

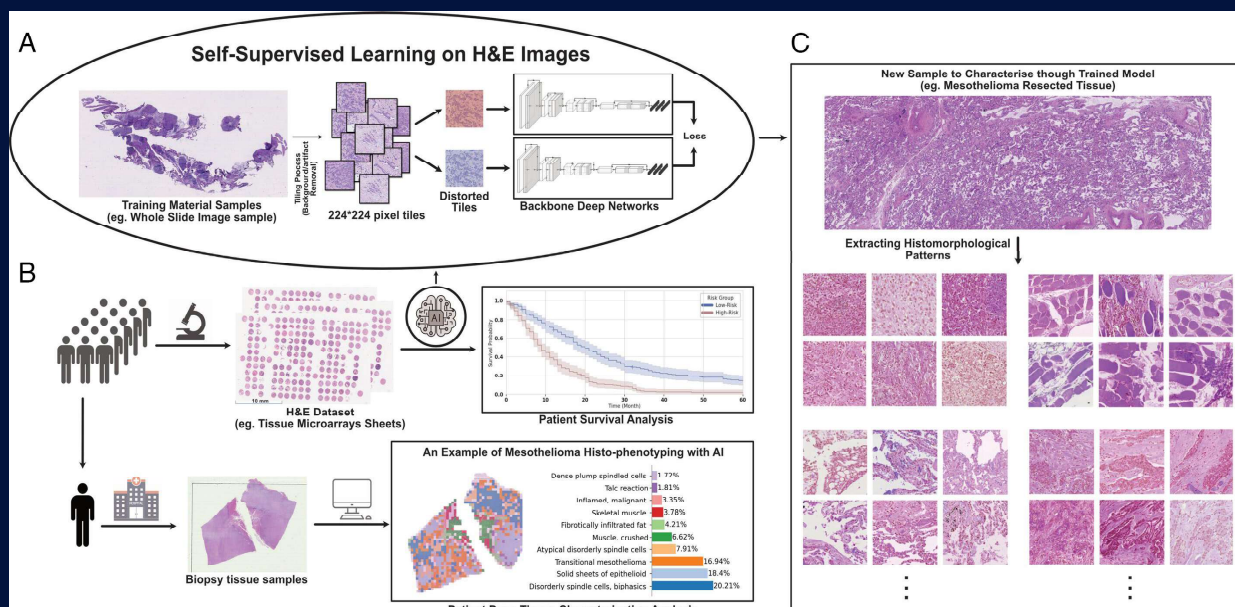
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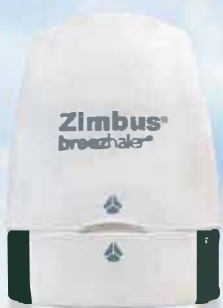
ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

com artigos do

ARCHIVES OF
DISEASE IN
CHILDHOOD

Edição Portuguesa





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

1 vez dia¹

**Zimbus[®]
breezhaler[®]**

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



**NOVA
ASSOCIAÇÃO
LABA/LAMA
/ICS¹**

Dá ritmo à vida^{2,3*}

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

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

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

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



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Editorial

O primeiro número de 2026, com uma seleção de artigos das Revistas *Thorax* e *Archives of Diseases in Childhood*, compila uma série de temas atuais, com impacto na decisão clínica, alguns como resultado de análises conjuntas de diversas publicações sobre os temas em questão, utilizando ferramentas de análise e de inteligência artificial, que permitem ir mais longe na discriminação de fatores de risco individuais e na percepção de aplicabilidade personalizada de diagnósticos e/ou terapêuticas.

Se estiver com uma agenda apertada e pouco tempo comece por ler os Editoriais. Neste número estão incluídos 5 editoriais, textos curtos de leitura rápida, em temas tão diversos como: 1. As revisões da OMS para a gestão da asma aguda em idade pediátrica; 2. influência do material particulado, sobretudo partículas ultrafinas na saúde e a necessidade de monitorizar; 3. melhoria da OLD, com evolução de dispositivos de ajuste automático de débito; 4. utilização de IA na personalização da terapêutica com azitromicina na DPOC e, finalmente, 5. visitar a interação entre atopia e asma e procurar entender os fenótipos, à luz da evolução do conhecimento, para melhor gerir a heterogeneidade da asma na criança.

Estimo que alguns destes editoriais convidam ao aprofundar dos temas sobre os quais se debruçam. Mas para além destes, este número permite ler artigos originais em mais 3 áreas do conhecimento:

1. Cancro do Pulmão, “Aplicações atuais e futuras da inteligência artificial no cancro do pulmão e no mesotelioma” e “Avaliação do risco de cancro do pulmão por meio de modelo de predição: uma perspetiva global”;

2. Prevenção da infeção por VSR na criança e no Adulto, “Efetividade e segurança no mundo real do nirsevimab, da vacina materna contra o VSR e das vacinas contra o VSR para adultos mais velhos: uma revisão sistemática viva e meta-análise”, a primeira revisão de evidência de vida real com demonstração de uma extraordinária efetividade do nirsevimab, na criança, na prevenção de visitas de urgência (80,7%), internamentos em enfermaria (80,7%) e em cuidados intensivos (75,6%), com efetividade extensível aos grupos de risco e pretermos e sobreponível para as vacinas para RSV no adulto, com eficiência comprovada. Embora ainda não existam resultados suficientes para a vacina materna (*bivalent RSV prefusion F (RSVpreF) protein-based vaccine*), existem dados robustos de que todas estas profilaxias demonstraram ser seguras.

3. Finalmente, um estudo de enorme relevância sobre a aplicabilidade das guidelines: “Guidelines only impact care if they are implemented in practice”. O artigo “Impacto das guidelines regionais de asma nos padrões de prescrição de SABA em toda a Inglaterra: uma análise de séries temporais interrompidas” analisa a influência das orientações regionais sobre os modelos de prescrição terapêutica de alívio para asma, numa fase em que no Reino Unido as Guidelines da Asma têm, desde final de 2024 uma Orientação colaborativa desenvolvida em conjunto pela Sociedade Torácica Britânica (BTS), pelo Instituto Nacional de Excelência em Saúde e Cuidados (NICE) e pela Rede Intercolegial Escocesa de Orientações (SIGN).

O artigo começa assim “Short-acting beta agonist (SABA) over-use and inhaled corticosteroid (ICS) under-use contribute to asthma exacerbation and mortality risk... The Global Initiative for Asthma (GINA) has recommended ICS-formoterol (ICS/long-acting beta agonist) combination inhalers as the preferred reliever (anti-inflammatory reliever; AIR) for adults and adolescents with asthma since 2019”.... De uma vez por todas, se ainda restam dúvidas, de forma simples e com recurso à transparência da prescrição nacional, o artigo sugere que é tempo para implementar a gestão baseada em AIR e melhorar os resultados para os doentes com asma.

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Série de revisões sistemáticas sobre asma aguda

Patrick Brian Murphy,^{1,2} Swapna Mandal^{3,4}

Esta série de revisões sistemáticas¹⁻⁴ foi encomendada pela OMS em julho de 2022 para informar o seu processo de revisão de *guidelines* (www.who.int). O objetivo foi identificar as evidências atuais para o desenvolvimento das *guidelines* da OMS para a gestão da asma aguda na infância. As revisões contribuíram para a atualização das *guidelines* e recomendações da OMS sobre asma em crianças e adolescentes. A reunião do Grupo de Desenvolvimento de *Guidelines* (GDG) ocorreu em Genebra, Suíça, em outubro de 2023. A equipa de revisão sistemática concluiu sete revisões. A maioria já passou pelo processo de avaliação editorial externa por pares, no *Archives of Disease in Childhood*, e foi aceite para publicação; as restantes estão em processo.

Os membros do GDG da OMS e a equipa da OMS são reconhecidos com

gratidão. Agradecemos à equipa da OMS pela sua contribuição para estas revisões sistemáticas e meta-análises: Dra. Sarah Rylance, Dr. Nuhu Omeiza Yaqub Jr. e Dr. Wilson Milton Were. Agradecemos também ao Professor Eddy Lang, da Cumming School of Medicine, Universidade de Calgary, Canadá, pelo seu apoio como metodologista de *guidelines*.

A equipa da OMS foi responsável por determinar a pergunta de investigação, a população, as intervenções, os comparadores e os desfechos de interesse para a revisão sistemática. A equipa da OMS não esteve envolvida na implementação da revisão sistemática nem diretamente no desenvolvimento dos artigos. Quaisquer opiniões apresentadas são exclusivamente dos autores e não representam as da OMS, salvo indicação específica em contrário.

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Partículas ultrafinas e saúde: a próxima fronteira na compreensão dos riscos da poluição do ar

Laura Nicolaou,^{1,2,3} William Checkley^{1,2,4}

A poluição do ar ambiente é um importante fator de risco para morbidade e mortalidade em todo o mundo. Entre os poluentes, o material particulado fino (PM_{2.5}) — partículas com diâmetro aerodinâmico $\leq 2,5 \mu\text{m}$ — é reconhecido como aquele que causa os maiores impactos na saúde. Em 2021, estimou-se que o PM_{2.5} ambiental foi responsável por 4,7 milhões de mortes e 120 milhões de anos de vida ajustados por incapacidade perdidos em todo o mundo.¹

O PM_{2.5} afeta negativamente a saúde porque penetra profundamente nos pulmões e pode entrar na corrente sanguínea, contribuindo para o desenvolvimento ou agravamento de doenças respiratórias e cardiovasculares.² Estudos também associaram a exposição ao PM_{2.5} ambiental a outras condições de saúde, como o desenvolvimento de diabetes mellitus e resultados adversos na gestação.² Em muitas cidades, o PM_{2.5} ambiental pode frequentemente exceder $35 \mu\text{g}/\text{m}^3$, um nível considerado prejudicial para grupos sensíveis pela Organização Mundial da Saúde.³ De fato, 41% das cidades com população mínima de 50 000 habitantes apresentaram, em 2019, médias anuais ponderadas pela população de PM_{2.5} acima de $35 \mu\text{g}/\text{m}^3$.⁴

Há evidências iniciais crescentes sugerindo que as partículas ultrafinas (UFP, $<0,1 \mu\text{m}$ de diâmetro aerodinâmico) são o componente mais perigoso do PM_{2.5}, pois conseguem penetrar ainda mais profundamente nos pulmões, permanecem retidas por mais tempo e entram na corrente sanguínea com maior facilidade.⁵ Além disso, as UFPs têm uma área de superfície maior por unidade de massa, o que lhes permite transportar maiores quantidades de materiais adsorvidos, resultando em potencialmente maior toxicidade.⁶ Ao contrário do PM_{2.5} ambiental, as UFPs não são comumente monitorizadas ou reportadas por agências ambientais, em parte porque são difíceis de detectar usando métodos convencionais baseados em massa e exigem instrumentos mais complexos e caros para medir a concentração numérica e a distribuição do tamanho das partículas.⁷

Além disso, não existem padrões universalmente aceites para a medição de UFPs nem diretrizes para valores-limite de UFP no ar ambiente.⁸ Como resultado, as evidências epidemiológicas que relacionam UFPs a efeitos na saúde estão menos desenvolvidas. O artigo de Bergmann e colegas, publicado nesta edição, procura fortalecer a base de evidências sobre a relação entre concentrações ambientais de UFP e a saúde respiratória de crianças com asma em Copenhaga, Dinamarca.⁹ Os autores utilizaram dados de UFP ambiental recolhidos num único local como parte do Programa Dinamarquês de Monitorização da Qualidade do Ar desde 2001. Esse programa mediu UFPs usando um *Differential Mobility Sizer* construído sob medida, que contou com precisão partículas de 11–700 nm e determinou a concentração total de partículas com resolução temporal de 2,5 minutos, agregada em médias de 30 minutos (média diária estimada de 5028 partículas/cm³, com IQR de 3223–6292 partículas/cm³). Os autores ligaram esses dados a registros de saúde sobre asma recolhidos entre 2002 e 2018 em oito hospitais de sete municípios. Especificamente, contabilizaram internamentos, consultas externas e visitas ao serviço de urgência separadas por mais de 28 dias entre crianças ≤ 18 anos com diagnóstico primário de asma e endereço registado em qualquer um dos sete municípios incluídos no estudo. Utilizaram ainda dados do Sistema Dinamarquês de Registro Civil para obter informações sobre idade, sexo e município de residência. Usando uma análise *case-crossover* estratificada no tempo, os autores relacionaram a série temporal de concentrações de UFP ambiente nos dias de hospitalização ou visita à urgência por asma às concentrações diárias nos mesmos dias da semana, do mesmo mês e ano civil em que não ocorreu hospitalização, ao longo de um período de 17 anos. Também analisaram janelas de exposição de médias de 2–7 dias de concentrações de UFP no dia e nos dias anteriores à hospitalização por asma, para avaliar efeitos de saúde retardados.

Os autores descobriram que um aumento equivalente ao intervalo interquartil (IQR) nas concentrações de UFP estava associado a um risco 12% maior (IC 95%: 6% a 19%) de internamentos hospitalares por asma em crianças no mesmo dia. Relações positivas de exposição–resposta entre concentrações de UFP e internamentos também foram observadas para janelas de exposição até médias de 7 dias, com a associação mais forte identificada para a média de 2 dias, que esteve ligada a um risco 17% maior (IC 95%: 15% a 38%) por aumento equivalente ao IQR.

Os autores relataram que ajustar para NO₂ ambiente ou PM_{2.5} ambiente não alterou as estimativas de risco relativo da associação entre concentrações de UFP e hospitalizações por asma. No entanto, as análises multipoluentes só puderam ser realizadas num subconjunto dos dados, já que o PM_{2.5} ambiente não estava disponível antes de 2009; e as estimativas de risco relativo tanto para UFP isoladamente quanto para modelos ajustados por NO₂ ou PM_{2.5} nesse subconjunto foram todas não significativas e mais próximas do nulo, levantando preocupações sobre confundimento temporal.

Os resultados apresentados por Bergmann e colegas fornecem mais evidências de que concentrações mais elevadas de UFP estão associadas a pior saúde respiratória em crianças com asma. Uma força deste estudo é o acesso a dados ao nível individual, o que permitiu uma análise *case-crossover*, na qual cada indivíduo serve como seu próprio controlo, reduzindo o confundimento através de comparações dentro da mesma pessoa. A análise *case-crossover* é eficiente para comparar exposições no momento de um evento com exposições em momentos sem evento; contudo, não é o método ideal para avaliar exposições cumulativas ou eventos repetidos dentro dos mesmos indivíduos.¹⁰ Uma abordagem complementar seria usar análises de séries temporais para compreender melhor os papéis da sazonalidade, tendências de longo prazo e efeitos defasados. Outras melhorias possíveis incluem imputação de séries temporais para dias com dados ausentes de UFP ambiente.

Melhores dados epidemiológicos, como os apresentados por Bergmann e colegas, continuarão a evidenciar a importância de integrar a monitorização de UFP na monitorização já existente de poluentes atmosféricos regulamentados. A Organização Mundial da Saúde reconhece que as UFP são prejudiciais à saúde, mas ainda não desenvolveu padrões.³ Aumentar a monitorização de UFP e a investigação sobre seus impactos na saúde é urgentemente necessário para preencher lacunas nas políticas atuais. Estudos epidemiológicos futuros devem considerar o uso de uma rede de monitores de UFP, em vez de um único ponto de medição, já que as concentrações de UFP são altamente localizadas e variam rapidamente, especialmente perto do tráfego.¹¹

É importante reconhecer, contudo, que monitorizar UFP no ambiente requer nova infraestrutura, formação e manutenção, o que muitos países atualmente não conseguem suportar. Ainda assim, a falta de dados é uma barreira significativa para o desenvolvimento de regulamentações sobre UFP. Investir em tecnologias de menor custo para detecção de UFP permitiria maior cobertura geográfica em áreas urbanas densas e em países de baixo e médio rendimento, fornecendo dados essenciais para orientar políticas e intervenções com potencial para gerar benefícios importantes para a saúde pública, a economia e o ambiente.

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Melhorando a oxigenoterapia domiciliar: automatização para facilitar a deambulação

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A oxigenoterapia de longa duração (OLD) é fornecida no domicílio para doentes com doença pulmonar obstrutiva crônica (DPOC) que apresentam hipoxemia em repouso ($\text{SpO}_2 < 88\%$, $\text{PaO}_2 < 60$ mmHg (8 kPa)). Nos EUA, a OLD é fornecida a aproximadamente 1,5 milhões de adultos, com um custo anual de cerca de 2 mil milhões de dólares.¹ A base de evidência para a OLD continua a ser dois estudos históricos de há quatro décadas, que demonstraram uma aparente relação dose-resposta entre a duração diária da terapêutica e a mortalidade.^{2,3} A OLD é frequentemente chamada de oxigénio “domiciliar”, o que oculta o facto de que, embora o tratamento seja fornecido em casa, o objetivo é permitir mobilidade, retorno a uma vida mais ativa e deslocamentos fora do domicílio.⁴

Os doentes expressam o desejo de serem móveis e participarem em atividades da vida diária (AVD).⁵ No entanto, essas atividades são frequentemente limitadas por fadiga, hipoxemia e dispnéia. Além disso, os sistemas portáteis de oxigénio podem limitar a atividade devido a fluxo insuficiente, curta duração de fornecimento, débito constante e questões de portabilidade.^{4,5} Os objetivos de aumentar a deambulação, contudo, precisam ser equilibrados com evidências de que a OLD para hipoxemia moderada ao esforço não oferece benefício de mortalidade nem outros desfechos importantes para o doente.⁶

Na edição original da *Thorax*, Kofod e colegas descrevem o uso de um sistema de oxigénio em circuito fechado para ajustar automaticamente o fluxo entre 1 e 8 L/min, comparado com fluxo constante, durante dois testes Glittre-ADL.⁷ O sistema utilizou um oxímetro de pulso via *Bluetooth* e, embora o oxigénio estivesse limitado a 8 L/min, os autores usaram uma cânula nasal comumente utilizada em oxigénio nasal de alto fluxo. O sistema automatizado tinha como alvo uma SpO_2 de 90–94%. Neste estudo randomizado, duplo-cego e cruzado, o tempo para realizar o teste de AVD foi reduzido em 38 segundos, o tempo dentro da SpO_2 alvo aumentou de 19% para 49%, e a escala de Borg sugeriram menor dispnéia a favor do sistema automatizado. Importante: o fluxo de oxigénio durante o teste triplicou com o controlo automático (5,4 vs 1,6 L/min).

Os achados não são inesperados e confirmam o trabalho de Lellouche e outros. Estes

autores encontraram maior tempo dentro da SpO_2 alvo e menos tempo em hipoxemia ($\text{SpO}_2 < 88\%$) com titulação automática de oxigénio.⁸ Também observaram maior distância percorrida, sugerindo melhor tolerância ao exercício. Em ambos os estudos, apenas foram incluídos indivíduos que necessitavam de oxigénio em repouso e apresentavam dessaturação ao esforço. A dispnéia de esforço relacionada com hiperinsuflação provavelmente ao oxigénio. A diferença clínica minimamente importante para o teste de AVD foi estabelecida em 23 segundos após um programa de reabilitação pulmonar de 8 semanas.⁹ Notavelmente, neste estudo, a diferença de 38 segundos ocorreu apenas ajustando o oxigénio.

Do ponto de vista fisiológico, a titulação automática deve manter a SpO_2 dentro do alvo de forma mais fiável do que o fluxo constante ou ajustado manualmente. O trabalho confirma essa suposição. As limitações desta abordagem são principalmente práticas. Kofod *et al.* encontraram nove pacientes com osteoartrite que não conseguiram carregar a mochila. Isto tem implicações reais, pois um sistema automatizado capaz de fornecer até 8 L/min não pode ser suportado por um concentrador portátil padrão.¹⁰ Os autores não testaram sistemas de dose pulsada, mas concentradores portáteis com essa tecnologia provavelmente não conseguem fornecer oxigénio suficiente para igualar sequer 6 L/min. Se o objetivo é portabilidade, o sistema só poderia ser usado em casa com um concentrador estacionário e 15 metros de tubo, ou

fora de casa com um cilindro de oxigénio comprimido. O volume do cilindro necessário para permitir tempo fora de casa a até 8 L/min implica aumentos proporcionais de tamanho e peso. Cilindros maiores que o tamanho D não podem ser transportados numa mochila e exigem um carrinho com rodas.

Doentes com DPOC e outras doenças respiratórias crônicas com hipoxemia frequentemente têm múltiplas comorbidades que limitam a deambulação e o exercício, incluindo disfunção cardíaca, doenças musculoesqueléticas e perda muscular. A vantagem comprovada do sistema descrito por Kofod *et al.* pode ser anulada pelas limitações da tecnologia atual. Se o doente não consegue deambular com o sistema devido ao tamanho e peso, a implementação torna-se inviável. Há também questões relacionadas com a aceitação da cânula de grande calibre, muito mais visível do que uma cânula padrão. Doentes já tendem a sentir-se constrangidos com o equipamento de oxigénio, e este aumento de tamanho é significativo. Finalmente, a aceitação do oxímetro de pulso no pulso pode ser problemática, pois chama atenção para a doença. Mesmo quem usa *smartwatch* frequentemente esquece de carregar ou colocar o dispositivo.

Melhorias na OLD são urgentemente necessárias. O ajuste automático do fluxo para prevenir hipoxemia é um passo na direção certa. No entanto, tecnologia inovadora e disruptiva será necessária para tornar isso viável.

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Figure 1 From left to right. Portable oxygen concentrator (4 lb, ~2 L/min), stationary concentrator (35 lb, 10 L/min), M-6 cylinder (2.2 lb, 164 L capacity), M-15 cylinder (5.3 lb, 425 L capacity), M-24 cylinder (7.9 lb, 680 L capacity), M-250 cylinder (114 lb, 7080 L capacity), average-sized woman requiring LTOT. (The individual depicted here is AI generated; it does not depict a person living or deceased.) AI, artificial intelligence; LTOT, long-term oxygen therapy.

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Será que “um tamanho serve para todos”? Personalizando a terapêutica com azitromicina através de aprendizagem automática (machine learning)

Anthony Paulo Sunjaya,^{1,2} William D-C Man^{3,4,5}

Os ensaios clínicos randomizados (RCTs) continuam a ser a base da prática baseada na evidência. No entanto, os RCTs normalmente reportam efeitos médios do tratamento, obscurecendo a variabilidade das respostas dos doentes. As tentativas tradicionais de identificar respondedores e não-respondedores limitam-se geralmente à realização de múltiplas análises de subgrupos com fatores isolados, como idade, sexo e gravidade da doença, mas muitas vezes têm poder estatístico insuficiente.¹ É prática comum extrapolar os resultados de um RCT com uma conclusão do tipo “um tamanho serve para a maioria” para orientar a gestão de doentes individuais.

No entanto, o uso crescente de aprendizagem automática e algoritmos capazes de identificar associações complexas e não lineares entre múltiplos fatores demonstrou que a forma tradicional de reportar RCTs pode mascarar heterogeneidade na resposta dos pacientes e no efeito individual do tratamento (ITE). Por exemplo, modelos de aprendizagem automática aplicados *post hoc* a grandes RCTs de terapias inaladas na doença pulmonar obstrutiva crónica (DPOC) identificaram que o efeito “médio” do tratamento pode ser explicado por um subgrupo de super-respondedores.²

Embora a profilaxia a longo prazo com azitromicina reduza exacerbações na DPOC³ e seja recomendada em *guidelines*⁴ clínicas, a sua utilização generalizada tem sido limitada⁵ devido a preocupações com potenciais efeitos adversos, como perda auditiva, arritmias cardíacas, resistência a antibióticos⁶ e análises de subgrupos sugerindo ausência de benefício em fumadores ativos.³ Assim, identificar o ITE da profilaxia com azitromicina pode ajudar clínicos e doentes a tomar decisões mais informadas sobre riscos e benefícios.

Na edição original da *Thorax*, Verstraete *et al.*⁷ realizaram uma análise *post hoc* do ensaio histórico MACRO (MACROlide Azithromycin to prevent COPD exacerba-

tions). Utilizando *causal forest*, um modelo de aprendizagem automática derivado de *random forest*, os autores identificaram cinco parâmetros que revelaram heterogeneidade no ITE,³ mostrando que a redução global das exacerbações com azitromicina profilática era impulsionada por um subgrupo de doentes respondedores. Os resultados foram ainda validados externamente no ensaio mais pequeno COLUMBUS (COPd: *inflUence of Macrolides on exacerBation frequency in patientS*) (n=83),⁸ conduzido numa coorte e contexto diferentes.

Os cinco parâmetros que determinaram um ITE positivo foram: menor pontuação de sintomas, contagem elevada de glóbulos brancos, níveis mais baixos de hemoglobina, proteína C-reativa elevada e capacidade vital forçada elevada. Nenhum destes parâmetros foi considerado entre as 22 análises de subgrupos pré-especificadas no ensaio MACRO,³ nem no ensaio COLUMBUS⁸ (que não reportou quaisquer análises de subgrupos). Os resultados sugerem um endotipo clínico, caracterizado por um estado “inflamatório crónico” com menor comprometimento espirométrico e menor carga sintomática, que é o mais provável de responder à azitromicina profilática. De particular relevância clínica, os autores verificaram que previsões futuras de ITE não pareciam ser determinadas de forma independente por taxas basais de agudizações, idade ou estado tabágico, o que desafia a suposição clínica atual de que doentes mais velhos, não fumadores, com doença grave e exacerbações frequentes são os mais propensos a beneficiar da azitromicina profilática.

Um ponto forte do estudo inclui o uso de *causal forest*, que permite modelar conjuntos de dados de alta dimensão (com um grande número de covariáveis) para identificar doentes mais propensos a beneficiar (ou ser prejudicados) por uma intervenção específica, sem pressupor fortes relações paramétricas entre covariáveis, tratamentos e resultados. Esta flexibilidade permite captar interações complexas e não lineares que modelos de regressão tradicionais podem não detetar.⁹ Em cuidados respiratórios e intensivos, *causal forest* já foi utilizado para identificar respondedores a terapêuticas inaladas na DPOC e a vasopressina com norepinefrina no choque séptico.¹⁰ O presente estudo é o primeiro a usar um enquadramento de aprendizagem automática para estabelecer uma ligação causal entre características dos doentes e resposta à

azitromicina, integrando estas características num modelo clinicamente aplicável. Os autores devem ser felicitados por disponibilizarem uma calculadora *online* para estimar o ITE da azitromicina profilática. Importante: isto permitirá uma avaliação prospetiva do modelo em contexto real.

Existiram algumas limitações no estudo. Modelos de aprendizagem automática dependem fortemente da qualidade e completude dos dados de treino, bem como das características da população estudada. Por exemplo, as populações dos ensaios MACRO e COLUMBUS eram compostas por participantes de ascendência caucasiana com DPOC relacionada com tabagismo, enquanto o pequeno tamanho amostral do COLUMBUS foi subótimo para validação externa. É importante não generalizar excessivamente os resultados e, inadvertidamente, agravar disparidades em saúde. Parâmetros biológicos potencialmente relevantes, como a contagem de eosinófilos no sangue, não estavam disponíveis e, portanto, não foram considerados no modelo.⁹ Isto limita a compreensão dos mecanismos biológicos subjacentes ao ITE e cria incerteza sobre o papel futuro da azitromicina profilática na era das terapias biológicas para DPOC. Variáveis comportamentais ou socioambientais também não foram consideradas, podendo ser mais relevantes na prática real do que em RCTs rigorosos. Embora o estudo não tenha usado os mesmos métodos para prever eventos adversos, isso seria possível e poderia permitir discussões ainda mais personalizadas sobre riscos e benefícios com os doentes. Finalmente, a validação deste modelo precisará de ser avaliada prospetivamente num RCT comparado com a prática atual de prescrição de azitromicina profilática.

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Esclarecendo os fatores de risco distintos da atopia e da asma na infância

Akihiro Shiroshta

Diversas exposições ambientais e relacionadas com o estilo de vida têm sido sugeridas como fatores de risco para o desenvolvimento de asma infantil. No entanto, a evidência sobre os fenótipos de asma atópica e não atópica tem sido limitada. O termo atópico aqui refere-se especificamente a uma reação exagerada do sistema imunitário mediada por IgE a alérgenos comuns, detetada por testes cutâneos (também conhecida como asma alérgica), e não a uma predisposição genética (ou seja, tendência inerente) para desenvolver condições alérgicas. Como diferentes mecanismos fisiopatológicos subjacentes podem exigir medidas preventivas e estratégias terapêuticas distintas, é importante explorar fenótipos e endotipos de asma, em vez de tratar a asma como uma condição única e homogênea. No entanto, as definições inconsistentes dos subtipos de asma resultaram em substancial heterogeneidade nos resultados dos estudos.

O estudo “Fatores de risco para asma atópica e não atópica em crianças em idade escolar de países de rendimentos altos, médios e baixos”, conduzido por Rutter e colegas, avançou este tema do ponto de vista metodológico. Dada a elevada prevalência de atopia, a sua presença entre crianças com asma não implica necessariamente um mecanismo alérgico subjacente ao desenvolvimento da asma. Os autores distinguiram fatores de risco específicos da asma daqueles relacionados com a atopia ao estratificar a população em quatro subgrupos: “sem atopia e sem asma”, “com atopia mas sem asma”, “com asma atópica” e “com asma não atópica”. Em outras palavras, definiram cuidadosamente os grupos de controlo através da estratificação, em vez de simplesmente comparar indivíduos com asma atópica com aqueles sem asma.

O estudo foi uma meta-análise de dados individuais de quatro estudos (uma coorte de nascimento, um estudo caso-controlo e dois estudos transversais) conduzidos em 23 países abrangendo contextos de rendimento alto, médio e baixo. Os autores ilustraram um valioso enquadramento conceptual (figura 1) dos quatro percursos distintos de desenvolvimento da asma (percurso 1: “sem atopia e sem asma” para “asma não atópica”; percurso 2: “sem atopia e sem asma” para “atopia sem asma”; percurso 3: “atopia sem asma” para “asma atópica”; percurso 4: “sem atopia e sem asma” para “asma atópica”). Aplicaram modelos de regressão logística

de efeitos mistos separados para diferentes comparações de subgrupos, ajustando para idade, sexo, estudo e nível de rendimento do país. Por exemplo, os fatores de risco para asma não atópica foram identificados comparando crianças com asma não atópica com aquelas sem atopia e sem asma. De forma semelhante, os fatores de risco para asma atópica foram avaliados comparando crianças com asma atópica com aquelas com atopia mas sem asma — isolando assim fatores de risco específicos da asma dos relacionados com a atopia. O estudo mostrou que os ORs entre fatores de risco e asma foram amplamente semelhantes para asma atópica e não atópica, uma vez contabilizados os fatores relacionados com a atopia. Em contraste, as exposições mostraram associações diferenciais com a atopia; por exemplo, o consumo de fruta pareceu prejudicial para a atopia, mas protetor contra ambos os tipos de asma.

O que sugerem estes resultados? Os autores propuseram duas interpretações. Primeiro, o desenvolvimento da asma pode ser impulsionado por fatores de risco semelhantes em fenótipos atópicos e não atópicos, sugerindo que estas condições podem ser mais semelhantes do que se supunha, com a atopia não desempenhando um papel principal. Alternativamente, a asma atópica e não atópica podem ter mecanismos fisiopatológicos distintos, mas as definições atuais podem resultar em classificação incorreta — em que crianças com asma não atópica que coincidentemente têm atopia são rotuladas como tendo asma atópica. Em qualquer dos casos, atopia e asma podem frequentemente coexistir por acaso em crianças diagnosticadas com asma atópica.

Uma abordagem de estratificação semelhante foi proposta por Pekkanen e colegas há mais de uma década. Utilizando dados da *Northern Finland Birth Cohort* 1966, Pekkanen et al. demonstraram que análises tradicionais poderiam produzir resultados enganadores, como associações espúrias entre posse de gatos, género feminino e asma. Recomendaram analisar atopia e asma como desfechos separados e depois comparar grupos com e sem asma estratificados pelo estado de atopia. As abordagens de Pekkanen et al. e Rutter et al. estão essencialmente alinhadas, visando dissociar as associações entre fatores de risco e asma daquelas relacionadas com a atopia. Os seus resultados foram consistentes.

Como os autores reconheceram, podem existir potenciais vieses, como confundimento não medido (por exemplo, nível socioeconómico individual) e classificação incorreta de atopia e asma. No entanto, o desenho sofisticado do estudo reforça a

importância de clarificar grupos de comparação em investigação epidemiológica. Um papel fundamental de estudos epidemiológicos de grande escala é gerar hipóteses sobre relações entre exposições e desfechos, que podem orientar investigação futura. Estudos de coorte prospetivos são necessários para esclarecer melhor o papel da atopia no desenvolvimento da asma utilizando esta abordagem analítica refinada. É também crucial distinguir o papel da atopia na iniciação da asma do seu papel na agudização da asma já existente. Para desvendar vias causais, futuros estudos prospetivos devem incorporar protocolos pré-definidos para avaliar o estado de atopia antes do início dos sintomas de asma. Estabelecer longitudinalmente o estado de atopia antes da manifestação da doença ajudaria a determinar se a atopia é um verdadeiro fator iniciador ou se apenas coexiste com a asma devido a fatores de risco partilhados.

Além disso, deve ser dada atenção cuidadosa aos métodos utilizados para avaliar a atopia (por exemplo, testes cutâneos vs IgE específica; aeroalérgenos vs outros alérgenos comuns como alimentos) e ao momento e frequência das avaliações, dado que a sensibilização pode surgir e mudar dinamicamente durante a infância. Em particular, definir com precisão asma verdadeiramente atópica e não atópica pode ser um desafio na prática.

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ARTIGO ORIGINAL

Uso de aminofilina intravenosa em complemento ao tratamento padrão de primeira linha em crianças e adolescentes com exacerbação aguda de asma: uma revisão sistemática e meta-análise de ensaios clínicos randomizados

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RESUMO

Importância O papel da aminofilina intravenosa na asma aguda na infância permanece incerto.

Objetivos Avaliar a segurança e a eficácia da aminofilina intravenosa para asma em crianças.

Métodos De 1966 a maio de 2024, foram pesquisadas as bases de dados MEDLINE, Embase, CINAHL, Web of Science e o Cochrane Central Register of Controlled Trials. Incluímos apenas ensaios clínicos randomizados que testaram o tratamento padrão em combinação com aminofilina e seguimos as *guidelines* internacionais para a realização de revisões sistemáticas. Os desfechos avaliados foram morbidade, escalonamento de cuidados, duração da hospitalização, eventos adversos, mortalidade e função pulmonar. Utilizamos o modelo de efeitos aleatórios para a análise dos dados e o modelo de efeitos fixos para avaliar a heterogeneidade.

Resultados Nove estudos (466 participantes) cumpriram os critérios de elegibilidade pré-definidos. Não foram encontradas diferenças significativas no resultado de gravidade da asma após o tratamento (diferença média (DM)=0,13; IC 95% -0,79 a 1,06; I²=0%), taxa de hospitalização (risco relativo (RR)=0,66; IC 95% 0,27 a 1,59; I²=0%), admissão em unidade de cuidados intensivos pediátricos (RR=0,73; IC 95% 0,51 a 1,05; I²=0%), taxa de intubação (RR=0,09; IC 95% 0,01 a 1,64; p=0,1) ou duração da hospitalização (DM=-3,62; IC 95% -13,05 a 5,82; I²=31%). Vômitos (RR=3,52; IC 95% 2,04 a 6,06; I²=0%) e náuseas (RR=4,92; IC 95% 2,41 a 10,06; I²=0%) ocorreram mais frequentemente no grupo da aminofilina. Um estudo mostrou melhoria da função pulmonar no grupo da aminofilina, enquanto os restantes não mostraram diferenças.

Conclusão Esta revisão mostrou evidência limitada do benefício da aminofilina intravenosa no tratamento da asma na maioria dos parâmetros de gravidade pré-intubação. No entanto, a possível redução da taxa de intubação e a melhoria da função pulmonar merecem maior atenção.

Número de registro PROSPERO: CRD42023405234.

INTRODUCTION

This is one of a series of systematic reviews commissioned by WHO to inform consolidated recommendations for managing common childhood illnesses. The recommendations will update the guidance in the second edition of the WHO Pocket Book of Hospital Care for Children, which was published in 2013,¹ and the Integrated Management of Childhood Illness charts.²

Asthma is one of the most common chronic diseases, with an estimated 262 million people affected in 2019.³ It is a common cause of morbidity in children and adolescents; hence, the acute and long-term management of asthma has

Key messages

What is known about this topic

- Using intravenous aminophylline for acute severe asthma does not improve the hospitalisation rate, asthma severity score, paediatric intensive care unit admission or length of hospital stay.

What this study adds

- This study confirms that intravenous aminophylline does not benefit children and adolescents with acute severe asthma.
- Only one study found that it may improve lung function and reduce the duration of intubation in critically ill children with acute severe asthma; however, for very sick children with acute severe asthma, intravenous aminophylline may still be helpful as an add-on therapy.

How this study might affect research practice or policy

- Intravenous aminophylline may benefit critically ill children with acute severe asthma when other medications fail.

been identified by WHO as a priority for evidence appraisal and guideline development. The standard first-line treatment of acute asthma exacerbations includes oxygen, inhaled beta-agonist medications and systemic corticosteroids.⁴ Additional medications are added to this first-line treatment in the management of more severe asthma exacerbations with varying levels of supportive evidence.^{4,5}

Aminophylline is a methylated xanthine derivative whose mechanisms of action still need to be fully understood. Its benefits include bronchodilation and reduced airway hypersensitivity.⁶

Aminophylline is only recommended as a last option for the management of children with severe or life-threatening asthma who fail to respond to bronchodilators and steroids given at maximal doses.⁷

There are variations in managing acute asthma in children when intravenous treatment is considered. A 2015 survey of emergency physicians in the UK and Ireland reported that 15% of responders preferred intravenous aminophylline as the

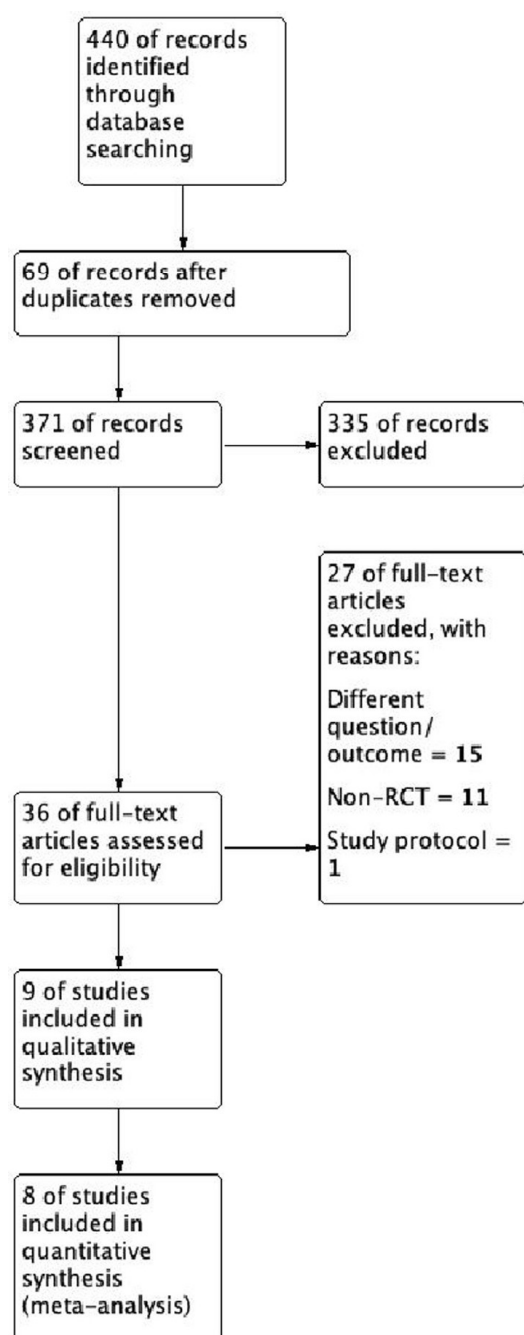


Figure 1 Study flow diagram. RCT, randomised controlled trial.

first-line intravenous treatment.⁸ This survey was conducted before the British Thoracic Society guideline update 2019; hence, the current situation may have changed.

The use of aminophylline is cautioned against due to concerns about side effects such as nausea and vomiting with other potentially serious side effects, especially in patients already on sustained release theophylline.⁹ A Cochrane review by Mitra et al concluded that adding intravenous aminophylline in children with acute severe asthma exacerbations who are unresponsive to maximum treatment with bronchodilators, supplemental oxygen and systemic steroids is beneficial. It improves lung function with improvement in symptoms maintained up to 8 hours after treatment.¹⁰ The review was published nearly 20 years ago; since then, at least one more randomised controlled trial (RCT) has been published.

This review aimed to assess the safety and efficacy of intravenous aminophylline in addition to standard first-line treatment with inhaled/nebulised Short-Acting Beta Agonist (SABA) and systemic steroids, compared with standard first-line therapy in children and adolescents with an acute asthma exacerbation aged 18 years and under.

MATERIALS AND METHODS

This study followed the international recommendations for conducting systematic reviews and meta-analyses.¹¹ The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under CRD42023405234.

Study selection and search strategy

We searched the MEDLINE, Embase, CINAHL, Web of Science and the Cochrane Central Register of Controlled Trials databases from inception to April 2023 and updated the search on 20 May 2024. We inspected the reference lists from retrieved articles to identify any additional citations the electronic searches may have missed. We also searched unpublished ongoing clinical trials on the websites www.clinicaltrials.gov and www.controlled-trials.com.

We used the standard recommended guidelines for our search strategy. Search terms included attack or exacerbation or acute or severe asthma or episode AND aminophylline (see online supplemental appendix 1 for complete search strategy).

Eligibility criteria

We included RCTs that assessed the safety and efficacy of intravenous aminophylline in addition to standard first-line treatment (inhaled/nebulised SABA and systemic steroids), compared with the first-line treatment and placebo for children and adolescents 18 years and under with acute asthma exacerbation.

The outcome measures were:

Primary outcomes

► Morbidity: symptoms, hospitalisation rate and school absence in days.

Secondary outcomes

► Escalation of care (ventilation/paediatric intensive care unit (PICU) admission).

► Length of hospital stay in hours.

► Adverse events.

► Mortality due to exacerbation.

► Lung function (change in per cent of predicted forced expiratory volume in 1 s (FEV₁) or FEV₁ in litres, and per cent of predicted peak expiratory flow (PEF) or PEF in L/min).

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

Data collection and analysis

Authors in pairs (RS, SA, AZZ, AT) assessed the relevant manuscripts using the above search strategy. They then independently assessed all trials' eligibility using the abovementioned prespecified criteria. Discussions with a third author (ISA or CP) resolved disagreements among authors.

Data extraction and management

Two authors (AA, NA) independently extracted data that included the following: risk of bias assessment, demographic information, methodology, intervention details and reported outcomes. They compared the extracted data, and any differences were resolved by consensus or discussion with a third author (KM) when needed. We used the Cochrane Collaboration's Review Manager for data analysis.¹²

Assessment of risk of bias in included studies

Two review authors (KM, AH) used the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions to assess the risk of bias.¹³ They independently evaluated the risk of bias for each study, and any disagreement was resolved through mutual discussion or involving a third author (ISA, CP) when needed. We assessed the risk of bias according to the following domains:

1. Random sequence generation.

2. Allocation concealment.

3. Blinding of participants and personnel.

4. Blinding of outcome assessment.

5. Incomplete outcome data.

6. Selective outcome reporting.

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

Table 1 Characteristics of included studies

Study, country and participants	Intervention	Comparison	Outcomes	Other treatments given to all patients	Criteria/Definition of acute severe asthma and timing of starting intravenous aminophylline
Bein <i>et al</i> ²⁴ USA (high-income country) ²⁷ 39 participants 2–10 years of age	A theophylline bolus (1.6 mg/mL in 5% dextrose water) and continuous infusion. Boluses and drip rates were calculated based on the algorithm of Weinberger <i>et al</i> . Therapeutic theophylline concentrations were considered 10–20 pg/mL.	Placebo bolus (5% dextrose water) and continuous infusion.	Clinical Asthma Score (PI). Number of albuterol aerosol required over the duration of the study.	Intravenous methylprednisolone, 2 mg/kg push at enrolment, and 1 mg/kg every 6 hours thereafter. Aerosolised albuterol as needed (2.5 mg/2.5 mL normal saline) with a maximum interval of every 6 hours. Supplemental humidified oxygen.	Participants were enrolled and aminophylline/placebo commenced if they had asthma exacerbation (as per the American Thoracic Society criteria) ²⁸ requiring admission to hospital excluding PICU admission. ASS used was introduced by Becker <i>et al</i> (PI). ²⁹
Carter <i>et al</i> ¹⁷ USA (high-income country) 21 participants 5–18 years of age	Theophylline loading dose based on the results of theophylline therapeutic monitoring, followed by intravenous infusion 0.8–1.0 mg/kg/hour. The loading dose was determined by calculating the increase in serum theophylline concentration to achieve a target level of 82.5 µmol/L (15 pg/mL).	Placebo.	FEV ₁ , clinical scores, total number of albuterol nebulisations, total dose of albuterol, hospital stay (inpatient stay in days after the initial emergency department treatment).	Intravenous infusions of methylprednisolone (1 mg/kg every 6 hours) and nebulised albuterol 2.5–5 mg. Oxygen was administered for patients with saturation <92%.	Participants were enrolled and aminophylline/placebo commenced if they had asthma exacerbation as per the American Thoracic Society criteria ²⁸ that required admission to hospital. Hospitalisation was decided if patients lacked response to three doses of nebulised albuterol. ASS that was used was introduced by Becker <i>et al</i> (PI). ²⁹
DiGiulio <i>et al</i> ¹⁸ USA (high-income country) 29 participants 2–16 years of age	Aminophylline was mixed in dextrose 5% and water at a concentration of 4.4 mmol/mL (0.8 mg/mL) that was administered at a rate of 6 mL/kg for 20 min, followed by a continuous infusion of the same solution at a rate of 1.0 mL/kg/hour if the patient was between 2 and 9 years of age, and 0.85 mL/kg/hour if the patient's age was >9 years.	Placebo dextrose 5% in water.	Number of hospital admissions. Hours elapsed until an asthma score of ~2 was achieved. Number of doses of nebulised beta-adrenergic drugs given to each subject. Adverse effects.	Three doses of nebulised albuterol initially, then four hourly. Methylprednisolone was given initially at a dose of (2 mg/kg; maximum 80 mg), patients subsequently received methylprednisolone intravenously, 0.5 mg/kg per dose every 6 hours, until the patient's condition allowed a change to prednisone, 1 mg/kg orally, once daily to complete a 5-day course.	ASS >3 (score was created by the authors) and lack of response to the emergency department treatment to allow discharge. Asthma was diagnosed by a physician and was defined as recurrent wheeze that was responsive to bronchodilators without any other cardiopulmonary disease.
Strauss <i>et al</i> ¹⁹ USA (high-income country) 31 participants 5–18 years of age Hospital admission after failure of ED treatment excluding patients needing PICU	Aminophylline bolus of 7 mg/kg of study drug in the ED with continuous cardiac monitoring. This was followed by a continuous infusion at an initial rate of: 1.2 mL/kg/hour in children <9 years of age; 1.0 mL/kg/hour in children 9 to 12 years old; and 0.75 mL/kg/hour in children older than 12 years.	Placebo as 5% dextrose.	Length of hospital stay (inpatient after initial ED treatment). Percentage of PEF recorded at 12 hours intervals. Number of albuterol treatments required. Adverse effects.	Beta-agonist inhalation therapy and glucocorticoids Methylprednisolone 1 mg/kg six hourly until switching to oral O ₂ as needed.	Aminophylline was started after failure to respond to three doses of albuterol. All patients had asthma as per the American Thoracic Society criteria and were able to perform PEF. All included patients had Wood-Downes asthma scores of 3–5. ³⁰
Needleman <i>et al</i> ²⁰ USA (high-income country) 42 participants 2–18 years of age	Aminophylline mixed in a dextrose and saline infusion to maintain serum theophylline levels at 55 to 110 µmol/L.	A placebo infusion of dextrose and saline at a similar rate.	Length of stay (inpatient stay in the paediatric ward). Asthma clinical scores.	Methylprednisolone, 2 mg/kg/day with a maximum of 125 mg; and 2.5 mg of albuterol nebulised initially every 2 hours, with the interval increased as tolerated. Oxygen was administered as needed.	Patients enrolled if they were previously diagnosed with asthma or reactive airway disease and were wheezing at presentation. Aminophylline/Placebo was started for lack of clinical improvement after three albuterol nebulisations at 20 min intervals. Asthma score was created by authors based on vital signs values reported by Iliff and Lee. ³¹
Nuhoğlu <i>et al</i> ²¹ Turkey (upper-middle-income country) 38 participants 2–16 years of age	Aminophylline in 5% dextrose in water (240 mg/10 mL). Dose was 6 mg/kg over 30 min followed by a continuous infusion of the same solution at a rate of 1.0 mg/kg/hour if the patient was between 2 and 9 years of age and 0.8 mg/kg/hour if the patient's age was >9 years.	Placebo group received 0.9% saline solution for the next 24 hours.	Number of salbutamol nebulisations needed at the end of 24 hours. Clinical asthma scoring at onset and at the end of the 24th hour.	Intravenous methylprednisolone 2 mg/kg in divided doses, maximum 60 mg/day and nebulised salbutamol 2.5 mg diluted with 2.5 mL of 0.9% saline solution.	All patients met the American Thoracic Society definition of asthma. Aminophylline/Placebo was started for lack of response to two doses of nebulised salbutamol and scored >3 in a clinical asthma scoring that was modified from DiGiulio <i>et al</i> . ¹⁸
Yung and South ²² Australia (high-income country) 163 participants 1–19 years of age	Intravenous aminophylline 10 mg/kg bolus then infusion (0.7–1.1 mg/kg/hour).	Sterile water at the same doses of the intravenous aminophylline.	Length of stay in hospital (inpatient stay in PICU). The second principal outcome measure was spirometry FEV ₁ , forced vital capacity, maximum mid-expiratory flow and peak flow were recorded and expressed as percentages of that predicted for the subject's age, height, sex and race.	Nebulised salbutamol 5 mg frequency determined by the treating physician, nebulised ipratropium bromide 250 µg every 4–6 hours and intravenous methylprednisolone 1 mg/kg every 6 hours, followed by oral prednisolone 1 mg/kg twice daily during convalescence.	Patients were considered as acute severe asthma and started on aminophylline/placebo, if they were unresponsive to three nebulised doses of 5 mg salbutamol, had an ASS of >6, spirometry (where possible) of <50% predicted or clearly sick and required PICU admission. We included data from this study after consensus despite having patients aged 19 years and under.

Continued

Table 1 Continued

Study, country and participants	Intervention	Comparison	Outcomes	Other treatments given to all patients	Criteria/Definition of acute severe asthma and timing of starting intravenous aminophylline
Viera <i>et al</i> ²³ Brazil (upper-middle-income country) 43 participants 1–7 years of age	Aminophylline bolus dose of 6 mg/kg followed by a maintenance dose of 1.2 mg/kg/hour throughout the protocol.	Placebo-saline solution.	Asthma clinical score. Length of stay in the emergency room. Admission rate.	Hydrocortisone (dose: 5 mg/kg, 6/6 hours) and nebulised fenoterol (0.1 mg/kg, 3/3 hours).	Patients were considered asthmatics if they had respiratory difficulty (expiratory) for <2 days with at least two previous similar episodes. Aminophylline/Placebo was started if patients scored 3–6 on a Modified Wood-Downes score, with three fenoterol nebulisations at 30 min intervals. ²⁸
D’Avila <i>et al</i> ²⁵ Brazil (upper-middle-income country) 60 participants 2–5 years of age Data were reported as mean and IQR. It was re-analysed into mean and SD using the formula by Hozo <i>et al</i> ²²	Two doses of intravenous aminophylline (5 mg/kg six hourly) diluted in saline solution (up to 20 mL).	Two infusions (at 6 hours interval) of normal saline solution (20 mL).	Length of supplemental oxygen, number of bronchodilator nebulisations or aerosol puffs, length of stay in the paediatric emergency room (in hours).	Oral dose of corticosteroids (prednisolone or prednisone 1 mg/kg) and three consecutive nebulisations with albuterol (150 mg/kg/dose), or three consecutive inhalations of metered-dose albuterol (50 mg/kg/dose).	Lack of response to three doses of salbutamol and one steroid dose. Aminophylline/Placebo was started if patients with acute asthma were refractory to an oral dose of corticosteroids (prednisolone or prednisone 1 mg/kg) and three consecutive nebulisations with albuterol (150 µg/kg/dose), or three consecutive inhalations of metered-dose albuterol (50 µg/kg/dose) over 1-hour period.

ASS, asthma severity score; PEF, peaked expiratory flow; PI, Pulmonary Index; PICU, paediatric intensive care unit.

Data management

We calculated the mean difference (MD) for continuous data when appropriate. For dichotomous data, we reported the risk ratio (RR). We highlighted all missing data within the ‘Results’ section. We used an intention-to-treat basis of analysis (ITT). Any dropout of included children was highlighted within the review. We planned to contact the authors for further clarification and to provide additional information when needed. We used the I² statistic to measure heterogeneity among the included trials.¹⁴ We considered an I² value of:

- ▶ 0%–40%: might not be as important.
- ▶ 30%–60%: represent moderate heterogeneity.
- ▶ 50%–90%: represent substantial heterogeneity.
- ▶ 75%–100%: represent considerable heterogeneity.

Heterogeneity was explored by performing sensitivity analyses when appropriate. We planned to investigate potential publication bias using funnel plots for each outcome if there were 10 or more studies.¹⁵

Data synthesis

We synthesised and analysed data using the statistical package Review Manager V.5.4, provided by the Cochrane Collaboration.¹² All measures were reported with 95% CIs. We synthesised data using a random-effects model. When data could not be combined, or significant heterogeneity existed, we reported results using a narrative description.

Subgroup analysis and investigation of heterogeneity

If data were available, the following subgroup was planned to be assessed: the timing of intravenous aminophylline administration, whether started at presentation or following a poor response to initial treatment.

Sensitivity analysis

We planned to perform sensitivity analysis to explore the potential impact of missing data and any methodological heterogeneity. We intended to do this by omitting the studies with a high risk of bias from the meta-analysis and analysing data using both random-effects and fixed-effects models to assess their impact on the overall results.

Summary of findings

We used the principles of the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system¹⁶ to assess the certainty of the body of evidence associated with specific outcomes. The grading was planned for the following outcomes:

Hospitalisation rate, asthma severity score at 24 hours postintervention, PICU admission rate, intubation and mechanical ventilation, length of hospital stay in hours and adverse events. We downgraded the certainty level of a body of evidence based on the following factors:

1. Methodological quality.
2. The directness of the evidence.

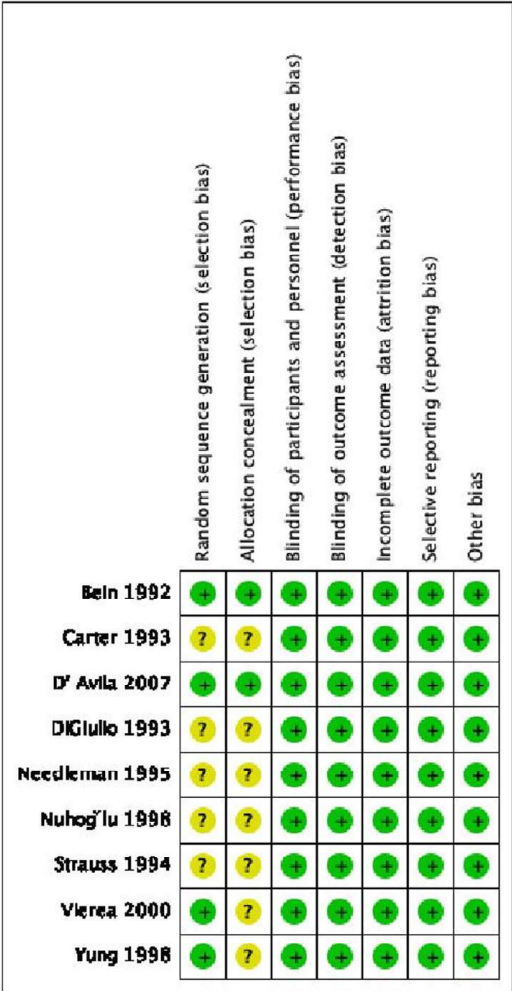


Figure 2 Risk of bias summary: review the authors’ judgements regarding each risk of bias item for each included study.

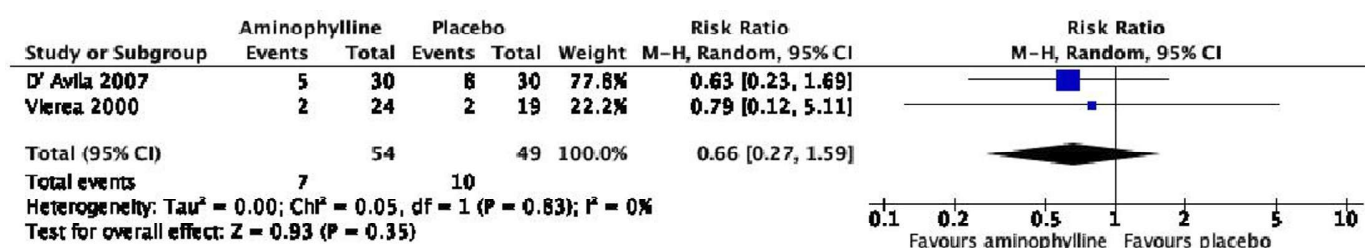


Figure 3 Forest plot of comparison: intravenous aminophylline for acute severe asthma, outcome: hospitalisation rate.

3. The heterogeneity of the data.
4. The precision of effect estimates.
5. The risk of publication bias.

RESULTS

We identified 440 citations, and full texts of 36 citations potentially meeting the inclusion criteria were assessed after duplicates were removed and titles and abstracts were screened. After the full-text assessment, 27 trials were excluded: 15 manuscripts assessed different research questions and/or outcomes, 11 were non-RCTs and one was a study protocol. We included nine studies, with total participants (n)=466. Figure 1 shows a flow diagram detailing the selection process.

Study characteristics

We included nine RCTs (n=466). Table 1 provides the characteristics of the included trials. The criteria used to define and assess asthma severity were the same as those used in the primary studies.

Risk of bias

All the included studies were assessed as low risk in terms of blinding of participants, outcome assessment, selective reporting, incomplete outcome data assessment and other biases. Random sequence generation and allocation concealment were unclear in five studies, as the primary authors did not share the details of randomisation and allocation concealment.^{17–21} Two studies^{22 23} had a low risk for random sequence generation but unclear allocation concealment due to a lack of details within the primary studies. Two studies^{24 25} were assessed as low risk for randomisation and allocation concealment (figure 2 and online supplemental figure 1).

Effect of interventions

Primary outcomes

Asthma severity scores

Asthma severity scores were used by primary studies to report morbidity symptoms. Five of the included studies reported this outcome.^{17 18 20 21 24} Only two studies were included in the meta-analysis.^{20 21} There was no difference between the aminophylline

Table 2 Summary of findings

The use of intravenous aminophylline in addition to standard first-line treatment compared with placebo for children 18 years or younger with acute asthma

Patient or population: children 18 years or younger with acute asthma

Setting: all studies were done in either high-income, middle-income or upper-income countries

Intervention: the use of intravenous aminophylline in addition to standard first-line treatment

Comparison: placebo or any other treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo or any other treatment	Risk with the use of intravenous aminophylline in addition to standard first-line treatment				
Asthma severity score at 24 hours postrandomisation		MD 0.13 higher (0.79 lower to 1.06 higher)	–	78 (2 RCTs)	⊕⊕○○ Low†‡	
Hospitalisation rate	204 per 1000	135 per 1000 (55 to 324)	RR 0.66 (0.27 to 1.59)	103 (2 RCTs)	⊕⊕⊕○ Moderate§	
PICU admission rate	375 per 1000	274 per 1000 (191 to 394)	RR 0.73 (0.51 to 1.05)	223 (2 RCTs)	⊕⊕○○ Low§¶	
Intubation and mechanical ventilation	61 per 1000	5 per 1000 (1 to 100)	RR 0.09 (0.01 to 1.64)	163 (1 RCT)	⊕⊕⊕○ Moderate**	
Length of hospital stay		MD 3.62 lower (13.05 lower to 5.82 higher)	–	154 (4 RCTs)	⊕⊕○○ Low†††	
Adverse events—emesis	33 per 1000	117 per 1000 (68 to 201)	RR 3.52 (2.04 to 6.06)	298 (5 RCTs)	⊕⊕⊕○ Moderate‡‡	
Adverse events—nausea	59 per 1000	289 per 1000 (142 to 592)	RR 4.92 (2.41 to 10.06)	233 (3 RCTs)	⊕⊕⊕○ Moderate‡‡	

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to the estimated effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimated effect, but there is a possibility that it could be substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimated effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimated effect.

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

†Downgraded for serious indirectness for variability of asthma severity score assessments.

‡Downgraded for serious impression for small sample size and wide CI.

§Downgraded for serious impression for small sample size.

¶Downgraded for inconsistency due to wide CI.

**Downgraded for serious imprecision as small sample size and wide CI were noted.

††Downgraded for serious inconsistency due to moderate heterogeneity.

‡‡Downgraded for unclear risk of randomisation and allocation concealment for most of the included studies.

GRADE, Grading of Recommendations, Assessment, Development and Evaluations; MD, mean difference; RR, risk ratio.

and placebo groups in clinical asthma severity score assessed at the 24th hour (low certainty evidence) (MD=0.13, 95% CI -0.79 to 1.06, $I^2=0\%$, $n=78$) (online supplemental figure 2). A narrative description of the asthma severity scores reported by the other three studies^{17 18 24} was included in the online supplemental files under the asthma severity scores further analysis.

Hospitalisation rate

Two studies reported this outcome.^{23 25} No difference between the intravenous aminophylline and placebo groups was found (moderate certainty evidence) (RR=0.66, 95% CI 0.27 to 1.59, $I^2=0\%$, $n=103$) (figure 3).

Secondary outcomes

PICU admission rate

Two studies reported this outcome.^{22 25} No significant difference was found between the groups (low certainty evidence) (RR=0.73, 95% CI 0.51 to 1.05, $I^2=0\%$, $n=223$) (online supplemental figure 3).

Intubation and mechanical ventilation

Only one study reported this outcome.²² Five patients were intubated and mechanically ventilated in the placebo group. The difference was insignificant among the groups (moderate certainty evidence) (RR=0.09, 95% CI 0.01 to 1.64, $p=0.1$, $n=163$) (online supplemental figure 4).

Length of hospital stay in hours

This outcome was reported by five RCTs.^{17 19 20 22 25} Only four studies^{17 19 20 25} were included in the meta-analysis. There was no significant difference among the studied groups (low certainty evidence) (MD=-3.62, 95% CI -13.05 to 5.82, $I^2=31\%$, $n=154$) (online supplemental figure 5). When sensitivity analysis was done using the fixed-effects model, patients who received aminophylline stayed longer than those who received other treatment (MD=-8.13, 95% CI -11.78 to -4.47, $I^2=31\%$, $n=154$).

One study²² reported the mean length of stay as numbers without CIs for both intravenous aminophylline and placebo groups. The authors provided the ratio of the aminophylline group's mean length of stay to the placebo mean length of stay; therefore, we could not include that in the meta-analysis. The mean length of stay for the placebo group was 2.87 days compared with 2.69 days for the aminophylline group; therefore, aminophylline could have reduced the length of stay by as much as 23% or increased it by as much as 14%.

Adverse events

Five studies investigated adverse events.^{18 19 21 22 24} All the above five studies reported emesis. It occurred significantly more in the aminophylline group (RR=3.52, 95% CI 2.04 to 6.06, $I^2=0$, $n=298$, moderate certainty evidence). Three studies reported nausea as an adverse event.^{19 22 24} Significantly more patients in the aminophylline group experienced nausea (RR=4.92, 95% CI 2.41 to 10.06, $I^2=0\%$, $n=233$, moderate certainty evidence). Other adverse events reported were headache, tremors, abdominal pain, arrhythmia, insomnia, irritability, aminophylline toxicity and seizures (online supplemental figure 6).

Percentage improvement of predicted forced expiratory volume in 1 s

Two of the included studies reported this outcome.^{17 22} Yung et al²² measured FEV₁ among other parameters and expressed the values as a percentage of that predicted for the candidate's age, height, sex and race. FEV₁ was better in the aminophylline group. At 24 hours, the mean percentage difference in FEV₁ was (MD=9.4%, 95% CI 1.0 to 17.9, $p=0.029$). The CIs were given only for the difference in FEV₁ between intravenous aminophylline and placebo. Therefore, we could not include that in the meta-analysis. The study by Carter et al¹⁷ showed improvement of FEV₁ from baseline at 36 hours (MD=7.00, 95% CI -7.55 to 21.55, $p=0.35$) (online supplemental figure 7).

Peaked expiratory flow change

Two studies reported this outcome.^{19 22} Strauss et al showed no difference in PEF at any of the studied time points¹⁹ ($p=0.16$, $n=31$). The overall result of PEF changes is shown in online supplemental figure 8.

Yung²² et al ($n=163$) measured PEF among other parameters and expressed the values as a percentage of that predicted for the candidate's age, height, sex and race. The aminophylline group showed significant improvement at all points measured compared with placebo. PEF MD measured at 24 hours was MD=10.2, 95% CI 0.3 to 19.9, $p=0.043$. The CIs were provided only for the difference in PEF between intravenous aminophylline and placebo. Therefore, we could not include this study in the meta-analysis.

Further analysis

Need and duration of supplemental oxygen in hours

This outcome result was shared and discussed in online supplemental figures 9 and 10.

Other outcomes

We could not find any data from the primary studies on school absence and mortality due to asthma exacerbation.

Subgroup analysis

No data were available for the planned subgroup analysis of the timing of administration of intravenous aminophylline.

Quality of evidence

The GRADE assessment showed low to moderate certainty evidence that asthma severity score, hospitalisation rate, PICU admission rate, intubation rate and length of hospital stay were not significantly different among the groups. Intravenous aminophylline use was associated with more emesis and nausea (moderate certainty evidence) (table 2).

DISCUSSION

This review assessed the efficacy and safety of adding intravenous aminophylline to the standard first-line treatment of acute severe asthma in children. Nine studies, including 466 children, were included in the review. The meta-analysis of this review showed no significant difference in the asthma severity scores, hospitalisation rate, PICU admission rate or length of hospital stay in hours between the aminophylline and placebo groups. However, the aminophylline group experienced more adverse events than the placebo group. A single high-dose aminophylline study showed more side effects than studies that used lower doses.²²

Yung and South²² reported no significant difference in the intubation rate between the groups, with a reduction in the duration of intubation and improvement in lung function tests in the intravenous aminophylline group. However, two other studies showed comparable lung function test results between the studied groups.^{21, 23}

Two systematic reviews conducted by Mitra et al¹⁰ and Craig et al²⁶ revealed an unclear effect on PICU admission when intravenous aminophylline was added to the first-line treatment of acute asthma. They reported that the risk of emesis and nausea was higher in the intravenous aminophylline group. Furthermore, intravenous aminophylline reduced the overall symptom score and improved the percentage of predicted FEV₁.^{10 26}

To our knowledge, we identified all the relevant studies in our search up to May 2024. A comprehensive literature search was performed, and two review authors independently assessed studies for inclusion, extracted data and rated the quality of included studies. We conducted meta-analyses of the data studied when available. We graded the certainty of evidence for each outcome with a 4-level rating scale using the GRADE classification.

Limitations

A limitation of this systematic review is the small sample size in some of the included studies. The studies were published over 15 years ago,

and both respiratory support and acute asthma management have evolved since then. Due to the format used, we could not incorporate data from some studies into our meta-analysis. No recent RCTs have been identified for inclusion in this review. Additionally, none of the studies were conducted in low-income countries, which limits the conclusions drawn from the current results. Furthermore, the primary studies exhibited variable methodologies; clinical heterogeneity was noted, outcome measures were inconsistent and asthma severity scores were assessed differently.

CONCLUSIONS

This meta-analysis shows no evidence that adjunctive intravenous aminophylline enhances early clinical markers of recovery. However, the reduction in intubation rates and improvement in lung function merit further investigation. We cannot rule out beneficial effects that may have gone undetected due to underpowering.

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Contributors CP is the guarantor of this work. CP developed the concept of the review. KM, AH, ISA, AH, AT, AZZ, NA, RS, SA and AKP selected studies for inclusion and abstracted data. KM wrote the first draft. ISA, AH, KM and CP did the data analysis, interpretation data and critically revised the paper for important intellectual content. All authors approved the final version of this article.

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ARTIGO ORIGINAL

Opção de tratamento de segunda linha para crianças até aos 18 anos com agudização grave de asma: uma revisão sistemática e meta-análise de ensaios clínicos randomizados

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RESUMO

Importância A evidência disponível sobre tratamentos de segunda linha para asma grave é limitada.

Objetivos Avaliar a segurança e a eficácia da aminofilina intravenosa, agonistas beta de curta duração intravenosos (SABA), sulfato de magnésio intravenoso, cetamina intravenosa ou adrenalina subcutânea como tratamento de segunda linha para asma grave.

Métodos Incluímos apenas ensaios clínicos randomizados (RCTs) e seguimos as diretrizes internacionais para a realização de revisões sistemáticas. Realizamos uma pesquisa bibliográfica abrangente até maio de 2024. Os desfechos incluíram morbidade, escalonamento de cuidados, duração da hospitalização, eventos adversos, mortalidade e alterações na função pulmonar. Resultados Foram incluídos nove RCTs (total de participantes = 546). Comparada com outros tratamentos, a aminofilina intravenosa não mostrou diferença significativa na duração da hospitalização em horas, exceto em doentes críticos ventilados, que tiveram uma estadia mais curta (diferença média (DM) = -12,99; IC 95% -33,13 a 7,15). A necessidade de medicação intravenosa adicional (RR = 2,17; IC 95% 0,48 a 9,71) e os resultados de gravidade da asma após as intervenções (DM = 0,97; IC 95% -0,91 a 2,85) foram semelhantes. Náuseas e vômitos foram mais frequentes no grupo da aminofilina intravenosa. O grupo SABA intravenoso não mostrou diferença na duração da hospitalização (DM = -10,12; IC 95% -45,74 a 25,49) ou necessidade de ventilação (RR = 0,25; IC 95% 0,03 a 2,21). Não ocorreram eventos adversos graves frequentes. O grupo do sulfato de magnésio intravenoso apresentou menor taxa de hospitalização (RR = 1,52; IC 95% 1,26 a 1,84), menor necessidade de medicação intravenosa adicional (RR = 6,30; IC 95% 2,62 a 15,17) e uma melhoria rápida nos resultados de gravidade da asma ($p < 0,05$).

Conclusão Existe evidência de baixa a muito baixa certeza demonstrando a superioridade de qualquer opção intravenosa de segunda linha para asma aguda. **Número de registo PROSPERO:** CRD42023405226.

INTRODUCTION

This is one of a series of systematic reviews commissioned by the WHO to inform consolidated recommendations for managing common childhood illnesses. The recommendations will update the existing guidance in the WHO Pocket Book of Hospital Care for Children¹ and Integrated Management of Childhood Illness charts.²

Asthma is a serious global health problem with increasing prevalence, especially among children.³ The first line of management of asthma exacerbation includes supportive treatment, administration of short-acting beta2 agonist (SABA), systemic

Key messages

What is known about this topic

- Second-line treatment options for acute severe asthma are limited.
- The choice of medication would be guided by availability, cost, drug system safety, critical care beds and local policies.

What this study adds

- Intravenous magnesium sulphate may lower hospitalisation rates, reduce the need for additional intravenous medications and accelerate the improvement in asthma severity scores. Therefore, it would be a suitable first option for the second-line treatment of acute asthma exacerbations.
- Intravenous short-acting beta agonist (SABA) demonstrated a comparable treatment effect to other therapies regarding the duration of hospital stay, asthma severity scores, paediatric intensive care admission rate and duration and the need for additional intravenous medications.
- Intravenous aminophylline is associated with more nausea and emesis. It could be considered for critically unwell children with acute severe asthma when other treatment modalities failed.

How this study might affect research practice or policy

- Multicentre research would be required to generate high-quality evidence regarding acute severe asthma treatment options.

steroids and consideration of inhaled ipratropium bromide.^{3,4} Children with acute severe asthma refractory to the above first-line management are to be considered for initiation of the second-line treatment/interventions.³⁻⁶ Many options are available for parenteral bronchodilators that were used as a second-line treatment for severe asthma exacerbation, including SABA; epinephrine (epinephrine); magnesium sulphate; methylxanthines such as theophylline or aminophylline; and ketamine.^{4,5} With a few treatment options available, wide variation in self-reported/actual practice and different guidelines and protocols to guide acute



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severe asthma exacerbation management, it is vital to have an updated new evidence synthesis that provides guidance on which to base clinical decisions.⁴

Intravenous SABA, namely terbutaline and salbutamol, is increasingly recommended;⁶ however, evidence is limited.⁷ Travers et al reported that intravenous SABA led to reductions in the need for recurrent inhaled SABA and no reductions in lengths of hospitalisation or paediatric intensive care (PICU) admission.⁷ A retrospective study found an association between early initiation of intravenous terbutaline and reduced respiratory failure, ICU admission and mechanical ventilation.⁸ Intravenous magnesium sulphate has been shown to shorten the length of hospital stay.⁵ Ketamine is a recognised bronchodilator indicated for children in truly refractory status asthmaticus with impending respiratory failure or death requiring mechanical ventilation.^{5,9} Intravenous aminophylline was found to increase nausea and vomiting,⁶ while intravenous SABA was associated with increased tremors, tachycardia and hypotension.^{6,10} This review aimed to assess the safety and efficacy of intravenous aminophylline, intravenous SABA, intravenous magnesium sulphate, intravenous ketamine and subcutaneous (SC) epinephrine as second-line treatment options for acute asthma exacerbation in children aged 18 years and under.

METHODS

We followed the international recommendations for conducting systematic reviews and meta-analyses.¹¹ The protocol was registered with the PROSPERO, registration number CRD42023405226.

Study design and participants, interventions and outcomes

We included randomised controlled trials (RCTs) that compared intravenous aminophylline, intravenous SABA, intravenous magnesium sulphate, intravenous ketamine or SC epinephrine as a second-line treatment in acute asthma exacerbation after the failure of first-line therapies that included supportive treatment, intermittent inhaled SABA and systemic corticosteroids.

We excluded placebo control comparator studies.

The outcome measures were:

- ▶ Morbidity (symptoms, hospitalisation, school absence).
- ▶ Escalation of care (ventilation/PICU admission).
- ▶ Length of stay in hours (in emergency department or hospital).
- ▶ Adverse events.
- ▶ Mortality.
- ▶ Changes in lung function (change in forced expiratory volume and peak expiratory flow).

Publication characteristics and search methods

We did not apply language restrictions and translated relevant studies into English when needed. From inception to June 2023 (updated on 25 May 2024), we searched the following databases: Medline, Embase, Cumulative Index to Nursing and Allied Health (CINAHL), Web of Science (WOS) and the Cochrane Central Register of Controlled Trials (CENTRAL).

We inspected reference lists from retrieved articles and searched the websites www.clinicaltrials.gov and www.controlled-trials.com for unpublished ongoing clinical trials.

Search strategy

Search terms included (attack or exacerbation or acute severe asthma or episodic) AND (SABA or salbutamol or albuterol or terbutaline or adrenaline or epinephrine or magnesium sulphate or aminophylline). See online supplemental appendix 1 for the complete search strategy.

Data extraction and management

Two review authors (NA and AH) independently extracted data that included risk of bias assessment, demographic information, methodology, intervention details and reported outcomes. Any differences in the extracted data were discussed and resolved by consensus and discussion with a third author if needed (ISA). We analysed the extracted data using the Cochrane Collaboration's Review Manager.¹²

Assessment of risk of bias in included studies

Two review authors (KM and AH) used the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions to assess the risk of bias.¹³ They independently evaluated the risk of bias for each study, and any disagreement was resolved by a mutual discussion or involving a third author (ISA and CP). We assessed the risk of bias according to the following domains:

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

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

Data management

For dichotomous data, we reported the risk ratio (RR) and the mean difference (MD) for continuous data. We highlighted all missing data within the Results section. We used an intention-to-treat (ITT) basis of analysis. We used the I^2 statistic¹⁴ to measure heterogeneity among the included RCTs. We considered an I^2 value of:

- ▶ 0%–40% might not be as important.
- ▶ 30%–60% represent moderate heterogeneity.
- ▶ 50%–90% represent substantial heterogeneity.
- ▶ 75%–100% represent considerable heterogeneity.

We explored potential explanations for heterogeneity using sensitivity analyses and subgroup analyses when appropriate. When 10 or more studies were included, we planned to investigate possible publication bias using funnel plots for each outcome.¹⁵

Sensitivity analysis

Sensitivity analyses were planned to explore the potential impact of missing data and any methodological heterogeneity. We assessed the effect of omitting the studies at high risk of bias from the meta-analysis, evaluating their impact on the overall results. We also used both random and fixed-effect models of data synthesis to assess for potential heterogeneity when present.

Summary of findings

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system¹⁶ principles to assess the quality of the body of evidence associated with specific outcomes. The estimate of effect considers the within-study risk of bias that included:

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

RESULTS

Study selection

We identified 2670 citations. Full texts of 91 citations potentially meeting the inclusion criteria were assessed after duplicates were removed and screening of titles and abstracts. 81 studies were excluded: 30 studies were duplicates, 2 were non-RCTs; 25 assessed different interventions, 3 included only adult participants and 22 assessed intravenous asthma medications compared with only placebo treatment option. We included nine RCTs consisting of a total of 546 participants ($n=546$). A flowchart detailing the studies' selection process is shown in figure 1.

Study characteristics

We included only RCTs; the characteristics of the included studies are shown in online supplemental table 1. Participants were children and adolescents aged 18 years and under with acute exacerbation of asthma. The assessment of asthma severity was based on the criteria used by the primary study included.

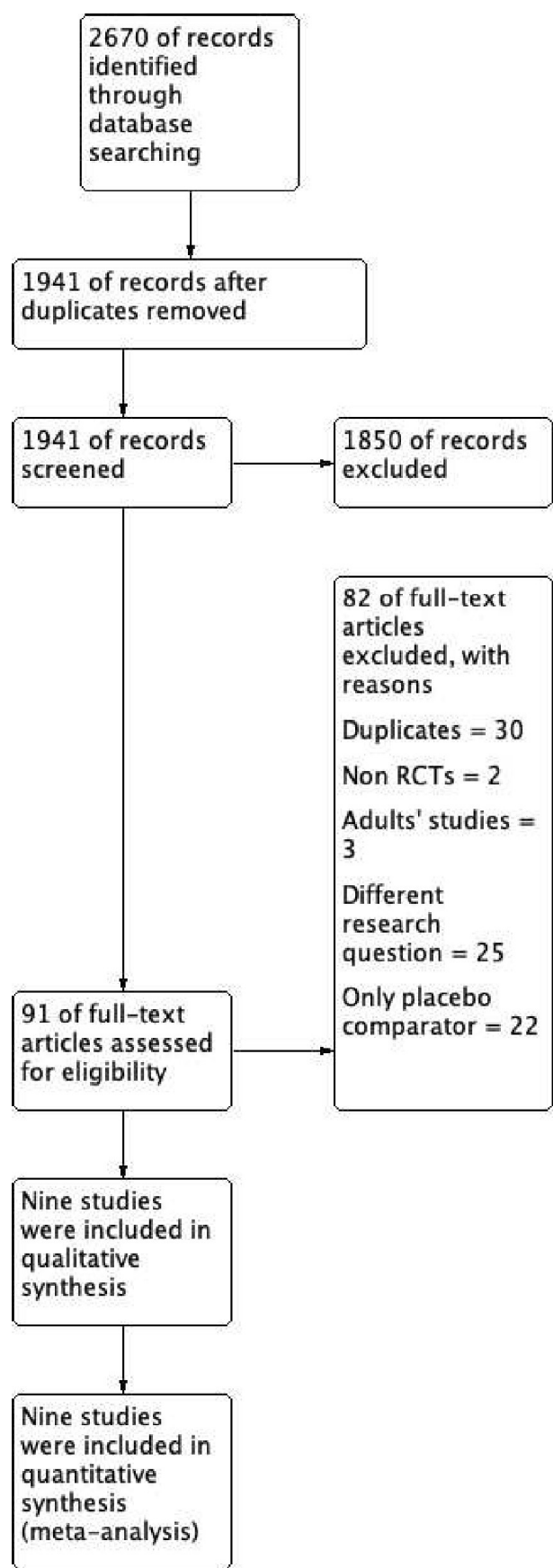


Figure 1 Study flow diagram. RCTs, randomised controlled trials.

Risk of bias

The risk of bias assessment is shown in figure 2 (online supplemental figure 1). Eight of the included studies were classified as low risk of bias regarding random sequence generation,^{17–24} and one study was classified as unclear risk as no further information was shared.²⁵ Six studies^{17–21 23} were classified as low risk for al-

location concealment, and three studies^{22 24 25} were of unclear risk as the authors shared no further information. Four studies^{18,19,23,25} were classified as having a low risk of bias regarding blinding of participants and personnel, while the other five studies were of high risk as these were unblinded studies.^{17 20–22 24} Five studies were classified as low risk for outcome assessments,^{17–19 23 25} and four were high risk.^{20–22 24} All included studies were classified as low risk for incomplete outcome data, selective reporting and other biases.^{17–25}

EFFECT OF THE INTERVENTIONS

Comparison 1: intravenous aminophylline versus other intravenous treatment options

Six studies were included in this comparison (n=410)^{17–22} that assessed intravenous aminophylline versus intravenous SABA, intravenous magnesium sulphate, intravenous ketamine or a combination of intravenous medications.

Hospitalisation rate

Only one study assessed this outcome, comparing intravenous aminophylline to intravenous magnesium sulphate (n=131).²² The hospitalisation rate was significantly lower in the intravenous a combination of intravenous aminophylline and intravenous SABA versus SABA alone.²¹ No significant difference was found (MD=−18.85, 95% CI −40.77 to 3.08, I²=0.57, n=139, low-quality evidence) (online supplemental figure 3a). Sensitivity analysis was done by reanalysing the data using the fixed effect model. The results showed a significantly shorter duration of hospital stay in favour of the intravenous aminophylline group, with substantial

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Boeschoten 2022	+	+	+	+	+	+	+
Daengsuwan 2017	+	?	+	+	+	+	+
Kassisse 2021	+	?	+	+	+	+	+
Ream 2001	+	+	+	+	+	+	+
Roberts 2003	+	+	+	+	+	+	+
Santana 2001	?	?	+	+	+	+	+
Singhi 2014	+	+	+	+	+	+	+
Thwari 2016	+	+	+	+	+	+	+
Wheeler 2005	+	+	+	+	+	+	+

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

heterogeneity ($MD=-1.48$, 95% CI -24.52 to -0.44 , $I^2=0.57$) (online supplemental figure 3b). When we omitted the data of the ventilated participants, results showed no significant difference between the studied groups, with low heterogeneity noted, as shown in online supplemental figure 3c.

PICU admission and duration in hours

PICU admission rate was reported by Kassisse et al²² No significant difference was found between the intravenous aminophylline and the intravenous magnesium sulphate groups ($RR=1.72$, 95% CI 0.53 to 5.61 , $p=0.37$, $n=131$) (online supplemental figure 4).

The duration of PICU admission in hours was reported by two studies^{17 19} that compared intravenous aminophylline, intravenous SABA or the combination of both intravenous SABA and intravenous aminophylline, and no significant difference was found ($MD=-8.16$, 95% CI -20.56 to 4.24 , $I^2=0$, $n=100$) (online supplemental figure 5).

The need for extra asthma intravenous medications

Three studies ($n=204$) reported this outcome that assessed intravenous aminophylline versus intravenous SABA or intravenous magnesium sulphate.^{18 19 22} No significant difference was found ($RR=2.17$, 95% CI 0.48 to 9.71 , $I^2=84\%$, $n=204$, very low-certainty evidence) (figure 3).

However, there was significantly less need for extra intravenous asthma medications when intravenous magnesium sulphate was used²² ($RR=6.30$, 95% CI 2.62 to 15.17 , $p<0.0001$, $n=131$).

Asthma severity score post-intervention

Four studies that assessed intravenous aminophylline versus intravenous SABA, intravenous ketamine or intravenous magnesium sulphate were included.^{18 19 21 22} No significant difference was noted ($MD=0.97$, 95% CI -0.91 to 2.85 , $I^2=94\%$, $n=252$, very low certainty evidence), figure 4. Sensitivity analysis was done by reanalysing data using a fixed effect model, which led to no significant difference in the results. Further analyses of asthma severity scores with relevant results were shared in online supplemental figure 6a, online supplemental figure 6b, and online supplemental figure 7.

The need for mechanical ventilation

One study¹⁸ reported no significant difference in the need for mechanical ventilation when comparing intravenous aminophylline to intravenous SABA (RR 0.35 , 95% CI 0.03 to 3.54 , $p=0.37$, $n=44$) (online supplemental figure 8).

Adverse events

Five studies^{17 19–22} assessed this outcome (online supplemental figure 9). The intravenous aminophylline group had significantly more nausea ($RR=2.80$, 95% CI 1.02 to 7.70 , $I^2=66\%$, $n=187$, low certainty evidence), emesis ($RR=1.74$, 95% CI 1.10 to 2.75 , $I^2=0\%$, $n=135$ moderate certainty evidence) and hypokalaemia that was reported by a single study ($RR=1.56$, 95% CI 1.14 to 2.15 , $p=0.006$, $n=39$). Other reported adverse events were tremors, hy-

pertension, arrhythmias and abdominal pain, with no significant differences noted among the studied groups (online supplemental figure 9).

Comparison 2: intravenous SABA versus other treatments (that were not included in comparison 1)

Two studies were included that assessed intravenous SABA versus: I. intravenous magnesium sulphate.²⁵

II. Intravenous SABA loading dose with SABA infusion versus intravenous placebo loading dose with intravenous SABA infusion.²³

Length of hospital stay in hours

Two studies were included.^{23 25} No significant difference was found between the studied groups ($MD=-10.12$, 95% CI -45.74 to 25.49 , $I^2=59\%$, $n=92$, low certainty evidence) (online supplemental figure 10a). Sensitivity analysis was done by reanalysing the data using the fixed-effect model, which did not affect the overall results (online supplemental figure 10b).

The need for mechanical ventilation

Two studies were included.^{23 25} No significant difference was found ($RR=0.25$, 95% CI 0.03 to 2.21 , $I^2=0\%$, $n=92$, low certainty evidence) online supplemental figure 11.

The need for extra intravenous asthma medications

One study assessed intravenous SABA loading dose with infusion versus intravenous placebo loading with intravenous SABA infusion and reported this outcome.²⁶ There was no difference among the studied groups (RR 4.00 95% CI 0.48 to 33.66 $p=0.20$, $n=58$) (online supplemental figure 12).

Asthma severity score

One study investigated this outcome for intravenous SABA loading dose added to intravenous SABA infusion compared with intravenous SABA infusion plus placebo loading dose.²³ As shown in online supplemental figure 13, the asthma severity score improved significantly in those who received intravenous SABA loading dose ($MD=1.00$, 95% CI 0.61 to 1.39 , $p=0.00001$, $n=58$).

Adverse events

Both included studies^{23 25} reported the following adverse events: arrhythmias, hypotension and tachycardia, as shown in online supplemental figure 14. However, as the total number of events was low, it is difficult to conclude their significance.

Comparison 3: intravenous magnesium sulphate versus other treatment

The single study's results that assessed intravenous magnesium sulphate versus nebulised magnesium sulphate as a second-line treatment were shared in the supplementary file.

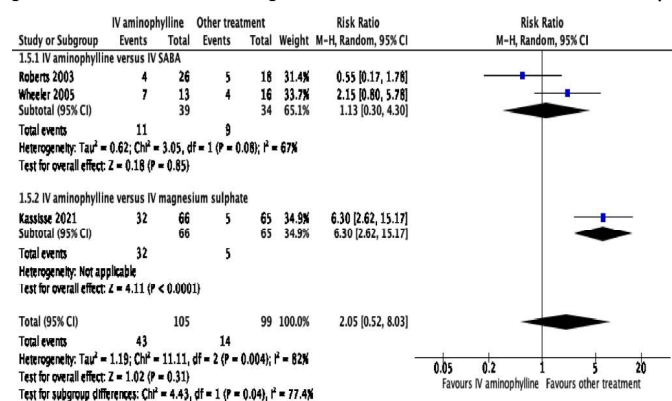


Figure 3 Forest plot of comparison: 1 intravenous aminophylline versus other treatment, outcome: the need for extra asthma intravenous medications. SABA, short-acting beta agonist.

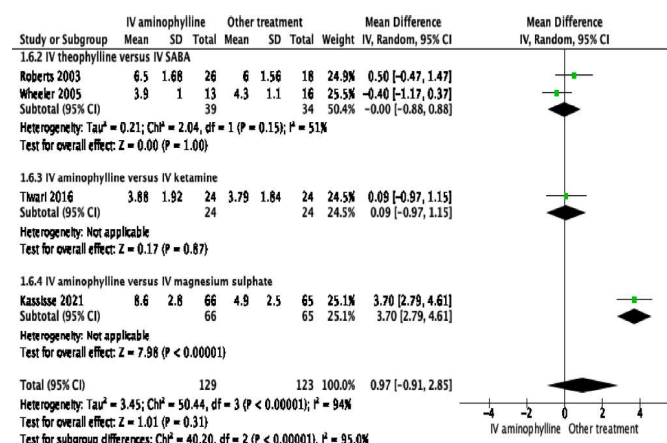


Figure 4 Forest plot of comparison: 1 intravenous aminophylline versus other treatment, outcome: asthma severity scores postintervention. SABA, short-acting beta agonist.

Other comparisons

No studies assessed SC epinephrine as a second-line treatment in acute severe asthma.

Quality of evidence

For the comparison of intravenous aminophylline versus other treatments, the GRADE quality of evidence for the outcome: the length of hospital stay in hours was graded as low certainty evidence, and no significant differences were noted. Asthma severity score, the change in asthma severity score postinterventions and the need for extra intravenous medications were similar between the groups and graded as very low certainty evidence. The outcome adverse events, nausea and emesis were more on the intravenous aminophylline group and graded as low and moderate certainty evidence, respectively, table 1.

For the comparison of intravenous SABA versus other treatments, the GRADE quality of evidence for the outcomes, the length of hospital stay in hours and the need for mechanical ventilation were graded as low certainty evidence, with no difference found between the studied groups.

No frequent serious adverse events were reported in both groups, table 1.

DISCUSSION

We included nine RCTs (n=546) that assessed the intravenous second-line treatment options for acute severe asthma. This review showed that the hospitalisation rate and the need for additional intravenous medications were lower in participants who received intravenous magnesium sulphate. Furthermore, the length of hospital stay was similar among different treatment options; however, further analysis suggested that intravenous aminophylline might have reduced the hospital stay for

critically ill and ventilated participants. Moreover, asthma severity scores improved with intravenous magnesium sulphate, intravenous aminophylline and an intravenous SABA loading dose followed by maintenance. PICU admission rates and duration were similar among all groups. More adverse events were reported with the use of intravenous aminophylline, including nausea, vomiting and hypokalaemia; however, intravenous SABA was associated with fewer reports of tachycardia, hypotension and arrhythmias.

Other systematic reviews reported comparable results to this review's findings. Travers et al concluded that there was no consistent evidence in favour of either intravenous SABA or intravenous aminophylline for children with acute severe asthma.²⁷ Craig and colleagues reported that intravenous magnesium sulphate reduces the length of hospital stay and the hospital admission rate.⁴ They concluded that none of the interventions reduced the PICU admission rate; moreover, nausea and vomiting were more common with intravenous aminophylline use.⁴

This is one of a series of reviews conducted to update the recommendations of paediatric asthma management plans. Network meta-analysis is another suitable option for assessing direct and indirect estimates across a network of interventions, which informs the comparative effectiveness of multiple interventions³³. However, this is beyond the scope of this review.

We performed a comprehensive literature search, and two review authors independently assessed the studies for inclusion, extracted data and rated their quality.

The limitations of this review are due to the small to modest size of the included studies. Furthermore, the primary studies used different methodologies, had clinical heterogeneity, used inconsistent outcome measures and assessed asthma severity scores differently.

Table 1 Summary of findings

Intravenous aminophylline [#] /intravenous SABA [§] as second line compared with other treatment for children with an acute asthma exacerbation						
Patient or population: children with an acute asthma exacerbation						
Setting: in-hospital admissions						
Intervention: intravenous aminophylline [#] /intravenous SABA [§] as second line						
Comparison: other treatment						
	Anticipated absolute effects* (95% CI)					
Outcomes	Risk with other treatment	Risk with intravenous aminophylline[#]/intravenous SABA[§] as second line	Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
Length of hospital stay in hours [#]		MD 18.85 lower (40.77 lower to 3.08 higher)	–	139 (3 RCTs)	⊕⊕○○ Low†‡	
The need for extra intravenous medication [#]	131 per 1000	285 per 1000 (63 to 1000)	RR 2.17 (0.48 to 9.71)	204 (3 RCTs)	⊕○○○ Very low†§¶	
Asthma severity score [#]		MD 0.97 higher (0.91 lower to 2.85 higher)	–	252 (4 RCTs)	⊕○○○ Very low†§¶	
Change in asthma severity score post interventions [#]		MD 0.05 higher (0.56 lower to 0.67 higher)	–	92 (2 RCTs)	⊕○○○ Very low†¶**	
Adverse events—nausea [#]	121 per 1000	340 per 1000 (124 to 936)	RR 2.80 (1.02 to 7.70)	187 (3 RCTs)	⊕⊕○○ Low†††	
Adverse events—emesis [#]	234 per 1000	408 per 1000 (258 to 645)	RR 1.74 (1.10 to 2.75)	135 (3 RCTs)	⊕⊕⊕○ Moderate†	
Length of hospital stay in hours [§]		MD 10.12 lower (45.8 higher to 25.5 higher)	–	92 (2 RCTs)	⊕⊕○○ Low†‡	
Need for mechanical ventilation [§]	65 per 1000	16 per 1000 (2 to 144)	RR 0.25 (0.03 to 2.21)	92 (2 RCTs)	⊕⊕○○ Low†§	

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

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

†Downgraded due to serious risk of bias as one study was unblinded.

‡Downgraded to serious inconsistency due to moderate heterogeneity and wide CI.

§Downgraded to serious imprecision due to high heterogeneity.

¶Downgraded to serious indirectness due to different study medications used.

**Downgraded to serious imprecision due to small sample size.

††Downgraded to serious inconsistency due to moderate heterogeneity.

§, IV SABA ; #, IV aminophylline ; GRADE, Grading of Recommendations Assessment, Development and Evaluation ; MD, mean difference; RR, risk ratio; SABA, short-acting beta agonist.

Conclusions

This review demonstrated that intravenous magnesium sulphate reduced hospitalisation rate and the need for additional intravenous medications. The length of hospital stay was comparable across different treatment options; however, further analysis indicated that intravenous aminophylline may have shortened the hospital stay for critically ill and ventilated participants. Asthma severity scores improved with intravenous magnesium sulphate, intravenous aminophylline and an intravenous SABA loading dose followed by maintenance. PICU admission rates and the duration were similar among all groups. Nausea, vomiting and hypokalaemia were higher among participants who received intravenous aminophylline, and intravenous SABA was associated with a few reports of tachycardia, hypotension and arrhythmias.

Few comparative studies exist on the treatment of acute severe asthma. More research would enable clinicians to draw more decisive conclusions about the most effective treatment options.

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Aplicações atuais e futuras da inteligência artificial no cancro do pulmão e no mesotelioma

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RESUMO

Contexto Existem desafios consideráveis na gestão do cancro do pulmão e do mesotelioma, incluindo complexidade diagnóstica, estratificação terapêutica, deteção precoce e quantificação imagiológica. A incidência variável do mesotelioma também dificulta a prestação equitativa de cuidados de elevada qualidade. Neste contexto, a inteligência artificial (IA) oferece uma variedade de funções assistivas/automatizadas que podem potencialmente melhorar a tomada de decisão clínica, reduzindo simultaneamente desigualdades e atrasos nos percursos assistenciais.

Objetivos Nesta revisão narrativa de ponta, sintetizamos a evidência sobre este tema, com foco particular em ferramentas que utilizam imagens de patologia e radiologia de rotina. Resumimos os pontos fortes e fracos da IA aplicada a funções comuns das equipas multidisciplinares (MDT), incluindo diagnóstico histológico, previsão de resposta terapêutica, deteção e quantificação radiológica e estimativa de sobrevivência. Também revemos métodos emergentes capazes de gerar novos conhecimentos biológicos e as barreiras atuais à implementação, incluindo o acesso a dados de treino de alta qualidade e a existência de infraestruturas regulatórias e técnicas adequadas.

Narrativa Redes neuronais treinadas em imagens de patologia demonstraram utilidade comprovada na classificação histológica, prognóstico, previsão de resposta e sobrevivência. Modelos auto-supervisionados também podem gerar novos conhecimentos sobre características biológicas responsáveis por desfechos adversos. As aplicações em radiologia incluem ferramentas para nódulos pulmonares, que oferecem suporte crítico para programas iminentes de rastreio do cancro do pulmão e para referências urgentes. A IA para segmentação tumoral oferece vantagens particulares no mesotelioma, onde a avaliação de resposta e o estadiamento volumétrico são difíceis para leitores humanos devido ao tamanho do tumor e à complexidade morfológica. A IA é também fundamental para a radiogenómica, permitindo a integração eficaz de características moleculares e radiómicas para a descoberta de marcadores não invasivos de subtipagem molecular e melhor estratificação.

Conclusões As soluções de IA oferecem benefícios potenciais consideráveis em toda a MDT, particularmente em tarefas repetitivas ou demoradas baseadas em imagens de patologia e radiologia. A utilização eficaz desta tecnologia é crucial para o rastreio do cancro do pulmão e para a prestação eficiente de funções diagnósticas e preditivas cada vez mais complexas nas equipas multidisciplinares. A investigação futura em IA deve envolver resultados transparentes e interpretáveis que ajudem a explicar a base da tomada de decisão apoiada por IA.

INTRODUCTION

In the UK, lung cancer remains the most common cause of cancer-related death¹ and mesothelioma incidence is among the highest globally.² Considerable progress has been made in both malignancies, but significant challenges remain, including maximising gains from screening and rapid diagnostic pathways for lung cancer, and delivery of equitable high-quality mesothelioma care in healthcare systems with variable incidence and associated exper-

tise.³ In mesothelioma, measurement of treatment response is also uniquely challenging due to tumour size and shape,⁴ while accurate stratification is of critical importance in both cancers, given the increasing toxicity and cost of available therapies.

To meet these challenges, clinicians and healthcare systems need to embrace new technologies, with many novel tools underpinned by 'artificial intelligence (AI)'. Broadly speaking, AI refers to predictive models capable of performing tasks that would otherwise require human intelligence. Within AI, machine learning (ML) enables computers to make predictions based on data without explicit task programming. Deep learning (DL) is a subset of ML, which uses layered structures to model non-linear relationships in large-scale data sets, while radiomics applies these methods to imaging data, typically allowing extraction of information not perceivable by human readers. With adequate training, AI tools demonstrate considerable performance in recognition, linkage and outcome prediction based on medical images, which form the substrate of many common multidisciplinary team (MDT) functions. Appropriately leveraged, AI can therefore enhance and support pathway delivery and clinical decision-making. In this narrative review, we summarise the current state of the art regarding the application of AI to lung cancer and mesothelioma. We focus on tools that address important clinical and healthcare system challenges and conclude by summarising implementation challenges and potential solutions that would accelerate progress and improve understanding of AI by clinicians and patients. To synthesise the available evidence, we searched PubMed and Google Scholar using combinations of the following terms 'AI', 'machine learning', 'deep learning', 'radiomics', 'lung cancer', 'mesothelioma'.

LUNG CANCER

The last decade has seen the development of robot-assisted and lung-sparing surgical resection,⁵ stereotactic ablative radiotherapy⁶ and an expanding armamentarium of systemic therapies for metastatic disease.⁷⁻⁸ However, reducing the recurrence rate and further extending survival remain considerable challenges, either through screening, better selection and/or more effective deployment of adjuvant therapies. Application of AI is well aligned with these goals.

Pathology AI in lung cancer

Pathology AI encompasses a broad range of applications and is therefore a useful starting point. These include networks trained for specific tasks using classical supervised methods, self-supervised models capable of generating new biological insights and large foundation models (see Self-supervised learning (SSL)). Visual-language models have also recently emerged, trained using pathology image-text pairs extracted from social media and prior publications.⁹⁻¹⁰



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Supervised learning has generally been used to train models that assist pathologists with defined clinical tasks, resulting in improved efficiency, accuracy or consistency. Supervised models are resource-intensive to train, requiring high-quality annotation ('ground truth') for every case, and a specific model for every task. In their purest form, supervised models are also limited by the accuracy of the human 'gold standard', which in many settings is neither perfect nor consistent. Their focused utility may be useful for an adjunctive diagnostic test, by facilitating direct evaluation against a reference standard (desirable for regulatory approval), but it is a poor surrogate for the actual function required. In 'real life', multiple tasks need to be performed on single images/samples (eg, diagnostic classification, grading, immunohistochemical scoring) and training from scratch for each task becomes prohibitive. Below, we discuss three tasks in which considerable progress has been made using supervised AI. Practical deployment may depend, in part, on the resources available, including pathologist time. In the medium term, they are likely to operate as assistive tools. However, the criteria for expert pathologist review may vary according to available resources and the relative risks and benefits of AI support.

Histological classification

Differentiation between lung squamous cell and lung adenocarcinoma (LUAD) is straightforward in most cases. However, the task becomes more difficult if biopsy material is limited, or the tumour is poorly differentiated. Coudray et al trained a convolutional neural network (CNN) to assist, reporting a very high area under the curve (AUC) of 0.913–0.977 on frozen sections, 0.833–0.975 on paraffin-embedded material and 0.834–0.928 on smaller biopsies¹¹ (where AUC 0.5=prediction value no better than guesswork and AUC 1=perfect prediction). Notably, the model's AUC was 0.809–0.822 in cases deemed 'unclassifiable' by a pathologist on morphological grounds. Models of this type are likely to have most clinical utility in morphologically difficult cases, and subsequent studies including small-cell¹² and large-cell neuroendocrine carcinoma¹³ are therefore important.

Prognostication

Histological grading is important for prognostication in LUAD, although imperfect as recently reported.¹⁴ The moderate prognostic value of grade in part reflects complex morphology and intratumour heterogeneity, which make consistent grading by pathologists difficult. Xiao et al reported one of the first efforts to automate grading using a graph convolutional network deployed on H&E-stained whole slide images (WSIs).¹⁵ More recently, Pan et al trained ANORAK to quantitatively encode growth patterns and automatically assign grade¹⁶ in 1372 stage I LUADs from four independent cohorts. ANORAK demonstrated reasonable agreement with pathologist-defined grade and added independent prognostic value beyond that derived from human scores.¹⁶ ANORAK also identified a new prognostically important growth pattern, called 'acinar scattering'.¹⁶ Less supervised methods have also been evaluated, allowing ML to discover new associations between morphology and adverse prognosis. Early studies used morphometry, including nuclear features^{17,18} or tumour contours,¹⁹ and while these methods can be easily understood, they, by definition, restrict learning to features that are preclassified as important. Unsupervised methods are not constrained by such hypotheses as discussed under 'Self-supervised Learning'.

Definition of PD-L1 status and prediction of immunotherapy response

Programmed death-ligand 1 (PD-L1) immunohistochemistry (IHC) is routinely performed in all non-small cell lung cancer (NSCLC) cases but is an imperfect biomarker for immunotherapy (IO) response, with a weighted AUC of only 0.65 reported in a recent meta-analysis.²⁰ This predictive uncertainty probably reflects multiple sources of variance, including tumour heterogeneity and inconsistency in PD-L1 assay performance and subsequent scoring by pathologists. Recent studies have successfully validated

automated PD-L1 reading using AI, with multiple models leading to improved interobserver concordance among pathologists.^{21–24} However, these results remain vulnerable to PD-L1 assay variances, including those related to the need for specific assays for specific drugs ('companion testing'). An alternative approach is to use AI to directly decipher undiscovered morphology in the original H&E slide, thereby predicting PD-L1 status based on the H&E, or ideally directly predicting subsequent IO response. Sha et al were able to predict PD-L1 status from H&E-stained WSIs with moderate success in a histologically mixed cohort of NSCLC (AUC 0.67–0.81).²⁵ Ligerio et al trained a weakly supervised DL model that demonstrated strong concordance with PD-L1 status (AUC 0.88 and 0.80 in independent cohorts) and improved prediction over human scoring. Explainability analyses in this study revealed that the model had integrated morphological features such as lymphocyte aggregates, not just the pigment on the PD-L1 slides.²⁶ Training new models on therapeutic response rather than PD-L1 status frees the model of the assumption that current assays entirely represent the ground truth. Hu et al reported moderate performance of such a model, with an AUC of 0.65 (0.49–0.78) for IO response. Tumour mutational burden (TMB) has recently emerged as an alternative predictor of IO response,^{27,28} but testing requires additional expense and use of finite tissue. Sadhwani et al recently reported a DL method that successfully inferred TMB status from LUAD growth patterns on H&E-stained WSI,²⁹ underscoring the importance of integrated histological patterns in biomarker prediction, a task to which AI is well suited.

Self-supervised learning

The shortcomings of supervised models can be addressed through SSL. This includes the generation of 'foundation models', which are large, general-purpose models, which after training (typically on tens of thousands of images) can be applied flexibly to downstream tasks with minimal additional training (see figure 1A for an example). While this approach initially requires access to large image resources, it delivers broader capabilities without the need for a bespoke model for each task, for example, recognition of histological features across cancer types and multiple magnifications (see figure 1B). Numerous large foundation models have been reported, performing well in standard tasks such as histological classification.^{10,30–34} The flexibility of these models has obvious clinical advantages, and the outputs of some can also help users understand how the model is learning. SSL-discovered features, typically groups of images displaying similar morphology, can be reviewed by pathologists, offering insight into the basis on which classifications are being made.^{33,34} While still exploratory, foundation models therefore hold enormous promise.

Radiology AI in lung cancer

Most patients with lung cancer present with advanced, incurable disease.³⁵ Improvements in early detection are therefore of critical importance, and successful implementation of lung cancer screening is one important means to achieve this.

Implementation of lung cancer screening and early detection

Computer-aided adjuncts to lung cancer screening include fully automated nodule detection and segmentation tools. Automated tools for CT have shown considerable diagnostic utility, including sensitivities between 0.705 and 0.987, AUCs of 0.856–0.96 and accuracies of up to 97.8%.^{36–42} AI-assisted nodule reading has also been shown to outperform human radiologists, irrespective of nodule size,^{43,44} supporting the deployment of AI tools for chest radiograph and CT interpretation in multiple National Health Service (NHS) trusts.⁴⁵ However, nodule segmentation algorithms are also associated with variation by software, leading to concerns regarding the consistency of the data input used for risk prediction algorithms. The best validated of these is the Brock model,⁴⁶ which codifies features like size, location and spiculation into a positive (referral for investigation needed), intermediate (surveillance recommended) or negative (not cancer) result. Recently, a CNN,

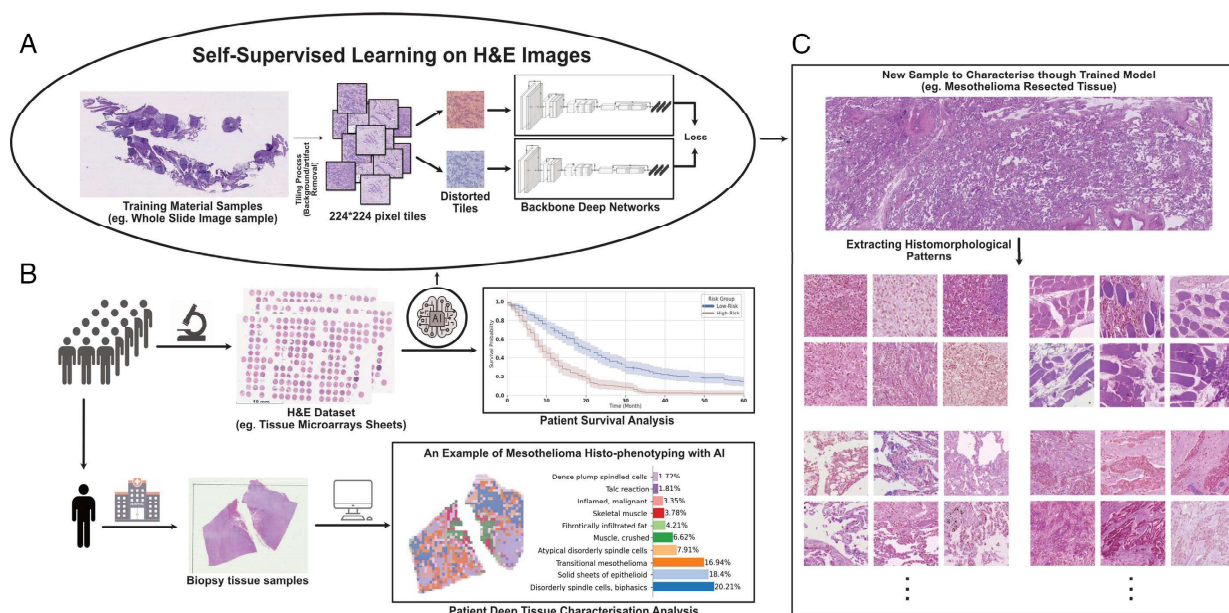


Figure 1 (A) A self-supervised learning approach can be applied to H&E-stained whole slide images or tissue microarrays allowing automated extraction of histomorphology patterns. This workflow begins with training of deep learning models on tissue samples, where images are tiled into small patches and augmented for robust feature learning. (B) AI-driven histophenotyping enables deep tissue characterisation, aiding in patient risk stratification and survival analysis. The insights gained facilitate precision oncology by identifying key tissue structures and their clinical relevance in lung cancer and mesothelioma. (C) To infer and evaluate, the trained model is applied to new samples. Extraction of histomorphological patterns associated with classification allows a pathologist to understand what the model has learnt and the basis of any classification made. AI, artificial intelligence.

trained on annotated NLST CT images, outperformed this traditional pipeline in predicting the outcome of 1397 nodules in 1187 patients in the IDEAL study.⁴⁷ A recent systematic review of CE-marked AI software has similarly reported increased sensitivity for identifying actionable or malignant nodules (+3%–20%) at the expense of reduced specificity (–3%–8%), potentially resulting in unnecessary surveillance and overdiagnosis.⁴⁸ The DOLCE study is currently prospectively evaluating an AI-assisted CT-based lung cancer prediction tool across 2000 patients in 12 UK centres, with early analyses aimed at determining whether AI guidance can safely increase discharge rates of benign nodules and expedite cancer diagnoses.⁴⁹ Depending on the results of studies like DOLCE, it is likely that AI engines will generate screening reports in the near future, including guidance on the frequency of surveillance imaging required, replacing iterative nodule measurement and risk protocols.⁵⁰ In the UK, the DART consortium is currently driving practical implementation.⁵¹

Nodule outcome prediction

CNNs have shown excellent performance in discriminating between subsolid nodules (SSNs) on CT scan that will persist and transitory lesions of little clinical significance. In this setting, Huang et al reported an accuracy of 85.9%⁵² based on a single baseline CT, with the AI network outperforming human readers. Qi et al reported similar performance in the assessment of pure ground glass SSNs (accuracy 96.5%).⁵³ Radiomic tools have also recently reported excellent capability in discriminating between benign and malignant CT nodules.^{54–55} The ongoing LungIMPACT study is assessing a class II CE-approved tool that flags pulmonary nodules detected on chest radiographs in real time, potentially reducing time to lung cancer diagnosis by enabling automated direct-to-CT scheduling.⁵⁶ These capabilities have obvious potential to reduce radiology workload and anxiety for patients referred for investigation or screening.

Tumour segmentation, including for radiotherapy planning

Lung tumour volume, measured without AI assistance, better predicts survival than a change in unidimensional RECIST (Response Evaluation Criteria in Solid Tumours) Score.⁵⁷ Trained DL models can automate volumetric segmentation, and a recent meta-analysis of 37 studies reported promising but varied per-

formance (pooled Dice Score 79%; 95% CI 76% to 83%, which equates to moderate accuracy).⁵⁸ Accuracy was generally highest in studies of smaller, earlier stage tumours, with improving performance over time (post-2022).⁵⁸ This highlights the need for continued improvement of AI segmentation tools, with additional training needed in diverse cohorts including more advanced disease, where discrimination between tumour and adjacent soft tissue structures is most challenging. AI-assisted segmentation has also shown considerable utility in radiotherapy planning. In 2022, Hosny et al reported training and validation of DL models based on 2208 patients from the USA, the Netherlands, Canada and China. The models yielded target volumes with equivalent dose coverage to that of expert manual annotators, and AI assistance led to a 65% reduction in segmentation time and a 32% reduction in interobserver variability.⁵⁹

Radiogenomics and prediction of response

Radiogenomics involves AI integration of radiological data with molecular and genomic information to extract actionable phenotypical labelling from non-invasive imaging, for example, the presence of a sensitising epidermal growth factor receptor (EGFR) mutation. This has the potential to democratise testing for precision therapies to lower resourced healthcare settings and to reduce delays in all systems. The latter is important because even in well-funded systems, sequential testing for single driver genes remains common, reflecting the costs of broader next generation sequencing (NGS) assays. This may result in weeks of testing before precision-guided therapy can be started. Shao et al recently reported successful training of a multilabel, multitask deep CNN, using NGS and IHC data combined with 1052 radiomic features extracted from CTs in 1096 patients. Using 20 radiomic features, the trained network was able to reliably identify genotypes defined by a 10-marker panel (AUC 0.856), with better performance based on a simpler panel of EGFR and PD-L1 only (AUC 0.868).⁶⁰

MESOTHELIOMA

Management of mesothelioma is complicated by extreme heterogeneity in survival outcomes,⁶¹ challenging histology and complex tumour morphology.⁶² Recent years have, however, seen considerable progress in understanding the molecular basis of the di-

sease^{63,64} and approval of combination IO as a new first-line therapy.⁶⁵ It is now understood that in patients with the more aggressive non-epithelioid histological subtype, selection of first-line IO over chemotherapy is important, with enduring benefits observed in some patients.⁶⁶ This progress highlights the need to deliver accurate histological subclassification, better prognostication and accurate disease quantification.

Pathology AI in mesothelioma

Diagnosis

Reliable discrimination between benign reactive pleural thickening and non-epithelioid mesothelioma is a considerable challenge for pathologists and one of the most common reasons for diagnostic delay. The tendency for rapid progression in non-epithelioid patients, combined with the potential for long-term survival extension with combination IO, makes accurate subtyping a major clinical priority. Naso et al recently reported SpindleMesoNet, a weakly supervised recurrent neural network trained to distinguish between subtypes. Each WSI was first divided into 512 × 512-pixel 'tiles', generating tens to hundreds of thousands of images. SpindleMesoNet demonstrated 92.5% accuracy (85.7% sensitivity, 100% specificity), which was superior to three expert pathologists.⁶⁷ This demonstrates AI's potential to extend subspecialty pathology expertise, typically limited to higher-volume mesothelioma centres, to all patients, reducing delay and improving access to therapy.

Histological classification

Current guidelines recommend histological classification into epithelioid and sarcomatoid subtypes based on cellular morphology, with biphasic arbitrarily defined by the presence of at least 10% sarcomatoid appearance. This has important therapeutic implications relating to IO and major prognostic implications but fails to acknowledge the spectrum of histologies present within patients. In 2023, Eastwood et al reported Meso-Graph, a graph neural network for automatic profiling of histological subtype from H&E-stained tissue microarray (TMAs)⁶⁸ instead of WSIs. TMAs are composed of multiple tissue cores on a single slide, providing a high-density, standardised data set ideal for DL. In this study, tissue structures were modelled as graphs, with nodes representing key cellular features (eg, intensity, neighbourhood-cell counts, nuclear morphometrics features) and edges capturing spatial and phenotypical relationships, with training performed on 234 cores from 90 patients and external validation on 258 cores from 77 patients.⁶⁸ Meso-Graph reliably predicted histological subtype (AUC>0.85) and produced a quantitative measure that positioned each tumour on the epithelioid-sarcomatoid spectrum. This derived 'MesoScore' then independently predicted survival.⁶⁸ Using the same cohort, the same group also reported a different approach to subtyping based on multiple-instance learning, called PINS,⁶⁹ which highlighted morphological patterns specific to each subtype.

Transitional mesothelioma (TM) is a rare histological subtype that has epithelioid-like morphology, but a prognosis closer to sarcomatoid cases. Recent guidelines tentatively positioned TM under both categories, pending more data, and the therapeutic implications of TM are therefore uncertain. A recent study by Galateau Salle et al combined bulk RNA sequencing with a weakly supervised AI method, CHOWDER,⁷⁰ to better characterise TM. Through iterative learning, CHOWDER was able to assign a transitional score to each tile based on its contribution to correct classification of cases as TM or not. It was then able to classify WSIs as TM or non-TM with 94% cross-validated accuracy.⁷¹ Interestingly, unsupervised clustering of the transcriptomic data revealed that TM was more closely aligned to sarcomatoid than epithelioid comparators in this cohort.

Survival prediction

Survival models in mesothelioma typically rely on clinical parameters, including histological subtype, performance status and selected blood parameters. However, the prognostic value of these

routinely available metrics is limited, being previously estimated to improve survival predictions over chance by only 22%.⁶¹ Recent advances in ML, coupled with increasing access to suitable data sets, have enabled survival modelling based on richer data sets, including genomic/molecular data and pathology images. In 2019, Courtiol et al reported the performance of MesoNet, a CNN trained using tiled images from 2300 cases (up to 10 000 tiles per WSI). Training the multilayered network based on the most extreme tile risk scores led to a single risk score per patient and superior prognostication compared with histological grading by expert pathologists.⁷² The study also highlighted that image tiles most powerfully associated with adverse prognosis were in the stroma, not tumour cells, emphasising the importance of the tumour microenvironment (TME).

The mesothelioma TME has a rich stromal component; however, the dynamic interactions between tumour cells and adjacent fibroblasts remain incompletely understood. Ollila et al evaluated location-specific expression of seven mesenchymal markers using multiplex immunofluorescence (mIF), then trained an AI model to detect mIF features that proved prognostically important (high platelet-derived growth factor receptor beta expression in tumour cells, and high-secreted protein acidic and cysteine rich in stromal fibroblasts).⁷³ This approach illustrates the potential for AI models to supplant more expensive tools like mIF, extending biological enquiry into archival tissue resources that could not be queried at scale with the more expensive methods.

Pathology AI studies have also been reported in peritoneal mesothelioma, including the recently reported MPeMSupervisedSurv model, which reported prediction survival in 131 cases with moderate success (C-index 0.66).⁷⁴

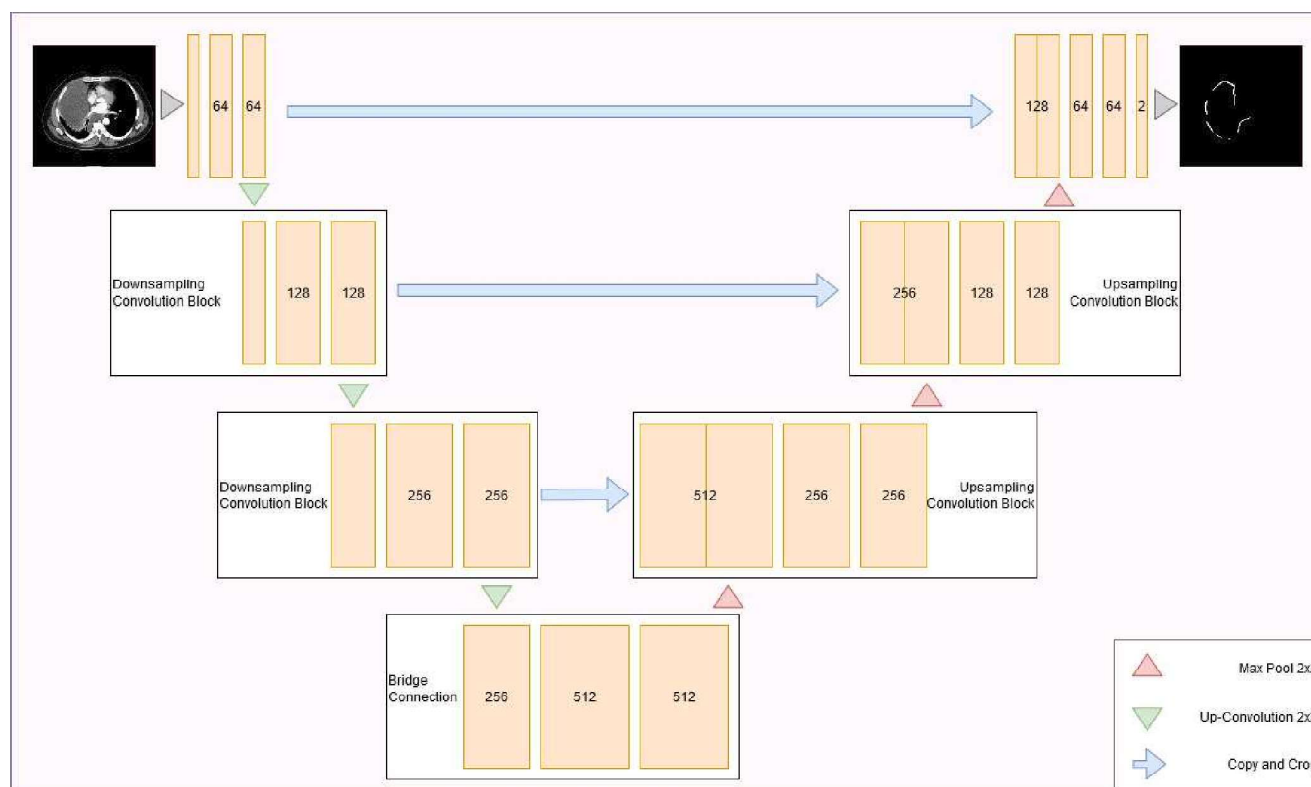
Radiology AI in mesothelioma

The radiological appearance of mesothelioma is variable, but the disease is classically associated with an ipsilateral pleural effusion (observed in 89% of cases in a recent large multicentre diagnostic study)^{75–76} and pleural thickening that is typically nodular and enhancing.⁷⁷ Archetypal 'rind-like' pleural tumour is absent in earlier stages of disease, and tumour visualisation is highly sensitive to contrast timing, with peak contrast uptake not occurring until 4 mins postcontrast injection.⁷⁷ In previous studies, the diagnostic sensitivity of CT for pleural mesothelioma was only 58%–68%,^{78,79} with up to 4 in 10 patients only reported to have a non-specific effusion. In one of these studies, reporting by an expert thoracic radiologist significantly improved performance,^{78–79} emphasising the variability of human readers. While volumetric assessment for staging is logical and supported by multiple prior studies,^{80–81} this remains aspirational in clinical practice. Deployment of volumetry has proven impractical using human readers, due to the time required and the interobserver variation associated with this workflow.^{82–83} In this context, AI-assisted and fully automated radiology pipelines have obvious potential for enhanced consistency and improved quality.

Detection and characterisation

Multiple studies have reported disease classifiers (mesothelioma present or not) based on ML models that combine clinical features with CT-derived features (eg, nodular pleural thickening, plaques, fissural or circumferential pleural abnormalities).^{84–87} While many of these studies report AUCs>0.9, suggesting excellent performance, the control cohorts used are frequently normal cases,^{84–85} or cases of uncertain aetiology,⁸⁷ and much of the classification relies on non-CT features. In the absence of a clinical rationale for population screening for mesothelioma, the most relevant clinical question for AI is whether mesothelioma can be discriminated from other forms of pleural disease in patients presenting with symptoms. In this setting, using an intention to diagnose, although retrospective cohort, Kitajima et al reported encouraging performance (AUC 0.825) of a CNN trained on integrated positron emission tomography (PET)/CT images only.⁸⁸ This study included appropriate patients and controls for training (n=525; 314 mesothelioma, 211 benign pleural disease) and validation (n=174;

A



B

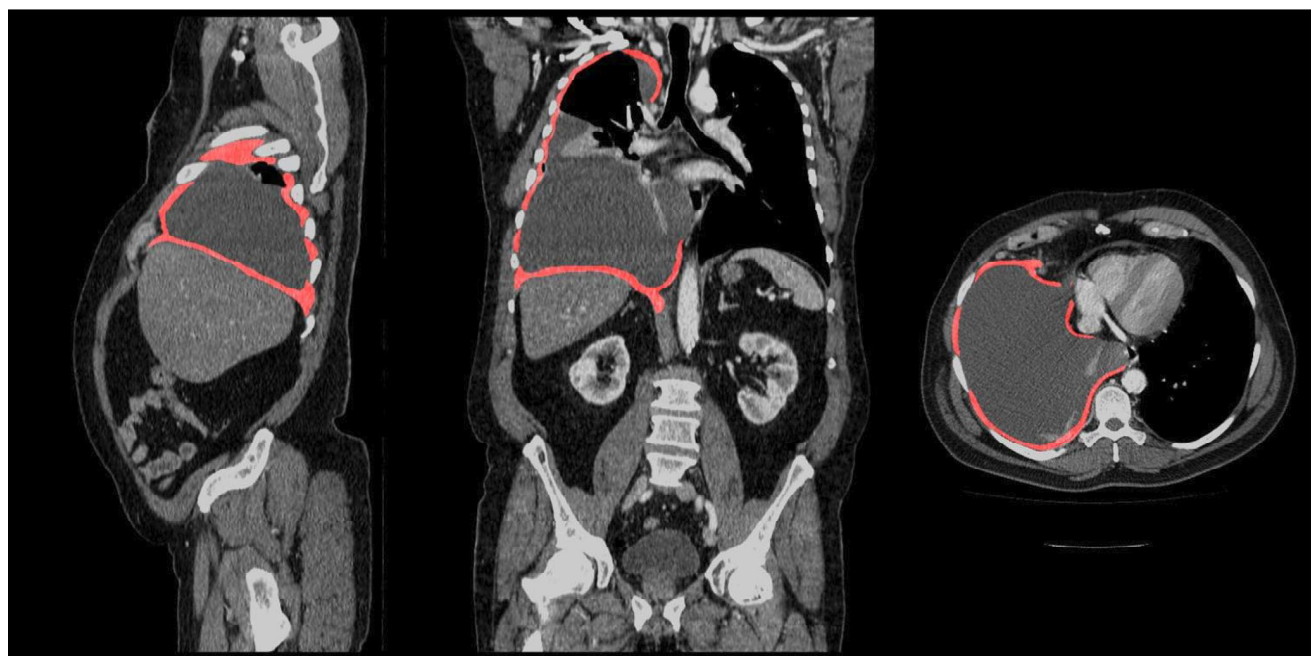


Figure 2 (A) A general U-Net architecture for image segmentation. A full 3D-CT scan (or a single 2D slice) is ingested into the convolutional neural network via successive downsampling blocks, reducing the spatial dimensions by half, but doubling the number of extracted features. To avoid loss of salient low-dimensional features, skip connections transfer features from the downsampling path to the corresponding upsampling blocks by copying and cropping around the central regions. This enables more accurate recovery of spatial detail, resulting in a refined binary segmentation map that delineates the target region with improved precision. (B) A contrast-enhanced CT scan from a patient with right pleural mesothelioma. Fully automated AI-generated tumour segmentation is shown in red. Selected sagittal (left), coronal (middle) and axial (right) slices are shown.

102 mesothelioma, 72 benign pleural disease), but classifier performance was still enhanced (AUC 0.896) by addition of clinical features (eg, age, gender). External validity of these data is, unfortunately,

negatively affected by the limited role of integrated PET/CT as a primary diagnostic modality. At present, therefore, the radiological detection of mesothelioma using AI remains a research

goal, but suitably trained models are likely to support radiologists in this task.

Volumetric quantification

Unlike most solid tumours, mesothelioma conforms to a non-spherical growth pattern, violating the assumptions underpinning use of simple unidimensional measurements as a surrogate for true volume, which is needed for accurate staging and response assessment. For response assessment, 'modified' RECIST (mRECIST) criteria⁸⁹ have been developed to mitigate confounding effects, in lieu of practical tools for true volumetric quantification. For staging, the latest (ninth) iteration of the staging system has introduced tumour thickness as a surrogate of volume,⁹⁰ but volumetric quantification remains the goal. Using mRECIST, measurements by radiologists vary by up to 30%,⁴ potentially leading to different response classification based on the same CT scan. Multiple computer-aided assists have therefore been tested, using linear and shape-based interpolations,^{91–93} hierarchical segmentation using diffusion and k-means,⁹⁴ random walk⁹⁵ and texture analysis.⁹⁶ However, these tools remain heavily reliant on expert radiologist input and curation of the final volume. CNNs have the potential to be less dependent, and several recent studies have reported semiautomatic, or two-stage processes based on CT^{97–98} and PET/CT.⁸⁸ Figure 2 shows an example of a typical CNN architecture, accompanied by an example of AI-generated tumour segmentation. In 2021, Kidd et al were the first to report the performance of a fully automated CNN for this purpose,⁹⁹ including excellent correlation and strong agreement with human annotations (validation $r=0.851$, Bland-Altman mean bias $+31\text{ cm}^3$, $p=0.182$). In more recent conference proceedings, Lipman et al reported encouraging performance using the ARTEMIS CNN to measure response on CTs from previous trials.¹⁰⁰ Moving forward, rigorous external validation studies are needed, including tuning of optimal thresholds for volumetric response, since previous data suggest that mRECIST criteria (partial response: -30% , progressive disease: $+20\%$) may be poorly calibrated to volumetric change. Both Kidd et al⁹⁹ and Frauenfelder et al⁹¹ observed a high rate of stable disease using volumetric measures, and different thresholds may be needed to leverage the higher sensitivity of these observations.

CHALLENGES AND FUTURE APPLICATIONS

AI tools have the potential to automate or assist in many of the image-based decisions made in the MDT. However, several important challenges remain, which, if not addressed, will slow the careful clinical validation still needed for many tools, subsequent deployment and the translation of benefits to patients and healthcare systems. From a technical standpoint, the foremost of these is data availability. AI network architectures and associated computational techniques are sufficiently advanced to learn most clinical tasks, but many state-of-the-art AI practitioners are based outside healthcare systems, including the NHS. This makes it difficult to engage the best models with the large volumes of data needed for training, optimisation and validation at scale. In the pathology setting, large-scale foundation models address this, in part, but the path to clinical validation using such models remains uncharted. Development of trusted research or secure data environments (including environments inside the NHS) that allow AI practitioners from industry and academic sectors to safely interact with large data sets is likely to be of critical importance. The recent Sudlow Review¹⁰¹ on UK health data research infrastructure highlighted the importance of linkage and integration of systems across the UK, removing unnecessary barriers and regulatory complexity. Extensive engagement with patients in the design and delivery of the governance and ethical controls for this infrastructure is clearly essential. AI methods and outputs also need to become more understandable to clinicians and patients. One major obstacle to trust in AI is the perception that AI decision-making is opaque, making 'explainability' an important aspect for future tools, alongside robust handling of sources of bias in validation studies. This will support clinical adoption

alongside traditional performance metrics needed for regulatory approval. AI will then be well positioned to support clinicians to make better decisions with their patients.

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ARTIGO ORIGINAL

Efetividade e segurança no mundo real do nirsevimab, da vacina materna contra o VSR e das vacinas contra o VSR para adultos mais velhos: uma revisão sistemática viva e meta-análise

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RESUMO

Contexto O anticorpo monoclonal de longa duração nirsevimab e as vacinas contra o vírus sincicial respiratório (VSR) tornaram-se disponíveis em 2023 para a prevenção de doença grave associada ao VSR. Embora os ensaios clínicos tenham demonstrado boa eficácia e segurança, os seus critérios de inclusão restritivos, tamanhos amostrais reduzidos e acompanhamento curto limitam a generalização dos resultados. O nosso objetivo foi sintetizar a evidência do mundo real sobre a eficácia e segurança do nirsevimab, da vacina materna contra o VSR e das vacinas contra o VSR para adultos mais velhos.

Métodos Foi realizada uma revisão sistemática e meta-análise, com pesquisas atualizadas mensalmente (cinco ciclos) em três bases de dados. Foram incluídos estudos publicados entre 1 de dezembro de 2022 e 10 de março de 2025. As meta-análises sobre a eficácia do nirsevimab e das vacinas contra o VSR foram conduzidas utilizando um modelo de efeitos aleatórios. Os dados de segurança foram sintetizados de forma narrativa.

Resultados Foram incluídas 50 publicações, abrangendo aproximadamente 7,6 milhões de pessoas. O nirsevimab demonstrou: 80,7% de eficácia (IC 95%: 75,7%–85,7%; sete estudos) contra visitas ao serviço de urgência relacionadas com VSR, 80,7% de eficácia (IC 95%: 76,1%–85,2%; 17 estudos) contra hospitalizações e 75,6% de eficácia (IC 95%: 63,3%–87,9%; oito estudos) contra admissões em unidades de cuidados intensivos. A eficácia das vacinas contra o VSR em adultos mais velhos contra hospitalizações relacionadas com VSR foi de 79,6% (IC 95%: 73,8%–85,3%; três estudos). Não foram encontrados dados de eficácia para a vacina materna contra o VSR. Nenhum evento adverso grave foi reportado para o nirsevimab. As vacinas contra o VSR em adultos mais velhos apresentaram menos de 10 casos de síndrome de Guillain-Barré por milhão de doses. Não foram reportados eventos adversos graves para a vacina materna contra o VSR, embora a evidência seja limitada.

Conclusões A nossa revisão demonstrou elevada eficácia do nirsevimab na redução da utilização de cuidados de saúde relacionados com o VSR em lactentes, bem como um perfil de segurança favorável. São necessários mais dados para avaliar as vacinas contra o VSR em grávidas e adultos mais velhos.

Número de registo PROSPERO: CRD42025643585.

INTRODUCTION

Respiratory syncytial virus (RSV) is a common seasonal cause of significant morbidity and mortality associated with acute lower respiratory tract illness (LRTI) in infants and older adults.^{1 2} The burden on healthcare systems is substantial, particularly among infants in their first year of life and adults aged 60 years and above.^{2 3} Each year, RSV is re-

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- In clinical trials, nirsevimab, the respiratory syncytial virus (RSV) maternal vaccine (ABRYSVO, Pfizer), and the RSV vaccine for adults aged 60 years or older showed great efficacy in reducing RSV-related lower respiratory tract infections, with no substantial safety concerns.
- However, restrictive inclusion criteria, small sample sizes and short follow-up in clinical trials limit the generalisability of efficacy and safety findings to the general population.

WHAT THIS STUDY ADDS

- This is the first living systematic review to evaluate effectiveness and safety of RSV immunisation programmes in the real world.
- Our study confirmed the high effectiveness of nirsevimab and RSV vaccines for older adults, as well as the favourable safety of these immunisation products in real-world conditions. No effectiveness data were available for RSV maternal vaccine.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- In addition to building public confidence in RSV immunisation approaches, our findings highlight areas for further research, such as the waning of immunisation effectiveness over time and population subgroups that need to be studied in more detail as new evidence emerges.

sponsible for approximately 33 million episodes of LRTI in children under 5 years old, leading to about 3.6 million hospitalisations and 118 200 deaths globally.³ Notably, over 95% of RSV-related LRTI cases and more than 97% of RSV-related deaths occur in low- and middle-income countries (LMICs), underscoring the substantial global health burden of RSV, especially in resource-limited settings.¹ For older adults, the burden of RSV is also significant, though not as extensively studied as in young children.²

Recent estimates indicate that, annually in the USA, RSV leads to approximately 60 000–160 000 hospitalisations and 6000–10 000 deaths among adults aged 65 years and older.⁴

In response, passive immunisation with nirsevimab for infants and the maternal vaccine (bivalent RSV prefusion F (RSVpreF) protein-based vaccine, (ABRYVVO, Pfizer)) for pregnant people between 24 and 36 completed weeks of gestation (varied by country) was approved in Europe in October 2022, the UK in November 2022 and the USA in July 2023. Several clinical trials have been conducted, demonstrating favourable safety and efficacy for these products.^{5–8} For the maternal vaccine, a clinical trial of the RSVpreF3 (AREXVY, GSK) was halted due to an observed increase in premature births.⁹ Only the ABRYVVO (Pfizer) vaccine has been licensed for use during pregnancy, but concerns about the risk of premature births remain. In addition, for older adults, three RSV vaccines—AREXVY (GSK), ABRYVVO (Pfizer) and mRESVIA (Moderna)—were also approved after demonstrating favourable efficacy and good safety profiles in clinical trials.^{10,11} However, clinical trials are often limited in their generalisability to real-world settings due to the exclusion of individuals with risk factors and the relatively small sample sizes as reflected in the wide 95% CIs. Rare or very rare serious adverse events such as hypersensitivity reactions, adverse pregnancy outcomes (eg, pre-eclampsia) or cardiovascular or neurological conditions (eg, atrial fibrillation, Guillain-Barré Syndrome (GBS)) may not have been detected in clinical trials. Furthermore, the efficacy of the performance of nirsevimab and vaccines needs to be established in scenarios reflecting those encountered by public health agencies. Since their approval, routine RSV immunisation campaigns have been implemented in countries across Europe, including the UK, and in North America, providing real-world evidence. A growing evidence base demonstrating effectiveness and safety is vital primarily to provide reassurance and build confidence in the vaccines and immunisation programmes, as well as inform decision-makers and policy. To our knowledge, no systematic review has yet assessed the effectiveness and safety of nirsevimab and RSV vaccines using real-world data. To inform immunisation policy, address gaps in evidence from clinical trials and help decision-making, we aimed to conduct a comprehensive review of the effectiveness and safety of RSV prophylaxis in reducing RSV-related healthcare utilisation among infants and older adults in real-world settings.

METHODS

Search strategy and selection criteria

This systematic review follows the PRISMA-P2020 (Preferred Reporting Items for Systematic Review and Meta-analysis Protocols) guidelines.¹² To capture the most up-to-date evidence, we conducted a living systematic review and meta-analysis. The searches were updated monthly over 5 months, from 5 November 2024 to 10 March 2025, following a pre-specified protocol. A protocol for this study was registered on PROSPERO (CRD42025643585).

We searched Ovid Embase, Ovid MEDLINE and Ovid Global Health for literature published between 1 December 2022 and 10 March 2025. Additionally, we hand-searched reference lists of the included studies to identify other relevant publications, including grey literature. Search terms included “respiratory syncytial virus”, “RSV”, “nirsevimab”, “vaccine”, “immunisation”, “effectiveness” and “safety”. The full search strategy is provided in online supplemental table S1.

Eligible studies reported either effectiveness or safety data for nirsevimab or RSV vaccines in real-world settings. Therefore, eligible study designs were observational studies including prospective or retrospective cohort studies, population-based studies using routinely collected healthcare data, registry-based studies or postmarketing surveillance studies. Studies were excluded if they were animal studies, modelling studies, cost-effectiveness analyses or clinical trials. No language or geographical restrictions were applied.

All retrieved studies were uploaded to Covidence, where duplicates were automatically removed.¹³ Title and abstract screening, followed by full-text screening, was conducted independently by

two of five reviewers (DT, BL, SE, HHYK and RP). Any disagreements were resolved by consensus or by a third reviewer.

Two reviewers independently extracted data using a prespecified data extraction form. Extracted information included study setting, study design, population characteristics and outcomes related to effectiveness and safety. Data extraction was performed using Microsoft Excel, and conflicts were resolved by consensus or by a third reviewer.

Risk of bias was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools, with checklists selected based on study design.¹⁴ Each checklist consisted of 8–11 items covering key domains of bias related to study design, conduct and analysis. As there is no standard JBI interpretation, studies were classified as high risk if they met fewer than 50% of the checklist criteria, moderate risk if they met 51–75% and low risk if they exceeded 75%. Two reviewers independently assessed the risk of bias, with discrepancies resolved through discussion or by a third reviewer.

Data analysis

We defined the effectiveness of nirsevimab and RSV vaccines as the relative reduction in the odds or risk of medical attendance due to RSV infection or LRTI, including bronchiolitis, following prophylaxis. Effectiveness (%) and corresponding 95% CIs using the effect estimates (OR, risk ratio (RR), HR and incidence rate ratio (IRR)) as reported by the studies: effectiveness (%) = $100 \times (1 - \text{adjusted effect ratio})$. Several sensitivity analyses were conducted: (1) stratified by different effect estimates (eg, OR, RR, HR or IRR); (2) by pooling unadjusted estimates into overall analysis. Some studies reported statistical estimates without explicitly providing the relative reduction in outcomes; in such cases, we calculated effectiveness based on the reported estimates. For multiple reports from the same study, only the most recent data were included in the meta-analysis.

A separate analysis was conducted for interrupted time series studies, as their comparisons were based on the odds or risk of outcomes at different time points. Different epidemic seasons were analysed in relation to the total number of patients with RSV-related LRTI who used healthcare services. The effectiveness was expressed as a reduction (%) in RSV-related healthcare visits.

We performed a subgroup meta-analysis for each outcome (primary care visits, emergency department (ED) visits, hospital admissions and intensive care unit (ICU) admissions), as well as by country, risk of bias and length of follow-up (≤ 5 months versus > 5 months, as 5 months was the mean follow-up). The I^2 statistic was used to measure the proportion of total variability attributable to between-study heterogeneity, and the τ^2 statistic was used to estimate the absolute between-study variance. Random-effects model was used to pool all estimates, with inverse-variance weighting incorporating an estimate of between-study variance. The impact of publication bias was assessed using Egger's test and funnel plots for meta-analyses containing at least 10 studies.¹⁵

For safety outcomes, we conducted a narrative analysis, as most data were reported narratively. Meta-analyses were performed using the ‘meta’ package in R (V.4.2.3).

Role of funding source

The funder was not involved in the design of this study, data collection, data analysis, interpretation, writing of the manuscript or decision to submit the study for publication.

RESULTS

A total of 1396 publications were retrieved. Following full-text screening, 50 studies were included in this review:^{16–65} 39 on nirsevimab (31 reporting exclusively on effectiveness, 6 reporting effectiveness and safety, 2 reporting exclusively on safety), 2 on the maternal RSV vaccine safety and 9 on RSV vaccines for older adults (5 reporting effectiveness and 4 reporting on safety) (figure 1). Studies with various and mixed designs were included: 19 cohort studies (36%), 13 test-negative case-control studies (25%), 14 interrupted time series studies (26%), 3 case-control stu-

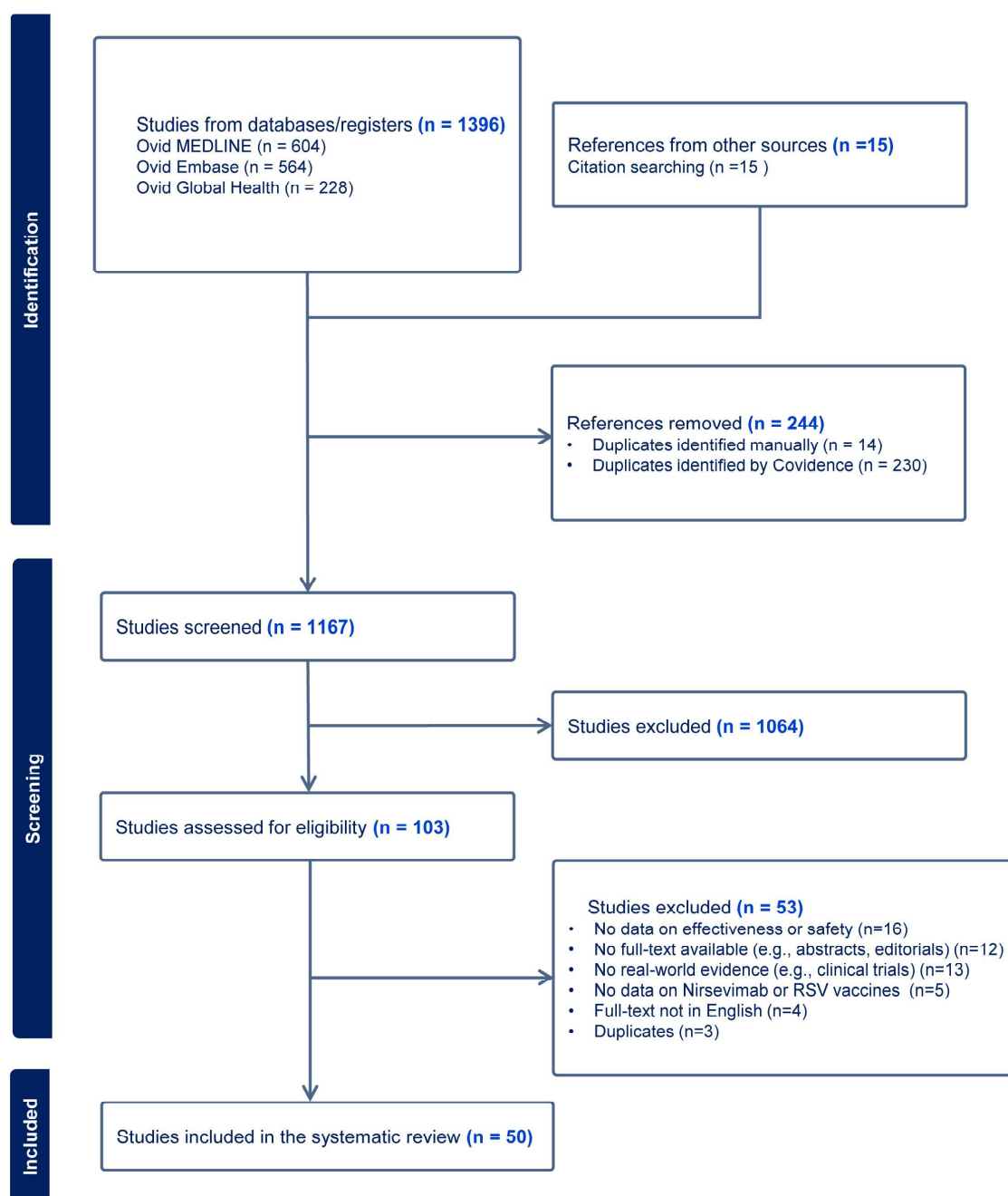


Figure 1 PRISMA flow diagram of study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RSV, respiratory syncytial virus.

dies (6%), 2 cross-sectional studies (4%), 1 case series (2%) and 1 quasi-experimental study (2%). Most studies were conducted in Europe (n=34, 68%), predominantly in Spain (n=21, 42%), and France (n=11, 22%). In North America, all included studies were conducted in the USA (n=13, 26%). Online supplemental table S2 provides an overview of the study characteristics.

Most studies were at low risk of bias (n=27, 54%), while 18 studies were classified as having a medium risk of bias (36%) and 5 studies (10%) as having a high risk of bias. Detailed results of the risk of bias assessment are presented in online supplemental table S3.

Effectiveness and safety of nirsevimab for infants

Of the 37 studies reporting the effectiveness of nirsevimab, 31 were included in the meta-analysis (the other 6 studies used interrupted time series design) (figure 2). Three studies were from the same cohort, so we used the latest report.^{19 42 44} For preventing RSV-related ED visits, the pooled effectiveness from seven studies was 80.7% (95% CI: 75.7% to 85.7%, $I^2=20.1\%$, $\tau^2<0.01$). The pooled effectiveness against RSV-related hospital admissions, derived from 17

studies, was 80.7% (95% CI: 76.1% to 85.2%, $I^2=82.8\%$, $\tau^2=56.11$). For prevention of RSV-related ICU admissions, the pooled effectiveness from eight studies was 75.6% (95% CI: 63.3% to 87.9%, $I^2=74.8\%$, $\tau^2=224.92$). For preventing RSV-associated primary care visits, two studies were available but could not be included in the meta-analysis due to highly heterogeneous study designs.^{21 41} In primary care settings, Lopez-Lacort et al study showed that the effectiveness of nirsevimab was 75.8% (95% CI: 40.4% to 92.7%) in infants under 10 months old.⁴¹ Additionally, Barbas Del Buey et al differentiated effectiveness by follow-up period (1–5 months) and age (0.5–5 months). Effectiveness ranged from 48.3% to 69.0% in the first month across all age groups, but declined with increasing age, from 69.0% (95% CI: 63.5% to 73.7%) at 0.5 months old to 48.3% (95% CI: 40.9% to 54.9%) at 5 months old.²¹

In sensitivity analyses stratified by different effect estimates of either ORs, RRs, HRs or IRRs, the pooled effectiveness of nirsevimab in preventing RSV-related hospital admissions remained consistent, ranging between 77.4% and 82.3%. The pooled effectiveness for reducing RSV-related ED visits was between 74.7%

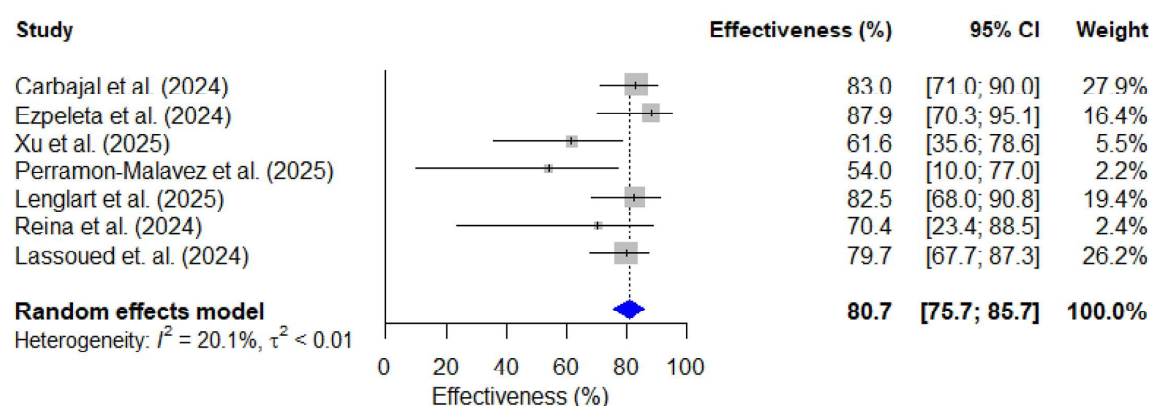
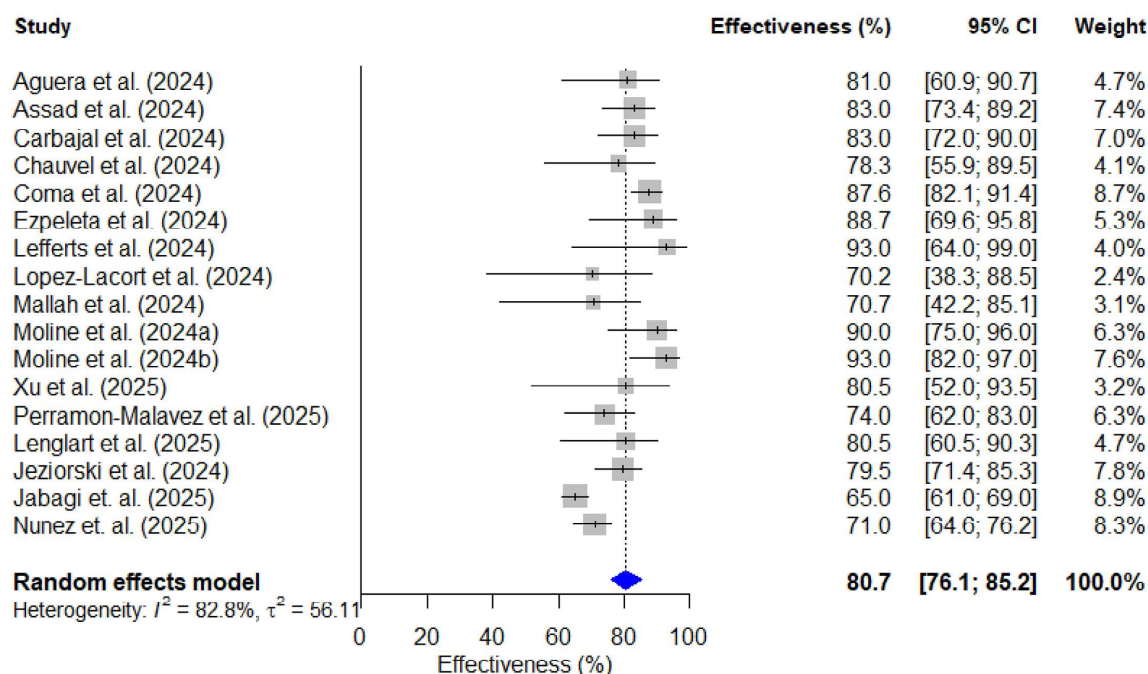
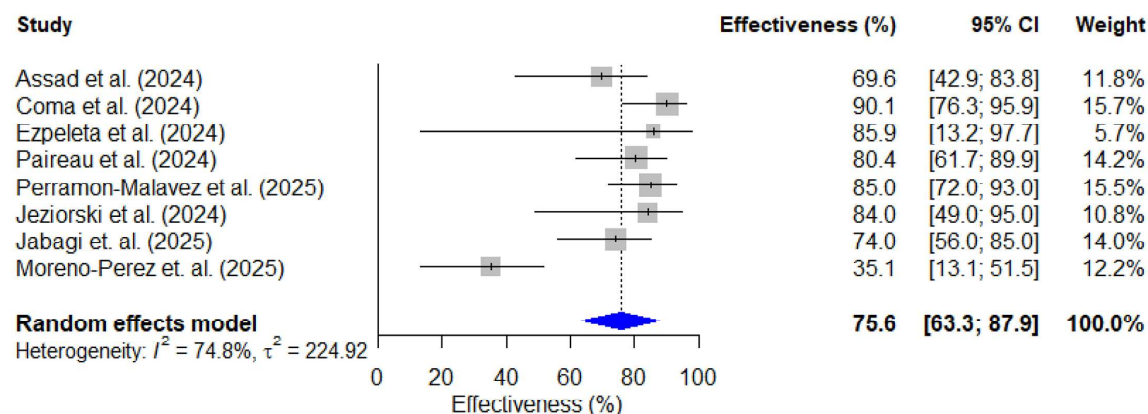
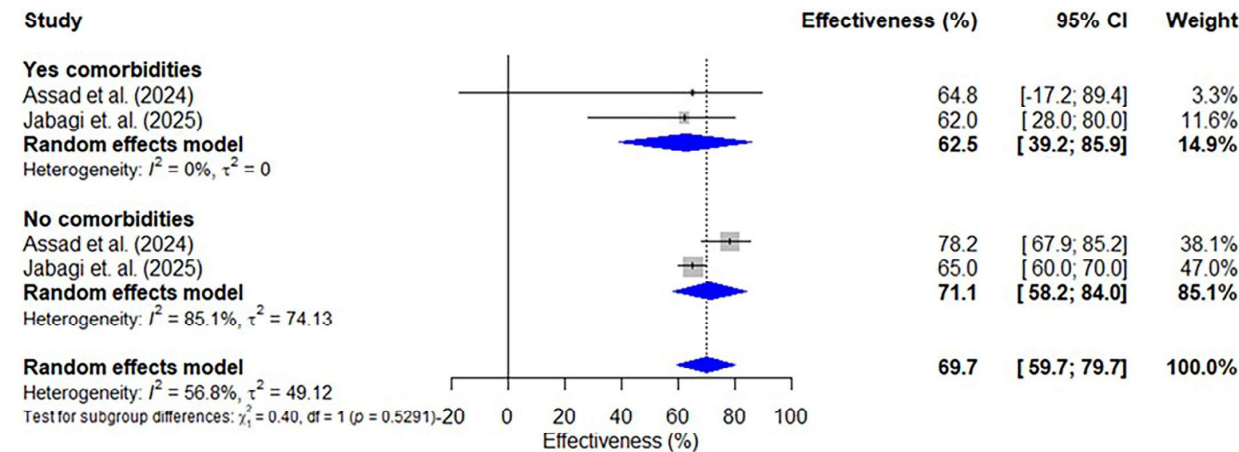
a RSV-related emergency department visits**b RSV-related hospital admissions****c RSV-related ICU admissions**

Figure 2 Effectiveness of nirsevimab in infants against respiratory syncytial virus (RSV)-related healthcare utilisation, including emergency department visits, hospital admissions and intensive care unit (ICU) admissions. Note: emergency department visits included data from emergency department, ambulatory care and/or outpatient clinics.

and 80.0%, and the pooled effectiveness against RSV-related ICU admissions was between 78.4% and 84.6% (online supplemental figure S1). Sensitivity analyses restricted to unadjusted estimates (online supplemental figure S2) or studies with low risk of bias did not significantly differ from the overall estimates (online supplemental figure S3). As funnel plots and Egger's test ($p=0.25$) were performed only for the meta-analysis of nirsevimab effectiveness on RSV-related hospital admissions ($n=17$), they indicated a low risk of publication bias (online supplemental figure S4).

We further analysed the studies based on the length of follow-up (online supplemental figure S5). The mean follow-up duration was 5 months, ranging from 15 weeks to 9 months. 18 studies with a follow-up period of 5 months or less and 5 studies with a follow-up period longer than 5 months after immunisation were analysed separately. The meta-estimates were not significantly different. Three studies reported the effectiveness of nirsevimab in preventing RSV-related hospital admissions by child's sex, indicating similar effectiveness: males (78.0%; 95% CI: 64.1% to 91.9%, $I^2=88.6\%$, $\tau^2=127.98$) and females (73.4%; 95% CI: 60.5% to 86.3%, $I^2=80.2\%$, $\tau^2=82.91$) (online supplemental figure S6).³¹ We obtained crude estimates using data provided in one study for preventing RSV-related primary care visits, showing greater effectiveness in males (86%; 95% CI: 40.0% to 97.0%, $n=102$) compared with females (68%; 95% CI: -42.0% to 93.0%, $n=58$), although CIs overlapped.⁴¹ The presence of comorbidities in children and preterm births did not significantly affect the overall results (figure 3).

a Comorbidities (yes vs no)



b Preterm vs term birth

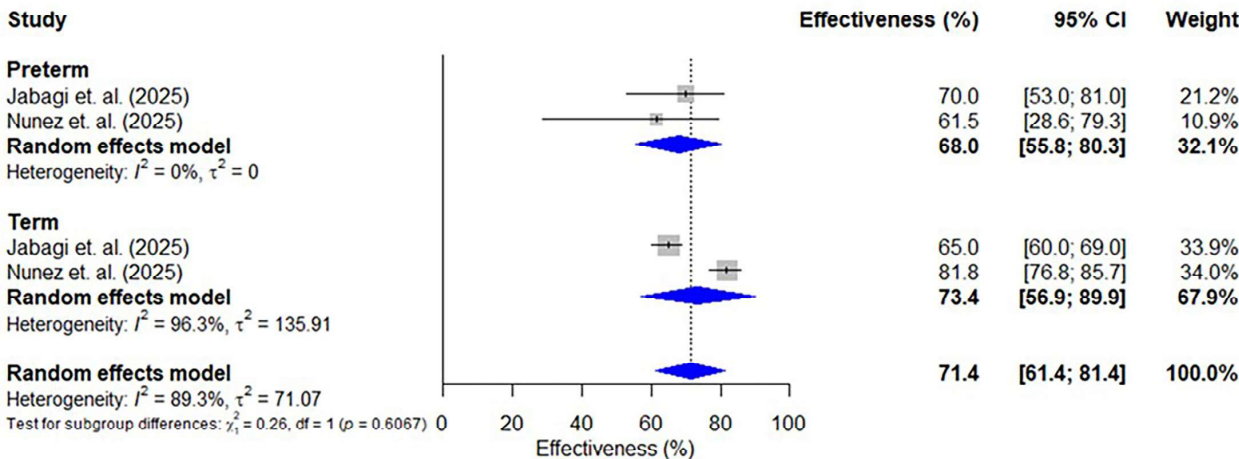


Figure 3 Effectiveness of nirsevimab in infants against respiratory syncytial virus (RSV)-related hospital admission by presence of comorbidities, including preterm births. Note: eligible age criteria varied across the included studies. Detailed eligibility criteria for age are available in online supplemental table S2. Comorbidities included chronic lung disease of prematurity, congenital heart disease or any other previously known comorbidities. Preterm birth was defined as birth at a gestational age of 36 weeks or less.

The pooled effectiveness of nirsevimab for preventing all-cause LRTI-related hospital visits, including non-RSV-related LRTI, is summarised in figure 4. The pooled effectiveness for preventing LRTI-related ED visits from four studies was 52.4% (95% CI: 46.1% to 58.6%, $I^2=12.5\%$, $\tau^2=4.86$),^{24 26 52 53} while the pooled effectiveness against LRTI-related hospital admissions from five studies was 54.0% (95% CI: 45.6% to 62.4%, $I^2=0.0\%$, $\tau^2=0.00$).^{24 42 43 52 56} Two studies reported effectiveness for the prevention of LRTI-related ICU admissions, with a pooled estimate of 68.1% (95% CI: 44.1% to 92.2%, $I^2=53.2\%$, $\tau^2=178.27$).^{43 52}

14 interrupted time series studies assessed impact of nirsevimab on RSV-related healthcare utilisation in the 2023/2024 season, compared with previous seasons (online supplemental table S4).¹⁷ 18 22 25 27–29 35 39 45 47 51 53 55 11 studies reported a reduction in RSV-related primary care visits, hospital admissions, ED visits or ICU admissions while one study found that the incidence rates of RSV-related hospitalisations were similar (due to low uptake of nirsevimab). One study reported a decrease in the number of all-cause bronchiolitis cases compared with the previous season (2022/2023).³⁹ Three studies reported a shift in the median age of infants with RSV-related healthcare utilisation to older ages (indicating fewer healthcare interventions required for younger children and therefore increasing the median age).^{22 25 45} The increase in median age ranged from 3 to 6 months for ED visits or hospital admissions.

Eight studies reported mild transient symptoms or no severe adverse events for nirsevimab.^{19 23 27 28 31 32 42 44} (online supplemental table S5). In a study from Australia, 47 (11.5%) of 410 parents

reported one or more adverse events during the 3 days post-nirsevimab administration.²³ The most frequently reported symptoms were fatigue (7.1%), local reaction (2.3%), fever (3.4%) and gastrointestinal issues, which included vomiting/diarrhoea (3.9%). In a study conducted in Italy with 369 children, fever was the most frequent symptom (6.4%), followed by local reaction (4.0%), while 89.2% had no severe adverse events.²⁷ Adverse events from these two studies are summarised in figure 5. The remaining six studies stated no severe adverse events.

Effectiveness and safety of maternal RSV vaccine

As of 10 March 2025, no studies reporting the effectiveness of maternal RSV vaccination were identified. However, two studies from the USA reported on the safety of the RSV maternal vaccine.^{32, 54} Homo et al did not find adverse outcomes after vaccination.³² Additionally, Son et al⁵⁴ found that RSV maternal vaccine was not associated with adverse pregnancy outcomes, including preterm birth (adjusted OR (aOR): 0.87, 95% CI: 0.62 to 1.20), pregnancy-related hypertension (aOR: 1.10, 95% CI: 0.90 to 1.35), small-for-gestational age birth weight (aOR: 1.16, 95% CI: 0.89 to 1.50) and neonatal outcomes including ICU admissions, jaundice, hypoglycaemia or sepsis (all $p > 0.05$). However, only in the time-dependent model, an increased risk of pregnancy-related hypertension was observed (HR: 1.43, 95% CI: 1.16 to 1.77).

Effectiveness and safety of RSV vaccine for older adults

Five studies reported RSV-related healthcare utilisation in older adults after receiving the RSV vaccines (figure 6).^{57, 59, 63–65} Four studies were included in the meta-analysis. The pooled effectiveness was 77.9% (two studies, 95% CI: 73.4% to 82.4%, $I^2 = 0.0\%$, $\tau^2 = 0.00$) for preventing RSV-related ED visits,^{57, 63} and 79.6% (three studies, 95% CI 73.8% to 85.3%, $I^2 = 0.0\%$, $\tau^2 = 0.00$) for the prevention of RSV-related hospital admissions.^{57, 63, 64} One study from the UK found a 62.1% (95% CI: 35.0% to 79.8%) reduction in RSV-related hospital admissions during the 2024/2025 RSV season (after introduction of the vaccine) compared with the 2023/2024 RSV season.⁵⁹ In a US study, vaccine effectiveness against RSV-related critical illness including ICU admissions and/or in-hospital deaths was 81% (95% CI 52% to 92%).⁶³ In the same study, effectiveness against RSV-related hospital admissions was similar between different vaccine types with overlapping confidence intervals: Study

AREXVY (83%, 95% CI: 73% to 89%) and ABRYSV0 (73%, 95% CI: 52% to 85%); and between different age groups with overlapping CIs: 60–74 years (81%, 95% CI: 66% to 90%) and 75 years and above (79%, 95% CI: 68% to 86%).⁶³

Four studies reported data on the safety of RSV vaccines in older adults.^{58, 60–62} Injection site symptoms and systemic symptoms (eg, fatigue/tiredness or muscle pain) constituted 30.0–33.5% and 26.0–29.8% of all reported adverse events, respectively.^{60, 62} One study reported no association between the RSV vaccine (AREXVY or ABRYSV0) and risk of new-onset atrial fibrillation (RR: 1.06, 95% CI: 0.90 to 1.25) or recurrent atrial fibrillation (RR: 0.94, 95% CI: 0.91 to 0.97) compared with influenza vaccines.⁵⁸ In a US study using a self-controlled case series approach, 95 incidents of GBS within 42 days after vaccination were observed among 3.2 million vaccine recipients.⁶¹ They observed the incidence of GBS following both AREXVY (attributable risk: 6.5 GBS cases per one million doses; IRR 2.46, 95% CI: 1.19 to 5.08, 24 cases in risk period, 11 cases in control period) and ABRYSV0 (attributable risk: 9 GBS cases per one million doses; IRR 2.02, 95% CI: 0.93 to 4.40, 18 cases in risk period, <11 cases in control period) vaccines within 42 days after vaccination compared with the period between 42 and 90 days postvaccination.⁶¹ Another US study using surveillance data sets found 4.4 and 1.8 GBS cases per one million doses of ABRYSV0 and AREXVY vaccine administered, respectively.⁶⁰

DISCUSSION

In this living systematic review, the effectiveness of nirsevimab in reducing medically attended RSV-related disease in real-world settings ranged from 75.6% to 80.7% and the safety profile was favourable. These findings were corroborated by interrupted time series studies comparing data on medically attended RSV-associated disease before and after the implementation of nirsevimab. Interestingly, nirsevimab was associated with over 50% reduction in all-cause LRTI-related hospital visits. In older adults, RSV vaccines showed effectiveness estimates between 77.9% and 79.6% for preventing RSV-related ED visits and RSV-related hospital admissions, respectively. GBS was an adverse event reported in fewer than 10 cases per one million vaccine doses. Despite our monthly updates in searches, no data reporting on the effectiveness of the RSV maternal vaccine in real-world settings was identified and only two studies reported safety outcomes. Although none of the two studies reported increased incidence of

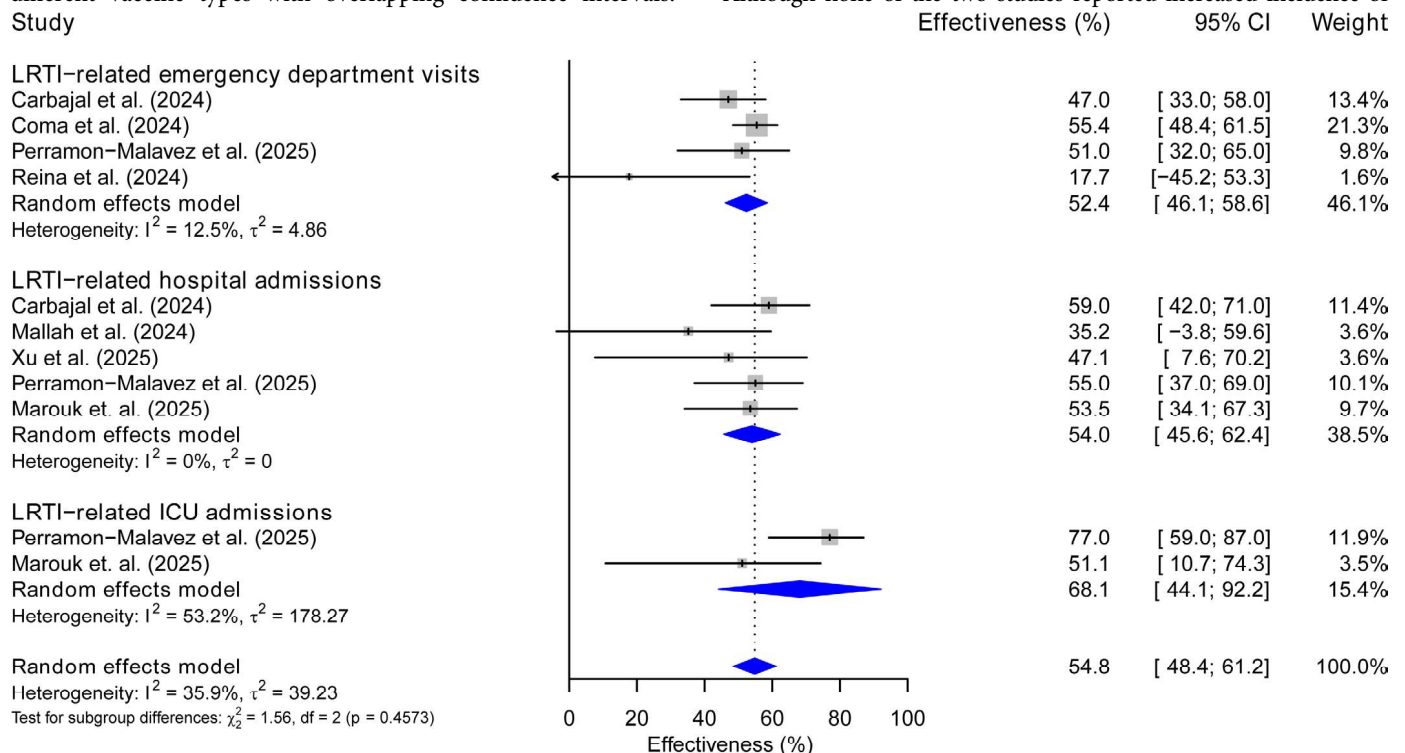


Figure 4 Effectiveness of nirsevimab in infants against all-cause lower respiratory tract illness (LRTI)-related healthcare utilisation, including emergency department visits, hospital admissions and intensive care unit (ICU) admissions.

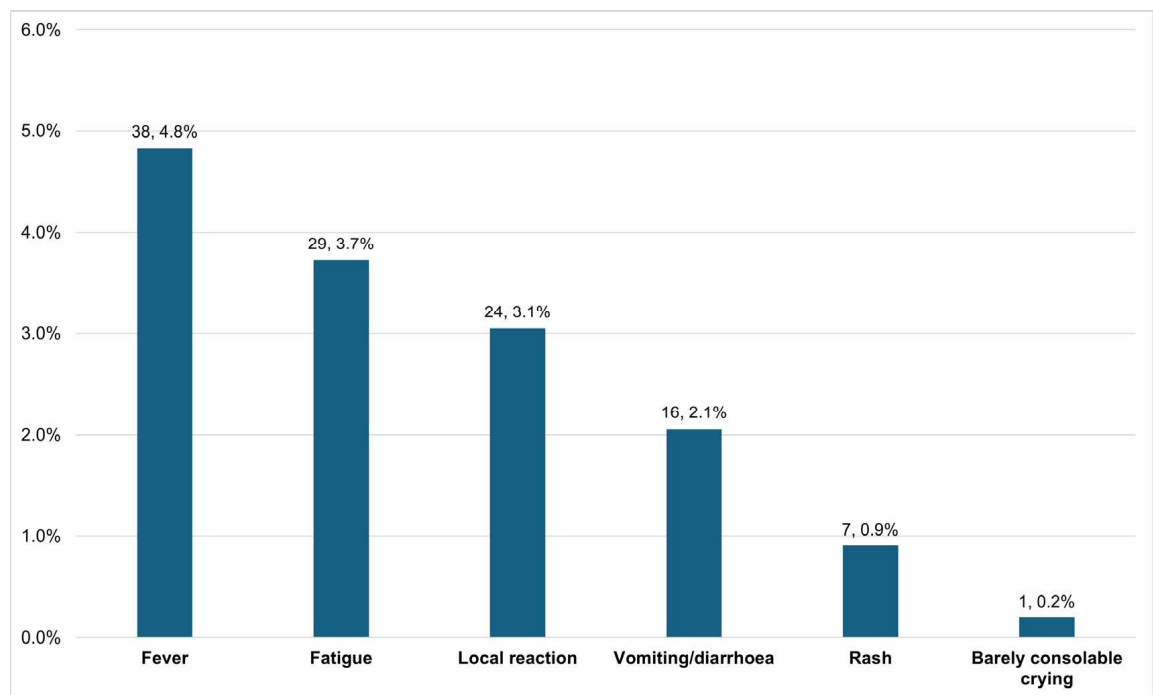


Figure 5 Adverse events of nirsevimab in infants reported in the included studies (n=2 studies*, 779 participants). Note: *among eight studies reporting adverse events of nirsevimab, six reported no adverse events and two reported adverse events.^{23 27} None of the reported cases required additional medical visits, and no major events were recorded. In one study, 1.2% (5/410) of children sought medical advice.²³

preterm births after the RSV maternal vaccination, current scarcity of data highlights the need for continuous monitoring.

In clinical trials, the efficacy of nirsevimab against RSV-related hospitalisation during the first RSV season ranged from 61% to 90% compared with standard care,^{5–8} which was similar to our pooled effectiveness estimates generated from population-based studies. However, it is important to note that the target population for immunisation with nirsevimab varied between the included studies. It was most commonly delivered at under 6 or under 8 months of age, depending on country-specific recommendations owing to factors including product supply, healthcare systems and immunisation service delivery models. For example, in France, soon after the start of the immunisation programme in September 2023, the recommendation shifted from all infants under 8 months of age to newborns in maternity wards only due to unexpectedly high demand and supply shortages.^{66 67} By contrast, Spain expanded the use of nirsevimab to premature infants up to 12 months old, achieving high uptake rates exceeding 90%.⁶⁸ The effectiveness of nirsevimab did not vary by follow-up length. Although some studies noted the

waning of effectiveness over time, there is no consensus on the time frame for this decline. In a study by Xu et al, the effectiveness decreased by 24.5% from 2 weeks to 14 weeks postimmunisation.⁵⁶ Barbas del Buey et al observed a 2–50% decrease over a 5-month follow-up, 21 whereas Jabagi et al found no such decline over follow-up of 2.5 months.³³ This decline can be expected, given the pharmacokinetics of nirsevimab⁶⁹ and the natural decrease in monoclonal antibody concentration over time, highlighting the importance of timing in nirsevimab immunisation.

The use of nirsevimab for children beyond 1 year old remains debated. The European Medicines Agency and the Australian Therapeutic Goods Administration have approved its use in infants up to 24 months of age who have risk factors for severe RSV disease.^{70 71} The US Center for Disease Control and Prevention does not currently recommend nirsevimab for infants aged 20 months or older.⁷² Evidence of the effectiveness during children’s second RSV season is limited. One study in the USA demonstrated effectiveness of 88.0% (95% CI: 48.0% to 97.0%) in preventing medically attended RSV-related acute respiratory infections during the second RSV sea-

Study

RSV-related emergency department visits
Payne et al. (2024)
Bajema et. al. (2025)
Random effects model
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$

RSV-related hospital admissions
Payne et al. (2024)
Surie et al. (2024)
Bajema et. al. (2025)
Random effects model
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$

Random effects model
Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0$
Test for subgroup differences: $\chi^2_1 = 0.21$, $df = 1$ ($p = 0.6482$)

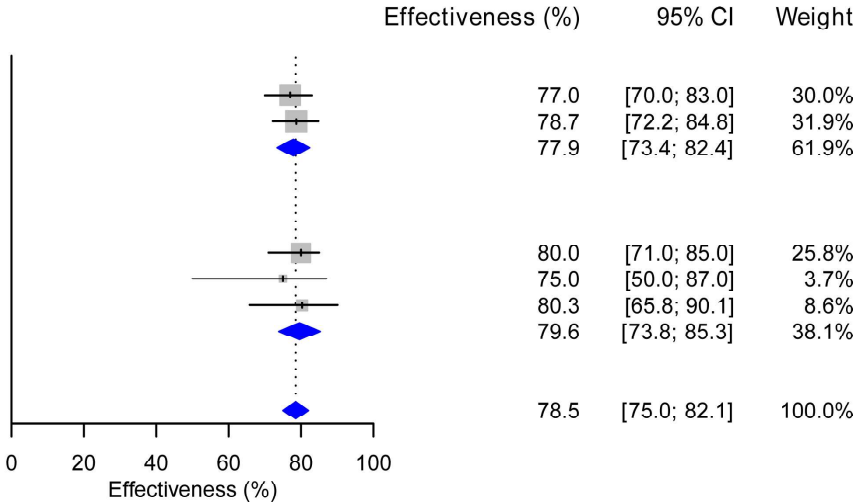


Figure 6 Effectiveness of RSV vaccine for older adults against respiratory syncytial virus (RSV)-related healthcare utilisation, including emergency department visits and hospital admissions. Note: eligible age criteria varied across the included studies. Detailed eligibility criteria for age are available in online supplemental table S2.

son.³⁷ In our review, we found an increased median age at the time of medically attended RSV infection after the implementation of nirsevimab, which may indicate the need to offer immunisation to older infants as well. More real-world evidence is required to assess how immunisation with nirsevimab impacts RSV-associated disease during children's first and second RSV seasons.

In current practice, a nirsevimab dose of 50 mg is administered to children weighing less than 5000 g and a dose of 100 mg is given to children weighing 5000 g or more. The appropriate dosage for infants with a very low body weight (eg, under 1000 g) has not been ascertained, and limited data are available for this population. In a US study, the effectiveness estimates for the 100 mg and 50 mg doses were comparable, with overlapping CIs.³⁰ In addition, the effectiveness for preterm infants appears to be similar to that of infants born at term.¹⁶ On the other hand, an increased dose of 200 mg is administered to children 8–19 months old with risk factors in their second RSV season.^{72–73} A brief report with 230 children observed a favourable safety profile for the second dose of 200 mg nirsevimab.^{72–74} Future research exploring the dose-effectiveness relationship would be beneficial to provide guidance for optimal use of this product depending on children's clinical characteristics.

A clinical trial of the RSVpreF vaccine (ABRYSVO, Pfizer) in pregnant people showed protective effects against medically attended severe LRTI in infants, with an efficacy of 81.8% within 90 days and 69.4% within 180 days after immunisation, compared with the placebo group.⁷⁵ While effectiveness has not yet been confirmed in real-world settings due to a lack of data, safety has been supported by the two included US studies.^{32–54} These studies found no significant increase in the risk of adverse pregnancy or neonatal outcomes, such as preterm births, small-for-gestational-age birth weight, stillbirth, ICU admissions, respiratory distress, hypoglycaemia, jaundice or hyperbilirubinaemia, or sepsis.^{32–54} However, it is important to note that the US vaccination programme only included pregnant people between 32 and 36 weeks of gestation, limiting the opportunity to generate data on preterm birth risk before 32 weeks. In one study, an increased risk of hypertensive disorders of pregnancy was observed only in the time-dependent model, which appeared to be linked to insurance type and hospital site.⁵⁴ Therefore, it remains unclear whether hypertensive disorders are a genuine safety concern related to the RSV vaccination. As real-world evidence in different populations and settings remains scarce, further monitoring is needed to assess any potential risks.

Limited evidence was available on the effectiveness and safety of the RSV vaccines for older adults. Our pooled effectiveness meta-estimates were 77.9% for preventing RSV-associated ED visits and 79.6% for preventing RSV-related hospital admissions, which are slightly different from estimates from clinical trials (efficacy of over 80% in preventing RSV-related LRTI).¹⁰ Additionally, the development of GBS after vaccination was reported in fewer than 10 cases per one million vaccine doses. It is recognised as a serious but rare adverse event in the product information documents for ABRYSVO (which may affect up to 1 in 1000 people).⁷⁶ GBS is also known to be an adverse event following the influenza vaccine, though the incidence is much lower, with fewer than one case per million doses.⁷⁷ As RSV vaccines become available for more people worldwide, further surveillance of the incidence of GBS and other rare safety signals in older adults will be crucial for accurate risk estimation.

The limited evidence could partially be attributed to poor linkage between healthcare databases or inadequate reporting systems for the older adult population in some countries. In the USA, reporting of influenza and RSV vaccination coverage for residents of nursing homes is optional, meaning that only facilities that voluntarily submit data are included. This can introduce potential selection bias, as facilities that report such data may be more likely to offer these vaccines.⁷⁸ Barriers such as high cost and vaccine hesitancy may also limit RSV vaccine uptake, contributing to the limited data. For instance, the high cost of RSV vaccines compared with the influenza or COVID-19 vaccines may create financial barriers for individuals and nursing homes. In the USA, the cost of RSV vaccines is significantly higher than that of the influenza vaccine (US\$75.54) or COVID vaccines (US\$141.80). The AREXVY

and ABRYSVO vaccines are priced at US\$294.00 and US\$295.00 per dose, respectively.⁷⁹ Beyond cost, vaccine hesitancy related to safety and efficacy concerns, along with general non-vaccination behaviours, may also contribute to low RSV vaccine uptake in this population.⁸⁰ As this is a new vaccine, it may take time for the vaccine programme to mature and for public trust to increase, highlighting the need for educational campaigns for vaccine recipients and providers and implementation of other strategies to address barriers to vaccine uptake.

Our comprehensive living systematic review and meta-analysis provides up-to-date evidence on the effectiveness and safety of RSV immunisation products against RSV-related severe disease. However, it is important to acknowledge several methodological limitations. First, most of the included studies in our review were peer-reviewed studies, and data from governmental and public health agencies were not sought out. New evidence on the effectiveness and safety of RSV prophylactics is rapidly emerging and may be reported by public health agencies before studies are published; therefore, it is possible that some data were missed in our review. However, we included studies published up to 10 March 2025, and will update the living systematic review as new studies are published. Second, the included studies were conducted in eight high-income countries which may limit generalisability to LMICs. For instance, most of the effectiveness data for nirsevimab were contributed by studies from Spain, which has high immunisation uptake rates (online supplemental figure S7). However, an early press release from a study on RSV maternal vaccine in Argentina suggests similar effectiveness to that observed in clinical trials: effectiveness of 72.7% (95% CI: 60.0% to 81.4%) and 68.0% (95% CI: 56.2% to 76.6%) in preventing RSV-associated LRTI hospitalisations in infants aged 0–3 months old and 0–6 months old, respectively.⁸¹ Estimates of immunisation effectiveness may vary across countries due to differences in uptake rates, immunisation strategies, monitoring systems or potential delays in data entry into healthcare databases. These factors are likely to contribute to the high heterogeneity observed between studies in the meta-analysis (high I^2 or τ^2 statistics). Third, models for effect estimates underlying the calculated vaccine effectiveness varied across studies. To address this limitation, we conducted sensitivity analyses by each effect estimate and unadjusted estimates but found no significant differences. Fourth, some duplication of study populations is possible; however, where possible, we only included the most recent data covering the same study population in the meta-analysis. For example, three studies reported data from the NIRSE-GAL population-based study, a longitudinal study initiated in collaboration with the Galician Directorate of Public Health of the Xunta de Galicia, but to avoid duplication, data only from Mallah et al were included.⁴² Finally, the RSVpreF maternal vaccine may be offered year-round in some countries, but on an extended seasonal or seasonal basis in others; additionally, in some countries, it may only be offered from a certain gestational age.⁸² As a result, data on effectiveness and safety may be limited initially for comparison as data accumulation may take an entire year or several RSV seasons. Especially, lack of studies reporting severe adverse events does not necessarily imply the absence of substantial safety signals—ongoing monitoring of the safety of RSV prophylactics is crucial. As more evidence becomes available from a wider range of geographical settings and population subgroups, more granular effectiveness and safety estimates, as well as insights into waning effects over time, will be possible.

CONCLUSION

This is the first comprehensive overview of the effectiveness and safety of nirsevimab, the RSV maternal vaccine and RSV vaccines for older adults in a real-world setting. Nirsevimab demonstrated a favourable safety profile and high effectiveness in preventing medically attended RSV-related disease, including ED visits, hospitalisations and ICU admissions in infants. For the RSV maternal vaccine and RSV vaccines for older adults, data on effectiveness and safety in real-world conditions are currently scarce; therefore, evaluation of the evidence in these populations is essential. Ongoing monitoring of effectiveness and safety is paramount for informing guidelines, public health agencies and clinical decision-making, as well as reassuring the public and building confidence in

immunisation programmes which have the potential to reduce the burden of RSV-associated disease in the most vulnerable groups.

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ARTIGO ORIGINAL

Fatores de risco para asma atópica e não atópica em crianças em idade escolar de países de elevadas rendas

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RESUMO

Contexto Está bem estabelecido que existem diferentes fenótipos de asma, mas enquanto os determinantes da asma atópica (AA) são bem estudados, pouco se sabe sobre a asma não atópica (NAA). Comparamos fatores de risco para atopia, AA em indivíduos atópicos e NAA em indivíduos não atópicos em crianças de uma grande variedade de países.

Métodos Utilizando quatro estudos, em 23 países, avaliamos o estado de asma e a atopia (testes cutâneos de hipersensibilidade) em crianças de 6 a 17 anos, além de fatores de risco relacionados com habitação, aquecimento, animais de estimação, família, dieta e qualidade do ar. Usando modelos de regressão logística com efeitos mistos, avaliamos fatores de risco ao longo de quatro trajetórias: trajetória 1 — de não atópico sem asma para NAA; trajetória 2 — de não atópico sem asma para atopia (sem asma); trajetória 3 — de atópico sem asma para AA; trajetória 4 — de não atópico sem asma para AA. Comparamos os log-odds dos fatores de risco entre trajetórias usando o coeficiente de correlação de Pearson (PCC).

Resultados A nossa amostra final de 32 741 crianças incluiu: 67% sem atopia nem asma, 15% com atopia mas sem asma, 8% com AA, 10% com NAA. Os fatores de risco foram semelhantes entre a trajetória 1 e a trajetória 3 (PCC = 0,81; IC 95%: 0,68 a 0,94). Em contraste, os fatores de risco diferiram entre a trajetória 2 e a trajetória 3 (PCC = -0,06; IC 95%: -0,29 a 0,17).

Discussão Estes resultados indicam que, embora a atopia aumente o risco de asma, os fatores de risco para desenvolver asma posteriormente são, em geral, os mesmos em indivíduos com e sem atopia. Isto levanta questões importantes sobre o papel da atopia na asma, particularmente se ela faz parte intrínseca do processo etiológico ou se é apenas coincidental.

INTRODUCTION

Although the importance of intrinsic (or non-allergic or non-atopic) asthma has been recognised since the early 20th century,¹ the focus of asthma research in the past 60 years has been predominantly on allergic mechanisms despite compelling evidence that at most half of asthma cases are attributable to atopy.^{2,3}

As a consequence, little is known about the causes and pathophysiological mechanisms of non-atopic asthma (NAA), hampering the development of effective prevention and treatment options for a large proportion of people with asthma.

Atopic asthma (AA) is associated with T helper type 2-mediated airway inflammation, with atopy often identified (with varying results) by skin prick test (SPT) positivity to common allergens or serum allergen-specific immunoglobulin E (IgE) measurement (commonly associated with airway eosinophilia).⁴ The mechanisms underlying NAA

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- It is well established that there are different phenotypes of asthma, but little is known about risk factors for non-atopic asthma.

WHAT THIS STUDY ADDS

- Using a novel approach, we found that lifestyle and environmental risk factors for developing asthma are generally similar in atopic and non-atopic children, but the risk factors for atopy are quite different.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Our findings suggest that atopy and asthma may be coincidental in a large proportion of children who are defined as having atopic asthma. This has important implications for our understanding of the causes and mechanisms of different asthma phenotypes, and therefore prevention and treatment of asthma.

remain unclear but may involve neutrophilic inflammation, neural mechanisms, infection-related responses or other currently unknown pathophysiological pathways.⁵⁻⁷ Different mechanisms may lead to different risk factors associated with disease. To make a valid comparison between NAA and AA, we first need to tease apart the risk factors for asthma from the risk factors for atopy.

Figure 1 shows a framework for pathways potentially involved in the development of AA and NAA.⁸ These are not often considered separately in studies of risk factors. Instead, most have done one of the following⁸: (1) compared all asthma cases with all non-atopic controls (a mix of all four pathways); (2) adjusted for atopy (an average of the effects of pathway 1 and pathway 3); (3) compared AA with all non-atopic controls (a mix of pathways 2-4); (4) compared NAA with all non-atopic controls (none of the indicated pathways); or (5) a few studies have stratified on atopy (yielding separate estimates for pathways 1 and 3).

A 2014 review of the evidence for NAA risk factors found that, of 30 risk factors evaluated in 43 studies, only three (family history of allergic disease, household dampness/mould and childhood lower respiratory tract infections) showed



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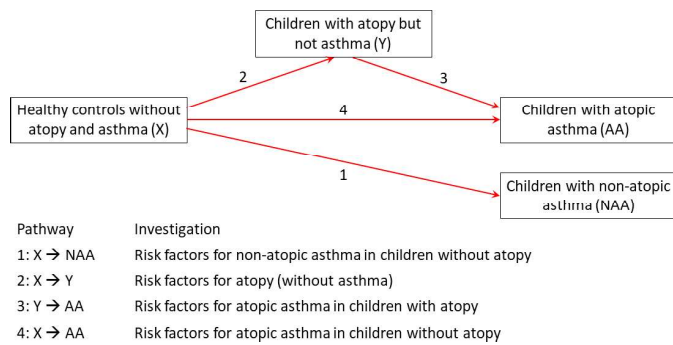


Figure 1 Pathways of possible asthma causation (adapted from

consistent associations with NAA. A lack of breastfeeding, or breastfeeding for a limited period, was less consistently associated with NAA. However, this review noted that most of these studies used inappropriate comparison groups.⁹ There was also considerable methodological heterogeneity with different definitions of atopy and asthma, and different study designs, hampering valid comparisons.⁹

Here, using data from four studies: the International Study of Asthma and Allergies in Childhood (ISAAC) Phase II, the World Asthma Phenotypes (WASP), the Social Change, Asthma and Allergy in Latin America (SCAALA) and the Avon Longitudinal Study of Parents and Children (ALSPAC), we aimed to separately assess and compare risk factors for the four pathways (figure 1), allowing the identification of modifiable factors that may increase/decrease the risk of NAA (pathway 1) and/or AA (pathways 2–4).

METHODS

Data sources

The ISAAC Phase II cross-sectional questionnaire survey (with additional objective tests) commenced in 1998, targeting children aged 10–11, and included 30 centres from a mix of high-income countries (HIC) and low- and middle-income countries (LMICs). Detailed methods have been published previously.^{10 11}

The WASP cross-sectional case-control study was conducted in five centres in HICs (UK, New Zealand (NZ)) and LMICs (Brazil, Ecuador, Uganda) between 2017 and 2020. Participants in Brazil, Ecuador and NZ were recruited from ongoing population-based cohort studies, with additional recruitment through the community (eg, surveys in schools). In Uganda, participants were recruited from a larger case-control study of children with and without asthma identified through a cross-sectional survey in schools. Full details of the questionnaire and methods have been published previously.⁴ The UK centre surveyed young adults (26–27 years) and has therefore been excluded from this analysis.

Table 1 Exclusions

	WASP	ISAAC	SCAALA	ALSPAC	Total
Total sample	1205	54 271	8266	8174*	71 916
Out of age range	177	864	553	93	1687
No SPT offered	0	21 801	0	478	22 279
Previous but not current asthma symptoms	84	4396	2175	2528	9183
Total ineligible	261	27 061	2728	3099	33 149
Eligible sample	944	27 210	5538	5075	38 767
Missing sex/age	0	9	0	12	21
Missing SPT data	21	0	216	1468	1705
Missing symptoms	0	3545	0	755	4300
Total missing data	21	3554	216	2235	6026
Final sample	923	23 656	5322	2840	32 741

*Individuals who completed the age 7 questionnaire, without second twin. ALSPAC, Avon Longitudinal Study of Parents and Children; ISAAC, International Study of Asthma and Allergies in Childhood; SCAALA, Social Change, Asthma and Allergy in Latin America; SPT, skin prick test; WASP, World Asthma Phenotypes.

The SCAALA study involved a cross-sectional survey in Ecuador and a longitudinal study in Brazil, with detailed protocols published previously. In Ecuador, data were collected in 2006 on children aged 5–16 years in the Esmeraldas province.¹² In Brazil, data were collected in 2005 on children aged 4–11 years at baseline in the city of Salvador, Northeastern Brazil.¹³

For the ALSPAC birth cohort study, pregnant women resident in Avon, UK, with expected dates of delivery between 1 April 1991 and 31 December 1992 were invited to take part in the study. The initial number of pregnancies enrolled was 14 541 from which 13 988 children were still alive at 1 year of age, consisting of 14 203 unique women (G0 mothers). Information was collected from 12 113 G0 partners (of the mothers), of which 3807 are currently enrolled on the study. After 7 years, efforts were made to find eligible pregnancies that were missing from the study. The total sample size for analyses using any data collected after the age of 7 is therefore 15 447 pregnancies, from which 14 901 children were still alive at 1 year of age. The study included regular surveys and tests throughout childhood, details of which have been reported previously.^{14 15} Here we use SPT data at age 7 and surveys collected up to age 7. Please note that the study website contains details of all the data that are available through a fully searchable data dictionary and variable search tool.¹⁶

From all sources, individuals with missing data on symptoms, SPT results, age or sex were excluded, along with those outside the target age group of 6–17 years, and those who did not fit into a category of case or control (ie, with previous asthma symptoms/diagnosis but not in the past year). Missingness was checked for associations with demographics.

Variable definitions

Children were defined as having current asthma if they had wheeze symptoms and/or used asthma medications in the past 12 months. They were defined as without asthma if they never had asthma or asthma symptoms, determined by negative responses to questions on ever having wheeze symptoms or diagnosed asthma (ISAAC and SCAALA) or by negative responses to questions on recent wheeze symptoms across all surveys in ALSPAC. Participants qualifying for neither status (eg, those who previously had asthma) were excluded from the analyses. More details on the exact definitions for each study are found in online supplemental table S1.

We defined atopy as SPT positivity (≥ 3 mm wheal in ISAAC, WASP and SCAALA, ≥ 2 mm wheal in ALSPAC) to at least one of a panel of five or more common allergens. Individuals testing positive for saline (negative control), negative for histamine (positive control) or with fewer than five allergens tested were excluded. Similar SPT methods were used in each study, and allergens appropriate for the local environment of each centre were used (online supplemental table S2).

Study participants were categorised into four outcome groups: healthy controls (no atopy and no asthma) (X), those with atopy but no asthma (Y), those with AA and those with NAA.

We included potential risk factors if they were available in ISAAC as it was by far the largest study. These were all binary variables and included housing condition (heating, cooling, insulation, cooking fuel, feather/synthetic bedding, damp), animal contact (pet cats, dogs, birds and farm animals), diet (meat, fish, fruit, vegetables, fast food), body mass index category, family (siblings, parental allergies/education/smoking) and early life factors (breastfeeding, birth weight, prematurity) (online supplemental table S1).

Statistical analyses

Four sets of models were used, representing each pathway in figure 1.

Pathway 1: comparing those with NAA to healthy controls (risk factors for NAA).

Pathway 2: comparing those with atopy but without asthma to healthy controls (risk factors for atopy).

Pathway 3: comparing those with AA to those with atopy but not asthma (risk factors for AA).

Pathway 4: comparing those with AA to healthy controls (risk factors for AA and atopy together).

Table 2 Distribution of main outcome by study

Study	Healthy controls, no atopy, no asthma (X) (%)	Atopy but no asthma (Y) (%)	Atopic asthma (AA) (%)	Non-atopic asthma (NAA) (%)	Total
WASP	171 (19)	66 (7)	422 (46)	264 (29)	923
ISAAC	16 239 (69)	3922 (17)	1584 (7)	1911 (8)	23 656
SCAALA	3860 (73)	560 (11)	203 (4)	699 (13)	5322
ALSPAC	1650 (58)	322 (11)	433 (15)	435 (15)	2840
Total	21 920 (67)	4870 (15)	2642 (8)	3309 (10)	32 741

ALSPAC, Avon Longitudinal Study of Parents and Children; ISAAC, International Study of Asthma and Allergies in Childhood; SCAALA, Social Change, Asthma and Allergy in Latin America; WASP, World Asthma Phenotypes.

For the first three pathways, we examined which risk factors were associated with NAA (figure 1, pathway 1), atopy (pathway 2) and AA in atopic children (pathway 3). Pathway 4 was more difficult to address as it is in addition to the two existing pathways, 2 and 3. It was assessed by estimating the overall association of non-atopic non-asthma (X) with AA (not adjusted or stratified on atopy) and comparing it with that predicted assuming no direct path, that is, the OR for pathway 2 multiplied by the OR for pathway 3. A difference between the two figures was considered to indicate a possible direct path (assuming the difference was not due to misclassification or residual confounding). In addition, we directly compared AA to NAA to see which factors differentiated them and how these compared with the risk factors for atopy alone.

Mixed-effects logistic regression models were fitted on the binary outcome representing each pathway, with a random intercept for centre and adjusting for age, sex, study and country income level (LMIC/HIC). In children, asthma prevalence is known to increase with age, peaking around 13–14 years, after which it decreases.¹⁷ Thus, using the models with no risk factors, we first tested for evidence against a linear trend for age by adding a quadratic term and then by adding a restricted cubic spline (RCS); the most appropriate form was then used for the models of each pathway.

Individual models were fitted for each risk factor in turn, and results compared between pathways. The sample size varies between models as the amount of missing data for each risk factor varies. In addition, some risk factors were not included for a particular study; as stated previously, all included risk factors were in the ISAAC study and at least one other study (online supplemental table S1). To assess the relationship between risk factors for each pathway, we plotted the OR estimates for one pathway against another (on the log scale as the log odds is usually normally distributed) and calculated the Pearson correlation coefficient (PCC) for the log odds and associated bootstrapped CIs (using bootstrap samples of the individual-level dataset to account for the uncertainty of the individual estimates as well as the uncertainty of the correlation) for 1000 replications.

Models stratified by country income group were fitted to test for interactions, and separate models were fitted for each study to assess consistency.

Sensitivity analyses were conducted on the main non-stratified models as follows:

1. To exclude borderline atopics, two stricter atopy definitions were applied to data from ISAAC and ALSPAC (due to data availability): any wheal of at least 5 mm in the core allergens; two or more wheals of at least 4 mm in the core allergens. Those originally classed as atopic but not meeting the new definition were excluded from that analysis. The definition for non-atopics remained the same. Results were compared with those using the standard atopy definition but limited to the two studies.
2. To check if there was an imbalance between studies, four analyses were conducted leaving out one study each time.
3. Lastly, an analysis was conducted that used a more lenient definition for the controls, allowing for a small amount of missing symptom data (either one past questionnaire missing for ALSPAC or the question 'Has the child ever been told they have asthma?' missing in ISAAC). Data were analysed using Stata V.18.¹⁸

RESULTS

From a total sample of 71 916 participants (1205 from WASP, 54 271 from ISAAC, 8266 from SCAALA and 8174 from ALSPAC), 33 149 were deemed ineligible for either being out of the age range, not being offered an SPT, or previously having asthma symptoms but not in the past year. This left a sample of 38 767 participants to be considered for analysis. Of these, 6026 (16%) were excluded due to missing data: demographics (21); SPT data (1705); and symptom data (4300) (table 1). There were some relatively weak associations between missing data and demographics; being male was associated with missing SPT data (OR=1.15, 95% CI 1.03 to 1.29), but not with missing symptom information. Older children were associated with a higher chance of missing SPT data (1.07 (1.02 to 1.13)) but a much lower chance of missing symptom information (0.63 (0.60 to 0.65)). Individuals with current asthma were more likely to be missing the SPT data than those who never had asthma (1.27 (1.09 to 1.47)) (online supplemental table S3).

The final sample of 32 741 comprised 66% healthy controls, 15% children with atopy but not asthma, 8% with AA and 10% NAA. The WASP sample had a higher proportion of children with asthma (75%) than the others (15–30%) due to its case-control design (table 2).

Participants in WASP were on average the oldest but with a wide range (9–18 years). Those in ALSPAC were 7–8 years, ISAAC participants were mainly 10–11 years and SCAALA ranged from 6 years to 16 years (online supplemental figures S1–S3). The WASP dataset was 55% female, SCAALA was 48% and ISAAC and ALSPAC were both 51%. In WASP, 64% of the individuals were from LMICs, and in ISAAC this was 32%. SCAALA participants were all from LMICs (Brazil and Ecuador) and ALSPAC were all from HICs (UK). Details of the final sample by country are found in online supplemental table S4.

The prevalence of each risk factor by study is presented in table 3 (expanded to include individual centres in online supplemental table S5). Each risk factor was available for a different subset of individuals, ranging from 14 060 for synthetic pillows to 31 175 for parental allergic diseases. There was considerable variation between centres for some variables, particularly indoor heating questions, as some centres in hot countries do not use heating at all.

Results from the mixed-effects logistic regression, with random intercepts for centre and adjusted for study, sex, age and country income level (LMIC/HIC), but without including risk factors, showed evidence that the effect of age was not linear for pathway 1 (quadratic $p=0.046$, RCS $p=0.17$) and for the AA/NAA comparison (quadratic $p=0.016$, RCS $p=0.23$), but there was no evidence against linearity for pathways 2–4 (quadratic $p=0.27$, $p=0.18$, $p=0.45$ and RCS $p=0.43$, $p=0.87$, $p=0.87$, respectively). Thus, a quadratic age term was included in all models for pathway 1 and the AA/NAA comparison.

Figure 2 compares the estimated ORs of each risk factor between AA in already atopic individuals (pathway 3) and the risk of NAA in non-atopic individuals (pathway 1). The associations for the included risk factors were generally similar for AA and NAA, with a high positive correlation between the estimated log odds (PCC=0.81, bootstrapped 95% CI 0.68 to 0.94).

Figure 3 compares risk factors for atopy (pathway 2) with risk factors for AA in atopic individuals (pathway 3) with no correlation between the two groups (−0.06 (−0.28 to 0.16)).

We also compared the risk factors for atopy (pathway 2) with the risk factors for AA compared with NAA, as in both of these groups

Table 3 Prevalence of potential risk factors by study

Category	Covariable	n	ISAAC	WASP	SCAALA	ALSPAC	Overall total
Study sample size			23 656	923	5322	2840	32 741
Confounder	Male sex	32 741	49%	45%	52%	49%	49%
House/bedding	Feather bedding	14 156	18%	25%	—	—	18%
	Synthetic bedding	14 155	43%	35%	—	—	43%
	Blankets	15 560	44%	45%	22%	—	43%
	Feather pillow	14 780	17%	32%	—	—	17%
	Synthetic pillow	14 060	39%	47%	—	—	40%
	Double glazing	20 831	55%	—	—	81%	58%
	Double glazing in 1st year	20 194	45%	—	—	59%	47%
	Urban	23 452	92%	—	45%	88%	81%
	Urban in 1st year	16 953	89%	—	—	93%	89%
Heating/cooking	Heating	16 979	68%	48%	—	—	67%
	Wood heating	18 386	14%	14%	—	—	14%
	Coal/coke heating	17 603	4%	0%	—	—	4%
	Gas heating	16 261	28%	34%	—	—	28%
	Heating in 1st year	15 523	68%	—	—	—	68%
	Wood heating in 1st year	16 894	20%	—	—	—	20%
	Coal/coke heating in 1st year	16 330	6%	—	—	—	6%
	Cooking electric	20 728	45%	11%	0%	—	43%
	Cooking gas	29 549	54%	77%	97%	61%	63%
	Cooking gas in 1st year	18 776	19%	—	99%	56%	27%
Animals	Pets	20 342	43%	58%	57%	70%	51%
	Cats	30 397	15%	31%	33%	30%	20%
	Dogs	30 379	14%	36%	42%	20%	20%
	Birds	24 130	14%	—	—	6%	13%
	Cat in 1st year	21 091	9%	—	7%	29%	12%
	Dog in 1st year	21 091	8%	—	18%	19%	10%
	Bird in 1st year	20 399	7%	—	—	5%	7%
	Farm animals	22 052	7%	60%	22%	—	11%
Diet/weight	Meat weekly	26 025	88%	95%	85%	—	87%
	Seafood weekly	26 507	57%	69%	81%	—	62%
	Green vegetables weekly	24 540	83%	—	68%	78%	79%
	Fruit weekly	25 019	90%	93%	87%	96%	90%
	Fast food weekly	17 878	25%	42%	7%	—	20%
	Fruit juice weekly	18 553	69%	—	55%	69%	69%
	Overweight	14 615	25%	22%	10%	14%	18%
	Obese	14 615	7%	5%	3%	3%	4%
Family/birth	Older siblings	29 536	52%	—	75%	52%	56%
	Younger siblings	29 470	49%	—	72%	52%	53%
	More than 1 sibling	29 528	40%	—	82%	34%	47%
	Ever breastfed	29 588	78%	—	97%	80%	82%
	Low birth weight	20 176	18%	—	—	4%	16%
	Premature	16 875	16%	—	8%	9%	14%
	Parental allergic diseases	31 175	36%	—	40%	74%	39%
	Maternal education	18 189	79%	—	34%	100%	70%
	Paternal education	18 389	80%	—	46%	100%	74%

Continued

Table 3 Continued

Category	Covariable	n	ISAAC	WASP	SCAALA	ALSPAC	Overall total
Air quality	Any smokers	29 371	45%	–	41%	29%	43%
	Maternal smoking	30 869	25%	–	13%	16%	22%
	Maternal smoking in 1st year	27 364	19%	–	11%	17%	17%
	Maternal smoking during pregnancy	28 545	12%	–	10%	16%	12%
	Damp	17 670	14%	28%	–	90%	20%
	Mould	15 021	9%	39%	–	52%	15%
	Damp or mould	15 512	18%	49%	60%	92%	28%
	Damp in 1st year	17 763	15%	–	–	49%	20%
	Mould in 1st year	14 599	10%	–	–	25%	13%
	Air conditioning	14 910	29%	3%	1%	–	27%

ALSPAC, Avon Longitudinal Study of Parents and Children; ISAAC, International Study of Asthma and Allergies in Childhood; SCAALA, Social Change, Asthma and Allergy in Latin America; WASP, World Asthma Phenotypes.

the difference is atopy. We found a moderate positive correlation (0.54 (0.34 to 0.74)) between the risk factor log odds of these groups (online supplemental figure S4).

The individual results for each risk factor and outcome are shown in online supplemental table S6, along with predictions of pathway 4, based on the results for pathways 2 and 3. The observed and the predicted values are similar, so there is likely no direct pathway 4 (non-atopic to AA) over and above the two separate pathways. Results comparing pathways 1–3 by category of risk factor are shown in online supplemental figures S5–S10.

The strongest risk factor for asthma was parental history of allergic disease (asthma, eczema or hay fever) (NAA OR=2.45 (95% CI 2.24 to 2.69); AA 2.05 (1.81 to 2.31)). Breastfeeding (ever) was associated with a lower risk of NAA (0.75 (0.67 to 0.85)). Premature birth (1.42 (1.19 to 1.69)) and low birth weight (1.25 (1.05 to 1.49)) were associated with an increased NAA risk (online supplemental figure S9).

Bedding-related risk factors included feather bedding (NAA 0.63 (0.52 to 0.76); atopy 0.87 (0.76 to 0.99); AA 0.64 (0.52 to 0.79)) and feather pillows (NAA 0.80 (0.66 to 0.96); atopy 0.88 (0.77 to 1.01);

AA 0.64 (0.50 to 0.81)) which were both associated with a lower risk of asthma and atopy across all pathways. Conversely, synthetic bedding was associated with a higher risk (NAA 1.33 (1.16 to 1.53); atopy 1.18 (1.05 to 1.31); AA 1.51 (1.28 to 1.79)) (online supplemental figure S5).

Current use of coal/coke heating was associated with an increased risk of developing AA among atopic individuals (1.75 (1.11 to 2.78)), but other heating factors did not show a strong association with asthma or atopy (online supplemental figure S6).

There was evidence that having pet birds in the first year of life was associated with higher risk of asthma (NAA 1.38 (1.13 to 1.68); AA 1.47 (1.15 to 1.87)), and having pet dogs in the first year of life was associated with a higher risk of AA (1.41 (1.15 to 1.72)). Many types of pets (both current and in first year of life) were associated with a lower risk of atopy (any pets 0.87 (0.79 to 0.95); cats 0.81 (0.74 to 0.89); dogs 0.90 (0.82 to 0.99); cats in first year 0.83 (0.72 to 0.95); dogs in first year 0.73 (0.63 to 0.84)). Farm animal contact showed no association with either asthma or atopy (online supplemental figure S7).

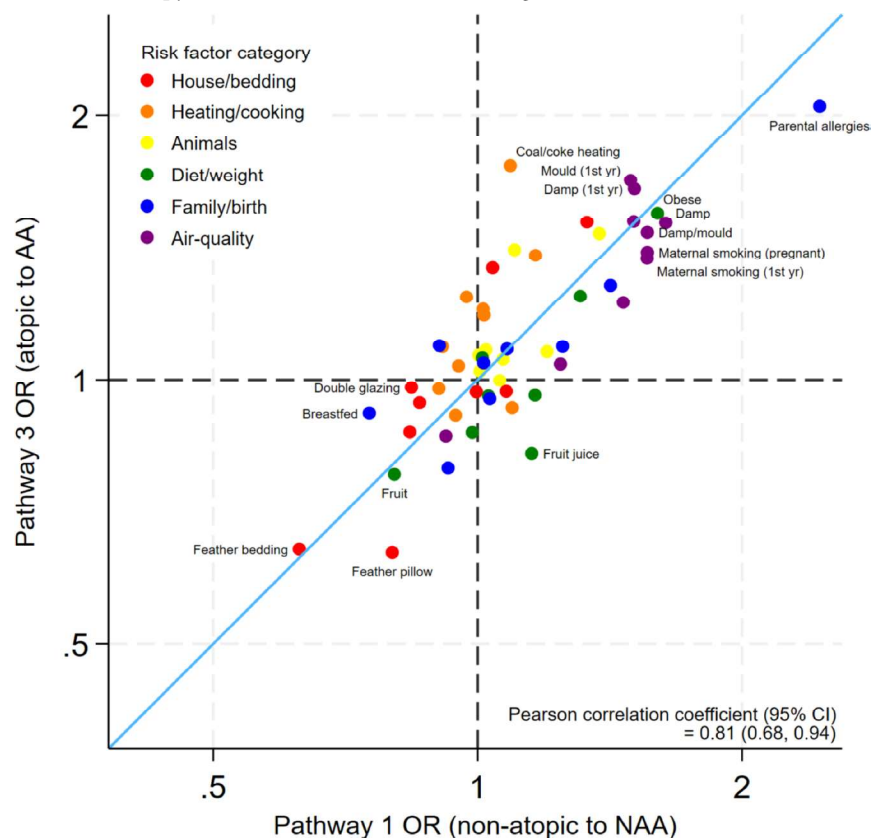


Figure 2 Estimated ORs of risk factors for atopic asthma (AA) compared with non-atopic asthma (NAA), excluding atopy risk (pathway 3 vs pathway 1). Axes are shown on the natural log scale.

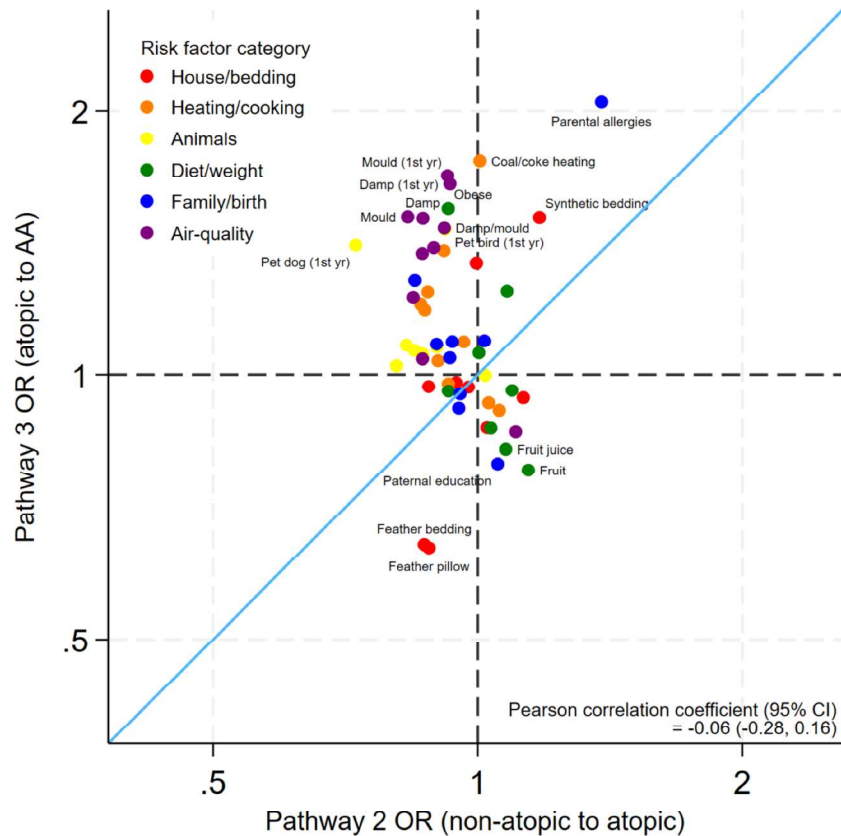


Figure 3 Estimated ORs of risk factors for asthma (in atopic individuals) compared with atopy (pathway 3 vs pathway 2). Axes are shown on the natural log scale. AA, atopic asthma.

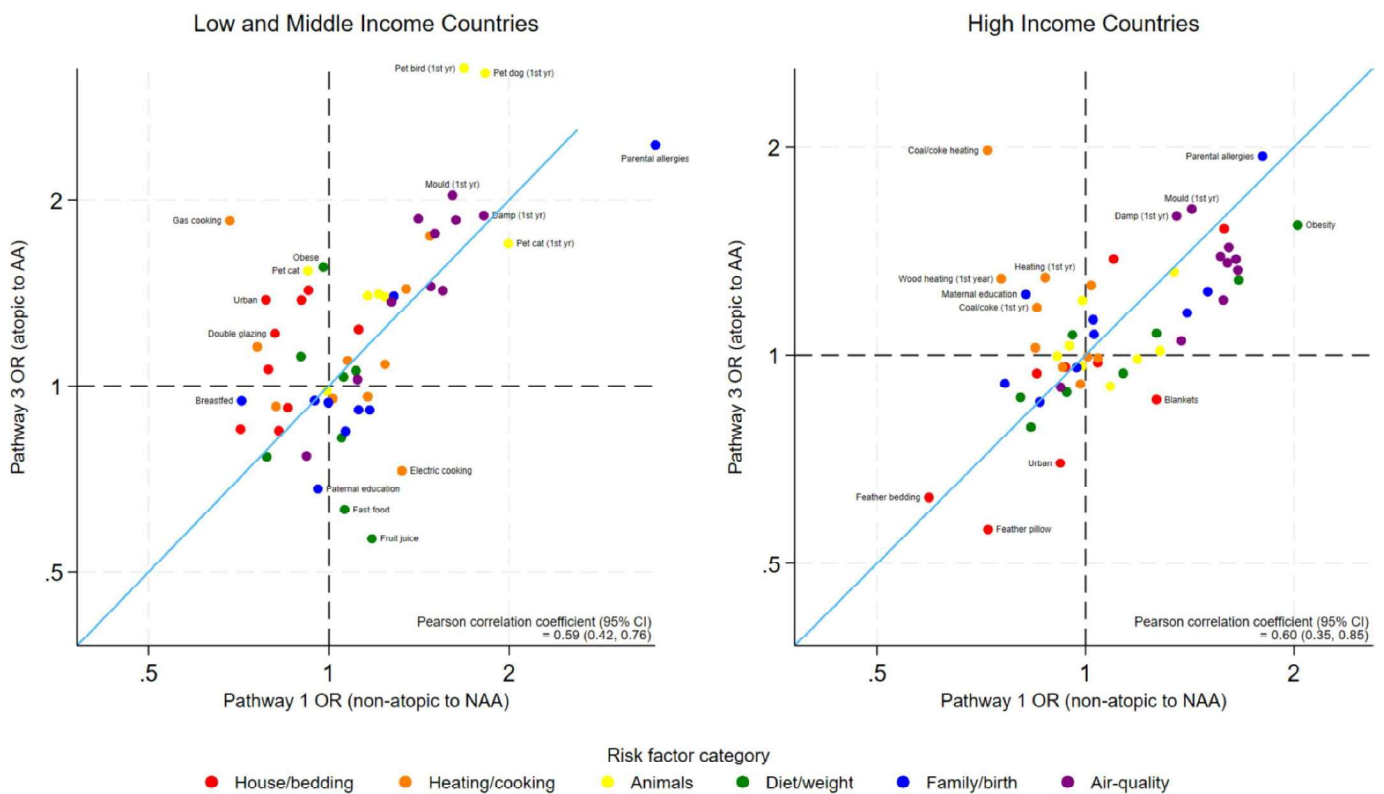


Figure 4 Estimated ORs of risk factors for atopic asthma (AA) compared with non-atopic asthma (NAA), excluding atopy risk (pathway 3 vs pathway 1) stratified by country affluence. Axes are shown on the natural log scale.

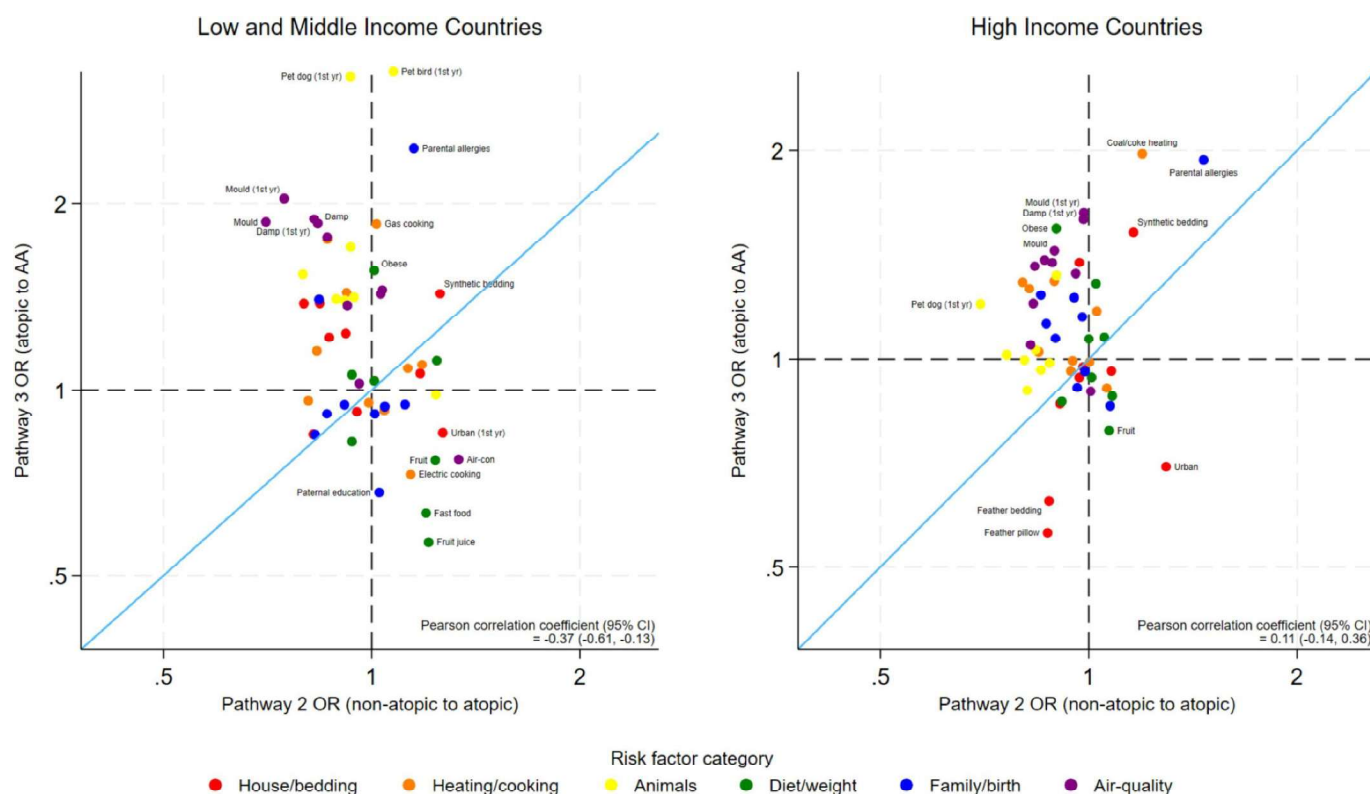


Figure 5 Estimated ORs of risk factors for asthma (in atopic individuals) compared with atopy (pathway 3 vs pathway 2) stratified by country affluence. Axes are shown on the natural log scale. AA, atopic asthma.

Obesity (NAA 1.60 (1.28 to 2.01); AA 1.55 (1.10 to 2.16)) and being overweight (NAA 1.31 (1.14 to 1.50); AA 1.24 (1.03 to 1.51)) were associated with higher risk of both forms of asthma but were not related to risk of atopy alone. Regular fruit consumption was associated with a lower risk of asthma and a weak but increased risk of atopy (NAA 0.80 (0.70 to 0.93); atopy 1.14 (0.99 to 1.31); AA 0.78 (0.63 to 0.97)) (online supplemental figure S8).

Almost all indoor air-related factors including damp (NAA 1.64 (1.41 to 1.90); atopy 0.87 (0.75 to 1.00); AA 1.51 (1.22 to 1.86)), mould (NAA 1.51 (1.29 to 1.75); atopy 0.83 (0.69 to 1.00); AA 1.51 (1.20 to 1.91)) and maternal smoking (current: NAA 1.46 (1.32 to 1.62); atopy 0.84 (0.78 to 0.92); AA 1.22 (1.07 to 1.40); in first year: NAA 1.56 (1.40 to 1.74); atopy 0.87 (0.78 to 0.96); AA 1.37 (1.18 to 1.60)) were associated with an increased risk of asthma (NAA and AA) and a slight protective effect on atopy (online supplemental figure S10).

Stratified by country affluence, there was still a positive correlation between risk factors for AA and NAA in both settings, but some of the strongest risk factors were quite different by setting (figure 4). The risk factors for atopy were unrelated to the risk factors of asthma in HICs, but in LMICs there was evidence of a negative association (figure 5).

Notably, pet birds and dogs were strong risk factors for asthma in LMICs but not in HICs. Coal/coke heating was a risk factor for AA in HICs but not LMICs. The protective effect of feather bedding and pillows was only found in HICs. Regular fast food was protective for AA (but not NAA) in LMICs only. Detailed results of these stratified models are found in online supplemental table S7.

Results for the separate studies (online supplemental table S8-11) showed some differences, though the WASP study alone was relatively small, resulting in wide CIs.

The sensitivity analyses with different atopy definitions showed similar outcomes. Using only ISAAC and ALSPAC but with the standard atopy definition ($n=26\,496$), the correlation between risk factors for AA in already atopic individuals (pathway 3) and NAA in non-atopic individuals (pathway 1) was lower but still very strongly positive (PCC=0.80, bootstrapped 95% CI 0.67 to 0.93), and the correlation between risk factors for atopy (pathway 2) and AA in atopic individuals (pathway 3) was still very low (-0.12 (-0.33 to

0.09)). Using wheal size ≥ 5 mm for any core allergen ($n=23\,188$), the correlation between risk factors for AA and NAA was slightly less strong (0.63 (0.45 to 0.81)) and there was no correlation between risk factors for AA and atopy (-0.13 (-0.36 to 0.10)). Using wheal size ≥ 4 mm for two or more core allergens ($n=22\,243$) resulted in similar findings (0.63 (0.45 to 0.81) and -0.17 (-0.41 to 0.07)) (online supplemental figure S11 and S12 and online supplemental table S12).

The second sensitivity analysis leaving out one study at a time also showed similar findings to the main analyses. The correlation between risk factors for AA and NAA was slightly lower when leaving out the ISAAC data (0.62 (0.36 to 0.88)), but the CI on the correlation coefficient was wider due to the lower sample size ($n=9085$) (online supplemental figure S13-S16 and online supplemental table S13).

The last sensitivity analysis, allowing for a small amount of missing symptom data, increased the sample size by 3668 ($n=36\,409$) and produced similar findings to the main analyses (online supplemental figure S17 and table S13).

DISCUSSION

We used a novel approach to assess risk factors for the different pathways to AA and NAA in a large and diverse population representing both HICs and LMICs.

Our findings from the available variables indicate that lifestyle and environmental risk factors are similar for NAA (in non-atopic children) and AA (in atopic children) but not for atopy. For example, dog contact in the first year of life showed a strong association for AA in atopics (OR=1.41), weaker evidence of effect for NAA in non-atopics (1.10) and a protective association with atopy (0.73); frequent fruit intake showed strong and consistent protective associations for asthma (NAA 0.80; AA 0.78) but a positive association with atopy (1.09); maternal smoking at various times in the child's life was strongly associated with increased risk of asthma (NAA and AA) but reduced risk of atopy. The exception was parental history of allergic diseases, which was a strong risk factor for both forms of asthma (NAA 2.45; AA 2.05) and atopy (1.38).

Although atopy (defined using SPT) is associated with increased risk of asthma, other risk factors are generally the same for AA and

NAA. There may be important risk factors that were not included in this study, particularly for NAA which has not been as extensively studied, and the results may have been different if these 'other' risk factors (eg, air pollution, viral infections, stress) had been examined. Nevertheless, we have included a large number of commonly recognised and studied risk factors in our analyses, including most of the risk factors that have been identified as being associated with asthma in major studies such as ISAAC.^{19 20} The fact that we have found these risk factors to have similar associations with both asthma in atopics (AA) and asthma in non-atopics (NAA) raises important questions about the role of atopy in asthma, particularly whether it is an inherent part of the aetiological process, or an exacerbating factor (or a mix of both), or is coincidental. Alternatively, NAA and AA could be separate phenotypes caused by different mechanisms for the initial onset of asthma but with similar exacerbating factors. However, this cannot be established from our cross-sectional studies as it is not possible to differentiate risk factors for initial onset from those for exacerbation of pre-existing asthma.

Risk factors in the animal and air quality categories showed a particularly striking pattern of negative associations with atopy but positive associations with asthma (both AA and NAA) (online supplemental figure S7 and S9). This is apparent for both early-life and current risk factors, making it unlikely to be due to reverse causation or specific to exacerbation of symptoms. In comparing our method of investigating different pathways to the other methods listed in the introduction, we found, as an example, that fruit intake (which was protective for NAA and AA but a risk factor for atopy) was protective when comparing all asthma to all non-asthma, also when adjusting for atopy, and when comparing NAA to all people without asthma. However, this effect was not seen when comparing AA to all people without asthma (as the effect was confounded by atopy). If the differences between risk factors for NAA and AA were greater than we observed, consideration of the separate pathways is even more important.

A strength of this study is the inclusion of data from 23 different countries, including both HICs and LMICs, as well as the resulting large sample size. Previous analyses of ISAAC data have generally found the risk factors for asthma to be similar in HICs and LMICs, providing for triangulation of findings²¹ and increasing the likelihood that the associations are causal. However, there are difficulties in ensuring the relevance of questions in varying settings, for example, heating questions in different climates. In addition, some risk factors may be differentially associated with socioeconomic position, which we partially assessed by stratifying the results by country income level, but we do not have the information to assess differences within countries.

The strongest risk factor for both types of asthma, and for atopy alone, was parental history of allergic disease, consistent with previously published findings.^{9 22} Other strong risk factors for asthma (AA and NAA), but not atopy, were damp and mould in the home, which are already established risk factors for childhood asthma (both aetiology and exacerbation).⁹ Obesity was a risk factor for both AA and NAA in HICs, which is consistent with literature,⁹ but we did not see this in LMICs, whereas pet birds and dogs were risk factors for AA and NAA only in LMICs. These differences could indicate that associations were due to confounding, or that there were other uncaptured differences between settings, for example, bird contact could mean one pet budgie or a brood of chickens.

Other limitations of these analyses should be considered. The associations reported here will likely be subject to residual confounding as not all asthma risk factors are known or were recorded in all the included studies. Furthermore, the questionnaire was relatively simple, and most questions were binary. For some risk factors, reverse causation is a possibility, for example, those with asthma (or family members) may have changed to synthetic bedding if feathers exacerbate symptoms. Selection bias could be a problem with males and younger people being more likely to have missing data, along with a higher chance of missing the SPT for those who never had asthma. Recall bias could also be an issue, with parents of children with asthma more likely to recall information on known risk factors than parents of children without asthma. There is evidence of a

disassociation between SPT and IgE in LMICs where some individuals with negative SPT are IgE positive to the same allergen.²³ In addition, the European Academy of Allergy and Clinical Immunology, in 2023, proposed a broader classification of allergy, including hypersensitivity reactions far beyond IgE-mediated phenomena (atopy).²⁴ Both these factors could indicate a higher proportion of asthma cases are in fact allergic (using the above definition) than that which we find here using SPT alone.

Our findings are important as they point towards similar mechanisms in AA and NAA, once the risk factors for atopy itself are removed. With SPT positivity defining atopy, there is no evidence that the risk factors differ between asthma phenotypes, even after using stricter definitions in sensitivity analyses. This suggests that atopy and asthma may be coincidental in a proportion of children who are defined as having AA. To confirm or refute these findings, further work on identifying different phenotypes of asthma should be undertaken in a variety of populations, including using other markers and data sources (eg, microbiome and epigenetics). IgE analysis could identify patterns in potential allergens, and clinical tests could investigate the role of neurological triggers.

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Data availability statement Data are available in a public, open access repository. Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. ISAAC data are publicly available at the UK Data Service archive (<http://discover.ukdataservice.ac.uk/catalogue?sn=8131>). ALSPAC data can be accessed after application to the ALSPAC Executive Team; application instructions and data use agreements are available at <http://www.bristol.ac.uk/alspac/researchers/access/>. The relevant data from the WASP and SCAALA studies will be shared on reasonable request to the corresponding author.

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ARTIGO ORIGINAL

Exposição de curto prazo a partículas ultrafinas e admissões hospitalares por asma em crianças em Copenhaga, Dinamarca

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RESUMO

Contexto As partículas ultrafinas (UFP; <0,1 µm de diâmetro) não são regulamentadas nem comumente monitorizadas, mas podem ser prejudiciais à saúde humana, especialmente para crianças. Neste estudo, o objetivo foi examinar a associação entre a exposição de curto prazo às UFP e as admissões hospitalares por asma em crianças.

Métodos As concentrações diárias de UFP (2002–2018) foram monitorizadas numa estação urbana de referência em Copenhaga, Dinamarca. As admissões hospitalares por asma, bem como informações demográficas e socioeconômicas das crianças (0–18 anos), foram obtidas a partir de registros. Foi aplicado um desenho de caso-crossover para estimar a associação entre admissões hospitalares e janelas de exposição às UFP de até 6 dias, para todas as crianças e estratificado por idade, sexo, rendimento familiar, escolaridade materna, asma prévia ou infecção respiratória prévia.

Resultados Foram observadas 15 903 admissões hospitalares por asma no total. Um aumento correspondente ao intervalo interquartil (IQR) nas UFP esteve significativamente associado às admissões hospitalares por asma, com efeito mais forte em janelas de exposição de 2 dias (razão de risco (RR): 1,17; IC 95%: 1,09–1,25). Estas associações mantiveram-se mesmo após ajuste para partículas finas <2,5 µm (PM_{2.5}) ou dióxido de azoto (NO₂), para os quais também foram detetadas associações positivas significativas. As associações com UFP foram mais fortes em crianças em idade escolar (5–14 anos: RR: 1,26; IC 95%: 1,15–1,38) do que em crianças com menos de 5 anos (RR: 1,01; IC 95%: 0,93–1,10).

Conclusões Neste grande estudo realizado num contexto de baixa exposição, verificou-se que a exposição de curto prazo às UFP pode desencadear admissões hospitalares por asma em crianças, independentemente das associações com PM_{2.5} ou NO₂. Este estudo reforça a necessidade de regulamentação e melhoria na avaliação da exposição a UFP para proteger a saúde infantil em áreas urbanas.

INTRODUCTION

Increasing evidence suggests that ultrafine particles (UFP; <0.1 µm in diameter) are harmful to human health.^{1–3} Their small size and large surface-area-to-mass ratio allow them to penetrate deep into the lung and translocate to other organs, while carrying relatively large amounts of potentially toxic organic compounds.¹ Exposure to UFP can cause oxidative stress in the body, leading to inflammation and tissue damage, and subsequently to respiratory diseases.^{1,2} However, epidemiological research on the health effects of UFP is hampered by a lack of monitoring data. Unlike particle metrics measured as mass and including larger particles, such as particulate matter with a diameter less than 2.5 µm (PM_{2.5}) or 10 µm (PM₁₀), for which health effects are more established, particle number in general and especially UFP are not regulated and routinely

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Previous studies suggest potential associations of short-term exposure to ultrafine particles and asthma hospital admissions, which might be strongest in children. Few studies have examined this association in children, of which two found significant increases in asthma emergency room and outpatient visits in children in China, robust to adjustment for copollutants. Others found weak, non-significant associations with asthma hospital admissions. It remains unclear whether these associations are independent from those with larger particles or nitrogen dioxide, as associations diminished after adjustment in some of these studies, or two-pollutant models were not presented.

WHAT THIS STUDY ADDS

► We add to the limited and inconclusive evidence base on the association between short-term exposure to ultrafine particles and asthma hospital admissions in children by presenting results of an exceptionally long time series (17 years) of monitoring data of ultrafine particles and detailed, individual-level sociodemographic and health data from comprehensive Danish registers. We apply state-of-the-art case-crossover models and analyse different lag structures, effect modification by age and sex, and two-pollutant models. Additionally, we examine possible effect modification by socioeconomic status and previous health conditions, which has not been done in previous studies.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► We find significant associations between short-term exposure to ultrafine particles and asthma hospital admissions in children in Copenhagen, robust to copollutant adjustment, with most pronounced effects in school-aged children. Our findings call for regulations and policies for improved air quality, which could reduce asthma morbidity in children.



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monitored. The recently updated WHO Air Quality Guidelines include a 'Good Practice Statement' on UFP, emphasising a need for more monitoring and epidemiological studies of UFP with homogeneous study designs and exposure assessment.⁴

Studies on short-term exposure to UFP and hospital contacts due to respiratory diseases have suggested that these effects may be strongest among children.^{2,5} This is likely explained by children's continuously developing respiratory system, immature defence mechanisms for detoxification and a different metabolism compared with adults, making children more susceptible to the adverse health effects of UFP.⁶ In addition, children's exposure patterns are different from those of adults, as they spend more time outdoors, are more physically active, and inhale more air volume per body weight than adults, leading to relatively higher exposures within the same environment.⁶ Studies have found that short-term exposure to UFP can lead to systemic inflammation, decreased lung function, alterations in airway inflammatory biomarkers or symptoms such as wheezing in children, especially in those with existing respiratory conditions such as asthma.^{6,7} There are only a few studies that examined the association of short-term exposure to UFP and asthma hospital admissions in children, and they show somewhat mixed results. Two Danish studies found weak, non-significant associations between UFP and asthma hospital admissions in children, which diminished after adjustment for larger particles or nitrogen dioxide (NO₂).^{8,9} A Finnish study detected associations between UFP and asthma emergency room visits in children, which were independent of PM_{2.5} but diminished after adjustment for NO₂.¹⁰ A US study detected associations between UFP and asthma exacerbation in children with asthma in single pollutant models but did not evaluate whether these were robust to adjustment for NO₂ or PM_{2.5}.¹¹ Lastly, two studies from China found significant increases in asthma emergency room and outpatient visits in children, which were robust to adjustment for NO₂ and PM_{2.5}.^{12,13}

There are a few factors that possibly alter the susceptibility to short-term exposure to UFP in children. Besides age and sex as known effect modifiers, socioeconomic status (SES) is an important determinant of children's health. A recent scoping review of SES as an effect modifier of the association between air pollution and children's respiratory health found increased risks for children in lower SES groups.¹⁴ Moreover, childhood acute respiratory infections such as respiratory viruses like human rhinovirus (HRV), respiratory syncytial virus (RSV), bocavirus or influenza, and bacterial infections have been hypothesised to affect children's risk of developing asthma later in life.¹⁵ While the differential susceptibility by sex and age groups has been examined in three studies on UFP and asthma hospital admissions in children,^{9,12,13} no study to date has considered SES, prior asthma or childhood respiratory infections. In Copenhagen, UFPs have been monitored as part of the Danish Air Quality Monitoring Programme since 2001. In addition, well-established Danish registries make it possible to access complete, validated information on the population's health status, as well as individual demographic and socioeconomic characteristics. In this study, we use 17 years of UFP routine measurements between 2002 and 2018 to examine the associations between short-term exposure to UFP and asthma hospital admissions in children and identify susceptible groups by age, sex, SES, prior asthma or prior acute respiratory infections.

METHODS

Study population, demographic data and SES

We included all asthma hospital admissions in children (0–18 years at admission) living in Greater Copenhagen (online supplemental figure S1). Information on municipality of residence, age and sex was available from the Danish Civil Registration System, which was linked to health registries based on individual civil registration numbers. In addition, we used two indicators of SES: household disposable income, which is the total income in a household weighed by the number of adults and children in a family, and mothers' highest attained education, extracted from income and education registers.^{16,17}

Health outcome data

Admissions to eight hospitals located within the study area (online supplemental figure S1) were obtained from the Danish National Patient Register¹⁸ for the years 2002 to 2018. We included inpatients, outpatients and emergency room visits, with a primary diagnosis of asthma (International Classification of Disease 10th revision (ICD-10) codes J45–46). ICD-10 codes have been used in Denmark since 1994. Readmissions for asthma within less than 28 days after a previous admission, likely follow-up visits, were excluded. We included only patients with a registered address within the study area at the time of admission. Moreover, we recorded previous hospital contacts (inpatients, outpatients and emergency room visits) for respiratory infections (HRV, RSV and influenza, which typically dominate in Denmark¹⁹) if they occurred before the age of 5, to represent early childhood and before the first asthma admission (ICD-10 codes in online supplemental table S1).

Exposure assessment

Detailed information on the study's exposure assessment can be found elsewhere.²⁰ In short, air pollution data used in this study originate from a regulatory urban background monitoring station in central Copenhagen (online supplemental figure S1), which is located on top of a building at a height of ca. 20 m. Measurements of UFPs were performed using a custom-built differential mobility particle sizer, which counts particles with an atmospheric diameter of 6–700 nm at 2.5 min time resolution, averaged to 30 min intervals, as total particle number concentration (PNC), which is a common proxy for UFP. It was found at a later stage that measurements below 11 nm were associated with high uncertainties in the size selection and in the counting statistics. This issue is based on the hardware used in the instrument, and for that reason, data below 11 nm in size were removed. Thus, the final dataset included PNC of particles with diameters of 11–700 nm. Additionally, we obtained daily mean concentrations of PM_{2.5}, NO₂ and ozone (O₃), as well as temperature and relative humidity, from the same monitoring station.

Statistical analysis

First, we calculated daily mean values for all exposure variables and merged them with numbers of hospital admissions on the same day. We summarised daily data as number of observations (n), median, arithmetic mean, SD, minimum and maximum values, percentiles and IQR. We calculated Spearman correlation coefficients to evaluate the correlation between air pollutants.

Next, we applied a time-stratified case-crossover design²¹ to estimate the association between air pollutants and asthma hospital admissions. Specifically, we compared the air pollution concentration on the day of a hospital admission to the concentration on the same weekdays of the same month and calendar year, using conditional logistic regression. Thus, each case served as its own control, which prevents confounding by personal characteristics that do not vary over time. Moreover, confounders that vary slowly over time, such as seasonality and long-term trends, are controlled for by choosing control days close to the admission day. To ensure that key assumptions for conditional logistic regression were met, we (1) assessed multicollinearity of predictor variables in the model through variance inflation factors (VIF), (2) tested the linearity of the exposure response function using the Akaike information criterion (AIC)²² and (3) assessed the independency of observations in our dataset. Assumption (1) was met with VIFs for included variables ranging from 1.00 to 1.04. Assumption (2) was met, as a comparison of AICs between a linear and non-linear exposure response function indicated a better model fit for a linear term. Assumption (3) was met through the nature of the case-crossover design, which matches weekdays of daily data of air pollution and numbers of hospital admissions within the same months. Both of these are independent observations within the strata. Effect estimates are reported as risk ratio (RR) and 95% CIs associated with IQR increases in daily mean concentrations of air pollutants. We adjusted for meteorological variables by including daily mean

Table 1 Summary of asthma hospital admissions of children in the Greater Copenhagen area between 2002 and 2018 by subgroups

Group	Total hospital admissions	Daily hospital admissions	
		Mean	SD
Age			
All (0–18)	15 903	3	4
0–4	7537	1	2
5–14	6881	1	3
15–18	1485	0	1
Sex			
Female	5919	1	2
Male	9984	2	3
Family income			
First quartile	3827	1	1
Second quartile	3621	1	1
Third quartile	3513	1	1
Fourth quartile	3682	1	1
Mother's education			
Primary	2592	0	1
Upper secondary	992	0	0
Vocational	4261	1	1
Short cycle higher education	4142	1	1
College +	3422	1	1
Prior asthma admission			
No	10 370	2	2
Yes	5533	1	3
Childhood infection			
No	15 618	3	4
Yes	285	0	0

temperature and relative humidity in the model. Furthermore, we included a categorical variable for public holidays or the day after a public holiday. In order to account for delayed health effects, we investigated exposure windows of 2-day moving averages (ie, lag 0–1: mean of the concentrations on the day before plus the day of the asthma hospital admission) to 7-day (ie, lag 0–6: mean of the concentrations on the day of the hospital admission plus six preceding days' concentrations) moving averages of air pollutants prior to an asthma hospital admission,²³ which have been identified as the period relevant for health effects of short-term exposure to air pollution.²⁴ These moving averages represent cumulative exposure to UFP prior to a hospital admission for up to a week. Exposure-response curves were plotted using generalised additive models with Poisson distributions, adjusting for temperature (using thin plate regression splines with four df, chosen based on the AIC), time trend (5 df per year) and categorical variables for the day of the week and public holidays. The attributable fraction of asthma cases was calculated by first determining the daily excess RRs relative to a counterfactual scenario of UFP concentration of zero. The daily fraction of asthma cases attributable to UFP was then computed using the formula $(RR - 1)/RR$.

Possible effect modification was examined by stratifying analyses by sex (female/male), age (0–4/5–14/15–18 years old), categories of disposable household income (quartiles, calculated separately for each year, to account for inflation), mother's education (primary/upper secondary/vocational/short cycle higher education/college+), prior asthma admission (first/second+admission) or prior acute respiratory infections (before age of 5 and prior to asthma admission). We then compared point estimates and CIs between groups to test whether differences were statistically significant.²⁵ In two-pollutant models, we additionally adjusted for $PM_{2.5}$ and NO_2 .

A comparison of single-pollutant and two-pollutant models was made based on a complete dataset of daily information on all three pollutants (UFP, $PM_{2.5}$ and NO_2).

We performed several sensitivity analyses. First, to account for possible exposure misclassification owing to the use of a single monitoring station, we restricted cases to children living in the two municipalities closest to the monitoring station (ie, in an 8 km radius) and repeated the analysis using the same models as described above. Second, to account for missing exposure data, we restricted our analysis to those days with at least three available control days with available daily mean UFP on the same weekdays within the same month and year as the event day, excluding all other days and repeating the same analysis as described above.

Statistical analyses were performed in R statistical software (V4.1.2; The R Foundation, 2021) using the season and mgcv functions.

RESULTS

Descriptive statistics

On 6209 days, we counted 15 903 asthma hospital admissions in children up to 18 years, with three daily admissions on average (table 1). The highest absolute number of admissions was observed in children younger than 5 years ($n=7537$), followed by children aged 5–14 years ($n=6881$). Boys were more often admitted for asthma than girls ($n=9984$ and 5919, respectively). Most admissions were first-time admissions ($n=10\,370$), while 5533 children were readmitted after a prior asthma admission. Moreover, 285 asthma hospital admissions occurred among children with a prior acute respiratory infection before the age of 5. Daily mean concentrations of air pollutants were 5028 (SD: 2592) $\mu\text{g}/\text{m}^3$ for UFP, 13 (8) $\mu\text{g}/\text{m}^3$ for $PM_{2.5}$, 10 (5) ppb for NO_2 and 33 (8) for O_3 (table 2). Mean concentrations of UFP and NO_2 decreased during the study period, while $PM_{2.5}$ showed no clear trend and ozone concentrations increased (online supplemental figure S2). Both UFP and asthma hospital admissions showed a decreasing trend during the study period (figure 1). Due to different monitoring periods and data removed during quality control, daily concentrations of UFP and $PM_{2.5}$ were missing for about 44% and 43% of the study period, respectively (see online supplemental figure S2). Days with missing UFP did not differ in terms of relative humidity, day of the week, or $PM_{2.5}$ or NO_2 concentrations, but were slightly warmer than days with available UFP (online supplemental table S3). UFP was moderately correlated with NO_2 (Spearman's r correlation, $r_s=0.55$, $p<0.001$) and $PM_{2.5}$ ($r_s=0.40$, $p<0.001$) (online supplemental figure S3) and weakly correlated with temperature and relative humidity (online supplemental table S2).

Associations between air pollutants and hospital admissions

One IQR increase in UFP was significantly associated with an increase in asthma hospital admissions in children up to 18 years on the same day (RR: 1.12 (95% CI: 1.06, 1.19)). We observed positive, significant associations for all exposure windows up to 7-day means (table 3), with the strongest associations at 2-day means of UFP (RR: 1.17 (95% CI: 1.09, 1.25)). The mean daily attributable fraction for the 2-day mean UFP exposure was 22%. Over the 17-year study period, this corresponded to an estimated total of 3526 asthma hospital admissions, with 207 admissions per year on average, attributable to UFP. Similarly, an IQR increase in $PM_{2.5}$ was positively, significantly associated with asthma hospital admissions in children up to 18 years on the same day and up to 6-day exposure windows, with the highest associations at 2-day means (RR: 1.13 (95% CI: 1.09, 1.18)). An IQR increase in NO_2 was associated with increases in asthma hospital admissions in children up to 18 years on the same day (RR: 1.04 (95% CI: 1.00, 1.07)) and at 2-day means (RR: 1.05 (95% CI: 1.01, 1.10)). Warm-season O_3 was associated with increases in asthma hospital admissions in the same age group at 4-day means (RR: 1.18 (95% CI: 1.02, 1.37)).

Among the age subgroups, associations were strongest for children aged 5–14 years, where an IQR increase in UFP on the same day was associated with an RR of 1.26 (95% CI: 1.15, 1.38) (figure 2).

Table 2 Summary of daily concentrations of air pollutants and meteorological variables monitored at an urban background station in central Copenhagen between 2002 and 2018

Exposure	N days (% missing)	Mean	SD	IQR	Percentiles		
					25th	50th	75th
UFP (pt/cm ³)	3496 (44)	5028	2592	3070	3223	4556	6292
PM _{2.5} (µg/m ³)	3563 (43)	13	8	8	7	10	15
NO ₂ (ppb)	6025 (3)	10	5	6	6	9	12
O ₃ (ppb, warm season)	2739 (12)	33	8	10	28	33	38
Temperature (°C)	6051 (3)	10	7	11	5	10	16
Relative humidity (%)	6051 (3)	72	11	15	65	73	81

N, number; NO₂, nitrogen dioxide; O₃, ozone; PM_{2.5}, particulate matter <2.5 µm in diameter; ppb, parts per billion; UFP, ultrafine particle.

Moreover, associations were positive and significant for adolescents aged 15–18 (RR: 1.24 (95% CI: 1.00, 1.54)) and children aged 0–14 (RR: 1.11 (95% CI: 1.05, 1.18)), while they were non-significant for children under the age of 5 (RR: 1.01 (95% CI: 0.93, 1.10)). Furthermore, associations were slightly, but not significantly, stronger for boys (RR: 1.15 (95% CI: 1.07, 1.24)) than for girls (RR: 1.07 (95% CI: 0.97, 1.19)). There were no significant differences in associations between the different categories of family income or mother's education. For children with a prior asthma admission, the associations between UFP (same day) and asthma hospital admissions were considerably higher than for those who were admitted for the first time (RR: 1.24 (95% CI: 1.12, 1.37) and RR: 1.06 (95% CI: 0.98, 1.14), respectively). Moreover, we found strong, yet non-significant associations for children with an acute respiratory infection before the age of 5 (RR: 1.45 (95% CI: 0.84, 2.49)).

Exposure-response curves of the association between UFP and asthma hospital admissions in children up to 18 years showed a steep increase up to UFP concentrations of approximately 5000 pt/cm³, whereafter CIs widened (online supplemental figure S4). In a comparison of single-pollutant and two-pollutant models using a subset of data with complete information on UFP, PM_{2.5} and NO₂ (n=2009 days), we did not observe significant changes after mutual adjustment of air pollutants (online supplemental figure S5).

In sensitivity analyses, we found that associations between UFP and asthma hospital admissions remained positive, but not significant, when restricting the analysis to children living close to the monitoring station (online supplemental table S4). In analyses restricted to those days that had at least three available control days (n=3033 days), we found a similar association to that in the main analysis (RR: 1.07 (95% CI: 0.99, 1.14), lag 0).

DISCUSSION

We analysed the associations of short-term UFP exposure and other air pollutants with asthma hospital admissions in children

based on 17 years of data from Copenhagen, Denmark. We found significant, positive associations between short-term UFP exposure and asthma hospital admissions on the same day, as well as for multiple-day exposure windows of up to 1 week. Those associations were strongest in children aged 5–14 years, and in boys. Moreover, we observed stronger associations for those with a prior asthma admission and those who had been admitted to the hospital for an acute respiratory infection (HRV, RSV or influenza) under the age of 5. Different indicators of SES, or adjustment for PM_{2.5} or NO₂, did not change associations significantly.

The few previous studies on short-term exposure to UFP and asthma hospital admissions in children found mostly positive, but non-significant associations. Specifically, a study from Helsinki, Finland, found a 6.60% (95% CI: 2.34, 11.00) increase in asthma-related emergency room visits of children younger than 15 years per 5760 pt/cm³ increase in PNC lagged 4 days that were independent of PM_{2.5} but diminished after adjustment for NO₂.¹⁰ In Copenhagen, two previous studies of shorter time series (4–8 years) found positive, but non-significant associations between UFP and asthma hospital admissions of children up to 18 years (OR: 1.06 (95% CI: 0.98, 1.14) per 3813 pt/cm³ increase in 5-day mean PNC),⁹ and children aged 5–18 years (RR: 1.07 (95% CI: 0.98, 1.17) per 3907 pt/cm³ increase in 6-day mean PNC), both of which diminished after copollutant adjustment.⁸ Two studies from Shanghai, China, found positive associations between 1800 pt/cm³ increases in 3-day mean PNC and asthma emergency room visits (RR: 1.35 (95% CI: 1.14, 1.59))¹² and outpatient visits (RR: 1.21 (95% CI: 1.07, 1.38))¹³ in children. Studies that included all respiratory hospital admissions in children, beyond asthma, generally found positive, but non-significant associations with UFP concentrations at longer exposure windows.^{26 27}

Generally, in research on air pollution, even a small risk estimate may correspond to a large number of cases attributed to air pollution due to the ubiquitous nature of the exposure. As such, we estimated that 22% of all asthma hospital admissions in children in our 17-year study period, corresponding to 207 admissions per year, were attributable to short-term increases in UFP concentrations.

For PM_{2.5}, both previous studies from Copenhagen found significant, positive associations similar to our study, where we, however, observed stronger associations for longer exposure windows. Our findings are also in line with a meta-analysis of studies on short-term PM_{2.5} exposure and children's asthma hospital admissions and emergency room visits, which found an RR of 1.05 (95% CI: 1.03, 1.07) per 10 µg/m³ increase in PM_{2.5}.²⁸ Similarly, our results for NO₂ are comparable to the previous findings from Copenhagen and to a meta-analysis of short-term exposure to NO₂ and hospital admissions or emergency room visits due to asthma.²⁹ The same meta-analysis also found positive, significant associations for O₃, in line with the positive associations in our current study.

Concentrations of air pollution are comparably low in Copenhagen, with mean UFP concentrations at ~5000 pt/cm³. Other studies using background monitor UFP data with comparable cut-offs for particle diameter found significantly higher mean

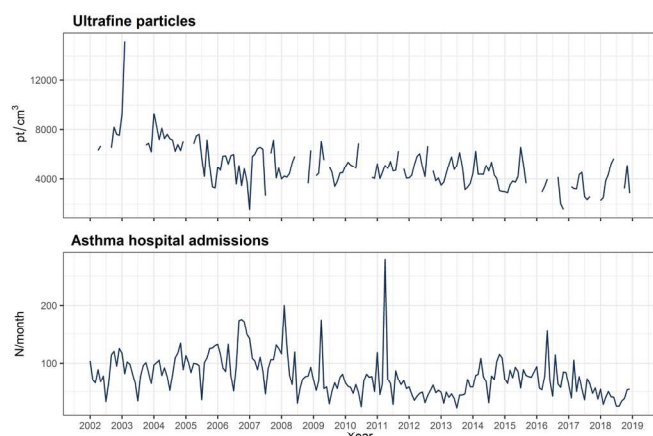


Figure 1 Monthly means of UFP and monthly number of asthma hospital admissions in children up to 18 years in Copenhagen in 2002–2018. UFP, ultrafine particles.

Table 3 Rate ratios and 95% CIs of the association between asthma hospital admissions in children per IQR increase in air pollutants on the same day and exposure windows of up to 7 days (moving averages)

Air pollutant	IQR	N days	RR (95% CI)						
			Lag 0	Lag 0-1	Lag 0-2	Lag 0-3	Lag 0-4	Lag 0-5	Lag 0-6
UFP (pt/cm ³)	3070	3496	1.12 (1.06, 1.19)*	1.17 (1.09, 1.25)*	1.15 (1.07, 1.24)*	1.16 (1.07, 1.26)*	1.12 (1.03, 1.22)*	1.13 (1.03, 1.24)*	1.13 (1.03, 1.25)*
PM _{2.5} (µg/m ³)	8	3563	1.05 (1.02, 1.09)*	1.13 (1.09, 1.18)*	1.13 (1.08, 1.18)*	1.12 (1.07, 1.18)*	1.11 (1.05, 1.17)*	1.10 (1.04, 1.16)*	1.04 (0.99, 1.11)
NO ₂ (ppb)	6	6025	1.04 (1.00, 1.07)†	1.05 (1.01, 1.10)*	1.04 (0.99, 1.08)	1.03 (0.98, 1.08)	0.99 (0.94, 1.04)	0.99 (0.94, 1.05)	1.00 (0.94, 1.06)
O ₃ (ppb, warm season)	10	2739	1.01 (0.90, 1.13)	1.09 (0.96, 1.23)	1.14 (1.00, 1.32)	1.18 (1.02, 1.37)†	1.08 (0.92, 1.27)	1.01 (0.85, 1.19)	1.03 (0.86, 1.23)

Model adjusted for temperature, relative humidity and public holidays.
 *Statistically significant with a p value below 0.01.
 †Statistically significant with a p value below 0.05.
 NO₂, nitrogen dioxide; O₃, ozone; PM_{2.5}, particulate matter <2.5 µm in diameter; ppb, parts per billion; RR, risk ratio; UFP, ultrafine particle.

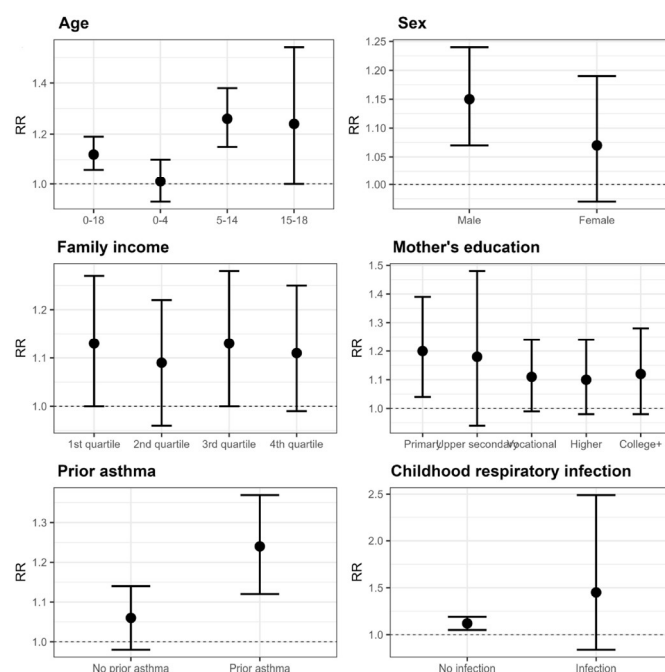


Figure 2 Rate ratios and 95% CIs of the association between asthma hospital admissions in different subgroups and an IQR increase in UFP on the same day, stratified by age (0–18/0–4/5–14/15–18 years), sex (female/male), categories (quartiles) of disposable family income, mother's education (primary/upper secondary/vocational/short cycle higher education/college+), prior asthma admissions (first admission/readmission) and childhood acute respiratory infections below the age of 5. Model adjusted for temperature, relative humidity and public holidays. RR, risk ratio; UFP, ultrafine particle.

concentrations, such as 6300–7700 pt/cm³ in three German cities,²⁷ 12 000 pt/cm³ (median) in London,³⁰ 8200 pt/cm³ in Helsinki¹⁰ or 11 400 pt/cm³ in Barcelona.³¹ This could be attributed to Copenhagen's policies for improving air quality, to its geographical location with no major UFP emission areas nearby, but also to the relatively high placement of the background monitor at 20 m height.

We assessed several possible effect modifiers in our study. First, differential susceptibility to short-term UFP exposure and asthma hospital admissions by age has been assessed in three previous studies, of which one found no differences between age groups,⁹ while two found stronger associations among school-aged children (<13 years).^{12,13} In our study, we found a clear difference in susceptibility among school-aged children compared with children under 5, where we found no associations. This could, among other factors, be related to difficulties in diagnosing asthma in children under 5,³² leading to outcome misclassification and bias towards the null. Second, findings indicate that pre-existing respiratory conditions (prior asthma or childhood respiratory infections) play an important role in children's susceptibility to adverse health effects of UFP. This is in line with a previous study from Rochester, New York, where a 2088 pt/cm³ increase in 4-day mean UFP was associated with an OR of 1.27 (95% CI: 0.90, 1.79) for asthma exacerbation in children.¹¹ In addition to that, studies of respiratory biomarkers, such as lung function and airway inflammation, suggest that asthmatic children are particularly susceptible to adverse health effects of short-term UFP exposure.^{33,34} Lastly, we did not find differential effects by SES in this study. This relationship has not previously been explored for UFP. However, a scoping review found that most available studies report greater associations between air pollution and respiratory diseases for children with lower SES,¹⁴ possibly related to a higher burden of existing health conditions. Nonetheless, SES could also have an effect in the opposite direction, as higher individual-level SES has been associated with higher UFP exposure in Denmark.³⁵

Strengths and limitations

Strengths of this study include the use of health and exposure data covering a long study period of 17 years. Furthermore, we were able to link to detailed pre-existing health conditions and individual-level indicators on SES to identify susceptible groups, which is not usually done in time-series studies.

Some limitations have to be acknowledged. First, a commonly discussed limitation of comparable studies is the use of a single urban background station for exposure assessment. In order to assess the city-wide representativeness of background-level UFP measurements, we have previously compared them to measurements from a street-level monitoring station in central Copenhagen (2002–2016) and found moderate correlation ($r=0.58$) of daily means, indicating that background-level UFP might accurately represent temporal variability of UFP throughout the city.²⁰ Additionally, a recent measurement campaign of UFP in Copenhagen found good agreement between daily mean concentrations at 7 fixed monitoring stations and 37 residential locations across Copenhagen.³⁶ Moreover, the current study's results did not change significantly when restricting the analysis to children living close to the monitoring station. Nonetheless, microenvironments and activity patterns play an important role in children's UFP exposure. As children spend most time indoors, at home and in schools, where UFP concentrations vary substantially based on location, on activities such as cooking or smoking inside, mould/dampness or pet ownership, those exposures should ideally be considered in epidemiological studies.¹⁶ Furthermore, outdoor UFP concentrations vary greatly by distance to traffic, and peak exposures can be experienced while moving through the city.³⁷ While it would be informative to examine children's exposure patterns in Copenhagen, we do not expect exposure misclassification to have led to an overestimation of effect estimates. In fact, exposure misclassification generally leads to a bias towards the null, which is why our results might be even higher without exposure misclassification.³⁸ A second limitation is the amount of missing air pollution data in our study, which was as high as 44% and 43% for UFP and $PM_{2.5}$, respectively. However, missing air pollution data did not follow a systematic pattern, such as by month, day of the week or meteorology, and sensitivity analyses suggested that associations for cases with at least three available control days were similar to our main analysis. Lastly, we did not explore possible interactions between UFP and other relevant exposures such as temperature or pollen, which should be addressed in future studies.

CONCLUSIONS

Short-term exposure to UFP may be associated with asthma hospital admissions in children in Copenhagen. Children aged 5–14 years and those with prior asthma might be most susceptible to the adverse health effects of UFP. Those findings suggest that preventive measures to reduce UFP exposure could reduce asthma morbidity in children and should specifically target the susceptible subgroups identified in our study. Finally, the body of evidence on this association is still small, and more studies in more diverse settings with detailed information on the distribution of UFP and other air pollutants are needed.

Contributors MB (guarantor) had full access to the study data and took responsibility for the integrity of the data and accuracy of the data analysis. ZJA, JZ, Y-HL and ST made substantial contributions to the conception, design, analysis and interpretation of the data. MB drafted the original article and ZJA, AM, SL, TC-H, CN, ST, JZ and Y-HL revised it critically for important intellectual content. All authors provided final approval of the version to be published.

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Avaliação do risco de cancro do pulmão por meio de modelo de predição: uma perspectiva global

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RESUMO

Contexto Numerosos modelos de predição de risco de cancro do pulmão têm sido desenvolvidos e validados em todo o mundo. É fundamental oferecer uma visão abrangente e uma análise comparativa dos seus desempenhos. **Métodos** Realizámos uma pesquisa extensa da literatura para identificar estudos que desenvolvessem e/ou validassem modelos de predição de risco de cancro do pulmão. Em seguida, resumimos e comparamos o desempenho externo desses modelos, com foco na precisão discriminativa (índice C) e no desempenho de calibração (rácio E:O).

Resultados Após uma triagem inicial de 10 210 artigos, foram identificados 35 estudos sobre 21 modelos de predição distintos, que utilizaram 42 tipos diferentes de preditores distribuídos por sete categorias. Foram observadas variações notáveis de desempenho nas validações externas. Nos grupos norte-americanos, o índice C variou entre 0,60 e 0,87, com rácios E:O entre 0,62 e 3,70. Entre os grupos europeus, o estudo de saúde Trøndelag (HUNT) e o CanPredict apresentaram índices C superiores a 0,870. Por outro lado, os modelos Bach, LCRAT (lung cancer risk assessment tool), PLCO_{m2012} e PLCO_{all2014} tiveram desempenho fraco nos registos eletrónicos de saúde do subgrupo da base de dados QResearch, com índices C abaixo de 0,60. O PLCO_{m2012} alcançou o melhor rácio E:O de 1,00 (IC 95%: 0,93–1,08) no subgrupo do UK Biobank. Nos grupos asiáticos, o índice C variou entre 0,54 e 0,87. Apenas três modelos — Korean Men, LCRAT e o modelo de risco de incidência do Liverpool Lung Project (LLPi) — atingiram um índice C superior a 0,80. O LCRAT demonstrou a melhor calibração, enquanto o modelo de Hoggart apresentou o pior desempenho.

Conclusões O desempenho dos modelos de predição de risco de cancro do pulmão, apesar de bem desenvolvidos e validados, varia entre diferentes populações. Persiste um desequilíbrio regional significativo no desenvolvimento destes modelos. Uma validação externa rigorosa ou um estudo de recalibração na população-alvo é essencial, de acordo com as orientações, antes da implementação do modelo.

Número de registo PROSPERO: CRD42022324602.

INTRODUCTION

Lung cancer is a leading worldwide cancer, accounting for 11.4% of the total cancer incidence and 18.0% of cancer-related deaths.¹ The US National Lung Screening Trial (NLST) demonstrated that screening high-risk individuals with low-dose CT (LDCT) reduced lung cancer mortality by 20%.² The US Preventive Services Task Force 2021 (USPSTF2021) recommends annual screening for lung cancer with LDCT for adults aged 50–80 years with a smoking history ≥20 pack-years, meanwhile current smoking individuals or former smoking individuals who ceased smoking within ≤15 years.³ Despite the expanded screening eligibility, these criteria may not fully identify all high-risk individuals. Growing evidence suggests that using individually calculated risk scores from lung cancer risk prediction models might be a more effective approach for screening selection.⁴

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► A wide array of lung cancer risk prediction models has been developed, with numerous validation studies published. However, the task of comprehensively assessing the performance of these existing models remains challenging.

WHAT THIS STUDY ADDS

► This study offers a comprehensive overview and comparative analysis of performances of lung cancer risk prediction models, in the perspective of discriminative ability and calibration accuracy, stratified by population and smoking status.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► This study demonstrated that, even for the lung cancer risk prediction models that are well developed and rigorously validated, their performance tends to diverge across diverse populations during validation. Therefore, it is imperative to conduct a well-designed validation or recalibration study in the target population and report the details strictly adhering to the guidance such as TRIPOD+AI (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis+artificial intelligence), prior to model implementation.

In the past two decades, numerous multivariable lung cancer risk prediction models have been successfully developed and validated globally.⁵ For reliability and generalisability, models ought to be implemented in wider populations that differ from development samples. Model performance in terms of calibration and discrimination may vary according to modelling methodology, risk factors included or population applied to. Hence, conducting systematic reviews to extract and evaluate model performance across multiple studies is crucial for comprehensive assessment.

Therefore, we conducted a systematic review with two aims. First, to offer a concise and comprehensive overview of lung cancer risk prediction models globally that had been externally validated. Second, to understand the performance of these models across diverse populations, delving into their potential for future application and calibration.

METHODS

We designed this systematic review in accordance with the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) statement.⁶ A protocol for this study was published with the PROSPERO (International Prospective Register of Systematic Reviews), under registration number CRD42022324602.

Search strategy and selection criteria

The literature was systematically searched through PubMed, Embase and Web of Science from database inception to 15 November 2023. The combination of the following key search terms was used for each database: “lung cancer”, “risk”, “prediction”, “model” and “valid”. The full search strategy is available in online supplemental file 1. Meanwhile, a manual search for reference lists of relevant articles was performed for further eligible studies.

Broad inclusion criteria for prediction modelling studies were used to include all possible models for predicting the risk of developing lung cancer in participants. All studies in the English language that met the following criteria were included: (1) studies designed to develop the new risk prediction models but without external validation in original studies; (2) studies developing and externally validating the same prediction models; (3) studies designed to develop the new risk prediction models and compare with the previously developed comparable models; (4) updating the previously developed models; (5) studies designed to validate the existing risk prediction models.

The exclusion criteria were as follows: (1) newly developed models without external validation either in the original model development study or the following studies designed to validate the existing models; (2) models incorporating lung nodule characteristics extracted from LDCT images; (3) conference abstracts, letters to editors, reviews and study protocols, in addition to other non-original studies were excluded.

Data extraction

Data extraction was conducted independently by two investigators (LZ, QC) and assessed by the other two investigators (MZ, CJ). Disagreements were resolved by consensus. From included articles, we extracted information on first author, publication year, derived or validated model name and validation data sets information. For all eligible models, we extracted information on the following domains: study information, model characteristics, model performance and validation. Full information on the extracted data was provided in table 1 and online supplemental file 1.

To evaluate the predictive performance, measures of discrimination and calibration were extracted from the original publication. Common measures of discrimination are the discrimination ability (C-index) and area under the curve (AUC) which typically ranges from 0.50 to 1.00. Calibration is usually assessed with calibration plots and the observed/expected ratio (E:O ratio). Detailed information was provided in the online supplemental file 1.

Quality assessment

For each prediction model, the prediction model risk of bias assessment tool (PROBAST) was used to assess risk of bias (ROB), or potential for inflated model performance estimates due to shortcomings in design/analysis.⁷ This tool evaluated ROB in four domains: participants, predictors, outcome and statistical analysis. Each domain was rated as high, low or unclear ROB. Overall ROB was judged as low if all domains were low risk, high if any domain was high risk and otherwise unclear risk.

RESULTS

Model selection and characteristics

Search by PRISMA guidance yielded 10 210 studies, of which 296 were screened the full text, and 35 studies were included (figure 1). Of these, 21 studies were designed to develop lung cancer risk prediction models, of which 3 studies proposed new models without external validation, 5 studies developed and externally validated the proposed model, 6 studies upgraded the previously developed models and the other 7 studies developed new models while comparing

with the existing ones. The other 14 studies validated these existing models independently (online supplemental file 1). Finally, 21 lung cancer risk prediction models with external validations were identified.

All 21 risk prediction models were applicable to ever smoking individuals; 13 of them were tailored for general population, including never smoking individuals. A total of 19 (90.48%) were developed in prospective cohorts and only 2 were trained from case-control studies. There were 9, 7 and 5 models for European, North American and Asian populations, respectively. All these models underwent internal validation, of which nine were tested in non-randomly split data sets, and the remaining models were tested in either randomly split data sets (n=3), or by cross-validation (n=4) or bootstrapping (n=5) approaches. Sample sizes of model development sets ranged from 1736 to 12 917 662, with lung cancer cases from 237 to 73 380.

Of note, 11 models were developed using Cox regression, 7 were by logistic regression, 1 was by Weibull regression; and the other two were developed by machine learning methods including eXtreme Gradient Boosting (XGBoost) and AutoPrognosis (table 1).

Evaluation for risk of bias

According to the PROBAST checklist, nine models had high overall ROB (figure 2), all of which were evaluated to have high ROB for the analysis domain. Details of domain evaluation are provided in online supplemental file 1.

Predictors

The 21 prediction models included, aimed at general populations or specific subpopulations, were derived from 28 individual models (figure 3, online supplemental file 1). Numbers of predictors ranged from a minimal of 2 (Spitz model for never smoking individuals) to a maximum of 18 (OWL+ as an extension of optimized early warning model for lung cancer risk (OWL) model), with an interquartile of 6–11 predictors per model. Overall, 42 unique predictors fell into seven categories according to their definition or functionality: (1) cancer history; (2) demographics; (3) environmental exposures; (4) laboratory and functional measurements; (5) medical activity; (6) medical history and symptoms; and (7) smoking. Details were provided in online supplemental file 1.

External validation data sets of the models

All models in this study underwent external validation. Each included model reported discrimination in external validation sets and reported at least one AUC or C-index. The prostate, lung, colorectal and ovarian cancer screening (PLCO)_{m2012}, Liverpool lung project V3 (LLPv3) and Bach models were the most frequently validated externally. Sample size in the external data sets ranged from 4 051 to 1 287 502 individuals, with lung cancer cases varying from 99 to 11 509. Regarding calibration, seven models had no E:O ratio reported in external validation studies. The maximum sample size for validation sets regarding E:O ratio evaluation varied from 25 653 to 3 69 650, with the number of lung cancer cases varying from 503 to 11 590 (online supplemental file 1).

Model performance in external validation

Stratified by populations

In the North American population, 13 models had C-index ranged from 0.60 to 0.87 in external validation. The PLCO family models, OWL, LCRAT and LLPv3 showed high C-index (>0.80) in the PLCO trial subgroup. However, the PLCO₂₀₁₂, PLCO_{m2012} and LLPv3 models performed poorly in the PLCO trial under different inclusion and exclusion criteria (C-index, 0.65–0.67). For calibration, models showed a clear difference in E:O ratio ranging from 0.62 to 3.70. The UCL-I and Bach models demonstrated satisfactory calibration in the PLCO Trial chest radiography arm (PLCO-CXR) and The National Institutes of Health and the American Association of Retired Persons data sets, with E:O ratios of 1.00 (95% CI: 0.92 to 1.07) and 1.00 (95% CI: 0.98 to 1.02), respectively (figures 4 and 5, online supplemental file 1).

In the European population, 14 models had C-index values in the external validation that ranged from 0.53 to 0.89. The HUNT

Table 1 Summarised information of 21 included prediction models

Model	Year	Study design	Modelling type	Targeted population smoking status	Country	Derived data set	External validation with best performance	
						N _{Lung cancer} / N _{Participants}	Discrimination AUC/C-index (95% CI)	Calibration E:O ratio (95% CI)
Bach	2003	Cohort	Cox proportional regression	Ever smokers	USA	1070/18 172	EPIC-UK 0.840 (0.810 to 0.870)	NIH-AARP 1.000 (0.980 to 1.020)
Spitz	2007	Case-control	Logistic regression	Never smokers Former smokers Current smokers	USA	1851/3852	EPIC-Germany 0.780 (0.730 to 0.830)	NLCS 3-year Ever smokers 1.010 (0.698 to 1.327)
PLCO ₂₀₁₁	2011	Cohort	Logistic regression	Model 1 General population Model 2 Ever smokers	USA	Model 1: 1040/70 962 Model 2: 964/38 260	Model 1 PLCO-CXR-Men 0.849 (0.815 to 0.883) Model 2 PLCO-CXR-Men 0.789 (0.743 to 0.835)	—
PLCO _{m2012}	2013	Cohort	Logistic regression	Ever smokers	USA	709/39 928	EPIC-UK 0.820 (0.770 to 0.850)	UKB Current smoker 1.000 (0.930 to 1.080)
PLCO _{all2014}	2014	Cohort	Logistic regression	General population	USA	1307/38 634	PLCO-CXR General population 0.869 (0.850 to 0.889)	PLCO-CTRL USPSTF-CN 1.027 (0.891 to 1.212)
Pittsburgh Predictor	2015	Cohort	Logistic regression	Ever smokers	USA	1854/51 577	Korea-NHIS 0.781 (0.778 to 0.784)	NIH-AARP 1.010 (0.980 to 1.030)
LCRAT	2016	Cohort	Cox proportional regression	Ever smokers	USA	1505/39 180	EPIC-UK 0.830 (0.810 to 0.870)	NLCS 3-year Ever smokers 1.006 (0.507 to 1.505)
UCL-I	2023	Cohort	AutoPrognosis	Ever smokers	USA	4409/243 330	PLCO-CXR Former smoker 0.791 (0.768 to 0.814)	PLCO-CXR 1.000 (0.920 to 1.070)
LLP	2008	Case-control	Logistic regression	General population	UK	579/1736	LLPC 0.820 (0.800 to 0.850) EPIC-UK 0.820 (0.780 to 0.850)	NLCS 5-year Ever smokers 0.953 (0.625 to 1.514)
LLPi	2015	Cohort	Cox proportional regression	General population	UK	237/8760	Korea-NHIS 0.803 (0.800 to 0.806)	NLCS 3-year Ever smokers 0.805 (0.348 to 1.458)
LLPv3	2020	Cohort	Logistic regression	General population	UK	599/75 958	PLCO-CXR General population 0.846 (0.824 to 0.869)	PLCO-CTRL USPSTF-CN 1.027 (0.884 to 1.224)
Hoggart	2012	Cohort	Weibull regression	General population	Western Europe	1124/151 005	CARET-high risk 1-year 0.753 (0.700 to 0.806)	NLCS 3-year Ever smokers 0.407 (0.381 to 1.394)
HUNT	2018	Cohort	Cox proportional regression	Ever smokers	Norway	583/58 343	CONOR General population 0.8915 (0.879 to 0.903)	—
Reduced HUNT	2019	Cohort	Cox proportional regression	Ever smokers	Northern Europe	227/12 091	DLCST Non-screened 0.709	—
OWL	2023	Cohort	XGBoost algorithm	General population Ever smokers	UK	General population 1655/323 344 Ever smokers 1371/144 304	General population PLCO-CXR 5-year 0.865 (0.844 to 0.887) Ever smokers PLCO-CXR 5-year 0.812 (0.763 to 0.861)	General population UKB-SW 5-year 1.002 (0.899 to 1.133) Ever smokers NLST-CTRL 6-year 0.989 (0.920 to 1.070)
CanPredict	2023	Cohort	Cox proportional regression	General population	UK	73 380/13 064 422	CPRD GOLD-men 0.878 (0.875 to 0.881)	—
Korean Men	2013	Cohort	Cox proportional regression	General population	Korea	10 007/1 309 144	KNHC-1998 to 1999 0.871 (0.867 to 0.876)	—
JPHC	2018	Cohort	Cox proportional regression	General population	Japan	1210/59 161	JPHC Cohort I 0.772	—
China NCC-LC _{m2021}	2022	Cohort	Cox proportional regression	Never smokers Ever smokers	China	Never smokers 925/425 626 Ever smokers 538/12 952	WHOLE 3-year Never smokers 0.673 (0.650 to 0.695) Ever smokers 0.752 (0.715 to 0.789)	Ever smokers 1.040 (0.680 to 1.410)

Continued

Table 1 Continued

Model	Year	Study design	Modelling type	Targeted population smoking status	Country	Derived data set	External validation with best performance	
						N _{Lung cancer} / N _{Participants}	Discrimination AUC/C-index (95% CI)	Calibration E:O ratio (95% CI)
LCRS	2023	Cohort	Cox proportional regression	Ever smokers Never smokers	China	Ever smokers 3133/159 715 Never smokers 2428/336 526	Ever smokers 0.774 (0.695 to 0.853) Never smokers 0.759 (0.675 to 0.842)	–
Shanghai-LCM	2023	Cohort	Cox proportional regression	Ever smokers	China	771/25 653	17 ACC 0.700 (0.670 to 0.720)	17 ACC 1.550 (1.240 to 1.930)

-, Not available.

ACC, Asia Cohort Consortium; AUC, area under the curve; CARET, Carotene and Retinol Efficacy Trial; China NCC-LCM2021, China National Cancer Center-Lung Cancer 2021 model; C-index, discrimination ability; CN, criteria negative; CONOR, Cohort of Norway; CPRD GOLD, Clinical Practice Research Datalink Gold database; CXR, chest X-ray; DLCST, Danish Lung Cancer Screening Trial; E:O, observed/expected ratio; EPIC, European Prospective Investigation into Cancer and Nutrition; HUNT, Nord-Trøndelag Health Study; JPHC, Japan Public Health Center-based study; KNHC, Korean National Health Corporation; Korea-NHIS, Korea National Health Insurance Service; LCRAT, Lung Cancer Risk Assessment Tool; LCRS, Lung Cancer Risk Score; LLP, Liverpool lung project; LLP, LLP population-based prospective cohort study; NIH-AARP, National Institutes of Health and the American Association of Retired Persons; NLCS, National Lung Cancer Screening; NLST, National Lung Screening Trial; NLST-CTRL, National Lung Screening Trial chest radiography arm; OWL, Optimized Early Warning Model for Lung Cancer Risk; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening; PLCO-CTRL, Prostate, Lung Colorectal, and Ovarian Screening Trial control arm; UCL-I, University College London-Incidence; UKB, UK Biobank; UKB-SW, UKB Scotland and Wales area; USPSTF, US Preventive Services Task Force; WHOLE, Whole Life Cycle of Cancer Screening; XGBoost, eXtreme Gradient Boosting.

and CanPredict models demonstrated excellent C-index (>0.87) in the Cohort of Norway and Clinical Practice Research Datalink Gold database (CPRD GOLD), respectively. The Bach, LCRAT, PLCO_{m2012} and PLCO_{all2014} models performed poorly in electronic health records of the Qresearch database subgroup (C-index <0.6). For calibration, the PLCO_{m2012} model reached the best E:O ratio of 1.00 (95% CI: 0.93 to 1.08) in UK Biobank (UKB) current smoking individuals. Conversely, the Hoggart model showed overprediction in the Generations Study (E:O ratio, 16.10; 95% CI: 6.69 to 38.60) (figures 4 and 5, online supplemental file 1).

In the Asian population, 14 models had C-index values from 0.54 to 0.87. Three models, including the Korean Men model in

the Korean National Health Corporation enrolled from 1996 to 1997 data set, LCRAT and LLPi in the Korea National Health Insurance Service, achieved well performance (C-index >0.80). LLP (C-index, 0.56; 95% CI: 0.50 to 0.69) and LLPi (0.57; 95% CI: 0.50 to 0.71) models showed poor performance in Whole Life Cycle of Cancer Screening ever smoking individuals. For calibration, LCRAT had the best calibration in the China National Lung Cancer Screening programme ever smoker subgroup (E:O ratio, 1.01; 95% CI: 0.51 to 1.51); while the Hoggart model showed the worst calibration in this data set (0.41; 95% CI: 0.38 to 1.39) (figures 4 and 5, online supplemental file 1).

Stratified by smoking status

For the general population, nine models had C-index values ranging from 0.66 to 0.89; of these, seven models, excluding Spitz and Bach models, had well performance (C-index >0.8). The CanPredict model showed notable C-index in the GOLD-Men subgroup (C-index, 0.878; 95% CI: 0.875 to 0.881). As for calibration, only the PLCO_{all2014}, OWL and LLPv3 models reported E:O ratio in the general population, ranging from 0.66 to 1.33 (figures 4 and 5, online supplemental file 1).

In ever smoking individuals, all models reported C-index values that varied from 0.54 to 0.84. OWL model showed outstanding discrimination with C-index of 0.84 (95% CI: 0.81 to 0.87) in UKB Scotland and Wales area (UKB-SW). Regarding the E:O ratio, 14 models were validated in external data sets yielding values from 0.41 to 16.10, with both the lowest and highest values attributed to the Hoggart model. Conversely, OWL, PLCO_{m2012}, UCL-I, Bach, LCRAT, Pittsburgh Predictor and Spitz models exhibited good calibration ability in some external data sets (E:O ratio ranging between 0.80 and 1.20) (figures 4 and 5, online supplemental file 1).

For never smoking individuals, six models were validated in this specific subpopulation. PLCO_{all2014}, LLPv3 and OWL models showed robust C-index in the PLCO trial (C-index >0.80). OWL also demonstrated satisfactory calibration in UKB-SW (E:O ratio,

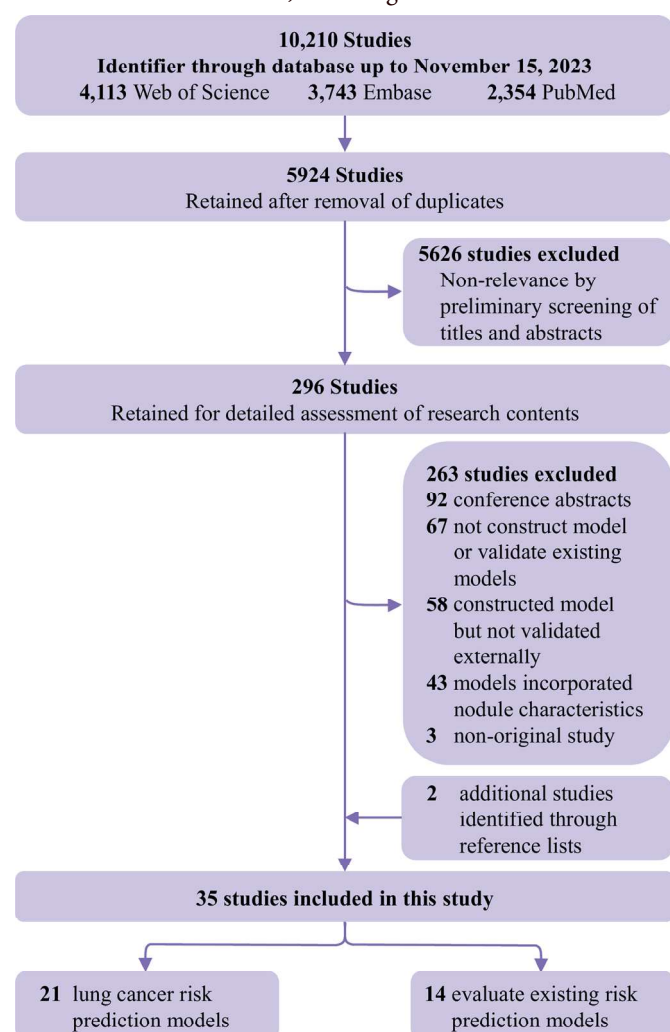


Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of study inclusions and exclusions.

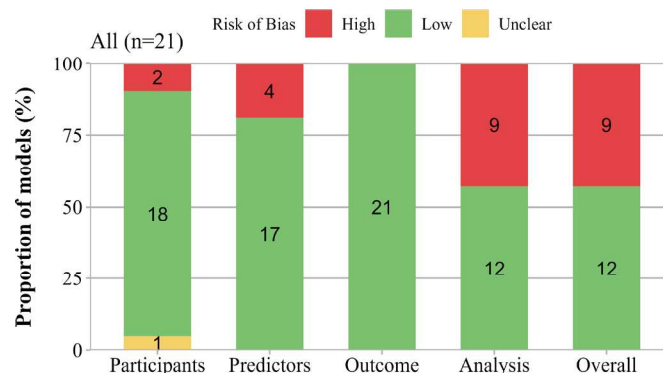


Figure 2 PROBAST (Prediction Model Risk Of Bias Assessment Tool) risk of bias for all included models (n=21).

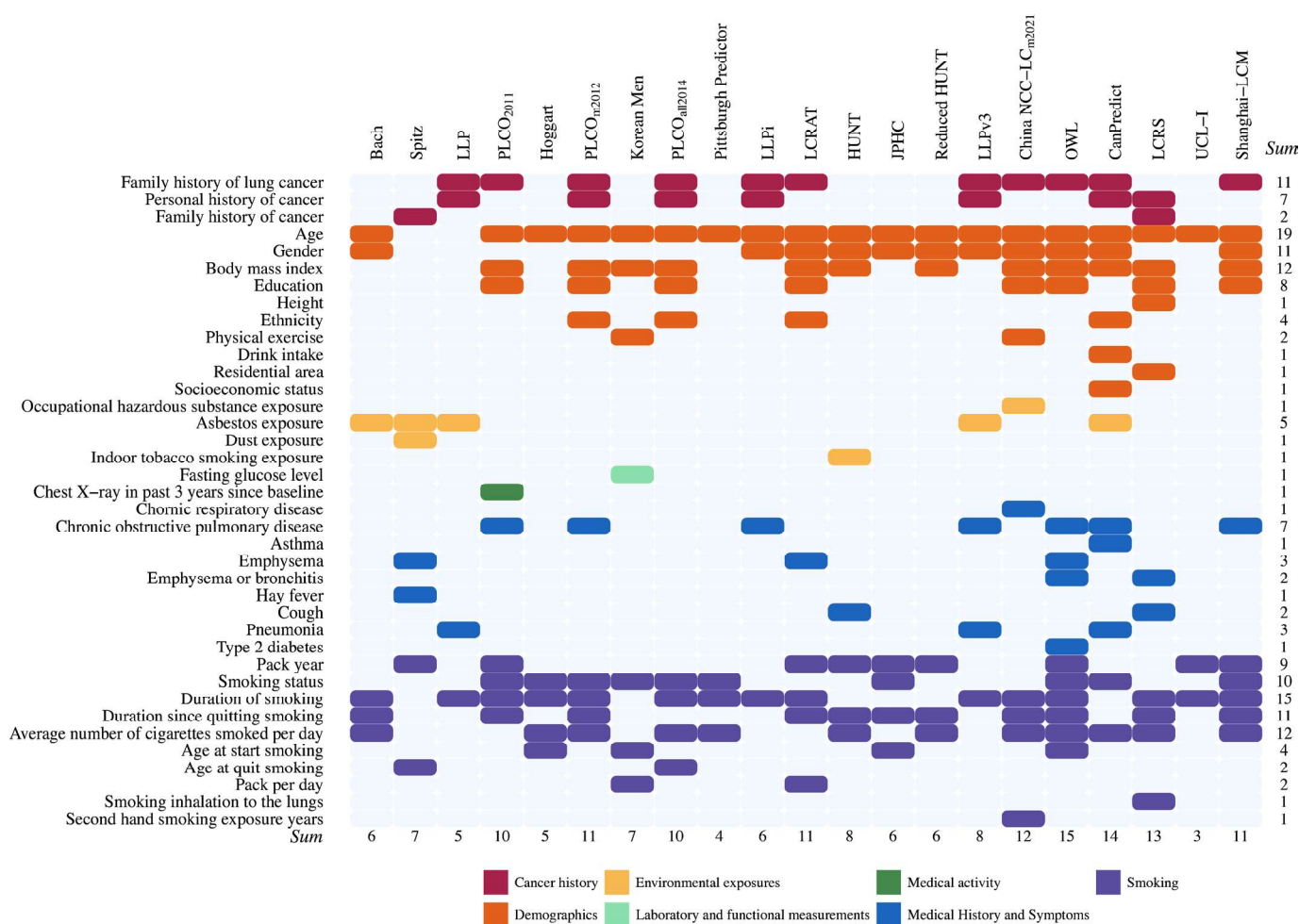


Figure 3 Matrix of risk predictors for the included lung cancer risk prediction models applying to ever smoking individuals. Spitz, PLCO₂₀₁₁ and China NCC-LC_{m2021} and LCRS models can be divided into different submodels aiming to different populations of smoking status. OWL and UCL-I models have extension versions. All details can be found in online supplemental file 1. Sum: the sum of a predictor or the number of predictors included in a model. PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening.

1.02; 95% CI: 0.85 to 1.27) (figures 4 and 5, online supplemental file 1).

DISCUSSION

This systematic review employed rigorous criteria to exclusively include externally validated prediction models. We provided an in-depth description of the selected models along with validation studies of these established models, summarising their performance across subgroups in external validation cohorts, to offer a precise assessment of their predictive capabilities.

Predictors incorporated in the models

Models incorporating easily obtainable predictors

Most included models leveraged easily obtainable predictors such as demographics, cancer history and smoking-related factors, which are key modifiable risk factors for lung cancer.⁸ These factors, like age and personal history of cancer, can be quickly gathered via interview or questionnaire and are commonly found in clinical practice and primary care records, facilitating their integration into prediction models.

Models incorporating lung function measurements

In this study, only two models incorporated laboratory and lung functional measurements. Forced expiratory volume in 1 second, which had the association with lung cancer incidence and mortality,⁹ only appeared in the OWL+ model. Muller et al developed and internally validated a prediction model incorporating spirometry data from a large UK prospective cohort, modestly enhancing discriminatory power.¹⁰ In addition, a study conducted in Canada with 2596 individuals having smoking exposure over 20 pack-years

found that incorporating lung function improved model discrimination (AUC: 0.77, 95% CI: 0.73 to 0.81) over the base model (AUC: 0.72, 95% CI: 0.67 to 0.77) (comparison $p=0.001$) in internal validation. 11 Assessing how lung function parameters enhance lung cancer risk prediction models is crucial.

Models incorporating biomarkers

Recent advancements in biomarker discovery have produced novel and effective means for personalised lung cancer risk assessment. Biomarkers involve identifying abnormal levels of specific molecules (eg, single nucleotide polymorphisms (SNPs), proteins or hormones) in blood, body fluids or tissues, signalling disease progression.¹² While some biomarkers have been integrated into risk prediction models, most of these models lack external validation.

K Gould et al developed a machine learning model incorporating distinctive laboratory variables, including white blood cell, platelet count and red cell distribution width. This model exhibited an AUC of 0.86 (95% CI: 0.84 to 0.87), surpassing the PLCO_{m2012} model's AUC of 0.79 (95% CI: 0.77 to 0.81) (comparison $p\text{ value}<0.001$) in an internal validation set.¹³ This study underscored the potential of routine laboratory measures as biomarkers for lung cancer risk.

Routine clinical and laboratory data can be complemented with genetic variants in predictive models. Genome-wide association studies (GWASs) have identified hundreds of SNPs linked to lung cancer across diverse ethnicities since 2008.¹⁴ Spitz et al enhanced their original model (Spitz) by incorporating DNA repair capacity and bleomycin sensitivity markers, boosting the AUC from 0.67 (95% CI: 0.63 to 0.71) to 0.70 (95% CI: 0.66 to 0.74) for former smoking individuals, and from 0.68 (95% CI: 0.64 to 0.72) to

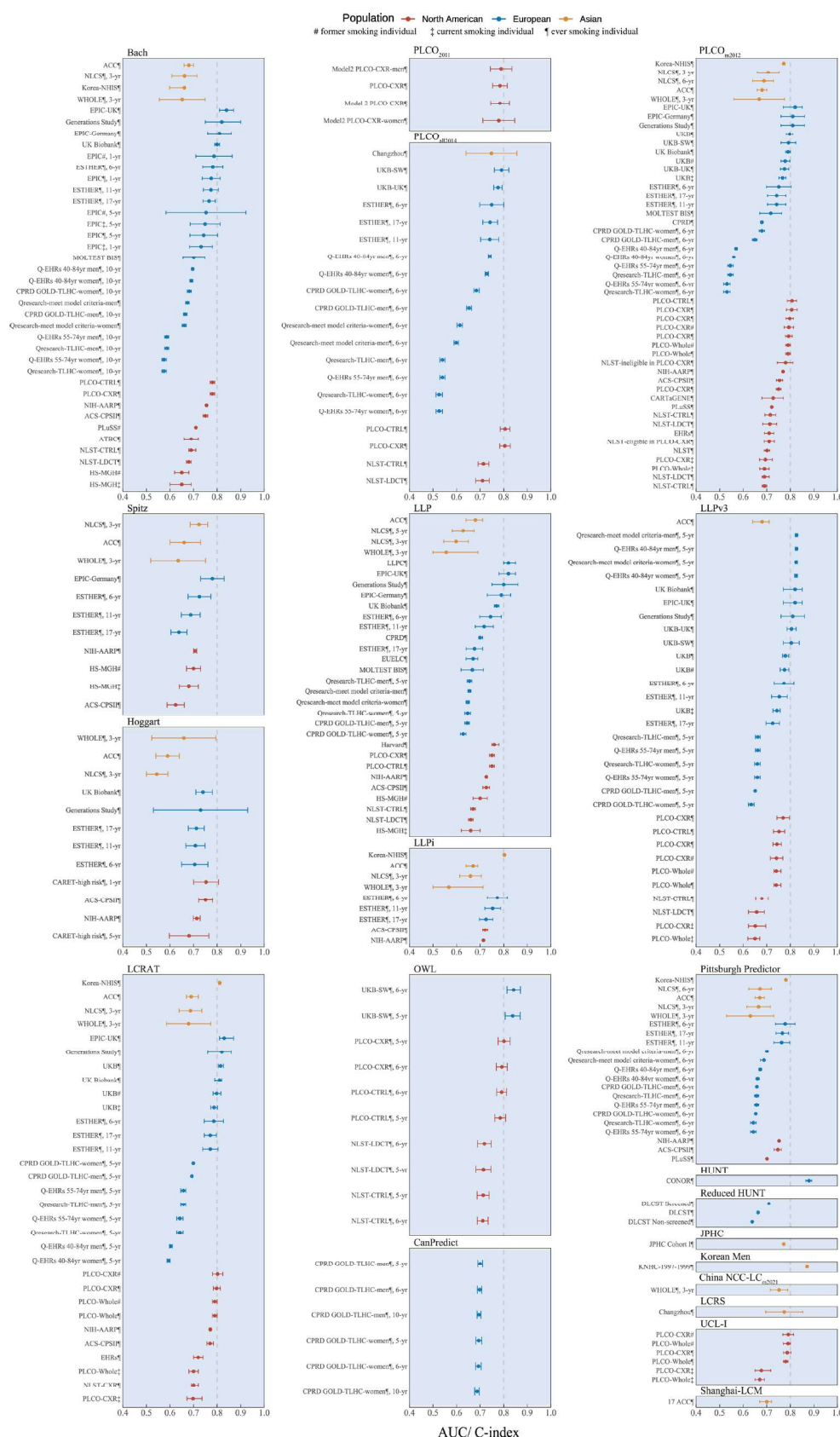


Figure 4 The forest plots of the model discrimination (AUC/C-index) of externally validated prediction models in ever smoking individuals. AUC, area under the curve; C-index, discrimination ability; CONOR, Cohort of Norway; CPRD-GOLD, Clinical Practice Research Datalink Gold database; CXR, chest X-ray; KNHC, Korean National Health Corporation; Korea-NHIS, Korea National Health Insurance Service; LDCT, low-dose CT; NIH-AARP, National Institutes of Health and the American Association of Retired Persons; NLCS, National Lung Cancer Screening; NLST, National Lung Screening Trial; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening; Q-EHR, Electronic Health Record of Qresearch database; TLHC, Targeted Lung Health Checks; UKB, UK Biobank; UKB-SW, UKB Scotland and Wales area; WHOLE, Whole Life Cycle of Cancer Screening.

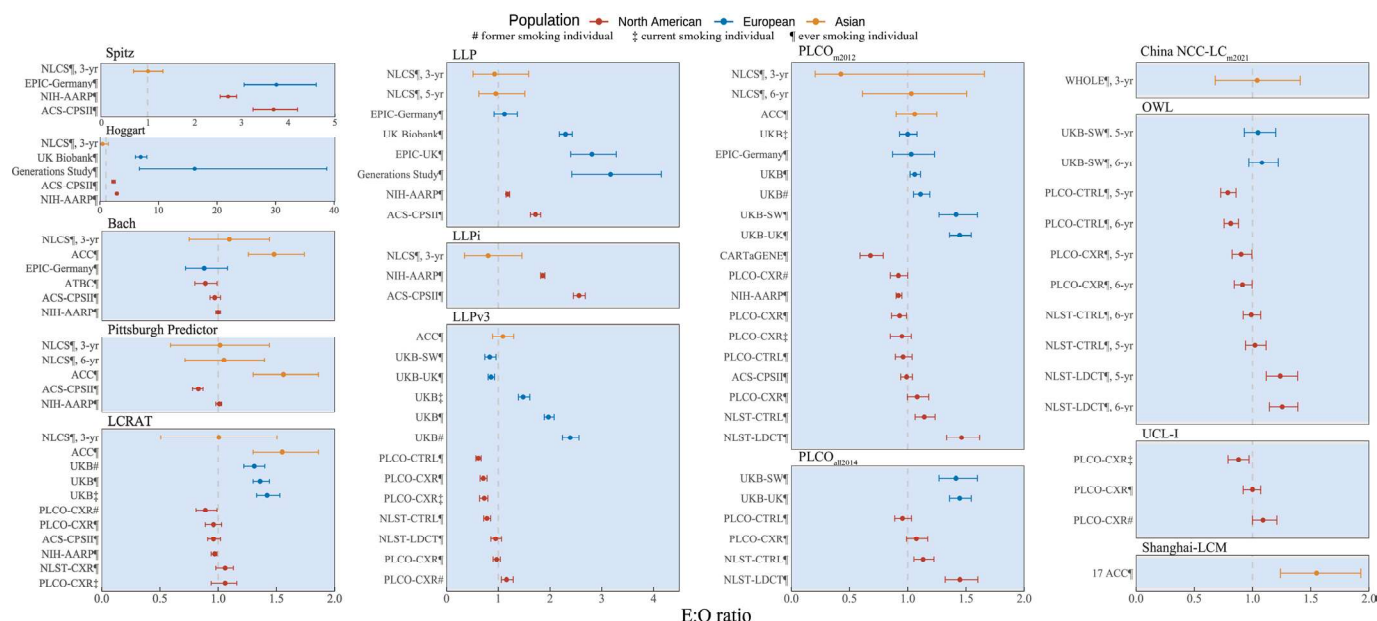


Figure 5 The forest plots of the model calibration (E:O ratio) of externally validated prediction models in ever smoking individuals. CXR, chest X-ray; E:O ratio, observed/expected ratio; LDCT, low-dose CT; NIH-AARP, National Institutes of Health and the American Association of Retired Persons; NLCS, National Lung Cancer Screening; NLST, National Lung Screening Trial; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening; UKB, UK Biobank; UKB-SW, UKB Scotland and Wales area; WHOLE, Whole Life Cycle of Cancer Screening.

0.73 (95% CI: 0.69 to 0.77) for current smoking individuals, respectively, in threefold cross-validation (comparison $p=0.006$, $p=0.0048$, respectively).¹⁵ Similarly, incorporating SNPs in seizure 6-like improved the LLP model's AUC from 0.72 to 0.75 in internal validation (comparison $p=0.01$).¹⁶ In our study, OWL+, which includes genetic indicators, significantly improved lung cancer risk discrimination. A polygenic risk score (PRS) effectively quantifies the cumulative effect of multiple risk-associated variants. Dai et al have shown for the first time in a Chinese population that GWAS-derived PRS can identify subpopulations at high risk for lung cancer, beyond traditional predictors like smoking.¹⁷

In a proof-of-principle study, Guida et al showed that a four-marker protein panel (4MP) comprising cancer antigen 125, carcinoembryonic antigen, cytokeratin-19 fragment and the precursor form of surfactant protein B could improve lung cancer risk assessment, achieving an AUC of 0.83 (95% CI: 0.76 to 0.90) in internal validation.¹⁸ Fahrman et al further showed that combining 4MP with PLCO_{m2012} yields further improved performance compared with PLCO_{m2012} alone and outperformed USPSTF₂₀₁₃ and USPSTF₂₀₂₁ criteria by increasing sensitivity by 11.9% and 9.9%, and specificity by 12.9% and 6.9%, respectively.¹⁹ Additionally, the 4MP validated its utility in predicting lung cancer-specific mortality risk and distinguishing benign from malignant indeterminate pulmonary nodules.²⁰

Biomarker-based risk stratification can be independently implemented, offering ease and speed in interpreting a single blood test compared with compiling extensive patient information. However, lung cancer's complex mechanisms suggest that combining biomarkers with other crucial risk factors may provide higher accuracy than relying solely on biomarkers.²¹ A biomarker-informed model usually yields moderate performance improvements over questionnaire-based models, hinting at undiscovered significant biomarkers for specific subpopulations and complex interactions between biomarkers and other factors. Thorough evaluation of the cost-effectiveness of such models is necessary.

Models incorporating environmental exposure predictors

Environmental exposure predictors have occupational-related, indoor and outdoor tobacco smoking exposure but lack air pollution predictors. Among the five models, one considered asbestos exposure, and another included the occupational hazardous substance exposure. Previous epidemiological studies have linked air pollution to lung cancer mortality,²² with PM pollution classified as a group 1 carcinogen by the International Agency for Research

on Cancer.²³ Huang et al revealed that high genetic risk combined with high air pollution exposure synergistically increased lung cancer risk, and 15–32% of lung cancer risk was attributed to the underlying interactions.²⁴ These studies offered a fresh perspective on the possibility of incorporating a blend of air pollution and genetic factors as predictors.

Risk prediction model versus categorical screening strategies

Current lung cancer screening strategies mainly target individuals by age and smoking history.³ Despite proving superiority over current guidelines, prediction models are rarely recommended or used in screening programmes. The Targeted Lung Health Checks screening programme uses the PLCO_{m2012} and LLPv2 models to select high-risk participants undergoing LDCT screening. The National Comprehensive Cancer Network guidelines endorse the use of risk prediction models in the USA.²⁵ Meza et al assessed the potential effects of screening with eligibility criteria based on three prediction models (PLCO_{m2012}, LCRAT and Bach models), which indicated that risk model-based strategies led to higher numbers of deaths averted and overdiagnosed lung cancer cases and to lower numbers of screenings per person and radiation-related lung cancer deaths. Similarly, Ten Haaf et al demonstrated that risk model-based strategies reduced lung cancer mortality more effectively and efficiently compared with USPSTF recommendations.²⁶ Toumazis et al proved that the PLCO_{m2012} model yielded more quality-adjusted life-years and cost savings than USPSTF₂₀₂₁.²⁷ However, these comparative studies overlook potential implementation challenges associated with risk model-based screening or whether such challenges may vary by setting or among different demographic groups. Moreover, current evidence is mainly retrospective. Ongoing implementation studies and trials are expected to provide further insights into the effectiveness and feasibility of risk model-based screening in clinical settings. Cost-effectiveness should also be evaluated by health economic modelling, which is currently under-represented in existing lung cancer risk prediction models.²⁸

Populations covered by the model

The majority of the included models originate from Western hemisphere populations, particularly the USA and the UK, with the NLST and PLCO cohorts in the USA frequently used for both model development and validation. Despite alarmingly high incidence of lung cancer in low- and middle-income countries/regions,

model building and validation in Asia and Africa remains limited. Etzel et al developed a risk prediction model in 2008 tailored for the African-American population.²⁹ Among five Asian models (JPHC, Korean Men, China NCC-LC_{m2021}, LCRS and Shanghai-LCM) included in our study, external validations are relatively scarce. Western models generally perform poorly in Asian populations, potentially attributable to the notable differences in genetic susceptibility, diet, alcohol consumption, physical activity, air pollution and occupational/environmental exposures.³⁰ Notably, the distinct smoking patterns and tobacco-related factors in the Asian population, characterised by low intensity, late initiation, bidi use and extremely low prevalence of female smoking, could shape unique and Asian-specific underlying lung cancer risk.³¹ Gandini et al found that in Asian countries such as China, Japan and Korea, the lung cancer risk among smoking individuals was about four times among never smoking individuals. By contrast, the risk of lung cancer in African-American smoking individuals was 10 times higher than in never smoking individuals. Notably, over 40% Asian lung cancer cases occur in never smoking individuals,³² possibly due to higher exposure to indoor and ambient air pollution and secondhand smoke.³³ These disparities highlight the need for region-specific model development, validation, recalibration and localisation in Africa and Asia.

Model development strategy

Existing models are developed using two main approaches: developing new models using known predictors in large-scale cohorts (such as OWL and CanPredict), or refining existing models like LLP, PLCO and HUNT. Prospective cohorts are ideal for constructing predictive models, whereas conventional case-control studies, though efficient for identifying predictors, are not optimal due to inability to determine absolute risk.³⁴ Only Spitz and LLP models derived from case-control studies.

Model performance metrics may be artificially inflated if based solely on the original sample used for model training. Internal validation techniques can mitigate this optimism. More than half of these models adopted a split-sample approach, despite its inefficiency.³⁵ External validation is crucial for assessing overfitting and generalisability, with no internal validation methods being a substitute.

Model performance in external validation

Classical models such as Bach, Spitz and LLP have served as benchmarks for model improvement, frequently used for validation and comparison. PLCO series models, LLPv3 and LCRAT have undergone multiple external validations yielding mixed results. The latest models, OWL and CanPredict, demonstrated significant performance, particularly OWL in North American and various smoking status populations. The CanPredict model showed outstanding discrimination in the general population but declined in the CPRD database, with an AUC below 0.70. Models derived from Asian countries, such as China NCC-LC m2021, LCRS and Shanghai-LCM, have unclear predictive accuracy and generalisability due to poor reporting performance statistics, which also warrants validation in other populations.

Indeed, it is impossible to definitively prove that all models are valid. A significant issue with external validation studies is that they frequently rely on small, localised data sets. Model performance consistency hinges on population characteristics similarity between validation and development sets, including age range, smoking status and race. Furthermore, the quality and integrity of these validation studies significantly influence model performance. Over time, participants' measurements and baseline risk factors may change, causing calibration drift and heterogeneity. Therefore, multiple validation studies are necessary to assess model generalisability. To ensure model reliability and transportability, researchers must scrutinise model adequacy and report the model's predictive performance across clinical settings, populations and subgroups. Design and report of high-quality external validation studies should adhere to certain standards or guidelines,³⁶ such as the extension to the TRIPOD+AI (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis+artificial intelligence).³⁷

Model implementation in medical practice

The ease of implementation of a model is a critical consideration, depending on the modelling methodology used. In this study, most included models built by conventional statistical methods, which had explicit modelling assumptions, features and complexities, but these methods could not be scaled to very large data sets.³⁸ OWL and UCL-I models, powered by machine learning algorithms, exhibited superior performance. Notably, the UCL-I model, using ensemble machine learning with three predictors (age, smoking duration and pack-years), matched the predictive prowess and clinical relevance of existing models. Machine learning and AI models excel in capturing non-linear and interaction effects of predictors, offering more precise outcomes than traditional statistical methods when dealing with high-dimensional and heterogeneous data. In contrast, machine learning models, heavily reliant on computers, are often perceived as black boxes, lacking transparency and reproducibility due to their inherent complexity. Thus, model developers should release the code and provide detailed documentation on model fitting and data usage, as exemplified by the UCL-I development team. This transparency fosters independent validation and seamless integration into clinical workflows.³⁹ Furthermore, AI models must undergo rigorous evaluation before deployment in medical practice.

Future research perspective

Given model performance heterogeneity arising from different populations, target settings or changing baseline risks, high-quality external validation is crucial for ongoing evaluation. Routinely monitoring performance and model updates are increasingly important.

Increasing availability of data and growing popularity of AI will further drive lung cancer risk prediction model development. Both enhancing model capabilities and facilitating model implementation merit thorough evaluation. Moreover, incorporating biomarkers in specific subpopulations and examining their interactions with other risk factors probably boosts model predictive accuracy.

Regional imbalance persists in the development of lung cancer risk prediction models. Recognising the need for an update or recalibration of the model across different target populations is crucial. Adhering to harmonised guidance when developing or validating the model would enhance study quality, transparency and reproducibility.

Limitations

Our study has several limitations. First, while the E:O ratio offers a comprehensive evaluation of model calibration, including estimates of calibration slope or other relevant metrics would improve the assessment. Second, due to the wide range of cohorts involved and the high heterogeneity among the populations within these cohorts, the limited validation metrics available hinder more precise evaluation and comparison of model performance. Third, our study restricted the language of studies to English, which may partially explain regional imbalance in model development as well as regional model performance variations.

CONCLUSIONS

Performance of lung cancer risk prediction models, despite being well developed and validated, varies in diverse populations. Significant regional imbalance persists in the development of these models. Rigorous external validation or recalibration study in the target population is crucial in accordance with the guidance prior to model implementation.

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Impacto das guidelines regionais de asma nos padrões de prescrição de SABA em Inglaterra: uma análise de séries temporais interrompidas

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RESUMO

As *guidelines* de asma de 2024 da British Thoracic Society, do National Institute for Health and Care Excellence e da Scottish Intercollegiate Guidelines Network recomendam um tratamento baseado em AIR (anti-inflamatório de alívio ICS/long-acting beta agonist), oferecendo a oportunidade de reduzir o uso excessivo de agonistas beta de curta duração (SABA). Muitas regiões inglesas também publicam *guidelines* locais. A análise de 34 *guidelines* regionais permitiu agrupá-las em três categorias, com base no tratamento inicial recomendado: SABA-primeiro, corticosteroide inalado (ICS) mais SABA e AIR (AIR conforme necessário). Uma análise de séries temporais interrompidas, utilizando dados publicamente disponíveis, demonstrou que a publicação de *guidelines* AIR resultou na maior redução na prescrição de SABA, expressa como a proporção de todas as prescrições de inaladores contendo ICS e de SABA (AIR: -0,26% (DP 0,09%) por mês; SABA-primeiro: -0,1% (DP 0,03%) por mês, $p=0,001$ vs AIR; e ICS mais SABA: -0,16% (DP 0,06%) por mês, $p=0,004$ vs AIR). Portanto, as *guidelines* regionais influenciam a prática local de prescrição, e o alinhamento com as recomendações nacionais mais recentes pode melhorar a prescrição para asma e os resultados clínicos dos doentes.

INTRODUCTION

Short-acting beta agonist (SABA) over-use and inhaled corticosteroid (ICS) under-use contribute to asthma exacerbation and mortality risk.^{1,2} The Global Initiative for Asthma (GINA) has recommended ICS-formoterol (ICS/long-acting beta agonist) combination inhalers as the preferred reliever (anti-inflammatory reliever; AIR) for adults and adolescents with asthma since 2019.³ British Thoracic Society/ National Institute for Health and Care Excellence/ Scottish Intercollegiate Guidelines Network (BTS/NICE/SIGN) published their first

collaborative UK asthma guideline in November 2024, endorsing a similar, AIR-based approach, providing opportunity to improve asthma care.

Guidelines only impact care if they are implemented in practice.⁴ In New Zealand, publication of national AIR-based guidelines positively impacted both ICS and SABA prescribing.⁵ However, following the 2017 NICE asthma guideline publication, UK prescribing data did not reveal any impact on montelukast prescribing, despite increased prominence in the treatment pathway.⁶ Previous NICE asthma guidance implementation may have been negatively impacted by several factors, including coexistence of alternative national guidelines (BTS/SIGN, 2016). Detecting prescribing change following guideline publication therefore requires guideline implementation/adoption in practice, access to accurate prescribing data and a responsive measure that reflects implementation.

While the collaborative BTS/NICE/SIGN guideline is now the sole UK national guideline, many English regional integrated care boards (ICBs) publish their own asthma guidelines, providing opportunity to tailor guidance to regional context. Some regional guidelines have endorsed GINA's recommended strategy for some time, with as-needed AIR as the initial treatment step, while others still endorse SABA-containing regimes.

In this study, we (1) establish the presence and content of regional asthma guidelines in England; (2) assess the impact of regional guideline publication on asthma prescribing; and (3) investigate the impact of guideline recommended treatment approaches on SABA and ICS prescribing.

METHODS

ICB adult and adolescent asthma management guidelines were identified through internet searches (key words: 'asthma', 'guideline' and 'manage-



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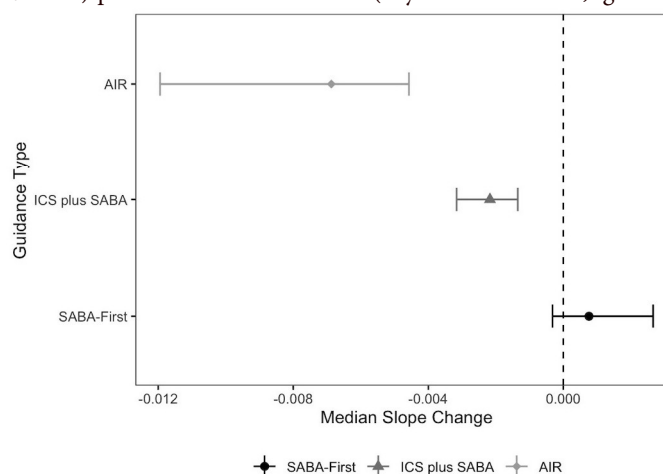


Figure 1 Forest plot providing pooled medians of slope change before and after guideline introduction for each group of ICB guideline. Error bars represent estimated 95% CIs. AIR, anti-inflammatory reliever; ICB, integrated care board; ICS, inhaled corticosteroid; SABA, short-acting beta agonist.

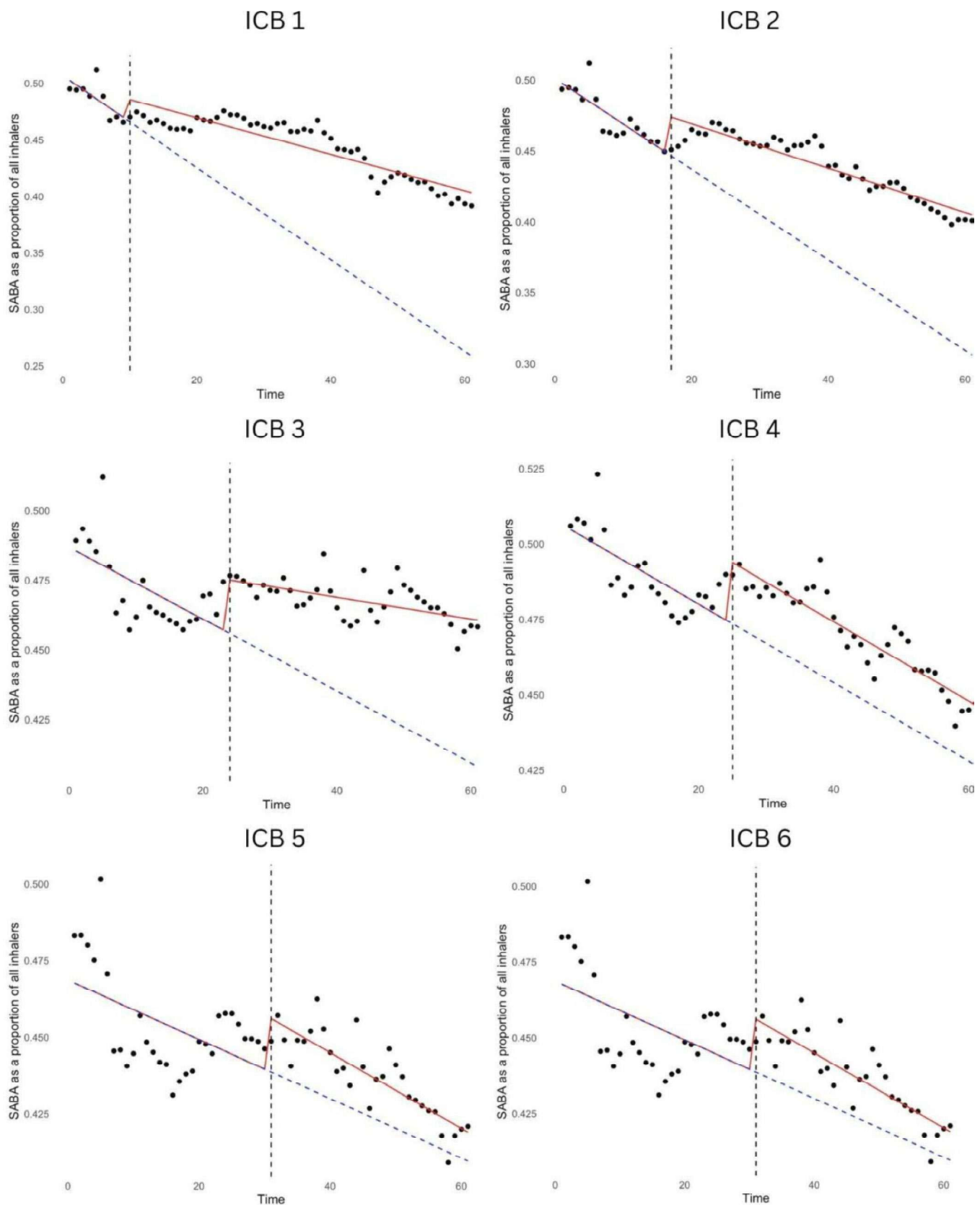


Figure 2 Interrupted time series analyses for ICBs with SABA-first guideline recommendations. The vertical dashed line represents the time of guideline introduction. The red line demonstrates average observed prescribing patterns, and the blue dashed line demonstrates the predicted pattern based on values prior to guideline introduction. ICB, integrated care board; SABA, short-acting beta agonist.

ment', and ICB names). ICB websites were also manually searched for guidelines. Searches were performed independently by two researchers and guidelines were classified into three categories based on the initial asthma management recommendation:

1. SABA-first: guidelines that recommended a SABA-reliever only.
2. ICS plus SABA: guidelines that recommend regular low-dose ICS with SABA-reliever.
3. AIR: guidelines that recommend as-needed AIR therapy.

Monthly prescribing data (OpenPrescribing.net, Bennett Institute for Applied Data Science, University of Oxford, 2023) were collected for each ICB from November 2019 to November 2024. The 'short acting beta agonist inhalers' dashboard metric, which displays SABA prescribing as a proportion of all ICS-containing and SABA inhaler prescriptions, was used

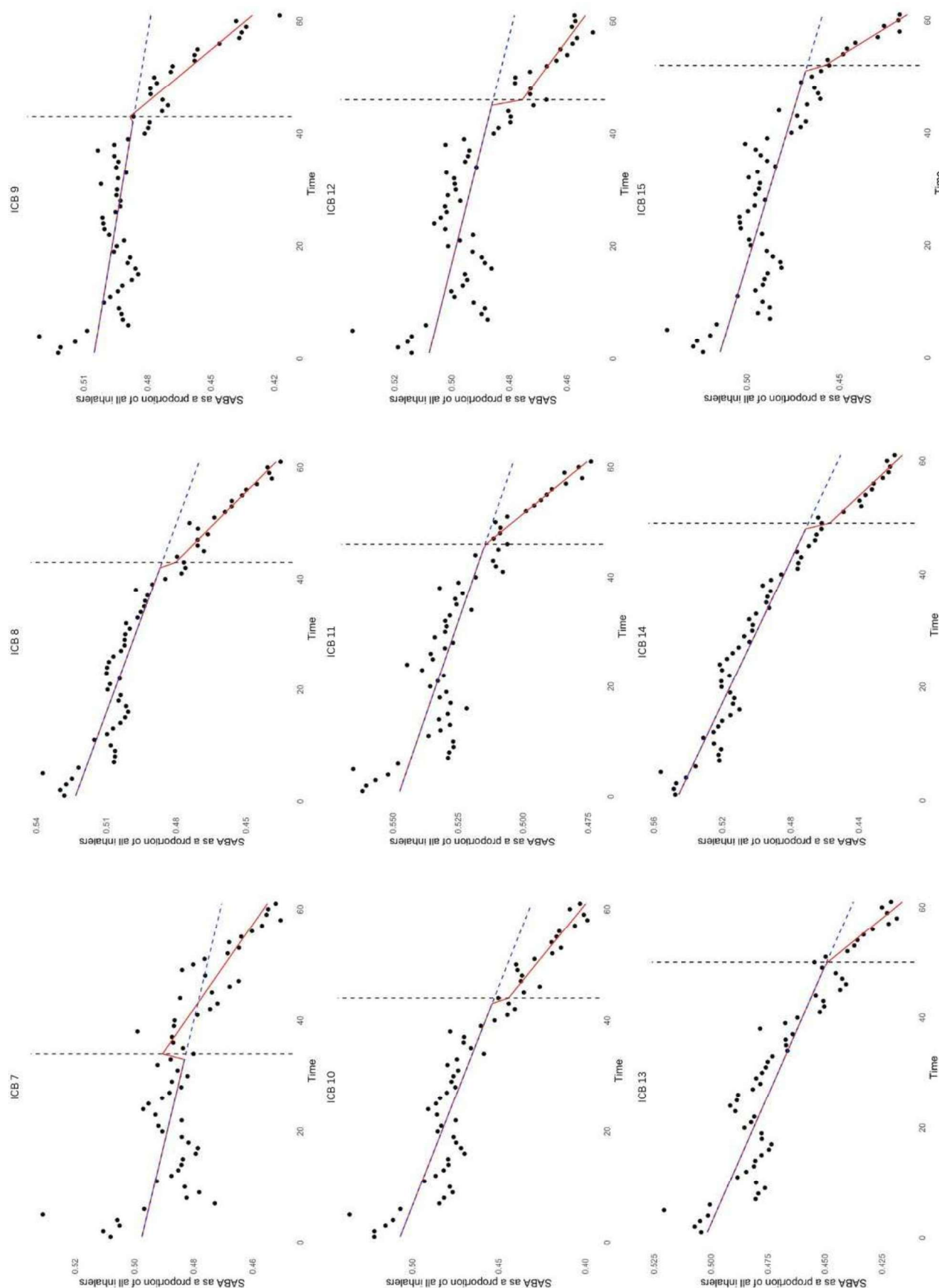


Figure 3 Interrupted time series analyses for ICBs with AIR-based guideline recommendations. The vertical dashed line represents the time of guideline introduction. The red line demonstrates average observed prescribing patterns, and the blue dashed line demonstrates the predicted pattern based on values prior to guideline introduction. AIR, anti-inflammatory reliever; ICB, integrated care board; SABA, short-acting beta agonist.

to investigate guideline publication impact. This metric was selected due to its sensitivity to detect change in both SABA and ICS-containing inhalers, with a reduction reflecting a positive change in prescribing practice. As this metric may be in-

fluenced by prescribing for other conditions, such as chronic obstructive pulmonary disease (COPD), we searched all ICBs for contemporaneous asthma and COPD guideline publication (within 6 months of each other).

Interrupted time series analyses (ITSA) were performed for all ICBs by fitting linear regression models to preguideline and postguideline data. Coefficients for both models were extracted to evaluate slope change. To compare slopes, postguideline slopes were adjusted to align with preguideline time scales and the slope change computed. A hypothetical 'no intervention' line was modelled by presenting predicted values based on preguideline models across the data collection period. Durbin-Watson and Augmented Dickey-Fuller tests were used to assess for autocorrelation and stationarity, respectively. Where data demonstrated autocorrelation, Newey-West standard errors were used. To address potential non-stationarity, sensitivity analyses were conducted using first-differenced data. Q-Q plots were generated to assess data for linearity. All data were tested for normality using Kolmogorov-Smirnov testing; normal data were compared using means and non-normal data were compared using medians.

Slope changes were aggregated and medians of the three guideline categories (ie, SABA-first, ICS plus SABA and AIR) were compared simultaneously using the Kruskal-Wallis test and post hoc testing with Dunn's test to provide p value adjustment for multiple testing. Individual guideline category medians were then directly compared using Mann-Whitney U testing. To quantify the prescribing change, the mean percentage changes in SABA as a proportion of all ICS-containing and SABA prescriptions per month since guideline implementation were calculated. Mean percentage changes were directly compared between guideline categories with independent t-tests and all three guideline categories were simultaneously compared using analysis of variance testing. Post hoc adjustment of p values was then performed using Bonferroni correction. All data were analysed using R statistical software V.4.4.2.

RESULTS

As of November 2024, 39 of 42 ICBs in England had a publicly available asthma management guideline. Of these, 34 guidelines were published at least 6 months after November 2019 and 6 months before November 2024, allowing sufficient prepublication and postpublication data. 6 (18%) were categorised as SABA-first, 19 (56%) as ICS plus SABA and 9 (26%) as AIR (as-needed AIR first). 9 (26%) ICBs had contemporaneously published COPD and asthma guidelines (1 SABA-first, 7 ICS plus SABA and 1 AIR).

The median slope change after guideline introduction differed significantly among the three categories (figure 1, $p<0.001$). AIR-based guidelines demonstrated a greater median slope change than SABA-first guidelines (SABA-first vs AIR: 0.00076 vs -0.00687 , $p<0.001$) and ICS plus SABA guidelines (ICS plus SABA vs AIR: -0.00217 vs -0.00687 , $p=0.042$), indicating greater reduction of SABA as a proportion of all ICS-containing and SABA prescriptions after AIR guideline introduction. Additionally, ICS plus SABA guidelines exhibited greater median slope change relative to SABA-first guidelines (ICS plus SABA vs SABA-first: -0.00217 vs 0.00076, $p=0.001$).

Figures 2 and 3 display the individual ITSA plots for SABA-first and AIR ICBs, respectively.

The mean change in SABA prescribing as a proportion of all ICS-containing and SABA prescriptions was significantly greater following AIR-based guideline publication compared with both ICS plus SABA (-0.26% (SD 0.09%) per month vs -0.16% (SD 0.06%) per month, $p=0.004$) and SABA-first guidelines (-0.26% (SD 0.09%) per month vs -0.1% (SD 0.03%) per month, $p=0.001$).

DISCUSSION

Regional asthma guideline publication significantly impacts inhaled therapy prescribing at an ICB level in England. The significant differences observed between SABA-first, ICS plus SABA and as-needed AIR first guidelines suggest that the Open-Prescribing, net 'Short acting beta agonist inhalers' metric is responsive to prescribing changes associated with guideline publication. While this reflects all-prescribing and is therefore not specific to asthma, and a general downward trend was observed across all ICBs both preguideline and postguideline publication, ITSA reveals a clear inflection point at the time of guideline publication across the studied ICBs. Only 9 of 34 studied ICBs published contempora-

neous COPD guidelines, supporting our assumption that the observed prescribing change relates to asthma guideline publication.

When considering how best to measure BTS/NICE/SIGN asthma guideline publication impact, the lack of read codes for as-needed AIR and inconsistent use of Maintenance and Reliever Therapy (MART) codes means they cannot be relied on to a curately assess guideline adoption. While this may change over time, and improved access to linked primary and secondary care data may allow more granular analysis, our data suggests that OpenPrescribing data provides useful insights. Indeed, such data has previously been used within a quality improvement framework to support MART-based guideline implementation, providing feedback to clinicians with the aim of supporting positive changes in prescribing behaviour,⁷ indicating potential value for both supporting and measuring change.

Our data support the potential for the new BTS/NICE/SIGN guideline to positively impact asthma prescribing, as was seen in New Zealand. However, we also confirm the impact of regional guidelines on local prescribing. Regional guidelines that continue to endorse SABA-first or ICS plus SABA regimes may prove barriers to national guideline implementation. ICBs should therefore consider urgently updating their guidelines to reflect national recommendations and developing formal implementation strategies to support positive practice change and the related clinical benefits.⁷

There are, of course, limitations to this study. Grouping guidelines into three broad categories risks oversimplifying the nuances of each local guideline. However, this method of grouping enables identification of guidelines aligned with the latest BTS/NICE/SIGN recommendations, in which as-needed AIR is the initial treatment step, and clear differences in prescribing impact were observed between the categories. Additionally, OpenPrescribing data details the number of prescriptions provided for individual medicines but does not provide data on whether these prescriptions were filled or taken.

In summary, our data suggest that regional guideline publication does influence local asthma care, and the impact of AIR-based guideline publication can be observed within publicly available UK prescribing data. BTS/SIGN/NICE asthma guideline publication offers an opportunity for a nationwide effort to implement AIR-based management and improve outcomes for patients with asthma.^{8,9}

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