 625 (17.5)	44 942 (20.9)	8.7	18 648 (19.0)	18 661 (19.0)	0
Fall	66 198 (26.5)	55 439 (25.8)	1.7	25 608 (26.1)	25 639 (26.1)	0
Disposable family income						
First quartile	62 317 (25.0)	53 730 (25.0)	0	24 374 (24.9)	24 402 (24.9)	0
Second quartile	62 843 (25.2)	53 206 (24.8)	1	24 488 (25.0)	24 516 (25.0)	0
Third quartile	61 927 (24.8)	54 120 (25.2)	0.8	24 543 (25.1)	24 573 (25.1)	0
Fourth quartile	62 264 (25.0)	53 784 (25.0)	0.1	24 538 (25.1)	24 577 (25.1)	0
Parental education in years						
<10	9295 (3.7)	7706 (3.6)	0.8	3554 (3.6)	3559 (3.6)	0
10–12	95 692 (38.4)	85 288 (39.7)	2.7	38 148 (38.9)	38 191 (38.9)	0
>12	144 364 (57.9)	121 846 (56.7)	2.4	56 241 (57.4)	56 318 (57.4)	0
Previous lower respiratory tract infections (LRTI)						
Outpatient contact for LRTI	18 603 (7.5)	11 729 (5.5)	8.1	6131 (6.3)	6139 (6.3)	0
Hospitalisation for LRTI	6344 (2.5)	3910 (1.8)	5	2041 (2.1)	2043 (2.1)	0
Comorbidities†						
Trisomy 21	316 (0.1)	288 (0.1)	0.2	122 (0.1)	122 (0.1)	0
Non-severe congenital heart disease	1802 (0.7)	1320 (0.6)	1.3	628 (0.6)	629 (0.6)	0
Severe congenital heart disease	144 (0.1)	92 (0.0)	0.7	47 (0.0)	47 (0.0)	0
Use of respiratory drugs in the last 18 months						
Short-acting beta-agonist	214 233 (85.9)	190 197 (88.5)	7.8	88 431 (90.3)	88 441 (90.2)	0.4
Long-acting beta-agonists	4035 (1.6)	5246 (2.4)	5.8	2168 (2.2)	2169 (2.2)	0
Leucotriene receptor antagonist	14 308 (5.7)	26 358 (12.3)	23	8698 (8.9)	8699 (8.9)	0
Oral corticosteroids	24 457 (9.8)	21 835 (10.2)	1.2	9879 (10.1)	9899 (10.1)	0
Respiratory drugs in the last 18 months, n						
0	138 786 (55.7)	58 944 (27.4)	59.8	38 499 (39.3)	38 623 (39.4)	0.2
1	94 076 (37.7)	135 633 (63.1)	52.5	51 571 (52.7)	51 572 (52.6)	0.1

Continued

Table 1 Continued

	Unweighted, n (%)			Weighted, n (%)		
2	14 951 (6.0)	18 453 (8.6)	10	7123 (7.3)	7123 (7.3)	0
3+	1538 (0.6)	1810 (0.8)	2.7	750 (0.8)	750 (0.8)	0
Other drugs in the last 18 months, n						
0	63 161 (25.3)	49 353 (23.0)	5.5	23 761 (24.3)	23 792 (24.3)	0
1–2	94 434 (37.9)	79 278 (36.9)	2	36 674 (37.4)	36 719 (37.4)	0
3–5	66 952 (26.9)	61 745 (28.7)	4.2	27 193 (27.8)	27 228 (27.8)	0
6+	24 804 (9.9)	24 464 (11.4)	4.7	10 314 (10.5)	10 329 (10.5)	0
Outpatient hospital contacts due to asthma in the last 12 months, n						
0	164 405 (65.9)	169 730 (79.0)	29.6	72 995 (74.5)	72 996 (74.4)	0.2
1	65 492 (26.3)	34 681 (16.1)	25	19 171 (19.6)	19 223 (19.6)	0.1
2+	19 454 (7.8)	10 429 (4.9)	12.1	5777 (5.9)	5849 (6.0)	0.3
Other outpatient hospital contacts in the last 12 months, n						
0–1	157 936 (63.3)	139 905 (65.1)	3.7	63 499 (64.8)	63 547 (64.8)	0.1
2–4	65 228 (26.2)	52 909 (24.6)	3.5	24 551 (25.1)	24 603 (25.1)	0
5+	26 187 (10.5)	22 026 (10.3)	0.8	9892 (10.1)	9918 (10.1)	0
Inpatient admissions due to asthma in the last 12 months, n						
0	248 201 (99.5)	213 936 (99.6)	0.6	97 539 (99.6)	97 664 (99.6)	0
1	1100 (0.4)	867 (0.4)	0.6	389 (0.4)	389 (0.4)	0
2+	50 (0.0)	37 (0.0)	0.2	15 (0.0)	15 (0.0)	0
Other inpatient admissions in the last 12 months, n						
0	235 901 (94.6)	203 838 (94.9)	1.2	92 869 (94.8)	92 985 (94.8)	0
1	11 340 (4.5)	9301 (4.3)	1.1	4291 (4.4)	4298 (4.4)	0
2+	2110 (0.8)	1701 (0.8)	0.6	783 (0.8)	785 (0.8)	0

*Absolute standardised mean difference.

†Based on data from the last 5 years before index. Number of respiratory drugs in the last 18 months do not include the index day. ICS, inhaled corticosteroids.

Subgroup analyses were performed based on sex, age group (2–5, 6–11, 12–17 years) and type of ICS initiated (ICS as monotherapy, combination therapy of ICS and long-acting beta-agonists (LABA), any budesonide and any fluticasone). These subgroup analyses were conducted to explore potential effect modification, as the association between ICS use and the risk of pneumonia may vary between demographic groups and types of ICS therapy. A few sensitivity analyses were performed. First, children younger than 2 years were not included in the primary analysis, but in a sensitivity analysis all children of age 0–17 years were included. Second, we adjusted for additional potential confounders that required full register coverage since birth, which was only available for a subset of patients born in Sweden in 2006 or later. We adjusted for prematurity, small for gestational age, parity, LRTI before and after age 2 years in inpatient and outpatient care, respectively, and sibling with confirmed asthma (online supplemental appendix eTable 4). The literature suggests that LRTI early in life may be associated with an increased risk for developing asthma and recurrent LRTIs.^{18–20} Third, we used a less restrictive definition of the outcome, which included inpatient contacts with pneumonia as secondary diagnosis. Fourth, we performed an analysis where we excluded the years of the COVID-19 pandemic (2020–2021) from the study period, when the background incidence of hospitalisation for pneumonia in children might have been different. All analyses were performed in SAS Enterprise Guide V.7.1

Study population

We identified 425 965 children with confirmed asthma during the study period. From these patients, we identified 249 351 ICS and 214 840 no-use episodes that met the inclusion criteria (figure 1). The mean follow-up time was 0.9 and 0.7 years in the ICS and no-use episodes, respectively (the median was 1.0 year in both groups). In the unweighted cohort, the most imbalanced covariates between ICS and no-use episodes included age, previous use of leucotriene receptor antagonists, number of respiratory drugs used and number of previous outpatient hospital contact for asthma (table 1). In the weighted cohort, nearly exact balance between ICS and no-use episodes was achieved for all covariates. In the weighted cohort, the mean age at baseline was 10.5 years for both ICS use and no-use episodes, with females accounting for 46% of ICS use and no-use episodes.

RESULTS

Primary analysis

In the ICS and no-use episodes, 369 and 181 incident hospitalisations for pneumonia were observed during follow-up, respectively (table 2). This translated to incidence rates of 15.8 and 11.5 events per 10 000 patient-years, respectively, and the unweighted HR associated with ICS use was 1.44 (95% CI 1.21 to 1.72; table 2). In the weighted cohort, the incidence rates were similar between

Table 2 Association between ICS use and the risk of hospitalisation for pneumonia (primary analysis) and hospitalisation or emergency outpatient contact for pneumonia (secondary analysis) in comparison with no use

	Unweighted			Weighted		
	Events/ episodes, n	Incidence rate	HR (95% CI)	Incidence rate	HR (95% CI)	Incidence rate difference (95% CI)
Primary analysis; hospitalisation for pneumonia						
ICS use	369/249 351	15.81	1.44 (1.21 to 1.72)	14.51	1.06 (0.88 to 1.28)	−0.06 (−2.83 to 2.72)
No use	181/214 840	11.49		14.57		
Secondary analysis: Hospitalisation or emergency outpatient contact for pneumonia						
ICS use	1104/249 351	47.40	1.60 (1.44 to 1.78)	41.90	1.10 (0.98 to 1.23)	−0.30 (−5.04 to 4.44)
No use	504/214 840	32.03		42.20		

ICS, inhaled corticosteroids.

the groups, 14.5 events per 10 000 patient-years (cumulative incidence 0.14%; figure 2) in the ICS episodes and 14.6 (cumulative incidence 0.13%) in the no-use episodes. We found no material difference between the groups, in relative or absolute terms. The weighted HR of hospitalisation for pneumonia associated with ICS use was 1.06 (95% CI 0.88 to 1.28; table 2 and figure 3), in comparison with no use. The absolute rate difference was −0.06 (95% CI −2.83 to 2.72) events per 10 000 patient-years.

Secondary and subgroup analyses

In the secondary analysis where both hospitalisations and emergency outpatient visits for pneumonia were considered, 1104 and 504 events in the ICS and no-use episodes were observed, respectively. The weighted HR associated with ICS use was higher than the primary analysis, 1.10 (95% CI 0.98 to 1.23; table 2). The weighted HRs by age groups were 0.88 (95% CI 0.68 to 1.13) among children of age 2–5 years, 0.99 (95% CI 0.68 to 1.45) for age 6–11 years and 1.28 (95% CI 0.82 to 2.02) for age 12–17 years (figure 3). The results were similar between boys and girls, HRs of 1.12 (95% CI 0.85 to 1.46) and 1.06 (95% CI 0.82 to 1.38), respectively.

We performed analyses stratified on the type of ICS that was initiated. In the analysis of ICS as monotherapy (222 872 episodes), the HR of hospitalisation for pneumonia was 1.04 (95% CI 0.86 to 1.26) and it was higher in the analysis of ICS and LABA as combination therapy (26 692 episodes), HR 1.18 (95% CI 0.68 to 2.07). The results were similar in the analyses of ICS types, budesonide (167 109 episodes) and fluticasone (80 699 episodes); we observed HRs of 1.03 (95% CI 0.81 to 1.30) and 1.05 (95% CI 0.83 to 1.34), respectively (figure 3).

Sensitivity analyses

In the sensitivity analysis where children under the age of 2 years were also included, higher weighted incidence rates of hospitalisation for pneumonia were observed; 36.6 events per 10 000 patient-years in the ICS episodes and 32.6 in the no-use episodes.

The HR associated with ICS use was higher in this cohort than in the primary analysis, 1.23 (95% CI 1.09 to 1.38). In the analysis where the outcome definition also included secondary diagnoses, we observed a similar result as in the primary analysis, HR 1.03 (95% CI 0.87 to 1.23). The sensitivity analysis where we adjusted for additional potential confounders was restricted to patients with available data since birth (44% of the ICS episodes; max age 16 years). The unweighted cohort was fairly balanced on the additional potential confounders (online supplemental appendix table 5) and the HRs with the same adjustment as in the primary analysis and with the additional adjustment were the same, 0.99 (95% CI 0.77 to 1.26) (figure 3). Finally, we found

no difference in relation to the primary analysis when the study period ended before the COVID-19 pandemic, HR 1.01 (95% CI 0.83 to 1.22).

DISCUSSION

In this Swedish nationwide cohort study, we assessed the potential association between ICS use and the risk of hospitalisation for pneumonia in children with asthma. The study was based on a sample of more than 425 965 patients from routine clinical practice during a study period of 15 years. Our results indicated no evidence of an association between ICS use and the risk of hospitalisation for pneumonia, as compared with no use. Based on the upper limit of the CI, our results were not compatible with an increased rate greater than 2.7 events per 10 000 patient-years.

The results obtained from this study of patients in routine clinical practice are in agreement with those of previous meta-analyses of RCTs providing children-specific results, which show a null or protective effect of ICS use on the risk of pneumonia.^{4,6} Cazeiro et al found no difference in risk of pneumonia between ICS and placebo groups (risk difference −0.1%; 95% CI −0.3% to 0.2%) among patients younger than 18 years.⁴ O'Byrne et al found a protective effect of ICS on the risk of pneumonia events in the age group 4–11 years, HR 0.54 (95% CI 0.33 to 0.90).⁶ For serious pneumonia events, the results were imprecise, and a null effect was observed, HR 0.93 (95% CI 0.31 to 2.78). The corresponding result was similar for pneumonia events in the analysis that included adults (age 4 to 78 years) HR 0.51 (95% CI 0.35 to 0.74); while it was higher but still imprecise for serious pneumonia events, HR 1.30 (95% CI 0.53 to 3.14).

Our results differed from those of previous observational studies, which showed an association between ICS use and increased risk for pneumonia: OR of 1.20 (95% CI 1.12 to 1.27) in adults⁷ and a rate ratio of 1.83 (95% CI 1.57 to 2.14) in patients aged 12–35 years.⁸ The observed differences between results could be due to important differences in the design (both previous studies used case-control designs), definition of the population (less strict definitions of asthma and no required use of respiratory medication in the no-use group in the previous studies), and in the confounding adjustment. Further, the previous studies analysed only or mostly adult populations. The impact of some design choices can be observed in the study by Qian et al.⁸ For example, the results of the primary analysis, a rate ratio of 1.83 (95% CI 1.57 to 2.14), was attenuated when the non-ICS users were restricted to current users of other respiratory medication, 1.61 (95% CI 1.38 to 1.89), and increased when the non-ICS users instead did not use any other respiratory medication, 4.81 (95% CI 3.56 to 6.51).

Asthma is a heterogeneous disease and manifestation, and severity varies greatly between age groups.^{21–23} Children in general and those under the age of 5 years in particular are prone to developing

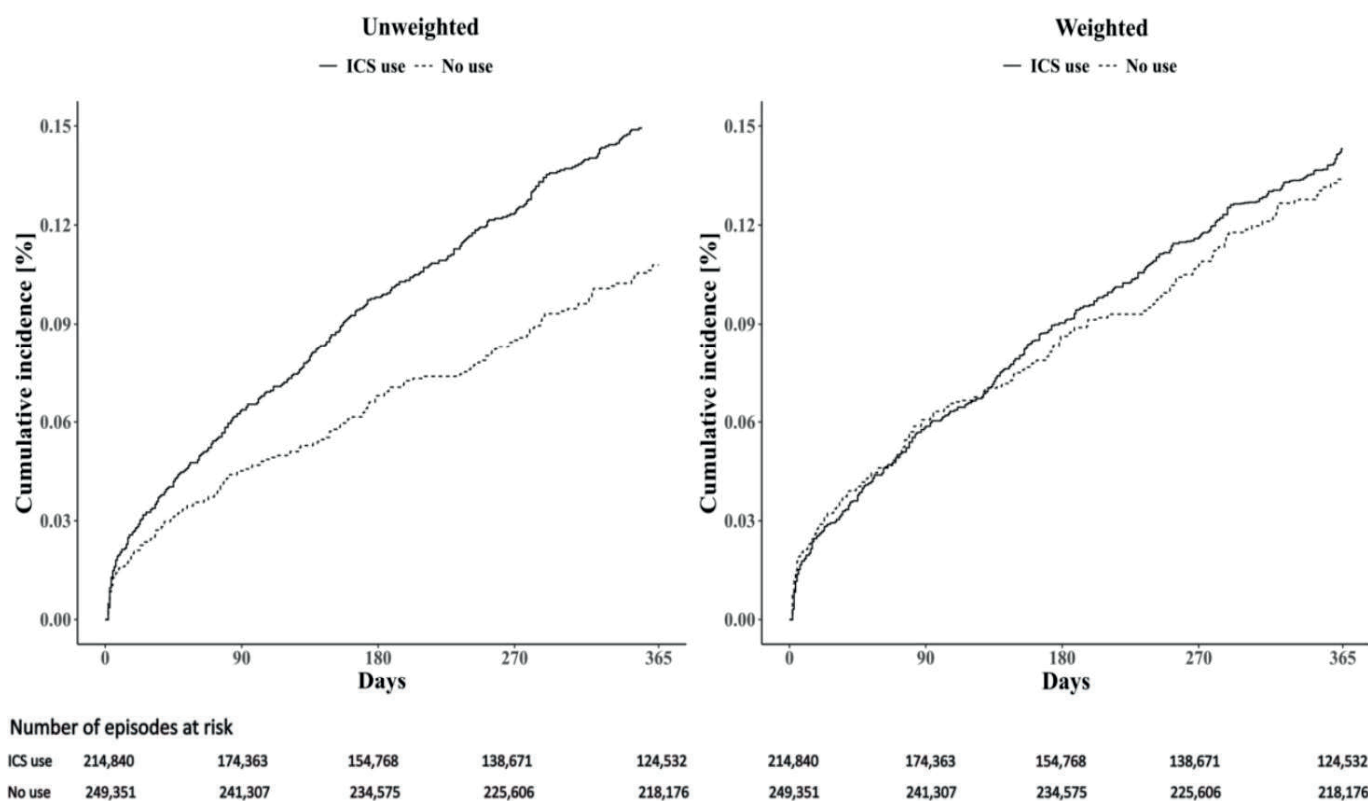


Figure 2 Cumulative incidence of hospitalisation for pneumonia in unweighted and weighted cohorts of ICS and no-use episodes. ICS, inhaled corticosteroids.

symptoms that may be misclassified as asthma when infected with respiratory viruses.^{10,11} In our analysis, children aged 2–5 years had the highest unweighted rates of hospitalisation for pneumonia, especially ICS users. Our sensitivity analysis that included patients under the age of 2 years showed an increased risk of hospitalisation for pneumonia associated with ICS use. However, this increased risk should be interpreted with caution given the difficulties in ascertaining both asthma and pneumonia in the youngest children.^{9–11} Further, we observed a higher but less precise HR in the age group 12–17 years. A similar imprecise (only 18 events in the

ICS episodes) result was observed for the subgroup of patients initiating a combination therapy of ICS and LABA. The combination therapy is indicated for children older than 6 years and generally targets patients with more severe disease.²⁴ Given the no-use design, this analysis might be subject to more extensive confounding by indication.

The study had limitations. As in all observational drug safety studies, the analysis was subject to potential unmeasured confounding and several measures were taken to limit this risk. In the study design, we included only patients with confirmed asthmatic disease based on

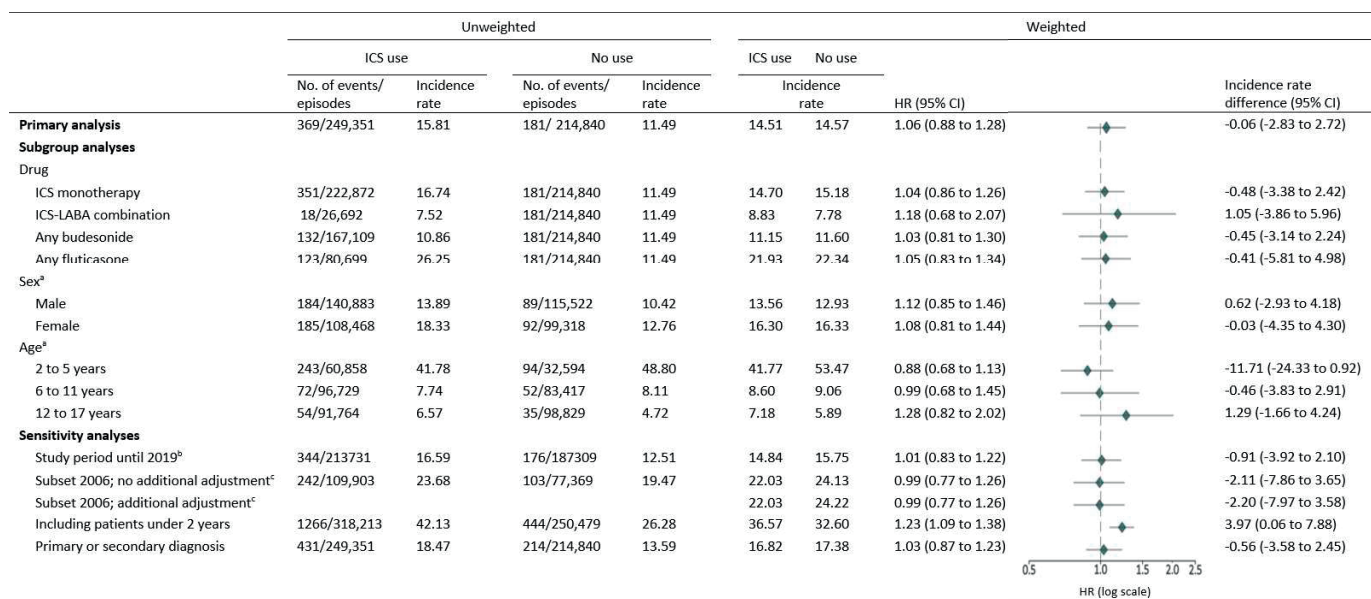


Figure 3 Subgroup and sensitivity analyses of association between ICS use and the risk of hospitalisation for pneumonia in comparison with no use. Incidence rates and rate differences are presented as events per 10 000 person years. Individual propensity score models and related weights were estimated for each sensitivity and subgroup analysis. ^aP values for test of differences between subgroups were 0.95 and 0.35 for sex and age, respectively. ^bEnd of study period was set before the COVID-19 pandemic. ^cSubset 2006 consisted of patients born in 2006 or later and with available data on additional potential confounders (prematurity, small for gestational age, parity, sibling with confirmed asthma and lower respiratory tract infections before the age of 2 years); the analysis was performed with the same adjustment as in the primary analysis and with the additional variables. ICS, inhaled corticosteroids; LABA, long-acting beta-agonists.

a validated algorithm.¹² The definition of asthma was comparably strict and to avoid including patients with very mild or transient disease we additionally required that patients received respiratory pharmacotherapy in the last 12 months. Due to the difficulties in distinguishing asthma from obstructive bronchitis or viral-induced wheeze in very young children, those under the age of 2 years were excluded from the analysis.

In the statistical analysis, we adjusted for a large number of potential confounders, including comorbidities, asthma drug history and proxies of disease severity. We used propensity score overlap weighting to achieve nearly exact balance on all covariates. With this method, we efficiently estimated the HR in the patients with the most propensity score overlap.¹⁵ Further, we performed a sensitivity analysis with adjustment for additional potential confounders, including LRTIs at age below and above 2 years, prematurity, parity, small for gestational age, and having a sibling with asthma, in patients with available data since birth. The additional adjustment did not change the results. Finally, the potential unmeasured confounding in the primary analysis was expected to bias the results away from the null, that is, unmeasured risk factors would be more prevalent in the ICS episodes than the no-use episodes. Hence, it is unlikely that the close-to null result of the study is explained by this bias. Nonetheless, the presence and impact of unmeasured confounding cannot be ruled out.

Outcome and exposure misclassification are other potential biases. Outcome events were ascertained based on physician-assigned diagnosis codes in the Swedish National Patient Register. Validation studies have shown that the ICD-10 codes for pneumonia have high positive predictive values (85%–95%).^{25–26} To increase specificity of the definition, we restricted our primary outcome to hospitalisations and required that pneumonia was the primary diagnosis, that is, the reason for admission. In a sensitivity analysis where secondary diagnosis codes were also included, the result did not change materially. A similar result was observed in the secondary analysis where we analysed the incidence of pneumonia in inpatient or emergency outpatient care. We did not analyse the risk of bacterial and viral pneumonia separately since the aetiology is difficult to distinguish in children due to inaccurate diagnostic methods and the specific diagnosis codes have low validity.

Our exposure definition was based on data of dispensed prescriptions of ICS as mono or combination therapy and low adherence would bias the results toward the null. Due to the great variability in dosing and general use patterns of ICS, we used a comparably short maximum follow-up of 12 months and to make sure that no patients used ICS recently we used a wash-out period of 18 months. It was not possible to investigate a potential association between the prescribed daily dose of ICS and the risk of pneumonia, since these data cannot be derived from the registers and the dose can vary over time within ICS dispensing. However, such an analysis would be of interest as higher ICS doses may be associated with greater immunosuppression.

In summary, based on nationwide data from routine clinical practice, we found no evidence of an association between ICS use and the risk of hospitalisation for pneumonia in children with asthma. The results were in accordance with results of previous RCTs on children, but not aligned with the previous observational data, which mainly included adults. To our knowledge, this is the first large study that provides paediatric-specific evidence on the potential association between ICS use and the risk of hospitalisation for pneumonia. Our findings further support the safety of ICS use for managing asthma in children.

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Contributors VW had full access to all the data in the study and was responsible for the integrity and accuracy of the data analysis. VW, K-HSK, SAR and CA contributed to the concept and design of the study as well as the acquisition and interpretation of the data. K-HSK and VW drafted the manuscript which was critically revised for important intellectual content by all authors. K-HSK and VW conducted the statistical analysis. Funding for the study was obtained by VW, who also supervised the study and is the guarantor.

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ARTIGO ORIGINAL

Emissões de gases com efeito de estufa associadas a cuidados de asma inadequados no Reino Unido: o estudo SABINA healthCARE-Based enviroNmental cost of treatment (CARBON)

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RESUMO

Contexto A asma mal controlada está associada a um aumento da morbilidade e da utilização dos recursos de saúde (URS). Por conseguinte, de modo a quantificar o impacto ambiental dos cuidados com a asma, este estudo retrospectivo de coorte sobre o custo ambiental do tratamento baseado em CARBON (healthCARE-Based enviroNmental cost of treatment) estimou as emissões de gases com efeito de estufa (GEE) no Reino Unido associadas à gestão da asma bem controlada e da asma mal controlada.

Métodos Foram incluídos doentes com asma atual (com idade ≥12 anos) registados no Clinical Practice Research Datalink (2008–2019). As emissões de GEE, medidas como equivalente de dióxido de carbono (CO₂e), foram estimadas para o uso de medicação relacionada com a asma, URS e agudizações durante o acompanhamento de doentes com asma classificados no início do estudo como bem controlados (<3 inaladores/ano de β₂-agonista de curta duração (SABA) e sem agudizações) ou mal controlados (≥3 inaladores/ano de SABA ou ≥1 agudização). O excesso de emissões de GEE devido a um controlo inadequado da asma incluiu ≥3 prescrições de recipientes de SABA/ano, agudizações e quaisquer consultas de clínica geral e de ambulatório no prazo de 10 dias após a hospitalização ou uma visita ao serviço de urgência.

Resultados Dos 236 506 doentes analisados, 47,3% apresentaram asma mal controlada no início do estudo. A nível nacional, a pegada de carbono global dos cuidados com asma no Reino Unido foi de 750 540 toneladas de CO₂e/ano, tendo a asma mal controlada contribuído com um excesso de emissões de GEE de 303 874 toneladas de CO₂e/ano, o que equivale às emissões de >124 000 casas no Reino Unido. A asma mal controlada em comparação com a asma bem controlada gerou uma pegada de carbono excessiva em 3,1 vezes em termos globais e 8,1 vezes em termos per capita, em grande parte induzida por SABA, com contribuições menores de URS.

Conclusões Estes achados sugerem que a abordagem do elevada carga da asma mal controlada, incluindo a redução do elevado uso de SABA e do risco associado de agudizações, pode aliviar significativamente as emissões de carbono relacionadas com os cuidados para asma.

INTRODUCTION

In an effort to combat climate change, countries are seeking to decarbonise their economies, and the healthcare sector has emerged as a central target of improvement.^{1 2} Any patient interaction with the healthcare system generates a carbon footprint. Healthcare is one of the largest sources of greenhouse gas (GHG) emissions in the public sector, with a carbon footprint equivalent to 4.4% of global net GHG emissions.² In 2020, the UK National Health Service established an ambitious

Key messages

What is the key question?

- Despite advances in evidence-based treatments, suboptimal asthma control is common.
- Poorly controlled asthma is associated with an increased risk of exacerbations, hospitalisations and mortality, resulting in significant healthcare resource utilisation (HCRU).
- To date, the environmental impact of asthma care, particularly poor disease control, has not been fully evaluated.

What is the bottom line?

- Our These study findings indicate that poorly controlled versus well-controlled asthma generated a larger overall and excess per capita carbon footprint, primarily contributed by short-acting β₂-agonist (SABA) use, with smaller contributions from inhaled corticosteroids use, exacerbations and HCRU.

Why read on?

- Targeting improved asthma outcomes by mitigating the high burden of poorly controlled asthma may elicit significant declines in carbon emissions, particularly through reducing high SABA use, enabling healthcare systems to meet their carbon emission reduction goals.

goal of 80% reduction in its carbon footprint by 2036–2039, with the aim of achieving a ‘net zero’ carbon footprint by 2045.³ The Sustainable Healthcare Coalition (SHC) in the UK supports this effort with its stepwise process of computing the carbon impact of numerous diverse activities associated with healthcare services to estimate the overall carbon footprint for a specific care pathway or patient population. This calculation affords policymakers and healthcare providers (HCPs), among others, the opportunity to understand and consider sustainability profiles when developing new models of care and clinical practice improvements that can support environmental targets.⁴ Understanding the carbon footprint of treatment interventions may assist in identifying practical strategies to reduce GHG emissions via patient-centric principles of improved disease management.

Despite advances in evidence-based treatments, asthma control remains suboptimal across all disease severities.^{5,6} In the UK and Europe, approximately 50% of patients experience uncontrolled asthma.⁷ Poorly controlled asthma is associated with a risk of avoidable asthma-related mortality and exacerbations,^{8,9} resulting in significant healthcare resource utilisation (HCRU).¹⁰ The environmental impact of asthma care, particularly poor disease control, has not been fully evaluated, with most of the attention directed towards the global warming potential (GWP) of the hydrofluoroalkane (HFA) propellants, which atomise the preventer medication in pressurised metered-dose inhalers (pMDIs).^{11–13} Patients with poorly controlled asthma incur greater asthma-related costs than those with well-controlled asthma.¹⁴ Intuitively, the same may hold true for the carbon impact of asthma care, where poorly controlled disease is recognised as associated with a higher carbon footprint. One manifestation of inadequate asthma control is the increased use of short-acting β_2 -agonist (SABA) reliever therapy.¹⁶ SABAs provide immediate bronchodilation but lack anti-inflammatory activity and, therefore, contribute little to achieving asthma control.¹⁷ Furthermore, SABA prescriptions of ≥ 3 canisters/year are associated with an increased risk of exacerbations, asthma-related mortality^{18,19} and incremental HCRU.¹⁸ Together, these factors imply that poorly controlled asthma and the consequent rise in exacerbations may increase the carbon footprint of asthma care in terms of increased HCRU and the requirement for additional pharmacotherapy. The environmental impact of this unmet need may be better understood by estimating the carbon footprint of managing poorly controlled asthma.

This study, which is part of the healthCARE-Based environmental cost of treatment (CARBON) programme,²⁰ is the first to quantify asthma care-based GHG emissions as illustrated by UK prescribing practices and HCRU, with the specific objective of estimating GHG emissions related to the management of well-controlled versus poorly controlled asthma.

METHODS

This retrospective, cohort study, based on the SABA use IN Asthma (SABINA) I UK study,¹⁸ extracted routinely collected, anonymised pseudonymised primary care data from the Clinical Practice Research Datalink (CPRD GOLD).²¹ Linked data on mortality from the Office for National Statistics (ONS),²² socioeconomic status (SES) from the Index of Multiple Deprivation (IMD 2015 in quintiles at practice level)²³ and secondary care from Hospital Episode Statistics (HES)²⁴ were provided by CPRD for patients residing in England (online supplemental methods).

Study population

Patients (aged ≥ 12 years) with a validated record of a current asthma diagnosis, current asthma (Read code²⁵ within 3 years of study entry) and registered in CPRD GOLD English general practice between 1 January 2008 and 31 December 2019 were included in the analysis (online supplemental methods).

Study variables

At baseline, defined as 12 months preceding the index date, patients were categorised based on their asthma control status as well-controlled (no asthma exacerbations and <3 SABA canister prescriptions/year) or poorly controlled (≥ 3 SABA canister prescriptions/year or ≥ 1 asthma exacerbation). The index date was defined as the latest date of any of the following: 13th birthday; start date of the study period; the date 12 months after the general practitioner (GP) commenced up-to-standard or research-quality data; the date 12 months after continuous CPRD GOLD record availability or the date 12 months after the first asthma Read code. Exacerbations were defined as a temporary worsening of asthma requiring a short course of oral corticosteroids (OCS), an emergency department (ED) visit or hospitalisation.²⁶ To balance differences between actuation counts across inhalers, the SABA canister cut-off was converted to 600 actuations/year according to the 200

actuations that would be expected in a SABA pMDI—the predominant device type prescribed for SABA in the UK.²⁷

Patient demographics captured age; sex; SES (IMD1 (least deprived) to IMD5 (most deprived²³)) and comorbidities, including anxiety, atopy, chronic obstructive pulmonary disease (COPD), gastro-oesophageal reflux disease (GORD), pneumonia, diabetes, osteoporosis and depression.

Asthma severity was determined based on treatments proposed in the 2016 Scottish Intercollegiate Guidelines Network (SIGN)/British Thoracic Society (BTS) guidelines.²⁸

All asthma medication prescriptions (SABA, inhaled corticosteroids (ICS), ICS/long-acting β_2 -agonist (LABA), ICS/LABA/long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonist (LTRA), maintenance OCS (with a daily dose <10 mg), theophylline, aminophylline and biologics) were evaluated at baseline. A cut-off of 10 mg was considered for maintenance OCS based on clinical experience and studies conducted in the UK that estimated the median daily dose of maintenance OCS for severe asthma to be 10–15 mg/day across several specialist centres.^{29,30}

Asthma exacerbations, medication prescriptions and HCRU were evaluated during the postindex follow-up period. Asthma-related HCRU included primary care or GP visits (overall and within 10 days of hospitalisation or an ED visit), outpatient visits (overall and within 10 days of hospitalisation or an ED visit), inpatient visits or hospitalisation and ED visits. Exacerbation-related HCRU included inpatient hospitalisations, ED visits and a GP-prescribed short course of OCS. Routine HCRU included asthma-related GP and outpatient visits (online supplemental methods).

GHG emissions, measured as carbon dioxide equivalent (CO_2e (95% CI)), were assessed during follow-up years (online supplemental methods). The quantification of GHG emissions associated with all asthma medications were based on the quantity and type of medications prescribed/possessed (as a surrogate for use) and the CO_2e emission value for each asthma treatment. The carbon footprint of all inhaled treatments, as well as oral and injectable medications (SABA, ICS, ICS/LABA, ICS/LABA/LAMA, LABA, LABA/LAMA, LTRA, maintenance OCS (with a daily dose <10 mg), theophylline, aminophylline and biologics), were quantified using the SimaPro software modelling resource, and energy consumption data, Ecoinvent datasets and certified published studies, together with modelled estimates^{12,31,32} and internal data, and are listed in online supplemental table S1. Calculations for the carbon footprint considered emissions from the entire life cycle of all asthma medications, including the manufacture and transport of the inhaler device (eg, pMDI or dry powder inhaler (DPI)), drug, propellants (for pMDIs) and end-of-life disposal of inhalers. As commonly practised,^{33,34} product life cycle assessments were carried out using GWP values of HFAs for a 100-year time period obtained from the Intergovernmental Panel on Climate Change Fifth Assessment Report.³⁵ GHG emissions associated with various HCRU components, including all healthcare visit types (GP visits, outpatient visits, ED visits and inpatient hospitalisation) were estimated by applying the methodology and data obtained from the SHC Care Pathway Guidance⁴ and related assumptions (online supplemental table S2). Primary care/GP visits were identified in the CPRD with asthma Read codes,²⁵ while asthma-related outpatient (specialist) visits were identified in the HES data with specialist code 340 (which identified respiratory medicine) and International Classification of Diseases 10th Revision codes, where available.

Since CO_2e emissions associated with different types of HCRU can vary considerably, we conducted a post hoc sensitivity analysis to demonstrate the potential range of asthma care-related GHG emissions, HCRU CO_2e at $0.1\times$ and $10\times$ of SHC values.

Statistical analysis

Mean (SD) and median (minimum, maximum) were used to describe continuous variables. Categorical data were expressed as numbers and percentages.

Overall GHG emissions, including emissions related to all asthma medication prescriptions and HCRU, were calculated as total annual measure and per 10 000 person-years (per capita) to facilitate comparison across groups. These values were also scaled up

Table 1 Demographics and baseline clinical characteristics stratified by asthma control in UK patients with asthma

	All (N=236 506)	Well-controlled asthma (n=124 662)	Poorly controlled asthma (n=111 844)
Age at index, years, n (%)			
12–17	33 295 (14.1)	21 394 (17.2)	11 901 (10.6)
≥18–54	129 734 (54.9)	71 452 (57.3)	58 282 (52.1)
≥55	73 477 (31.1)	31 816 (25.5)	41 661 (37.3)
Sex, n (%)			
Female	135 324 (57.2)	70 373 (56.5)	64 951 (58.1)
Missing values	5 (<0.1)	2 (<0.1)	3 (<0.1)
Socioeconomic status, n (%)			
IMD1 (least deprived)	39 850 (16.9)	23 207 (18.6)	16 643 (14.9)
IMD2	43 983 (18.6)	23 707 (19.0)	20 276 (18.1)
IMD3	45 727 (19.3)	24 237 (19.4)	21 490 (19.2)
IMD4	48 098 (20.3)	25 076 (20.1)	23 022 (20.6)
IMD5 (most deprived)	58 848 (24.9)	28 435 (22.8)	30 413 (27.2)
Comorbidities, n (%)			
Anxiety	44 361 (18.8)	20 038 (16.1)	24 323 (21.8)
Atopy	116 823 (49.4)	61 098 (49.0)	55 725 (49.8)
COPD	17 133 (7.2)	4205 (3.4)	12 928 (11.6)
GORD	23 146 (9.8)	10 417 (8.4)	12 729 (11.4)
Pneumonia	4457 (1.9)	1373 (1.1)	3084 (2.8)
Diabetes	14 486 (6.1)	5549 (4.5)	8937 (8.0)
Osteoporosis	6338 (2.7)	2313 (1.9)	4025 (3.6)
Depression	53 040 (22.4)	23 201 (18.6)	29 839 (26.7)
Asthma duration at index date, years			
Mean (SD)	12.1 (11.7)	10.8 (10.7)	13.5 (12.5)
Asthma severity based on BTS steps, n (%)			
Step 0	68 621 (29.0)	53 773 (43.1)	14 848 (13.3)
Step 1	77 650 (32.8)	40 006 (32.1)	37 644 (33.7)
Step 2	32 713 (13.8)	12 971 (10.4)	19 742 (17.7)
Step 3	41 993 (17.8)	14 642 (11.8)	27 351 (24.5)
Step 4	15 529 (6.6)	3270 (2.6)	12 259 (11.0)
All-cause mortality, n (%)			
Dead	22 177 (9.4)	7514 (6.0)	14 663 (13.1)
Alive	214 329 (90.6)	117 148 (94.0)	97 181 (86.9)
Cause of death, n (%)			
Asthma	384 (1.7)	87 (1.2)	297 (2.0)
COPD	2986 (13.5)	482 (6.4)	2504 (17.1)
Other/unspecified	18 807 (84.8)	6945 (92.4)	11 862 (80.9)
Any SABA*	3.2 (3.9)	0.9 (0.9)	5.7 (4.3)
SABA monotherapy*	0.3 (1.3)	0.2 (0.6)	0.4 (1.8)
Any ICS*†	3.1 (3.6)	1.7 (2.5)	4.7 (4.0)
ICS monotherapy*	1.4 (2.5)	0.9 (1.7)	2.0 (3.0)
Any ICS/LABA*‡	1.7 (3.3)	0.8 (2.2)	2.7 (4.0)
ICS/LABA*	1.5 (3.1)	0.8 (2.1)	2.3 (3.7)
Any ICS/LABA/LAMA*	0.2 (1.2)	0.0 (0.5)	0.3 (1.6)
OCS maintenance*	0.0 (0.1)	0.0 (0.1)	0.0 (0.2)
LTRA*	0.2 (1.5)	0.1 (0.9)	0.4 (2.0)
Other treatments*	0.1 (1.3)	0.0 (0.7)	0.2 (1.8)

Continued

Table 1 Continued

All (N=236 506)	Well-controlled asthma (n=124 662)	Poorly controlled asthma (n=111 844)
*Data are presented as mean number of prescriptions (SD).		
†Any ICS represents ICS-containing therapies, including ICS, ICS/LABA or ICS/LABA/LAMA in combination or as separate inhalers.		
‡Any ICS/LABA represents ICS/LABA-containing therapies, including ICS/LABA or ICS/LABA/LAMA in combination or as separate inhalers.		
BTS, British Thoracic Society; COPD, chronic obstructive pulmonary disease; GORD, gastro-oesophageal reflux disease; ICS, inhaled corticosteroid; IMD, Index of Multiple Deprivation; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β_2 -agonist.		

to the national UK asthma population of 5.4 million.³⁶ To assess whether GHG emissions varied based on follow-up year, we also quantified these measures for the second and third years of follow-up.

GHG emissions during the first year of follow-up were stratified by baseline variables, including asthma control and BTS treatment steps (online supplemental table S3). Excess GHG emissions due to suboptimal asthma control included emissions from ≥3 SABA canister prescriptions/year, exacerbations and any GP and outpatient visits within 10 days of hospitalisation or an ED visit.

As a sensitivity analysis, multivariable HCRU incidence rates—adjusted for prespecified covariates (sex, age, anxiety, atopy, COPD, GORD, pneumonia, depression, SABA canister count, SES and proportion of days covered by ICS prescriptions)—were quantified using a negative binomial regression model and multiplied with the relevant CO₂e emission values to quantify total GHG emissions. These covariates were selected a priori based on literature and modelling data from the SABINA I study.¹⁸

RESULTS

Of the 236 506 patients analysed, 47.3% were categorised as having poorly controlled asthma (table 1). At baseline, patients with poorly controlled asthma versus those with well-controlled asthma received a greater number of prescriptions for SABA, ICS monotherapy and ICS/LABA. Demographics and baseline clinical characteristics stratified by BTS steps are provided in online supplemental table S4.

GHG emissions during the follow-up period

Overall GHG emissions attributed to asthma care were 27 108 tonnes CO₂e (range: (0.1×) 26 084–(10×) 37 343 tonnes CO₂e; 95% CI 26 969 to 27 247), with poorly controlled asthma (21 363 tonnes CO₂e; range: (0.1×) 20 568–(10×) 29 315 tonnes CO₂e; 95% CI 21 244 to 21 482) associated with higher emissions versus well-controlled asthma (5745 tonnes CO₂e; range: (0.1×) 5517–(10×) 8028 tonnes CO₂e; 95% CI 5702 to 5788; figure 1A). Poorly controlled asthma was associated with 3.1-fold higher per capita GHG emissions than well-controlled asthma (1997 (95% CI 1985.9 to 2008.1) vs 652.4 (95% CI 647.5 to 657.3) tonnes CO₂e/10 000 person-years). SABA relievers accounted for 60.7% of the per capita GHG emissions, with smaller contributions from other pharmacotherapies, exacerbations and routine HCRU (figure 1B). For all components, GHG emissions were greater for poorly controlled asthma. SABA relievers contributed 1264.7 (95% CI 1257.3 to 1272.0) vs 332.5 (95% CI 329.8 to 335.3) tonnes CO₂e/10 000 person-years in poorly controlled versus well-controlled asthma, respectively. Inpatient hospitalisations accounted for the highest per capita exacerbation-related GHG emissions, followed by ED visits and short courses of OCS (figure 1C). For routine HCRU, GP visits accounted for higher per capita GHG emissions than outpatient visits (figure 1D). Overall per capita GHG emissions increased with greater asthma severity, with emissions being greater in poorly controlled versus well-controlled asthma across all BTS steps (0–4; online supplemental figure S1A).

Scaled to the UK asthma population, overall emissions were equivalent to 750 540 tonnes CO₂e (range: (0.1×) 722 202–(10×)

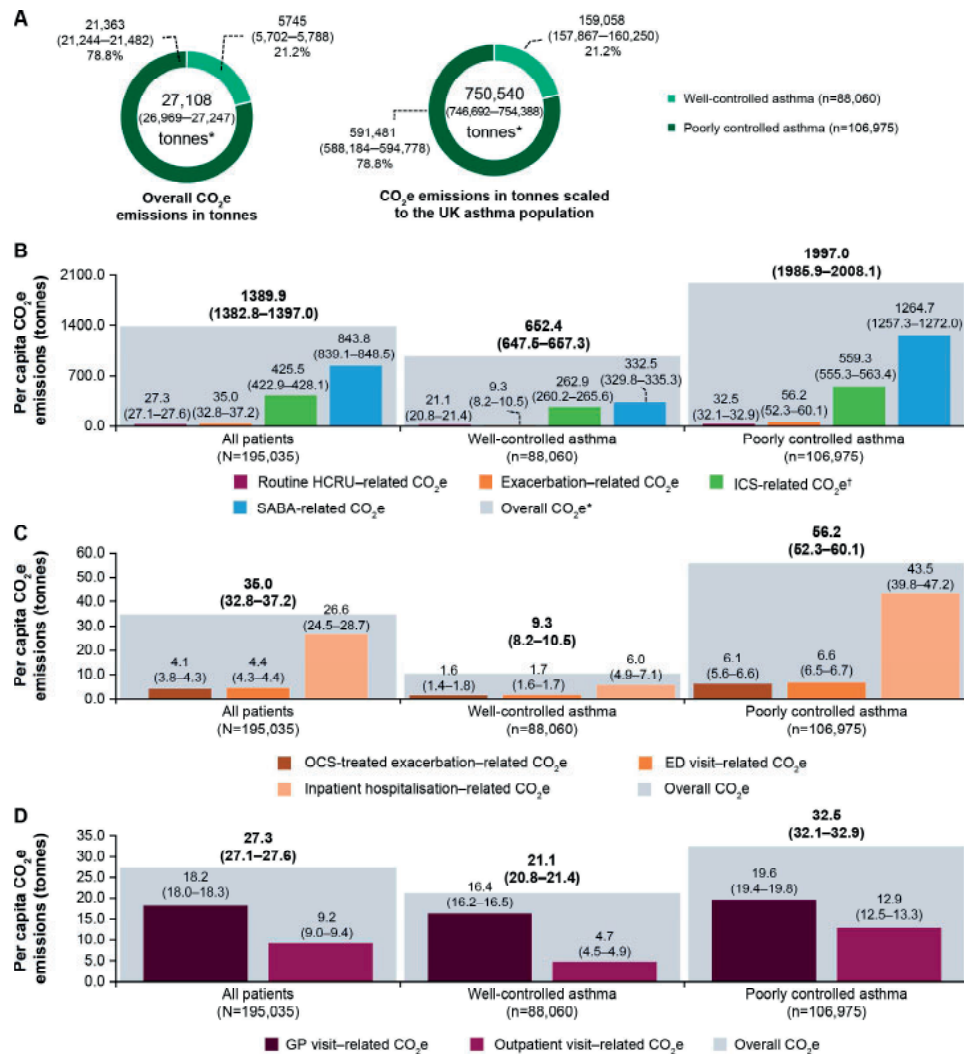


Figure 1 Greenhouse gas emissions during the first year of follow-up stratified by asthma control in UK patients with asthma. (A) Overall CO₂e emissions in tonnes and CO₂e emissions in tonnes scaled to the UK asthma population. (B) Overall CO₂e emissions per capita. (C) Exacerbation-related CO₂e emissions per capita. (D) Routine HCRU-related CO₂e emissions per capita. Estimates are subject to rounding. Values in parentheses represent 95% CI unless otherwise stated. *Includes emissions from other asthma medications, including LABA, LAMA, LABA/LAMA, LTRA, OCS maintenance, theophylline, aminophylline and biologics. †ICS-related CO₂e emissions include all ICS-containing therapies (ICS, ICS/LABA or ICS/LABA/LAMA in combination or as separate inhalers). CO₂e, carbon dioxide equivalent; ED, emergency department; GP, general practitioner; HCRU, healthcare resource utilisation; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; per capita, per 10 000 person-years; SABA, short-acting β_2 -agonist.

1 033 921 tonnes CO₂e; 95% CI 746 692 to 754 388), with poorly controlled asthma as the major contributor (figure 1A).

Similar findings were observed in the second and third years of follow-up (online supplemental figures S1C,D, S2 and S3). In a sensitivity analysis, modelling HCRU incidence rates adjusted for prespecified covariates did not substantially alter the GHG emissions observed (online supplemental figure S4).

Excess GHG emissions during the first year of follow-up

Excess GHG emissions due to suboptimal asthma control, defined as ≥ 3 SABA canisters and exacerbation-related care, accounted for 12 085 tonnes CO₂e overall (range: (0.1 $\times$) 11 533–(10 $\times$) 17 602 tonnes CO₂e; 95% CI 11 979 to 12 191), with poorly controlled asthma (10 975 tonnes CO₂e; range: (0.1 $\times$) 10 485–(10 $\times$) 15 873 tonnes CO₂e; 95% CI 10 880 to 11 070) associated with higher emissions versus well-controlled asthma (1110 tonnes CO₂e; range: (0.1 $\times$) 1048–(10 $\times$) 1729 tonnes CO₂e; 95% CI 1087 to 1133; figure 2A). Poorly controlled asthma was associated with 8.1-fold higher per capita excess GHG emissions than well-controlled asthma (1026.0 (95% CI 1017.1 to 1034.9) vs 126.0 (95% CI 123.4 to 128.7) tonnes CO₂e/10 000 person-years). SABA relievers accounted for 94.3% of the per capita excess emissions, with poorly controlled asthma and well-controlled asthma contributing 969.0 (95% CI

961.6 to 976.4) and 116.6 (95% CI 114.3 to 118.9) tonnes CO₂e/10 000 person-years, respectively (figure 2B). Inpatient hospitalisations accounted for the highest per capita exacerbation-related excess GHG emissions (figure 2C). Per capita routine HCRU-related excess GHG emissions were 8.7-fold higher in poorly controlled asthma versus well-controlled asthma (figure 2D). Across disease severities, poorly controlled asthma was associated with greater excess emissions than well-controlled asthma (BTS steps 0–4; online supplemental figure S1B).

Scaled to the national level, excess GHG emissions of 334 604 tonnes CO₂e (range: (0.1 $\times$) 319 329–(10 $\times$) 487 351 tonnes CO₂e; 95% CI 331 670 to 337 537) were observed, with poorly controlled asthma contributing to 90.8% of these emissions (figure 2A).

GHG emissions during the first year of follow-up stratified by medication use, SES and care pathway

When stratified by SABA prescriptions (0 to >12 SABA canisters), per capita GHG emissions increased with higher SABA canister counts (online supplemental table S5). High SABA use of 3–12 canisters/year accounted for 58.3% of overall GHG emissions (figure 3A). High SABA use of >12 canisters/year contributed most to per capita GHG emissions versus high SABA use of 3–12 canisters/year and optimal SABA use (figure 3B). Across

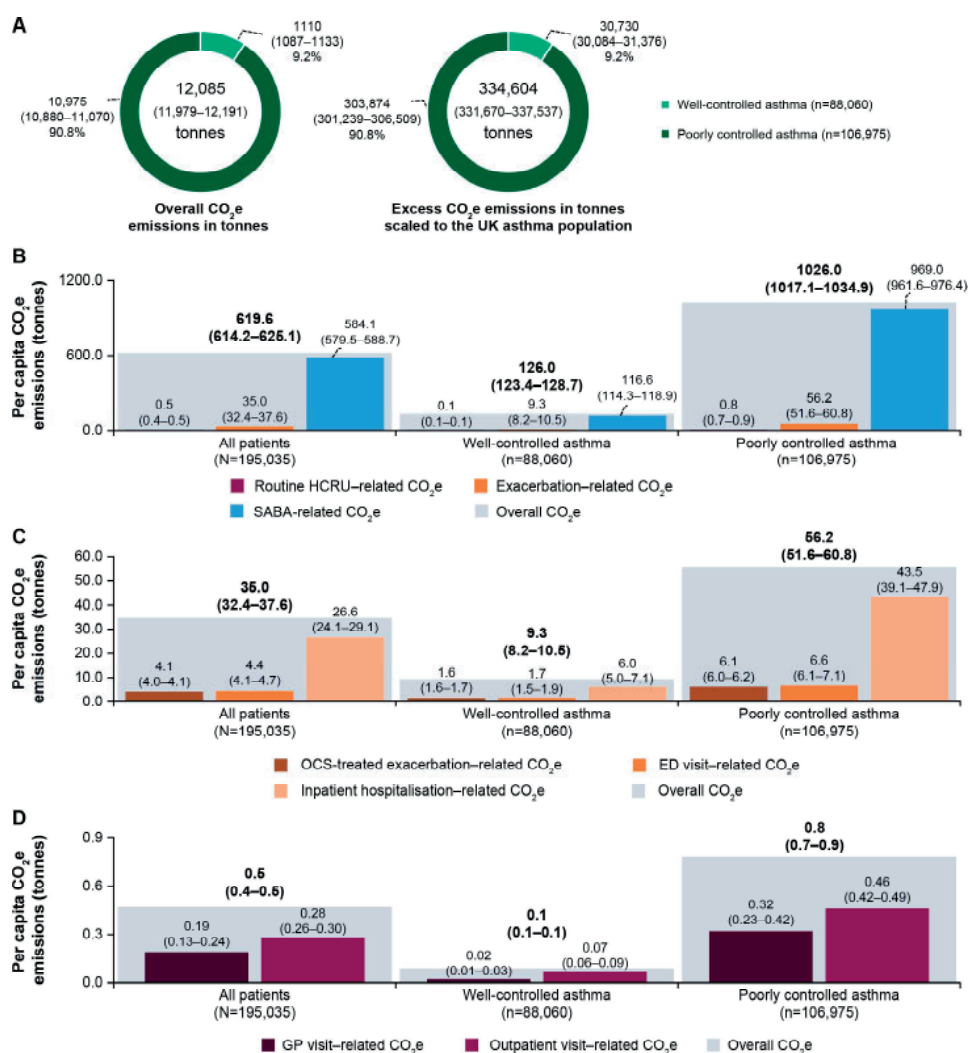


Figure 2 Excess greenhouse gas emissions due to suboptimal asthma control during the first year of follow-up stratified by asthma control in UK patients with asthma. (A) Overall excess CO₂e emissions in tonnes and excess CO₂e emissions in tonnes scaled to the UK asthma population. (B) Overall excess CO₂e emissions per capita. (C) Exacerbation-related excess CO₂e emissions per capita. (D) Routine HCRU-related excess CO₂e emissions per capita. Estimates are subject to rounding. Values in parentheses represent 95% CI unless otherwise stated. CO₂e, carbon dioxide equivalent; ED, emergency department; GP, general practitioner; HCRU, healthcare resource utilisation; OCS, oral corticosteroid; per capita, per 10 000 person-years; SABA, short-acting β_2 -agonist.

prescription volumes, SABA relievers contributed most to per capita GHG emissions, with smaller fractions from ICS use, exacerbations and routine HCRU (figure 3B). Inpatient hospitalisations accounted for the highest per capita exacerbation-related GHG emissions (figure 3C). For routine HCRU, the majority of per capita GHG emissions were contributed by GP visits for optimal SABA use and high SABA use of 3–12 canisters/year (figure 3D).

Stratification by SES indicated that per capita GHG emissions increased from least deprived (IMD1) to most deprived (IMD5) areas of the UK (figure 4A). Regardless of SES, SABA use and ICS use contributed most to overall GHG emissions (figure 4B). Although GHG emissions were not notably different across IMD groups, they were highest in the most deprived areas. Per capita exacerbation-related GHG emissions were lowest in IMD1 and highest in IMD5 (figure 4C). Per capita routine HCRU-related GHG emissions were lowest in IMD5 and highest in IMD4 (figure 4D). The GHG emissions stratified by ICS dose and care pathway are provided in online supplemental tables S6 and S7.

DISCUSSION

In this nationwide study, asthma care accounted for 750 540 (95% CI 746 692 to 754 388) tonnes CO₂e annually when scaled to the UK asthma population, with poorly controlled asthma contributing nearly 80% of these emissions. At the national level, poorly controlled asthma was associated with excess GHG emissions of

303 874 (95% CI 301 239 to 306 509) tonnes CO₂e annually, which was equivalent to emissions from >124 000 houses in the UK in 2020.^{37 38} Poorly controlled asthma was associated with approximately eightfold higher per capita excess GHG emissions versus well-controlled asthma. SABA relievers represented the largest contributors to per capita asthma-related GHG emissions, accounting for >60% of overall GHG emissions and >90% of excess GHG emissions. These findings indicate that efforts to improve asthma treatment practices to curtail high SABA use as part of an overall management strategy that seeks to implement evidence-based treatment recommendations and address other contributing factors to poor asthma control, such as suboptimal adherence to medication and poor inhaler technique,⁸ could result in substantial carbon savings. This concept of coupling optimised patient outcomes with environmental targets to decrease GHG emissions would enable healthcare systems to meet their carbon emission reduction goals and might also be extended to other chronic progressive diseases, particularly those associated with multimorbidities. Notably, in an attempt to balance environmental sustainability with respiratory healthcare, the European Respiratory Society in its recent position statement on asthma and the environment introduced the concept of the ‘green asthma patient’ and recommended that patients should be supported by greener healthcare regulations to make lifestyle changes and conscious choices to reduce the environmental impact of their treatment, without compromising their health.³⁹

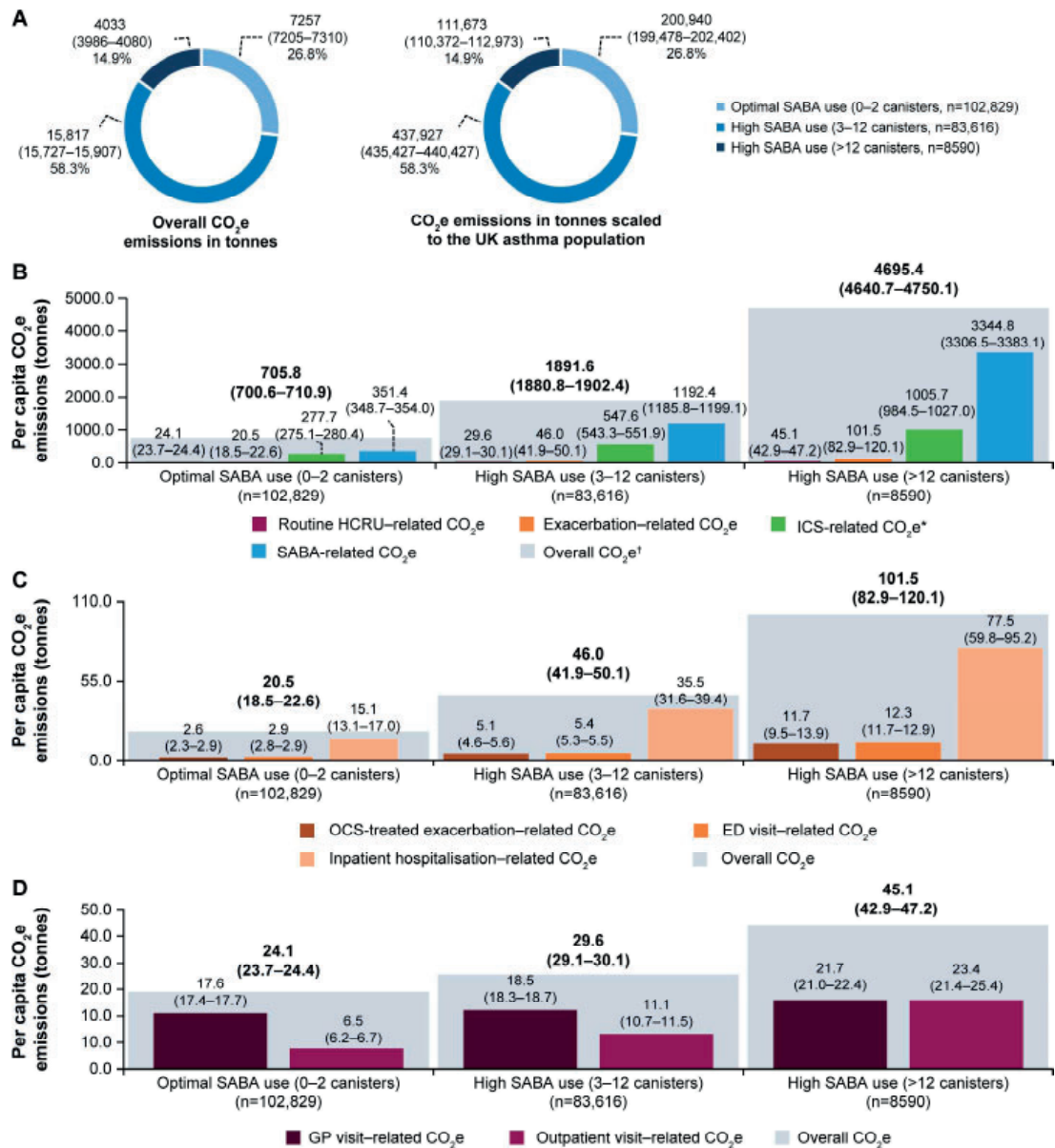


Figure 3 Greenhouse gas emissions during the first year of follow-up stratified by SABA use groups in UK patients with asthma. (A) Overall CO₂e emissions in tonnes and CO₂e emissions in tonnes scaled to the UK asthma population. (B) Overall CO₂e emissions per capita. (C) Exacerbation-related CO₂e emissions per capita. (D) Routine HCRU-related CO₂e emissions per capita. Estimates are subject to rounding. Values in parentheses represent 95% CI unless otherwise stated. *ICS-related CO₂e emissions include all ICS-containing therapies (ICS, ICS/LABA or ICS/LABA/LAMA in combination or as separate inhalers). †Includes emissions from other asthma medications, including LABA, LAMA, LABA/LAMA, LTRA, OCS maintenance, theophylline, aminophylline and biologics. CO₂e, carbon dioxide equivalent; ED, emergency department; GP, general practitioner; HCRU, healthcare resource utilisation; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; per capita, per 10 000 person-years; SABA, short-acting β_2 -agonist.

To our knowledge, no other study has attempted to quantify the carbon footprint of all aspects of asthma care, although the carbon footprint of healthcare systems has been estimated on a global⁴⁰ as well as a country level.^{41–45} In the current study, routine HCRU and exacerbations contributed to overall GHG emissions, although in comparatively lower proportions than inhaled asthma pharmacotherapies. Poorly controlled asthma generated higher emissions associated with routine HCRU and exacerbations than well-controlled asthma. Inpatient hospitalisations contributed most to exacerbation-related emissions. Per capita GHG emissions associated with routine HCRU and exacerbations were higher among patients seen in both primary and specialty care settings versus primary care alone. Overall, these results align with previous research on asthma-related HCRU.^{10,46}

In line with previous studies,^{47,48} higher asthma care-related GHG emissions were observed among residents of the most socioeconomically deprived areas of the UK. Although GHG emissions were not notably different across IMD groups, SABA and ICS use

largely contributed to emissions, followed by exacerbations and routine HCRU. Therefore, targeted interventions designed to increase healthcare access for patients living in socioeconomically disadvantaged areas could promote improved clinical outcomes and deplete the carbon footprint of the UK health system.

Our study indicates that poorly controlled asthma contributes to a large proportion of asthma care-related GHG emissions, with SABA use emerging as the single largest contributor, irrespective of asthma control or SES. Since 2019, the Global Initiative for Asthma (GINA) no longer recommends SABA as the preferred reliever for acute asthma symptoms based on evidence of an increased risk of severe exacerbations and asthma-related mortality associated with SABA-only treatment.⁴⁹ Adoption of GINA-guided treatment strategies could assist healthcare systems to decarbonise care pathways. In addition, self-management of asthma, supported by asthma action plans and regular clinical evaluations, is fundamental to asthma control and has been shown to reduce asthma symptoms and HCRU, including unscheduled primary care vi-

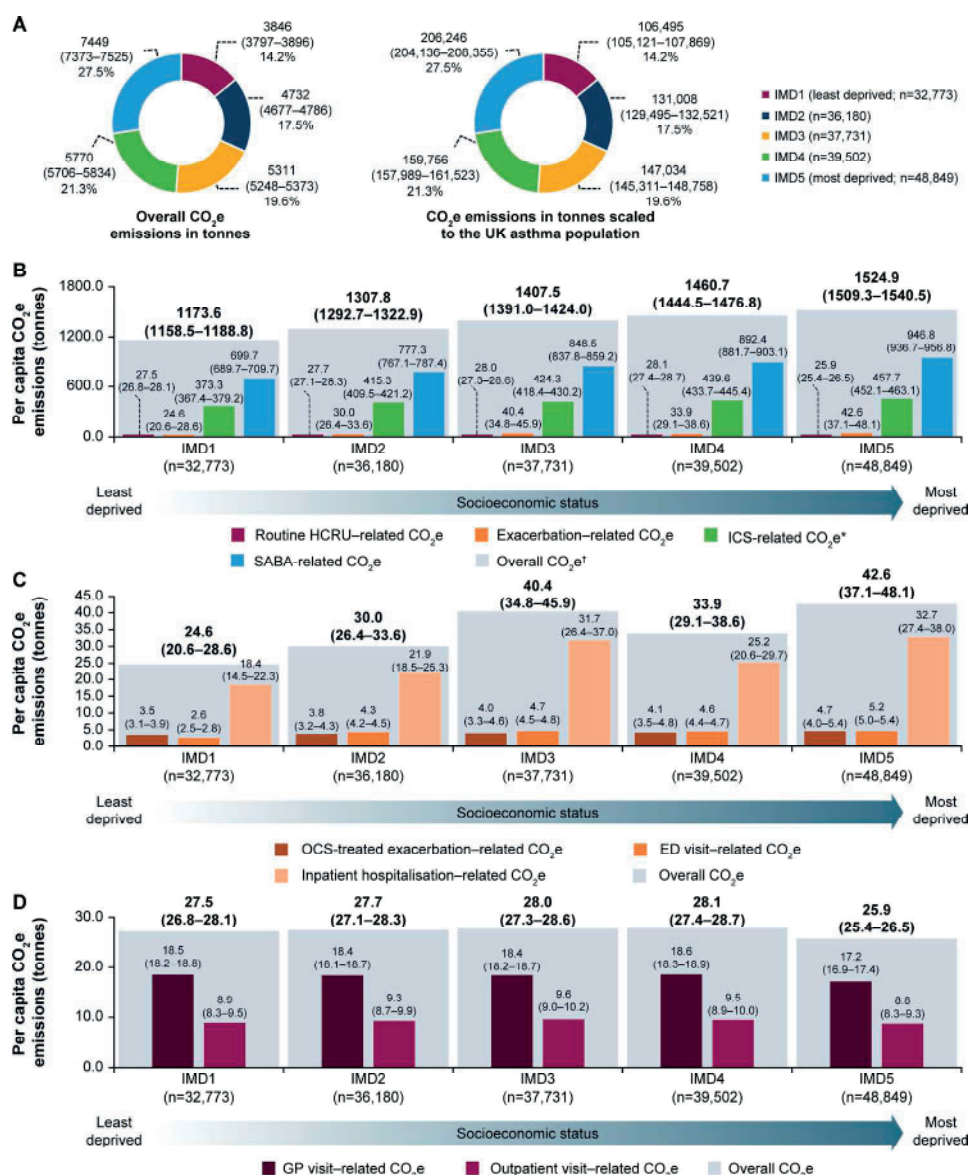


Figure 4 Greenhouse gas emissions during the first year of follow-up stratified by SES (based on IMD) in UK patients with asthma. (A) Overall CO₂e emissions in tonnes and CO₂e emissions in tonnes scaled to the UK asthma population. (B) Overall CO₂e emissions per capita. (C) Exacerbation-related CO₂e emissions per capita. (D) Routine HCRU-related CO₂e emissions per capita. Estimates are subject to rounding. Values in parentheses represent 95% CI unless otherwise stated. *ICS-related CO₂e emissions include all ICS-containing therapies (ICS, ICS/LABA or ICS/LABA/LAMA in combination or as separate inhalers). †Includes emissions from other asthma medications, including LAMA, LABA, LABA/LAMA, LTRA, OCS maintenance, theophylline, aminophylline and biologics. CO₂e, carbon dioxide equivalent; ED, emergency department; GP, general practitioner; HCRU, healthcare resource utilisation; ICS, inhaled corticosteroid; IMD, Index of Multiple Deprivation; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; per capita, per 10 000 person-years; SABA, short-acting β_2 -agonist; SES, socioeconomic status.

sits, ED visits and hospitalisations.⁵⁰ Therefore, prioritising asthma care through early and accurate diagnosis; use of recommended effective therapies and process improvements in asthma management by clinicians, healthcare decision-makers and policymakers can foster better and sustained clinical outcomes and subsequently reduce excess GHG emissions.

The extraction of patient data from CPRD yielded results generalisable to the asthma population across the UK,⁵¹ and access to anonymised data routinely collected as part of patient care mitigated participation and recording biases. However, certain limitations must be acknowledged. In spite of using validated Read codes with a high positive predictive value²⁵ to identify an asthma diagnosis, all patients with mild disease may not have been captured. However, given the lower carbon footprint at BTS step 0 (~10% of the scaled national value), the omission of some patients with mild disease is expected to minimally impact overall GHG emissions. Although CO₂e emissions were stratified by ICS use and BTS treatment steps, this analysis did not account for potential confounding by ICS dose. While a reduction in SABA use may be accompanied

by an increase in ICS uptake,⁵² the decline in SABA-related carbon emissions is unlikely to be accompanied by an equivalent increase in GHG emissions associated with ICS-containing medications. This may be explained by the fact that pMDIs, which are more commonly prescribed in the UK as reliever therapy than preventer therapy (>80% vs ~65%),²⁷ have a considerably higher carbon footprint than DPIs (16.0–37.0 vs 0.8–2.0 kg CO₂e per device),^{11 31 53 54} commonly used for ICS-containing medications. While it is a challenge to quantify differences in the carbon footprint associated with reliever and preventer inhaler use in a retrospective analysis, our findings indicate that curbing high SABA use may be accompanied by an overall reduction in asthma care-related carbon emissions. The CPRD provides nationally representative and comprehensive real-world data from GP practices across the UK⁵⁵; however, some aspects of health may be recorded infrequently, and certain patient groups may not be captured.⁵¹ Due to a lack of alternative measures of asthma symptom control in the CPRD, poorly controlled disease was defined based on prescription of ≥ 3 SABA canisters/year or ≥ 1 asthma exacerbation at baseline. Since the

carbon footprint of poorly controlled asthma was largely SABA-induced, high reliever use at baseline, as part of the definition for poorly controlled disease, may partially explain the increased GHG emissions observed during follow-up. Patients with severe asthma and chronic OCS use were excluded from the study due to the inherent challenges of documenting their complete treatment regimen in primary care records. These patients likely experience higher asthma exacerbation rates and HCRU; however, as they were <0.3% of the study population, their exclusion would not have substantially altered the results. Finally, results from this study were largely descriptive in nature. Additionally, allowances must be made for several uncertainties. Factors other than the level of asthma symptom control, such as high reliever prescribing patterns that have been observed in some primary care networks in the UK, may also have contributed to high SABA use.⁵² Prescription data may not reflect actual dispensing in the real world which may contribute to an overestimation of the carbon footprint from prescribed medication. However, once dispensed, the carbon impact of the inhaler device is already largely apparent regardless of inhaler use as manufacture and transport comprises the majority of the cradle-to-grave carbon footprint of inhaler devices.³¹ For a pMDI, the propellant contained within the inhaler will almost inevitably be released into the atmosphere, either through prescribed use or because patients commonly dispose of their dispensed inhalers (whether empty or not) in the general waste due to a lack of inhaler recycling schemes in the UK,³¹ where degradation of the canister will eventually result in the release of the contained propellant into the atmosphere, thereby contributing to global warming. Data on medication use during a hospital admission or an ED visit were not available. CO₂e emissions were calculated by applying approximations based on published guidelines and estimates, which are susceptible to variability and tend to evolve over time. CO₂e emissions were calculated for standard types of HCRU, which may have lower or higher CO₂e emissions than asthma-related HCRU and may also vary between healthcare institutions given regional and local differences in routine clinical practice. These uncertainties were overcome, at least in part, by performing a sensitivity analysis to demonstrate the potential range of GHG emissions from 10-fold to one-tenth of current values. Finally, certain individual patients (in either the well-controlled or poorly controlled asthma groups) may have been classified differently, as evidenced by the fact that a small proportion of patients categorised as having well-controlled asthma at baseline experienced exacerbations during the first year of follow-up. Nevertheless, the definition of poorly controlled asthma used in this study reflects a level of SABA prescriptions that has clearly been associated with inadequate disease control and adverse outcomes.^{18 19}

In conclusion, the present findings demonstrate that targeting improved asthma outcomes by mitigating the high burden of poorly controlled asthma may elicit significant declines in carbon emissions. HCPs and policymakers are in a unique position to assist in resolving the current climate emergency by improving the quality of treatment across asthma severities through actionable process improvements and policies to ensure broader access to guideline-directed controller therapies, with a view towards optimising patient-centric asthma care, curtailing high SABA use and minimising the risk of severe exacerbations.

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Competing interests AJKW is a member of the Montreal Protocol Medical and Chemical Technical Options Committee and has made unpaid contributions to publications on the carbon footprint of inhalers and respiratory treatment, which were sponsored by GlaxoSmithKline and AstraZeneca. CJ has received personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis and Teva outside the submitted work. VR is an employee of ZS Associates India Pvt. Ltd. JKQ has received grants from The Health Foundation, MRC, GlaxoSmithKline, Bayer, Boehringer Ingelheim, British Lung Foundation, IQVIA, Chiesi, AstraZeneca, Insmad and Asthma UK and personal fees for advisory board participation or speakers' fees from GlaxoSmithKline, Boehringer Ingelheim, AstraZeneca and Bayer. AM-G has attended advisory boards for AstraZeneca, GlaxoSmithKline, Novartis, Sanofi and Teva; has received

speaker fees from AstraZeneca, Novartis, Sanofi and Teva; has participated in research with AstraZeneca, for which his institution has been remunerated; has attended international conferences with Teva and has consultancy agreements with AstraZeneca and Sanofi. AM-G is an employee of AstraZeneca. EM, NB, TNT, YX, JPB and AM-G are employees of AstraZeneca and own stocks in AstraZeneca.

Patient consent for publication Not applicable.

Ethics approval The protocol for this research was approved by the Independent Scientific Advisory Committee (ISAC) for the Medicines and Healthcare Products Regulatory Agency (MHRA) Database Research (protocol 18_080RAR) on 24 March 2020. Generic ethical approval for observational research using Clinical Practice Research Datalink (CPRD) with approval from ISAC was granted by the Health Research Authority Research Ethics Committee (East Midlands Derby, REC reference number 05/MRE04/87). This non-interventional study (NIS) was performed in accordance with the ethical principles consistent with the Declaration of Helsinki, International Conference on Harmonisation (ICH) guideline for Good Clinical Practice, Good Pharmacoeconomics Practice (GPP) and the applicable legislation on NIS.

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Data availability statement Data are available on reasonable request. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at <https://astrazeneca-group.trials.pharm.mcm.com/ST/Submission/Disclosure>. Data for studies directly listed on Vivli can be requested through Vivli at <https://www.vivli.org/>. Data for studies not listed on Vivli could be requested through Vivli at <https://vivli.org/members/enquiries/aboutstudies-not-listed-on-the-vivli-platform/>. AstraZeneca Vivli member page is also available outlining further details: <https://vivli.org/ourmember/astrazeneca/>.

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ARTIGO ORIGINAL

Trajetória reprodutora da mulher e o risco de doença pulmonar obstrutiva crônica

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RESUMO

Contexto Os fatores reprodutores da mulher poderão influenciar o desenvolvimento da doença pulmonar obstrutiva crônica (DPOC) através do ambiente hormonal, mas os estudos sobre este tema são limitados. Este estudo teve como objetivo avaliar se a idade da menarca, o número de filhos, a infertilidade, o aborto espontâneo, os nascidos-mortos e a idade da menopausa natural estavam associados ao risco de DPOC.

Métodos Foram incluídas mulheres de três coortes com dados sobre fatores de reprodução, DPOC e covariáveis. Os modelos de regressão de Cox específicos para cada causa foram ajustados para o ano de nascimento, a raça, o nível de escolaridade, o índice de massa corporal e os anos de consumo de tabaco, estratificados por asma, e incorporando a interação entre o ano de nascimento e o tempo. Foram tidas em conta as diferenças entre coortes e as correlações dentro das coortes.

Resultados No total, foram incluídas 283 070 mulheres e 10 737 (3,8%) desenvolveram DPOC após um seguimento médio de 11 (IQR 10–12) anos. As análises revelaram uma associação em forma de U entre a idade da menarca e a DPOC (≤ 11 vs. 13: HR 1,17, IC 95% 1,11 a 1,23; ≥ 16 vs. 13: HR 1,24, IC 95% 1,21 a 1,27). Mulheres com três ou mais filhos (3 vs. 2: HR 1,14, IC 95% 1,12 a 1,17; ≥ 4 vs. 2: HR 1,34, IC 95% 1,28 a 1,40), abortos múltiplos (2 vs. 0: HR 1,28, IC 95% 1,24 a 1,32; ≥ 3 vs. 0: HR 1,36, IC 95% 1,30 a 1,43) ou nascidos-mortos (1 vs. 0: HR 1,38, IC 95% 1,25 a 1,53; ≥ 2 vs. 0: HR 1,67, IC 95% 1,32 a 2,10) apresentaram maior risco de DPOC. Entre as mulheres pós-menopáusicas, a idade mais precoce da menopausa natural foi associada a um risco acrescido de DPOC (<40 vs. 50–51: HR 1,69, IC 95% 1,63 a 1,75; 40–44 vs. 50–51: HR 1,42, IC 95% 1,38 a 1,47).

Conclusões Vários fatores de reprodução feminina, incluindo idade da menarca, número de filhos, aborto espontâneo, nascidos-mortos e idade na menopausa natural, foram associados ao risco de DPOC.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive lung disease characterised by respiratory symptoms associated with chronic airflow limitation.¹ Globally, the estimated prevalence of COPD was about 3.9% in 2017, and the prevalence among men and women was 3.7% and 4.2%, respectively.² Recent evidence indicates substantial gender differences in the susceptibility to, and severity of, COPD.³ Women appear to develop severe COPD at younger ages than men, and non-smokers with COPD are more likely to be women, indicating that women may be more susceptible.³

Female sex hormones are crucial modulators of lung development and diseases. Oestrogen and progesterone are involved in formation and maintenance of a full complement of alveoli.⁴ Female sex hormones may influence the development of COPD through the properties of

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Gender differences in the susceptibility to, and severity of, chronic obstructive pulmonary disease (COPD) have been documented.
- Female reproductive factors may influence the development of COPD through the female hormonal environment, which varies according to different phases and events in women's reproductive life stages, but studies on this are limited.

WHAT THIS STUDY ADDS

- Women with earlier or later age at menarche had an increased risk of COPD, as well as women with three or more children.
- A history of infertility, miscarriage or stillbirth, especially multiple miscarriages or stillbirths, was associated with a higher risk of COPD.
- Among women who had experienced natural menopause, earlier age at menopause was associated with an increased risk of COPD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This study demonstrated that multiple female reproductive factors were associated with the risk of COPD, which could have important practical implications for identifying women at a higher risk of COPD.

modulating bronchodilation, inflammation, proliferation and cigarette smoke metabolism.^{5–6} The female hormonal environment varies according to different phases and events in women's reproductive life stages, such as menarche, pregnancy and menopause, and women with infertility or pregnancy loss often have diminished ovarian reserve and oestrogen deficiency.^{7,8}

A growing number of studies have revealed a higher risk of asthma among women during puberty, at pregnancy or after menopause, which indicates the role of sex hormones in the development of asthma.^{9–11} However, studies on COPD are limited. As far as we know, there have been only five studies on this topic, which showed that several reproductive histories (eg, age at menarche, high

parity, pregnancy loss and age at natural menopause) were associated with the risk of COPD. But two of the studies were cross sectional and in the three longitudinal studies the female reproductive factors were not assessed with fine grained categories due to limitation in sample size.^{12–16} The follow-up periods varied from 6 to 15.8 years, and the analyses did not include important confounding factors, such as asthma and pack years of smoking.

Therefore, this study used individual level data from the International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events (InterLACE) consortium to investigate whether women with earlier age at menarche, higher number of children, infertility, miscarriage, stillbirth or earlier age at menopause were at higher risk of COPD.

METHODS

Study design and participants

The InterLACE consortium is composed of 27 observational studies, pooling individual level data of more than 850 000 women from 12 countries.¹⁷ For our analysis, three cohorts with data on reproductive factors and COPD were included. These were the Australian Longitudinal Study on Women's Health 1946–51 cohort (ALSWH-mid), UK Biobank, and the Swedish Women's Lifestyle and Health Study (WLH). Cohort characteristics are presented in online supplemental e-Table 1.

Two cohorts collected information on infertility and miscarriage, while only one cohort had data on stillbirths (online supplemental e-Table 1 and online supplemental e-Figure 1). Other reproductive histories were available in all three cohorts. Since the ages of infertility, miscarriage, stillbirths, and parity were not available, women who had COPD at or before the age of 40 years were excluded from the analyses of these variables. Analyses of miscarriages and stillbirths were restricted to women who had ever been pregnant. Analyses of age at menopause were restricted to women with natural menopause, and those with COPD before natural menopause were excluded. In the analysis of each reproductive factor, women with missing data on that factor, COPD or the covariates of birth year, race/ethnicity, education level, pack years of smoking, body mass index (BMI) and asthma were excluded. In ALSWH-mid and UK Biobank, women were followed up until 31 December 2019 to exclude the potential influence of COVID-19 infection. Women in WLH were followed up to the end of 2010.

Reproductive histories

Reproductive histories were collected at baseline or at follow-up surveys. Women were considered to experience infertility if they reported failure to establish a pregnancy after 12 months of regular unprotected sexual intercourse, were diagnosed with infertility or were receiving fertility treatment. Age at menarche was determined as the age of the first menstrual period, and age at natural menopause was defined as the age of the last menstrual period in the absence of hysterectomy or oophorectomy. The number of each pregnancy outcome (ie, live birth, miscarriage and stillbirth) were self-reported. These reproductive histories were categorised as age at menarche (≤ 11 , 12, 13, 14, 15 and ≥ 16 years), number of children (0, 1, 2, 3 and ≥ 4), infertility (never and ever), number of miscarriages (0, 1, 2 and ≥ 3), number of stillbirths (0, 1 and ≥ 2), and age at menopause (< 40 , 40–44, 45–47, 48–49, 50–51, 52–53 and ≥ 54). Three or more miscarriages were defined as recurrent miscarriages, and two or more stillbirths were defined as recurrent stillbirths. Menopause age < 40 and 40–44 years were defined as premature and early menopause, respectively.

Chronic obstructive pulmonary disease

COPD was retrospectively and prospectively identified through self-reported and health administrative data, including pharmaceutical scripts, hospital admissions, hospital emergency presentations and death registry data (online supplemental e-Table 1). All cohorts had hospital admission data, one cohort (ALSWH-mid) had hospital emergency data and two cohorts (ALSWH-mid and UK Biobank) provided death registry data. Hospital admissions, hospital emergency presentations and death registry data were coded using the ninth or 10th version of the International

Classification of Diseases (ICD-9 and ICD-10). ICD-9 codes 491, 492 and 496, and ICD-10 codes J41, J43 and J44 were used to identify COPD cases. ALSWH-mid and UK Biobank also collected information on doctor diagnosed COPD and age at diagnosis through questionnaire items, and ALSWH-mid further identified COPD cases through pharmaceutical data (Anatomical Therapeutic Chemical codes R03AC18, R03AL03, R03AL04, R03AL05, R03AL06 and R03AL08). Age at the earliest record of COPD (eg, self-reported, pharmaceutical, hospital or death record) was taken as the age of COPD onset.

Covariates

Covariates were collected at cohort entrance, including birth year (≤ 1950 and > 1950), race or ethnicity (Caucasian, Asian and other), educational level (≤ 10 , 11–12 and > 12 years), pack years of smoking (0, 1–9, 10–19, 20–29 and ≥ 30 pack years) and asthma (never and ever). BMI (kg/m²) at cohort entrance was categorised as < 18.5 , 18.5–22.9, 23.0–27.4 and ≥ 27.5 for Asian women, and < 18.5 , 18.5–24.9, 25.0–29.9 and ≥ 30.0 for Caucasian and other women.

Statistical analysis

Continuous variables are summarised as median (IQR) and categorical variables as number (%). Cause specific Cox regression models were used to estimate HRs and two sided 95% CIs for the association between each reproductive variable and COPD. Age was used as a time scale. Survival time was from birth to the age at COPD or age at the last follow-up, whichever came first. The proportional hazards assumption was assessed using the Schoenfeld residuals and found to be violated for birth year and history of asthma on COPD (online supplemental e-Table 2). Therefore, an interaction term between birth year and survival time was used to account for its time varying effect. The analyses were stratified by asthma status. This assumed that the coefficients of exposure were the same among women with and without asthma, but the function of time might differ. All models were adjusted for potential confounders (ie, birth year, race/ethnicity, education level, BMI and pack years of smoking; figure 1).^{18–20} Cohort differences were taken into account by including a fixed effect for cohort, and a robust sandwich estimate was used to account for within cohort correlation.²¹

Several sensitivity analyses were conducted. Firstly, random effects for the cohorts were fitted. Secondly, Fine–Grey competing risk models were used to take competing risks of death of other causes (except COPD) into account. For this analysis, women from WLH were excluded because death registry data were not available. Thirdly, the analysis was restricted to women without asthma at cohort entrance. Fourthly, analysis by smoking status at cohort entrance was conducted to separate never smokers, past smokers, and current smokers. Fifthly, analyses of single reproductive factors were further restricted by or adjusted for potential confounding factors (figure 1). Analysis of number of children was restricted to women who did not have infertility. Miscarriage and stillbirth were included in the same model, when the previous pregnancy ending in miscarriage or stillbirth was associated with a higher risk of later stillbirth or miscarriage and subsequent COPD.¹⁸ Analysis of age at natural menopause was further adjusted for age at menarche and number of children, or a single fertility issue (ie, infertility, miscarriage or stillbirth), which have previously been shown to be associated with age at natural menopause.²²

Sixthly, multiple imputation was conducted to account for missing data. Missing data in each cohort were imputed separately. The imputation model included all of the variables in the main analysis except for fertility issues (ie, infertility, miscarriage and stillbirth) and age at natural menopause, because none of the included cohorts had data on all three fertility issues and women who had a hysterectomy or oophorectomy could not experience natural menopause. A fully conditional method was used, in which the imputation methods for continuous and categorical variables were linear regression and logistic regression, respectively. Ten times imputed datasets for each cohort were combined to assess the robustness of the findings. Additionally, two supplementary

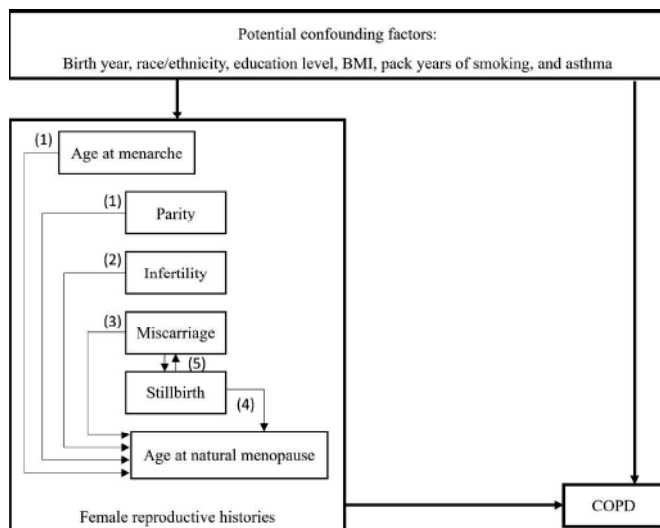


Figure 1 Directed acyclic graph: exploring the associations between female reproductive histories and chronic obstructive pulmonary disease (COPD), with sensitivity analyses accounting for the associations among female reproductive histories. Sensitivity analysis of the association between age at natural menopause and COPD were conducted: (1) with additional adjustment for age at menarche and number of children; (2) with additional adjustment for history of infertility; (3) with additional adjustment for miscarriage; and (4) with additional adjustment for stillbirth. Sensitivity analysis of the association of miscarriage and stillbirth separately with COPD: (5) included miscarriage and stillbirth in the same model. BMI, body mass index.

analyses were conducted. Women with bilateral oophorectomy before menopause, who were excluded from the analysis of age at natural menopause, were included with age at bilateral oophorectomy as an explanatory variable. Associations for COPD in each study were assessed separately, and the effects in a single study were combined using a random effects meta-analysis.

All tests of hypotheses were reported using a two sided 5% level of significance. No adjustment for multiplicity of statistical tests was performed. All statistical analyses were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA), with PROC PHREG for Cox regression.

RESULTS

Overall, 283 070 women were included at a median (IQR) age of 54 (46–62) years and followed up for a median (IQR) of 11 (10–12) years. Among them, 10 737 (3.8%) women developed COPD at a median (IQR) age of 63 (55–70) years. Of these COPD cases, 7983 were identified through a single data source (1729 from survey data, 95 from pharmaceutical scripts, 6102 from hospital data and 57 from death registry) and 2754 were identified through at least two data sources. The characteristics of the women at cohort entrance are shown in table 1. Women with COPD were more likely to be older at cohort entrance, have ≤ 10 years of education, BMI ≥ 30.0 kg/m² (≥ 27.5 kg/m² for Asian women), have ≥ 10 pack years of smoking and have asthma. In total, 53 205 (15.8%) women were excluded due to missing data, mainly for smoking and BMI (online supplemental e-Tables 3 and 4).

There was a U shaped pattern of association for age at menarche and COPD. Women with age at menarche ≤ 11 had a higher risk of COPD (HR 1.17, 95% CI 1.11 to 1.23) compared with women experiencing menarche at age 13 years (table 2). Among women experiencing menarche after age 13 years, the HR for COPD increased from 1.10 (95% CI 1.07 to 1.13) to 1.24 (95% CI 1.21 to 1.27) when age at menarche increased from 14 to 16 years or more.

Women with children were at higher risk of COPD than women without children (HR 1.13, 95% CI 1.11 to 1.15; table 2). Compared with women with two children, women with three (HR 1.14, 95% CI 1.12 to 1.17) or more children (HR 1.34, 95% CI 1.28 to 1.40) were at increased risk of COPD, as well as women with one child (HR 1.18, 95% CI 1.14 to 1.21; table 2).

Women who experienced infertility had a higher risk of COPD (HR 1.13, 95% CI 1.10 to 1.16) than women who did not experience infertility (table 2). Among women who had ever been pregnant, a history of miscarriage was associated with a higher risk of COPD (HR 1.15, 95% CI 1.15 to 1.16) compared with women without miscarriage, and the risk of COPD further increased in women with more miscarriages (miscarriage=1: HR 1.08, 95% CI 1.08 to 1.09; miscarriage=2: HR 1.28, 95% CI 1.24 to 1.32; miscarriage ≥ 3 : HR 1.36, 95% CI 1.30 to 1.43; table 2). Similarly, compared with women without stillbirth, women with stillbirth had a higher risk of COPD (HR 1.42, 95% CI 1.29 to 1.56), and the HRs for COPD associated with single and recurrent stillbirths were 1.38 (95% CI 1.25 to 1.53) and 1.67 (95% CI 1.32 to 2.10), respectively (table 2).

Among women with natural menopause, the risk of COPD was inversely associated with age at menopause, ranging from 1.69 (1.63–1.75) for menopause before the age of 40 to 0.79 (0.78–0.79) for menopause at or over the age of 54, compared with women experiencing natural menopause at age 50–51 years (table 2).

Sensitivity analyses

Firstly, the models with random effects for the cohorts revealed almost the same estimated HRs and slightly wider 95% CIs (online supplemental e-Table 5). Secondly, results from Fine–Grey competing risk analysis were consistent with the results from the main analysis, although the association for infertility was no longer statistically significant (online supplemental e-Table 6). Thirdly, analysis restricted to women without asthma at cohort entrance revealed similar results (online supplemental e-Table 7). Fourthly, associations observed in the main analysis persisted among never smokers, past smokers and current smokers, while the effect of infertility was only observed in current smokers (online supplemental e-Table 8). Fifthly, after restricting the analysis to women without infertility issue, the association between number of children and COPD did not change except for an increase in HR for the effect of no children (online supplemental e-Table 9). The estimated HRs (95% CIs) for miscarriage and stillbirth decreased slightly when both miscarriage and stillbirth were included in the same model (online supplemental e-Table 10). The association for age at natural menopause remained the same after additional adjustment of age at menarche and number of children or fertility issue (ie, infertility, miscarriage or stillbirth; online supplemental e-Tables 11 and 12). Sixthly, findings from the multiple imputed datasets were consistent with the main analysis (online supplemental e-Tables 13 and 14, online supplemental e-Text 1). Supplementary analysis showed that younger age at bilateral oophorectomy was associated with a higher risk of COPD (online supplemental e-Table 15). The associations of female reproductive histories with COPD in the individual studies are presented in online supplemental e-Figures 2–6, as well as the overall effects from random effects meta-analysis. The estimated effect sizes in each cohort separately were generally consistent, except for age at menarche. In the ALSWH-mid cohort, the adjusted HRs did not show a U shaped association for age at menarche, but the data still indicated a higher risk of COPD among women experiencing menarche at age ≥ 15 years.

DISCUSSION

In this pooled analysis of individual level data from 283 070 women, several female reproductive factors were found to be associated with the risk of COPD. Women with earlier or later age at menarche had an increased risk of COPD, as well as women with three or more children. A history of infertility, miscarriage or stillbirth, especially multiple miscarriages or stillbirths, was associated with a higher risk of COPD. Among women who had experienced natural menopause, earlier age at menopause was associated with an increased risk of COPD.

As far as we know, there were three previous studies assessing the association between female reproductive factors and COPD. Tang et al's study included 271 271 female participants in UK Biobank, and found that age at menarche < 12 years (HR 1.15, 95% CI 1.00 to 1.32) or > 15 years (HR 1.37, 95% CI 1.11 to 1.71), number of children > 3 (HR 1.45, 95% CI 1.16 to 1.82) and age at natural menopause < 47 years (HR 1.44, 95% CI 1.19 to 1.75) or 47–49 years (HR 1.25,

Table 1 Characteristics at cohort entrance

	COPD			COPD	
	No (n=2 72 333)	Yes (n=10 737)		No (n=2 72 333)	Yes (n=10 737)
Age (years)			No of children*		
	54 (46–61)	61 (53–65)	0	47 029 (17.3)	1256 (12.7)
Race			1	35 674 (13.1)	1463 (14.8)
Caucasian	259 833 (95.4)	10 482 (97.6)	2	118 817 (43.7)	3820 (38.6)
Asian	5672 (2.1)	89 (0.8)	3	51 257 (18.8)	2141 (21.6)
Other	6828 (2.5)	166 (1.5)	≥4	19 238 (7.1)	1227 (12.4)
Education (years)			Infertility*		
≤10	126 176 (46.3)	7380 (68.7)	Never	40 945 (80.3)	754 (79.0)
11–12	41 784 (15.3)	1058 (9.9)	Ever	10 030 (19.7)	200 (21.0)
>12	104 373 (38.3)	2299 (21.4)	Miscarriage*		
Body mass index (kg/m ²)†			Never	142 618 (74.8)	5866 (71.5)
<18.5	2536 (0.9)	232 (2.2)	Ever	48 130 (25.2)	2339 (28.5)
18.5–24.9	118 566 (43.5)	3467 (32.3)	No of miscarriages*		
25.0–29.9	93 410 (34.3)	3627 (33.8)	0	142 618 (74.8)	5866 (71.5)
≥30.0	57 821 (21.2)	3411 (31.8)	1	34 503 (18.1)	1510 (18.4)
Smoking (pack years)			2	8743 (4.6)	488 (5.9)
0	179 763 (66.0)	2894 (27.0)	≥3	4884 (2.6)	341 (4.2)
1–9	23 749 (8.7)	637 (5.9)	Stillbirth*		
10–19	26 626 (9.8)	1198 (11.2)	Never	176 259 (96.9)	7312 (94.1)
20–29	22 479 (8.3)	1676 (15.6)	Ever	5645 (3.1)	455 (5.9)
≥30	19 716 (7.2)	4332 (40.3)	No of stillbirths*		
Asthma			0	176 259 (96.9)	7312 (94.1)
Never	244 270 (89.7)	6642 (61.9)	1	4895 (2.7)	382 (4.9)
Ever	28 063 (10.3)	4095 (38.1)	≥2	750 (0.4)	73 (0.9)
Age at menarche* (years)			Age at natural menopause* (years)		
≤11	49 737 (18.8)	2351 (22.7)	<40	2301 (1.7)	197 (3.9)
12	53 188 (20.2)	1741 (16.8)	40–44	9027 (6.8)	646 (12.8)
13	67 347 (25.5)	2148 (20.8)	45–47	14 263 (10.8)	765 (15.1)
14	51 874 (19.7)	2100 (20.3)	48–49	16 256 (12.3)	681 (13.5)
15	27 677 (10.5)	1268 (12.3)	50–51	31 774 (24.0)	1110 (22.0)
≥16	14 124 (5.4)	735 (7.1)	52–53	26 194 (19.8)	727 (14.4)
Parity*			≥54	32 616 (24.6)	930 (18.4)
Never	47 029 (17.3)	1256 (12.7)			
Ever	225 159 (82.7)	8666 (87.3)			

Data are number (%) or median (IQR).

*Reproductive history whose association with COPD was assessed in this study.

†Body mass index was categorised as <18.5, 18.5–22.9, 23.0–27.4 and ≥27.5 kg/m² for Asian women, and <18.5, 18.5–24.9, 25.0–29.9 and ≥30.0 kg/m² for Caucasian and other women.

COPD, chronic obstructive pulmonary disease.

95% CI 1.00 to 1.57) were associated with a higher risk of COPD.¹² Findings from our study were mainly consistent with Tang et al's finding. In their study, women were aged 40–69 years at baseline, and 2170 women with COPD at baseline were excluded.¹² Some of these COPD cases might have occurred after the relevant reproductive events. In our study, only women with COPD before the age of 40 years were excluded (n=1122). Also, the follow-up period in our study was longer than that in Tang et al's study (median follow-up period 6 vs 11 years). With more COPD cases, our study had enough power to assess the association for less common reproductive events, such as premature menopause, early menopause, recurrent miscarriages and stillbirths, which had not been assessed by Tang et al's study.

For fertility problems, Westergaard et al's study enrolled 1 370 896 women from Denmark who had ever been pregnant, and found that those with primary recurrent pregnancy loss (≥3 consecutive pregnancy losses before a live birth) had an increased risk of COPD (incidence rate ratio 1.56, 95% CI 1.24 to 1.96).¹³ Similarly, a cross sectional study enrolled 302 510 women from China and showed that ≥2 pregnancy losses was associated with the risk of COPD (OR 1.25, 95% CI 1.17 to 1.32), while the associations for ≥2 miscarriages and ≥2

stillbirths did not persist after adjustment.¹⁵ In our study, longitudinal data showed that miscarriage and stillbirth were associated with an increased risk of COPD, and the risk of COPD tended to be higher among women with recurrent miscarriages or recurrent stillbirths.

COPD and asthma have some similar symptoms and inflammatory mechanisms. Worsening asthma symptoms have been associated with oestrogen changes through several female reproductive stages (eg, menarche, pregnancy and menopause).⁵ Similarly, in this study, the risk of COPD was associated with multiple female reproductive factors, indicating the role of oestrogen changes in COPD development. Oestrogen might influence the development of COPD in a complex way. In infancy and childhood, oestrogen accelerates lung maturation and termination of lung growth.²³ Girls with early menarche might experience insufficient lung growth in early life, lower lung function and greater predisposition to COPD in later life.²⁴ Meanwhile, in the presence of allergens, oestrogen augments airway inflammation by enhancing Th2 cell differentiation, upregulating proinflammatory cytokines (eg, interleukin (IL)-1 β and IL-17A) and downregulating anti-inflammatory cytokines (eg, IL-10) among asthmatic women.²⁵ Sensitised individuals might be at greater risk of COPD due to airway hyperresponsiveness, neutrophilic inflamma-

Table 2 Association between female reproductive histories and risk of chronic obstructive pulmonary disease

		Sample size	Cases	IR*	Crude HR (95% CI)†	Adjusted HR (95% CI)‡
Age at menarche (years)	≤11	52 088	2351	0.68	1.35 (1.28 to 1.41)	1.17 (1.11 to 1.23)
	12	54 929	1741	0.49	1.02 (1.00 to 1.03)	1.01 (1.00 to 1.02)
	13	69 495	2148	0.48	Reference	Reference
	14	53 974	2100	0.59	1.18 (1.13 to 1.23)	1.10 (1.07 to 1.13)
	15	28 945	1268	0.66	1.30 (1.20 to 1.40)	1.12 (1.08 to 1.17)
	≥16	14 859	735	0.75	1.50 (1.41 to 1.61)	1.24 (1.21 to 1.27)
Parity	Never	48 285	1256	0.41	Reference	Reference
	Ever	233 825	8666	0.56	1.17 (1.14 to 1.20)	1.13 (1.11 to 1.15)
No of children	0	48 285	1256	0.41	1.02 (0.99 to 1.05)	0.97 (0.95 to 1.00)
	1	37 137	1463	0.61	1.45 (1.41 to 1.49)	1.18 (1.14 to 1.21)
	2	122 637	3820	0.47	Reference	Reference
	3	53 398	2141	0.61	1.25 (1.22 to 1.27)	1.14 (1.12 to 1.17)
	≥4	20 465	1227	0.90	1.79 (1.71 to 1.87)	1.34 (1.28 to 1.40)
Infertility	Never	41 699	754	0.30	Reference	Reference
	Ever	10 230	200	0.33	1.25 (1.12 to 1.39)	1.13 (1.10 to 1.16)
Miscarriage	Never	148 484	5866	0.59	Reference	Reference
	Ever	50 469	2339	0.70	1.26 (1.21 to 1.31)	1.15 (1.15 to 1.16)
No of miscarriage	0	148 484	5866	0.59	Reference	Reference
	1	36 013	1510	0.63	1.12 (1.10 to 1.15)	1.08 (1.08 to 1.09)
	2	9231	488	0.80	1.47 (1.36 to 1.58)	1.28 (1.24 to 1.32)
	≥3	5225	341	0.99	1.88 (1.76 to 1.99)	1.36 (1.30 to 1.43)
Stillbirth	Never	183 571	7312	0.59	Reference	Reference
	Ever	6100	455	1.09	1.68 (1.53 to 1.85)	1.42 (1.29 to 1.56)
No of stillbirths	0	183 571	7312	0.59	Reference	Reference
	1	5277	382	1.06	1.61 (1.46 to 1.79)	1.38 (1.25 to 1.53)
	≥2	823	73	1.32	2.15 (1.70 to 2.70)	1.67 (1.32 to 2.10)
Age at menopause (years)	<40	2498	197	1.18	2.72 (2.63 to 2.81)	1.69 (1.63 to 1.75)
	40–44	9673	646	0.98	2.07 (2.03 to 2.11)	1.42 (1.38 to 1.47)
	45–47	15 028	765	0.75	1.60 (1.55 to 1.66)	1.25 (1.19 to 1.31)
	48–49	16 937	681	0.59	1.32 (1.27 to 1.38)	1.12 (1.06 to 1.19)
	50–51	32 884	1110	0.49	Reference	Reference
	52–53	26 921	727	0.39	0.79 (0.77 to 0.82)	0.83 (0.80 to 0.86)
	≥54	33 546	930	0.39	0.72 (0.70 to 0.75)	0.79 (0.78 to 0.79)

*Incidence rate per 1000 person years.

†Crude HR: models took cohort difference and within cohort correlation into account.

‡Adjusted HR: models were additionally adjusted for birth year (≤1950 and >1950), race (Caucasian, Asian, and others), education level (≤10, 11–12, and >12 years), body mass index (<18.5, 18.5–22.9, 23.0–27.4, and ≥27.5 for Asian women; <18.5, 18.5–24.9, 25.0–29.9, and ≥30.0 for Caucasian and other women), and pack years of smoking (0, 1–9, 10–19, 20–29, and ≥30 pack years), and included the interaction term between birth year and survival time, and were stratified by asthma (never and ever).

tion and remodelling.²³ Oestrogen's proliferative effects on airway smooth muscle could further worsen airway structure.²⁵

Also, oestrogen has been implicated in the two phase metabolism of cigarette smoke. Oestrogen may upregulate the phase I enzymes without alerting the expression of phase II enzymes, resulting in the accumulation of intermediate metabolites and greater airway damage.⁶ However, oestrogen has been demonstrated to mediate an anti-inflammatory response (eg, suppressing neutrophilic inflammation and alveolar cell apoptosis), which would be protective in COPD.²³ Given oestrogen's multiple effects on the lung, the overall effect of oestrogen might differ depending on the timing. In the early or middle reproductive stage, long or higher accumulated exposure to oestrogen would be detrimental to the lung, leading to a higher risk of COPD among women with early menarche or multiple live births. In the later stage, oestrogen may be protective, since earlier age at menopause or bilateral oophorectomy (indicates shorter exposure to oestrogen) were associated with a higher risk of COPD.

Some common factors might also have a role in the association between reproductive factors and COPD. Autoimmune diseases,

such as antiphospholipid syndrome, autoimmune thyroid disease and type 1 diabetes mellitus, may affect all stages of fertility and pregnancy, commonly manifesting as delayed puberty, infertility and pregnancy loss.^{26–27} Autoimmune components also exist in COPD and underlie chronic mucosal inflammatory responses of bronchitis.²⁸ A pre-existing autoimmune condition that persisted after a complicated reproductive stage could be involved in the development of COPD. Other social and environmental factors, such as smoking, air pollution, underweight, low socioeconomic status, poor health related quality of life and low social support, which are associated with later menarche, low parity and pregnancy loss, are also well established risk factors for COPD.^{19–20–29} Some factors (ie, smoking, BMI and educational level) were adjusted in our study, and explained part of the associations of reproductive histories with COPD, but data on other factors, such as air pollution, were not available.

This study had several limitations. Volunteer bias could exist. Participants with poor health might be less likely to take part in the study. Compared with the general population, participants over represented women with a better socioeconomic status and healthier

lifestyle, which might affect the generalisability of the findings.^{30–32} Detailed data on contraceptive medications and hormone replacement therapy (eg, type, dose, time and duration of use) were not available, so their effect on COPD could not be explored. Other reproductive histories in this study were self-reported, which might introduce recall bias. For the outcome event, there might be unidentified COPD cases since COPD may often be undiagnosed until it is clinically apparent, and COPD cases identified through hospital data could represent more severe cases. This might limit the generalisability of the current findings to the risk of COPD across all levels of severity.

Heterogeneity might exist in the diagnosis of COPD, which was inconsistent among the three cohorts during the research periods. Additionally, other potential confounders, such as parental history of COPD, childhood respiratory infection, secondhand smoking, occupational exposure and tuberculosis, were not available in all cohorts. Finally, women being excluded due to missing data might lead to sample bias. Findings from the imputed dataset and complete dataset were similar, and so it is plausible that the influence of sample bias was small.

CONCLUSION

This study showed that female reproductive factors, including age at menarche, number of children, infertility, number of miscarriages and stillbirths, and age at natural menopause, were associated with an increased risk of COPD. Health professionals should consider the potential risk of COPD among women with such reproductive histories. Further research is needed to understand the mechanisms linking multiple female reproductive histories and COPD.

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ARTIGO ORIGINAL

Implicações clínicas da obstrução das vias aéreas com FEV₁ normal ou baixo na infância e adolescência

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RESUMO

Contexto A obstrução das vias aéreas é definida pela espirometria como uma razão baixa entre o volume expiratório forçado em 1 s (FEV₁) e a capacidade vital forçada (FVC). Esta razão baixa pode ter origem num FEV₁ baixo (clássico) ou num FEV₁ normal em combinação com uma grande FVC (dissinápica). As implicações clínicas da obstrução dissinápica durante a infância e a adolescência na população em geral permanecem pouco claras.

Objetivos Investigar a associação entre obstrução das vias aéreas com um FEV₁ baixo ou normal na infância e adolescência, e asma, pieira e hiperresponsividade brônquica (BHR).

Métodos Nas coortes de nascimento BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology; Suécia) e PIAMA (Prevention and Incidence of Asthma and Mite Allergy; Países Baixos), a obstrução (rácio FEV₁:FVC inferior ao limite inferior do normal, LLN) aos 8, 12 (apenas PIAMA) ou 16 anos foi classificada como obstrução clássica (FEV₁ <LLN) ou dissinápica (FEV₁ ≥LLN). As associações transversais e longitudinais entre estes dois tipos de obstrução e os resultados de saúde respiratória foram estimadas por regressão logística ajustada à coorte em dados agrupados.

Resultados A prevalência de obstrução clássica aos 8, 12 e 16 anos nas duas coortes foi de 1,5%, 1,1% e 1,5%, respetivamente. A obstrução dissinápica foi ligeiramente mais prevalente: 3,9%, 2,5% e 4,6%, respetivamente. A obstrução, independentemente do FEV₁, foi consistentemente associada a maiores probabilidades de asma (obstrução dissinápica: OR 2,29, IC 95% 1,40 a 3,74), pieira, uso de medicação para a asma e BHR em comparação com o grupo de função pulmonar normal. Aproximadamente um terço dos indivíduos com obstrução dissinápica na infância permaneceu dissinápico durante a adolescência.

Implicações clínicas As crianças e adolescentes com obstrução das vias aéreas apresentaram, independentemente do nível de FEV₁, maior prevalência de asma e pieira. O seguimento e o tratamento nestas idades devem ser orientados pela presença de obstrução das vias aéreas.

INTRODUCTION

Airway obstruction is widely recognised as a key characteristic and prognostic marker of childhood wheezing and asthma.^{1–3} Obstruction is defined as a low ratio of forced expiratory volume in 1 s (FEV₁) over forced vital capacity (FVC) and is generally considered to be the result of airway narrowing.⁴ Consequently, FEV₁, as a marker of airway calibre, is frequently low in subjects with obstruction. Airway obstruction with normal FEV₁ could be a sign of physiological variability (ie fluctuations) in lung function resulting from airway hyperresponsiveness, or could be the result of anatomical unequal growth of the airways and lung parenchyma, also referred to as dysanapsis.^{4,5} Regardless, it has not been well established if subjects who fulfil the criteria of an FEV₁ to FVC ratio less than the lower limit of normal (LLN) originating from a low FEV₁ have

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Airway obstruction (forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC) ratio less than the lower limit of normal) is widely recognised as a key characteristic of childhood asthma.
- The obstructive ratio may originate from a low FEV₁ or a normal FEV₁ in combination with a large FVC.

WHAT THIS STUDY ADDS

- Children and adolescents with airway obstruction, defined by low FEV₁ to FVC ratio, have higher risks of asthma, wheezing, use of inhaled corticosteroids and bronchial hyperresponsiveness independent of their FEV₁ levels.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- We recommend a careful evaluation of the FEV₁ to FVC ratio in the diagnostic workup of children, similar to its application in the diagnosis of chronic obstructive pulmonary disease in adults.

a greater risk of asthma and wheezing in comparison with subjects with an FEV₁ to FVC ratio less than the LLN originating from a normal FEV₁ with a relatively larger FVC.

Dysanapsis was first described by Green et al⁵ in 1974 and refers to within and between-individual differences in the growth of airway calibre and lung size. To a certain extent, dysanapsis is normal during development as lung function parameters reflecting flow and volume grow at different rates during childhood and adolescence.⁶ While FVC grows faster than FEV₁ in childhood, the opposite trend is observed in adolescence. Additionally, the interpretation of differing growth rates in FEV₁ and FVC becomes more complex due to variations in growth between males and females at different stages of development. Dysanapsis has been associated with obesity regardless of asthma status, greater use of asthma medication and asthma disease exacerbations in children with obesity.⁷ In the adult population, dysanapsis has been identified as a risk factor for the development of chronic obstructive pulmonary disease (COPD).⁸ However, the clinical implications of airway obstruction



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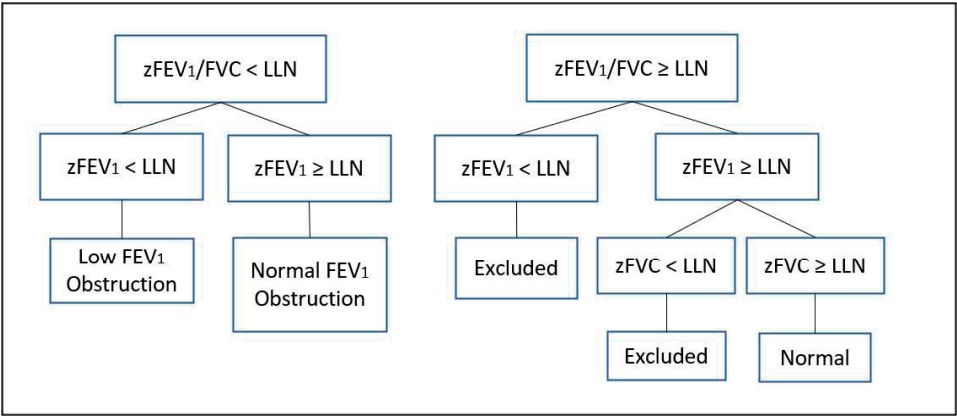


Figure 1 Definition of airway obstruction groups. LLN, lower limit of normal; zFEV₁, z-score for forced expiratory volume in 1 s; zFEV₁:FVC, z-score for forced expiratory volume in 1 s to forced vital capacity ratio.

with a normal FEV₁ during childhood and adolescence in the general population remain unclear.⁴

We therefore aimed to investigate the association between airway obstruction originating from either a low FEV₁ (classic obstruction) or a normal FEV₁ (dysanaptic obstruction) in childhood and adolescence, and respiratory health outcomes. Furthermore, we investigated the stability of these obstruction phenotypes from childhood to adolescence. We hypothesised that both classic and dysanaptic obstructions in childhood and adolescence were associated with a higher prevalence of asthma and wheezing compared with those without airway obstruction.

METHODS
Study population

This study uses data from the population-based BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology; Sweden) and PIAMA (Prevention and Incidence of Asthma and Mite Allergy; the Netherlands) birth cohorts. The BAMSE birth cohort consists of 4089 subjects born between 1994 and 1996 in Stockholm, Sweden.^{9–10} Follow-up was performed by questionnaires at ages 1, 2, 4, 8, 12 and 16 years, and clinical assessment was performed at ages 4, 8 and 16 years. The PIAMA cohort consists of 3963 newborns from 1996/1997 in the Netherlands.^{11–12} Questionnaires were completed by parents during pregnancy, at 3 months, annually until the age of 8, and at ages 11, 14 and 16 years. Clinical examinations were performed at ages 4, 8, 12 and 16 years. In the PIAMA cohort, informed (parental) consent was obtained as summarised in Wijga et al.¹³

Clinical assessment

Lung function testing was performed by spirometry according to the American Thoracic Society/European Respiratory Society criteria in both cohorts.¹⁴ Additional information regarding lung function testing at each measurement point in both cohorts is provided in online supplemental file S1. We calculated the z-scores for FEV₁, FVC and FEV₁:FVC using the Global Lung Function Initiative (GLI) reference equations.¹⁵ To improve comparability of the data, mean centring of the z-scores was performed separately for each cohort and age group. This was done by calculating the mean z-score (FEV₁, FVC and FEV₁:FVC) in healthy subjects (ie, never asthma, no wheezing in the past year and never smoking (age 16 only)) and subsequently subtracting this mean z-score from each individual z-score.¹⁶ Bronchial hyperresponsiveness (BHR) was tested in all high-risk and in a random selection of low-risk children of the PIAMA cohort at age 8.¹³ Definitions for BHR, allergic sensitisation and allergic rhinitis for both cohorts are provided in online supplemental file S2.

Definition of airway obstruction groups

Subjects with a z-score for FEV₁:FVC (zFEV₁:FVC) <LLN (defined as the fifth percentile of the distribution, which corresponds to a z-score of -1.645) were classified as obstructive (figure 1). Subjects with both zFEV₁:FVC <LLN and zFEV₁ <LLN were classified

as classic obstructive, whereas those with zFEV₁:FVC <LLN and zFEV₁ ≥LLN were classified as dysanaptic obstructive. The normal lung function group was identified by zFEV₁:FVC ≥LLN and both zFEV₁ and zFVC ≥LLN. Subjects with zFEV₁:FVC ≥LLN and zFEV₁ and/or zFVC <LLN were excluded from subsequent analyses (online supplemental file S3).

Asthma and wheezing

Asthma was defined as fulfilling two of the following three criteria, according to the Mechanisms of the Development of ALLergy (MeDALL) definition,¹⁷ as agreed by international experts: ever had doctor-diagnosed asthma, wheezing within the last 12 months and use of any asthma medication within the last 12 months. All these variables were defined using data collected by questionnaires (online supplemental file S2).

Statistical analysis

Cohort-specific descriptive analyses were reported as mean and SD for normally distributed continuous variables and as percentages for categorical variables. Pearson's χ^2 and independent sample t-test were used to compare differences between the obstruction groups. We analysed the cross-sectional association between classic and dysanaptic obstruction and the prevalence of asthma according to the MeDALL definition and its components separately (ie, ever doctor-diagnosed asthma, wheezing and use of asthma medication in the past 12 months; online supplemental file S2) and use of inhaled corticosteroids (ICS) at ages 8, 12 and 16.¹⁷ To analyse these associations, we performed a cohort-adjusted logistic regression on pooled data to estimate the OR using the normal lung

Table 1 Prevalence of obstructive groups at ages 8, 12 and 16 in the BAMSE and PIAMA birth cohorts			
	Normal	Classic obstruction	Dysanaptic obstruction
Age 8			
BAMSE, % (n)	96.1 (1668)	1.0 (18)	2.9 (50)
PIAMA, % (n)	92.3 (935)	2.2 (22)	5.5 (56)
Total, % (n)	94.7 (2603)	1.5 (40)	3.9 (106)
Age 12			
PIAMA, % (n)	96.4 (1178)	1.1 (13)	2.5 (31)
Age 16			
BAMSE, % (n)	93.6 (1830)	1.5 (29)	5.0 (97)
PIAMA, % (n)	94.9 (658)	1.4 (10)	3.6 (25)
Total, % (n)	93.9 (2488)	1.5 (39)	4.6 (122)
Classic obstruction defined at each measurement point as subjects with zFEV ₁ :FVC <LLN and zFEV ₁ <LLN. Dysanaptic obstruction defined as zFEV ₁ :FVC <LLN and zFEV ₁ ≥LLN.			
BAMSE, Barn/Child, Allergy, Milieu, Stockholm, Epidemiology; LLN, lower limit of normal; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; zFEV ₁ , z-score for forced expiratory volume in 1 s; zFEV ₁ :FVC, z-score for forced expiratory volume in 1 s to forced vital capacity ratio.			

Table 2 Characteristics of airway obstruction groups at age 8 in the BAMSE and PIAMA cohorts

Cohort	BAMSE			PIAMA		
	Normal (ref)	Classic obstruction	Dysanaptic obstruction	Normal (ref)	Classic obstruction	Dysanaptic obstruction
Demographics						
Subjects, n	1668	18	50	935	22	56
Age, mean (SD)	8.3 (0.5)	8.1 (0.5)	8.3 (0.5)	8.1 (0.3)	8.0 (0.3)	8.2 (0.3)**†
Male, % (n)	48.9 (816)	61.1 (11)	46.0 (23)	49.1 (459)	50.0 (11)	42.9 (24)
Height (cm), mean (SD)	132.3 (6.0)	127.8 (6.2)**	131.4 (6.5)†	132.8 (5.6)	133.1 (4.6)	134.5 (5.3)*
BMI (kg/m ²), mean (SD)	17.21 (2.2)	17.40 (2.1)	18.07 (2.7)**	16.3 (1.9)	16.3 (2.7)	17.3 (2.3)**
BMI z-score, mean (SD)	0.60 (0.96)	0.75 (1.04)	0.94 (1.09)*	0.05 (0.93)	−0.05 (1.23)	0.50 (0.87)**
Maternal asthma, % (n/N)	12.1 (202/1668)	16.7 (3/18)	6.0 (3/50)	16.0 (149/932)	22.7 (5/22)	17.9 (10/56)
Environmental tobacco smoke exposure, % (n)	17.1 (283/1668)	5.6 (1/18)	38.0 (19/50)**†	22.8 (200/877)	14.3 (3/21)	24.0 (12/50)
Respiratory infections, % (n)	9.2 (153/1668)	11.1 (2/18)	12.0 (6/50)	23.3 (215/923)	45.5 (10/22)*	23.6 (13/55)
SES						
Low, % (n/N)	2.2 (37/1668)	0.0 (0/18)	0.0 (0/50)	9.8 (91/933)	9.1 (2/22)	14.3 (8/56)
Intermediate, % (n/N)	42.9 (715/1668)	55.6 (10/18)	54.0 (27/50)	35.0 (327/933)	22.7 (5/22)	44.6 (25/56)
High, % (n/N)	54.9 (916/1668)	44.4 (8/18)	46.0 (23/50)	55.2 (515/933)	68.2 (15/22)	41.1 (23/56)
Early life risk factors						
Maternal smoking during pregnancy, % (n/N)	11.8 (197/1668)	11.1 (2/18)	24.0 (12/50)**	17.6 (163/925)	13.6 (3/22)	14.3 (8/56)
Premature birth, % (n/N)	5.2 (87/1668)	11.1 (2/18)	10.0 (5/50)	4.7 (44/932)	0 (0/22)	7.3 (4/55)
Birth by caesarean section, % (n/N)	12.2 (204/1668)	22.2 (4/18)	28.0 (14/50)**	10.2 (94/926)	9.1 (2/22)	7.3 (4/55)
Birth weight (kg), mean (SD)	3.5 (0.54)	3.5 (0.51)	3.5 (0.80)	3.5 (0.54)	3.5 (0.54)	3.6 (0.55)
Breast feeding more than 16 weeks, % (n/N)	93.8 (1515/1616)	88.9 (16/18)	84.0 (42/50)**	36.6 (342/935)	40.9 (9/22)	35.7 (20/56)
Wheezing in the first year of life, % (n/N)	14.4 (235/1632)	33.3 (6/18)*	32.0 (16/50)**	22.4 (204/909)	38.1 (8/21)	26.4 (14/53)
Respiratory infections in the first year of life						
Pneumonia, % (n/N)	2.9 (47/1631)	0.0 (0/18)	6.0 (3/50)	2.7 (25/928)	4.8 (1/21)	3.8 (2/53)
Bronchitis, % (n/N)	7.1 (116/1629)	5.6 (1/18)	10.0 (5/50)	14.2 (132/927)	14.3 (3/21)	18.9 (10/53)

n/N: number of subjects with positive response/total number with data available from both cohorts.

BMI (kg/m²) z-scores were based on WHO reference equations for the BAMSE cohort and national reference equations for the PIAMA cohort.^{38,39} SES was based on the highest attained educational level of the father or the mother—low: primary school, lower vocational or lower secondary education; intermediate: vocational education or intermediate/higher secondary education; high: higher vocational education and university. Respiratory infections: in BAMSE, defined as current respiratory tract infection/cough at the time of spirometry; in PIAMA, defined as respiratory infections or colds 3 weeks prior to lung function testing.

*P<0.05, **P<0.01, for comparisons of classic or dysanaptic obstructive vs normal.

†P<0.05, ††P<0.01, for comparisons of dysanaptic vs classic obstructive.

BAMSE, Barn/Child, Allergy, Milieu, Stockholm, Epidemiology; BMI, body mass index; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; ref, reference; SES, socioeconomic status.

function group as reference. To investigate differences between classic and dysanaptic obstruction, we repeated the analysis with the dysanaptic group as reference. We investigated the role of body mass index (BMI) as a possible confounder by means of meta-analysing cohort-specific estimates using inverse-variance weighted averages with the 'meta' package (V.4.15.1) in R (V.4.0.5) reporting fixed effects.¹⁸ We also analysed the prospective association between obstructive groups at age 8 and the risk of asthma, wheezing and medication use at age 16 by means of logistic regression using subjects with normal lung function as the reference group. For subjects with two lung function measurements available, we compared obstructive group membership at ages 8 and 16 years by means of cross-tabulation. Statistical analyses were performed using SPSS (V.27.0) and R (V.4.2.2). Statistical significance was set at a 5% level.

RESULTS

Study population

From the BAMSE and PIAMA cohorts, 1736 and 1013 participants were included in the cross-sectional analysis at the age of 8 years (table 1). At the age of 16 years, the number of subjects included was 1956 (BAMSE) and 693 (PIAMA). Additionally, we included 1222 subjects at the age of 12 years from the PIAMA cohort. Based on atypical lung function patterns (figure 1), we excluded 109, 45 and 123 subjects at the ages of 8, 12 (PIAMA only) and 16 (online supplemental file S3). The longitudinal analysis of the transition

between the obstructive groups from ages 8 to 16 included 1131 subjects from the BAMSE cohort and 308 subjects from the PIAMA cohort (online supplemental file S4).

The included subjects at age 16 in the BAMSE cohort and at all ages in the PIAMA cohort were more likely to be female compared with the excluded participants. Additionally, the included subjects from both cohorts were more likely to have higher socioeconomic status and to be breastfed in the first 16 weeks of life, less likely to be exposed to maternal smoking during pregnancy or have a mother who smoked at each follow-up point. Subjects included at age 8 in the PIAMA cohort more often had a mother with asthma (online supplemental file S5).

Prevalence of airway obstruction groups

Most subjects in both cohorts (between 92.3% and 96.4%) had a normal lung function at ages 8–16 years (table 1). The prevalence of classic and dysanaptic obstruction ranged from 1.0% to 2.2% and from 2.5% to 5.5%, respectively, throughout the 8–16 years age range. Lung function levels for all groups, including mean-centred z-scores, are provided in online supplemental file S6.

Characteristics of classic and dysanaptic obstruction

At the 8-year follow-up, the dysanaptic obstruction group in the PIAMA cohort was on average older and taller compared with subjects with a normal lung function. Subjects with dysanaptic obstruction had a higher BMI in both cohorts at age 8 compared

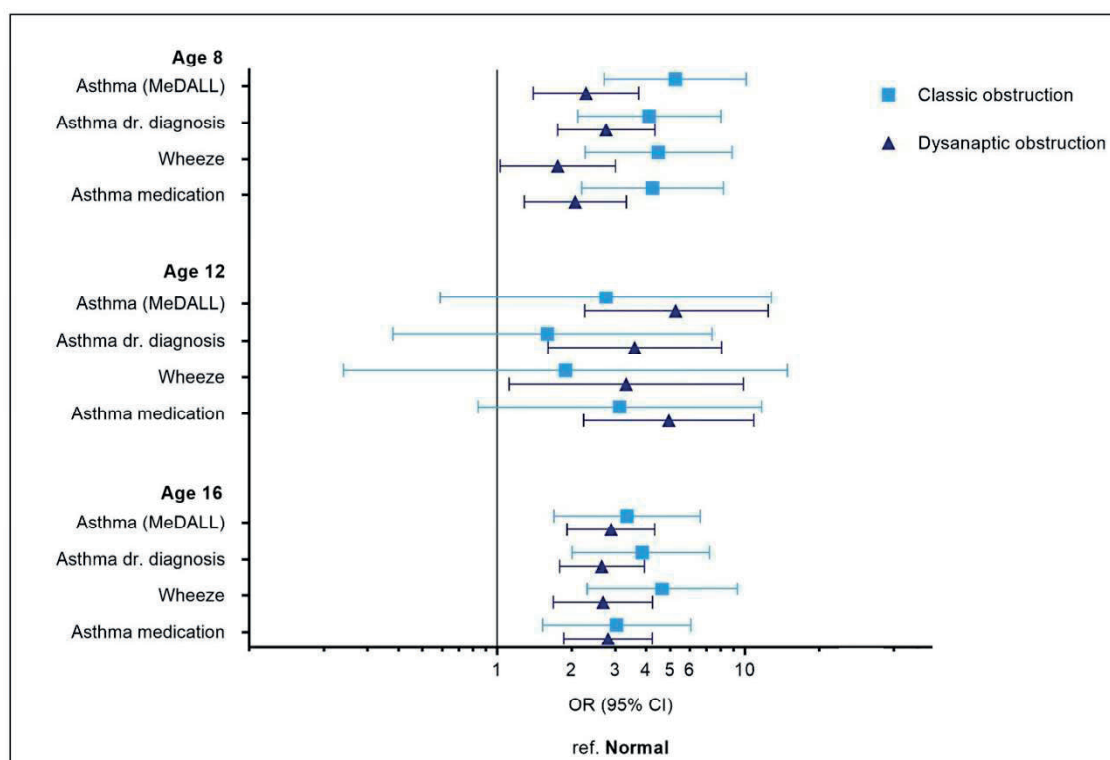


Figure 2 OR of the cross-sectional association at ages 8, 12 and 16 of the obstructive groups with asthma and wheezing in the BAMSE and PIAMA cohorts. Asthma in the last 12 months was defined as fulfilling at least two of the following three criteria: doctor (dr) diagnosis of asthma ever, wheezing in the last 12 months and/or use of asthma medication during the last 12 months (MeDALL definition). BAMSE, Barn/Child, Allergy, Milieu, Stockholm, Epidemiology; MeDALL, Mechanisms of the Development of ALLergy; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; ref, reference.

with the normal group (table 2). In contrast, subjects with classic obstruction did not have a different BMI compared with the dysanaptic obstructive or normal group at any measurement point. In both cohorts at age 8, dysanaptic obstruction was associated with higher $zFEV_1:FVC$ compared with classic obstruction (online supplemental file S7). This association was also seen at age 12 in PIAMA and at age 16 in BAMSE. Dysanaptic obstruction was associated with a higher prevalence of environmental tobacco smoke exposure at ages 8 and 16 in the BAMSE cohort and a higher prevalence of personal smoking at age 16 in the PIAMA cohort. There was no significant difference in the proportion of male and female subjects between the obstructive groups at ages 8, 12 and 16 (online supplemental files S8 and S9).

In the BAMSE cohort, subjects with dysanaptic obstruction more frequently had a mother who smoked during pregnancy compared with the normal group. Also, birth by means of a caesarean section was more prevalent in the dysanaptic obstruction group at age 8 compared with normal in the BAMSE cohort. Additionally, breastfeeding for more than 16 weeks was less prevalent in BAMSE subjects with dysanaptic obstruction at age 8 compared with subjects with normal lung function.

Airway obstruction groups and cross-sectional associations with asthma and wheezing

Subjects with either classic or dysanaptic obstruction had higher odds of having asthma compared with subjects with normal lung function at ages 8 and 16 (age 8: classic, OR 5.25, 95% CI 2.71 to 10.15; dysanaptic, OR 2.29, 95% CI 1.40 to 3.74) (figure 2, online supplemental file S10). Furthermore, subjects with either form of airway obstruction were more likely to experience wheezing and use ICS in the past 12 months at ages 8 and 16 (online supplemental file S10). At age 12 years in the PIAMA cohort, dysanaptic, but not classic, obstruction was associated with higher odds of asthma, wheezing and asthma medication use. Both classic and dysanaptic obstructions were associated with higher odds of ICS use at age 12 in the PIAMA cohort (online supplemental file S10). Additional adjustment for BMI resulted in similar estimates, and all associations remained significant (online supplemental file S11).

Comparing asthma and wheezing between the two obstructive groups, subjects with classic obstruction had higher odds of asthma (OR 2.29, 95% CI 1.03 to 5.12) and wheezing in the past 12 months (OR 2.56, 95% CI 1.09 to 5.98) at the age of 8 years compared with subjects with dysanaptic obstruction (online supplemental file S12).

Bronchial hyperresponsiveness

Of the subjects with classic and dysanaptic obstruction at age 8, 82.4% ($n=14$) and 60.0% ($n=30$) were BHR-positive, compared with 40.4% ($n=339$) in the normal group (online supplemental files S13 and S14). Both types of airway obstruction were associated with higher odds of BHR compared with the normal group (table 3), with no significant difference between the obstructive groups.

Allergic rhinitis

At age 8, classic, but not dysanaptic, obstruction was associated with higher odds of allergic rhinitis compared with the normal group (table 3). This association was not observed at ages 12 and 16 for either obstructive group (online supplemental files S15 and S16).

Allergic sensitisation

In the cross-sectional analysis of obstructive groups and allergic sensitisation at age 8, subjects with dysanaptic obstruction showed higher odds of sensitisation to common inhalant allergens (OR 1.86, 95% CI 1.22 to 2.77) and allergic polysensitisation (OR 1.85, 95% CI 1.18 to 2.89) compared with the normal group (table 3). Allergic sensitisation did not differ between the obstructive groups (online supplemental file S13).

Obstruction groups and their longitudinal association with asthma and wheezing

Subjects with either classic or dysanaptic obstruction at age 8 had higher odds of having asthma, wheezing, asthma medication use and use of ICS in the past 12 months at age 16 compared with subjects with normal lung function (table 4). The association between airway obstruction at age 8 and wheezing and medication use at age 16 was similar between subjects with classic and dysanaptic obstruction; however, classic obstruction was associated with

Table 3 OR of the cross-sectional associations at age 8, 12 (PIAMA only) and 16 of the obstructive groups with BHR, allergic rhinitis and sensitisation (pooled data)

	Normal		Classic obstruction		Dysanaptic obstruction	
	n/N	OR (95% CI)	n/N	OR (95% CI)	n/N	OR (95% CI)
Age 8						
Allergic rhinitis	218/2326	Ref	7/34	2.72 (1.16 to 6.35)*	7/86	0.90 (0.41 to 1.99)
Allergic sensitisation to food	471/2331	Ref	10/34	1.67 (0.79 to 3.51)	18/91	0.98 (0.58 to 1.66)
Allergic inhalant sensitisation	682/2332	Ref	12/33	1.30 (0.63 to 2.66)	41/92	1.86 (1.22 to 2.77)**
Allergic sensitisation: food or inhalant	900/2329	Ref	14/33	1.10 (0.55 to 2.21)	43/91	1.36 (0.89 to 2.07)
Allergic polysensitisation	491/2329	Ref	11/33	1.88 (0.90 to 3.90)	30/91	1.85 (1.18 to 2.89)**
BHR (PIAMA only)	339/839	Ref	14/17	6.88 (1.96 to 24.13)**	30/50	2.21 (1.24 to 3.96)**
Age 12 (PIAMA only)						
Allergic rhinitis	96/802	Ref	2/12	1.47 (0.32 to 6.81)	1/21	0.37 (0.05 to 2.78)
Allergic sensitisation to food	286/1011	Ref	3/13	0.76 (0.21 to 2.78)	9/26	1.34 (0.59 to 3.05)
Allergic inhalant sensitisation	423/1018	Ref	6/13	1.21 (0.40 to 3.61)	14/26	1.64 (0.75 to 3.58)
Allergic sensitisation: food or inhalant	525/1015	Ref	6/13	0.80 (0.27 to 2.40)	16/26	1.49 (0.67 to 3.32)
Allergic polysensitisation	295/1011	Ref	4/13	1.08 (0.33 to 3.53)	12/26	2.08 (0.95 to 4.55)
Age 16						
Allergic rhinitis	466/1868	Ref	10/33	1.31 (0.62 to 2.77)	26/87	1.28 (0.80 to 2.05)
Allergic inhalant sensitisation	1068/2412	Ref	19/38	1.26 (0.66 to 2.39)	55/118	1.10 (0.76 to 1.59)
Allergic polysensitisation	707/2412	Ref	11/38	0.98 (0.48 to 1.99)	37/118	1.10 (0.74 to 1.64)

n/N: number of subjects with positive response/total number with data available from both cohorts.

* $P < 0.05$, ** $P < 0.01$, for comparisons between classic or dysanaptic obstructive and normal lung function groups (ref).

BHR, bronchial hyperresponsiveness; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; ref, reference.

a higher OR of doctor-diagnosed asthma at age 16 compared with dysanaptic obstruction (online supplemental file S17).

Transition between obstructive groups in childhood and adolescence

In both the BAMSE and PIAMA cohorts, majority of the participants with a normal lung function at age 8 also had a normal lung function at follow-up in adolescence (ie, at age 16). Most subjects with classic and dysanaptic obstruction at age 8 showed normal lung function in subsequent measurements (66.7% and 54.7%, respectively). However, one-third (34.0%) of the subjects with dysanaptic obstruction at age 8 remained in this group in adolescence (table 5). Of the subjects with normal lung function at age 8, 0.7% and 4.1% developed classic and dysanaptic obstruction at age 16, respectively. Transition between lung function groups for each cohort is presented in online supplemental file S18. Lung function levels per subject ($zFEV_1$ and $zFEV_1:FVC$) for those who changed group membership are presented in online supplemental files S19 and S20.

DISCUSSION

In this study, we show that airway obstruction in childhood and adolescence, defined by low FEV_1 to FVC ratio, with either a low or a normal FEV_1 was associated with a higher prevalence of asthma, wheezing, use of ICS and BHR. Furthermore, obstructive lung function in childhood was, regardless of FEV_1 , associated with a higher prevalence of asthma, wheezing and medication use in adolescence. Dysanaptic obstruction was associated with higher BMI in childhood in both cohorts and in adolescence in the BAMSE cohort, an association not seen in classic obstructive lung function. Of subjects with a dysanaptic obstructive lung function in childhood, one-third remained in the same group in adolescence.

A low or below-normal FEV_1 is widely recognised as a key characteristic and prognostic marker of childhood wheezing and asthma,^{2,3,19–23} and the Global Initiative for Asthma guidelines identify low FEV_1 as a risk factor for asthma exacerbations and persistent airflow limitation in adolescents and children ages 6–11 years.² However, low FEV_1 is often not observed in childhood asthma.¹⁶ Our findings support this observation, showing that airway obstruction, defined by low FEV_1 to FVC ratio, with a normal FEV_1 was two to three times more frequent than the combination of a low ratio with a low FEV_1 at the ages of 8, 12 and 16 years.

Growth of FEV_1 and FVC during development is non-parallel.⁶ This divergence is attributed to differences in body composition during growth, timing of growth spurt and dimensions and muscular strength of the thoracic cage.²⁴ Ongoing growth may account for the relatively higher prevalence of normal versus low FEV_1 in obstruction during childhood and adolescence. In our study, subjects with a low FEV_1 to FVC ratio carried a similar prevalence of wheezing, asthma and ICS use regardless of their FEV_1 level. Importantly, both classic and dysanaptic obstructions were associated with a higher prevalence of BHR at age 8. The precise mechanism explaining the association between a relatively narrow airway calibre to lung volume and BHR is not fully understood. This may result from abnormalities in airway smooth muscle contractility such as a myogenic contractile response to greater stretching, or the mechanisms of autonomic regulation could play a role.^{25–26} Based on our findings, we recommend a careful evaluation of the FEV_1 to FVC ratio, even if FEV_1 is normal, while considering the unique characteristics of each patient, to assess the risk of current or future respiratory disease.

In both cohorts, dysanaptic obstruction was associated with higher BMI, particularly at age 8, although BMI values were generally within the normal range. This is consistent with previous studies showing a positive association between childhood BMI and relatively higher growth of FVC compared with FEV_1 .²⁷ Meanwhile, in adults with obesity, the opposite pattern is seen as the physical effects of abdominal obesity reduce the chest wall compliance and obstruct the downward displacement of the diaphragm during inspiration, resulting in a lower FVC.^{28,29} The precise mechanisms underlying the association between a greater FVC in children and a higher BMI are uncertain. According to a meta-analysis of 25 000 children from 24 birth cohorts, greater infant weight gain could be associated with greater FVC compared with FEV_1 at age 8.5 years.³⁰ Alternatively, a higher BMI could be a proxy for a greater muscle mass.

Dysanaptic obstruction was found to be associated with early childhood risk factors, including birth by caesarean section and a lower prevalence of breastfeeding, although results varied across cohorts. Notably, dysanaptic obstruction was associated with a higher prevalence of wheezing in the first year of life. This suggests that factors contributing to airway obstruction in childhood may partly originate from the first years of life. Future studies should

Table 4 OR of the prospective association of the obstructive groups at age 8 with asthma and wheezing at age 16 in the BAMSE and PIAMA cohorts (pooled data)

	Normal		Classic obstruction		Dysanaptic obstruction	
	n/N	OR (95% CI)	n/N	OR (95% CI)	n/N	OR (95% CI)
Age 16						
Asthma (MeDALL)	284/2061	Ref	13/32	4.72 (2.29 to 9.74)**	25/85	2.86 (1.75 to 4.67)**
Asthma doctor diagnosis	373/2156	Ref	18/32	6.44 (3.16 to 13.10)**	31/86	2.81 (1.78 to 4.44)**
Wheezing in the past 12 months	199/2130	Ref	8/35	2.78 (1.25 to 6.24)*	20/87	2.83 (1.64 to 4.77)**
Asthma medication use in the past 12 months	282/2136	Ref	12/33	3.88 (1.88 to 7.98)**	24/86	2.63 (1.61 to 4.30)**
ICS use in the past 12 months	182/2158	Ref	9/32	4.45 (2.02 to 9.80)**	21/87	3.62 (2.16 to 6.087)**
Allergic rhinitis	387/1351	Ref	5/23	0.82 (0.30 to 2.26)	17/56	1.15 (0.64 to 2.07)
n/N: number of subjects with positive response/total number with data available from both cohorts. *P<0.05, **P<0.01, for comparisons between classic or dysanaptic obstructive and normal lung function groups (ref.). BAMSE, Barn/Child, Allergy, Milieu, Stockholm, Epidemiology; ICS, inhaled corticosteroids; MeDALL, Mechanisms of the Development of ALLergy; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; ref, reference.						

investigate the association between early life exposures and the differential development of FEV₁ and FVC. In lung development, dysanapsis has been suggested to be caused by differential airway and lung growth velocities during childhood and adolescence.⁴ While FVC grows faster than FEV₁ in childhood, the opposite trend is observed in adolescence. Additionally, prepubescent girls have larger airway size relative to lung size than boys.^{31, 32} Conversely, growth of airways relative to volume is enhanced in adolescent boys. These differences in lung development may partially explain the sex shift in asthma prevalence and disease severity observed in adolescence. We did not find any differences in the prevalence of dysanaptic obstruction between the sexes during childhood or adolescence. This could be due to the LLN as a cut-off not capturing longitudinal differences in FEV₁ and FVC growth between the sexes. Alternatively, we did not see these differences in our data as the reference equations adjusted for differential growth differences in FEV₁ and FVC between the sexes.⁶ We did observe that approximately half of the subjects with dysanaptic obstruction transitioned to a normal state in adolescence, indicating plasticity of lung function growth during this period.³³ In contrast, 34% remained dysanaptic obstructive during adolescence, while only 11.1% remained classic obstructive, suggesting an early childhood origin of dysanaptic obstruction.^{31, 32}

This study has strengths and limitations that should be considered when evaluating our findings. First, we used population-based birth cohorts with multiple lung function measurements and included a validated asthma definition based on multiple variables.³⁴ As the GLI fit differs between cohorts,¹⁶ we performed mean centring to improve comparability. Previous research on dysanapsis in the paediatric population has applied a more stringent definition of dysanaptic obstruction using higher cut-off levels for FEV₁ and FVC; however, this was done in clinical cohorts enriched with patients with asthma.⁷ In our population-based cohorts, stricter definitions of dysanaptic obstruction yielded insufficient numbers of subjects to investigate different forms of airway obstruction and respiratory health outcomes. Regardless, we observed significant differences

in the distribution of the FEV₁ to FVC ratio and FVC between these two forms of airway obstruction, indicating that they are distinct from each other.

We realise that dysanapsis in our cohorts may reflect ongoing bronchial constriction as opposed to non-reversible differences in airway calibre and volume. A subject with large FEV₁ and FVC could be classified as dysanaptic obstructive if FEV₁ is lowered (due to increased variability) while FVC remains high. Consequently, subjects with both high FEV₁ and FVC may be classified as dysanaptic obstructive, partly due to lung function variability in subjects with asthma-like symptoms. Additionally, the accuracy of spirometry reflecting airway calibre and lung size in the paediatric population remains uncertain. Further elucidation of anatomical versus physiological obstructive lung function patterns requires reversibility testing and imaging studies. Furthermore, it would be interesting to compare established biomarkers of asthma disease such as fractional exhaled nitric oxide (FeNO) and blood eosinophils between the airway obstruction groups. The prevalence of allergic sensitisation and allergic rhinitis was higher in dysanaptic obstruction compared with normal; however, this analysis was complicated by low statistical power. The prevalence of BHR at age 8 reflects the selection of high-risk children and is not applicable to the general population; however, the comparison between lung function groups is informative. Additionally, both cohorts are of primarily Caucasian descent. Future studies should investigate the generalisability of our findings to populations of other ancestries. Furthermore, although we strive to reflect the general population, the external validity of our findings may be impacted by attrition bias. Consequently, we recommend validation of our results in other population-based cohorts.

The objective of this study was to examine the co-occurrence of two respiratory phenotypes, that is, airway obstruction and asthma/wheezing/medication use/BHR, from a clinical perspective. As both phenotypes are likely to have the same underlying aetiology and/or causative agents, we did not adjust for any covariates. However, we examined BMI as a potential confounder and observed that associations remained materially unchanged in the adjusted analyses.

Previous studies have shown that in children, adolescents and young adults, a subgroup with an obstructive lung function and normal FEV₁ parameters exists.^{35, 36} A normal FEV₁, in the case of airway obstruction, may make physicians less inclined to pursue medical follow-up. However, our results showing associations between airway obstruction, irrespective of the level of FEV₁, and a higher prevalence of asthma, wheezing and ICS use led us to conclude that the ratio between FEV₁ and FVC is more important than FEV₁ when evaluating the risk of adverse respiratory health outcomes in childhood and adolescence. Therefore, we recommend a careful evaluation of the FEV₁ to FVC ratio in the diagnostic workup of children with wheezing, similar to its application in COPD diagnosis in adults.³⁷ Future research should address if dysanaptic obstruction during childhood and adolescence is associated with subsequent development of COPD.

Table 5 Transition between obstructive groups between the ages of 8 and 16 in the BAMSE and PIAMA cohorts (pooled data)

	Age 8		
	Normal (n=1368)	Classic obstruction (n=18)	Dysanaptic obstruction (n=53)
Age 16			
Normal (n=1344), % (n)	95.2 (1303)	66.7 (12)	54.7 (29)
Classic obstruction (n=17), % (n)	0.7 (9)	11.1 (2)	11.3 (6)
Dysanaptic obstruction (n=78), % (n)	4.1 (56)	22.2 (4)	34.0 (18)
BAMSE, Barn/Child, Allergy, Milieu, Stockholm, Epidemiology; PIAMA, Prevention and Incidence of Asthma and Mite Allergy.			

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Ethics approval This study involves human participants. BAMSE received ethical approval from the Stockholm Ethical Review Board (ref 2016/1380-31/2), and all participants and/or their parents provided consent. The PIAMA study was approved by the medical ethics committee at each respective measurement point, and informed (parental) consent was obtained as summarised in Wijga et al13 (METC protocol number 07-337/ K). Participants gave informed consent to participate in the study before taking part.

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Os programas de reabilitação pulmonar melhoram os resultados em doentes com DPOC após a alta hospitalar por agudização: uma revisão sistemática e uma meta-análise

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RESUMO

Introdução Revisões sistemáticas anteriores forneceram estimativas heterogêneas e diferentes sobre a eficácia da reabilitação pulmonar após agudizações de doença pulmonar obstrutiva crônica (DPOC). O objetivo desta revisão foi examinar a eficácia dos programas de reabilitação pulmonar iniciados nas 3 semanas seguintes à alta hospitalar após uma exacerbação de DPOC.

Métodos Foi realizada uma atualização de uma revisão de Cochrane anterior utilizando o Cochrane Airways Review Group Specialised Register. As pesquisas foram realizadas entre outubro de 2015 e agosto de 2023 relativamente a estudos que iniciaram a reabilitação pulmonar no prazo de 3 semanas após a alta hospitalar. Foram excluídos os estudos que avaliaram o impacto da reabilitação pulmonar exclusivamente em regime de internamento. Os gráficos de floresta foram criados utilizando um método genérico de efeitos aleatórios de variância inversa.

Resultado Foram incluídos dezassete estudos. A reabilitação pulmonar após a alta hospitalar reduziu as readmissões hospitalares (OR 0,48, IC 95% 0,30 a 0,77, $I^2=67\%$), melhorou a capacidade de exercício (teste de caminhada de 6 minutos, diferença média (DM) 57 m, IC 95% 29 a 86, $I^2=89\%$; teste de caminhada incremental, DM 43 m, IC 95% 6 a 79, $I^2=81\%$), a qualidade de vida relacionada com a saúde (Questionário da Doença Respiratória do Hospital Saint George, DM -8,7 pontos, IC 95% -12,5 a -4,9, $I^2=59\%$; Questionário das Doenças Respiratórias Crônicas (CRQ)-emoção, DM 1,0 pontos, IC 95% 0,4 a 1,6, $I^2=74\%$; CRQ-fadiga, DM 0,9 pontos, IC 95% 0,1 a 1,6, $I^2=91\%$), e dispneia (CRQ-dispneia, DM 1,0 pontos, IC 95% 0,3 a 1,7, $I^2=87\%$; Escala de dispneia modificada do Medical Research Council, DM -0,3 pontos, IC 95% -0,5 a -0,1, $I^2=60\%$). Não foram observados efeitos significativos no CRQ-mastery, no teste de avaliação da DPOC, no EuroQol-5 Dimension-5 Level e na mortalidade. Não foram registados quaisquer eventos adversos relacionados com a intervenção.

Discussão A reabilitação pulmonar efetuada após a alta hospitalar por agudização de DPOC resulta numa redução das readmissões hospitalares e em melhorias na capacidade de exercício, na qualidade de vida relacionada com a saúde e na dispneia, na ausência de quaisquer eventos adversos relacionados com a intervenção.

Número de registo do ensaio CRD42023406397.

INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are significant events in the trajectory of the disease. These events can lead to rapid deteriorations in patient health status, often resulting in hospital admissions and mortality.^{1–3} Acute exacerbations of COPD are associated with reduced health-related quality of life and exercise capacity.⁴ Mortality and rehospitalisation rates during the year following an initial hospitalisation in patients with COPD were approximately 35% and 60%, respectively.^{5–11}

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Previous versions of a Cochrane review have demonstrated the efficacy of pulmonary rehabilitation during or following an acute exacerbation of COPD in terms of reducing hospital re-admissions and improving exercise capacity and health-related quality of life.
- However, the latest version of the review in 2016 presented updated evidence which reduced confidence in the observed benefits of pulmonary rehabilitation in the context of an acute exacerbation of COPD.

WHAT THIS STUDY ADDS

- This systematic review provides an update of a Cochrane review assessing the effects of pulmonary rehabilitation following an acute exacerbation of COPD.
- Adopting ‘refined’ inclusion and exclusion criteria to better reflect pulmonary rehabilitation programmes commonly delivered in clinical practice, this review demonstrates benefits of pulmonary rehabilitation initiated within 3 weeks post-hospital discharge on reducing hospital re-admissions and improving exercise capacity and health-related quality of life with no reported adverse events related to the intervention.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This review was used to inform the American Thoracic Society Clinical Practice Guideline on Pulmonary Rehabilitation.
- Pooled analyses were used to make policy recommendations on the delivery of pulmonary rehabilitation following an acute exacerbation of COPD.
- Pooling of studies permitted specific future research recommendations to be considered in the context of pulmonary rehabilitation delivery following an acute exacerbation of COPD.

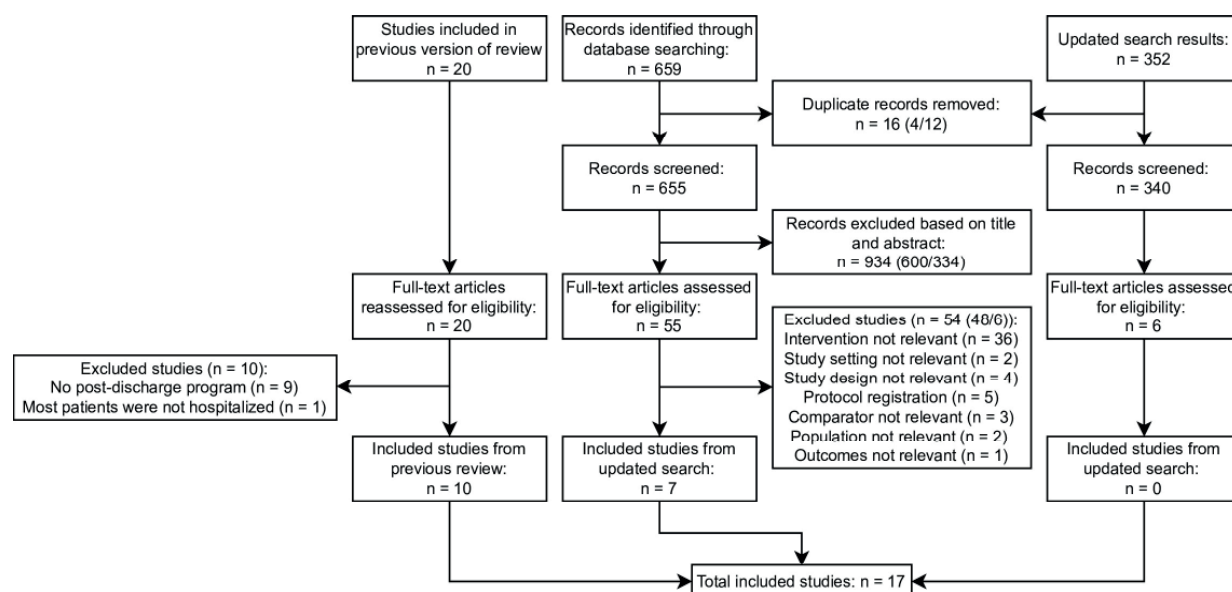


Figure 1 Flow diagram of study selection including both the previous review and the updated search.

It has been long proposed that pulmonary rehabilitation could be an effective intervention in the posthospitalisation phase in patients with COPD as it encompasses elements that are known to improve health status and prognosis, such as physical exercise and self-management education.^{12–13} This has been reiterated by previous versions of a Cochrane review^{14–15} and recent reviews^{16–19} which demonstrated favourable effects of pulmonary rehabilitation during hospital admission and/or following discharge on clinical and patient-reported outcomes. Subsequently, guidelines and position statements provided positive recommendations for the use of pulmonary rehabilitation following exacerbations of COPD.^{12–13} However, the latest update of the aforementioned Cochrane review²⁰ reported reduced confidence in observed estimates with heterogeneity present across the majority of outcomes.

Evidence to date has mainly focused on pulmonary rehabilitation programmes delivered during hospitalisation for acute exacerbation of COPD or combined these studies with posthospital discharge programmes. Acute hospital rehabilitation is not a widely available model in most parts of the world, and evidence is currently conflicting with regards to the risks and benefits.^{19–21} Therefore, it is important to understand the evidence based on studies which conducted pulmonary rehabilitation programmes taking place in the posthospital discharge phase, which is a more commonly available model.

The purpose of this systematic review was to summarise evidence relating to whether pulmonary rehabilitation delivered posthospital discharge for exacerbation of COPD improved clinical outcomes compared with no pulmonary rehabilitation.

METHODS

This systematic review conformed to the methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions.²² The protocol for this review (CRD42023406397) was pre-registered on PROSPERO (International Prospective Register of Systematic Reviews; www.crd.york.ac.uk/PROSPERO/) and was undertaken as part of a clinical guideline.²³ This systematic review was an update of a previous Cochrane review,²⁰ although with a refined protocol as detailed below. The systematic review was funded by the American Thoracic Society (ATS).

Population

Patients with COPD following inpatient or outpatient care for acute exacerbation. For studies that included patients with mixed diagnoses, the study was included if >90% of participants had COPD.

Intervention

Outpatient pulmonary rehabilitation programmes which comprised of at least physical exercise (endurance and/or strength exercise), delivered to patients with COPD following hospital discharge for an exacerbation. Studies incorporating an inpatient rehabilitation programme were included if a rehabilitation programme was continued following discharge, with solely inpatient pulmonary rehabilitation programmes excluded from both the Puhan et al²⁰ review and the updated search. Pulmonary rehabilitation programmes were required to commence within 3 weeks of hospital discharge as the efficacy of pulmonary rehabilitation in ‘stable’ COPD (ie, >4 weeks postexacerbation) has been demonstrated.²⁴ Studies which had an upper limit that fell outside this 3-week timeframe were conservatively included. No limits on the minimum number of exercise sessions were set as an inclusion/exclusion criterion. Pulmonary rehabilitation programmes could include additional elements such as self-management education, dietary advice, breathing exercises and psychological support. Pulmonary rehabilitation programmes which only included inspiratory muscle training or neuromuscular stimulation, but no whole-body physical exercise training programmes were excluded.

Comparator

The comparator was any concurrent control group labelled as usual care, provided that an exercise programme was not implemented as part of usual care. Trials with comparator groups which received or were offered ‘delayed’ pulmonary rehabilitation were eligible for inclusion if data were obtainable up to the point the comparator group were offered pulmonary rehabilitation.

Outcomes

The primary outcome was hospital re-admissions. Secondary outcome measures were functional exercise capacity (6 min walk test (6MWT), incremental shuttle walk test (ISWT), endurance shuttle walk test (ESWT)), health-related quality of life (St. George’s Respiratory Questionnaire (SGRQ), Chronic Respiratory Disease Questionnaire (CRQ), COPD Assessment Test (CAT), EuroQol-5 Dimension-5 Level (EQ-5D-5L)), dyspnoea (dyspnoea domain of CRQ, modified Medical Research Council (mMRC) Dyspnoea Scale), mortality and adverse events.

Study design

Studies were included if they were randomised controlled trials. Trials which used a randomised cross-over design were eligible up to the point of cross-over.

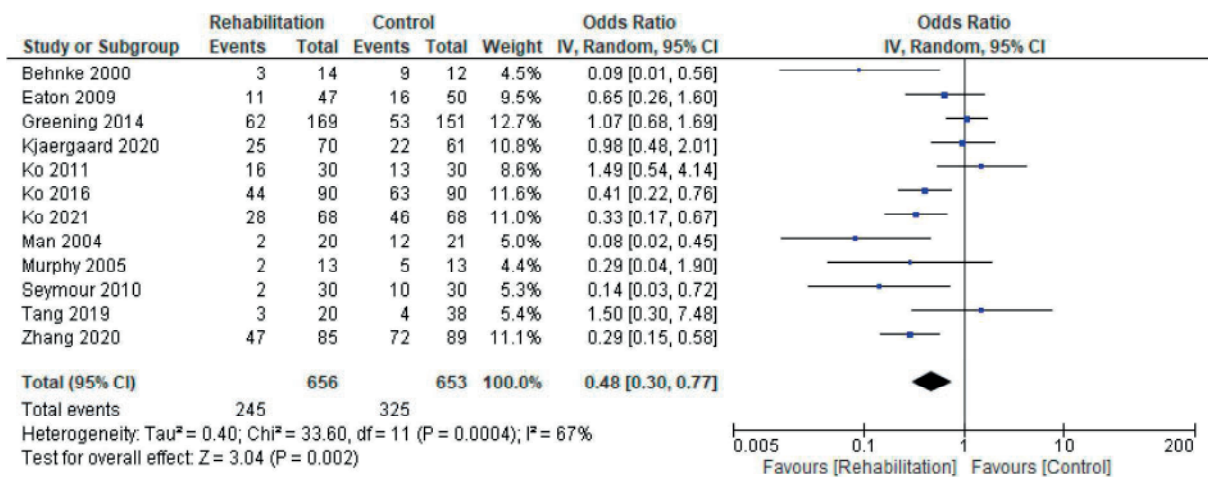


Figure 2 Trial-level data, effect estimates and forest plot of comparison for the odds of hospital re-admission (up to 12 months) following posthospital discharge pulmonary rehabilitation.

Search strategy

The details of search strategies from previous versions of the Puhan et al^{14,20} review can be found in the freely accessible Cochrane Library. The search period for this update covered from October 2015 to February 2022, with an additional updated search from February 2022 to August 2023.

Searches for this update were conducted using the Cochrane Airways Review Group Specialised Register (CAGR) (see online supplemental material). The search strategy for the CAGR is outlined in online supplemental table S1 with no restrictions placed on language. Searches of ClinicalTrials.gov and the WHO trials portal were also undertaken. Supplementary searches in the form of asking guideline committee members to identify any further potentially relevant studies were undertaken as well as screening reference lists of included studies. Included studies from Puhan et al²⁰ were re-screened independently by two reviewers for inclusion against the criteria of this review. Updated search results were screened using Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). After removal of duplicate citations, articles were independently screened based on title and abstract by two reviewers. Full texts were retrieved for studies not excluded based on title and abstract and reviewed independently by two reviewers. Discrepancies between reviewers were resolved through inclusion of a third reviewer.

Data extraction and management

For included studies from the updated search, data extraction was completed using an adapted Microsoft Excel form based on the Cochrane Data Extraction Template. Details extracted included study author, publication years, study design, interventions, participants and outcome measures. Data for the outcomes of hospital re-admissions, mortality and adverse events were extracted to the timepoint of 12 months of follow-up within relevant studies. For outcomes relating to functional exercise capacity, health-related quality of life and dyspnoea, data were extracted from the end of rehabilitation or nearest follow-up time point. Discharge was considered the baseline in all studies. Included studies from Puhan et al²⁰ had data duplicated into forest plots if data conformed to the methods outlined in this review, if not, then data were re-extracted for analyses.

Quality appraisal and risk of bias assessment

The Puhan et al²⁰ review was critically appraised for methodological quality using the AMSTAR 2 tool.²⁵ Risk of bias was assessed using the Cochrane 'Risk of bias' tool²⁶ (see online supplemental material). Risk of bias was independently assessed by two reviewers with disagreements resolved through inclusion of a third reviewer. The addressing of discrepancies with Puhan et al²⁰ are outlined in the supplementary material.

Data synthesis

Meta-analyses were performed using Review Manager V.5.4. Study authors were contacted to obtain any missing data. ORs were used for dichotomous outcomes. Measures of effect were computed using mean differences (MDs) or postintervention values in a generic inverse variance random effects method. Statistical heterogeneity was interpreted using the I² value. Where the I² statistic was >50%, and there were more than three studies included, data were reported with potential sources of heterogeneity explored using the subgroup analyses of Puhan et al.²⁰ Prespecified subgroup analysis was undertaken for programme characteristics and risk of bias (online supplemental material). Where heterogeneity could not be explained by subgroup analyses, sensitivity analyses were performed removing outliers provided there were distinguishing clinical intervention features that warranted removal (eg, poor intervention adherence). Funnel plots were created when data from more than 10 studies were available.

Quality of evidence

The Grading of Recommendations, Assessment, Development, and Evaluation approach (GRADE) was used in accordance with recommended guidelines²⁷ to assess the quality of the evidence (see online supplemental material).

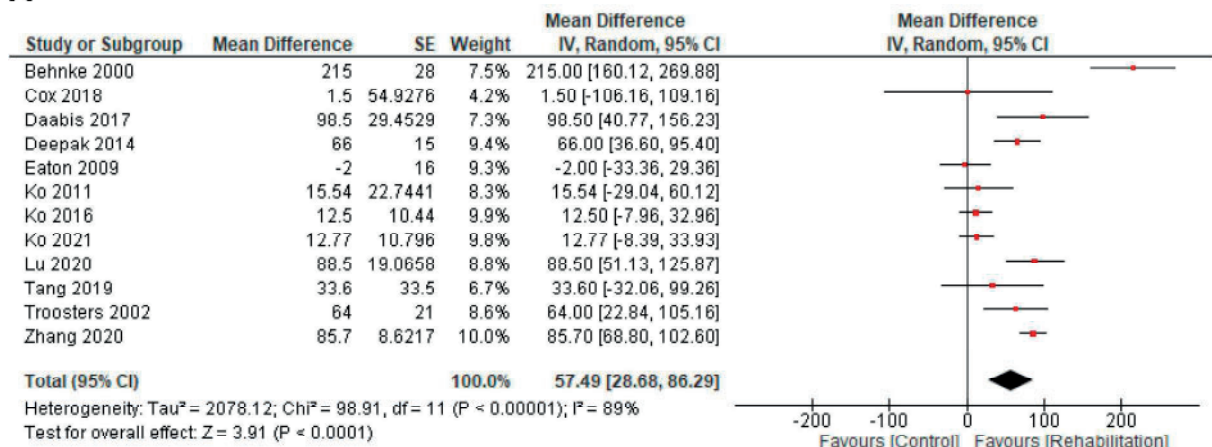
RESULTS

Ten studies included in Puhan et al²⁰ did not meet the criteria of the current review (online supplemental table S2), with 10 studies included. With the updated search, following screening for title, abstract and full-text, seven met the inclusion criteria with reasons for excluding full texts provided in online supplemental table S2. These were combined with the studies included from Puhan et al²⁰ for a total of 17 studies included in the current review (figure 1).

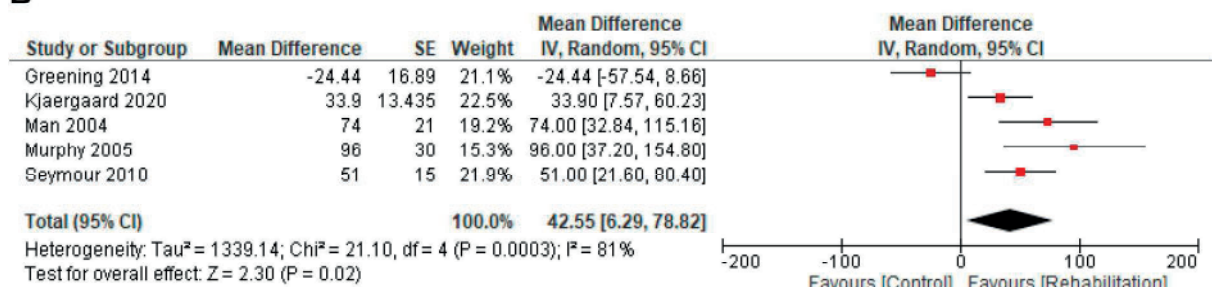
Characteristics of included studies

The characteristics of included studies are reported in online supplemental table S3.^{28–44} A total of 1724 patients with chronic respiratory disease were randomised following hospitalisation for an exacerbation of which 96% had a primary diagnosis of COPD. Sample sizes ranged from 26 to 389. Six studies commenced an inpatient acute care rehabilitation programme and continued to offer an outpatient rehabilitation programme postdischarge,^{28–32} whereas the other included studies offered an outpatient rehabilitation programme between discharge and 4 weeks postdischarge.^{29–31, 33–36, 38–43} Four included studies^{28, 30, 35, 44} offered 'delayed' pulmonary rehabilitation in the control group. One study³⁵ included data from chronic respiratory diseases other than COPD, for which data were obtained pertaining to the COPD population

A



B



C

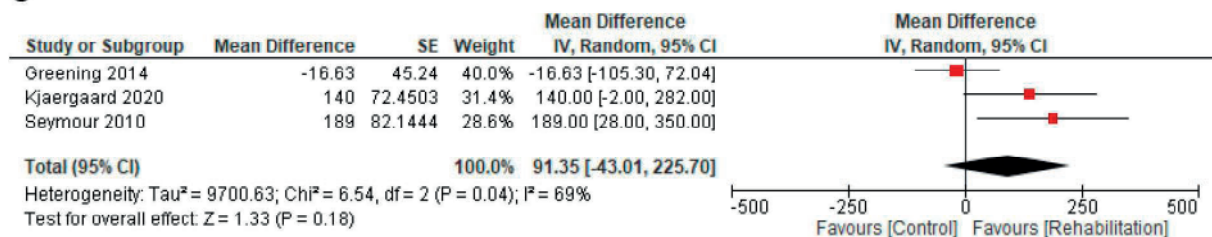


Figure 3 Trial-level data, effect estimates and forest plot of comparison for change in (A) 6 min walk test (6MWT), (B) Incremental shuttle walk test (ISWT) and (C) endurance shuttle walk test (ESWT) following posthospital discharge pulmonary rehabilitation.

only. Another study²⁸ had multiple intervention arms of relevance, so these intervention groups were combined for comparison in the meta-analyses. Details surrounding the extensiveness of pulmonary rehabilitation programmes are provided in online supplemental table S4.

The systematic review of Puhan et al²⁰ was deemed to be of high methodological quality. Risk of bias judgements within individual studies can be found in online supplemental figure S1 with 12 studies presenting with a high risk of bias^{28–30 34 36–38 40–44} and 5 studies presenting with a moderate risk of bias.^{31–33 35 39} Risk of bias assessments were hindered due to the inability to blind participants to exercise training introducing performance bias, as well as inadequate reporting of methods and outcomes.

Primary outcome

Hospital re-admissions

Thirteen studies reported hospital re-admissions up to 12 months as an outcome^{28 30 31 33–35 37–42 44} of which 12 studies (1309 participants) were able to be included in a meta-analysis.^{30 31 33–35 37–42 44} Moderate quality evidence, downgraded due to the presence of substantial heterogeneity, showed that posthospital discharge pulmonary rehabilitation reduced hospital re-admission (OR 0.48, 95% CI 0.30 to 0.77, $p = 0.002$, $I^2 = 67\%$, figure 2). There was no evidence of publication bias (online supplemental figure S2A). Subgroup analyses for programme characteristics and risk of bias did not explain heterogeneity (online supplemental figure S2).

Secondary outcomes

Exercise capacity

6 min walk test

Twelve studies including 943 participants reported 6MWT as an outcome.^{28 29 31–34 36–39 43 44} Low-quality evidence, downgraded due to the presence of substantial heterogeneity as well as selection, performance and detection bias across included studies, showed that posthospital discharge pulmonary rehabilitation improved 6MWT (MD 57.49 m, 95% CI 28.68 to 86.29 m, $p < 0.001$, $I^2 = 89\%$, figure 3A). There was no evidence of publication bias (online supplemental figure S3A). Subgroup analyses for programme characteristics and risk of bias did not explain heterogeneity (online supplemental figure S3).

Incremental shuttle walk test

Five studies including 560 participants reported ISWT as an outcome.^{30 35 40–42} Low-quality evidence, downgraded due to the presence of substantial heterogeneity as well as performance and detection bias across included studies, showed that posthospital discharge pulmonary rehabilitation significantly improved ISWT (MD 42.55 m, 95% CI 6.29 to 78.82 m, $p = 0.02$, $I^2 = 81\%$, figure 3B). Subgroup analyses showed that studies with unclear or high risk of bias favoured an effect with rehabilitation as opposed to a single study³⁵ with low risk of bias showing no effect (online supplemental figure S4D). Remaining subgroup analyses of programme characteristics and other risk of bias domains did not explain heterogeneity (online supplemental figure S4). Sensitivity analysis with

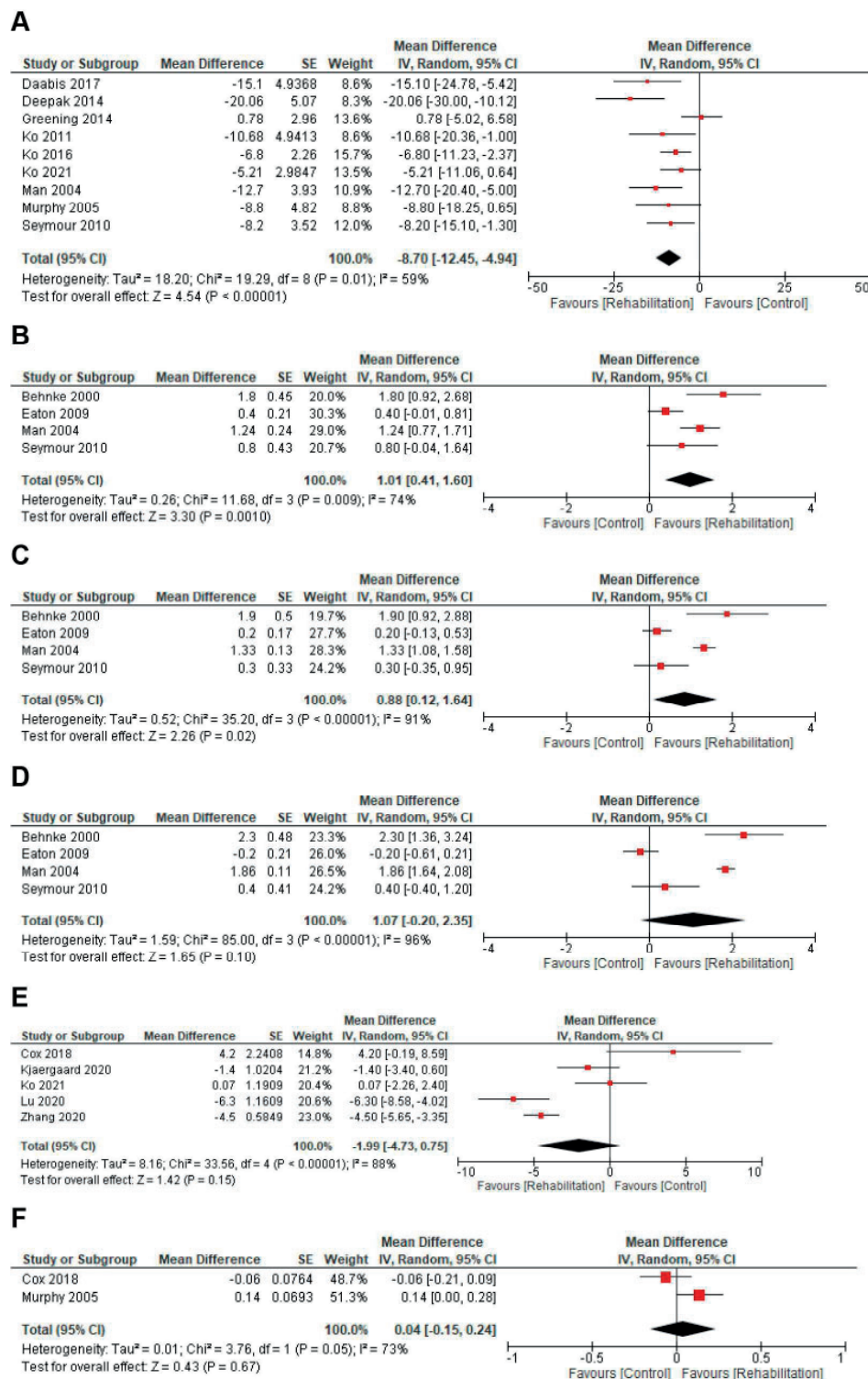


Figure 4 Trial-level data, effect estimates and forest plot of comparison for change in (A) St. George's Respiratory Questionnaire (SGRQ)-Total, (B) Chronic Respiratory Disease Questionnaire (CRQ)-emotion, (C) CRQ-fatigue, (D) CRQ-mastery, (E) chronic obstructive pulmonary disease (COPD) Assessment Test (CAT), and (F) EuroQol-5 Dimension-5 Level (EQ-5D-5L) following posthospital discharge pulmonary rehabilitation.

the removal of Greening et al³⁵ which reported low intervention adherence reduced heterogeneity to levels deemed unimportant and demonstrated a significant improvement in ISWT with post-hospital discharge pulmonary rehabilitation (MD 55.59 m, 95% CI 32.26 to 78.93 m, $p < 0.001$, $I^2 = 41\%$) (online supplemental figure S4E).

Endurance shuttle walk test

Three studies including 500 participants reported ESWT as an outcome.^{30 35 42} Very low-quality evidence, downgraded due to the presence of substantial heterogeneity, imprecision in effect estimates, and performance and detection bias across included

studies, showed that posthospital discharge pulmonary rehabilitation did not significantly improve ESWT (MD 91.35 s, 95% CI -43.01 to 225.70 s, $p = 0.18$, $I^2 = 69\%$, figure 3C). Subgroup analyses to investigate heterogeneity were not undertaken due to the low number of included studies. Sensitivity analysis with the removal of Greening et al³⁵ which reported low intervention adherence reduced heterogeneity to levels deemed unimportant and demonstrated a significant improvement in ESWT with posthospital discharge pulmonary rehabilitation (MD 161.44 s, 95% CI 54.94 to 267.94 s, $p = 0.003$, $I^2 = 0\%$) (online supplemental figure S5). For Greening et al,³⁵ data were obtained from the study authors.

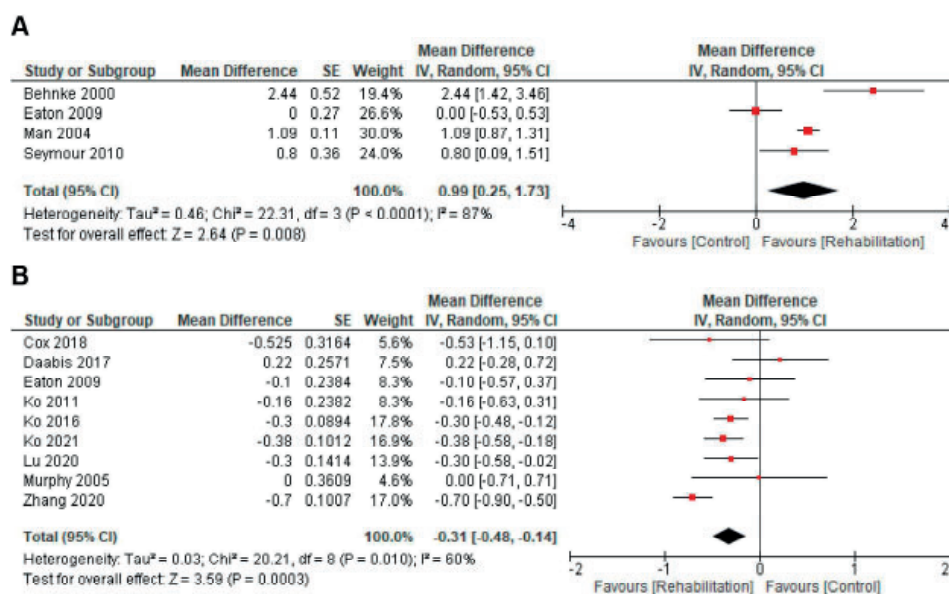


Figure 5 Trial-level data, effect estimates and forest plot of comparison for change in (A) Chronic Respiratory Disease Questionnaire (CRQ)-dyspnoea score and (B) Modified Medical Research Council (mMRC) score following posthospital discharge pulmonary rehabilitation.

Health-related quality of life

St. George's Respiratory Questionnaire

Nine studies including 888 participants reported SGRQ as an outcome.^{29 31 35 36 38–42} Low-quality evidence, downgraded due to the presence of substantial heterogeneity as well as performance and detection bias across included studies, showed that posthospital discharge pulmonary rehabilitation significantly reduced SGRQ total score (MD -8.70 points, 95% CI -12.45 to -4.94 points, $p < 0.001$, $I^2 = 59\%$, figure 4A). Subgroup analyses demonstrated a significantly greater decrease in SGRQ total score following posthospital discharge pulmonary rehabilitation in studies demonstrating unclear or high risk of bias compared with studies with a low risk of bias for the domains of random sequence generation or blinding of outcome assessment (online supplemental figure S6C,E). Remaining subgroup analyses of programme characteristics and other risk of bias domains did not explain heterogeneity (online supplemental figure S6). Sensitivity analysis with the removal of Greening et al³⁵ which reported low intervention adherence reduced heterogeneity to levels deemed unimportant and demonstrated a significant reduction in SGRQ total score with posthospital discharge pulmonary rehabilitation (MD -9.69 points, 95% CI -12.80 to -6.57 points, $p < 0.001$, $I^2 = 29\%$) (online supplemental figure S6F).

CRQ (emotion, fatigue and mastery domains)

Four studies including 205 patients with COPD reported CRQ as an outcome.^{34 37 40 42} Low-quality evidence, downgraded due to the presence of substantial heterogeneity as well as performance and detection bias across included studies showed that posthospital discharge pulmonary rehabilitation improved CRQ-emotion (MD 1.01 points, 95% CI 0.41 to 1.60 points, $p = 0.001$, $I^2 = 74\%$, figure 4B) and CRQ-fatigue (MD 0.88 points, 95% CI 0.12 to 1.64 points, $p = 0.02$, $I^2 = 91\%$, figure 4C). Very low quality evidence, downgraded due to the presence of substantial heterogeneity, imprecision in effect estimates, and performance and detection bias across included studies showed that posthospital discharge pulmonary rehabilitation did not significantly improve CRQ-mastery (MD 1.07 points, 95% CI -0.20 to 2.35 points, $p = 0.10$, $I^2 = 96\%$, figure 4D). Subgroup analyses demonstrated a significantly greater increase in CRQ-emotion, CRQ-fatigue and CRQ-mastery following posthospital discharge pulmonary rehabilitation in studies classified as having extensive rehabilitation programmes compared with a single study with a less-extensive rehabilitation programme (online supplemental figure S7A,E and I). Remaining subgroup analyses of programme characteristics and risk of bias domains did not explain heterogeneity (online supplemental figure S7).

COPD Assessment Test

Five studies including 533 participants reported CAT as an outcome.^{28 30–33} Low-quality evidence, downgraded due to the presence of heterogeneity and imprecision in effect estimates showed that posthospital discharge pulmonary rehabilitation did not improve CAT Score (MD -1.99 points, 95% CI -4.73 to 0.75 points, $p = 0.15$, $I^2 = 88\%$, figure 4E). Subgroup analyses for programme characteristics and risk of bias did not explain heterogeneity (online supplemental figure S8).

EuroQol-5 Dimension-5 Level

Two studies including 60 participants reported EQ-5D-5L as an outcome.^{28 41} Very low quality evidence, downgraded due to the presence of substantial heterogeneity, imprecision in effect estimates, as well as performance, detection and attrition bias across included studies showed that posthospital discharge pulmonary rehabilitation did not improve EQ-5D-5L Score (MD 0.04 points, 95% CI -0.15 to 0.24 points, $p = 0.67$, $I^2 = 73\%$, figure 4F). Due to the small number of included studies, subgroup analyses to investigate heterogeneity could not be performed. For Cox et al,²⁸ data were obtained from the study authors.

Dyspnoea

CRQ (dyspnoea domain)

Four studies including 205 participants reported CRQ-dyspnoea as an outcome.^{34 37 40 42} Low-quality evidence, downgraded due to the presence of substantial heterogeneity as well as performance and detection bias across included studies showed that posthospital discharge pulmonary rehabilitation significantly improved CRQ-dyspnoea score (MD 0.99 points, 95% CI 0.25 to 1.73 points, $p = 0.008$, $I^2 = 87\%$, figure 5A). Subgroup analyses demonstrated a greater increase in CRQ-dyspnoea score following posthospital discharge pulmonary rehabilitation with extensive rehabilitation programmes compared with a single study with a less-extensive rehabilitation programme (online supplemental figure S9A). A single study with a follow-up period > 3 months and unclear or high risk of bias for random sequence generation and allocation concealment demonstrated significantly greater increases in CRQ-dyspnoea score following posthospital discharge pulmonary rehabilitation compared with studies with a follow-up period ≤ 3 months and low risk of bias for random sequence generation and allocation concealment (online supplemental figure S9B–D).

modified Medical Research Council

Nine studies including 798 participants reported mMRC as an outcome.^{28 29 31–33 37–39 41} Low quality evidence, downgraded

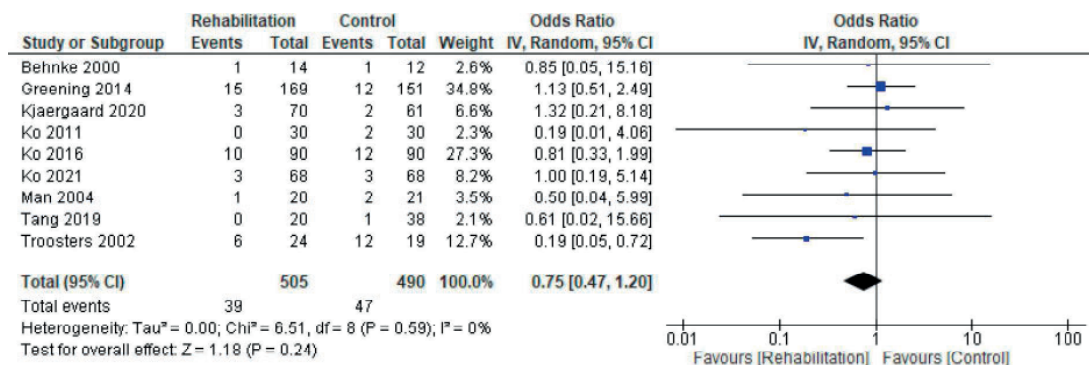


Figure 6 Trial-level data, effect estimates and forest plot of comparison for change in (A) Chronic Respiratory Disease Questionnaire (CRQ)-dyspnoea score and (B) Modified Medical Research Council (mMRC) score following posthospital discharge pulmonary rehabilitation.

due to the presence of substantial heterogeneity as well as performance and detection bias across included studies showed that posthospital discharge pulmonary rehabilitation improved mMRC score (MD -0.31 points, 95% CI -0.48 to -0.14 points, $p < 0.001$, $I^2 = 60\%$, figure 5B). Subgroup analyses demonstrated greater reductions in mMRC score following posthospital discharge pulmonary rehabilitation in studies with low risk of bias compared with studies with unclear or high risk of bias for random sequence generation or blinding of outcome assessment (online supplemental figure S9G,I). Remaining subgroup analyses of programme characteristics and other risk of bias domains did not explain heterogeneity (online supplemental figure S9).

Mortality

Nine studies including 995 participants reported mortality as an outcome.^{30 31 34 35 38–40 43 44} Moderate-quality evidence, downgraded due to the presence of imprecision in effect estimates, showed that posthospital discharge pulmonary rehabilitation did not significantly affect mortality (OR 0.75, 95% CI 0.47 to 1.20, $p = 0.24$, $I^2 = 0\%$, figure 6). For three studies,^{30 35 44} data were obtained from study authors.

Adverse events

Four studies including 229 participants reported adverse events as an outcome.^{28 34 37 40} Three studies reported no adverse events^{34 37 40} with one study²⁸ reporting no differences between pulmonary rehabilitation and usual care groups, of which none were attributed to the intervention. The evidence was graded as moderate quality.

The full evidence profile comprising the GRADE assessment on a per outcome basis is reported in the supplementary material (online supplemental table S5).

Summary of main findings

This latest data synthesis suggests that, on average, pulmonary rehabilitation delivered posthospital discharge for exacerbation of COPD reduces hospital re-admissions ($\downarrow 52\%$), improves exercise capacity (6MWT, $\uparrow 57$ m; ISWT, $\uparrow 43$ m), health-related quality of life (SGRQ, $\downarrow 9$ points; CRQ-Emotion, $\uparrow 1$ point; CRQ-Fatigue, $\uparrow 0.9$ points), and dyspnoea (CRQ-Dyspnoea, $\uparrow 1$ point; mMRC, $\downarrow 0.3$ points) with values often exceeding reported minimal clinically important differences (MCID) of 30 m for 6MWT,⁴⁵ 0.5 points for CRQ domains⁴⁶ and 4 points for SGRQ.⁴⁷ However, heterogeneity was apparent among most pooled analyses, and the lower ends of CIs did not exceed the MCID for exercise capacity, health-related quality of life and dyspnoea outcomes, meaning the findings should be interpreted with a degree of caution. Not all outcomes for exercise capacity (ie, ESWT) and health-related quality of life (CRQ-Mastery, CAT, EQ-5D-5L) significantly favoured an effect with pulmonary rehabilitation, but these analyses were based on smaller sample sizes and number of included studies. There is no evidence that pulmonary rehabilitation programmes delivered posthospital discharge for COPD exacerbations significantly reduces mortality. There is also no evidence to suggest that posthospital discharge pulmonary rehabilitation presents a risk of

harm in patients with COPD, as evidenced by a lack of adverse events.

Comparison with other reviews

There are five previous relevant reviews of pulmonary rehabilitation following exacerbation of COPD.^{16–20} The current review agrees with previous pooled evidence, in terms of reduced hospital admissions, improvements in health-related quality of life, exercise capacity and dyspnoea with pulmonary rehabilitation following an exacerbation of COPD.^{16–18 20} Our review provides the latest updated evidence in this area leveraging criteria for a clinically relevant, and more widely available pulmonary rehabilitation programme model which can be implemented in practice. Previous reviews^{17 19 20} have incorporated studies focused on pulmonary rehabilitation during admission, which is a model not widely available in clinical care. Other reviews^{16 18} also excluded pulmonary rehabilitation programmes which were of a largely unsupervised nature, while the current review included these studies given the increasing evidence surrounding the efficacy of unsupervised exercise in COPD.⁴⁸

Strengths and limitations

A key strength of the current review is that successful efforts were made to obtain data from authors for inclusion in meta-analyses. Data were able to be obtained before the point of cross-over to include studies in which 'delayed' pulmonary rehabilitation was offered in the control group. A limitation of the review was heterogeneity which was reported across a majority of outcomes, which reduces confidence in where the 'true' observed effect lies. For outcomes such as hospital re-admissions, 6MWT and CAT, heterogeneity could not be explained by subgroup analyses and there were no clear distinguishing intervention features (eg, frequency, intensity, time and type of exercise intervention) to warrant a sensitivity analysis to explore heterogeneity. Broadly speaking, it is worth noting that subgroup analyses on the extensiveness of pulmonary rehabilitation programmes tended to favour those that were extensive compared with those that were less extensive. Sensitivity analyses that were able to be performed with the removal of Greening et al³⁵ on the basis of poor intervention adherence did address heterogeneity for the outcomes of SGRQ, ISWT and ESWT, suggesting intervention adherence could be an important factor in explaining the underlying heterogeneity. Several outcomes were graded as very low to low quality evidence due to the presence of unclear or high risk of bias, heterogeneity and/or imprecision in estimated effects meaning some observed effects must be interpreted with caution. With regards to performance bias, it is important to note that blinding of participants is not possible with exercise-based interventions such as pulmonary rehabilitation. The data relating to mortality, as well as that presented in other relevant reviews, needs to be interpreted with caution as trials were not powered to detect differences in mortality. Finally, the interpretation of estimated effects in line with MCIDs needs to be undertaken with caution as the MCIDs are based on pulmonary rehabilitation for people with stable COPD, and it is not clear as to

whether MCIDs for included outcomes differ significantly in the postexacerbation population.

Implications for clinical practice

The findings from the current review support the implementation of pulmonary rehabilitation initiated within 3 weeks of hospital discharge for patients admitted with an exacerbation of COPD. Improvements in key clinical outcomes such as hospital re-admission, exercise capacity and health-related quality of life in the absence of adverse events support the use of pulmonary rehabilitation in the postacute exacerbation phase. Hospital re-admissions in particular pose a significant burden on patients, families and the healthcare system with emphasis placed on avoiding these events. The evidence presented in the current review demonstrates the utility of pulmonary rehabilitation in achieving this goal. Recent evidence has demonstrated the substantial cost savings of pulmonary rehabilitation in patients with COPD following hospital discharge⁴⁹ meaning pulmonary rehabilitation should be considered as part of the COPD postexacerbation treatment pathway. However, with the presence of heterogeneity, which can be partially explained by pulmonary rehabilitation components such as programme extensiveness (eg, largely supervised, at least twice a week for a minimum of 16 sessions, include progressive aerobic and resistance exercise training, and provide comprehensive self-management education) and adherence to pulmonary rehabilitation programmes, such programmes need to adhere to guidance and the frequency, intensity, time and type principles of exercise training while promoting/ensuring compliance throughout.¹²

Implications for future research

The quality of evidence presented in this review ranges from very low to moderate. Poor reporting of information pertaining to risk of bias assessments and appropriate blinding of outcome assessors are areas which should be addressed in future research. Unexplained heterogeneity for several outcomes suggests that future research is required to ascertain the optimal intervention components and true effect estimates. Such studies should conform to guidance on pulmonary rehabilitation¹² and adopt a design based on a minimum of two supervised exercise sessions a week for at least 6–8 weeks ensuring to achieve 16 or more sessions in total. Exercise training should include both aerobic and resistance-based components ensuring that intensity is progressed in a measurable way. Furthermore, if assessing outcomes such as hospital re-admissions and mortality, clinical trials need to be appropriately powered for such outcomes and allow a suitable observation period for events to be measured. Intervention compliance should be a key measure of future research alongside healthcare use, exercise capacity, health-related quality of life, dyspnoea and adverse event outcomes. Despite the benefits demonstrated, studies need to ascertain the correct timing for implementing pulmonary rehabilitation following hospitalisation for an exacerbation of COPD.

Conclusions

In conclusion, this systematic review and meta-analyses provide evidence that pulmonary rehabilitation delivered posthospital discharge for an exacerbation of COPD results in a reduction in hospital re-admissions and improvements in exercise capacity, health-related quality of life and dyspnoea in the absence of any intervention-related adverse events. However, unexplained heterogeneity for several outcomes means results should be interpreted with caution. Nevertheless, these findings support the need to develop strategies to ensure that people with COPD are offered pulmonary rehabilitation following hospital discharge for an exacerbation.

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Asma, condicionamento clássico e sistema nervoso autónomo - uma hipótese para a razão pela qual as crianças têm pieira

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RESUMO

A asma pediátrica é um problema de saúde global crescente, para o qual os atuais tratamentos nem sempre são eficazes. Esta revisão explora como o desencadeamento anormal do reflexo autonómico de mergulho pode ser importante para explicar os resultados da investigação e a experiência da asma no mundo real. Coloca-se a hipótese de que o stresse durante a gravidez está associado à asma infantil. Isto resulta num aumento da capacidade de resposta parassimpática e, especificamente, no trigger excessivo do reflexo de mergulho em resposta ao humedecimento e ao arrefecimento da face e do nariz, como ocorre com infecções das vias aéreas superiores e rinite alérgica. Nos mamíferos aquáticos, o reflexo inclui, sobretudo, a contração do músculo liso das vias respiratórias para minimizar o volume dos pulmões e evitar a narcose por nitrogénio em mergulhos em profundidade.

INTRODUCTION

Asthma is the most common chronic disease among children globally and the number of children affected is increasing in developing countries.^{1,2} UK data from the Royal College of Physicians' national asthma audit suggests that children are presenting with more severe asthma attacks than recorded in previous audits.³ UK asthma mortality is much higher than other European countries. These concerns have driven efforts to improve the delivery of asthma care.⁴ Exploring new hypotheses about the cause of asthma might usefully result in changes in treatment to the benefit of patients. This paper explores the possibility that asthma might occur because of antenatally determined changes in autonomic development resulting in increased triggering of the parasympathetic components of the diving reflex and its subsequent triggering by classically conditioned reflex responses. Such a hypothesis might explain counterintuitive findings from research into asthma heritability, the role of allergy and the ineffectiveness of inflammometry.

Registry-based twin studies, using well-established methods to estimate the relative genetic (nature) versus environmental (nurture) determinants of asthma, suggest that genetic factors account for approximately 60%–80% of asthma susceptibility, with only a modest or no effect attributable to environmental effects shared between family members.⁵ Despite such findings, genome-wide and epigenome-wide association studies fall short of explaining the disease's polygenic heritability.^{6,7}

Atopy is highly associated with asthma, but there is little evidence that the association is causal. Studies comparing changes in asthma incidence within geographical locations over time show significant rises in the number of patients with asthma, with little change in the incidence of atopy and vice versa.⁸ Authors of British Thoracic Society (BTS) asthma guidelines do not recommend allergen avoidance to treat asthma symptoms and highlight the paradoxical effects of removing cats and dogs from the homes of children with evidence of sensitisation to their

pets.⁹ Metanalyses of allergen avoidance confirm a lack of evidence for the benefits of allergen control in treating asthma and allergic rhinitis.^{10,11} Such findings suggest that while allergically triggered symptoms might be important in initiating asthma, they are less important as an ongoing cause of symptoms.

While there is good evidence that airways inflammation is associated with the asthma phenotype, there are significant shortcomings in managing asthma according to indices of airways inflammation. Raised fractional exhaled nitric oxide (FeNO) levels in steroid-naïve patients might usefully suggest an asthma diagnosis, but paediatric studies have found that such levels are insensitive and will miss up to 50% of affected children.¹² Randomised controlled trials consistently fail to demonstrate benefits for FeNO levels in decision making about the use of asthma therapies.¹² Routine measurement of FeNO as part of asthma care is not recommended in BTS/Scottish Intercollegiate Guidelines Network guidelines. While this failure of inflammometry to improve asthma outcomes is commonly attributed to poor adherence, it might also be due to the limited efficacy of high-dose versus low-dose steroids. Cochrane analyses of dose responses to inhaled corticosteroids identified 89 studies with negative results for clinically important outcome measures and just one study suggesting high doses versus low doses of budesonide reduced acute exacerbations in severe asthma.^{13–15}

These findings are difficult to explain within the prevailing narrative of asthma as a genetically determined, allergically driven, inflammatory disease process. The following hypothesis addresses these shortcomings. Three components are suggested as relevant to the development and persistence of asthma (figure 1). The first is the impact of maternal stressors on early life development during pregnancy. These stressors affect the antenatal development of the nervous system favouring increased parasympathetic stress responses. The second is the impact of this predisposition on the bronchoconstrictive component of the diving reflex as triggered by wetting and cooling of the face and nostrils. Third, classically conditioned autonomic reflexes result in recurrent wheezing. These reflexes occur in response to neutral stimuli that were present at the time of initial wheezy episodes.

Step 1: Antenatal stressors result in fetal programming favouring increased parasympathetic responsiveness

This hypothesis builds on the developmental origins of disease concept proposed by Barker.¹⁶ His observation that nutritional indices at birth were associated with chronic diseases in later life, spurred many prospective cohort studies to identify the important risk factors for diseases across the life course. Antenatal stress has been consistently identified as an important risk factor for childhood asthma¹⁷ but the cause is not clear.¹⁸ Suggested mechanisms include effects on immune, neuroendocrine and oxidative stress systems. Effects on the



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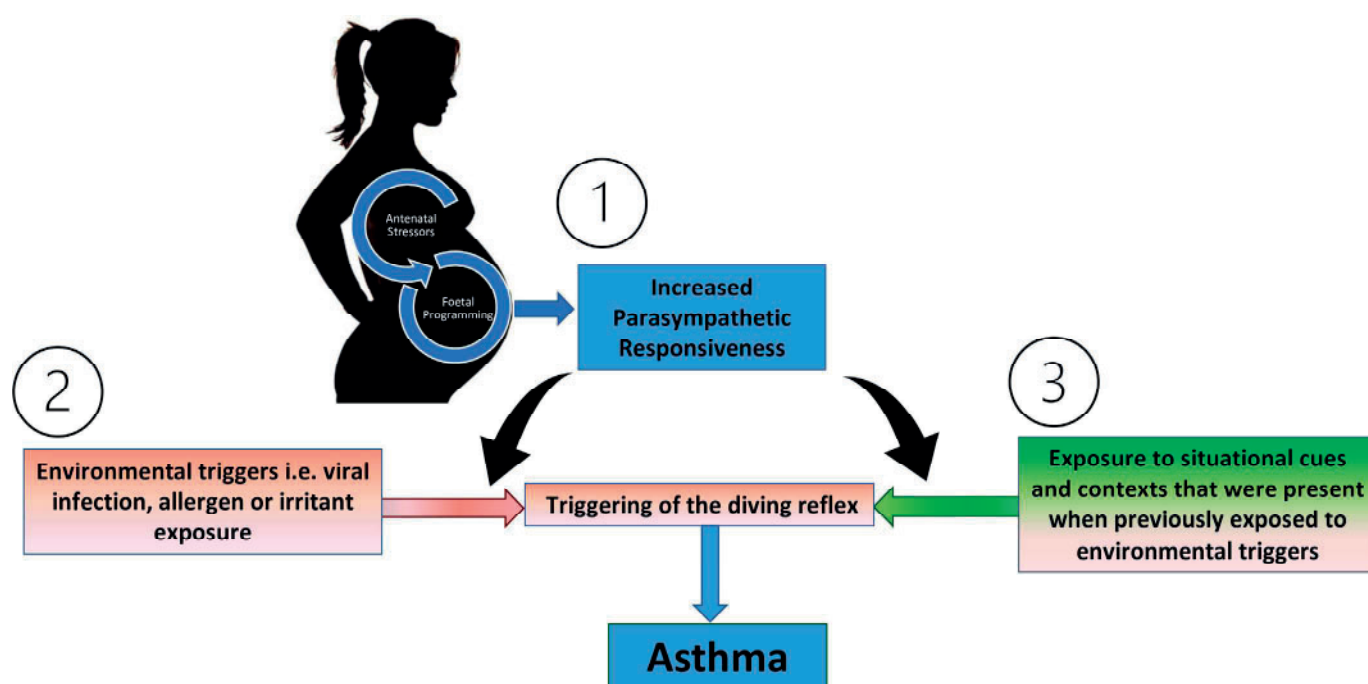


Figure 1 The autonomic basis for asthma. (1) Prenatal stressors alter autonomic development favouring parasympathetic pathways. (2) Increased vagal responsiveness after exposure to environmental triggers cause triggering of the diving reflex. (3) Situational cues and contexts cause reflex bronchoconstriction without the need for allergic sensitisation.

development of the autonomic nervous system might also be important. Vulnerable fetuses, stressed in utero at a critical period for the development of autonomic homeostatic mechanisms, could be predisposed to neurally derived mechanisms which, when triggered by postnatal factors, result in asthma.

An important component of acute asthma attacks is neurally driven contraction of bronchial smooth muscle via the vagus nerve. The anticholinergic drug ipratropium bromide works as a bronchodilator in addition to the effects of β -2 agonist drugs by blocking these neural pathways.¹⁹ Heart rate variability indices have been used in many studies as a marker of parasympathetic responsiveness. These markers are associated with increased asthma severity.²⁰

There is evidence suggesting the sympathetic part of the autonomic nervous system, (the classical 'fight or flight' response), is diminished in patients with asthma. While circulating epinephrine levels in heart failure, septicaemia and hypoglycaemia typically increase to 17 times above basal levels, in acute asthma attacks epinephrine levels have been reported to be at the lower end of the normal range.²¹ Although findings are not consistent across all studies, patients with asthma have reduced adrenergic responses after exercise, antigen bronchoprovocation and hyperventilation.²²

Antenatal stress might be an important confounder for other antenatal risk factors for asthma (table 1). For example, extreme preterm birth is highly associated with asthma.²³ While chronic lung disease of prematurity among such infants might adversely impact on lung growth and result in bronchial hyper-reactivity, these infants spend what would have been their third trimester ex utero. They have therefore been exposed to more stressful circumstances than most infants during this critical period for the development of the autonomic nervous system.²⁴ Studies characterising outcomes for autonomic function after preterm birth are inconsistent. However in one, a subgroup of premature infants who went on to have acute life-threatening events had distinct autonomic development trajectories characterised by increased parasympathetic and decreased sympathetic tone.²⁵ Similar trajectories might be important risk factors for asthma.

A maternal history of asthma is strongly associated with asthma in her offspring. Many studies report that anxiety disorders are more common in patients with asthma and particularly among women. Anxiety increases the perception of respiratory symptoms and thus the likelihood of an asthma diagnosis.²⁶ Although smokers state that cigarettes help them relax, there is good evidence

that tobacco dependency is associated with higher stress levels.²⁷ There are similar associations for obesity²⁸ and pre-eclampsia.²⁹

Although it has been suggested that the association between caesarean section (CS) and asthma might be due to changes in microbiota, recent research suggests that maternal vaginal strains make up a small and transient fraction of the neonatal intestinal microbiota after birth.³⁰ A systematic review has shown that women who request a CS have significantly raised anxiety and depression.³¹ These feelings are not alleviated by them knowing they can have their chosen mode of delivery. There are many confounding medical factors determining whether women opt for a CS, but the only published study assessing the risk of childhood asthma in women opting for CS without medical indication, had a higher OR for childhood asthma than all other CS studies (OR 1.58; 95% CI 1.17 to 2.13).³¹

Exposure to air pollutants is increasingly recognised as having adverse respiratory health effects, but thus far antenatal exposure appears to only have a weak association with subsequent asthma³² except in male offspring with mothers who had experienced antenatal stress.³³

Step 2: Increased vagal responsiveness after exposure to environmental triggers results in an exaggerated diving reflex

The parasympathetic nervous system subserves more complex functions than 'rest and digest' as is commonly popularised. It is active in many autonomic reflexes including the diving reflex. This is present in all mammals. It is greater in infants, who instinctively trigger the response when submerged, and aquatic mammals. In clinical settings, cold water facial immersion is used to trigger the reflex to treat supraventricular tachycardia. The resulting bradycardia is part of an adaptive survival response to maximise time spent underwater.³⁴ The reflex is triggered by chilling or wetting the nostrils and face. Studies in rats have shown how the reflex is initiated by excitation of nerves in the anterior nasal passages.³⁵

Less well appreciated is that bronchoconstriction is part of the diving reflex. Reducing lung volume through airway narrowing reduces the systemic absorption of nitrogen when diving at depth to prevent nitrogen narcosis—the bends.³⁶ There is no good explanation for why humans and other land mammals have smooth muscle in their airways. It might be that its presence is an evolutionary remnant of our aquatic past. The diving reflex in humans, when exaggerated by increased parasympathetic responsiveness, might

Table 1 Antenatal risk factors for the early life origins of asthma

Risk factors for wheeze in childhood	OR (95% CI)	Outcome
Maternal stress/stressors ¹⁷ *	1.56 (1.36 to 1.80)	Childhood asthma or wheeze
Maternal smoking ⁶² *	1.23 (1.12 to 1.36)	Asthma aged >5 years
Socioeconomic status ⁶³ *	1.38 (1.37 to 1.39)	Asthma prevalence
Low birth weight ⁶⁴ *	1.13 (1.01 to 1.27)	School-aged asthma
Maternal history of asthma*	3.15 (2.53 to 3.93)	Asthma aged >5 years
Paternal history of asthma ⁶⁵ *	2.60 (2.28 to 2.96)	Asthma aged >5 years
Prematurity (22–31 weeks)*	4.92 (2.91 to 8.31)	Asthma aged 6–9 years
Prematurity (32–36 weeks) ²³ *	2.04 (1.38 to 3.01)	Asthma aged 6–9 years
Exposure to inhaled pollutants ³³	1.28 (1.15 to 1.41)	Diagnosed asthma by 6 years (male only)
Emergency caesarean section*	1.18 (1.07 to 1.29)	Childhood asthma
Elective caesarean section ⁶⁶ *	1.23 (1.20 to 1.26)	Childhood asthma
Caesarean section without medical indication ⁶⁷	1.58 (1.17 to 2.13)	Asthma aged 4–12 years
Pre-eclampsia ⁶⁸	1.23 (1.07 to 1.43)	Ever or recurrent wheeze (up to 24 months)
Maternal obesity (BMI≥30 kg/m ²) ⁶⁹	1.36 (1.08 to 1.68)	Current asthma or wheeze (14 months to 16 years)

*Asterisk labelled references are the most recently published systematic reviews or meta-analyses for antenatal risk factors. Non-asterisked references are case series addressing risk factors for which there are no published systematic reviews. BMI, body mass index.

be the mechanism whereby bronchospasm occurs in relation to being exposed to cooling and wetting of the face and nostrils as occurs after coryzal or allergic symptoms.

Bradycardia, as elicited by the diving reflex, is increased in a subgroup of patients with asthma compared with non-asthmatic controls and decreases in heart rate are associated with the underlying degree of hyper-responsiveness measured by methacholine challenge.³⁷ One small study has demonstrated that bronchoconstriction is also a component of the diving response in man but whether this occurs to a greater extent in patients with asthma has not been studied.³⁸ Asthma prevalence is high among elite swimmers and winter sports athletes, but this is thought to be largely an effect of breathing at high ventilation rates and volumes.³⁹ Swimming in public pools is also associated with increased asthma but this is likely to be due to chlorine exposure. Interestingly, there is emerging evidence that open water swimming alleviates asthma.⁴⁰ This might be due to improvements in mental well-being but might also occur through resetting of the diving reflex after repeat immersions in the cold water environment within which it originated.

The most important postnatal risk factors for asthma are wheezy illnesses in early childhood, often caused by rhinovirus, and evidence of allergic sensitisation. Initial wheezy illnesses are unresponsive to bronchodilators.⁴¹ Why the pathophysiology changes, and reversible smooth muscle contraction becomes a cause of recurrent viral-associated wheeze, has not been explained. It is possible that initial infections predispose to the development of reflex vagal bronchoconstriction in response to further episodes of wetting of the nostrils. The association between asthma and allergic rhinitis might also be due to wetting of the nostrils by nasal secretions.

Step 3: Situational cues and contexts cause recurrent, classically conditioned activation of the diving reflex

Classical conditioning is a form of associative learning. Subjects learn something about the causal fabric of their environment or, in an experimental setting, the relationship of stimuli. Stimuli can be arranged so that one stimulus provides information about the likely occurrence of another. Over time learning becomes incorporated into the nervous system's autonomic brainstem pathways and causes involuntary physiological changes in response to what were previously neutral stimuli.

Classical conditioning is also known as Pavlovian conditioning in recognition of research by the Russian physiologist Ivan Pavlov. He elicited an involuntary parasympathetic reflex; salivation, in response to a previously neutral stimulus; the sound of a bell. Similarly, asthma could be an involuntary parasympathetic reflex in response to neutral stimuli present at a time when airways obstruction occurred after infection or allergen exposure.

This type of reflex is well characterised in guinea pig research models of asthma.^{43–45} Animals can be sensitised to egg albumen by intraperitoneal injections of egg white. Two weeks later, placing the animals in a chamber and exposing them to a fine mist of egg white produces asthma-like symptoms. Most develop tolerance to the mist after repeated exposure but among those that don't, many develop respiratory symptoms after inhaling saline mist and eventually just by being in the chamber. This is an example of cue and context conditioning. The cue is the saline aerosol mist, and the context is the chamber in which the mist had previously been given. Smaller chambers cause more severe symptoms.

Studies have used other neutral stimuli as cues introduced at the same time as the albumen mist including bells and smells. Responses to these stimuli are accompanied by rises in histamine levels and prevented by atropine injection.⁴¹ Wheezing is greater in stressed animals but stressing animals without exposure to a conditioned stimulus does not cause respiratory symptoms. Such findings have implications for the way in which stress during childhood might exacerbate wheezing but is not the underlying cause.

Similar cue and context conditioning occurs in adults with allergic rhinitis after just one learning session exposing subjects to a strong smell at the same time as an unconditioned stimulus (allergen) to which the subjects were sensitised.⁴⁶ Such studies have not been replicated in patients with asthma but patients with asthma have been induced to have asthma attacks by suggestion after inhaling saline which they believe is a solution of an allergen to which they are allergic.⁴⁷ Symptoms occurred in almost half of those challenged and reversed after inhaling normal saline which the subjects were told was a bronchodilator. Patients with asthma, having associated inhaling specific allergens with the occurrence of asthma attacks, might reasonably be assumed to have suffered airways obstruction through a classically conditioned reflex.

The significant improvements in lung function in the placebo arms of randomised controlled asthma trials might also be explained as a cue conditioned response to taking an inhaler for which there is belief in there being a high probability of effectiveness. There are likely to be individuals who continue to have asthma symptoms because of ongoing allergic sensitisation, but the extent to which this occurs might be less than appreciated.⁹

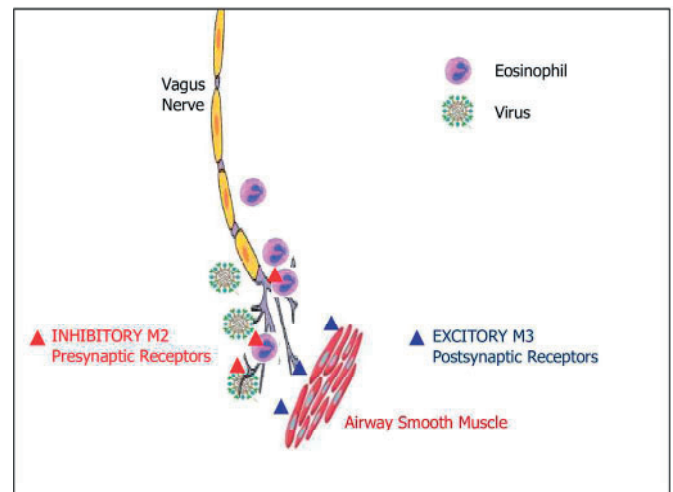


Figure 2 Vagal nerve impulses excite M3 post synaptic receptors and cause smooth muscle contraction. Viruses and eosinophils increase cholinergic induced airways obstruction through blocking M2 receptor inhibition of the vagus nerve.

Implications

If asthma has a significant neurobehavioural component, the highly inheritable nature of asthma, as suggested by twin studies in which identical twins are far more likely to both have asthma than non-identical twins, could be due to mimicry. While psychologists define mimicry as the unconscious automatic repetition of behaviour performed by others, mimicry can also result in the repetition of autonomic responses.^{48,49} Identical twins are more empathic to each other than non-identical twins. An identical twin is therefore more likely to have autonomically driven bronchoconstriction than a non-identical twin when confronted by their wheezy sibling. Such a mechanism might explain why the heritability of asthma cannot be explained genetically.⁵

While allergic nasal symptoms as a trigger for the diving reflex might in part explain the relationship between atopy and asthma, this relationship is far more complex. There is now increasing epidemiological evidence suggesting that the atopic march's prevalence has been overstated and that the hygiene hypothesis is incorrect. These findings have reignited discussion about alternative models to better explain the pathophysiological and epidemiological processes that result in what may or may not be ongoing allergic disease.⁵⁰

There is a strong association between stress and asthma but the extent to which this occurs in developing countries and the associated morbidity is underappreciated.⁵¹ Similarly, there is evidence for an association between post-traumatic stress disorders and asthma most clearly demonstrated among 9/11 responders to the destruction of the twin towers in New York.⁵² In the few studies that have investigated the phenomena, asthma is increased in war zones.⁵³ Mirroring the association between inequality and poor mental health, there is an association between asthma and increasing inequality at a national level.⁵⁴ These data are consistent with the way in which asthma is increasingly recognised in many parts of the developing world and becoming more severe in developed countries where young people increasingly suffer from stress-related mental health problems.

Vagally induced bronchoconstriction is exacerbated by viral infections⁵⁵ and eosinophil mediators.⁵⁶ The anti-inflammatory benefits of inhaled corticosteroids could be through downregulating such mechanisms. The lack of a dose response for inhaled corticosteroids⁵⁷ could be because these drugs do not prevent ongoing reflex vagal excitation of smooth muscle. The effectiveness of precision biologics might be a result of anti-inflammatory effects that restore presynaptic M2 receptor suppression of vagal activity (figure 2).

High doses of anticholinergics are effective adjuncts to β -2 agonists for acute asthma but are less effective than β -adrenergics. This is because they act on the neurogenic cause of bronchoconstriction as opposed to directly reversing the contraction of smooth muscle. Regular use of the anticholinergic tiotropium for chronic asthma has modest clinical benefits although it has been shown to be as effective as long-acting β -2 agonists in preventing symptoms in adults.⁵⁸ The limited efficacy of anticholinergics is probably due to insufficient dose and the non-selective blocking of receptors that inhibit the vagal nerve as well as those causing smooth muscle contraction (figure 2).^{59,60} The development of selective M3 postsynaptic receptor antagonists might result in more effective treatment.⁶¹

CONCLUSION

This hypothesis is consistent with much of what is known about asthma. The evidence base in support of it is limited but studies could readily be done to confirm or refute it. These might usefully further characterise how the autonomic nervous system is altered in patients with asthma, the extent to which bronchoconstriction exists as a component of the diving reflex in patients with asthma, and whether cue and context conditioning occurs in the same way it has been demonstrated in allergic rhinitis. Interventional studies to suppress the diving reflex and classically conditioned wheezing might result in new effective treatments with less reliance on medication.

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