

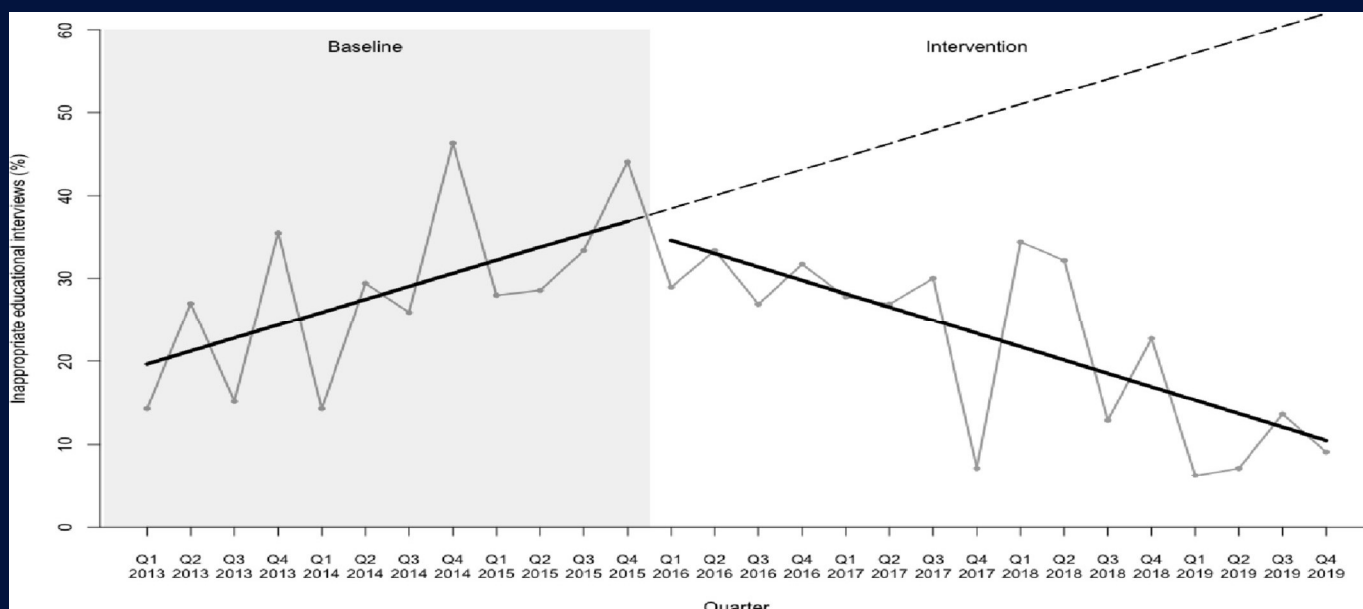
Thorax

ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

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ARCHIVES OF
DISEASE IN
CHILDHOOD

Edição Portuguesa



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

Zimbus Brezhaler 114 microgramas/46 microgramas/136 microgramas pó para inalação, cápsulas
NBTA: Antes de preservar consulte o RCM do medicamento. APRESENTAÇÃO: Pó para inalação, cápsula (pó para inalação). Cada cápsula contém 150 microgramas de indacaterol, 50 microgramas de glicopirrónio 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 glicopirrónio equivalente a 46 microgramas de glicopirrónio e 136 microgramas de furoato de mometasona. **Excipiente(s) com efeito conhecido:** Cada cápsula contém 25 mg de lactose mono-hidratada. **INDICAÇÕES:** Zimbus Brezhaler está indicado como terapêutica de manutenção da asma em doentes adultos não controlados adequadamente com uma associação de um agonista beta₂ de ação prolongada e uma dose alta de corticosteroide inalado em regime de manutenção que experimentaram uma ou mais exacerbações da asma no ano anterior. **POSOLOGIA: Adultos:** A dose recomendada é uma cápsula inalada uma vez por dia. A dose máxima recomendada é de 114 µg/46 µg/136 µg uma vez por dia. **Doentes pediátricos (< 18 anos):** Não recomendado em doentes com menos de 18 anos de idade. **Populações especiais: População idosa:** Não é necessário ajuste de dose em doentes idosos (65 anos de idade ou mais). **Compromisso renal:** Não é necessário ajuste de dose em doentes com compromisso renal ligeiro a moderado. Deve ter-se precaução em doentes com compromisso renal grave ou doença renal terminal que necessitem de diálise. **Compromisso hepático:** Não é necessário ajuste de dose em doentes com compromisso hepático ligeiro a moderado. Não existem dados disponíveis sobre a utilização deste medicamento em doentes com compromisso hepático grave, como tal deve ser utilizado nestes doentes apenas se o benefício esperado superar o risco potencial. **Modo de administração:** Apenas para utilização por via inalatória. As cápsulas não podem ser engolidas. Os doentes que não sintam melhorias na sua respiração devem ser questionados se estão a engolir o medicamento em vez de o inalar. As cápsulas têm de ser administradas usando apenas o inalador Zimbus Brezhaler. 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 Brezhaler devem ser sempre conservadas no blister para proteger da luz e humidade, e só podem ser removidas do blister imediatamente antes da utilização. **CONTRAINDICAÇÕES:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **ADVERTÊNCIAS/PRECAUÇÕES:** ♦ **Asma aguda:** não deve ser utilizado para tratar sintomas agudos de asma, incluindo episódios agudos de broncospasma, para os quais é necessário um broncodilatador de curta ação. ♦ **Hipersensibilidade:** Se ocorrer uma reação de hipersensibilidade, Zimbus Brezhaler deve ser descontinuado imediatamente e deverá ser instituída terapêutica alternativa. ♦ **Broncospasma paradoxal:** Tal como com outra terapêutica inalatória, a administração deste medicamento pode resultar em broncospasma paradoxal, o qual pode colocar a vida em risco. Se tal ocorrer, o tratamento deve ser interrompido imediatamente e deverá ser instituída terapêutica alternativa. ♦ **Efeitos cardiovasculares:** Tal como outros medicamentos contendo agonistas adrenérgicos beta₂, este medicamento pode produzir um efeito cardiovascular clinicamente significativo em alguns doentes conforme avaliado através de aumentos na frequência cardíaca, pressão arterial e/ou sintomas, alterações do electrocardiograma (ECG). Este medicamento deve ser usado com precaução em doentes com patologias cardiovasculares (doença arterial coronária, enfarte agudo do miocárdio, arritmias cardíacas, hipertensão, suspeita ou confirmação de prolongamento do intervalo QT, distúrbios convulsivos ou tirotóxicose e em doentes com resposta aumentada aos agonistas adrenérgicos beta₂). ♦ **Hipocalcemia:** Os agonistas adrenérgicos beta₂ podem causar uma hipocalcemia significativa em alguns doentes, o que potencialmente pode levar a reações adversas cardiovasculares. Em doentes com asma grave, a hipocalcemia pode ser potenciada pela hipoxia e pela terapêutica concomitante, o que pode aumentar a suscetibilidade a arritmias cardíacas. ♦ **Hiperglicemia:** A inalação de doses elevadas de agonistas adrenérgicos beta₂ e corticosteroides pode produzir um aumento da glicose plasmática. Nos doentes diabéticos, ao iniciar o tratamento, a glicose plasmática deve ser monitorizada mais cuidadosamente. ♦ **Efeitos anticolinérgicos:** Tal como com outros medicamentos anticolinérgicos, este medicamento deve ser utilizado com precaução em doentes com glaucoma de ângulo fechado ou retenção urinária. ♦ **Doentes com compromisso renal grave:** Nos doentes com compromisso renal grave (taxa de filtração glomerular estimada inferior a 30 ml/min/1,73 m²), incluindo aqueles com doença renal terminal que necessitam de diálise, deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. ♦ **Prevenção de infeções orofaríngeas:** De modo a reduzir o risco de infeção orofaríngea por *Candida albicans*, os doentes devem ser aconselhados a lavar a boca ou a gargarejar com água, sem a engolir, ou a lavar os dentes após inalar a dose prescrita. ♦ **Efeitos sistémicos dos corticosteroides:** Podem ocorrer efeitos sistémicos dos corticosteroides inalados, principalmente no caso de doses elevadas prescritas por períodos prolongados. Os efeitos sistémicos possíveis podem incluir: síndrome de Cushing, manifestações Cushingoides, supressão adrenal, atraso do crescimento em crianças e adolescentes, diminuição da densidade mineral óssea, cataratas, glaucoma e, mais raramente, uma série de efeitos psicológicos ou comportamentais incluindo hiperatividade psicomotora, distúrbios do sono, ansiedade, depressão ou agressão (especialmente em crianças). Como tal, é importante que a dose de corticosteroide inalado seja titulada para a dose mais baixa na qual o controlo efetivo da asma é mantido. Podem ser notificados distúrbios visuais como o uso de corticosteroides sistémicos ou tópicos (incluindo intranasais, inalados ou intraculares). Doentes que apresentem sintomas como visão turva ou outros distúrbios visuais, devem ser considerados para encaminhamento a um oftalmologista para avaliação de possíveis causas dessas perturbações visuais, as quais podem incluir cataratas, glaucoma ou doenças raras como a coriorretinopatia central serosa (CRCS), que foram notificadas após o uso de corticosteroides sistémicos ou tópicos. Este medicamento deve ser administrado com precaução em doentes com tuberculose pulmonar ou em doentes com infeções crónicas ou não tratadas. ♦ **Gravidez:** Este medicamento deve ser utilizado durante a gravidez apenas se o benefício esperado para o doente justificar o potencial risco para o feto. ♦ **Amamentação:** Tem que ser tomada uma decisão sobre a descontinuação da amamentação ou a descontinuação/abstenção da terapêutica, tendo em conta o benefício da amamentação para a criança e o benefício da terapêutica para a mulher. ♦ **Trabalho de parto:** Como outros medicamentos contendo agonistas adrenérgicos beta₂, o indacaterol pode inibir o trabalho de parto devido a um efeito relaxante no músculo liso uterino. **INTERAÇÕES:** ♦ **Bloqueadores adrenérgicos beta:** este medicamento não deve ser administrado com bloqueadores adrenérgicos beta₂ (incluindo gotas para os olhos) a menos que existam razões importantes para a sua utilização. ♦ **Medicamentos conhecidos por prolongarem o intervalo QTc:** este medicamento deve ser administrado com precaução a doentes que estejam a ser tratados com inibidores da monoamina oxidase, antidepressivos tricíclicos ou medicamentos conhecidos por prolongar o intervalo QT. ♦ **Tratamento hipocalcémico:** O tratamento hipocalcémico concomitante com derivados da metilxantina, esteróides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocalcémico dos agonistas adrenérgicos beta₂. ♦ **Interação com inibidores do CYP3A4 e da glicoproteína P:** A inibição do CYP3A4 e da glicoproteína P (gp-P) não tem impacto na segurança de doses terapêuticas de Zimbus Brezhaler. ♦ **Outros antimuscarínicos de ação prolongada e agonistas adrenérgicos beta₂ de ação prolongada:** A coadministração deste medicamento com outros medicamentos contendo antagonistas muscarínicos de ação prolongada ou agonistas adrenérgicos beta₂ de ação prolongada não foi estudada e não é recomendada. ♦ **Cimetidina ou outros inibidores do transporte de cationes orgânicos:** Não é esperada qualquer interação medicamento-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, distonia, gastroenterite, dor musculoesquelética, espasmos musculares, pirexia. ♦ **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. **Escalaão de comparticipação:** Escalão B. **Titular da AM:** Novartis Europharm Limited. **Representante local:** Laboratório Medifar - Produtos Farmacêuticos, S.A. - Rua Henrique de Paiva Couceiro, N.º 29, Venda Nova, 2700-451 Amadora Informações Essenciais Compatíveis com o Resumo das Características do Medicamento ZIM_RCM20210422_MEC_V2).



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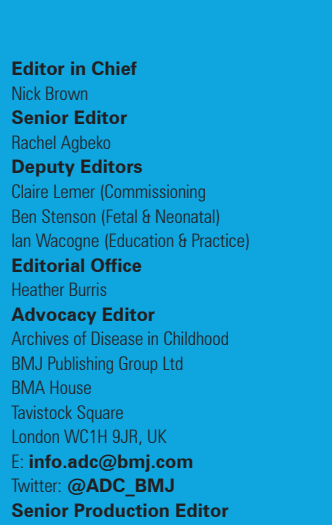
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The priorities are originality, rigour and excellence.

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Editorial

Após um outono e inverno onde se verificou que o impacto das alterações climáticas é uma realidade que não pode ser ignorada por ninguém, e tendo sido esta uma época muito atribulado em termos de infeções respiratórias, atingindo grupos etários habituamente mais “imunes”, como é o caso dos adolescentes e dos adultos jovens, eis-nos chegados à Primavera.

Os alérgenos circulam agora em força na atmosfera e vieram novamente acompanhados por poeiras do deserto. E com concentrações que, por vezes, são elevadíssimas. Para a população em geral estes podem ser meses complicados, competindo a todos nós informar e aconselhar.

E este número abre precisamente com um editorial que traz à discussão a importância dos profissionais de saúde que “devem ser defensores poderosos tanto da recuperação da biodiversidade como da luta contra as alterações climáticas para o bem da saúde”, realçando que “os líderes políticos devem reconhecer tanto as graves ameaças que a crise planetária representa para a saúde como os benefícios que podem advir para a saúde do facto de se combater a crise”, sendo esta uma emergência sanitária de âmbito mundial. Mas política e boas práticas sanitárias nem sempre evidenciam uma adequada correlação.

A relação entre o tabagismo e a fibrose pulmonar idiopática, ou a reflexão sobre os hábitos tabágicos de adolescentes e adultos jovens, iniciados e mantidos através do consumo inicial de “tabaco eletrónico”, fator de risco principal para a DPOC, são um excelente enquadramento para uma pertinente reflexão crítica sobre as últimas recomendações GOLD, efetuada pela nossa colega Elsa Fragoso.

Artigos versando o tratamento da sibilância pediátrica após a alta dos serviços de urgência hospitalar, e sobre asma, nomeadamente sobre a “relação entre a qualidade do ar e as admissões nas urgências hospitalares relacionadas com a asma, na Cidade do México” e a “influência da idade nas características clínicas, no tratamento farmacológico e nas agudizações em crianças com asma”, são apenas alguns dos temas adicionais que Vos propomos para leitura.

E, como não a podemos esquecer, recomendamos igualmente o artigo “Impacto da pandemia de SARS-CoV-2 na sobrevivência ao cancro do pulmão em Inglaterra”. Porque a COVID-19 mantém a sua memória entre nós...

Até já.

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É altura de tratar a crise climática e natural como uma emergência de saúde global indivisível

Chris Zielinski, em nome do grupo de autoria abaixo indicado

Mais de 200 revistas da área da saúde apelam à Organização das Nações Unidas (ONU), aos líderes políticos e aos profissionais de saúde para que reconheçam que as alterações climáticas e a perda de biodiversidade são uma crise indivisível e que devem ser combatidas em conjunto para preservar a saúde e evitar uma catástrofe. Esta crise ambiental global é atualmente tão grave que constitui uma emergência sanitária mundial.

O mundo está atualmente a responder à crise climática e à crise da natureza como se fossem desafios separados. Este é um erro perigoso. A 28ª *Conference of the Parties* (COP) sobre as alterações climáticas está prestes a realizar-se no Dubai, enquanto a 16ª COP sobre a biodiversidade deverá ter lugar na Turquia em 2024. As comunidades de investigação que fornecem as provas para as duas COP estão, infelizmente, em grande parte separadas, mas foram reunidas num workshop em 2020, onde concluíram que: «Só considerando o clima e a biodiversidade como partes do mesmo problema complexo [...] é possível desenvolver soluções que evitem a má adaptação e maximizem os resultados benéficos».¹

Tal como o mundo da saúde reconheceu com o desenvolvimento do conceito de saúde planetária, o mundo natural é constituído por um sistema global interdependente.

Por exemplo, a seca, os incêndios florestais, as inundações e outros efeitos do aumento das temperaturas globais destroem a vida vegetal e conduzem à erosão do solo, inibindo assim o armazenamento de carbono, o que significa mais aquecimento global.²

As alterações climáticas deverão ultrapassar a desflorestação e outras alterações do uso do solo como principal fator de perda de natureza.³

A natureza tem um poder de recuperação notável. Por exemplo, as terras desflorestadas podem voltar a ser florestas através da regeneração natural e o fitoplâncton marinho, que atua como armazém natural de carbono, transforma mil milhões de toneladas de biomassa fotossintetizante de 8 em 8 dias.⁴

A gestão das terras e dos mares indígenas tem um papel particularmente importante a desempenhar na regeneração e nos cuidados continuados.⁵

O restabelecimento de um subsistema pode ajudar outro, como por exemplo, a reconstituição do solo pode ajudar a remover os gases com efeito de estufa da atmosfera em grande escala.⁶

Mas as ações que podem beneficiar um subsistema podem prejudicar outro, por exemplo, plantar florestas com um tipo de árvore pode remover o dióxido de carbono do ar, mas pode prejudicar a biodiversidade que é fundamental para ecossistemas saudáveis.⁷

OS IMPACTOS NA SAÚDE

A saúde humana é diretamente prejudicada tanto pela crise climática, como as revisitas descreveram em editoriais anteriores,^{8,9} como pela crise da natureza.¹⁰

Esta crise planetária indivisível terá efeitos importantes na saúde em resultado da rutura dos sistemas sociais e económicos, escassez de terras, de abrigo, de alimentos e de água, agravando a pobreza, o que, por sua vez, conduzirá a migrações em massa e a conflitos. O aumento das temperaturas, os fenómenos meteorológicos extremos, a poluição atmosférica e a propagação de doenças infecciosas são algumas das principais ameaças para a saúde agravadas pelas alterações climáticas.¹¹

«Sem a natureza, não temos nada», foi o resumo contundente do Secretário-Geral da ONU, António Guterres, na COP da biodiversidade em Montreal, no ano passado.¹²

Mesmo que conseguíssemos manter o aquecimento global abaixo de um aumento de 1,5°C em relação aos níveis pré-industriais, poderíamos causar danos catastróficos à saúde ao destruir a natureza.

O acesso à água potável é fundamental para a saúde humana e, no entanto, a poluição prejudicou a qualidade da água, causando um aumento das doenças transmitidas pela água.¹³

A contaminação da água em terra também pode ter efeitos de grande alcance em ecossistemas distantes quando essa água escorre para o oceano.¹⁴

A boa nutrição é sustentada pela diversidade na variedade de alimentos, mas tem-se registado uma perda notável de diversidade genética no sistema alimentar. A nível mundial, cerca de um quinto das pessoas depende das espécies selvagens para a sua alimentação e subsistência.¹⁵

O declínio da vida selvagem é um grande desafio para estas populações, particularmente nos países de baixo e médio rendimento. O peixe fornece mais de metade das proteínas alimentares em muitos países de África, do Sul da Ásia e de pequenas ilhas,

mas a acidificação dos oceanos reduziu a qualidade e a quantidade de peixe.¹⁶

As alterações na utilização dos solos forçaram dezenas de milhares de espécies a entrar em contacto mais estreito, aumentando o intercâmbio de agentes patogénicos e o aparecimento de novas doenças e pandemias.¹⁷

A perda de contacto das pessoas com o ambiente natural e o declínio da biodiversidade têm sido associados ao aumento de doenças não transmissíveis, autoimunes e inflamatórias, bem como de doenças metabólicas, alérgicas e neuropsiquiátricas.^{10,18}

Para os povos indígenas, cuidar da natureza e ligar-se a ela é especialmente importante para a sua saúde.¹⁹

A natureza também tem sido uma importante fonte de medicamentos, pelo que a redução da diversidade também limita a descoberta de novos medicamentos.

As comunidades são mais saudáveis se tiverem acesso a espaços verdes de elevada qualidade que ajudem a filtrar a poluição atmosférica, a reduzir a temperatura do ar e do solo e a proporcionar oportunidades de atividade física.²⁰

A ligação com a natureza reduz o stresse, a solidão e a depressão, enquanto promove a interação social.²¹ Estes benefícios estão ameaçados pelo aumento contínuo da urbanização.²²

Por último, os impactos das alterações climáticas e da perda de biodiversidade na saúde serão sentidos de forma desigual entre os países e no interior dos mesmos, sendo que as comunidades mais vulneráveis suportarão frequentemente os maiores encargos.¹⁰

Associada a este facto, a desigualdade está também, sem dúvida, a alimentar estas crises ambientais. Os desafios ambientais e as desigualdades sociais e de saúde são desafios que partilham os mesmos fatores e que podem ter benefícios comuns de os abordar.¹⁰

UMA EMERGÊNCIA SANITÁRIA MUNDIAL

Em dezembro de 2022, a COP da biodiversidade acordou na conservação e gestão eficazes de, pelo menos, 30% das terras, zonas costeiras e oceanos do mundo até 2030.²³

Os países industrializados concordaram em mobilizar 30 mil milhões de dólares por ano para apoiar os países em desenvolvimento a fazê-lo.²³

Estes acordos refletem as promessas feitas nas COP sobre o clima. No entanto, muitos dos compromissos assumidos nas COP não foram cumpridos. Isto permitiu que os ecossistemas fossem empurrados ainda mais para o seu limite, aumentando consideravelmente o risco de se chegar a «pontos de rutura» e rupturas abruptas no funcionamento da natureza.^{2,24}

Se estes acontecimentos se verificassem, os impactos na saúde seriam globalmente catastróficos.

Este risco, combinado com os graves impactos na saúde que já estão a ocorrer, significa que a OMS deve declarar a crise indivisível do clima e da natureza como

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uma emergência de saúde global. As três condições prévias para que a OMS declare uma situação como emergência de saúde pública de âmbito internacional²⁵ são: (1) ser grave, súbita, invulgar ou inesperada, (2) ter implicações para a saúde pública para além da fronteira nacional do Estado afetado, e (3) poder exigir uma ação internacional imediata. As alterações climáticas parecem preencher todas estas condições.

Embora a aceleração das alterações climáticas e a perda de biodiversidade não sejam súbitas ou inesperadas, são certamente graves e invulgares. Por isso, apelamos à OMS para que faça esta declaração antes ou durante a 77.^a Assembleia Mundial da Saúde, em maio de 2024.

Para fazer face a esta emergência, é necessário harmonizar os processos da COP. Como primeiro passo, as respetivas convenções devem promover uma melhor integração dos planos climáticos nacionais com os equivalentes em matéria de biodiversidade.³

Como concluiu o workshop de 2020, que reuniu cientistas do clima e da natureza, «os pontos de alavancagem críticos incluem a exploração de visões alternativas de boa qualidade de vida, repensar o consumo e os resíduos, mudar os valores relacionados com a relação homem-natureza, reduzir as desigualdades e promover a educação e a aprendizagem».¹ Tudo isto seria benéfico para a saúde.

Os profissionais de saúde devem ser defensores poderosos tanto da recuperação da biodiversidade como da luta contra as alterações climáticas para o bem da saúde. Os líderes políticos devem reconhecer tanto as graves ameaças que a crise planetária representa para a saúde como os benefícios que podem advir para a saúde do facto de se combater a crise.²⁶ Mas, antes de mais,

temos de reconhecer esta crise pelo que ela é: uma emergência sanitária mundial.

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REFERÊNCIAS

- Otto-Portner H, Scholes B, Agard J, et al. Scientific outcome of the IPBES-IPCC co-sponsored workshop on biodiversity and climate change. 2021.
- Ripple WJ, Wolf C, Lenton TM, et al. Many risky feedback loops amplify the need for climate action. *One Earth* 2023;6:86–91.
- European Academies Science Advisory Council. Key messages from European science academies for UNFCCC COP26 and CBD COP15. 2021. Available: <https://easac.eu/publications/details/key-messages-from-european-science-academies-for-unfccc-cop26-and-cbd-cop15> [Accessed 01 Oct 2023].
- Falkowski P. Ocean science: the power of Plankton. *Nature* 2012;483:S17–20.
- Dawson NM, Coolsaet B, Sterling EJ, et al. The role of indigenous peoples and local communities in effective and equitable conservation. *E&S* 2021;26.
- Bossio DA, Cook-Patton SC, Ellis PW, et al. The role of soil carbon in natural climate solutions. *Nat Sustain* 2020;3:391–8.
- Levia DF, Creed IF, Hannah DM, et al. Homogenization of the terrestrial water cycle. *Nat Geosci* 2020;13:656–8.
- Atwoli L, Baqui AH, Benfield T, et al. Call for emergency action to limit global temperature increases, restore biodiversity, and protect health. *BMJ* 2021;374:m1734.

- Atwoli L, Erhabor GE, Gbakima AA, et al. COP27 climate change conference: urgent action needed for Africa and the world. *BMJ* 2022;379:o2459.
- WHO, UNEP. Convention on Biological D. Connecting global priorities: biodiversity and human health: a state of knowledge review. 2015. Available: <https://www.cbd.int/health/SOK-biodiversity-en.pdf> [Accessed 1 Oct 2023].
- Magnano San Lio R, Favara G, Maugeri A, et al. How antimicrobial resistance is linked to climate change: an overview of two intertwined global challenges. *Int J Environ Res Public Health* 2023;20:1681.
- Jelskov U. “Without nature, we have nothing”: UN chief sounds alarm at key UN Biodiversity event [UN News]. 2022. Available: <https://news.un.org/en/story/2022/12/1131422> [Accessed 01 Oct 2023].
- World Health Organization. State of the world’s drinking water: an urgent call to action to accelerate progress on ensuring safe drinking water for all [World Health Organization]. 2022. Available: <https://www.who.int/publications/i/item/9789240060807> [Accessed 01 Oct 2023].
- Comeros-Raynal MT, Brodie J, Bainbridge Z, et al. Catchment to sea connection: impacts of terrestrial run-off on Benthic Ecosystems in American Samoa. *Mar Pollut Bull* 2021;169:112530.
- IPBES. Assessment report on the sustainable use of wild species. 2022. Available: <https://www.ipbes.net/sustainable-use-assessment>
- Falkenberg LJ, Bellerby RGJ, Connell SD, et al. Ocean acidification and human health. *Int J Environ Res Public Health* 2020;17:4563.
- Dunne D. Climate change “already” raising risk of virus spread between mammals. 2022. Available: <https://www.carbonbrief.org/climate-change-alreadyraising-risk-of-virus-spread-between-mammals/> [Accessed 01 Oct 2023].
- Altves S, Yildiz HK, Vural HC. Interaction of the microbiota with the human body in health and diseases. *Biosci Microbiota Food Health* 2020;39:23–32.
- Schultz R, Cairney S. Caring for country and the health of aboriginal and Torres Strait Islander Australians. *Med J Aust* 2017;207:8–10.
- Macguire F, Mulcahy E, Rossington B. The lancet countdown on health and climate change - policy brief for the UK. 2022. Available: https://s41874.pcdn.co/wp-content/uploads/Lancet-Countdown-2022-UKPolicy-Brief_EN.pdf [Accessed 01 Oct 2023].
- Wong FY, Yang L, Yuen JWM, et al. Assessing quality of life using WHOQOL-BREF: a cross-sectional study on the association between quality of life and neighborhood environmental satisfaction, and the mediating effect of health-related behaviors. *BMC Public Health* 2018;18:1113.
- Simkin RD, Seto KC, McDonald RI, et al. Biodiversity impacts and conservation implications of urban land expansion projected to 2050. *Proc Natl Acad Sci U S A* 2022;119:e2117297119.
- Secretariat of the Convention on Biological Diversity. COP15: nations adopt four goals, 23 targets for 2030 in landmark UN Biodiversity agreement [Convention on Biological Diversity]. 2022. Available: <https://www.cbd.int/article/cop15-cbd-press-release-final-19dec2022> [Accessed 01 Oct 2023].
- Armstrong McKay DI, Staal A, Abrams JF, et al. Exceeding 1.5°C global warming could trigger multiple climate tipping points. *Science* 2022;377:eabn7950.
- WHO guidance for the use of annex 2 of the International health regulations [World Health Organization]. 2005. Available: [https://www.who.int/publications/m/item/who-guidance-for-the-useof-annex-2-of-the-international-health-regulations-\(2005\)](https://www.who.int/publications/m/item/who-guidance-for-the-useof-annex-2-of-the-international-health-regulations-(2005)) [Accessed 01 Oct 2023].
- Australian Government Department of Health and Aged Care. Consultation on Australia’s first national health and climate strategy [Australian Government Department of Health and Aged Care]. 2023. Available: <https://www.health.gov.au/news/consultation-on-australias-first-national-health-andclimate-strategy> [Accessed 01 Oct 2023].

Tabagismo: a prova irrefutável para a FPI?

Ian Hall^{1,2}

A incidência da FPI está a aumentar a nível mundial.¹ Estudos epidemiológicos identificaram uma série de fatores de risco para o desenvolvimento de fibrose pulmonar idiopática (FPI), incluindo: sexo masculino, avanço da idade e historial de trabalho em ambientes industriais poeirentos ou de exposições agrícolas.^{2,3} Há muito que o tabagismo também é considerado um fator de risco, mas tem sido difícil obter provas irrefutáveis, uma vez que o comportamento tabágico também está associado a um risco acrescido de outras exposições devidas a fatores sociodemográficos. Por conseguinte, é difícil distinguir as contribuições relativas de cada fator de risco.

Nos últimos anos, vários estudos de associação do genoma (GWAS) também identificaram fatores de risco genético para o desenvolvimento de FPI⁴⁻⁵ e, além disso, foram encontrados fatores de risco genético associados a taxas de progressão da doença. As abordagens de mapeamento de variantes para genes implicaram uma série de genes suscetíveis de sustentar estas associações genéticas, incluindo MUC5B, TERT, TERC e KIF15 para o início da doença e PCSK⁶ para a progressão da doença.⁶

A probabilidade de um indivíduo começar a fumar a longo prazo também é, em parte, determinada geneticamente, tendo sido identificado um grande número de variantes genéticas ligadas ao comportamento tabágico. O mapeamento de variantes para genes identificou, em geral, genes envolvidos nas vias de recompensa e dependência do sistema nervoso central ou variantes diretamente ligadas às ações e ao metabolismo da nicotina, incluindo o bem estudado locus CHRNA3/5 no cromossoma 15.⁷

A existência de conjuntos bem validados de variantes genéticas associadas quer ao comportamento tabágico quer ao risco de FPI permite adotar uma abordagem diferente para avaliar se as associações observadas entre a FPI e o comportamento tabágico são causais ou não. Ao definir conjuntos não sobrepostos de variantes associadas a cada característica, é possível gerar um instrumento genético que explica pelo menos uma parte do risco de começar a fumar ou de desenvolver FPI.

Uma vez que as variantes genéticas em que estes instrumentos se baseiam são atribuídas à nascença, não estão obviamente sujeitas à confusão, o que representa um problema para muitos fatores de risco identificados em estudos epidemiológicos. Esta abordagem é designada por

aleatorização mendeliana (MR, do inglês *Mendelian randomisation*).

É possível encontrar mais informação sobre as abordagens MR num editorial anterior da *Thorax* original.⁸ No número de fevereiro da *Thorax*, Zhu *et al.*⁹ utilizaram duas amostras de RM com um modelo ponderado inverso e, de seguida, realizaram uma análise de sensibilidade utilizando MR-Egger e MR-PRESSO, para examinar se o comportamento tabágico era ou não um fator de risco no desenvolvimento de FPI. Em geral, são necessárias amostras de grandes dimensões nos estudos de MR, uma vez que a proporção absoluta do risco de uma determinada característica ou fenótipo explicada pelos instrumentos genéticos é normalmente bastante reduzida. Os investigadores criaram instrumentos genéticos para a iniciação ao tabagismo com 378 variantes do GWAS and *Sequencing Consortium of Alcohol and Nicotine Use Study*⁷ e, para a exposição ao tabagismo ao longo da vida, um instrumento não sobreposto de 126 variantes do UK Biobank. Apesar de 1,2 milhões de indivíduos terem contribuído para o primeiro instrumento e mais de 426 000 terem contribuído para o segundo instrumento, estes instrumentos apenas explicaram 2,3 % e 1,3 % da variância, respetivamente, para cada característica.

Então, os investigadores utilizaram dados resumidos de GWAS de 2 consórcios de FPI com um total de 10 382 casos e 968 080 controlos para explorar se os instrumentos que previam o comportamento tabágico estavam ou não associados ao risco de FPI. Concluíram que a predisposição genética para a iniciação ao tabagismo (OR 1,29) ou a exposição ao tabagismo ao longo da vida (OR 1,63) estavam ambas significativamente associadas ao aumento do risco de desenvolver FPI. Estes resultados sugerem que é provável que o tabagismo seja um fator de risco independente para o desenvolvimento de FPI.

Existe uma série de questões que tem de ser considerada ao avaliar estudos de MR como este. A questão mais importante é o facto de os instrumentos genéticos para o comportamento tabágico utilizados na análise de MR não conterem variantes genéticas que também prevejam o risco de desenvolver FPI, independentemente dos efeitos induzidos pelo comportamento tabágico. As análises de sensibilidade efetuadas pelos investigadores são importantes para tentar excluir este facto. No entanto, embora o MR-PRESSO ajude a resolver este problema através da remoção de valores aberrantes, pode não ter em conta toda a pleiotropia, sendo que outras abordagens podem ser mais adequadas para lidar com esta questão da correlação genética parcial, como por exemplo o método da variável causal latente.¹⁰

Também existem algumas limitações na conceção do estudo, tanto em termos de

coortes (sendo a principal a falta de dados de coortes sobre a exposição ao tabagismo em todas as pessoas e outros dados demográficos), como na análise, em particular se é ou não razoável efetuar uma meta-análise global com efeitos aleatórios para resumir as outras duas meta-análises que foram realizadas.

Abordagens semelhantes baseadas na MR tornar-se-ão uma forma cada vez mais comum de tentar resolver os potenciais problemas de confundidores que podem causar dificuldades na interpretação de muitos estudos epidemiológicos. É também de salientar que existem outras utilizações potenciais da abordagem por MR que ajudarão a compreender melhor as doenças respiratórias (e outras). Um bom exemplo é a forma como a MR pode acrescentar valor à análise da quantidade crescente de dados ómicos que estão a ficar disponíveis, por exemplo, mais de 50 000 indivíduos no UK Biobank têm agora dados Olink sobre 1463 marcadores do proteomaplasmático.¹¹

É provável que, ao gerar instrumentos genéticos que expliquem alguma da variabilidade dos níveis dos biomarcadores, seja possível explorar mais pormenorizadamente a relação entre os biomarcadores, o início da doença e/ou a progressão da doença.

Esta abordagem pode, por exemplo, fornecer informações sobre o facto de os níveis alterados dos biomarcadores estarem ou não causalmente envolvidos no início da doença ou serem apenas um marcador do desenvolvimento de uma determinada doença.¹²

Adicionalmente, outras potenciais associações causais para a FPI, como o comprimento dos telómeros, podem ser exploradas utilizando a MR.¹³

Em conclusão, o artigo de Zhu *et al.* acrescenta significativamente à literatura sobre tabagismo e FPI, fornecendo mais provas de que o tabagismo é um fator de risco independente para o desenvolvimento de FPI. Também fornece um exemplo de como as abordagens de MR podem ser utilizadas de forma mais geral para explorar questões de causalidade para associações observadas em estudos epidemiológicos transversais. No entanto, subsiste uma questão fundamental: como é que o conhecimento da provável contribuição do tabagismo altera a nossa gestão da FPI? Do ponto de vista clínico, é pouco provável que isto tenha implicações importantes, uma vez que a redução da exposição ao tabagismo já é um objetivo fundamental de saúde pública. No entanto, é possível que uma exploração mais aprofundada dos mecanismos pelos quais a exposição ao fumo do tabaco contribui para o desenvolvimento da FPI forneça novos alvos terapêuticos para intervir numa fase precoce do desenvolvimento da doença.

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REFERÊNCIAS

1 Hutchinson J, Fogarty A, Hubbard R, et al. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *Eur Respir J* 2015;46:795–806.
2 Kaul B, Lee JS, Zhang N, et al. Whooley MA epidemiology of idiopathic pulmonary fibrosis among U.S. *Ann Am Thorac Soc* 2022;19:196–203.
3 Pergolizzi JV, LeQuang JA, Varrassi M, et al. Varrassi G what do we need to know about rising rates of idiopathic pulmonary fibrosis. *Adv Ther* 2023;40:1334–46.
4 Allen RJ, Porte J, Braybrooke R, et al. Oldham JM et al genetic variants associated with susceptibility to idiopathic pulmonary fibrosis in people of European ancestry. *The Lancet Respiratory Medicine* 2017;5:869–80.
5 Allen RJ, Guillen-Guio B, Oldham JM, et al. Genome-wide Association study of susceptibility to idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2020;201:564–74.

6 Oldham JM, Allen RJ, Lorenzo-Salazar JM, et al. Pcsk6 and survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2023;207:1515–24.
7 Liu M, Jiang Y, Wedow R, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nat Genet* 2019;51:237–44.
8 van der Plaat DA. Mendelian Randomisation supports causal link between obesity and asthma. *Thorax* 2020;75:194–5.
9 Zhu J, Zhou D, Yu M, et al. Appraising the causal role of smoking in idiopathic pulmonary fibrosis: a Mendelian Randomisation study. *Thorax* 2024;79:179–81.
10 O'Connor LJ, Price AL. Distinguishing genetic correlation from causation across 52 diseases and complex traits. *Nat Genet* 2018;50:1753:50.
11 Sun BB, Chiou J, Traylor M, et al. Genetic regulation of the human plasma proteome in 54,306 uk biobank participants. *Genetics* [Preprint].
12 Zheng J, Haberland V, Baird D, et al. Phenome-wide Mendelian randomization mapping the influence of the plasma Proteome on complex diseases. *Nat Genet* 2020;52:1122–31.
13 Liu M, Luo P, Liu L, et al. Immune-mediated inflammatory diseases and Leukocyte Telomere length: A Mendelian randomization study. *Front Genet* 2023;14:1129247.

Utilização de cigarros eletrônicos em jovens adultos e adolescentes: será assim tão seguro?

Rachel Nadif

Há várias décadas que se sabe que o tabagismo causa lesões pulmonares obstrutivas irreversíveis nos adultos¹ e está associado a uma obstrução ligeira das vias aéreas e a um desenvolvimento mais lento da função pulmonar nos adolescentes.²

Apesar do declínio de mais de 1% ao ano na exposição ao fumo do tabaco padronizada por idade entre 2010 e 2019, o estudo *Global Burden of Diseases, Injuries and Risk Factors Study* relatou que o tabaco (fumado, passivo e mastigado) foi o principal fator de risco global para mortes atribuíveis, sendo responsável por 8,71 milhões de mortes, ou seja, 15,4 % de todas as mortes em 2019.³

Este panorama do tabagismo ainda não teve em conta o cigarro eletrônico, inventado pelo farmacêutico chinês Hon Lik no início da década de 2000.

A popularidade dos cigarros eletrônicos tem vindo a aumentar de forma constante em todo o mundo, em parte devido ao seu interesse como alternativa aos cigarros e como instrumento para deixar de fumar, uma vez que são considerados mais seguros do que os cigarros. Os aparelhos estão agora disponíveis em múltiplos formatos e modelos e em vários sabores atrativos para os jovens consumidores.

A aparente segurança dos cigarros eletrônicos tem sido posta em causa nos últimos anos.

Em 2021, uma revisão integrada baseada em estudos epidemiológicos - na sua maioria transversais - e laboratoriais concluiu que existe uma relação real entre o uso de cigarros eletrônicos e a doença pulmonar obstrutiva crónica (DPOC) entre adultos e a asma entre adolescentes, sobretudo estudantes do ensino secundário.⁴

Os estudos transversais sofrem de falta de temporalidade e de causalidade inversa. No entanto, dois dos estudos foram longitudinais e revelaram um aumento do risco de bronquite crónica, DPOC, enfisema e declínio da função pulmonar entre os utilizadores de cigarros eletrônicos. Apesar do problema de saúde pública que representa o consumo de cigarros eletrônicos entre os jovens consumidores, são escassas as coortes populacionais longitudinais centradas na saúde respiratória e que tenham em conta outros consumos de produtos do tabaco. Em 2022, a partir de um estudo prospetivo baseado nos dados do *California Children's Health Study* (CHS), Islam *et al.*⁵ mostraram que a exposição em segunda mão ao vapor

de nicotina em casa estava associada a um risco acrescido de sintomas bronquíticos e de falta de ar em jovens adultos, mesmo depois de se ter em conta o tabagismo ativo e a vaporização. Utilizando dados da mesma coorte, a questão da investigação sobre a utilização de cigarros eletrônicos e os sintomas respiratórios em adolescentes e jovens adultos foi bem explorada na presente edição da *Thorax* por Tackett *et al.*⁶

Os autores investigaram as associações transversais e longitudinais entre o consumo de cigarros eletrônicos e a pieira, os sintomas bronquíticos e a falta de ar entre os jovens consumidores, controlando o consumo de canábis e de cigarros, bem como a exposição passiva a qualquer tipo de fumo ou vapor de cigarros eletrônicos. Entre 2014 e 2018, foram recolhidas quatro vagas de dados sobre a utilização de cigarros eletrônicos e sintomas respiratórios de 2097 participantes do CHS com uma idade média de 17,3 anos na onda 1. Foram recolhidas informações de acompanhamento de 1609 participantes em 2015 (onda 2), de 1502 em 2017 (onda 3) e de 1637 na onda 4 (2018). Em cada inquérito, os participantes indicaram se nunca, há algum tempo e nos últimos 30 dias tinham consumido cigarros, cigarros eletrônicos ou canábis. Foram construídos modelos estatísticos adequados, tendo em conta observações repetidas, e ajustados em função do sexo, raça/etnia, idade, diagnóstico de asma ao longo da vida, educação parental, onda de recolha de dados e exposição passiva a qualquer tipo de fumo ou vapor de cigarro eletrônico.

Foram efetuadas análises de sensibilidade (1) para eliminar o potencial fator de confusão do consumo simultâneo e nos últimos 30 dias de cigarros e/ou canábis, (2) para avaliar se a perda de seguimento resultava em análises tendenciosas e (3) para avaliar a influência da asma. A prevalência do consumo de cigarros eletrônicos nos últimos 30 dias aumentou de 11,7 % na onda 1 para 15,6 % na onda 4, enquanto o relato do consumo de produtos do tabaco nos últimos 30 dias diminuiu de 25,6 % para 20,6 % durante o mesmo período.

Foram observados aumentos na prevalência de sintomas bronquíticos (de 19,4% para 26%) e de pieira (de 12,2% para 14,8%) da onda 1 para a onda 4, enquanto a prevalência de falta de ar se manteve em cerca de 17% em todas as ondas. As análises transversais mostraram que os participantes que relataram uso de cigarros eletrônicos nos últimos 30 dias apresentavam um aumento estatisticamente significativo do risco de pieira (OR 1,81, IC 95% 1,28 a 2,56), sintomas bronquíticos (OR 2,06, IC 95% 1,58 a 2,69) e falta de ar (OR 1,78, IC 95% 1,23 a 2,57), controlando para a onda, idade, sexo, raça e educação parental. Uma vez que o

relato da utilização de cigarros eletrônicos se referia aos últimos 30 dias, um período num passado recente, é improvável que haja um viés de memória. Após um ajustamento adicional para o consumo de cigarros e de canábis, bem como para a exposição passiva a cigarros eletrônicos, cigarros e canábis, as associações foram atenuadas e permaneceram significativas para os sintomas bronquíticos (OR 1,55, IC 95% 1,18 a 2,05) e a falta de ar (OR 1,48, IC 95% 1,01 a 2,18), mas não para a pieira (OR 1,41, IC 95% 0,99 a 2,01). Restringir as análises aos participantes que não relataram consumo de cigarros ou de canábis nos últimos 30 dias não revelou um aumento significativo do risco de sintomas respiratórios, apesar de os OR serem mais elevados (um resultado provavelmente devido, em parte, à falta de poder (n=1235), mesmo que não se possa excluir o viés de confusão). A exclusão dos participantes perdidos durante o seguimento produziu os mesmos resultados que as análises que incluíram a população total. Curiosamente, as associações persistiram quando os participantes com uma história de asma de base ao longo da vida foram excluídos (n=1618), indicando que as associações também estavam presentes nos participantes sem asma. As análises longitudinais mostraram que a utilização de cigarros eletrônicos durante 30 dias, avaliada na onda anterior, esteve associada a um aumento estatisticamente significativo do risco de pieira (OR 1,77, IC 95% 1,14 a 2,74)). A consideração dos efeitos independentes e conjuntos do consumo de cigarros eletrônicos nos últimos 30 dias, com uma onda anterior e atual, mostrou que o consumo de cigarros eletrônicos nos últimos 30 dias, tanto na onda anterior como na atual, esteve associado a um aumento significativo do risco de pieira e de falta de ar, com OR de 3,08 (IC 95% 1,52 a 6,25) e 2,29 (IC 95% 1,23 a 4,29), respetivamente. Isto é sugestivo do impacto da exposição crónica. Os autores reconhecem que a autoavaliação do consumo de cigarros eletrônicos, de cigarros e de canábis, bem como dos sintomas respiratórios, pelo questionário, apresenta limitações, tal como a falta de disponibilidade de dados sobre o consumo de canábis e o falta de ar até às ondas 2 e 3.

Os resultados do estudo de Tackett *et al* complementam a revisão dos estudos humanos e toxicológicos emergentes efetuada por Ali *et al*⁷ que mostram os efeitos adversos da utilização de cigarros em múltiplos sistemas de órgãos.

Em comparação com os cigarros de combustão, os cigarros eletrônicos parecem ter menos efeitos adversos na saúde, mas faltam dados sobre a exposição a longo prazo. O uso de cigarros eletrônicos pode ter alguma toxicidade pulmonar com o uso crónico, especialmente quando o uso começa na adolescência. De facto, os componentes do líquido encontrado nos cigarros eletrônicos incluem nicotina, compostos aromatizantes, solventes como a glicerina ou o propilenoglicol e potenciais compostos tóxicos, como metais pesados, componentes

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carbonílicos, compostos voláteis e partículas.⁷

Em 2022, os Centros de Controlo e Prevenção de Doenças comunicaram que os cigarros eletrónicos eram o produto do tabaco mais utilizado entre os jovens: cerca de 1 em cada 30 estudantes do ensino básico (3,3%) e cerca de 1 em cada 7 estudantes do ensino secundário (14,1%) comunicaram ter utilizado cigarros eletrónicos pelo menos 1 dia nos últimos 30 dias.⁸

Dentro dessas populações, são de particular importância os aumentos constantes daqueles que relatam usar o seu dispositivo com frequência (≥ 20 dias/mês) ou diariamente, de 2014 a 2022.⁹

Também existem fortes indícios de que os jovens não fumadores que utilizam cigarros eletrónicos têm mais probabilidades de começar a fumar e de se tornarem fumadores regulares do que os não fumadores.¹⁰

De um modo geral, a literatura recente de estudos epidemiológicos e toxicológicos justifica a preocupação com o impacto dos cigarros eletrónicos na saúde das populações jovens. Reconhecemos que a utilização de cigarros eletrónicos pode ajudar os fumadores adultos a deixarem de fumar, mas, sem dados sobre a vaporização a longo prazo

provenientes de estudos toxicológicos e de segurança realizados com jovens consumidores, é impossível afirmar com certeza que os cigarros eletrónicos são mais seguros do que os cigarros de combustão. Entretanto, de acordo com o princípio da precaução, os dados de estudos epidemiológicos e toxicológicos recentes devem ser utilizados para fundamentar políticas e abordagens regulamentares destinadas a limitar ainda mais o acesso dos jovens aos cigarros eletrónicos.

Sendo a utilização de cigarros eletrónicos uma exposição evitável, é tempo de agir eficazmente para preservar a saúde das gerações futuras.

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REFERÊNCIAS

- 1 Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J 1977;1:1645–8.
- 2 Gold DR, Wang X, Wypij D, et al. Effects of cigarette smoking on lung function in adolescent boys and girls. N Engl J Med 1996;335:931–7.
- 3 GBD. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. Lancet 2020;396:1223–49.
- 4 Wills TA, Soneji SS, Choi K, et al. E-cigarette use and respiratory disorders: an integrative review of converging evidence from Epidemiological and laboratory studies. Eur Respir J 2021;57:1901815.
- 5 Islam T, Braymiller J, Eckel SP, et al. Secondhand nicotine Vaping at home and respiratory symptoms in young adults. Thorax 2022;77:663–8.
- 6 Tackett AP, Urman R, Barrington-Trimis J, et al. Prospective study of E-cigarette use and respiratory symptoms in adolescents and young adults. Thorax 2023;79:135–40.
- 7 Ali N, Xavier J, Engur M, et al. The impact of E-cigarette exposure on different organ systems: a review of recent evidence and future perspectives. J Hazard Mater 2023;457:131828.
- 8 Available: https://www.cdc.gov/tobacco/data_statistics/fact_sheets/youth_data/tobacco_use/index.htm [Accessed 7 Aug 2023].
- 9 Boakye E, Erhabor J, Obisesan O, et al. Comprehensive review of the national surveys that assess E-cigarette use domains among youth and adults in the United States. Lancet Reg Health Am 2023;23:100528.
- 10 Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: umbrella and systematic review of the global evidence. Med J Aust 2023;218:267–75.



A DPOC em 2024:

Uma reflexão crítica sobre as últimas recomendações GOLD

O Projecto Global Initiative for Chronic Obstructive Lung Disease (GOLD) publica anualmente um documento que reúne as normas internacionais de boa prática para a gestão da Doença Pulmonar Obstrutiva Crónica (DPOC). A actualização de 2024 não apresenta alterações de fundo, no entanto, é importante visitar aspectos-chave da gestão da doença, bem como reflectir sobre alguns dos temas desenvolvidos no último documento.

A definição de DPOC mantém-se inalterada em relação a 2023, bem como a classificação taxonómica por etiotipos, que procura relembrar as diversas origens da doença. A classificação espirométrica e a ferramenta ABE também não sofreram alterações, permitindo identificar os principais traços tratáveis e adequar a estratégia terapêutica inicial, que continua a ser a dupla broncodilatação, na maioria dos casos. Manteve-se a recomendação prática de considerar a terapêutica inalatória tripla ab initio no doente GOLD E com contagens de eosinófilos $>300/\mu\text{L}$. Os ajustes terapêuticos subsequentes baseiam-se no traço dominante, sendo certo que, a haver indicação para transitar para terapêutica tripla na DPOC, essa mudança deve ser efectuada o mais precocemente possível, à luz da evidência actual.

As principais alterações introduzidas em 2024 podem agrupar-se em quatro grandes categorias: 1) Função respiratória; 2) Soluções para o subdiagnóstico; 3) Prevenção; 4) Tratamento.

No que respeita à avaliação da função respiratória, o conhecimento mais detalhado sobre o PRISm (Preserved Ratio Impaired Spirometry) permitiu a expansão desta secção. O termo PRISm descreve indivíduos com relação FEV1/FVC normal e FEV1 diminuído no estudo pós-BD. Estima-se uma prevalência de 10.4% a 11.3% em fumadores e ex-fumadores. O conceito de trajetórias de função pulmonar recorda-nos permanentemente que o factor tempo é determinante. Com efeito, não sendo um fenótipo estável, 20% a 30% dos indivíduos com PRISm evoluem para DPOC. Além disso, a evidência disponível demonstra, nos doentes com PRISm, aumento do risco de doença cardiopulmonar, aumento da mortalidade por todas as causas e causa cardiovascular e aumento do risco de internamento, pelo que é fundamental a vigilância destes indivíduos. Muitos são sintomáticos e têm evidência de doença estrutural pulmonar, pelo que devem ser medicados. Fica por estabelecer a melhor solução terapêutica, dado não existirem estudos nesta população, sendo certo que a abordagem deverá ser personalizada e, provavelmente, passar pela broncodilatação. A insuflação pulmonar é um tema central quando se discute a função respiratória e a DPOC não é excepção. Correlaciona-se com a dispneia, sobretudo no esforço, pelo que tem de ser considerada no doente sintomático, que se apresente com espirometria normal, doença das pequenas vias aéreas ou PRISm. Numa última nota referente à avaliação da função pulmonar, continua a ser recomendada genericamente a espirometria pós-broncodilatação, embora seja considerada a possibilidade de avaliar indivíduos com suspeita diagnóstica de DPOC exclusivamente com espirometria basal, recorrendo à prova de broncodilatação apenas se for identificada obstrução das vias aéreas. Continua a ser utilizado o valor fixo de 70% para a relação FEV1/FVC pós-BD, embora seja fundamental interpretar o valor obtido recorrendo aos intervalos de confiança a 95% e Z-scores, utilizando como referencial as equações GLI (Global Health Initiative), de forma a melhorar a acuidade diagnóstica.

No que respeita às soluções para melhorar o subdiagnóstico, foi introduzido um capítulo sobre o rastreio espirométrico de populações-alvo: indivíduos sintomáticos, com factores de risco, com eventos nos primeiros anos de vida ou infecções respiratórias recorrentes. A criação de sinergias parece determinante, sendo recomendada a realização sistemática de espirometria em indivíduos com identificação incidental de alterações imagiológicas compatíveis com DPOC ou submetidos a rastreio imagiológico de neoplasia do pulmão. A implementação de programas de rastreio activo deve, no entanto, assegurar a existência de recursos para providenciar um seguimento apropriado e intervenções específicas atempadas e custo-efectivas nos indivíduos identificados pelo rastreio.

No âmbito da prevenção, as estratégias de vacinação integram, actualmente, a vacinação contra o vírus sincicial respiratório (VSR). Tendo por base as premissas de elevada prevalência, do impacto significativo como causa de exacerbação de DPOC e da eficácia elevada e consistente da vacina na prevenção da doença grave em idosos, foi estabelecida a indicação de vacinação para indivíduos com mais de 60 anos e/ou com presença de doença cardíaca ou respiratória crónicas.

Também a terapêutica da DPOC mereceu algumas considerações no documento GOLD 2024. Salienta-se o alargamento da secção dedicada aos dispositivos inalatórios, enfatizando assim a relevância da selecção do inalador apropriado a cada doente, aspecto determinante da efectividade do tratamento. A terapêutica farmacológica para a cessação tabágica é abordada numa secção nova. Por último, o estudo BOREAS demonstrou a eficácia do dupilumab (anticorpo monoclonal humanizado anti-receptor da IL-4 e IL-13) na redução das exacerbações da DPOC e melhoria da qualidade de vida em doentes sintomáticos com DPOC moderada a grave com >300 eosinófilos/ μL e que mantêm exacerbações apesar da terapêutica tripla. Ainda que seja reforçada a necessidade de confirmar os resultados do BOREAS, fica definitivamente aberta a porta para a terapêutica biológica na DPOC com fenótipo inflamatório TH2.

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ARTIGO ORIGINAL

Resultados a longo prazo de um programa educativo de gestão antimicrobiana pediátrica: um estudo de melhoria da qualidade

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RESUMO

Contexto e objetivos Os programas de gestão de antimicrobianos (ASP) resultaram na redução do consumo de antimicrobianos (AMC) e na melhoria da qualidade da prescrição (QOP). No entanto, as evidências do impacto da ASP em pediatria são ainda limitadas. Este estudo tem por objetivo avaliar os resultados a longo prazo de uma ASP pediátrica.

Métodos Foi realizado um estudo de melhoria da qualidade, avaliado por uma análise de séries temporais interrompidas, num hospital pediátrico terciário. O QOP expresso como proporção de prescrições adequadas, o AMC medido pela incidência de doses diárias definidas por 1000 dias de cama ocupados, a densidade de incidência de infeções da corrente sanguínea (ICS) e a respetiva taxa bruta de mortalidade por todas as causas (TBM) foram comparados entre o período anterior (de janeiro de 2013 a dezembro de 2015) e posterior (de janeiro de 2016 a dezembro de 2019) à intensificação das atividades do ASP, que incluiu um médico especialista em doenças infecciosas pediátricas para realizar ativamente entrevistas educativas com os prescritores.

Resultados A prescrição desadequada mostrou uma mudança significativa para baixo associada à intervenção, com uma redução de -51,4% (-61,2% a -41,8%) em relação aos valores esperados. O AMC global não registou qualquer alteração de tendência após a intervenção. Relativamente à neonatologia, foi observada uma redução de 28,8% (-36,8% a -20,9%). A utilização global de cefalosporinas anti-pseudomonas registou uma redução de -51,2% (-57,0% a -45,4%). Foram observadas tendências decrescentes para a utilização de carbapenemes, com uma variação percentual trimestral (QPC) de -2,4% (-4,3% para -0,4%) e TBM relacionada com ICS (QPC=-3,6%; -5,4% para -1,7%) durante o período de estudo. As ICS multirresistentes associadas aos cuidados de saúde mantiveram-se estáveis (QPC=2,1; -0,6 a 4,9%).

Conclusões A intensificação das atividades educativas de aconselhamento no âmbito de um ASP sugere a melhoria da QOP e a redução parcial do AMC em doentes pediátricos. As tendências decrescentes da mortalidade mantiveram-se inalteradas.

INTRODUCTION

Antimicrobial stewardship programmes (ASPs) involve multidisciplinary approaches focused on optimisation of anti-infective therapy.¹⁻² Their implementation has proved beneficial in reducing antimicrobial consumption (AMC) and improving the quality of prescription (QOP).^{1,3-6}

In paediatrics, evidence supporting ASP efficacy on clinical outcomes is incomplete, displaying lack of harmonisation on the approaches and impact indicators used.^{3,4,7,8}

The Institutional Programme for the Optimisation of Antimicrobial Treatment (PRIOAM) is

Key messages

What is the key question?

- ▶ Antimicrobial stewardship programmes are effective in reducing antimicrobial consumption.
- ▶ In children, there are scarce data of their impact beyond this aspect and results are often presented after short-term periods of follow-up.

What is the bottom line?

- ▶ This study provides long-term results of a paediatric antimicrobial stewardship programme.
- ▶ Benefits of paediatric antimicrobial stewardship programmes not only on antimicrobial consumption but also on quality of prescription, ecological outcomes and mortality are reported.

Why read on?

- ▶ Study results support the use of counselling educational activities as part of paediatric antimicrobial stewardship programmes to improve quality of antimicrobial prescription and clinical outcomes.
- ▶ This study discusses the need to harmonise paediatric antimicrobial stewardship programmes practices and outcome measurement tools to obtain impact results in the paediatric population.

a 12-year-old educational ASP.³⁻⁸ After its implementation, sustained reduction in AMC, hospital-acquired bloodstream infections (BSIs) and mortality have been reported in adults.^{3,8} This study presents obtained results in children.

METHODS

Study design

A quality improvement study, based on an ecological time-trend analysis, was conducted.

Setting

The study was performed in the Paediatric Hospital of the University Hospital Virgen del Rocío (Seville, Spain), a tertiary centre distributed in five principal areas: paediatric wards (78 beds, including general paediatrics, infectious diseases, oncology, cardiology, nephrology, neurology,

pneumology and gastroenterology), paediatric haematology (8 beds), paediatric surgery wards (34 beds, including general surgery, traumatology and neurosurgery), paediatric intensive care unit (PICU) (17 beds) and neonatology unit (includes 14 beds for neonatal intensive care unit (NICU) and 40 beds for general neonatology).

Antimicrobial stewardship programme

The PRIOAM was implemented in January 2011. It is a consensus-formative institutional supported programme which includes the following activities: one-to-one educational interviews with the prescribers following a structured questionnaire (online supplemental figure 1), monitoring antibiotic use and incidence of bacterial resistance in each department, update, publication and dissemination of local guidelines for the management of the most frequent paediatric infectious syndromes (www.guiaprioam.com) and regular meetings between the ASP team members (paediatric infectious diseases physicians (PIDP), adult infectious diseases physicians, pharmacy specialists and microbiologists) to discuss microbiology results and treatment selection.

Study period

Data obtained between January 2013 and December 2019 (28 quarters) were included. Data from 2020 onwards were excluded to avoid possible interference of COVID-19 pandemic in prescribing practices. Study was divided into two periods: pre-intervention (from January 2013 to December 2015) and post-intervention (from January 2016 to December 2019).

Intervention

In January 2016, activity intensification of the ASP already in place was performed. This included the full-time assignment of a PIDP to carry out PRIOAM activities and intensification of collaboration with the different paediatric hospital units. Differences in ASP activities from the pre-intervention and post-intervention periods are summarised in table 1.

Study measures

Study primary outcomes were QOP, AMC and mortality. QOP data were obtained directly from educational interviews assessing antibiotic treatment appropriateness (indication, dose, spectrum, duration) according to antimicrobial treatment guidelines adapted to

Table 1 Differences before and after intensification of paediatric ASP

ASP activity	Period before ASP intensification (all areas except for neonatology unit)	Period before ASP intensification in neonatology unit	Period after ASP intensification
Tool for prescription assessment	Educational interview, postprescription review with feedback.	Educational interview, postprescription review with feedback.	Educational interview, post-prescription review with feedback and evolutive assessment with follow-up of patients on antibiotic treatment until infection resolution.
Person in charge of prescription assessment	Part-time dedicated paediatric infectious diseases physician and other paediatric specialties assigned antimicrobial stewards.	Independent review by assigned neonatologist antimicrobial stewards.	A reference full-time dedicated PRIOAM paediatric infectious diseases physician assigned to each unit working in close collaboration with other paediatric specialties assigned antimicrobial stewards and all paediatric hospital prescribers.
Identification of patients under antimicrobial prescription (selection of antimicrobial prescriptions for assessment)	Passive identification on prescribers' demand and by notification of patients with invasive bacterial infection. Only these antimicrobial prescriptions were assessed.	Passive identification on prescribers' demand and by notification of patients with invasive bacterial infection. Only these antimicrobial prescriptions were assessed.	Active identification by review of all patients under antimicrobial prescription with each unit antimicrobial stewards and prescribers. Notification of patients with invasive bacterial infection. Notification of patients with broad-spectrum antibiotics. All antimicrobial prescriptions in hospitalised children were assessed.
Organisation of PRIOAM activities	Activities developed on demand of prescribers and 2 days per week.	Activities independently developed by neonatal unit with no specific timetable.	Development of timetable for PRIOAM activities, covering 5 days per week (working days) with specific timeframes to evaluate clinical cases of patients under antimicrobial prescription, performing educational interviews with prescribers in all units and daily multidisciplinary meetings with microbiology, adult infectious disease specialist, pharmacy and preventive medicine.
Other activities complementary to PRIOAM base activities* and prescription review	None.	None.	Active advice on infection source identification and source control. Collaborative work with microbiology and prescribers to improve microbiological diagnosis by correct technique and timing. Collaborative work with pharmacy for therapeutic drug monitoring and dose adjusting in special circumstances.
Additional situations and interventions from other units	Outbreak of extended-spectrum beta-lactamases producing <i>Klebsiella pneumoniae</i> in the whole paediatric hospital. Horizontal transmission was the main source of acquisition. It was declared in October 2015 and continued as an endemic pathogen through the entire study period. A parallel transmission control programme† was started by preventive medicine unit in October 2015.	Outbreak of extended-spectrum beta-lactamases producing <i>K. pneumoniae</i> in the whole paediatric hospital (including neonatology unit). Horizontal transmission was the main source of acquisition. It was declared in October 2015 and continued as an endemic pathogen through the entire study period. A parallel transmission control programme† was started by preventive medicine unit in October 2015.	A parallel transmission control programme† conducted by preventive medicine unit was in place due to ongoing long-term endemic of extended-spectrum beta-lactamases producing <i>K. pneumoniae</i> . An outbreak of <i>Serratia marcescens</i> was declared in the neonatology unit lasting from July 2018 to September 2018. Attack rate was 9.7%, all strains were the same and an environmental primary source was identified (neonatal unit sinks and pipes), while horizontal transmission was also detected. A parallel transmission control programme† was started by preventive medicine unit in July 2018.

Pre-intervention period was from January 2013 to December 2015 and post intervention period was from January 2016 to December 2019. Intervention (ASP intensification) started on January 2016.
*PRIOAM base activities included monthly meetings for results assessments, trimonthly reports of results, setting and adjustment of annual antimicrobial consumption objectives per unit, review and update of antimicrobial use guide adapted to local microbiology.
†Parallel transmission control programme included active surveillance and screening of asymptomatic carriers of either extended-spectrum beta-lactamases producing *K. pneumoniae* or *Serratia marcescens* performing rectal swabs at admission in paediatric intensive care unit and neonatology intensive care unit; in addition to alert systems of previously identified colonised or infected patients to put in place isolation and contact precautions using personal protective equipment. Weekly monitoring of hand hygiene adherence by direct observation and compliance with environmental cleaning activities were performed.
ASP, antimicrobial stewardship programme; PRIOAM, Institutional Programme for the Optimisation of Antimicrobial Treatment.

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local epidemiology (www.guiaprioam.com) (online supplemental figure 1). AMC data were recorded quarterly as defined daily doses (DDDs) per 1000 occupied bed days (OBDs) calculated according to the Anatomical Therapeutic Chemical classification system,⁹ for total antimicrobials (J01+J02) and four groups of key ecological antibiotics: anti-pseudomonal cephalosporins (ceftazidime and ceftipime), carbapenems, piperacillin/tazobactam and vancomycin.

Antimicrobial resistance was assessed as the incidence density per 1000 OBDs of hospital-acquired BSIs produced by the six most frequent microorganisms (coagulase-negative *Staphylococci* excluded): *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida spp.* Strains were classified as multi-drug resistant (MDR) or non-MDR according to European definition.¹⁰ Mortality rates were assessed as the all-cause crude death rate (CDR) as deaths on day +14 after BSI diagnosis per 1000 OBDs per quarter.

Potential confounders related to healthcare complexity and patients' medium age changes during the study period were assessed (online supplemental table 1).

Statistical analysis

An interrupted time series analysis (ITSA) was performed for each variable to estimate changes in the level and trends before and after the start of the activity intensification of the ASP.¹¹ We used a generalised least-squares segmented regression approach with autoregressive moving-average models to account for autocorrelation, using the nlme package in R, V.3.5.1 (R Core Team, 2020). To assess whether the changes in the outcomes were attributable to the intervention, we calculated both absolute and relative effects with 95% CI, as the differences between observed changes and estimated values that would have been expected 4 years after starting the intervention.¹²

To assess the robustness of the findings from the ITSA, we also performed a joinpoint regression analysis to model trend patterns over time and identify significant points of change in the slope of each dependent variable time series and assess whether it occurred over the same period as the intervention,¹³ with the Joinpoint Regression Program, V.4.7.0.0 (National Cancer Institute, USA), accounting for autocorrelation between quarters. Trend segments were characterised by the quarterly per cent change (QPC) with their corresponding 95% CI. The permutation method was used to identify any point in time at which trends changed.

RESULTS

Quality of prescription

Total performed educational interviews between 2013 and 2015 were 424 (median of inadequate treatments: 28% (IQR 26–33%)) com-

pared with 506 educational interviews performed between 2016 and 2019 (median of inadequate treatments: 22% (IQR 11–30%)).

A change from an increasing pre-intervention trend with a slope of 1.6% (95% CI 1.1% to 2.0%) to a decreasing trend (change in slope=−3.2%; −3.6% to 2.7%) was observed in the ITSA associated with the intervention, leading to a final absolute effect of −51.4% (−61.2% to −41.8%) reduction of inappropriate prescribing with respect to the expected values according to the pre-intervention trend 4 years after the inception of the intervention (figure 1 and online supplemental figure 2.1).

AMC according to different areas

No significant change in trend after the intervention was observed for the overall AMC. An increasing trend throughout the ASP period was found for overall DDD/1000 OBDs: QPC=0.6% (95% CI 0.1% to 1.0%) (figure 2A). When analysing AMC per hospital area (figure 2B–F), no changes in trend were noted for paediatric wards, haematology, paediatric surgery and PICU. For paediatric wards, an increasing trend throughout the ASP period was observed: QPC=1.0% (0.4% to 1.6%). Haematology, paediatric surgery and PICU showed a stable trend throughout the ASP period: QPC=0.9% (−0.3% to 2.2%); QPC=0.2% (−0.6% to 1.0%) and QPC=0.4% (−0.6% to 1.4%), respectively. As for neonatology, ITSA showed a significant downward shift associated with the intervention from a stable pre-intervention slope to a decreasing trend, with a final relative reduction of −28.8% (−36.8% to −20.9%) with respect to the expected values according to the pre-intervention trend (figure 2F, table 2 and online supplemental figures 2.2–2.5).

AMC according to antibiotic group

For the entire paediatric hospital, anti-pseudomonal cephalosporin consumption showed a significant downward shift, with a final effect of −51.2% (−57.0% to −45.4%) reduction with respect to the expected values 4 years after the start of the intervention. No changes were found for the other key antibiotic groups. Trends were observed to be decreasing for carbapenems (QPC=−2.4%; −4.3% to −0.4%), increasing for piperacillin/tazobactam (QPC=1.7%; 0.5% to 2.9%) and stable for vancomycin (QPC=0.1%; −1.5% to 1.7%), throughout the ASP period (table 2). AMC outcomes per group and hospital area are summarised in table 2, online supplemental figures 2.2–2.9 and 3. All the significant shifts are supported by the joinpoint regression analysis identifying the change of slope after the evaluated intervention started, except for piperacillin–tazobactam consumption in paediatric haematology, (from increasing to stable trend, occurring before the intervention) (online supplemental figure 2.8).

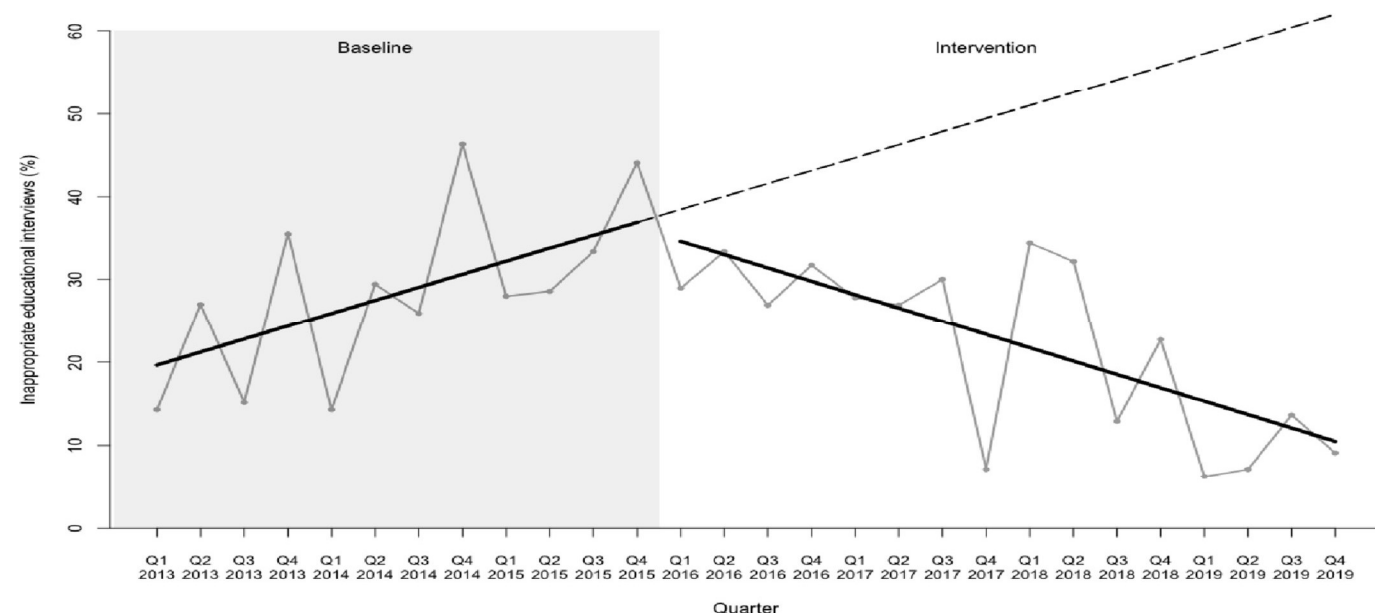


Figure 1 Quality of prescription interrupted time series analysis. Dashed line represents expected values without the intervention when a significant change in trend is observed. Solid straight black lines depict pre-post intervention modelled regression lines.

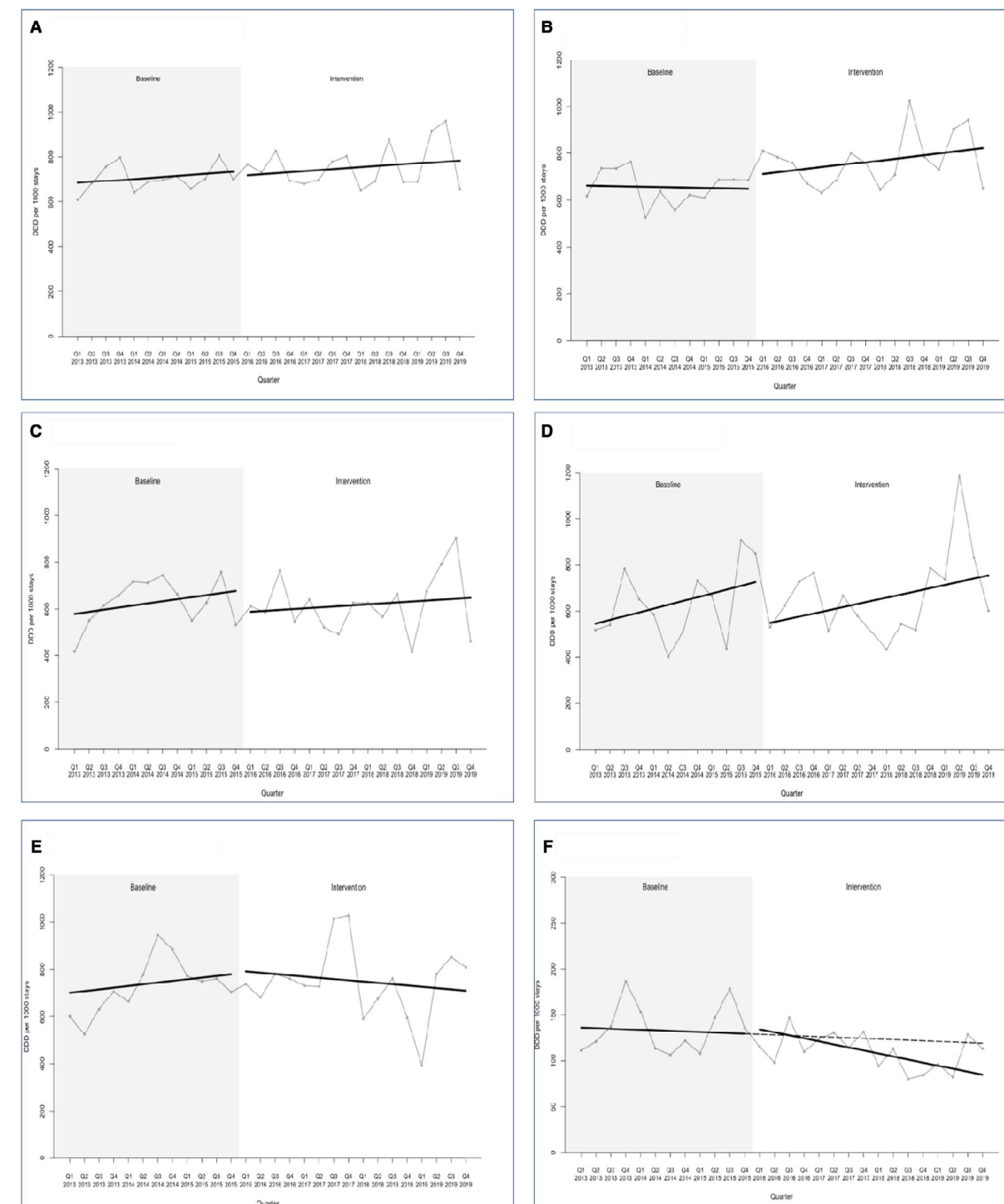


Figure 2 Antimicrobial consumption (defined daily dose (DDD) per 1000 stays) per area interrupted time series analysis. No change in trend was observed for overall antimicrobial consumption between the period pre-intervention (grey background) and the period post-intervention (white background) (A). No change in trend was observed between the period pre-intervention (grey background) and the period post-intervention (white background) for any area (B–E) except for neonatology unit (F). Dashed line represents expected values without the intervention when a significant change in trend is observed. Metric used for antimicrobial consumption was DDD.

Ecological outcomes

No significant effect was observed in the ITSA for the antimicrobial resistance variables (table 3, online supplemental table 2 and figure 4). Healthcare-associated MDR BSI remained stable (QPC=2.1%; −0.6% to 4.9%). Overall BSI showed an increasing trend throughout the whole ASP period (QPC=2.1%; 0.7% to 3.6%).

Mortality

No significant change in mortality was observed in the ITSA for the CDR. A decreasing trend throughout all the ASP period was observed for overall BSI-related CDR (QPC=−3.6%; −5.4% to −1.7%) and for non-MDR BSI-related CDR (QPC=−4.2%;

−6.7% to −1.7%), whereas MDR BSI-related CDR remained stable (QPC=−1.0% (−4.9% to 3.0%)) (table 3, online supplemental table 2 and figure 4).

Complexity

Significant increases of extracorporeal membrane oxygenation procedures in the PICU, kidney transplants and dialysis were observed. Medium age per unit showed non-influencing increasing or stable trends (online supplemental table 1). Other studied parameters showed a stable trend through the study (online supplemental table 1). There was an outbreak of extended-spectrum beta-lactamases (ESBL) producing *K. pneumoniae* (ESBL-KP) in the paediatric hos-

Table 2 Antimicrobial consumption according to antibiotic group and in different paediatric hospital areas interrupted time series analysis

	Regression intercept	Pre-intervention trend	Level change*	Change in trend†	Absolute effect‡	Relative effect (%)‡	Overall trends§
(A) Paediatric hospital							
Overall antimicrobials	680.11 (629.68 to 730.54)	4.47 (−2.78 to 11.72)	19.43 (−84.87 to 46.01)	0.10 (−7.01 to 6.81)	21.02 (−170.82 to 128.77)	2.6 (−2.1 to 15.4)	Increasing
Anti-pseudomonal cephalosporins	26.11 (17.85 to 34.36)	3.18 (2.03 to 4.33)	21.54 (11.91 to 31.17)	5.03 (−6.00 to −4.06)	58.94 (−81.44 to −36.43)	51.2 (−57.0 to −45.4)	Change from increasing to decreasing
Carbapenems	34.02 (26.66 to 41.39)	0.50 (−1.56 to 0.56)	10.89 (−20.38 to −1.40)	0.81 (−0.20 to 1.81)	2.04 (−19.72 to 23.79)	10.2 (−113.2 to 133.5)	Decreasing
Piperacillin–tazobactam	10.96 (5.79 to 16.13)	0.48 (−0.23 to 1.18)	1.03 (−7.36 to 5.31)	0.29 (−1.13 to 0.55)	5.67 (−21.47 to 10.14)	23.3 (−70.7 to 24.1)	Increasing
Vancomycin	22.82 (17.99 to 27.64)	0.15 (−0.84 to 0.53)	2.48 (−3.61 to 8.56)	0.07 (−0.76 to 0.62)	1.39 (−13.01 to 15.79)	7.5 (−77.8 to 92.9)	Stable
(B) Paediatric wards							
Overall antimicrobials	663.45 (591.06 to 735.83)	1.16 (−11.48 to 9.16)	55.70 (−35.04 to 146.44)	8.41 (−1.67 to 18.49)	190.19 (−24.66 to 405.05)	30.1 (−17.5 to 77.8)	Increasing
Anti-pseudomonal cephalosporins	14.78 (2.51 to 27.06)	3.36 (1.64 to 5.08)	26.25 (7.34 to 3.58)	5.31 (−6.68 to −3.94)	58.73 (−91.75 to −25.71)	54.0 (−61.3 to −46.6)	Change from increasing to decreasing
Carbapenems	10.59 (6.31 to 14.86)	0.34 (−0.96 to 0.27)	3.58 (−1.95 to 9.10)	0.22 (−0.37 to 0.80)	7.05 (−5.61 to 19.72)	7.7 (−130.9 to 145.3)	Stable
Piperacillin–tazobactam	5.06 (2.06 to 8.05)	0.11 (−0.52 to 0.30)	0.39 (−3.31 to 4.10)	0.50 (0.03 to 0.97)	8.40 (−0.69 to 17.48)	4.3 (−25.6 to 34.2)	Increasing
Vancomycin	11.40 (8.42 to 14.39)	0.21 (−0.62 to 0.20)	3.94 (0.62 to 7.26)	0.004 (−0.33 to 0.32)	3.87 (−3.93 to 11.68)	7.1 (−22.2 to 36.6)	Stable
(C) Paediatric haematology							
Overall antimicrobials	529.11 (461.43 to 596.78)	16.37 (−14.72 to 47.45)	190.22 (−537.41 to 156.96)	2.70 (−53.26 to 47.87)	233.35 (−1118.57 to 651.87)	23.6 (−94.0 to 46.7)	Stable
Anti-pseudomonal cephalosporins	270.93 (198.21 to 343.66)	4.19 (−14.07 to 5.70)	72.23 (−16.97 to 161.43)	2.31 (−14.09 to 9.47)	35.25 (−187.20 to 257.70)	22.9 (−161.6 to 207.5)	Stable
Carbapenems	41.71 (10.61 to 72.81)	1.98 (−2.27 to 6.23)	18.03 (−20.55 to 56.62)	3.96 (−8.90 to 0.98)	45.32 (−139.96 to 49.316)	46.7 (−92.5 to 1.0)	Stable
Piperacillin–tazobactam	11.74 (−21.60 to −1.89)	6.39 (4.97 to 7.80)	30.55 (−43.21 to −17.89)	5.91 (−7.25 to −4.57)	125.05 (−154.12 to −95.98)	74.9 (−78.3 to −71.4)	Change from increasing to stable
Vancomycin	7.98 (3.16 to 12.65)	0.01 (−0.67 to 0.69)	6.58 (−12.77 to −0.39)	0.22 (−0.43 to 0.88)	3.01 (−17.17 to 11.15)	36.8 (−127.2 to 53.7)	Stable
(D) Paediatric surgery							
Overall antimicrobials	570.60 (427.62 to 713.58)	8.92 (−10.51 to 28.34)	93.09 (−268.47 to 82.29)	4.96 (−28.12 to 18.19)	172.46 (−609.80 to 264.88)	21.0 (−61.2 to 19.2)	Stable
Anti-pseudomonal cephalosporins	5.23 (−29.99 to 19.53)	4.77 (1.17 to 8.38)	8.09 (−25.45 to 41.64)	5.62 (−9.33 to −1.92)	81.86 (−158.87 to −4.85)	63.7 (−79.2 to −48.2)	Change from increasing to decreasing
Carbapenems	34.58 (21.89 to 47.28)	0.18 (−6.04 to 5.68)	6.84 (−72.24 to 58.55)	0.65 (−10.21 to 8.91)	17.26 (−184.44 to 149.93)	58.5 (−340.8 to 223.8)	Decreasing
Piperacillin–tazobactam	16.30 (−0.92 to 33.52)	0.21 (−2.13 to 2.55)	5.37 (−15.75 to 26.49)	0.09 (−2.88 to 2.70)	3.91 (−48.76 to 56.58)	17.7 (−270.9 to 306.3))	Stable
Vancomycin	26.90 (17.59 to 36.21)	0.77 (−0.57 to 2.11)	4.15 (−16.25 to 7.94)	0.92 (−2.20 to 0.35)	18.94 (−46.62 to 8.74)	39.1 (−67.2 to 11.0)	Stable
(E) Paediatric intensive care unit							
Overall antimicrobials	695.14 (599.07 to 791.22)	7.12 (−6.47 to 20.70)	17.62 (−97.66 to 132.90)	12.56 (−24.37 to −0.75)	183.38 (−452.98 to 86.23)	20.5 (−42.1 to 1.1)	Stable
Anti-pseudomonal cephalosporins	4.97 (−5.75 to 15.68)	3.07 (−2.07 to 8.21)	20.76 (−68.65 to 27.13)	0.69 (−8.04 to 9.41)	74.99 (−156.76 to 137.21)	10.7 (−156.5 to 135.1)	Increasing
Carbapenems	46.53 (35.82 to 57.25)	0.68 (−5.49 to 4.14)	29.66 (−87.06 to 27.75)	3.89 (−3.73 to 11.50)	32.52 (−103.48 to 168.52)	117.8 (−93.5 to 170.2)	Stable
Piperacillin–tazobactam	28.31 (24.74 to 31.88)	0.40 (−0.89 to 0.09)	5.49 (1.54 to 9.45)	0.06 (−0.46 to 0.34)	4.57 (−24.50 to 33.64)	26.8 (−49.7 to 103.4)	Stable
Vancomycin	51.61 (31.73 to 71.49)	1.97 (−4.76 to 0.83)	3.69 (−20.03 to 27.41)	3.47 (0.50 to 6.45)	59.29 (−0.62 to 119.2)	170.1 (−384.6 to 350.4)	Stable
(F) Neonatology unit							
Overall antimicrobials	137.18 (130.59 to 143.78)	0.65 (−1.53 to 0.23)	8.19 (1.53 to 14.85)	2.66 (−3.35 to −1.96)	34.32 (−50.74 to −17.89)	28.8 (−36.8 to −20.9)	Change from stable to decreasing
Anti-pseudomonal cephalosporins	0.07 (−0.65 to 0.50)	0.22 (−0.04 to 0.49)	2.35 (−5.36 to 0.66)	0.004 (−0.42 to 0.43)	2.28 (−9.76 to 5.19)	36.7 (−117.3 to 43.9)	Increasing
Carbapenems	5.68 (4.91 to 6.45)	0.28 (0.18 to 0.39)	2.62 (−3.43 to −1.81)	0.43 (−0.51 to −0.35)	9.52 (−11.48 to −7.56)	69.8 (−71.8 to −67.8)	Change from increasing to decreasing
Piperacillin–tazobactam	3.61 (3.18 to 4.04)	0.01 (−0.05 to 0.07)	0.87 (−1.34 to −0.41)	0.09 (−0.14 to −0.04)	2.31 (−4.25 to −0.37)	58.9 (−64.1 to −53.6)	Change from stable to decreasing
Vancomycin	3.73 (2.95 to 5.41)	0.34 (0.11 to 0.57)	2.46 (−4.51 to −0.40)	0.43 (−0.70 to −0.16)	9.39 (−14.51 to −4.26)	70.8 (−82.7 to −59.0)	Change from increasing to decreasing

Data are presented as quarterly defined daily doses (DDD) per 1000 OBD per day with 95% CIs, unless otherwise specified.
Paediatric wards includes: general paediatrics, infectious diseases, oncology, cardiology, nephrology, neurology, and gastroenterology. Paediatric surgery includes: general surgery, traumatology and neurosurgery.
*Increase or decrease in the first quarter after the start of the intervention with respect to the expected value.
†Change in slope for the intervention period.
‡DDD/1000 OBD and percentage differences between the expected pre-intervention trend of antibiotic prescription and the observed trend 4 years after the start of the intervention.
§All the significant shifts are supported by the jointpoint regression analysis identifying the change of slope after the evaluated intervention started, except for piperacillin–tazobactam consumption in paediatric haematology, occurring before the start of the intervention (online supplemental figure 2.8).
OBD, occupied bed day.

pital (all units included) and of *Serratia marcescens* in the neonatology Unit, both described in table 1.

DISCUSSION

Intensification of paediatric ASP activities improved the QOP and changed AMC trends reducing anti-pseudomonal cephalosporins use. In neonates, ASP reduced overall AMC, especially those with high ecological impact (carbapenems, piperacillin/tazobactam and vancomycin). Mortality maintained a stable decreasing trend. Our results contribute to the growing paediatric ASP experience.^{4 14–21} Most paediatric ASP studies have proven efficacy by means of AMC reduction,^{4 14–18 20 21} and very few have analysed its effect on QOP and clinical variables.^{4 16 18 19 21} Our study was carried out through a prolonged period of time (7 years) in comparison to previous studies with a median assessment period of 2 years (IQR: 1–2.5).^{4 16 17 20 21} The intervention had no effect in overall AMC, which remained stable through the ASP period for the entire paediatric hospital, except for neonatology, where a significant change in trend from stable to decreasing was observed. This may be explained by (1) the ongoing effect of PRIOAM which was already in place since 2011, (2) increased case-mix complexity during the study period and (3) pre–post ASP initiation situation for neonatology. When analysing AMC by key ecological antimicrobial groups, variability of results was a consequence of QOP improvement, considering the reported outbreaks of ESBL-KP and *S. marcescens*. Intervention resulted in an overall significant reduction of unnecessary anti-pseudomonal cephalosporins use, especially in paediatric wards and paediatric surgery. Subsequently, the increasing trend for piperacillin/tazobactam and decreasing trend for carbapenems suggest that despite the increase of ESBL-KP infections, the first antibiotic was widely used as a carbapenem sparing option, indicating a positive intervention effect.^{22 23} Likewise, antimicrobial treatment optimisation in neonatology aiming to control AmpC-hyperproducer *S. marcescens* outbreak resulted in cefepime consumption increase while significantly reducing carbapenems and piperacillin/tazobactam consumption. No major changes in the *P. aeruginosa* resistance profile were observed during the study period (online supplemental table 3). Unfortunately, no comparison assessments can be made with other centres, which is a common problem in paediatric ASP reports.^{4 14–21} There is high variability in the methodology used and there are no harmonised quality endpoints, which are urgently required.^{1 424} Moreover, the optimal metric for aggregate AMC measurement is not yet determined for paediatrics.^{24–26} While days of therapy (DOT) have been replacing DDD as the preferred metric for children granted that they are not affected by weight-dosing variations, it does not discern between antibiotic spectrum of activity.^{24–26} Some authors have proposed the use of more than one metric for paediatric patients, but this seems unpractical on daily

basis.^{25 26} Our centre uses DDD as the metric to evaluate AMC in both adults and children, but efforts are currently underway to calculate DOT. Some centres have also reported paediatric ASP outcomes using DDD, and similarly, our results could be influenced by weight-dosing variability.^{14 17 27} Nonetheless, the long-term follow-up hypothetically allows an even distribution of weight-dosing variability, and the changes in AMC trends have a plausible explanation other than this confounder. The high variability observed in AMC in the long-term suggests its inexorable link to changes in case-mix complexity, seasonality and epidemiology.^{24 28} Moreover, AMC differences found between neonatology and other units suggest that an initial effect on AMC reduction is attainable, but there may be a quantifiable limit to that effect in time, bound to the mentioned variables. Thus, evaluation of ASP in paediatrics should transcend AMC; quality and clinical markers still being an unmet need.^{4 19 24} The few reports analysing QOP use treatment guidelines adapted to local epidemiology to define a correct treatment.^{4 19 24 28 29} This is the current gold standard, although existing evidence about optimal antimicrobial choice and duration of treatment for several infectious syndromes in childhood are under review.^{19,23,30} The preferred method for QOP evaluation is the use of point prevalence surveys, but its timing for assessment varies between studies.^{4 18 19 28 31} The PRIOAM method performing counselling educational interviews alongside prescribers allows QOP real-time data collection, permitting the assessment of QOP trends rather than single comparisons between evaluation timepoints.^{3 8} Intensification of paediatric ASP activities showed a positive change in trend with reduction of inappropriate prescriptions, outside of AMC variations. The appointment of a full-time dedicated PIDP was important, allowing the expansion of the programme to the whole paediatric centre, assessing and counselling antimicrobial prescriptions, keeping active education and involvement of prescribers, which was key to obtain a successful sustained decreasing trend of inappropriate treatments with a median value of 21.9%, below from what have been previously reported (25–50%).^{4 18 19 28} Continuing medical education in the management of infectious diseases, microbiology result interpretation and non-related antimicrobial procedures to control and prevent infections are key to obtain clinical success and are expected to decrease antimicrobial resistance and its related mortality like reported in adults.^{3 8} We observed no significant effect of ASP intensification neither for the incidence density of MDR BSI nor its related mortality, yet the low number of cases may justify these findings (online supplemental table 4). Observed trends during the ASP period must be put in perspective, as the increase in the incidence density of BSI could be related to an improvement in microbiology diagnosis resulting from the educational activities of the programme, above all,

Table 3 Ecological outcomes and mortality interrupted time series analysis							
(A) Ecological outcomes measured by incidence density of bacterial bloodstream infections time series segmented regression analysis							
Cases per 1000 OBD	Regression intercept	Pre-intervention trend	Level change*	Change in trend†	Absolute effect‡	Relative effect (%)‡	Overall trend
Overall bloodstream infections§	1,538 (1,281 to 1,794)	0,052 (0,017 to 0,087)	0,441 (0,163 to 0,719)	0,037 (−0,066 to −0,009)	0,155 (−0,822 to 0,512)	5,2 (−25,8 to 15,4)	Increasing
Multi-resistant healthcare-associated bloodstream infections	0,121 (0,068 to 0,173)	0,008 (0,001 to 0,015)	0,102 (0,045 to 0,158)	0,009 (−0,015 to −0,003)	0,040 (−0,176 to 0,096)	11,7 (−44,9 to 21,5)	Stable
Non-multi-resistant healthcare-associated bloodstream infections	0,972 (0,542 to 1,402)	0,002 (−0,057 to 0,061)	0,038 (−0,481 to 0,557)	0,033 (−0,042 to 0,108)	0,564 (−0,778 to 1,906)	54,8 (−160,2 to 271,3)	Increasing
(B) Mortality measured by crude death rate related to bacterial bloodstream infections time series segmented regression analysis							
Deaths per 1000 OBD	Regression intercept	Pre-intervention trend	Level change*	Change in trend‡	Absolute effect‡	Relative effect (%)‡	Overall trend
Overall bloodstream infections§	0,300 (0,263 to 0,337)	0,007 (−0,012 to −0,002)	0,024 (−0,014 to 0,063)	0,001 (−0,005 to −0,003)	0,010 (−0,084 to 0,104)	10,7 (−108,3 to 129,6)	Decreasing
Multi-resistant healthcare-associated bloodstream infections	0,019 (−0,064 to 0,013)	0,002 (−0,069 to 0,135)	0,033 (−0,069 to 0,135)	0,005 (−0,018 to 0,009)	1,037 (−2,162 to 0,089)	68,7 (−197,0 to 59,7)	Stable
Non-multi-resistant healthcare-associated bloodstream infections	0,207 (0,137 to 0,277)	0,013 (−0,023 to −0,003)	0,042 (−0,049 to 0,132)	0,011 (0,001 to 0,020)	0,22 (0,009 to 0,42)	133,6 (−243,2 to 24,0)	Decreasing
Data are presented as quarterly BSI cases per 1000 OBD with 95% CIs, unless otherwise specified. *Increase or decrease in the first quarter after the start of the intervention with respect to the expected value. †Change in slope for the intervention period. ‡Cases per 1000 OBD and percentage differences between the expected pre-intervention trend of incidence density and the observed trend 4 years after the start of the intervention. §Overall bloodstream infections include both community bloodstream infections and healthcare-associated bloodstream infections. OBD, occupied bed day.							

considering the reported stable trend in MDR BSI. Like previous reports, we obtained a sustained decreasing CDR related to BSI throughout the whole ASP period.^{3 6 18}

Our study has certain limitations. This was a single-centre experience, so small numbers are expected for clinical outcomes. The parameter used for AMC was DDD, while for most paediatric studies DOT may offer additional information. There were differences in the pre-intervention state between neonatology and other paediatric units. As per design, ecological bias is a possibility, nonetheless, a detailed analysis of potential confounding factors was conducted, not dismissing the possible influence of other uncontrolled confounders. Although the ASP was initiated in 2011, this study started in January 2013 since the available data between 2011 and 2012 referring to the children’s hospital were insufficient to be included in the ITSA. The possible positive effect on ASP between 2011 and 2012 is therefore not included. The strengths of this study rely on its long-term follow-up, the inclusion of all paediatric units (including high ecological impact units like surgery, PICU and NICU), and the previous reported experience and reliability of the PRIOAM method in non-paediatric population.^{3 8} For AMC and QOP, influence of the parallel transmission control programmes is not expected, given the nature of the interventions related to it (table 1), which could have a potential role on reducing MDR BSI and related CDR. However, no change in trend was observed for these parameters.

CONCLUSION

Intensification of counselling educational activities within along-term paediatric ASP may optimise AMC and appears to improve QOP. No change in decreasing mortality trends was observed. Further prospective multicentre studies are needed to harmonise and define best paediatric ASP practices and outcome measurement tools.

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REFERENCES

- Bielicki J, Lundin R, Patel S, et al. Antimicrobial stewardship for neonates and children: a global approach. *Pediatr Infect Dis J* 2015;34:311–3.
- Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the infectious diseases society of America and the society for healthcare epidemiology of America. *Clin Infect Dis* 2016;62:1197–202.
- Molina J, Peñalva G, Gil-Navarro MV, et al. Long-term impact of an educational antimicrobial stewardship program on hospital-acquired candidemia and multidrug-resistant bloodstream infections: a Quasi- experimental study of interrupted time-series analysis. *Clin Infect Dis* 2017;65:1992–9.
- Velasco-Arnaiz E, Simó-Nebot S, Ríos-Barnés M, et al. Benefits of a pediatric antimicrobial stewardship program in antimicrobial use and quality of prescriptions in a referral children's hospital. *J Pediatr* 2020;225:222–30.
- Rodríguez-Baño J, Pérez-Moreno MA, Peñalva G, et al. Outcomes of the PIRASOA programme, an antimicrobial stewardship programme implemented in hospitals of the public health system of Andalusia, Spain: an Ecologic study of time-trend analysis. *Clin Microbiol Infect* 2020;26:358–65.
- Cox JA, Vlieghe E, Mendelson M, et al. Antibiotic stewardship in low- and middle-income countries: the same but different? *Clin Microbiol Infect* 2017;23:812–8.
- Morris AM, Brenner S, Dresser L, et al. Use of a structured panel process to define quality metrics for antimicrobial stewardship programs. *Infect Control Hosp Epidemiol* 2012;33:500–6.
- Martin-Gutiérrez G, Peñalva G, Ruiz-Pérez de Pipaón M, et al. Efficacy and safety of a comprehensive educational antimicrobial stewardship program focused on antifungal use. *J Infect* 2020;80:342–9.
- World Health Organization. WHO collaborating centre for drug statistics methodology, ATC classification index with DDDs, 2021 [Oslo, Norway]. 2020. Available: [https:// www.whocc.no/](https://www.whocc.no/) [Accessed 16 Jun 2021].
- Magiorakos A-P, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and Pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012;18:268–81.
- Penfold RB, Zhang F. Use of interrupted time series analysis in evaluating health care quality improvements. *Acad Pediatr* 2013;13:S38–44.
- Zhang F, Wagner AK, Soumerai SB, et al. Methods for estimating confidence intervals in interrupted time series analyses of health interventions. *J Clin Epidemiol* 2009;62:143–8.
- Kim HJ, Fay MP, Feuer EJ, et al. Permutation tests for Joinpoint regression with applications to cancer rates. *Stat Med* 2000;19:335–51.
- Seah XFV, Ong YLR, Tan SW, et al. Impact of an antimicrobial stewardship program on the use of carbapenems in a tertiary women's and children's hospital, Singapore. *Pharmacotherapy* 2014;34:1141–50.
- Klatte JM, Kopczka K, Knee A, et al. Implementation and impact of an antimicrobial stewardship program at a non-freestanding children's hospital. *J Pediatr Pharmacol Ther* 2018;23:84–91.
- Horikoshi Y, Suwa J, Higuchi H, et al. Sustained pediatric antimicrobial stewardship program with consultation to infectious diseases reduced carbapenem resistance and infection-related mortality. *Int J Infect Dis* 2017;64:69–73.
- Di Pentima MC, Chan S, Hossain J. Benefits of a pediatric antimicrobial stewardship program at a children's hospital. *Pediatrics* 2011;128:1062–70.
- Donà D, Barbieri E, Daverio M, et al. Correction to: implementation and impact of pediatric antimicrobial stewardship programs: a systematic scoping review. *Antimicrob Resist Infect Control* 2020;9:59.
- Tribble AC, Lee BR, Flett KB, et al. Appropriateness of antibiotic prescribing in United States children's hospitals: a national point prevalence survey. *Clin Infect Dis* 2020;71:e226–34.
- Hersh AL, De Lurgio SA, Thurm C, et al. Antimicrobial stewardship programs in freestanding children's hospitals. *Pediatrics* 2015;135:33–9.
- Smith MJ, Gerber JS, Hersh AL. Inpatient antimicrobial stewardship in pediatrics: a systematic review. *J Pediatr Infect Dis Soc* 2015;4:e127–35.
- Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I, et al. Treatment of infections caused by extended-spectrum-beta-lactamase-, ampC-, and carbapenemase-producing enterobacteriaceae. *Clin Microbiol Rev* 2018;31.
- Aguilera-Alonso D, Escosa-García L, Goycochea-Valdivia WA, et al. Position statement of the Spanish Association of Paediatrics-Spanish society of Paediatric infectious diseases (AEP-SEIP) on the treatment of multidrug-resistant bacterial infections. *Anales de Pediatría (English Edition)* 2019;91:351.
- Gerber JS, Jackson MA, Tamma PD, et al. Antibiotic stewardship in pediatrics. *Pediatrics* 2021;147:e2020040295.
- Velasco Arnaiz E, Simó Nebot S, López Ramos MG, et al. Antimicrobial defined daily dose adjusted by weight: a proposal for antibiotic consumption measurement in children. *Enfermedades Infecciosas y Microbiología Clínica* 2019;37:356–7.
- Goycochea-Valdivia W-A, Montecatine-Alonso E, Gil-Navarro M-V, et al. In reply to: "antimicrobial defined daily dose adjusted by weight: a proposal for antibiotic consumption measurement in children." *Enfermedades Infecciosas y Microbiología Clínica (English Ed)* 2019;37:357–8.
- Zhang ZG, Chen F, Chen JZ. Introducing an antibiotic stewardship program in a pediatric center in China. *World J Pediatr* 2018;14:274–9.
- Goycochea-Valdivia WA, Moreno-Ramos F, Paño-Pardo JR, et al. Identifying priorities to improve paediatric in-hospital antimicrobial use by cross-sectional evaluation of prevalence and appropriateness of prescription. *Enferm Infecc Microbiol Clin* 2017;35:556–62.
- Bielicki JA, Cromwell DA, Sharland M. Fifteen-minute consultation: the complexities of empirical antibiotic selection for serious bacterial infections - a practical approach. *Arch Dis Child Educ Pract Ed* 2017;102:117–23.
- McMullan BJ, Andresen D, Blyth CC, et al. Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines. *Lancet Infect Dis* 2016;16:e139–52.
- Versporten (ARPEC) point prevalence survey: developing hospital-quality indicators of antibiotic prescribing for children. *J Antimicrob Chemother* 2016;71:1106–17.

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

**TRAVA
antes que
seja tarde**

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

*após alta hospitalar

**BEVESPI
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(glicopirrónio/fumarato de formoterol)
Suspensão Pressurizada para Inalação

DPOC, doença pulmonar obstrutiva crónica

Referências: **1.** Riltrava Aerosphere 5 microgramas/7,2 microgramas/160 microgramas, suspensão pressurizada para inalação [Resumo das Características do Medicamento]. AstraZeneca AB, SE-151 85 Södertälje Suécia; outubro 2023. Acedido em www.infarmed.pt em novembro 2023. **2.** Bevespi Aerosphere 5 microgramas/7,2 microgramas, suspensão pressurizada para inalação [Resumo das Características do Medicamento]. Astrazeneca AB, SE-151 85 Södertälje Suécia; setembro 2023. Acedido em www.infarmed.pt em novembro 2023. **3.** Ho TW, Tsai YJ, Ruan SY, Huang CT, Lai F, Yu CJ. In-Hospital and One-Year Mortality and Their Predictors in Patients Hospitalized for First-Ever Chronic Obstructive Pulmonary Disease Exacerbations: A Nationwide Population-Based Study. *Bai C. editor. PLoS ONE.* 2014 Dec 9;9(12):e114866.

Informações essenciais compatíveis com o Resumo das Características do Medicamento

Bevespi Aerosphere 7,2 microgramas/5 microgramas, suspensão pressurizada para inalação. Cada dose única (dose libertada, a dose que sai do aplicador bucal) contém 9 microgramas de brometo de glicopirrónio, equivalente a 7,2 microgramas de glicopirrónio, e 5 microgramas de fumarato de formoterol di-hidratado. Isto corresponde a uma dose calibrada (isto é, a dose que sai da válvula) de 10,4 microgramas de brometo de glicopirrónio, equivalente a 8,3 microgramas de glicopirrónio, e 5,8 microgramas de fumarato de formoterol di-hidratado.
Indicações terapêuticas: Bevespi Aerosphere é indicado como tratamento broncodilatador de manutenção para o alívio de sintomas em doentes adultos com doença pulmonar obstrutiva crónica (DPOC).
Posologia e modo de administração: **Posologia:** A dose recomendada é duas inalações duas vezes por dia (duas inalações de manhã e duas inalações à noite). Os doentes devem ser aconselhados a não fazer mais de 2 inalações duas vezes por dia. Se for omitida uma dose, esta deve ser tomada assim que for possível e a dose seguinte deve ser tomada no horário habitual. Não deve tomar-se uma dose a dobrar para compensar uma dose esquecida.
Populações especiais: *Idosos:* Não é necessário qualquer ajuste de dose em doentes idosos. *Compromisso renal:* Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso renal ligeiro a moderado. Em doentes com compromisso renal grave ou com doença renal em fase terminal com necessidade de diálise, só deve ser utilizado se o benefício esperado for superior ao risco potencial. *Compromisso hepático:* Bevespi Aerosphere pode ser utilizado na dose recomendada em doentes com compromisso hepático ligeiro a moderado. Não existem dados relevantes sobre a utilização de Bevespi Aerosphere em doentes com compromisso hepático grave e o medicamento deve ser utilizado com precaução nestes doentes.
População pediátrica: Não existe utilização relevante de Bevespi Aerosphere em crianças e adolescentes (com idade inferior a 18 anos) para a indicação de DPOC.
Modo de administração: Utilização por via inalatória. *Instruções de utilização:* Ao acionar Bevespi Aerosphere, um volume de suspensão é expelido do recipiente pressurizado a alta velocidade. Quando o doente inala através do aplicador bucal ao mesmo tempo que aciona o inalador, a substância segue o ar inspirado para as vias respiratórias. Os doentes devem ser instruídos sobre a técnica de inalação correta. É importante instruir o doente para: Ler com atenção as instruções de utilização no folheto informativo, que se encontra dentro da embalagem de cada inalador. Não utilizar o inalador se o agente exsicante, contido na bolsa de alumínio, tiver vazado da sua embalagem. Preparar o inalador agitando-o e acionando-o quatro vezes para o ar antes da primeira utilização ou duas vezes quando o inalador não tenha sido utilizado há mais de sete dias, tenha sido exposto a temperaturas baixas ou tenha caído. Para obter uma deposição pulmonar adequada das substâncias ativas, o carregamento da dose tem de ser coordenado com a inalação. Doentes com dificuldade em coordenar o carregamento da dose com a inspiração podem utilizar Bevespi Aerosphere com uma câmara expansora para garantir a administração adequada do produto. Foi demonstrada compatibilidade com a câmara expansora Aerochamber Plus Flow-Vu.
Contraindicações: Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes.
Advertências e precauções especiais de utilização: Não indicado para utilização em situações agudas. Bevespi Aerosphere não é indicado para o tratamento de episódios agudos de broncospasma, isto é, como terapêutica de alívio.
Asma: Bevespi Aerosphere não deve ser utilizado no tratamento da asma.
Broncospasma paradoxal: Tal como com outra terapêutica inalatória, a administração deste medicamento pode resultar em broncospasma paradoxal, o qual pode colocar a vida em risco. Se ocorrer broncospasma paradoxal, o tratamento com o medicamento deve ser interrompido e devem ser considerados outros tratamentos.
Efeitos cardiovasculares: Podem ser observados efeitos cardiovasculares, após a administração de antagonistas dos recetores muscarínicos e simpaticomiméticos, incluindo glicopirrónio ou formoterol. Bevespi Aerosphere deve ser utilizado com precaução em doentes com doenças cardiovasculares graves, tais como cardiopatia isquémica, taquiarritmias ou insuficiência cardíaca grave. Recomenda-se também precaução em doentes com tirototoxicose ou com prolongamento do intervalo QTc conhecido ou suspeito.
Hipocalcemia: Os agonistas β₂-adrenérgicos podem causar hipocalcemia significativa, o que pode aumentar a suscetibilidade para arritmias cardíacas. A diminuição do potássio sérico é normalmente transitória, não necessitando de suplementação. Em doentes com DPOC grave, a hipocalcemia pode ser potenciada por hipoxia e tratamento concomitante.
Hiperlipcemia: A inalação de doses elevadas de agonistas β₂-adrenérgicos pode provocar o aumento da glicose plasmática.
Atividade anticolinérgica: Devido à sua atividade anticolinérgica, Bevespi Aerosphere deve ser utilizado com precaução em doentes com hiperplasia da próstata sintomática, retenção urinária ou glaucoma de ângulo fechado.
Doentes com compromisso renal grave: Como o glicopirrónio é excretado predominantemente por via renal, os doentes com compromisso renal grave (depuração de creatinina <30 ml/min), incluindo aqueles com doença renal em fase terminal com necessidade de diálise, apenas devem ser tratados com Bevespi Aerosphere se o benefício esperado superar o risco potencial.
Doentes com compromisso hepático grave: Em doentes com compromisso hepático grave, Bevespi Aerosphere só deve ser utilizado se o benefício esperado superar o risco potencial. Estes doentes devem ser monitorizados para potenciais reações adversas.
Interações medicamentosas e outras formas de interação: **Interações farmacocinéticas:** O potencial para interações metabólicas é considerado baixo. Como o glicopirrónio é eliminado principalmente por via renal, podem ocorrer potencialmente interações com medicamentos que afetam os mecanismos de excreção renal.
Interações farmacodinâmicas: *Outros antimuscarínicos e simpaticomiméticos:* A coadministração de Bevespi Aerosphere com outros medicamentos contendo anticolinérgicos e/ou agonistas β₂-adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas β₂-adrenérgicos inalados. Não existe evidência clínica de interações quando utilizado concomitantemente com outros medicamentos para a DPOC, incluindo broncodilatadores β₂-adrenérgicos de curta duração de ação, metilxantinas e esteroides orais e inalados.
Hipocalcemia induzida por fármacos: O tratamento concomitante com derivados da metilxantina, esteroides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocalémico inicial dos agonistas β₂-adrenérgicos, pelo que se recomenda precaução na sua utilização concomitante.
Bloqueadores β-adrenérgicos: Os bloqueadores β-adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito dos agonistas β₂-adrenérgicos, tal como o formoterol. O uso simultâneo de bloqueadores β-adrenérgicos não seletivos ou seletivos deve ser evitado, a não ser que existam razões determinantes para a sua utilização. Se forem necessários bloqueadores β-adrenérgicos (incluindo colírios), dá-se preferência a bloqueadores β-adrenérgicos cardioseletivos, embora também estes devam ser administrados com precaução.
Outras interações farmacodinâmicas: Bevespi Aerosphere deve ser administrado com precaução em doentes que estejam a ser tratados com medicamentos conhecidos por prolongar o intervalo QTc.
Fertilidade, gravidez e aleitamento: **Gravidez:** Não existem dados sobre a utilização de Bevespi Aerosphere em mulheres grávidas. Bevespi Aerosphere só deve ser utilizado durante a gravidez se os benefícios esperados superarem os potenciais riscos.
Amamentação:

ARTIGO ORIGINAL

Alta hospitalar com salbutamol, conforme necessário, após ataques agudos de pieira em crianças: uma avaliação do serviço

Gary Connett,¹ Stephanie Harper,¹ Bhargav Raut,² David James²

RESUMO

Objetivo A maioria dos hospitais do Reino Unido dá alta às crianças após uma crise aguda de pieira, aconselhando-as a administrar salbutamol regularmente, utilizando um regime de desmame de dose fixa. Introduzimos e avaliámos a segurança e a eficácia da mudança de prática para a utilização de broncodilatadores apenas quando necessário, após avaliações de 4 em 4 horas.

Desenho Uma equipa multidisciplinar de profissionais de saúde trabalhou com oito famílias de crianças que tinham necessitado de tratamento hospitalar devido a pieira aguda para desenvolver orientações para a utilização de salbutamol, conforme necessário, após 4 avaliações horárias. Os dados sobre o salbutamol utilizados com esta abordagem foram comparados com um período semelhante do ano anterior.

Resultados Os dados de 103 famílias mostraram uma redução de 73% do salbutamol ao dia 1, 69% ao dia 2 e 50% ao dia 3, em comparação com o que teria sido utilizado de acordo com o aconselhamento anterior. As famílias consideraram os conselhos fáceis de seguir. Verificou-se uma tendência para taxas de reatendimento mais baixas no prazo de uma semana, em comparação com as registadas no ano anterior. As pessoas que já tinham participado anteriormente preferiram esta mudança de prática.

Conclusões Estes dados sugerem que, com informações que apoiem a utilização de salbutamol, conforme necessário, após a assistência hospitalar, as crianças podem ser geridas em segurança pelos pais/tutores com doses de salbutamol muito mais baixas do que as recomendadas nos regimes de desmame de dose fixa habitualmente utilizados.

INTRODUCTION

While paediatric care plans for acute wheeze advise treating worsening symptoms with salbutamol every 4 hours as needed, discharge care plans typically advise reducing doses of bronchodilator according to predetermined, fixed dose regimes.^{1,2} There is no clear discharge advice for salbutamol use in national guidelines, but advice that patients can be discharged when stable on regular 3–4 hourly bronchodilators has resulted in many hospitals recommending continued use of regular bronchodilators after leaving hospital.³ There is no evidence to support this practice. We have recently changed our local care pathways and assessed the safety and efficacy of introducing written information to aid parents’ decision-making about the use of salbutamol as needed in children aged 1 to < 18 years.

METHOD

Our development group included eight families with children who had suffered from acute wheeze, and a multidisciplinary team of healthcare professionals attending to wheezy children across our locality who worked according to guidance for the development, implementation, and evaluation of safe asthma discharge care pathways.⁴

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

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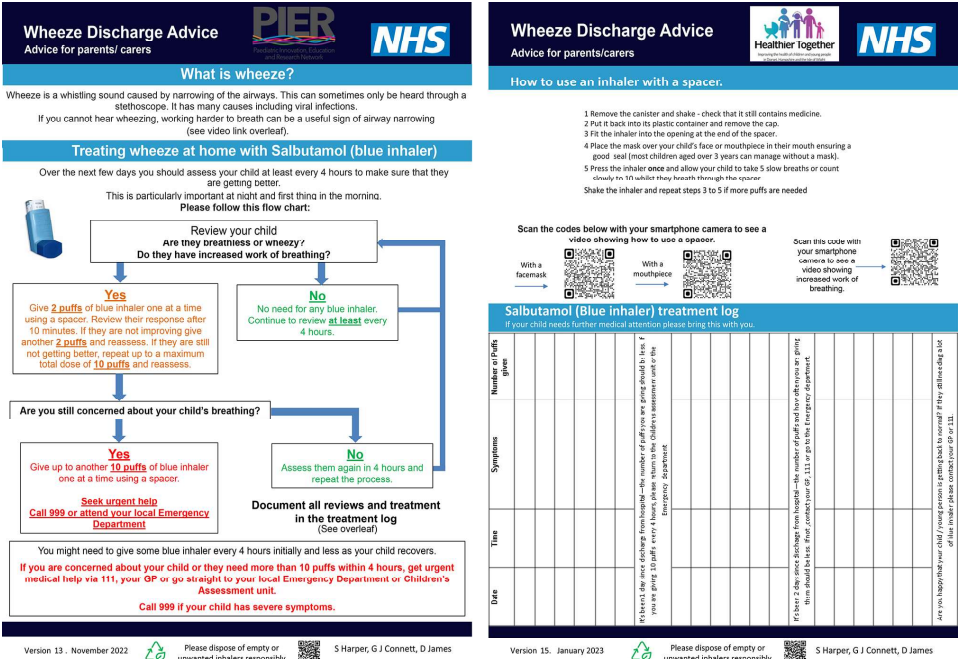


Figure 1 Wheeze discharge advice.

were approved by the Clinical Governance Board of Southampton Children's Hospital and the subsequent service evaluation of these changes was commissioned and approved by the Division of Respiratory Paediatrics. Parents who provided feedback at telephone follow-up appointments gave oral consent for the use of the information provided for evaluation purposes.

RESULTS

We obtained feedback from 103 families. Based on their reports, using salbutamol as required resulted in significant reductions in bronchodilator use. Compared with the expected use of salbutamol according to previous fixed dose 4 hourly weaning plans (day 1: 10 puffs, day 2: 5 puffs, day 3: 2 puffs), significantly lower doses were reported (figure 2). Mean estimated dose reductions were by 73% on day 1, 69% on day 2 and 50% on day 3. Only 13 children still required salbutamol after 3 days. Eight visited their General Practitioner over the next 2 weeks because of ongoing symptoms. In most cases, this was not because of concern about wheeze.

All parents/carers reported that written information was easy to follow. Only 23% used the table to record salbutamol use but all parents were able to recall the amounts used. All parents of children who had previously attended the hospital and been discharged on fixed dose weaning regimes said they preferred the new advice and confirmed that it had resulted in using less salbutamol. Those parents who had kept a written record of salbutamol use said they found this useful.

Comparative effectiveness of the new intervention was assessed by comparing reattendance rates for a similar group of children with a discharge diagnosis of acute wheeze or asthma and who

were treated for severe asthma in the same 6 months in the year before we introduced our new advice. The readmission rate for asthma in 2021 was 12.5 per 1000 and following the introduction of an 'as required' approach it fell to 8.3 per 1000. The OR for re-admission following the intervention was 0.66 (0.37–1.14), p=0.12 (table 1). No children reattended more than once within a week of their initial attendance with acute wheeze. The number of children attending the hospital was less in 2022 among children aged >5 years (446 in 2021 vs 247 in 2022). Numbers attending among children aged <5 years were similar (571 in 2021 vs 510 in 2022). The overall ratio of men to women was 1127/657 (1.71).

DISCUSSION

Advice for symptom management after acute wheezing attacks using as required doses of salbutamol has recently been published by one centre and has been recommended in a recent review, but objective evaluation of the safety and effectiveness of this approach has not been previously reported.^{5,6} The most recent Cochrane review of educational interventions for children with asthma recommends that education about managing wheezing attacks should be incorporated into routine asthma care but highlights the lack of evidence for specific components.⁷ Although we have not conducted a clinical trial, we believe this evaluation provides evidence that families can safely treat their children during the recovery period of acute wheeze without having to follow a predefined weaning regime. It is important to note that many of the children included in this study were preschool wheezers. Those with a history of recurrent wheezing and red flags for suspected asthma were commenced on regular inhaled corticosteroids and not treated with short acting bronchodilators alone.

Our data provide evidence that a more measured use of bronchodilators after hospital discharge results in less salbutamol being used. Empowering and supporting families with clear advice

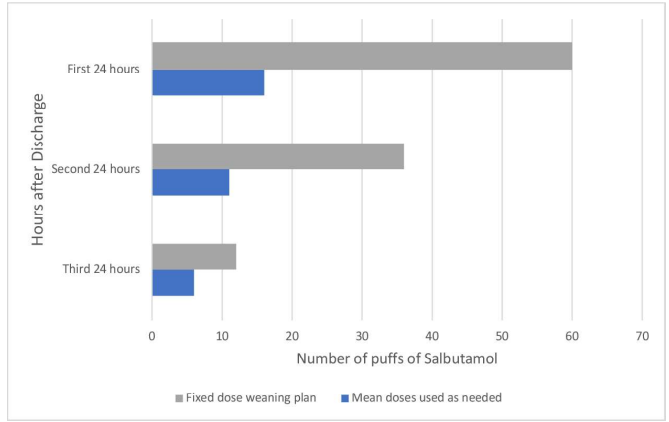


Figure 2 Salbutamol use with fixed dose and as needed regimes.

Table 1 Number of children with acute wheeze reattending within 1 week as a proportion of all wheezy children attending each month using salbutamol fixed dose (2021) and as needed (2022) treatment regimes		
Month	2021 (%)	2022 (%)
July	2/100 (2.0)	3/90 (3.3)
August	4/104 (3.8)	0/37 (0)
September	13/275 (4.7)	5/156 (3.2)
October	9/260 (3.5)	6/127 (4.7)
November	7/179 (3.9)	6/216 (2.8)
December	3/109 (2.7)	3/131 (2.3)

combined with respiratory nurse telephone follow up might also result in safely decreasing salbutamol use for subsequent wheezy episodes. Our reattendance rates to the emergency department varied between 0% and 4.7% monthly and are comparable to those reported in a study of nurse-led interventions to reduce the use of hospital services after acute asthma admissions.⁸ We suspect that the trend towards lower short-term readmission rates did not reach statistical significance because of the relatively small numbers of children reattending for the same acute episode. Those who did reattend were identified by our respiratory nurse specialists for follow-up care.

The number of school-aged children attending our hospital with wheeze was considerably less in 2022. This might in part have been a result of introducing NHS National bundle of care initiatives to improve asthma management in our locality. As well as the reported benefits to patients, we also helped achieve important environmental benefits.⁹ MDIs contain powerful greenhouse gases, accounting for approximately 13% of the NHS's carbon footprint.¹⁰ Guidelines to safely reduce the use of reliever medication might help reduce the UK's per capita use of short-acting bronchodilators, which is currently treble that of many other European countries.¹¹ Further studies might usefully confirm our clinical findings and explore how the information provided could be made available on handheld electronic devices for families who are familiar with using information in this format.¹²

An important limitation of this study is that much of the data for salbutamol use depended on parental recall with only 23% of families using the treatment log to record the treatment given. Reassuringly, however, the average doses used among those who did keep a written record were very similar to those who did not.

A potential problem with the use of MDIs is that they do not have a dose counter. There is a risk that families who have not kept records of the number of puffs of salbutamol used risk 'running on empty' with up to 100 additional actuations when using a 200 dose device.¹³ This was not an acute risk for our patients because the inhalers used for initial burst therapy were given to the families. These inhalers would have contained sufficient doses to continue treatment at home. Families were advised to count the doses given, but there was a risk that using devices for future episodes might result in them being used when empty.

In conclusion, these data provide good evidence to support a widespread change in practice in all UK centres to as required

dosing regimes during the recovery phase of acute wheeze after hospital discharge. This approach is safe and results in lower doses of salbutamol than those recommended in common fixed dose weaning regimes.

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Contributors All authors made substantial contributions to the work described. GC led on the conception and design of the change in practice, the delivery of the project on hospital wards and the preparation of the manuscript. As guarantor for this study he accepts full responsibility for the work and conduct of the study, had access to all data and controlled the decision to publish. SH led on developing materials and the follow-up collection of data. BR collected ED data and worked on changing practice within the ED. DJ helped develop materials and led on the delivery of the project within the ED.
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REFERENCES

- 1 Trust RdAENF. Discharge information following an asthma attack 2020. n.d. Available: [atient-information-leaflet-paediatric-asthma-discharge-rde-20-191-001.pdf](#)
- 2 Kennedy L, Gallagher G, Maxwell B, et al. Implementation of a children's safe asthma discharge care pathway reduces the risk of future asthma attacks in children-a retrospective quality improvement report. *Front Pediatr* 2022;10:865476.
- 3 British Thoracic Society and Scottish Intercollegiate Guidelines Network (SIGN). British guideline on the management of asthma. A national clinical guideline (SIGN publication No.158). n.d. Available: <https://www.brit-thoracic.org.uk/qualityimprovement/guidelines/asthma/>
- 4 Dexheimer JW, Borycki EM, Chiu KW, et al. A systematic review of the implementation and impact of asthma protocols. *BMC Med Inform Decis Mak* 2014;14:82.
- 5 Hospital GNCs. Emergency management flow charts. 2023. Available: <https://www.beatasthma.co.uk/resources/secondary-healthcare-professionals/exacerbationmanagement/6> Durrant N. Salbutamol: hero or villain. *Paediatrics and Child Health* 2023;33:97–103.
- 7 Wolf FM, Guevara JP, Grum CM, et al. Educational interventions for asthma in children. *Cochrane Database Syst Rev* 2003;2002:CD000326.
- 8 Pinto JM, Navallo LJ, Petrova A. Does participation in the community outreach for asthma care and healthy lifestyles (COACH) program alter subsequent use of hospital services for children discharged with asthma? *J Asthma* 2021;58:231–9.
- 9 Carroll WD, Gilchrist FJ, Horne R. Saving our planet one puff at a time. *Lancet Respir Med* 2022;10:e44–5.
- 10 Wilkinson A, Woodcock A. The environmental impact of Inhalers for asthma: a green challenge and a golden opportunity. *Br J Clin Pharmacol* 2022;88:3016–22.
- 11 Wilkinson A, Menzies-Gow A, Sawyer M, et al. S26 an assessment of short-acting B2-agonist (SABA) use and subsequent greenhouse gas (GHG) emissions in five European countries and the consequence of their potential Overuse for asthma in the UK. *Thorax* 2021;76:A19–A.
- 12 Ferrante G, Licari A, Marseglia GL, et al. Digital health interventions in children with asthma. *Clin Exp Allergy* 2021;51:212–20.
- 13 Rubin BK, Durotoye L. How do patients determine that their metered-dose Inhaler is empty? *Chest* 2004;126:1134–7.

ARTIGO ORIGINAL

Relação entre a qualidade do ar e as admissões nas urgências hospitalares relacionadas com a asma, na Cidade do México entre 2017 e 2019

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RESUMO

Contexto Estudos anteriores concluíram que a exposição à poluição atmosférica conduz à exacerbação da asma em pacientes adultos e pediátricos e aumenta as admissões nas urgências hospitalares relacionadas com a asma (AREHA, do inglês Asma-Related Emergency Hospital Admissions)

Métodos Foram recolhidos as AREHA e os níveis de poluentes atmosféricos (PM₁₀, PM_{2.5} e NO₂) na Cidade do México para o período entre 2017 e 2019. Foi utilizada uma abordagem temporal para explorar a relação entre os poluentes atmosféricos e as AREHA. Os riscos relativos de AREHA foram estimados recorrendo a uma regressão binomial negativa em crianças pequenas (com menos de 5 anos) e adultos (com mais de 18 anos).

Resultados Verificou-se uma associação positiva entre as AREHA e PM₁₀, PM_{2.5} e NO₂ em adultos, que se manteve após o ajuste mútuo para estes poluentes. O risco relativo (RR) de admissão em adultos aumentou em 3% (IC 95% de 1% a 4%) num aumento de 10 µg/m³ em PM₁₀, 1% (0,03% a 3%) num aumento de 5 µg/m³ em PM_{2.5} e 1% (0,06% a 2%) num aumento de 5 µg/m³ em NO₂. Em sentido contrário, em crianças pequenas, as AREHA estiveram negativamente associadas a PM₁₀ após ajuste para NO₂ (RR 0,97 (0,95 a 0,99) num aumento de 10 µg/m³ e com NO₂ depois de ajuste para PM₁₀ e PM_{2.5} (RR 0,98 (0,96 a 0,99) e 0,97 (0,96 a 0,99), respetivamente, para um aumento de 5 µg/m³ em NO₂). As AREHA em crianças não estiveram associadas a PM_{2.5} após ajuste para NO₂.

Conclusões A poluição atmosférica, durante a semana anterior, esteve associada a admissões hospitalares de emergência por asma em hospitais públicos de adultos na Cidade México. A relação nas crianças foi menos consistente. São necessários estudos mais aprofundados para explorar o motivo da existência de diferenças entre adultos e crianças, de modo a informar intervenções adequadas em prol da saúde pública.

INTRODUCTION

Asthma is defined as inflammation of the airways associated with wheeze, chest tightness, coughing and breathlessness.¹ Moderate or severe asthma exacerbations, an important health outcome for individuals with asthma, typically require attendance at a hospital emergency department (ED) and/or hospital admission.² Asthma is a leading cause of emergency hospitalisation in children aged less than 5 years and its prevalence has increased over the last 20 years, especially in developing countries.^{3,4}

Previous research has suggested that outdoor air pollution is an established risk factor for asthma exacerbations in children⁵ and adults,⁶ although the evidence remains equivocal.⁷ Fine particulate matter (PM_{2.5}), coarse particulate matter (PM₁₀) and nitrogen dioxide (NO₂) are widely used by international bodies as indicators of air pollution.⁸ Several previous studies from a range of different settings

Key messages

What is the key question?

► Globally measures are being implemented to reduce air pollution in cities due to its negative impact on the respiratory health of the population. Mexico was previously identified as the most polluted city in the world and interventions to improve air quality have been implemented over the past 30 years. Previous work found that ambient PM_{2.5}, O₃ and NO₂ were associated with emergency asthma admissions in Mexico City in 2010-2015.

What is the bottom line?

► This study demonstrated that in the period 2017-2019 levels of air pollution remain associated with emergency asthma admissions in adults in Mexico City.

Why read on?

► This study shows that despite improvements in air quality as a result of interventions put in place in Mexico City further air quality improvements are needed.

have reported that higher levels of PM_{2.5}, PM₁₀ and NO₂ are associated with poor respiratory health in both children and adults and are positively associated with asthma-related ED visits.⁷⁻¹¹ However, a systematic review and meta-analysis concluded that PM_{2.5} and NO₂, but not PM₁₀ show significant associations with asthma exacerbations.¹²

Previous work has also demonstrated the role of meteorological factors in exacerbations of asthma. For example, it has been reported that asthma admissions increase in cold temperatures^{13,14} and both high and low humidity are associated with an increase in asthma admissions.¹⁵

A recently published study demonstrated that respiratory health (defined as respiratory ED visits) was associated with levels of PM_{2.5}, O₃ and NO₂ in Mexico City in the period 2010-2015.¹⁶ The aim of this study was to explore the relationship between PM_{2.5}, PM₁₀ and NO₂ and asthma-related emergency hospital admissions (AREHA) for children aged less than 5 years and adults aged greater than 18 years, in Mexico City between 2017 and 2019. This was of particular interest in the context of city-wide interventions to improve air quality (AQ), including the recent introduction of a health-based AQ index to communicate information on levels of pollution to the population, to explore if this relationship still persisted.

Table 1 Asthma-related hospital admissions for the period 2017–2019

Year	Annual number of cases		Range, per day		Median (Q1, Q3), per day			
	0-4 years	>18 years	0-4 years	>18 years	0-4 years		>18 years	
2017	3078	13 512	0–28	7–120	7	(5, 11)	34	(26, 45)
2018	3137	14 242	0–29	10–122	7	(5, 12)	35	(26, 48)
2019	2721	14 033	0–25	9–115	6	(4, 10)	37	(28, 48)
Overall	8936	41 787	0–29	7–122	7	(4,11)	35	(27, 47)

Q1=quartile 1; Q3=quartile 3.

METHODS
Study location

Mexico City is the capital and largest city in Mexico, situated at an average altitude of 2240 m above sea level. It is also the most densely populated city in North America with a population of 21 828 944 and a high population density of 2559.8 inhabitants per km². It was once the most polluted city in the world. Mexico City's Metropolitan Environmental Commission implemented several policies, under two programmes (Comprehensive Programme Against Air Pollution: PICCA, 1990–1995; and ProAire, from 1995) aimed at reducing air pollution. For example, since 1990 catalytic converters have been required in new cars, cleaner unleaded fuels have been widely distributed, natural gas has been substituted for heavy oil in industry and power plants, liquefied petroleum gas has been reformulated for residential use, driving restrictions within the city were strengthened in 2006 and the public transport infrastructure was improved with the introduction of the Metrobus system that uses environmentally friendly buses, which also began in 2006. Data from Mexico City's automatic atmospheric monitoring network suggests that these measures have reduced air pollution levels by 58% by 2017.¹⁷ Despite this significant improvement in AQ, current PM_{2.5}, PM₁₀ and NO₂ levels are frequently found to exceed Mexican AQ standards.¹⁸ The Ministry for the Environment in Mexico City continues to take public health measures to reduce the impact of pollution on health, including the recent introduction of a health-based AQ index to communicate information on levels of pollution to the population.¹⁶ It is anticipated that this information tool will encourage the population to take measures to reduce their exposure to air pollution when it is indicated that levels are high.

AQ indicators and meteorological data

Ambient ground-level concentrations of PM_{2.5}, PM₁₀ and NO₂ were obtained from ten fixed-site AQ monitoring stations in different geographical areas across Mexico City from the automatic atmospheric monitoring network (RAMA).¹⁷ All measurements were taken by precision AQ monitoring equipment with quality assurance and quality control protocols for data sampling, analysis and calibration. Daily average concentrations were calculated from data downloaded at hourly intervals. The monitoring sites included were selected because they provided data from across Mexico City for at least 80% of the days and time period covered.

Table 2 Descriptive data for PM₁₀ concentration, PM_{2.5} concentration, NO₂ concentration, temperature, humidity and wind speed in Mexico City, 2017–2019

	Mean	(SD)	Median	(Q1, Q3)	Min	Max	Days exceeded WHO AQG
PM ₁₀ µg/m ³	43.97	(17.31)	41.60	(30.34, 55.39)	9.71	119.36	484 (44.4%)
PM _{2.5} µg/m ³	23.01	(9.53)	21.82	(16.49, 27.98)	5.46	78.94	886 (81.4%)
NO ₂ µg/m ³	44.75	(12.72)	43.69	(35.24, 51.74)	15.41	99.91	1061 (97.4%)
Temperature (°C)	17.80	(2.49)	17.94	(16.39, 19.33)	6.22	24.5	
Humidity (%)	51.48	(13.70)	52.20	(41.60, 61.80)	12.40	89.30	
Wind speed (m/s)	2.07	(0.42)	2.00	(1.77, 2.26)	1.23	4.29	

µg/m³, micrograms per cubic metre.
*World Health Organisation Air Quality Guidelines (AQG) ([https://www.who.int/news-room/fact-sheets/detail/ambient-\(outdoor\)-air-quality-and-health#:~:text=The current WHO guideline value, effects of gaseous nitrogen dioxide](https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health#:~:text=The current WHO guideline value, effects of gaseous nitrogen dioxide)): PM₁₀=45 µg/m³; PM_{2.5}=15 µg/m³; NO₂=25 µg/m³.

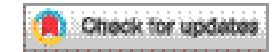
Humidity and temperature data were obtained from the Mexico City meteorological network stations for the period 2017–2019.¹⁹ The climate in Mexico City is temperate, with a wet season in summer, from May to October.

AREHA data

Data on all public hospital admissions in Mexico City during the period 2017–2019, including age, sex and International Classification of Diseases (ICD-10) code for diagnosis were obtained from the Registry Department of the Instituto Mexicano del Seguro Social (IMSS). Cases with a primary diagnosis of asthma (ICD-10 J45 and J46) were included in the study. The IMSS is the largest health institution in Mexico, and covers 42.4% of the population of Mexico City.²⁰ All the IMSS Hospitals of the Greater Valley of Mexico were included in the present analysis. Records of daily AREHA were available for the study period.

Statistical analysis

Descriptive statistics (means or medians, as appropriate) were produced to summarise the number of admissions during the study period and average PM_{2.5}, PM₁₀, NO₂ and selected environmental variables. As the number of admissions was not normally distributed, Spearman correlations were calculated to explore the relationship between these and the AQ and environmental variables. We conducted an ecological time series study. Time series analysis was conducted using generalised linear models with negative binomial (type II) regression, to take account of overdispersion of the data,²¹ while allowing model comparison using Akaike Information Criterion (AIC). The method was adapted from that described by Tadano et al.²² Mean daily relative humidity, wind speed, temperature and season (calendar day) were controlled for using a smooth function in the analyses. In addition, day of the week and public holidays were controlled for. Relative risks of an AREHA associated with a 10 unit increase in PM₁₀, and a 5 unit increase in PM_{2.5} and NO₂ were calculated. In addition, relative risks for an IQR increase in the pollutants were calculated. Lag times of 0–7 days were considered. The AIC was used to identify the best-fitting model. The best fitting model was identified as that with the lowest AIC. Multipollutant models were used to study the effect of adjusting for the other pollutants on hospital admissions. Due to collinearity (variance inflation factor>4) in regression analysis between PM₁₀ and PM_{2.5} in children each of these pollutants were adjusted only for NO₂ in separate two pollutant models.



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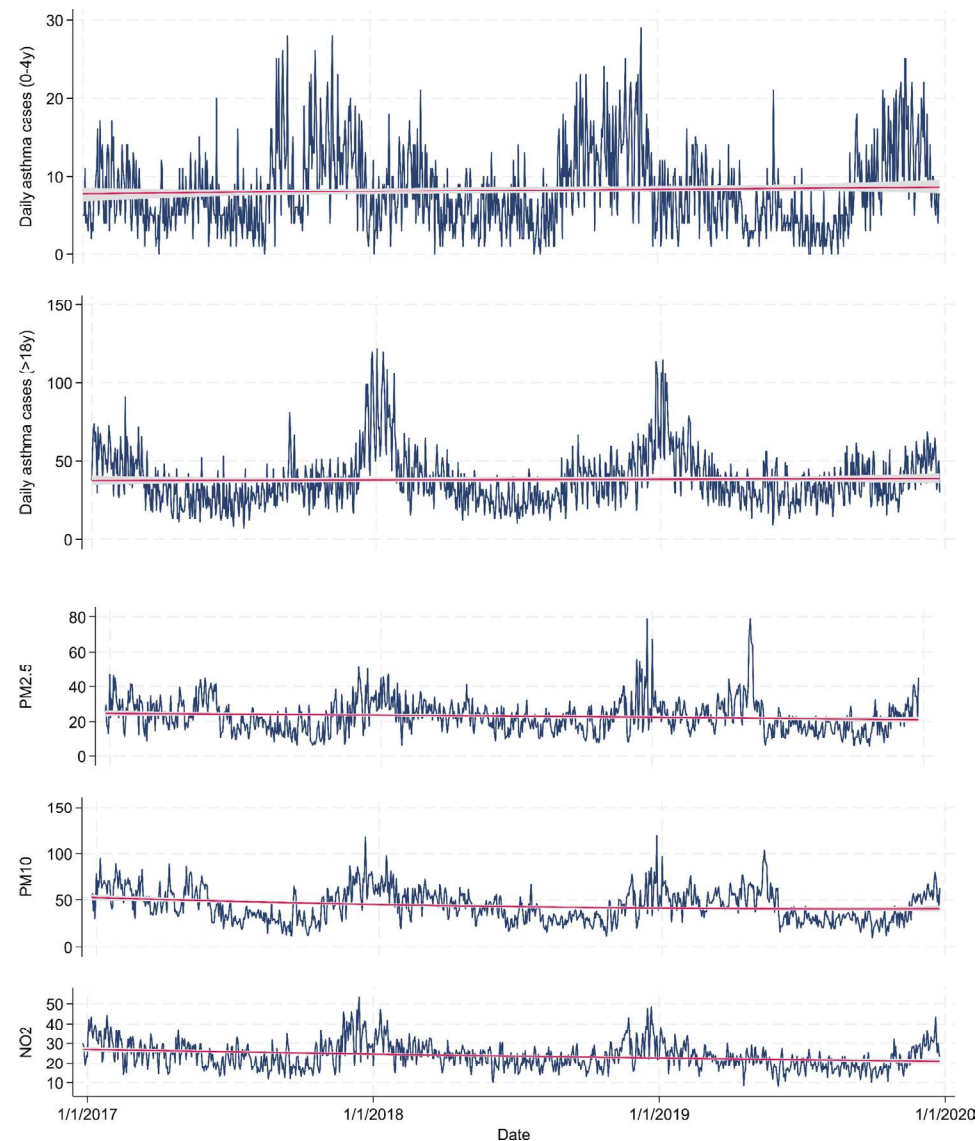


Figure 1 Time series plots of daily asthma admissions and pollutant concentrations, 2017–2019.

Analyses were conducted separately for adults (aged>18 years) and for children aged 0–4 years. This group of young children was studied because of their high asthma prevalence and increased risk of asthma-related hospitalisation.³

All analyses were conducted in Stata V.17.²³ A p value of <0.05 was used to indicate statistical significance.

RESULTS

A total of 50 723 AREHA (41 787 adults and 8936 children) were recorded in the period 2017–2019. The median number of AREHA per day was 7 in children and 35 in adults (table 1).

Table 2 shows descriptive data for the pollutants considered in this study and for meteorological variables. Recommended 24-hour thresholds (online supplemental table S1) were exceeded for the vast majority of days during the study period for PM_{2.5} and NO₂ (81% and 97%, respectively). PM₁₀ thresholds were exceeded on 44% of days during this period.

Daily emergency hospital admissions for asthma showed a clear seasonal pattern, with a greater number of cases recorded in the cold season (October–February) (figure 1). The median number of cases recorded per day in the cold season was 58 compared with 35 and 37 in the rainy and hot seasons, respectively (p<0.001). Sea-

Table 3 Spearman correlations between monthly or daily asthma admissions and PM ₁₀ concentration, PM _{2.5} concentration, NO ₂ concentration, temperature, humidity and wind speed, 2017–2019								
	Admissions>18 years	Admissions 0–4 years	PM ₁₀	PM _{2.5}	NO ₂	Temperature	Humidity	Wind speed
Admissions>18 years	1.00							
Admissions 0–4 years	0.375*	1.00						
PM ₁₀	0.362*	0.094*	1.00					
PM _{2.5}	0.232*	0.035	0.855*	1.00				
NO ₂	0.386*	0.198*	0.728*	0.730*	1.00			
Temperature	–0.387*	–0.243	–0.066*	–0.069*	–0.338*	1.00		
Humidity	–0.176*	0.046	–0.664*	–0.358*	–0.286*	–0.266*	1.00	
Wind speed	–0.175*	–0.090*	–0.203*	–0.427*	–0.596*	0.396*	–0.253*	1.00

*p<0.05.

Table 4 Relative risks (RR) for asthma-related hospital admissions for a 10 (PM ₁₀) or 5 unit (PM _{2.5} and NO ₂) and IQR, adjusted for day of the week, national holiday, temperature, humidity, season and wind speed, 2017–2019						
	Adults >18 years*			Children 0–4 years†		
	RR	95% CI	P	RR	95% CI	P value
PM ₁₀ (10 µg/m ³ increase)	1.04	1.02 to 1.05	<0.001	0.96	0.94 to 0.98	<0.001
PM _{2.5} (5 µg/m ³ increase)	1.03	1.02 to 1.04	<0.001	0.98	0.96 to 0.99	0.028
NO ₂ (5 µg/m ³ increase)	1.02	1.01 to 1.03	<0.001	0.97	0.96 to 0.99	<0.001
PM ₁₀ (IQR; 25.1 µg/m ³)	1.10	1.06 to 1.14	<0.001	0.90	0.85 to 0.96	<0.001
PM _{2.5} (IQR; 11.5 µg/m ³)	1.06	1.04 to 1.09	<0.001	0.95	0.91 to 0.99	0.028
NO ₂ (IQR; 16.5 µg/m ³)	1.06	1.03 to 1.09	<0.001	0.91	0.86 to 0.96	<0.001

*Best fitting model for adults for PM₁₀ was 1-day lag, for PM_{2.5} was 2-day lag and for NO₂ was 6-day lag.
†Best fitting model for children for PM₁₀ was 1-day lag, for PM_{2.5} was 2-day lag and for NO₂ was 6-day lag.

sonal patterns in PM₁₀, PM_{2.5} and NO₂ were also apparent. Mean daily PM10 concentrations were highest in the cold season and lowest in the rainy season (June–September). Mean daily PM_{2.5} concentrations were lowest in the rainy season and consistently higher between November and May. The pattern for NO₂ was similar to that for PM₁₀ (figure 1).

Daily asthma admissions were positively correlated with PM₁₀ and NO₂ concentrations in both adults and children. However, PM_{2.5} was positively correlated with asthma admissions in adults only. Mean wind speed was negatively associated with asthma admission in both adults and children. Mean temperature and humidity were negatively associated with asthma admissions in adults, but not in children (table 3).

The AIC values for models with 1–7 day lags indicated that in adults the model with the effect of a 1-day lag fitted the data best for PM₁₀ and for PM_{2.5} the best fitting model had a 2-day lag. For NO₂, the best fitting model was that with a 6-day lag. In children, the model with a 6-day lag was the best fitting model for PM₁₀ and PM_{2.5} and for NO₂ the best fitting model had a 5-day lag (online supplemental table S2).

Statistically significant increased relative risks of asthma admissions were found in the single pollutant models for increased PM₁₀, PM_{2.5} and NO₂ in adults. The relative risk (95% CI) for an increase of 10 µg/m³ in PM₁₀ was 1.04 (1.02, 1.05) and for an IQR increase was 1.10 (1.06–1.14) (table 4). For PM_{2.5} the relative risk (95% CI) of an asthma-related hospital admission was 1.03 (1.02 to 1.04) and 1.06 (1.04 to 1.09) for a 5 µg/m³ and IQR increase, respectively. The figures for NO₂ were 1.02 (1.01 to 1.03) and 1.06 (1.03 to 1.09).

Statistically significant decreased relative risks of asthma admissions were found for increased PM₁₀, PM_{2.5} and NO₂ in children

Table 5 Relative risks (RR) for asthma admissions for a 10 (PM ₁₀) or 5 unit (PM _{2.5} and NO ₂) and IQR, adjusted for day of the week, national holiday, temperature, humidity, season and wind speed, 2017–2019: mutually adjusted* results (adults, >18 years)			
	RR	95% CI	P value
PM ₁₀ (10 µg/m ³ increase)	1.03	1.01 to 1.04	0.003
PM _{2.5} (5 µg/m ³ increase)	1.01	1.00 to 1.03	0.016
NO ₂ (5 µg/m ³ increase)	1.01	1.01 to 1.02	0.001
PM ₁₀ (IQR; 25.1 µg/m ³)	1.06	02 to 1.11	0.003
PM _{2.5} (IQR; 11.5 µg/m ³)	1.03	1.01 to 1.06	0.015
NO ₂ (IQR; 16.5 µg/m ³)	1.05	1.02 to 1.08	<0.001

*Each pollutant mutually adjusted for the other two pollutants; collinearity of variables was not found (variance inflation factors (VIF)<4 observed in linear regression analysis).

Table 6A Relative risks (RR) for asthma admissions for a 10 (PM ₁₀) or 5 unit (NO ₂) and IQR, adjusted for day of the week, national holiday, temperature, humidity, season and wind speed, 2017–2019: two-pollutant model* results (children; 0–4 years)			
	RR	95% CI	P value
PM ₁₀ (10 µg/m ³ increase)	0.97	0.95 to 0.99	0.028
NO ₂ (5 µg/m ³ increase)	0.98	0.96 to 0.99	0.011
PM ₁₀ (IQR; 25.1 µg/m ³)	0.93	0.87 to 0.99	0.029
NO ₂ (IQR; 16.5 µg/m ³)	0.93	0.88 to 0.99	0.012

*PM₁₀ and NO₂ mutually adjusted for; collinearity of variables was not found (variance inflation factors (VIF)>4 observed in linear regression analysis when PM₁₀ and PM_{2.5} included in the same model).

Table 6B Relative risks (RR) for asthma admissions for a 5 unit increase in PM ₁₀ and NO ₂ and IQR, adjusted for day of the week, national holiday, temperature, humidity, season and wind speed, 2017–2019: two-pollutant model* results (children)			
	RR	95% CI	P value
PM _{2.5} (5 µg/m ³ increase)	0.99	0.97 to 1.01	0.458
NO ₂ (5 µg/m ³ increase)	0.97	0.96 to 0.99	0.002
PM _{2.50} (IQR; 11.5 µg/m ³)	0.98	0.94 to 1.03	0.461
NO ₂ (IQR; 16.5 µg/m ³)	0.92	0.87 to 0.97	0.003

*PM_{2.5} and NO₂ mutually adjusted for; collinearity of variables was not found (variance inflation factors (VIF)>4 observed in linear regression analysis when PM₁₀ and PM_{2.5} included in the same model).

aged less than 5 years (0.96 (0.94 to 0.98), 0.98 (0.96 to 0.99) and 0.97 (0.96 to 0.99), respectively) (table 4).

Results from the analysis with mutual adjustment for the pollutants are shown in table 5 (adults) and tables 6A and 6B (children). The associations between the pollutants and asthma-related hospital admissions observed in the single pollutant models remained statistically significant in the adjusted models for PM₁₀, PM_{2.5} and NO₂ in adults. Relative risks (95% CI) of 1.03 (1.01 to 1.04), 1.01 (1.00 to 1.03) and 1.01 (1.01 to 1.02) for a 10 µg/m³ in PM₁₀ increase in PM₁₀ and a 5 µg/m³ in PM_{2.5} and NO₂ respectively, were found, suggesting an independent effect of these pollutants on asthma-related admissions. In children, after adjustment for NO₂, PM₁₀ remained statistically significantly negatively associated with asthma-related admissions (relative risk (95% CI): 0.97 (0.95 to 0.99) for a 10 µg/m³ increase) and NO₂ remained statistically significantly negatively associated with asthma-related admissions after adjustment for PM₁₀ (0.98 (0.96 to 0.99) for a 5 µg/m³ increase). PM_{2.5} was no longer statistically significantly associated with asthma-related admissions after adjustment for NO₂, although NO₂ remained statistically significantly negatively associated with asthma-related admissions (relative risk (95% CI): 0.97 (0.96 to 0.99) for a 5 µg/m³ increase) after adjustment for PM_{2.5}. Relative risks associated with an IQR increase in each of the pollutants are shown in table 4 (single pollutant model) and table 6A, table 6B (two-pollutant models).

DISCUSSION

Main findings

The main findings of this study suggest that, in Mexico City in recent years, risk of hospital admission for an exacerbation of asthma in adults, aged over 18 years, increases with increasing ambient levels of PM_{2.5}, PM₁₀ and NO₂. The relationship between these pollutants and hospital admissions for asthma in children (aged less than 5 years) was less clear. A negative and statistically significant relationship between PM₁₀ and NO₂ and asthma-related admissions was observed in both single pollutant analysis and after adjustment for the other pollutants. A negative association between asthma-related admissions and PM_{2.5} was found when this pollutant was considered separately. This relationship was no longer statistically significant after adjustment for NO₂.

Models using different lag days were found to best fit the data for different pollutants and for children compared with adults. This

was particularly notable for NO₂, where a 6-day lag was identified as providing the best fit in adults compared with a 1-day and 2-day lag, respectively, for PM₁₀ and PM_{2.5}. For children, the relationship between ambient NO₂ and asthma-related admissions differed according to lag days. However, a comparison of results from the best fitting model (5 lag days) and the next best fitting model (6 lag days), based on AIC, has very similar findings.

Exposure to airborne pollutants is well established as contributing to poor health, including increased hospital admissions and emergency room visits for patients experiencing respiratory symptoms and exacerbation of chronic respiratory diseases.²⁴ Our findings in adults are consistent with those reported in other settings. There is a large body of evidence from studies conducted in a range of settings that asthma-related hospital visits increase as levels of particulate matter and NO₂ increase.^{7 25–29}

Albalawi et al reported that ambient levels of PM_{2.5}, PM₁₀ and NO₂ were associated with asthma-related visits to the ED independently of one another in Jubail Industrial City in Saudi Arabia.³⁰ In Albalawi’s study, data on all age groups were combined, in contrast to the present study in which young children and adults were considered separately, so a comparison with our findings in young children is not possible. However, these findings are broadly consistent with our findings in adults. A systematic review and meta-analysis published in 2015 found a significant positive association between PM₁₀, PM_{2.5} and NO₂ with asthma-related emergency visits or hospitalisations for all ages.³¹ In contrast, a 2017 systematic review and meta-analysis concluded that PM_{2.5} but not PM₁₀ was associated with asthma exacerbations in both children and adults.¹² This conflicts with our finding that NO₂, but not PM_{2.5} nor PM₁₀, was positively associated with asthma admissions in young children. A possible explanation for this is that we considered only asthma-related hospital admissions, while studies included in these systematic reviews included asthma-related emergency visits and asthma exacerbations.

Also in contrast to our findings, a study of ambient air pollutants and asthma-related hospitalisations in Hong Kong, including almost 70 000 admissions over a 5-year period, found that the relative risk of admission as PM_{2.5} and PM₁₀ increased was slightly higher (1.024 compared with 1.018 for PM_{2.5} and 1.023 compared with 1.014 for PM₁₀) in children (aged 0–14 years) than in adults aged 15–65 years.³² Other studies in children have reported similar findings of a positive association between ambient PM₁₀^{33–36} and PM_{2.5}^{35 37} and asthma admissions. In our study, we included only children aged under 5 years, which raises the possibility that, in this group of very young children, the relationship between particulate matter and asthma exacerbation does not exist. Silverman found that age was important in terms of risk of asthma-related hospital admissions associated with AQ in children, and that children aged 6–18 years have the highest risk.³⁸ This might help to explain the lack of or inverse association we found in children as we focused only on children aged less than 5 years in the present study, due to the high and increasing levels of asthma and related hospital admissions in this group. We cannot, however, discount the possibility that we did not observe a relationship between PM_{2.5} and asthma admission in children aged less than 5 years because statistical power was limited due to fewer hospitalisations in this group nor that unmeasured confounders masked this relationship.

The recent introduction of a health-based AQ index to communicate information on levels of pollution to the population¹⁶ might also account for the lack of association between fine particulate matter and paediatric asthma admissions. It is possible that parents are acting on the information provided on pollution levels within Mexico City and taking measures to limit their young children’s exposure to pollution, for example, by keeping them indoors during periods when pollution is high. It could be speculated that adults are less able to avoid exposure due to the need to be outdoors for work, travel to work and other commitments. This is an important area for future research to address.

Previous studies of the association between ambient NO₂ and paediatric asthma-related hospital admissions have generally pro-

vided evidence that admissions increase with increasing levels of NO₂, although the association has not always been as consistent as in our analysis. Samoli et al, for example, reported a non-statistically significant association between increasing levels of NO₂ and asthma admission in 0–14 year olds in Athens, Greece,³³ although others have reported that a significant association does exist.^{34 37}

Mexico City was once the most polluted mega-city worldwide, although improvements in AQ have been achieved in recent years, pollutant levels still frequently exceed Mexican AQ standards.¹⁸ This is not unexpected, given that the impact of measures to reduce air pollutants is typically seen on long-term pollutant concentrations, rather than on peaks. We found that asthma-related hospital admissions were higher in the cool, dry season in Mexico (November to February), which corresponds to the time of year when AQ is at its worst, reinforcing the need for continued action to address this.

Strengths of this study

The major strengths of this study are that we included data on AREHA to public hospitals in Mexico City during the period of interest and obtained precise data on AQ from monitoring equipment across the city that is consistently subject to strict assurance and control procedures. The AREHA data were obtained from the IMSS, which is the largest Health Institution in the country, and covers over 40% of the population of Mexico City. The strength of this is that individuals covered by IMSS are guaranteed access to treatment. The costs of medical care are paid directly by employers, meaning individuals are not denied care if they cannot pay. It must be noted, however, that a substantial proportion of the population receive their care outside this system and would not therefore be included in our analyses. It is possible that these individuals differ systematically from those who do receive care within the IMSS system, raising the possibility that our findings are not generalisable to the wider population of Mexico City.

Limitations of this study

Despite the high-quality data available on both pollutants and hospital admissions, our study is subject to some limitations. As with other similar studies, the ecological nature of the study means that information on individuals’ exposure to pollutants and subsequent asthma exacerbation is not available. In addition, data on characteristics of individuals who were admitted to hospitals, such as occupation and other potential confounders, were not available for inclusion in our analyses. We did not include children aged 5–17 years in our study and focused on those aged less than 5 years and those aged greater than 18 years. The reasons for this are that children under 5 years of age are the population most susceptible to their lung capacity being compromised as a result of exposure to environmental pollution³⁹ and it has been demonstrated that those over 18 years of age require the greatest steroid use and experience the highest number of hospitalisations for asthma exacerbations, due, in part, to comorbidities, such as obesity and smoking.⁴⁰ In addition, in this study we did not differentiate between first and subsequent admissions. This is important as it is known that allergic factors are strongly associated with initial asthma admissions in children, but in adults the effect of environmental factors is more important at initial admission.⁴¹

The possibility exists that, although we included a large proportion of the adult population in our study, we had a smaller sample size for children under 5 years of age. This raises the possibility that the lower number of cases meant we lacked statistical power to detect associations in this age group.

Finally, our approach to analysis, in which pollutants were mutually adjusted for each other, while consistent with previous literature in this area and facilitating comparison, may not enable the effects of individual pollutants to be disentangled sufficiently due to their being correlated with one another.

CONCLUSIONS

This study of the relationship between air pollution and asthma-related hospital admissions in Mexico City indicates that

ambient levels of NO₂ are associated with an increase in asthma-related admissions in both adults and young children and that PM_{2.5} and PM₁₀ levels are associated with asthma-related admissions in adults. These findings demonstrate the importance of continuing to implement measures to improve AQ and ways to minimise the impact of air pollution on the population’s health in Mexico City. Since being identified by the United Nations as the world’s most polluted city in 1992, improvements in AQ have been observed following the implementation of a wide range of measures including the introduction of low-emission transport zones, promotion of cycling and introduction of congestion charges. Today, Mexico is ranked as the 917th most polluted city. It is essential that work to improve AQ continues to reduce the global health burden associated with air pollution. It is imperative that the impact of interventions to improve AQ on pollutant levels is monitored and that research is undertaken to study if this translates into lower rates of asthma related hospital admissions. We suggest qualitative work to explore the barriers and motivators to individuals changing their behaviour in response to warnings of high pollutant levels being issued would be valuable.

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REFERENCES

- 1 World Health Organisation. Effects of Air Pollution on Children’s Health and Development: A Review of the Evidence. Bonn Office: European Centre for Environment Health, 2005.
- 2 Pollart SM, Compton RM, Elward KS. Management of acute asthma exacerbations. *Am Fam Physician* 2011;84:40–7.
- 3 Ferrante G, La Grutta S. The burden of pediatric asthma. *Front Pediatr* 2018;6:186. 4 Pitchon RR, Alvim CG, Andrade CR de, et al. Asthma mortality in children and adolescents of Brazil over a 20-year period. *Jornal de Pediatria* 2020;96:432–8.
- 5 Forno E, Celed3n JC. Predicting asthma exacerbations in children. *Curr Opin Pulm Med* 2012;18:63–9.
- 6 Meng Y-Y, Rull RP, Wilhelm M, et al. Outdoor air pollution and uncontrolled asthma in the San Joaquin valley, California. *J Epidemiol Community Health* 2010;64:142–7.
- 7 Fan J, Li S, Fan C, et al. The impact of PM_{2.5} on asthma emergency department visits: a systematic review and meta-analysis. *Environ Sci Pollut Res Int* 2016;23:843–50.
- 8 European Environment Agency. Outdoor air quality in urban areas. 2019. Available: <https://www.eea.europa.eu/airs/2018/environment-and-health/outdoor-air-qualityurban-areas> [Accessed 26 Jan 2022].
- 9 Anderson HR, Favarato G, Atkinson RW. Long-term exposure to air pollution and the incidence of asthma: meta-analysis of cohort studies. *Air Qual Atmos Health* 2013;6:47–56.
- 10 Mölter A, Simpson A, Berdel D, et al. A Multicentre study of air pollution exposure and childhood asthma prevalence: the ESCAPE project. *Eur Respir J* 2015;45:610–24.
- 11 Gasana J, Dillikar D, Mendy A, et al. Motor vehicle air pollution and asthma in children: a meta-analysis. *Environ Res* 2012;117:36–45.
- 12 Orellano P, Quaranta N, Reynoso J, et al. Effect of outdoor air pollution on asthma exacerbations in children and adults: systematic review and multilevel meta-analysis. *PLoS ONE* 2017;12:e0174050.
- 13 Guo Y, Jiang F, Peng L, et al. The association between cold spells and pediatric outpatient visits for asthma in Shanghai, China. *PLoS ONE* 2012;7:e42232. 14 Zhang Y, Peng L, Kan H, et al. Effects of meteorological factors on daily hospital admissions for asthma in adults: a time-series analysis. *PLoS ONE* 2014;9:e102475.
- 15 Lam HC, Li AM, Chan EY, et al. The short-term association between asthma Hospitalisations, ambient temperature, other meteorological factors and air pollutants in Hong Kong: a time-series study. *Thorax* 2016;71:1097–109.
- 16 Cromar K, Gladson L, Jaimes Palomera M, et al. Development of a health-based index to identify the association between air pollution and health effects in Mexico city. *Atmosphere* 2021;12:372.
- 17 Rama. 2022. Available: <http://www.aire.cdmx.gob.mx/default.php?opc=%27aKBh%27>
- 18 Sedema: Secretaria del Medio Ambiente. Calidad del Aire en La Ciudad de México, informe 2018. Direcci3n general de Calidad del Aire, Direcci3n de Monitoreo de Calidad del Aire: 2020.
- 19 Calidad del Aire. 2022. Available: <http://www.aire.cdmx.gob.mx/default.php> [Accessed Jan 2022].
- 20 Inegi. 2022. Available: https://www.inegi.org.mx/temas/derechohabiciencia/#Informacion_general
- 21 Errington A, Einbeck J, Cumming J, et al. The effect of data aggregation on dispersion estimates in count data models. *Int J Biostat* 2022;18:183–202.
- 22 TadanoYSet al. Methodology to Assess Air Pollution Impact on Human Health Using the Generalized Linear Model with Poisson Regression, Air Pollution—Monitoring, Modelling and Health. InTech: Croatia, 2012: 281–304.
- 23 Statacorp. Stata statistical software. Statacorp LLC College Station, TX,
- 24 Kim K-H, Kabir E, Kabir S. A review on the human health impact of airborne particulate matter. *Environ Int* 2015;74:136–43.
- 25 Bell ML, Levy JK, Lin Z. The effect of sandstorms and air pollution on cause-specific hospital admissions in Taipei, Taiwan. *Occup Environ Med* 2008;65:104–11.
- 26 Peel JL, Tolbert PE, Klein M, et al. Ambient air pollution and respiratory emergency department visits. *Epidemiology* 2005;16:164–74.
- 27 Galán I, Tobias A, Banegas JR, et al. Short-term effects of air pollution on daily asthma emergency room admissions. *Eur Respir J* 2003;22:802–8.
- 28 Castner J, Guo L, Yin Y. Ambient air pollution and emergency department visits for asthma in Erie County, New York 2007–2012. *Int Arch Occup Environ Health* 2018;91:205–14.
- 29 Tian Y, Xiang X, Juan J, et al. Fine particulate air pollution and hospital visits for asthma in Beijing, China. *Environ Pollut* 2017;230:227–33.
- 30 AlBalawi SM, Namdeo A, Hodgson S, et al. Short-term effects of air pollution on daily asthma-related emergency department visits in an industrial city. *J Public Health (Bangkok)* 2021;43:e45–53.
- 31 Zheng X, Ding H, Jiang L, et al. Association between Air Pollutants and asthma emergency room visits and hospital admissions in time series studies: A systematic review and meta-analysis. *PLoS One* 2015;10:e0138146.
- 32 Ko FWS, Tam W, Wong TW, et al. Effects of air pollution on asthma hospitalization rates in different age groups in Hong Kong. *Clin Exp Allergy* 2007;37:1312–9.
- 33 Samoli E, Nastos PT, Paliatatos AG, et al. Acute effects of air pollution on pediatric asthma exacerbation: evidence of association and effect modification. *Environ Res* 2011;111:418–24.
- 34 Giovannini M, Sala M, Riva E, et al. Hospital admissions for respiratory conditions in children and outdoor air pollution in Southwest Milan, Italy. *Acta Paediatr* 2010;99:1180–5.
- 35 Lee SL, Wong WHS, Lau YL. Association between air pollution and asthma admission among children in Hong Kong. *Clin Exp Allergy* 2006;36:1138–46.
- 36 Norris G, YoungPong SN, Koenig JQ, et al. An association between fine particles and asthma emergency department visits for children in Seattle. *Environ Health Perspect* 1999;107:489–93.
- 37 Li S, Batterman S, Wasilevich E, et al. Association of daily asthma emergency department visits and hospital admissions with ambient air Pollutants among the pediatric medicaid population in detroit: time-series and time-stratified case-crossover analyses with threshold effects. *Environ Res* 2011;111:1137–47.
- 38 Silverman RA, Ito K. Age-related association of fine particles and ozone with severe acute asthma in New York City. *Journal of Allergy and Clinical Immunology* 2010;125:367–373.
- 39 Brauer M, Davaakhuu N, Escamilla Nuñez MC, et al. Clean air, smart cities, healthy hearts: action on air pollution for cardiovascular health. *Glob Heart* 2021;16:61.
- 40 Azim A, Freeman A, Lavenu A, et al. New perspectives on difficult asthma; sex and age of asthma-onset based phenotypes. *J Allergy Clin Immunol Pract* 2020;8:3396.
- 41 Dharmage SC, Perret JL, Custovic A. Epidemiology of asthma in children and adults. *Front Pediatr* 2019;7:246.

ARTIGO ORIGINAL

Influência da idade nas características clínicas, no tratamento farmacológico e nas exacerbações em crianças com asma

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RESUMO

Contexto Os ensaios e as diretrizes sobre a asma não distinguem frequentemente entre adolescentes e crianças mais novas. Utilizando um grande conjunto de dados ingleses, avaliamos o impacto da idade nas características, tratamento e exacerbações da asma.

Métodos Os registros médicos dos cuidados primários, de 2004 a 2021, foram associados aos registros hospitalares. As crianças foram classificadas por idade no momento do diagnóstico e seguidas até ao escalão etário seguinte. As idades (com base nas diretrizes de gestão) foram 5-8 anos, 9-11 anos e adolescentes (12-16 anos). As características avaliadas incluíram o índice de massa corporal, alergias e eventos antes e depois do diagnóstico (sintomas, medicação). Foi calculada a incidência de exacerbações. A análise multivariada de riscos proporcionais de Cox determinou as associações com as exacerbações.

Resultados Foram elegíveis 119 611 crianças: 61 940 (51,8%) de 5-8 anos, 32 316 (27,7%) de 9-11 anos e 25 355 (21,2%) adolescentes. Várias características diferiram consoante a idade; as crianças com idades entre os 5 e 8 anos apresentaram a maior proporção de eczema, alergia alimentar/fármacos e tosse, mas os adolescentes apresentaram a maior proporção de excesso de peso/obesidade, sensibilização a aeroalergénios, dispneia e utilização exclusiva de beta-agonistas de curta duração. As taxas de exacerbação foram mais elevadas nas crianças mais novas (por 100 pessoas-ano (IC 95%): 5-8 anos =13,7 (13,4-13,9), 9-11 anos =10,0 (9,8-10,4), adolescentes =6,7 (6,5-7,0)). Os fatores de risco de exacerbação também diferiram consoante a idade; 5-8 anos: sexo masculino, eczema e alergia a alimentos/fármacos estiveram fortemente associados, mas para crianças ≥9 anos, a obesidade e a sensibilização a aeroalergénios estiveram fortemente associadas. Para todas as crianças, a privação socioeconómica mais elevada foi significativamente associada à ocorrência de uma exacerbação. O diagnóstico tardio foi mais comum em crianças com idades entre os 5 e 8 anos e esteve associado a um aumento das exacerbações em todas as idades.

Conclusão As características de base das crianças e as taxas de exacerbação variaram consoante o seu grupo etário. As diretrizes clínicas devem considerar a idade no momento do diagnóstico de forma mais discreta do que o intervalo alargado de 5-16 anos, uma vez que a idade parece ter impacto na gravidade e no tratamento da asma.

INTRODUCTION

School-age asthma is common, with a prevalence of around 7% in the UK.¹ Some studies have reported differences in patient characteristics and comorbidities depending on the age of asthma onset.²⁻⁵ However, these studies have focused either solely on children compared with adults, or ‘early-onset’ as compared with ‘late-onset’ asthma.³⁻⁶ The effect of age at diagnosis within the broad range included in school age (usually 5–16 years) has not been assessed. The age of onset (childhood or adult) influences the natural history and disease progression of asthma²⁻⁵ and may also influence outcomes within

Key messages

What is the key question?

► The age at onset is known to impact the natural history of asthma and proceeding management; management of preschool children (aged 1–5 years) is distinct to school age (6–16 years), we sought to determine if discrete ages within school age also influence management and outcomes.

What is the bottom line?

► This study informs clinicians about the impact of age at asthma diagnosis for schoolchildren, as it was associated with management risk factors and exacerbation risk.
► The youngest children (5–9 years) were most likely to have a delayed diagnosis and were at greatest risk of exacerbations; adolescents (12–16 years) were most likely to have suboptimal pharmacological management.
► Although high body mass index (BMI) was a major exacerbation risk factor, BMI was not measured in over a third.

Why read on?

► Younger school-age children and adolescents should not be considered as a homogeneous group in clinical guidelines and trials.

the childhood period. Critically, there is a huge period of growth and development within this window which is likely to impact both pathophysiology and psychosocial factors determining asthma management. Although most children have mild–moderate disease, many suffer from asthma exacerbations requiring oral corticosteroids and/or hospital admissions.¹ Real-life data on the incidence rate and risk factors for asthma exacerbations among children stratified by age are limited,^{4,7} although key risk factors such as atopy and obesity have been proposed to play different roles depending on the child’s age.⁸ We therefore hypothesised that age during childhood influences asthma characteristics at diagnosis, subsequent asthma management, and exacerbation risk and risk factors. To address this hypothesis, we used a large nationally representative cohort of children with asthma.

METHODS

Data source

The cohort was selected using primary care electronic healthcare records which were obtained from the Clinical Practice Research Datalink

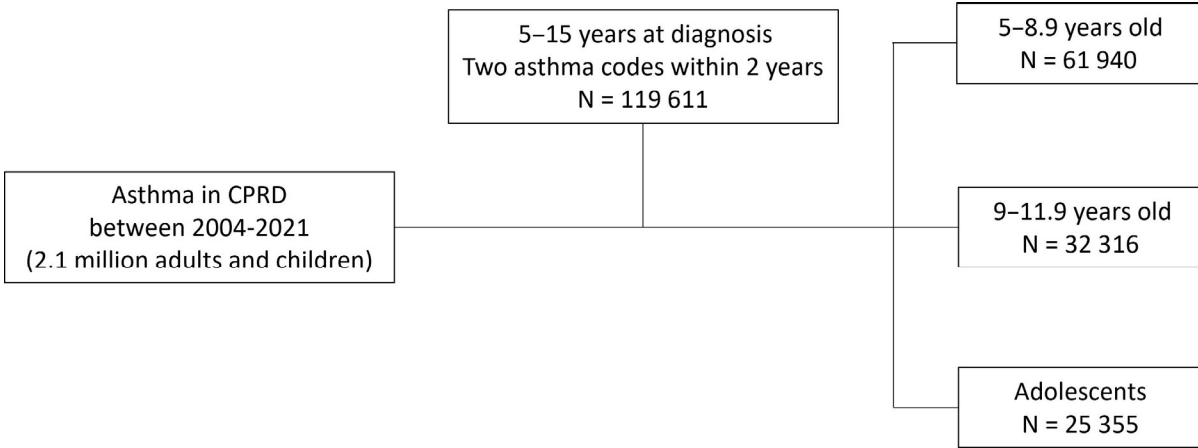


Figure 1 Flow chart of the eligible cohort. CPRD, Clinical Practice Research Datalink.

(CPRD). The CPRD is the largest longitudinal healthcare database worldwide; it is broadly representative of the UK population and includes over 19 million patients.⁹ Hospital admissions and accident and emergency (A&E) visits to English hospitals were obtained from Hospital Episode Statistics data; mortality data were obtained from Office for National Statistics death registration data.⁹

Study population and study design

The study population included patients identified between January 2004 and January 2021. Children were eligible to enter the study if they were aged 5 years or older, had continuous registration in a CPRD-linked general practice and had two validated asthma codes within 2 years and at least 1 year of data prior to study entry, and at least 1 year of data after diagnosis (figure 1 and online supplemental table E1).¹⁰ Follow-up was censored at the first date of reaching the end of their assigned age bracket, the end of the study (1 January 2022) or the end of their data collection. Asthma diagnosis date was defined as the first recorded asthma code within their general practice. The cohort was categorised into age groups based on UK asthma management guidelines¹¹ which include children (5–12 years), which we further arbitrarily divided into: 5–8.9 years and 9–11.9 years, and adolescents, defined as 12–15.9 years old.

Characteristic variables

Body mass index (BMI) was categorised using percentiles and z score as ‘normal weight’, ‘overweight’ and ‘obese’; z scores were derived using 1990 UK data and converted according to WHO cut-offs.¹² Indices of multiple deprivation (IMDs), as calculated by the English government, provide a relative score of socioeconomic deprivation; for this study we used the score categorised into quintiles, with level 5 considered as the most deprived area.¹³ Smoking status was considered for the children aged 12–15.9 years and categorised as ‘smoker’ or ‘never smoker’; passive smoke exposure was considered for all children (online supplemental tables E2 and E3). Three atopy variables were included: ‘aeroallergen sensitisation’, defined as receiving a code for allergic rhinitis, or allergy to pets, pollen or house dust mites (although information on how that diagnosis was obtained was not available); ‘food/drug allergy’, defined as receiving a code for allergy to food or drugs; or ‘eczema’ (online supplemental table E4). Reported respiratory symptoms were measured in the year prior to diagnosis, including cough, wheeze/chest tightness or dyspnoea.

An asthma exacerbation was defined as general practitioner (GP)-managed (short course of oral corticosteroids (OCS)) or hospital-managed (A&E visit or hospital admission for asthma, using International Classification of Disease (ICD)-10 codes J45 and J46; A&E data, using a specific asthma code (diagnosis 251), was only available from 2015 onwards).⁴ Exacerbations were categorised as either ‘at the time of diagnosis’, arising 30 days before or on the day of diagnosis, or as ‘post-diagnosis exacerbation’, arising any time after asthma diagnosis.

Asthma medications included short-acting beta-agonist (SABA), inhaled corticosteroids (ICS) and add-on medications: long-acting beta-agonist or leukotriene receptor antagonist (LTRA). The dose of each ICS-containing inhaler was classified, using budesonide equivalence, as very low (≤ 200 $\mu\text{g/day}$), low (200–400 $\mu\text{g/day}$), medium (>400 –800 $\mu\text{g/day}$) or high (≥ 800 $\mu\text{g/day}$). Courses of OCS were also recorded for the year before receiving a formal asthma diagnosis by the child’s GP practice.

Statistical analyses

Baseline data were presented as percentages, or medians and IQR. For ease of clinical interpretation, postdiagnosis asthma medications were described as percentages within a fixed 2-year follow-up, therefore only children with at least 2 years of follow-up were included in that analysis. Asthma exacerbations were described using incidence rates and displayed using Kaplan-Meier graphs for time to first exacerbation. The association between the first asthma exacerbation and patient characteristics and prior management was estimated using multivariable Cox proportional hazards models. Proportional hazards assumption were not violated, as confirmed by plotting the Schoenfeld residuals. All variables included were considered a priori to be risk factors. Two models were conducted, in Model 1, only baseline characteristics were simultaneously included: gender, age at diagnosis, IMD, BMI, smoking, aeroallergen sensitisation, food/drug allergy and eczema. In Model 2, additional prediagnosis covariates were added: symptoms, ICS prescriptions, OCS prescriptions and exacerbations at the time of diagnosis. Due to the large number of missing values for the BMI variable, a ‘missing’ BMI stratum was applied to the main models to determine if there was any impact from having missing BMI. In addition, a sensitivity analysis was conducted, excluding BMI from the models. An additional sensitivity analysis was conducted, including all exacerbations as the outcome, not just the first one: the Andersen-Gill extension to the Cox proportional hazards model was used. All analyses were conducted in Stata V.17 (StataCorp, College Station, Texas, USA).

RESULTS

Patient characteristics at the time of diagnosis

The total number of children included in the study was 119 611. Of these 61 940 (51.8%) received an asthma diagnosis between ages 5–8.9 years, 32 316 (27.7%) between ages 9–11.9 years and 25 355 (21.2%) during adolescence (12–15.9 years). The youngest had the lowest proportion of girls (41.8%) and the adolescents had the highest proportion (54.7%) (table 1). The percentage of children with aeroallergen sensitisation increased with age, 14.0% in the 5–8.9 years group, to 21.4% of adolescents. The proportion of children with eczema was highest in the youngest group and decreased with age, 37.3% in the 5–8.9 group to 33.0% of adolescents. The proportion that was overweight/obese increased with age, approximately 1 in 5 adolescents as compared with 1 in 10 of the youngest children (5–8.9 years), however, nearly 40% of the

Table 1 Baseline characteristics and prediagnosis events by age groups				
Baseline characteristics	Total N (%)	5–8.9 years N (%)	9–11.9 years N (%)	Adolescents* N (%)
	n=119 611 (100.0%)	n=61 940 (51.8%)	n=32 316 (27.7%)	n=25 355 (21.2%)
Mean age at diagnosis (SD; years)	9.7 (3.4)	6.8 (1.2)	10.4 (0.9)	13.7 (1.7)
Gender				
Male	65 886 (55.1%)	36 514 (58.9%)	17 868 (55.2%)	11 504 (45.3%)
Female	53 725 (44.9%)	25 426 (41.1%)	14 448 (44.8%)	13 851 (54.7%)
BMI				
Normal	52 668 (44.1%)	26 341 (42.5%)	14 229 (44.0%)	12 098 (47.7%)
Overweight	11 367 (9.5%)	4419 (7.1%)	3703 (11.4%)	3245 (12.8%)
Obese	7575 (6.3%)	3065 (4.9%)	2471 (7.6%)	2039 (8.0%)
Missing	48 001 (40.1%)	28 115 (45.5%)	11 913 (37.0%)	7973 (31.5%)
IMD (socioeconomic deprivation status)				
1	22 880 (19.1%)	11 548 (18.6%)	6420 (19.9%)	4912 (19.4%)
2	21 567 (18.0%)	11 083 (17.9%)	5757 (17.8%)	4719 (18.6%)
3	21 433 (17.9%)	10 962 (17.7%)	5752 (17.8%)	4719 (18.6%)
4	25 100 (21.0%)	13 143 (21.2%)	6763 (20.9%)	5194 (20.5%)
5	28 631 (24.0%)	15 204 (24.5%)	7624 (23.6%)	5803 (22.9%)
Aeroallergen sensitisation				
Yes	20 348 (17.1%)	8616 (14.0%)	6308 (19.6%)	5424 (21.4%)
Eczema				
Yes	40 814 (34.1%)	23 108 (37.3%)	10 651 (33.0%)	7055 (27.8%)
Food/drug allergy				
Yes	9548 (8.0%)	5561 (9.0%)	2344 (7.3%)	1643 (6.5%)
Passive smoking				
Yes	2503 (2.1%)	1292 (2.1%)	726 (2.3%)	486 (2.0%)
Smoking				
Yes	4225 (3.5%)	NA	1597 (5.0%)	2628 (10.4%)
Exacerbation at time of diagnosis				
No	114 303 (95.6%)	58 560 (94.5%)	31 102 (96.0%)	24 641 (97.1%)
GP-managed exacerbation	3620 (3.0%)	2178 (3.5%)	889 (2.7%)	553 (2.1%)
Hospital-managed exacerbation	1688 (1.4%)	1202 (1.9%)	325 (1.0%)	161 (0.6%)
Year before diagnosis				
Dyspnoea				
Yes	8650 (7.2%)	2954 (4.8%)	2755 (8.5%)	2941 (11.6%)
Wheeze/chest tightness				
Yes	14 532 (13.2%)	8592 (13.9%)	3536 (11.0%)	2404 (9.5%)
Cough				
Yes	41 767 (34.9%)	24 703 (39.9%)	10 347 (31.9%)	6717 (26.5%)
OCS course				
≥1 short course	6403 (5.3%)	4269 (6.9%)	1357 (4.2%)	777 (3.0%)
Unscheduled hospital visit coded as ‘asthma’ ≥1 visit	1542 (1.3%)	1134 (1.8%)	273 (0.8%)	134 (1.2%)

*Adolescents =12–15.9 years
BMI, body mass index; GP, general practitioner; IMD, Index of Multiple Deprivation; OCS, oral corticosteroids.

whole cohort did not have a recorded BMI. Regarding socioeconomic deprivation, the largest proportion, 24.0%, fell within the most deprived quintile across all ages. Ten percent of adolescents reported smoking but a surprisingly low proportion, under 3%, had recorded passive smoking in all age categories.

Of the whole cohort, 4.4% received their asthma diagnosis at the time of, or straight after, being treated for an exacerbation; the highest proportion were in the youngest group (approximately 6% in the 5–8.9 years group, 4% in the 9–11.9 years group and 3% of adolescents; table 1).

Respiratory symptoms in the year before diagnosis

Cough was the most common symptom and was most prevalent in the youngest children (5–8.9 years group: 39.9%, 9–11.9 years group: 31.9%, adolescents: 26.5%; table 1). Wheeze/chest tightness was also most common in the younger children (5–8.9 years group: 13.9%, 9–11.9 years group: 11.0%, adolescents: 9.5%). Adolescents were more likely to attend the GP with dyspnoea than were younger children (5–8.9 years group: 4.8%, 9–11.9 years group: 8.5%, adolescents: 11.6%).

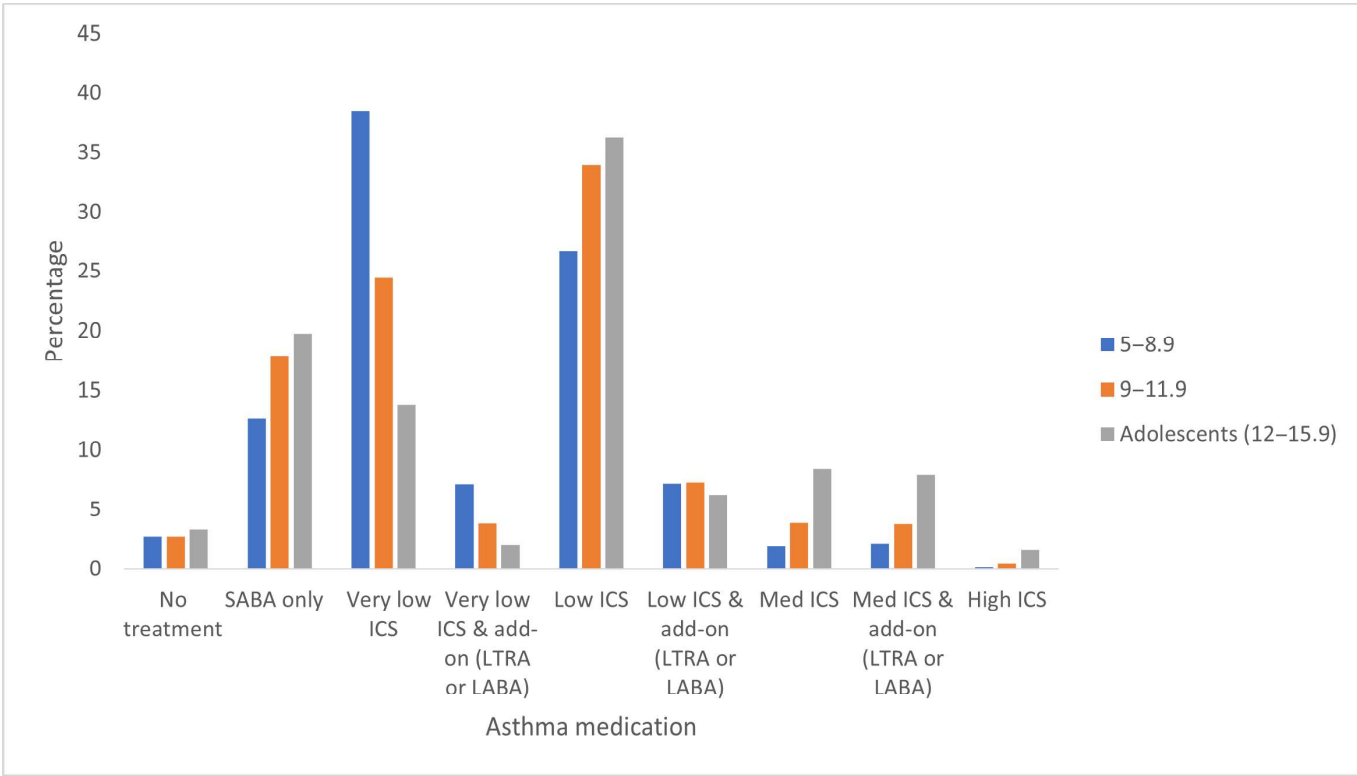


Figure 2 Asthma medication by age group. ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LTRA, leukotriene receptor antagonists; SABA, short-acting beta-agonist.

OCS and unscheduled hospital visits prediagnosis

Children in the 5–8.9 years group were most likely to be prescribed OCS (5–8.9 years group: 6.9%, 9–11.9 years group: 4.2%, adolescents: 3.0%) or have an unscheduled hospital visit coded for ‘asthma’ (5–8.9 years group: 1.8%, 9–11.9 years group: 0.8%, adolescents: 1.2%) in the year before receiving an asthma diagnosis within their GP practice (table 1).

Asthma medication in the first two years after diagnosis

Over 95% of all children were prescribed at least one asthma medication during the first 2 years after their recorded diagnosis

(figure 2 and online supplemental table E5). The youngest group was most likely to be prescribed an ICS inhaler but nearly a quarter of adolescents were not prescribed ICS ever during the first 2 years (online supplemental table E6). Adolescents were also most likely to be prescribed SABA only for the duration of the first 2 years (5–8.9 years group: 12.7%, 9–11.9 years group: 18.1%, adolescents: 19.8%); 42% of adolescents managed with SABA alone were prescribed ≥3 SABA and 17% ≥5 SABA. Of those prescribed ICS, most were prescribed very low or low dose ICS, although up to one in six adolescents were prescribed medium dose ICS (5–8.9 years group: 4.0%, 9–11.9 years group:

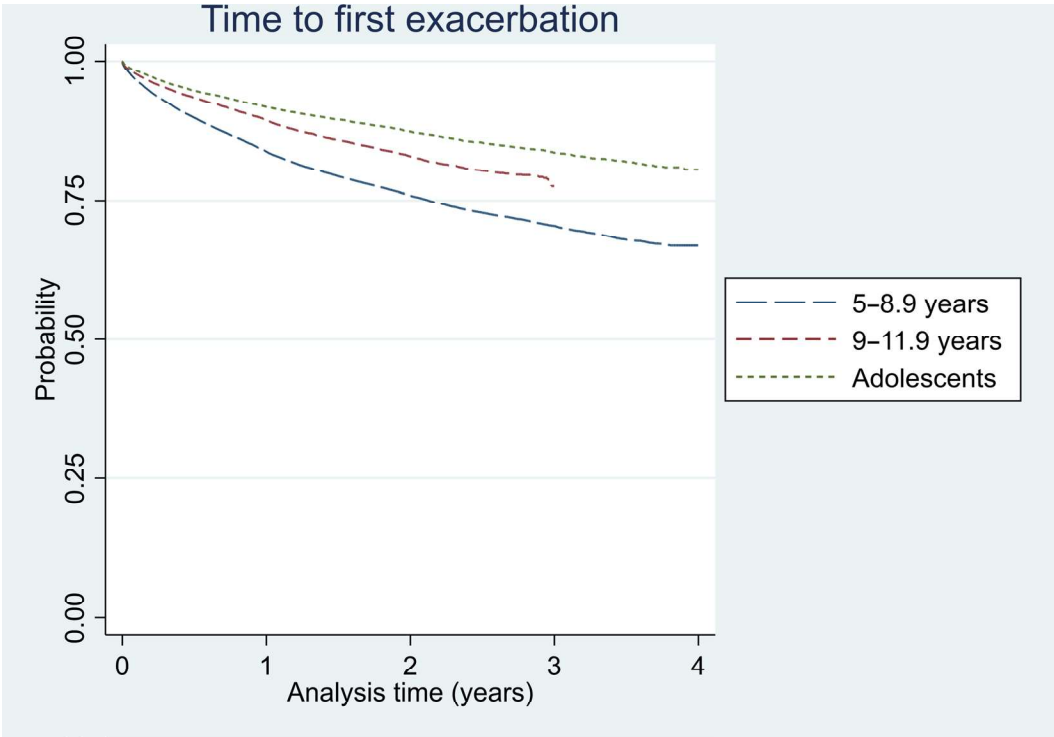


Figure 3 Kaplan-Meier plots of time to first exacerbation, by age.

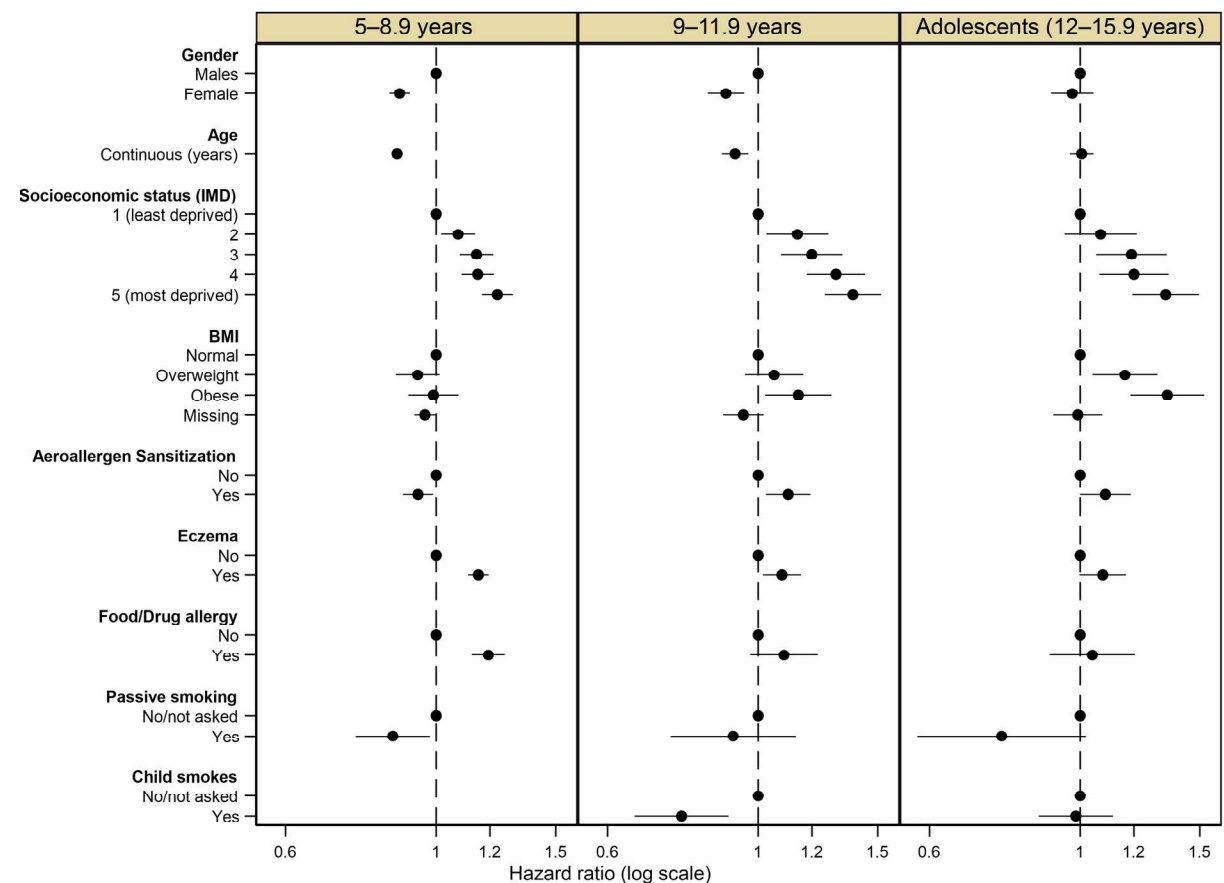


Figure 4 Forest plots showing the association between characteristics and first exacerbation by age (Model 1). BMI, body mass index; IMD, Index of Multiple Deprivation.

7.7%, adolescents: 16.3%; figure 2 and online supplemental table E5). Of those children that had an exacerbation postdiagnosis, 21% were not prescribed an ICS before or including ≤ 1 month after the exacerbation.

Exacerbation incidence

The youngest age group, 5–8.9 years, were the most likely to exacerbate (figure 3). The incidence rate fell with increasing age (5–8.9 years group =13.7 per 100 person-years (95% CI 13.4 to 13.9, $p<0.001$), 9–11.9 years group =10.0 per 100 person-years (95% CI 9.78 to 10.4, $p<0.001$), adolescents =6.7 per 100 person-years (95% CI 6.5 to 7, $p<0.001$; online supplemental table E7)).

Exacerbation risk factors

In Model 1 (including characteristics and demographics), in the 5–8.9 years group, factors significantly associated with exacerbations were being male, having eczema and food/drug allergy; in the 9–11.9 years group, the factors were being male, obese, and having aeroallergen sensitisation and eczema; in adolescents, the factors were being overweight, obese and having aeroallergen sensitisation (figure 4, online supplemental tables E8,9). In all age groups, higher levels of socioeconomic deprivation were significantly associated with an increased risk of an exacerbation.

In Model 2 (additionally including events in the year prediagnosis), across all ages there was a strong association between exacerbations and receiving asthma treatment prediagnosis (multiple ICS prescriptions and a single OCS prescription) and unscheduled hospital visits for asthma (figure 5 and online supplemental tables E10,11). Reporting of dyspnoea was associated with an increased risk of exacerbations in the youngest age group but reduced the risk in those 9 years old and above.

In the sensitivity analyses, excluding BMI, there was negligible difference to effect estimates. There was also very little difference in baseline characteristics between the children with

and without BMI measurements (online supplemental table E12). In a model, including all exacerbations as the outcome, there were negligible differences to the effect estimates except a slight increase HR for prior exacerbation variables (online supplemental table E13).

DISCUSSION

In this large population-based real-world cohort, we have found that age influences children's characteristics at the time of their diagnosis, their subsequent management, exacerbation rates and exacerbation risk factors. Younger children, 5–8 years, were at the highest risk of having an exacerbation and of receiving a delayed asthma diagnosis (defined as prescription of asthma treatments prior to receiving a diagnosis), whereas one in five adolescents were only prescribed a reliever (SABA), with no preventer medication (ICS or LTRA), in the 2 years following their diagnosis. Our study has shown diagnosis, and management after diagnosis, are often suboptimal. There are many areas that need improving and these differ according to the age of the children. Healthcare professionals should focus on certain areas for particular age groups, including, timely diagnosis, weight management and overuse of SABA, as well as socioeconomic deprivation, which was significantly associated with exacerbation risk across all ages.

Concerningly, a third of adolescents with a recorded BMI were categorised as overweight or obese, similar to national statistics for all adolescents. However, almost more worrying, 40% of children did not have a single recorded BMI, even though obesity is a potentially modifiable risk factor associated with both exacerbations and asthma development.¹⁴

In terms of socioeconomic deprivation, although the whole cohort was broadly equally spread across all quintiles, the largest proportion (22%) resided in the most deprived areas. Socioeconomic deprivation was also a significant independent risk factor for exacerbations, reflecting findings from previous studies,^{4,15,16} but was independent of age.

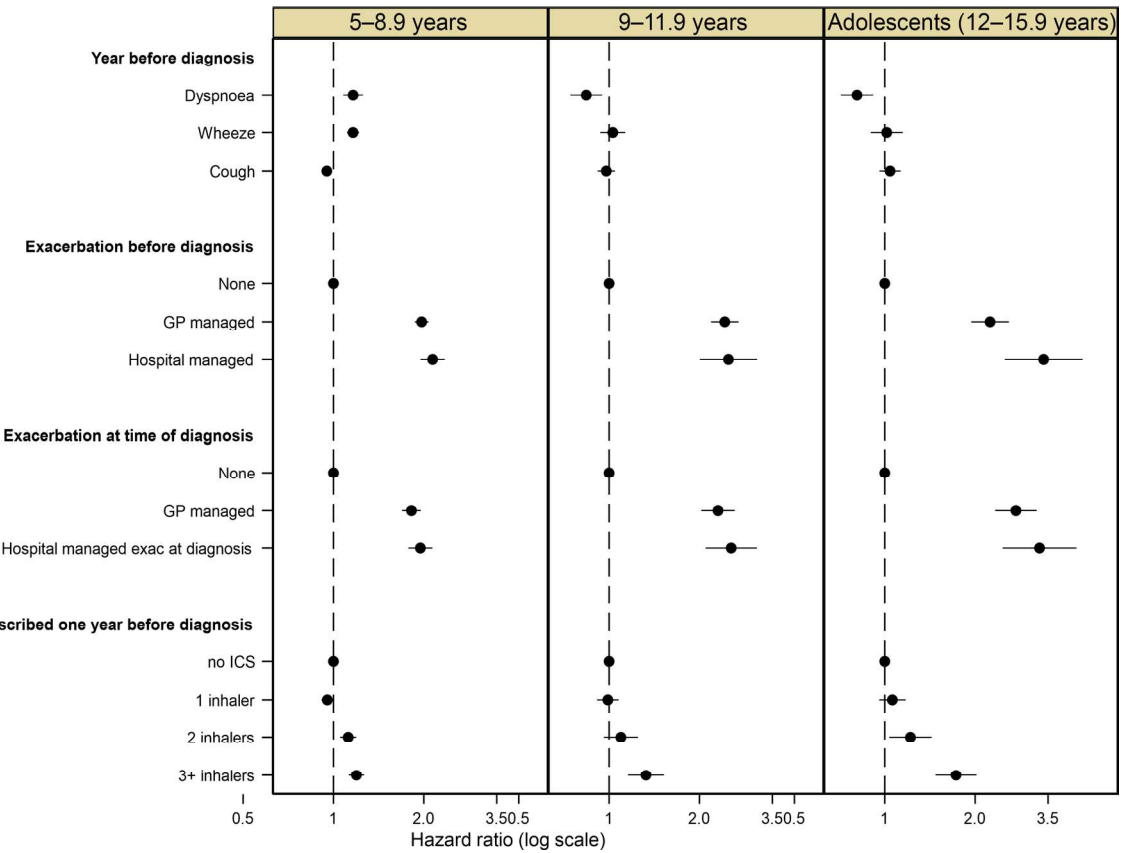


Figure 5 Forest plots showing the association between characteristics and prediagnosis events and first exacerbation by age (Model 2: includes all the variables in Model 1 and the additional variables shown in the plot). ICS, inhaled corticosteroids; GP, general practitioner.

One in 10 adolescents was documented in their primary care records as having smoked cigarettes. This proportion is similar to national statistics on childhood smoking¹⁷ but patient records currently do not distinguish between traditional cigarette smoking and vaping, which has seen a surge in popularity among young people in recent years.¹⁸ A very low percentage across all age groups was recorded as being passively exposed to cigarette smoke. We suspect these results are biased due to multiple factors, including lack of inquiry by the healthcare professional, poor documentation in records and bias in reporting by the children's families or carers. A history of eczema was prevalent in all age categories, occurring in approximately a third of children, with a 10% higher proportion in the youngest children compared with adolescents; but was only a strong exacerbation risk factor for the youngest children (5–8 years). It was also much higher than the reported prevalence of aeroallergen sensitisation and food/drug allergy, 17% and 8%, respectively, across the whole cohort. Food/ drug allergy was higher in the youngest age group; a reverse of the prevalence of aeroallergen sensitisation. Our prevalence of allergy and eczema align with those from the Global Asthma Network (GAN) Phase I Study.^{1,19} The GAN Phase I Study results are based on self-reporting of symptoms, whereas our findings are dependent on patient reporting and physician recording. Agreement of findings using such different data sources provides some confidence in the finding's accuracy. Perhaps unexpectedly, we found aeroallergen sensitisation not to be a particularly strong exacerbation risk factor, and only for children aged over 9 years. However, food/drug allergy was one of the strongest exacerbation factors for the youngest children, increasing the risk of an exacerbation by around 20%; but was not a risk factor for children over 9 years old. Food allergies are known to be more common in children with asthma and some previous studies have also suggested an association with more severe asthma.^{20,21}

Although, most children (around 80%) were prescribed an ICS at least once during the next 2 years, over a third were prescribed SABA, without ICS, as their first-line treatment. Over 20% of

children were not prescribed ICS even up to 1 month after their first exacerbation. Adolescents were most likely to be managed on SABA alone, with one in five never receiving an ICS during the first 2 years after diagnosis. While these findings do not follow current asthma management guideline recommendations,²² this may be because much of the data available were before 2016, when guidelines did recommend SABA as first-line treatment. Another area of concern was the dose of ICS prescribed; 8% of the whole cohort received medium or high dose, often receiving this dose as their first ever ICS prescription.

Interestingly, cough was reported to a healthcare professional in around one in three children prediagnosis. Wheeze/chest tightness (just over 10%) and dyspnoea (just under 10%) were less commonly recorded. Several children were prescribed OCS, or had an unscheduled hospital visit that was coded for asthma, yet were not diagnosed with asthma by their GP practice. This delayed diagnosis was most common for the youngest children, where nearly 1 in 10 were given OCS but no asthma diagnosis. Such delayed diagnosis may have contributed to poor management including no annual review, asthma management plan or education, resulting in missed opportunity to prevent further OCS prescriptions. Particularly important in these children as prediagnosis OCS use was the largest risk factor for a future exacerbation, paralleling findings in adult cohorts.^{23,24}

As with all observational studies, there are strengths and limitations to our study. The study strengths include, a large and unselected cohort of children, representing real clinical practice. One limitation was possible misclassification; we tried to reduce misclassification of asthma by only including children with two asthma codes within 2 years. Although we did not have information on objective tests, we were able to establish that just over 70% of the cohort had either a peak flow measurement (majority) or spirometry (minority) around the time of their diagnosis. Some of the short courses of OCS may have been prescribed for conditions other than asthma but <1% of children had a code for another steroid-managed condition on the day of their OCS prescription. Al-

lergy variables also relied on patient and physician reporting, and we had limited information regarding whether sensitisation tests were performed or not. There were missing values of the variables BMI and smoking, as discussed above. The missingness of BMI may have biased the exacerbation risk factor analysis, however, a model excluding BMI made negligible difference to the effect estimates for the rest of associations in the model. There was also missing data on A&E visits as described in the methods. We did not know if asthma prescriptions were dispensed or adhered to, however, these provided the healthcare professional’s perception on the child’s asthma control.

In conclusion, we have shown that children’s characteristics, management and exacerbations are influenced by the age of their asthma diagnosis. Younger children are at the highest risk of exacerbations, yet currently the anti-inflammatory reliever strategy is only recommended for adolescents; we urgently need trials to assess this effective approach in younger children too. For adolescents, weight management should be a key part of asthma management due to a strong association between overweight/obesity and exacerbations; yet BMI was not recorded in a third of adolescents. Younger children are most likely to receive a delayed diagnosis: 1 in 10 were prescribed at least one course of OCS before receiving an asthma diagnosis. Pharmacological management was also often suboptimal and varied according to diagnosis age: a quarter of adolescents were managed without any ICS, using reliever inhalers only.

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REFERENCES

1 Bloom CI, Saglani S, Feary J, et al. Changing prevalence of current asthma and inhaled corticosteroid treatment in the UK: population-based cohort 2006–2016. *Eur Respir J* 2019;53:1802130.
2 Tan DJ, Walters EH, Perret JL, et al. Clinical and functional differences between early-onset and late-onset adult asthma: a population-based Tasmanian longitudinal health study. *Thorax* 2016;71:981–7.
3 Baan EJ, de Roos EW, Engelkes M, et al. Characterization of asthma by age of onset: a multi-database cohort study. *J Allergy Clin Immunol Pract* 2022;10:1825–34.
4 Bloom CI, Nissen F, Douglas JJ, et al. Exacerbation risk and characterisation of the UK’s asthma population from infants to old age. *Thorax* 2018;73:313–20.
5 Tan DJ, Walters EH, Perret JL, et al. Age-of- asthma onset as a determinant of different asthma phenotypes in adults: a systematic review and meta-analysis of the literature. *Expert Rev Respir Med* 2015;9:109–23.
6 Miranda C, Busacker A, Balzar S, et al. Distinguishing severe asthma phenotypesrole of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol* 2004;113:101–8.
7 Jackson DJ, Sykes A, Mallia P, et al. Asthma exacerbations: origin, effect, and prevention. *J Allergy Clin Immunol* 2011;128:1165–74.
8 Buelo A, McLean S, Julious S, et al. At-risk children with asthma (ARC): a systematic review. *Thorax* 2018;73:813–24.
9 Wolf A, Dedman D, Campbell J, et al. Data resource profile: clinical practice research datalink (CPRD). *Int J Epidemiol* 2019;48:1740–1740g.
10 Nissen F, Morales DR, Mullerova H, et al. Validation of asthma recording in the clinical practice research Datalink (CPRD). *BMJ Open* 2017;7:e017474.
11 British Thoracic Society. BTS/SIGN British Guideline on the Management of Asthma. 2019.
12 Toolkit DM. Percentiles and Z-scores. 2022 Available: <https://dapa-toolkit.mrc.ac.uk/ anthropometry/ anthropometric-indices/growth>
13 Agency MaHPR. Small area level data based on patient Postcode (version 3.2). 2022.
14 Lang JE, Bunnell HT, Hossain MJ, et al. Being overweight or obese and the development of asthma. *Pediatrics* 2018;142:e20182119.
15 Sears MR. Descriptive epidemiology of asthma. *The Lancet* 1997;350:S1–4.
16 Serebrisky D, Wiznia A. Pediatric asthma: A global epidemic. *Ann Glob Health* 2019;85:6.
17 People RCoPaCHRSY. Smoking in young people. 2019. Available: <https://stateofchildhealth.rcpch.ac.uk/ evidence/health-behaviours/smoking-young-people/#page-section-12>
18 Lyzwinski LN, Naslund JA, Miller CJ, et al. Global youth Vaping and respiratory health: epidemiology, interventions, and policies. *NPJ Prim Care Respir Med* 2022;32:14.
19 Mortimer K, Lesosky M, Garcia-Marcos L, et al. The burden of asthma, hay fever and eczema in children in 25 countries: GAN phase I study. *Eur Respir J* 2022;60:2102865.
20 Wang J, Liu AH. Food allergies and asthma. *Curr Opin Allergy Clin Immunol* 2011;11:249–54.
21 Roberts G, Patel N, Levi-Schaffer F, et al. Food allergy as a risk factor for life-threatening asthma in childhood: a case-controlled study. *J Allergy Clin Immunol* 2003;112:168–74.
22 British Thoracic Society. BTS/SIGN British Guideline on the Management of Asthma,. 2003Available: <https://www.brit-thoracic.org.uk/quality-improvement/guidelines/ asthma>
23 Bloom CI, Palmer T, Feary J, et al. Exacerbation patterns in adults with asthma in England. A population-based study. *Am J Respir Crit Care Med* 2019;199:446–53.
24 Lowden R, Turner S. Past asthma exacerbation in children predicting future exacerbation: a systematic review. *ERJ Open Res* 2022;8:00174-2022.

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ARTIGO ORIGINAL

Estudo prospetivo da utilização de cigarros eletrônicos e sintomas respiratórios em adolescentes e jovens adultos

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RESUMO

Fundamentação O aerossol dos cigarros eletrônicos (e-cigarros) contém aldeídos voláteis, incluindo aromatizantes e metais oxidantes com conhecida toxicidade pulmonar.

Objetivos Avaliar as associações entre o consumo de cigarros eletrônicos e os sintomas de pieira, sintomas bronquíticos e falta de ar (SOB) ao longo de 4 anos de dados prospectivos.

Métodos Os participantes preencheram questionários sobre sintomas respiratórios e consumo de cigarros eletrônicos, cigarros e canábis nos últimos 30 dias em 2014 (onda 1; N=2094; idade média de 17,3 anos, DP=0,6 anos). Foram recolhidas informações de seguimento em 2015 (onda 2; n=1609), 2017 (onda 3; n=1502) e 2018 (onda 4; n=1637) através de inquéritos online. Os modelos de regressão logística de efeitos mistos avaliaram as associações entre a utilização de cigarros eletrônicos e os sintomas respiratórios.

Medições e principais resultados Os participantes foram maioritariamente brancos hispânicos (51,8%) e uniformemente representativos por sexo (49,6% mulheres; 50,4% homens). Quando comparados com os participantes que nunca tinham utilizado cigarros eletrônicos, os que relataram o uso de cigarros eletrônicos nos últimos 30 dias apresentaram um aumento estatisticamente significativo do risco de pieira (OR 1,81, IC 95% 1,28 a 2,56), sintomas bronquíticos (OR 2,06, IC 95% 1,58 a 2,69) e falta de ar (OR 1,78, IC 95% 1,23 a 2,57), controlando para a onda do estudo, idade, sexo, raça e educação parental. As estimativas de efeito foram atenuadas (pieira (OR 1,41; IC 95% 0,99, 2,01), sintomas bronquíticos (OR 1,55; IC 95% 1,18, 2,05), falta de ar (OR 1,48; IC 95% 1,01, 2,18)), após ajuste adicional para o consumo atual de cigarros, consumo de canábis e exposição passiva a cigarros eletrônicos/cigarros/canábis. **Conclusões** O uso de cigarros eletrônicos em jovens adultos esteve associado a sintomas respiratórios, independentemente da exposição à canábis combustível e ao cigarro.

INTRODUCTION

Use of electronic cigarettes (e-cigarettes) has increased in recent years among adolescents and young adults. In the USA, prevalence of past 30-day e-cigarette use among high school students 9th–12th grades in the US National Youth Tobacco Survey increased from 1.5% in 2011¹ to a high of 27.5% in 2019,2 later decreased to 19.6% in 2020,² and in 2022 estimates suggest 14.1% of youth currently used e-cigarettes.³ Components of the e-cigarette aerosol, including volatile aldehydes in flavourings, and oxidant metals, have known lung toxicity.^{4–5} For example, diacetyl and related diketone flavourings that cause bronchiolitis obliterans in occupationally exposed populations have also been found in e-cigarette liquids.⁴ E-cigarette aerosol has high concentrations of fine

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► E-cigarette use has been associated with increased respiratory symptoms like wheeze, bronchitic symptoms and shortness of breath, but limited studies have examined these associations in prospective, longitudinal population cohorts.

WHAT THIS STUDY ADDS

► This study identified prospective associations between e-cigarette use and wheeze, bronchitic symptoms and shortness of breath, even when controlling for use of combustible cannabis and cigarette use and secondhand exposure to e-cigarettes/ cigarettes/cannabis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► This study contributes to emerging evidence from human and toxicological studies that e-cigarettes cause respiratory symptoms that warrant consideration in regulation of e-cigarettes. It suggests that regulatory assessments of the population health cost underestimate the effects of late adolescent and young adult e-cigarette, cannabis and tobacco product use.

and ultrafine particles that can deliver these toxicants to the distal airways and alveoli,⁶ making the lung a target organ for injury and increasing risk for adverse respiratory health effects in e-cigarette users. To date, several cross-sectional and longitudinal studies have reported respiratory symptoms (eg, chronic cough, wheeze, asthma, shortness of breath) among both adolescent^{7–14} and young adult^{10,15} e-cigarette users. Most studies to date have focused on e-cigarette use without examining how multiple product use (eg, cigarette and/or cannabis prior or co-use) may impact respiratory health.^{16,17}

A 2018 report from the National Academies of Sciences, Engineering, and Medicine concluded that there was not enough evidence to determine whether e-cigarettes cause human respiratory diseases, although the report found moderate evidence that e-cigarette use increases cough, wheeze and asthma exacerbations in adolescents.¹⁸ These conclusions were based on a few cross-sectional studies.^{7–11,14} In a study of adolescents,



we found that a history of e-cigarette use was associated with increased prevalence of bronchitic symptoms, including among study participants with no history of cigarette use,⁷ consistent with findings in another cross-sectional study.¹⁴

Other studies found associations of e-cigarette use with asthma prevalence,^{9 11 13} and two recent prospective studies^{19 20} found associations of e-cigarette use with respiratory symptoms in the USA, controlling for combustible tobacco use. One cross-sectional study¹⁰ found that using e-cigarettes at least 5 days in the past 30 days was associated with bronchitis and shortness of breath after controlling for both combustible cigarette and cannabis use. However, to date, there has been little study of associations of e-cigarette use with respiratory symptoms in prospective investigations while also controlling for exposure to cannabis and combustible cigarette use.

In this study prospective data spanning 4 years of follow-up (2014–2018) were collected on e-cigarette use and respiratory symptoms in the Southern California Children’s Health Study (CHS).²¹ Analyses used prospectively collected data to evaluate the associations of e-cigarette use with subsequent symptoms of chronic bronchitis, shortness of breath and wheeze, controlling for co-use of combustible tobacco and cannabis and secondhand exposure to combustibles and e-cigarettes in these young adults. The primary hypothesis was that current e-cigarette use compared with never use of e-cigarettes would be associated with subsequent wheeze, bronchitic symptoms and shortness of breath at each wave of data collection, independent of use of or secondhand exposure to combustible cannabis and other tobacco products.

METHODS
Study design

There were 2097 CHS participants who completed a school-based survey on tobacco products and respiratory symptoms in 2014 (wave 1) when study participants were in 11th and 12th grades (mean age 17.3 years, SD=0.6). Follow-up information was also collected from 1609 participants in 2015 (wave 2), from 1502 in 2017 (wave 3) and from 1637 in 2018 (wave 4) using online surveys.²² At each survey wave, data were collected on ever and past 30-day use of e-cigarettes and cigarettes. At wave 3, cannabis use was added to the survey. There were 2094 participants who contributed to the analytical sample (see online supplemental figure S1), based on reporting of e-cigarette use and respiratory outcomes at each wave; at wave 4 there were 1438 participants who provided information on wheeze, 1383 who provided information on bronchitic symptoms and 1445 who provided information on shortness of breath. Additional description of the

cohort, including initial study recruitment, has been reported previously.⁷

Measures
Respiratory symptoms

Participants were considered to have had symptoms of chronic bronchitis during the previous wave based on the report of a daily cough for 3 months in a row or bronchitis in the previous 12 months, or congestion or phlegm other than when accompanied by a cold, as previously described.⁷ Wheeze was assessed based on a report of wheezing or whistling in the chest during the previous 12 months.²³ Shortness of breath was evaluated by a question asking if participants were troubled by shortness of breath when hurrying on level ground or walking up a slight hill. This question was added in wave 2.

Cigarette, e-cigarette and cannabis exposure

At each survey, participants reported never, ever and past 30-day use of cigarettes, e-cigarettes and cannabis. Specifically, participants were asked if they had ever used the products, and if participants indicated yes, they were asked a follow-up question about the number of days they had used the product(s) in the past 30 days. Participants who had never tried a product were classified as never users. Participants who had used a product on at least one of the past 30 days were classified as ‘past 30-day users’ of that product(s), a classification consistent with prior study of e-cigarette use and respiratory symptoms.⁷ Use of cannabis was first reported at wave 3 (coded as a three-level variable: missing, past 30-day use, no use).

Covariate information

Information was available on participants’ sex, ethnicity (Hispanic, non-Hispanic white, other) and parental education (highest level of education of either parent, categorised as high school diploma/general educational development (GED) or less, some college, college degree or more), as previously described.⁷ Report of any lifetime asthma was assessed at wave 1.²⁴ At each wave, second-hand exposure to e-cigarette vapour and to cigarette (and cannabis smoke starting at wave 3) at home was assessed by whether anyone in the household (other than the participant) used these products in their presence.

Statistical analysis

Separate mixed-effects logistic regression models were used to relate each respiratory symptom (wheeze, bronchitic symptoms and shortness of breath) to past 30-day e-cigarette use assessed at the same wave (lag 0) or at the prior wave (lag 1). All models

Table 1 Demographic characteristics of 2094 participants and by report of wheeze, bronchitic symptoms, shortness of breath or past 30-day e-cigarette use during the study period (2014–2018)					
	Total sample N=2094	Respiratory symptoms			Past 30-day e-cigarette use
		Wheeze	Bronchitic symptoms	Shortness of breath	
Race	Frequency (%)				
Asian	72 (3.4)	16 (3.1)	27 (3.3)	19 (4.0)	17 (3.5)
Black	31 (1.5)	9 (1.8)	12 (1.5)	2 (0.4)	4 (0.8)
Hispanic white	1083 (51.8)	214 (42.0)	379 (46.7)	254 (53.0)	228 (46.9)
Non-Hispanic white	734 (35.1)	222 (43.5)	321 (39.5)	168 (35.1)	208 (42.8)
Another race	172 (8.2)	49 (9.6)	73 (9.0)	36 (7.5)	29 (6.0)
Parental education at baseline					
Completed grade 12 or less	575 (27.5)	113 (22.2)	185 (22.8)	142 (29.6)	108 (22.2)
Some college	649 (31.0)	164 (32.2)	268 (33.0)	154 (32.1)	168 (34.6)
Completed college or more	623 (29.8)	183 (35.9)	280 (34.4)	136 (28.3)	153 (31.5)
Missing	247 (11.8)	50 (9.8)	80 (9.8)	48 (10.0)	57 (11.7)
Sex					
Female	1038 (49.6)	258 (50.6)	419 (51.5)	337 (70.2)	210 (43.2)
Male	1056 (50.4)	252 (49.4)	394 (48.5)	143 (29.8)	276 (56.8)
Another race includes Hispanic black, Hispanic Asian/Pacific Islander, missing, two or more racial/ethnic identities and Native American/American Indian. Respiratory symptoms are an average of reported symptoms across the study period.					

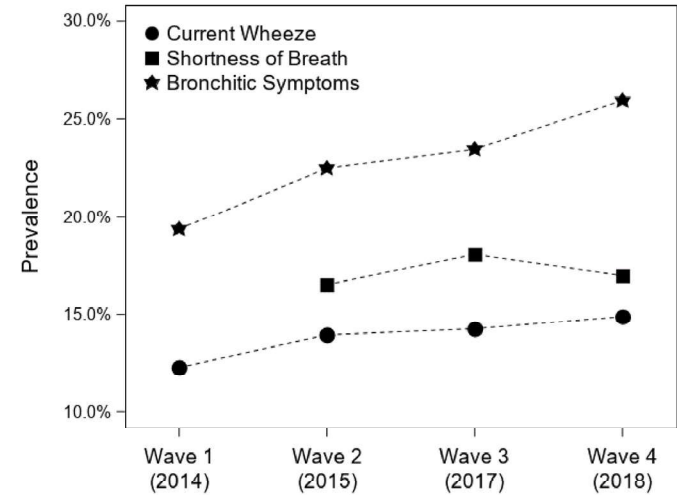


Figure 1 Prevalence of current respiratory symptoms (wheeze, shortness of breath and bronchitic symptoms) among study participants across each wave.

included a participant-level random intercept (random effect) to account for repeated observations over time within participant, and adjusted (fixed effects) for sex, race/ethnicity, age, lifetime asthma diagnosis, parental education and wave; additional models also adjusted for concurrent (lag 0) past 30-day use of cigarettes and/or cannabis, and secondhand exposure to e-cigarettes/cigarettes/cannabis. Although the sample size varied from wave to wave, all available data for each participant in each wave were included in the initial analysis. In sensitivity analyses conducted on associations of concurrent (lag 0) past 30-day e-cigarette use, we additionally restricted the sample to participants (1) without concurrent past 30-day (lag 0) cigarette or cannabis use, in order to remove potential confounding effects of coexposure, (2) who participated both in waves 1 and 2, in order to assess whether loss to follow-up resulted in biased estimates and (3) with no history of physician-diagnosed asthma at wave 1, in order to assess the influence of asthma on the patterns of observed associations. Further, multiplicative interactions between concurrent and 1-year lagged past 30-day e-cigarette use were tested. To assess associations with the joint distribution of one-wave lagged and current past 30-day e-cigarette use we also estimated the effects of a four-level e-cigarette use variable: no past 30-day e-cigarette use in the previous and current waves (reference group), past 30-day e-cigarette use in previous wave only, past 30-day e-cigarette use in current wave only and past 30-day e-cigarette use in both previous and current waves. Statistical analyses were conducted using SAS V.9.4 (SAS Institute).

RESULTS

Among the analytical sample of 2094 participants, 49.6% were female, and the largest ethnic group (51.8%) was Hispanic white, as shown in table 1. At wave 1 (the only time this question was asked), 22.7% (n=476) participants reported a lifetime history of physician-diagnosed asthma. Current wheeze (12.2%, 13.9%, 14.2% and 14.8%, waves 1–4, respectively) and shortness of breath (16.5%, 18.1% and 17.0%, waves 2–4, respectively) symptoms varied by wave, with bronchitic symptoms remaining the most commonly reported symptom across each wave (19.4%, 22.5%, 23.5% and 26%, waves 1–4, respectively), as shown in figure 1. Prevalence of respiratory symptoms by sociodemographic characteristics is reported in table 1. Prevalence of past 30-day e-cigarette use was 9.6% (wave 1), 12.9% (wave 2) and 9.4% (wave 3), and increased to 14.8% at wave 4 (figure 2). Past 30-day cigarette use was reported by 5.7% (wave 1), 9.6% (wave 2), 11.1% (wave 3) and 9.8% (wave 4) of participants. Finally, cannabis use was reported by 21.7% of participants at wave 3 (when participants were first asked) and increased to 25.7% at wave 4 (figure 2). Frequency of past-30 day use (mean number of days (SD)) is reported in table 2.

Table 2 Participant age, frequency of nicotine/tobacco and cannabis use by study wave (2014–2018)				
	Wave 1 (N=2094)	Wave 2 (n=1609)	Wave 3 (n=1502)	Wave 4 (n=1637)
Participant age (M, SD)	17.3 (0.6)	18.9 (0.6)	20.2 (0.6)	21.9 (0.7)
Secondhand exposure				
E-cigarettes	242 (11.7)	184 (11.8)	161 (11.0)	223 (15.6)
Cigarettes	552 (26.6)	402 (25.9)	309 (21.1)	293 (20.6)
Cannabis use	–	–	301 (20.5)	375 (26.3)
Past 30-day product use (number of days in past 30 days; M, SD)				
E-cigarettes	5.5 (7.3)	8.5 (10.0)	10.6 (11.1)	11.9 (11.2)
Cigarettes	9.7 (10.8)	8.6 (10.1)	8.2 (9.0)	7.7 (9.9)
Cannabis	–	–	12.3 (10.7)	11.9 (10.7)

Table 3 Adjusted ORs relating past 30-day e-cigarette use to respiratory symptoms, from mixed-effects logistic regression models			
Model	Wheeze OR (95% CI)	Bronchitic symptoms OR (95% CI)	Shortness of breath OR (95% CI)
Concurrent wave e-cigarette use (lag 0)			
Model 1*	1.81 (1.28, 2.56)	2.06 (1.58, 2.69)	1.78 (1.23, 2.57)
Model 2†	1.41 (0.99, 2.01)	1.55 (1.18, 2.05)	1.48 (1.01, 2.18)
Prior wave e-cigarette use (lag 1)			
Model 1*	2.17 (1.41, 3.35)	1.51 (1.07, 2.14)	1.59 (1.08, 2.34)
Model 2†	1.77 (1.14, 2.74)	1.23 (0.86, 1.74)	1.41 (0.96, 2.09)
*Model included participant-level random intercept and adjustment for wave, age, sex, race and parental education.			
†Additional adjustment for concurrent (lag 0) use of cigarettes and cannabis and secondhand exposure to e-cigarettes, cigarettes and cannabis.			

Participants who currently (lag 0) reported past 30-day e-cigarette use (table 3, model 1) had increased odds of wheeze (OR 1.81, 95% CI 1.28, 2.56), bronchitic symptoms (OR 2.06, 95% CI 1.58, 2.69) and shortness of breath (OR 1.78, 95% CI 1.23, 2.57), controlling for wave, age, sex, race and parental education. After further adjustment for concurrent (lag 0) use of cigarettes and cannabis and secondhand exposure to e-cigarettes, cigarettes and/or cannabis (table 3, model 2), all associations with lag 0 past 30-day e-cigarette use were attenuated but all except wheeze (p=0.06) remained significant (wheeze, OR 1.41, 95% CI 0.99, 2.01; bronchitic symptoms, OR 1.55, 95% CI 1.18, 2.05; shortness of breath, OR 1.48, 95% CI 1.01, 2.18). In models (table 3) using past 30-day

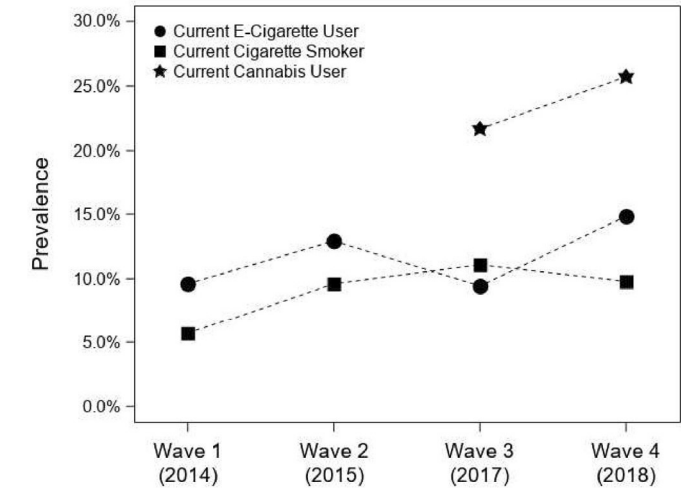


Figure 2 Prevalence of current e-cigarette, cigarette and cannabis use among study participants across each wave.

Table 4 Sensitivity analyses showing adjusted ORs relating past 30-day e-cigarette use (lag 0) to respiratory symptoms, from mixed-effects logistic regression models*			
Sensitivity analysis subgroup	Wheeze* OR (95% CI)	Bronchitic symptoms* OR (95% CI)	Shortness of breath* OR (95% CI)
No past 30-day cigarette or cannabis use, n=1235†	2.92 (0.85, 10.10)	1.86 (0.83, 4.19)	1.53 (0.65, 3.63)
Participated in both waves 1 and 2, n=1609‡	1.43 (0.99, 2.05)	1.52 (1.14, 2.02)	1.52 (1.03, 2.24)
No asthma, n=1618§	1.66 (1.11, 2.48)	1.53 (1.10, 2.12)	1.61 (1.04, 2.48)
*OR and 95% CI are based on mixed-effects logistic regression model with person-specific random intercept and adjustment (fixed effect) for wave, age, sex, race, parental education and secondhand exposure to cigarettes, e-cigarettes or cannabis.			
†Sensitivity analysis 1: restricted to participants without any concurrent cigarette and/or cannabis use in the past 30 days.			
‡Sensitivity analysis 2: participants were included if they participated in both waves 1 and 2, adjusted additionally for concurrent cigarette and/or cannabis use.			
§Sensitivity analysis 3: participants who reported no history of physician-diagnosed asthma at wave 1, adjusted additionally for concurrent cigarette and/or cannabis use.			

e-cigarette use from the previous wave (lag 1), associations were stronger for wheeze (OR 2.17, 95% CI 1.41, 3.35; and OR 1.77, 95% CI 1.14, 2.74 with additional adjustment for lag 0 use of cigarette/cannabis and secondhand exposures) than in lag 0 models; associations of lag 1 e-cigarette use with bronchitic symptoms and wheeze were weaker than lag 0 exposures, and after adjustment (for lag 0 coexposures) lag 1 associations with bronchitic symptoms and wheeze were no longer significant.

Sensitivity analyses were conducted on lag 0 past 30-day e-cigarette use. Estimated effects in the subset of participants reporting no concurrent (lag 0) cigarette or cannabis use (sensitivity analysis 1 in table 4) were substantially larger than the effects coadjusted for combustible use in the full sample (from table 3). For example, the OR for bronchitic symptoms in the participants without concurrent combustible use was 1.86 (95% CI 0.85, 10.1) compared with estimates (reported above) adjusted for combustibles (OR 1.55, 95% CI 1.18, 2.05). In models restricted to participants who were not lost to follow-up in wave 2 (n=1609; table 4, sensitivity analysis 2), estimated effects of concurrent past 30-day e-cigarette use (with adjustment for concurrent use of combustibles and secondhand exposures) were almost identical to effects in the full sample. In the subset asthma at wave 1 (n=1618),²⁴ the effects of e-cigarette use were generally similar in magnitude to associations in the full sample.

Between wave 1 and wave 2, there were 485 participants who were lost to follow-up (online supplemental table S1). Participants who were not included in wave 2 differed little from those included in rates of each outcome and in rates of exposure to current e-cigarette use at wave 1. Those lost to follow-up were more likely to be male, Hispanic white and to have a parent completing 12th grade or less. We adjusted for these sociodemographic characteristics that varied between those included and lost to the analysis, and the effect estimates (shown in table 3) were quite similar in size to the unadjusted estimates (results not shown). In addition, in a sensitivity analysis excluding these 485 participants, the effect estimates were similar in magnitude in the subset of participants with the same data at both waves 1 and 2 (table 4).

Finally, when considering the history of past 30-day e-cigarette use in the current wave (lag 0) only, in the prior wave (lag 1) only and in both waves, participants who reported past 30-day use at both waves had the largest OR (reference: no past 30-day e-cigarette use in both waves), particularly for wheeze and shortness of breath (online supplemental table S2, although the interaction of lag 0 × lag 1 exposure was not statistically significant).

DISCUSSION

This study used 4 years of prospective data to examine the association of e-cigarette use and respiratory symptoms in late adolescence and early young adulthood. Past 30-day e-cigarette use at the time of the assessment of outcome was associated with increased risk of wheeze, bronchitic symptoms and shortness of breath, after adjusting for use of and secondhand exposure to combustibles. Associations persisted in a sensitivity analysis excluding participants with a baseline lifetime history of asthma, indicating that associations were present in all participants, not just those with asthma. Past 30-day use of e-cigarettes the year prior to symptom assessment had a stronger association with the current year

wheeze, but weaker (and not significant) associations with bronchitic symptoms and shortness of breath. The estimated effect of persistent past 30-day e-cigarette use in the previous (lag 1) wave and the current (lag 0) wave was larger for all three outcomes than for either previous or current use alone. Results were consistent with another recent prospective study in adults showing e-cigarette use was an independent risk factor for poor respiratory outcomes.²⁰

The associations between past 30-day e-cigarette use and symptoms were moderately attenuated after controlling for concurrent use of or exposure to secondhand cigarettes and/or cannabis. Increasing frequency of co-occurrence of adult use of e-cigarettes with cannabis^{17 25 26} and cigarettes²⁰ makes it difficult to establish that respiratory associations with e-cigarettes are independent of coexposures. Recent analyses of the Population Assessment of Tobacco and Health Study data found that in adults e-cigarette use was associated with development of respiratory disease, independent of cigarette smoking,²⁰ but that past 30-day e-cigarette use among adolescents was not statistically significantly associated with self-reported symptoms of wheeze after controlling for cannabis vaping.²⁶ In our study, a causal interpretation was strengthened by sensitivity analysis showing that estimates of e-cigarette effects were stronger in participants with no (potentially confounding) past 30-day use of cigarettes or cannabis. Our observational results are supported by experimental studies. In cultured human airway epithelial cells, ex vivo immune cells and mice, e-cigarette vapour increased markers of oxidative stress and inflammatory effects and decreased cell viability.^{27 28} Further, recent human laboratory studies conducted among adult users of e-cigarettes showed that e-cigarette exposure causes short-term adverse respiratory effects²⁹ and immune suppression.^{30–32}

This study has some limitations. First, these data were collected via self-reported questionnaires. Second, questionnaire items for shortness of breath and cannabis were not available until waves 2 and 3, respectively, so analyses of these variables made use of more limited data than other analyses. Unlike cigarettes, which can be quantified by number of cigarettes smoked per day, validated questionnaire-based methods for assessing e-cigarette use frequency, for example, by reporting the number of e-cigarette inhalations/vaping sessions or duration of inhalation, were not available to us.^{33 34} Even when self-reported e-cigarette puffs are available, these estimates under-reported objectively collected user puffs from an e-cigarette device by approximately twofold.³⁵ It is likely that such misclassified exposure estimates from our self-report of any past 30-day use would result in underestimation of a true causal effect. In addition, e-cigarettes come in a variety of device types (eg, pod mods, tank systems, disposables), e-liquid flavours (fruit, mint, fruit ice, menthol) and various nicotine types (eg, synthetic nicotine, free-base nicotine, nicotine salt, various nicotine strength), which impact the user experience³⁶ and frequency of use³⁷ and may cause heterogeneous respiratory effects.^{4 10 19} For example, devices that offer greater power to heat e-liquids can generate substantially greater concentrations of aldehydes and other lung toxicants compared with lower powered devices.^{38 39} Recent cross-sectional data from four study populations across the USA found that e-cigarette use was associated with bronchitic symptoms and shortness of

breath, and device types did not substantially affect the strength of these associations.¹⁰ Finally, the direction of possible selection bias due to loss to follow-up is not clear. Those lost to follow-up differed little either in rates of outcome or exposure at wave, suggesting that the pattern of e-cigarette effects would have been similar had the entire cohort been included in the prospective analysis. Some sociodemographic covariates varied by symptom outcomes between those retained and lost to wave 2 follow-up, but sensitivity analyses found that the effect estimates of e-cigarette effects varied very little between models with and without these covariates. Estimates excluding in wave 1 those subjects that were lost to follow-up were also very similar to the analyses including all available information.

DISCUSSION

This Data collected from 2014 to 2018 among a diverse sample of young adults in southern California showed that e-cigarette use was associated with respiratory symptoms after accounting for concurrent cigarette and cannabis use as well as secondhand exposure to each of these products and secondhand exposure to e-cigarettes. The results strengthen epidemiological evidence of adverse respiratory effects of e-cigarettes that is consistent with known effects of e-cigarette ingredients.^{7 10}

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REFERENCES

1. Wang TW, Gentzke A, Sharapova S, et al. Tobacco product use among middle and high school students - United States, 2011–2017. *MMWR Morb Mortal Wkly Rep* 2018;67:629–33.
2. Choi BM, Abraham I. The decline in E-cigarette use among youth in the United States—an encouraging trend but an ongoing public health challenge. *JAMA Netw Open* 2021;4:e2112464.
3. Cooper M, Park-Lee E, Ren C, et al. Notes from the field: E-cigarette use among middle and high school students—United States, 2022. *MMWR Morb Mortal Wkly Rep* 2022;71:1283–5.

4. Allen JG, Flanigan SS, LeBlanc M, et al. Flavoring chemicals in E-cigarettes: diacetyl, 2, 3-pentanedione, and acetoin in a sample of 51 products, including fruit-, candy-, and cocktail-flavored E-cigarettes *Environ Health Perspect* 2016;124:A102–3.
5. Lee M-S, LeBouf RF, Son Y-S, et al. Nicotine, aerosol particles, carbonyls and volatile organic compounds in tobacco- and menthol-flavored E-cigarettes. *Environ Health* 2017;16:42.
6. Marini S, Buonanno G, Stabile L, et al. Short-term effects of electronic and tobacco cigarettes on exhaled nitric oxide. *Toxicol Appl Pharmacol* 2014;278:9–15.
7. McConnell R, Barrington-Trimis JL, Wang K, et al. Electronic cigarette use and respiratory symptoms in adolescents. *Am J Respir Crit Care Med* 2017;195:1043–9.
8. Tackett AP, Keller-Hamilton B, Smith CE, et al. Evaluation of respiratory symptoms among youth E-cigarette users. *JAMA Netw Open* 2020;3:e2020671.
9. Alnajem A, Redha A, Alroumi D, et al. Use of electronic cigarettes and secondhand exposure to their aerosols are associated with asthma symptoms among adolescents: a cross-sectional study. *Respir Res* 2020;21:300.
10. Chaffee BW, Barrington-Trimis JL, Liu F, et al. E-cigarette use and adverse respiratory symptoms among adolescents and young adults in the United States. *Preventive Medicine* 2021;153:106766.
11. Schweitzer RJ, Wills TA, Tam E, et al. E-cigarette use and asthma in a multiethnic sample of adolescents. *Preventive Medicine* 2017;105:226–31.
12. Choi K, Bernat D. E-cigarette use among Florida youth with and without asthma. *Am J Prev Med* 2016;51:446–53.
13. Osei AD, Mirbolouk M, Orimoloye OA, et al. The association between E-cigarette use and asthma among never combustible cigarette smokers: behavioral risk factor surveillance system (BRFSS). *BMC Pulm Med* 2019;19:1–6.
14. Wang MP, Ho SY, Leung LT, et al. Electronic cigarette use and respiratory symptoms in Chinese adolescents in Hong Kong. *JAMA Pediatr* 2016;170:89–91.
15. Gotts JE, Jordt S-E, McConnell R, et al. What are the respiratory effects of E-cigarettes? *BMJ* 2019;366:l5275.
16. Chadi N, Schroeder R, Jensen JW, et al. Association between electronic cigarette use and marijuana use among adolescents and young adults: a systematic review and meta-analysis. *JAMA Pediatr* 2019;173:e192574.
17. Braymiller JL, Barrington-Trimis JL, Leventhal AM, et al. Assessment of nicotine and Cannabis Vaping and respiratory symptoms in young adults. *JAMA Netw Open* 2020;3:e2030189.
18. National Academies of Sciences, Engineering, and Medicine. Public health consequences of e-cigarettes, paperback, 680 pages, ISBN 9780309468312 0309468310. Washington, DC: Committee on the review of the health effects of electronic cigarettes of electronic nicotine delivery systems, National Academies Press, 2018: 680.
19. Xie W, Tackett AP, Berlowitz JB, et al. Association of electronic cigarette use with respiratory symptom development among US young adults. *Am J Respir Crit Care Med* 2022;205:1320–9.
20. Bhatta DN, Glantz SA. Association of E-cigarette use with respiratory disease among adults: a longitudinal analysis. *Am J Prev Med* 2020;58:182–90.
21. McConnell R, Berhane K, Yao L, et al. Traffic, susceptibility, and childhood asthma. *Environ Health Perspect* 2006;114:766–72.
22. Barrington-Trimis JL, Berhane K, Unger JB, et al. Psychosocial factors associated with adolescent electronic cigarette and cigarette use. *Pediatrics* 2015;136:308–17.
23. ISAAC Steering Committee. International study of asthma and allergies in children: phase II modules. Muenster, Germany: Institute of Epidemiology and Social Medicine, University of Muenster, 1998.
24. Islam T, Braymiller J, Eckel SP, et al. Secondhand nicotine vaping at home and respiratory symptoms in young adults. *Thorax* 2022;77:663–8.
25. Roberts ME, Tackett AP, Singer JM, et al. Dual use of E-cigarettes and Cannabis among young people in America: A new public health hurdle? *J Stud Alcohol Drugs* 23, 2022.
26. Boyd CJ, McCabe SE, Evans-Polce RJ, et al. Cannabis, vaping, and respiratory symptoms in a probability sample of U.S. J Adolesc Health 2021;69:149–52.
27. Rowell TR, Reeber SL, Lee SL, et al. Flavored E-cigarette liquids reduce proliferation and viability in the CALU3 airway epithelial cell line. *Am J Physiol Lung Cell Mol Physiol* 2017;313:L52–66.
28. Clapp PW, Pawlak EA, Lackey JT, et al. Flavored E-cigarette liquids and cinnamaldehyde impair respiratory innate immune cell function. *Am J Physiol Lung Cell Mol Physiol* 2017;313:L278–92.
29. Wills TA, Pagano I, Williams RJ, et al. E-cigarette use and respiratory disorder in an adult sample. *Drug Alcohol Depend* 2019;194:363–70.
30. Vardavas CI, Anagnostopoulos N, Kougias M, et al. Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest* 2012;141:1400–6.
31. Dicipinigitis PV, Lee Chang A, Dicipinigitis AJ, et al. Effect of E-cigarette use on cough reflex sensitivity. *Chest* 2016;149:161–5.
32. Rebuli ME, Glista-Baker E, Hoffman JR, et al. Electronic-cigarette use alters nasal mucosal immune response to live-attenuated influenza virus. A clinical trial. *Am J Respir Cell Mol Biol* 2021;64:126–37.
33. Weaver SR, Kim H, Glasser AM, et al. Establishing consensus on survey measures for electronic nicotine and non-nicotine delivery system use: current challenges and considerations for researchers. *Addictive Behaviors* 2018;79:203–12.
34. Halpern-Felsher B, Kim H. Measuring E-cigarette use, dependence, and perceptions: important principles and considerations to advance tobacco regulatory science. *Addict Behav* 2018;79:201–2.
35. Li Z, Benowitz-Fredericks C, Ling PM, et al. Assessing young adults’ ENDS use via ecological momentary assessment and a smart bluetooth enabled ENDS device. *Nicotine Tob Res* 2021;23:842–8.
36. Park-Lee E, Ren C, Sawdey MD, et al. Notes from the field: E-cigarette use among middle and high school students—national youth tobacco survey, United States, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1387–9.
37. Vogel EA, Ramo DE, Rubinstein ML. Prevalence and correlates of adolescents’ E-cigarette use frequency and dependence. *Drug Alcohol Depend* 2018;188:109–12.
38. Geiss O, Bianchi I, Barrero-Moreno J. Correlation of volatile carbonyl yields emitted by E-cigarettes with the temperature of the heating coil and the perceived Sensorial quality of the generated vapours. *Int J Hyg Environ Health* 2016;219:268–77.
39. Ogunwale MA, Li M, Ramakrishnam Raju MV, et al. Aldehyde detection in electronic cigarette aerosols. *ACS Omega* 2017;2:1207–14. 168



Avaliação do papel causal do tabagismo na fibrose pulmonar idiopática: um estudo de aleatorização mendeliana

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RESUMO

O tabagismo tem sido considerado um fator de risco para a fibrose pulmonar idiopática (FPI) em estudos observacionais. Para avaliar se o tabagismo desempenha um papel causal na FPI, realizámos um estudo de aleatorização mendeliana utilizando dados de associação genética de 10 382 casos com FPI e 968 080 controles. Verificámos que a predisposição genética para o início do tabagismo (com base em 378 variantes) e o tabagismo ao longo da vida (com base em 126 variantes) estiveram associados a um maior risco de FPI. O nosso estudo sugere um potencial efeito causal do tabagismo no aumento do risco de FPI de uma perspetiva genética.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a lethal lung disease characterised by progressive fibrosis of lung parenchyma for which there is currently no cure.¹ Although the cause of IPF is unclear, tobaccosmoking is thought to play a part in the pathogenetic processes of IPF.¹ However, whether smoking represents a causal determinant remains uncertain, because the available evidence is scarce and originates mainly from observational studies, which are vulnerable to confounding bias and reverse causation. Mendelian randomization (MR) is an increasingly used approach that overcomes these challenges by exploiting randomly allocated genetic variants as instruments to make reliable causal inferences. Here, we conducted a MR study to investigate the causal association between smoking and the risk of IPF.

METHODS

In this study, we applied a two-sample design based on summary data from genome-wide association studies (GWASs). As genetic instruments, 378 independent, genome-wide significant ($p < 5 \times 10^{-8}$) single-nucleotide polymorphisms (SNPs) associated with smoking initiation (ever vs never being a regular smoker) were identified from the GWAS and Sequencing Consortium of Alcohol and Nicotine use (GSCAN), involving 1.2 million individuals.² In a secondary analysis, we used 126 independent SNPs associated with lifetime smoking (a continuous measure that takes into account smoking initiation, duration, heaviness, and cessation) as genetic instruments from the UK Biobank with 462 690 participants.³ These instrumental SNPs explained 2.3% of the variance in smoking initiation and 1.3% in lifetime smoking and have been treated as robust instruments with F -statistics > 10 in prior MR studies.⁴ GWAS summary data for IPF were derived from a meta-analysis of 5 cohorts (UK, Chicago, Colorado, UUS [US, UK, and Spain], and Genentech Study) by the International IPF Genetics Consortium (4125 cases and 20 464 controls)⁵ and another meta-analysis of 9 biobanks (BioVU, Colorado Centre for Personalised Medicine, Estonian Biobank, FinnGen, HUNT Study, Michigan Genomics Initiative, Mass General Brigham, UCLA Precision Health Biobank, and UK Biobank) by the Global Biobank Meta-analysis Initiative (6257 cases and 947 616 con-

trols).⁶ IPF was defined using European Respiratory Society/American Thoracic Society guidelines in the International IPF Genetics Consortium and using International Classification of Diseases codes (515 and 515.0 for ninth Revision and J84.1, J84.8, J84.89, J84.17, J84.1, and J84.10 for 10th Revision) in the Global Biobank Meta-analysis Initiative. GWAS models have adjusted for age, sex, and study-specific covariates where possible in the original studies. All participants included in the study were of European ancestry. The smoking and IPF studies involved some overlapping participants (43% of subjects in the Global Biobank Meta-analysis Initiative from the UK Biobank where the instruments for lifetime smoking were identified). However, sample overlap is not expected to introduce significant bias, because strong instruments (eg, F -statistics > 10) for smoking were used and these overlapping samples were from large biobanks (eg, UK Biobank).

The principal analysis was performed using the inverse-variance weighted (IVW) method. Sensitivity analyses robust to pleiotropy were conducted, including weighted median, MR-pleiotropy residual sum and outlier (MR-PRESSO), and MR-Egger (summarised in table 1). The estimates from two IPF datasets were combined using random-effects meta-analysis. We examined horizontal pleiotropy and heterogeneity using the MR-Egger intercept and the Cochran’s Q statistic, respectively. Reverse MR was performed to test for the potential reverse causation using 23 SNPs associated with IPF as genetic instruments.⁵ Characteristics of instrumental SNPs are given in online supplemental tables 1–3. Statistical analyses were conducted using R (version 3.6.3) with “TwoSampleMR” and “MR-PRESSO” packages. The significant threshold was 2-tailed $p < 0.05$.

RESULTS

The IVW results showed that genetic predisposition to smoking initiation (OR (OR) = 1.29; $p = 0.002$) and lifetime smoking (OR=1.63; $p < 0.001$) were associated with an increased risk of IPF in the meta-analysis of two datasets (table 2). The direction of effect was consistent across datasets, although the association in the International IPF Genetics Consortium did not reach the significant threshold. There were indications of horizontal pleiotropy or heterogeneity for some associations (table 3). MR-PRESSO identified only rs6948707 at MAD1L1 (a known IPF susceptibility signal) as an outlier and showed an effect directionally consistent with the IVW method after correction (table 2). Results were relatively stable in other sensitivity analyses although with wide confidence intervals. In the reverse MR analysis, genetic predisposition to IPF showed a null association with smoking initiation (OR=1.00; $p = 0.720$) and lifetime smoking (beta=0.002; $p = 0.378$), indicating the unidirectionality of the inferred relationship (online supplemental table 4). The leave-one-out analysis demonstrated that no single SNP (including rs69-

Table 1 Summary of applied Mr methods

Method	Assumptions	Strengths	Weaknesses	PubMed ID
IVW	All genetic instruments are valid.	Has optimal statistical power.	Estimates are biased if there is directional pleiotropy.	24114802
Weighted median	More than 50% of the weight comes from valid genetic instruments.	Informs the estimate supported by the majority of evidence.	May be less efficient.	27061298
MR-PRESSO	The largest group of candidate instruments with similar estimates is the group of valid instruments.	Detects outliers and provides an estimate after removal of outliers	May have high false-positive rate.	29686387
MR-Egger	Associations of genetic instruments with the exposure are uncorrelated with any pleiotropic effects of the instruments on the outcome (InSIDE assumption).	Quantifies directional pleiotropy and provides a consistent estimate even if all genetic variants are pleiotropic.	Has low precision and can be strongly influenced by outliers.	29040600
IVW, inverse variance weighted; MR, Mendelian randomization; PRESSO, pleiotropy residual sum and outlier.				

Table 2 Associations of genetic predisposition to smoking initiation and lifetime smoking with the risk of IPF

	IVW (random effects)		Weighted median		MR-PRESSO		MR-Egger	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Smoking initiation*								
International IPF Genetics Consortium	1.17 (0.95, 1.43)	0.137	1.08 (0.85, 1.29)	0.523	1.12 (0.92, 1.36)	0.253	1.50 (0.64, 3.48)	0.349
Global Biobank Meta-analysis Initiative	1.37 (1.17, 1.60)	<0.001	1.30 (1.05, 1.59)	0.014	1.37 (1.17, 1.60)	<0.001	1.77 (0.91, 3.47)	0.096
Meta-analysis (random effects)	1.28 (1.10, 1.49)	0.002	1.21 (1.01, 1.43)	0.034	1.25 (1.03, 1.52)	0.025	1.67 (0.98, 2.81)	0.059
Lifetime smoking†								
International IPF Genetics Consortium	1.37 (0.93, 2.02)	0.109	0.97 (0.56, 1.67)	0.913	1.37 (0.93, 2.02)	0.112	0.54 (0.12, 2.56)	0.443
Global Biobank Meta-analysis Initiative	1.79 (1.34, 2.41)	<0.001	1.51 (0.98, 2.32)	0.060	1.79 (1.34, 2.41)	<0.001	10.29 (3.49, 30.36)	<0.001
Meta-analysis (random effects)	1.62 (1.25, 2.09)	<0.001	1.25 (0.81, 1.92)	0.306	1.62 (1.25, 2.09)	<0.001	2.50 (0.14, 44.44)	0.533

*ORs are expressed per one unit increase in log odds of smoking initiation.

†ORs are expressed per one SD increase (equivalent to an individual smoking 20 cigarettes a day for 15 years and stopping 17 years ago or an individual smoking 60 cigarettes a day for 13 years and stopping 22 years ago) in the lifetime smoking index.

IPF, idiopathic pulmonary fibrosis; MR, Mendelian randomization; PRESSO, pleiotropy residual sum and outlier.

48707) substantially influenced the overall estimate (online supplemental figures 1–4). Scatter plots are presented in online supplemental figures 5–8.

DISCUSSION

Because of the low incidence of IPF, to date only two cohort studies have evaluated the longitudinal association of smoking with IPF.^{7 8} Both studies showed that smoking could increase the risk of IPF in a dose-response manner. However, a recent one-sample MR study reported that smoking is unlikely to be a causal factor for IPF, based on 871 IPF cases from the UK Biobank and an instrument constituted of 52 SNPs (explaining 0.7% of the variance in smoking volume).⁹ The limited power of this study may have prevented detection of a causal effect. In contrast, our two-sample MR analysis had a much larger sample size (10 382 IPF cases) and utilised stronger instruments that explain more variance in smoking, providing additional evidence for a potential causal effect of smoking on IPF. Several potential pathways may explain the role of cigarette smoke in the pathogenesis of IPF, including oxidative stress, inflammation, and telomere shortening.¹⁰ A common limitation in the MR setting is the presence of horizontal pleiotropy, which cannot be fully addressed even with sensitivity analyses based on different assumptions, because pleiotropy is widespread across the genome. Moreover, due to the use of summary data, we were unable to conduct a stratified analysis by smoking status or a nonlinear analysis to explore the threshold effect.

Table 3 Heterogeneity, horizontal pleiotropy, and outlier tests

Exposure	Outcome	IVW Q statistic (P-value)	MR-Egger intercept (P-value)	Outliers detected by MR-PRESSO
Smoking initiation	IPF (International IPF Genetics Consortium)	516 (<0.001)	−0.005 (0.551)	rs6948707
Smoking initiation	IPF (Global Biobank Meta-analysis Initiative)	366 (<0.001)	−0.005 (0.436)	NA
Lifetime smoking	IPF (International IPF Genetics Consortium)	140 (0.141)	0.014 (0.229)	NA
Lifetime smoking	IPF (Global Biobank Meta-analysis Initiative)	118 (0.262)	−0.034 (0.002)	NA
IVW, inverse variance weighted; MR, Mendelian randomization; NA, not available; PRESSO, pleiotropy residual sum and outlier.				

Impacto da pandemia de SARS-CoV-2 na sobrevivência ao cancro do pulmão em Inglaterra: uma análise do conjunto de dados de registo rápido do cancro

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RESUMO

As alterações precoces nos cuidados de cancro do pulmão podem afetar a sobrevivência. Dada a diminuição do diagnóstico durante os confinamentos, calculámos o seu impacto na sobrevivência utilizando os dados da Auditoria Nacional do Cancro do Pulmão. A percentagem de sobrevivência e as taxas de mortalidade foram comparadas entre 2019 e os períodos de confinamento de 2020. Foi observada uma diminuição da sobrevivência a partir do primeiro confinamento nacional e no prazo de 90 dias após o diagnóstico. Os HR foram mais elevados para as pessoas diagnosticadas no final de 2020, com 1,26 (IC 95% 1,20 a 1,32) para morte no prazo de 90 dias e 1,51 (IC 95% 1,42 a 1,60) para morte entre 91 e 270 dias. É necessário continuar a trabalhar em medidas para atenuar este impacto.

INTRODUCTION

In England during 2020, there were fewer lung cancer diagnoses and those who presented tended to be less fit with more advanced disease, likely due to a combination of public fear and the essential advice to ‘Stay at Home’.^{1,2} The true impact of this on survival is unclear. Using the rapid cancer registration dataset (RCRD), we compared lung cancer survival for 2019 and 2020 to evaluate the impact.

METHODS

The RCRD was extracted by the National Cancer Registration and Analysis Service for 2019 and 2020 to allow timely observation of the effect of COVID-19, in place of the usual National Lung Cancer Audit (NLCA). The NLCA collates multiple data sources, with the aim to capture data for all people diagnosed with lung cancer across England and Wales. The RCRD was more rapidly collated with shorter validation time.¹ Compared with usual NLCA data, some diagnoses are not captured, the majority of which are advanced stage or death certificate only diagnoses.² The differences between the RCRD and NLCA are detailed by Conibear et al.¹

We included people aged 18 or older diagnosed with lung cancer between 1 January 2019 and 31 December 2020. Data were collected until death or registry censor date (7 October 2021). People were excluded where the censor date was missing or occurred before the diagnosis date. Stata/SE V.17.0 (StataCorpLLC) was used for analysis. All analysed variables were included in the RCRD.

Data were subdivided into five groups according to COVID-19 policy: all of 2019; 1 January to 25 March 2020 (‘Pre-pandemic’); 26 March to 10 May 2020 (‘first National Lockdown’); 11 May to 7 October 2020 (‘Local Lockdowns’).³ Data from 8 October 2020 to 31 December 2020 (‘Late 2020’) were considered separately owing to the shorter follow-up period.

Percentage survival was calculated at set points following diagnosis: 90 days, 6 months, 9 months and 1 year. Kaplan-Meier curves were produced and log rank was used to calculate significance. HRs were calculated using cox regression, adjusting for sex, age, performance status (PS), stage and comorbidities (using Charlson comorbidity index). HRs were calculated for death within 365 days of diagnosis, or 270 days where 1 year of follow-up was unavailable.

RESULTS

Over the two years 2019–2020, 64 462 people were diagnosed with lung cancer. Following inclusions and exclusions as described above, 63 808 were included in the analysis. Demographics are included in online supplemental table 1. As 2020 progressed, PS at presentation worsened and stage was more frequently missing; all other demographics were similar. There was no statistical difference in survival probabilities between 2019 and ‘Pre-Pandemic’ 2020 (figure 1). Survival probabilities worsened as 2020 progressed, with the worst in those diagnosed during late 2020.

For the whole cohort and non-small cell lung cancer, the difference in survival was evident within 90 days of diagnosis and worsened as 2020 progressed (table 1). For small cell lung cancer, 1-year survival was similar throughout 2020. When stratified by stage, the difference in 1-year survival was more pronounced for stages III–IV compared with stages I–II (table 1).

As proportional hazards assumption were not met, separate HRs were calculated from 0 to 90 days, and 91–365 days or 91–270 days as applicable. Compared with 2019, the risk of death within 90 days of diagnosis was increased for all time points in 2020 (table 2). During lockdown, the excess risk normalised 91–365 days from diagnosis (HR=1.00; 95% CI 0.93 to 1.08). The excess risk of death was highest for those diagnosed during late 2020, with HR=1.26 during the first 90 days of diagnosis and HR=1.51 for the remainder.

DISCUSSION

This demonstrates how measures taken to control the SARS-CoV-2 pandemic impacted lung cancer survival, from as early as the first national lockdown. Between March and May 2020, when restrictions were most stringent, the risk of dying was greatest in the first 90 days following diagnosis, returning to baseline between 91 and 365 days. The excess risk of early death continued throughout 2020 and was worst for those diagnosed after October 2020.

Changes early in the patient journey are known to be important for long-term outcomes, contributing to the early deaths observed.⁴ The

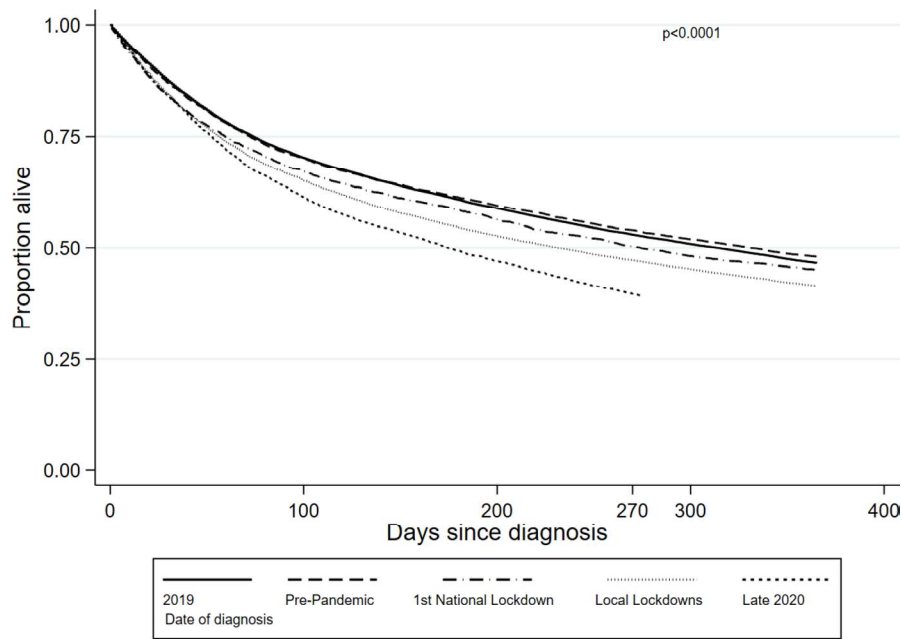


Figure 1 Unadjusted Kaplan-Meier graphs for people diagnosed with lung cancer in England in 2019 and 2020, divided by COVID-19 restrictions at time of diagnosis; ‘Late 2020’ data are censored at 270 days due to shorter follow-up time; log-odds $p<0.0001$.

worsening survival as time progressed is likely to have been contributed to by worsening PS throughout 2020, an indicator of poor prognosis as well as determining treatment eligibility.^{2,5} A small but significant stage shift occurred following the first national lockdown, which will have altered treatment intent.^{2,6} The demonstrated worsening survival could be explained by a delay in presentation and subsequently worsening fitness. Ongoing lockdowns throughout the year may have also impacted this. The greater impact observed in advanced stage disease compared with early stage may be influenced by the shorter prognosis of this group without treatment and decreased use of systemic anti-cancer therapy during 2020.^{2,7,8}

The worsened survival reported here is in line with, and even exceeds, those from modelling estimates. These suggested that diagnostic delays caused by pathway changes could result in a 6.0%–7.7% rise in lung cancer deaths in 1 year.⁹ Here, we observed a

6% absolute decrease in 1 year survival between May and October 2020, and a 13% decrease in 9-month survival between October and December.

Limitations of the RCRD should be noted. Compared with quality-assured previous NLCA data, the 2019 dataset is missing approximately 4300 diagnosed patients, which includes death certificate diagnoses. As 2019 and 2020 data were prepared in the same way, the same number can be assumed to be missing from 2020.² Therefore, survival figures produced here are not comparable with previous years and will overestimate actual results.

During the first national lockdown, there was a 26% reduction in lung cancer incidence, as previously published by our group.⁶ In the assumption that the true incidence remained static, it is likely these missing people died without diagnosis. The true survival for 2020 is therefore likely worse than the figures here, and does not fully represent the impact of the pandemic. These missing cases

Table 1 Unadjusted percentage survival at 90 days, 6 months, 9 months and 1 year following diagnosis with lung cancer for 2019 and 2020

	Survival	2019	Pre-Pandemic	First national lockdown	Local lockdowns	Late 2020
Total	90 days	72%	71%	69%	67%	64%
	6 months	61%	61%	58%	55%	49%
	9 months	53%	54%	50%	47%	40%
	1 year	47%	48%	45%	41%	
NSCLC	90 days	72%	72%	68%	66%	64%
	6 months	61%	62%	58%	54%	49%
	9 months	53%	55%	50%	47%	40%
	1 year	48%	49%	45%	42%	
SCLC	90 days	69%	65%	72%	67%	60%
	6 months	56%	53%	60%	53%	46%
	9 months	42%	39%	43%	40%	29%
	1 year	29%	29%	35%	30%	
NSCLC						
Stage I	1 year 9 months*	86%	86%	87%	83%	82%*
Stage II		71%	73%	70%	67%	66%*
Stage IIIA		57%	58%	57%	50%	50%*
Stage IIIB/C		41%	38%	34%	35%	36%*
Stage IV		22%	23%	21%	19%	16%*
Missing		50%	49%	39%	44%	41%*

*Results refer to 9-month survival due to shorter follow-up.
NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.



Table 2 HRs for risk of death following diagnosis of lung cancer, compared with 2019						
Death within	Time period	2019	Pre-Pandemic	First national lockdown	Local lockdowns	Late 2020
0–90 days	Unadjusted HR	1	1.02	1.16	1.23	1.35
	95% CI	–	0.97 to 1.07	1.08 to 1.24	1.18 to 1.27	1.29 to 1.41
	Adjusted HR	1	1.08	1.16	1.11	1.26
	95% CI	–	1.03 to 1.13	1.08 to 1.24	1.07 to 1.15	1.20 to 1.32
91–365 days*	Unadjusted HR	1	0.91	0.97	1.12	1.55*
	95% CI	–	0.87 to 0.94	0.90 to 1.05	1.07 to 1.16	1.46 to 1.65*
	Adjusted HR	1	0.95	1.00	1.06	1.51*
	95% CI	–	0.91 to 1.00	0.93 to 1.08	1.02 to 1.10	1.42 to 1.60*
Calculated using Cox regression and adjusted for age, sex, comorbidities, performance status and stage at diagnosis.						
*It indicates HR for 91–270 days due to shorter follow-up.						

likely represent those with the most aggressive disease and the worst prognosis.

In addition, the lack of longer-term follow-up limits the analysis of outcomes for people with early-stage disease. A decrease in curative treatments in this group has the potential for worse long-term outcomes not captured by 1 year survival.²

CONCLUSIONS

People who were diagnosed with lung cancer in 2020 were more likely to die in the year following diagnosis than those in 2019 even after adjustment for stage and PS, with those diagnosed in the final quarter of 2020 having the worst survival. It is likely the observed reduction in survival is multifactorial, being influenced both by delayed presentation and subsequent diagnosis, poorer PS and decreased treatment eligibility.

As, lockdowns and healthcare pressures continued into 2021, it will be beneficial to establish survival patterns in this period. Moving forward, a focus on awareness campaigns and prompt access to diagnostic pathways is essential to return to the pre-pandemic trajectory of improving lung cancer survival.

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REFERENCES

1. Conibear J, Nossiter J, Foster C, et al. The National lung cancer audit: the impact of COVID-19. *Clinical Oncology* 2022;34:701–7.
2. Royal College of Physicians. National lung cancer annual report (for the audit period 2019 and 2020 England only). London: Royal College of Physicians, 2022.
3. Institute for Government. Timeline of UK government Coronavirus lockdowns and restrictions 2021. n.d. Available: <https://www.instituteforgovernment.org.uk/charts/ukgovernment-coronavirus-lockdowns>
4. Holmberg L, Sandin F, Bray F, et al. National comparisons of lung cancer survival in England, Norway and Sweden 2001-2004: differences occur early in follow-up. *Thorax* 2010;65:436–41.
5. Sculier J-P, Chansky K, Crowley JJ, et al. The impact of additional Prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th edition of the TNM classification of malignant tumors and the proposals for the 7th edition. *J Thorac Oncol* 2008;3:457–66.
6. Gysling S, Morgan H, Ifesemen OS, et al. The impact of COVID-19 on lung cancer incidence in England: analysis of the National lung cancer audit 2019 and 2020 rapid cancer registration Datasets. *Chest* 2023;163:1599–607.
7. Cancer Research UK. Lung cancer statistics. Available: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer> [Accessed 24 Nov 2021].
8. National Disease Registration Service. Systemic anti-cancer therapy COVID-19 dashboard: NHS Digital. 2022. Available: <https://www.cancerdata.nhs.uk/covid-19/sact>
9. Maringe C, Spicer J, Morris M, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. *Lancet Oncol* 2020;21:1023–34.

A ingestão de mel local pode reduzir os sintomas de rinite alérgica (febre dos fenos) em crianças e jovens?

CENÁRIO CLÍNICO

Um rapaz de 14 anos com rinite alérgica (RA), comummente conhecida como febre dos fenos, apresenta-se com espirros, corrimento nasal e comichão nos olhos. Apresenta sensibilidade ao pólen de gramíneas, árvores e bétulas em testes cutâneos de picada. Os seus sintomas afetam-no durante os meses de primavera e verão, interferindo com o seu desempenho escolar. Apesar das terapias médicas que incluem anti-histamínicos orais, spray nasal e gotas para os olhos, há alguns dias em que continua sintomático e a mãe está interessada em encontrar um tratamento melhor. A mãe ouviu dizer que o consumo de mel local pode melhorar os sintomas da febre dos fenos e pede aconselhamento. Perguntamo-nos se o consumo de mel local, não pasteurizado, pode ajudar a reduzir os sintomas de RA ou mesmo curar os sintomas da febre dos fenos.

PERGUNTA CLÍNICA ESTRUTURADA

Em crianças e jovens com menos de 16 anos de idade com sintomas de RA e sensibilização aos pólenes (febre dos fenos) (doente), a ingestão de mel local não pasteurizado (intervenção) reduz os sintomas e/ou a necessidade de tratamentos farmacológicos para ajudar a melhorar os sintomas (resultado)?

ESTRATÉGIA DE PESQUISA E RESULTADOS

Foi efetuada uma pesquisa bibliográfica em outubro de 2021 e foram pesquisadas as bases de dados Medline, Embase e CINAHL, utilizando os seguintes termos de pesquisa: ((Honey OR Honey* OR local honey OR (ingest* OR consume OR eat) adj3 honey)) AND ((Hayfever OR Hay fever OR Rhinitis OR Allergic rhinitis OR Seasonal rhinitis OR Seasonal allergic rhinitis OR Rhinoconjunctivitis OR Rhino-conjunctivitis OR Allergic rhinoconjunctivitis OR Allergic rhino-conjunctivitis OR Seasonal allerg* OR Sensitive nose)).

Table 1 Summary of studies featuring children and young people and adults					
Citation	Study group	Study type (level of evidence)	Outcome	Key result	Comments
Saarinен <i>et al</i> ¹	61 patients with AR, aged 8–79 years randomised to BPH or RH or no honey (control). Invited through public announcements/advertisements.	Single blinded RCT (1b)	Symptom score graded (range 0–3) in April and May. Symptom-free days. Use of additional antihistamine medications for symptoms.	BPH patients reported a 60% lower total symptom score (p<0.01). More symptom-free days in honey groups: BPH mean 32.1 days±14.2; RH median 26.6 days±16.5; control median 14.1 days±12.6 (p=0.004). Use of antihistamine medication was less in BPH (19.3 days±15.7) and RH (32.3 days±18.4) groups compared with control (43.3 days±20.0), p=0.001. Fewer common colds and stomach upsets and better general health reported by 35% of the BPH group and by 38% of the RH group compared with 7% in the control group.	11 dropped out due to sweetness of the honey and unspecified personal reasons. Only 72% sensitised to birch pollen shown via a positive skin prick test. It is not clear how many paediatric patients the results relate to.
Asha’ari <i>et al</i> ²	40 patients with AR, aged 20–50 years randomised to 1 g/kg body weight of local honey daily (case) or honey-flavoured corn syrup as a placebo (control) across 4 weeks. Recruited from otolaryngology clinic.	Prospective placebo-controlled double blinded RCT (1b)	Comparison of mean difference of symptom scores for seven symptoms using a 7-point validated scale between start (week 0), week 4 and week 8. Comparisons of the improvement of the mean symptoms score between case and control at 0, 4 and 8 weeks and scores for 4 of the cardinal symptoms of AR (nasal itchiness, sneezing, rhinorrhoea and nasal blockage).	Mean differences of the total symptom score between weeks 0 and 8 were 5.35 (SD 4.98) for the case and 3.13 (SD 4.10) for the control, p=0.00 and p=0.003, respectively. Mean differences of the four cardinal symptom scores between weeks 0 and 8 for the case vs control were: nasal itchiness—0.75 (SD 0.97), p=0.003, vs 0.55 (SD 0.94), p=0.17; sneezing—0.80 (SD 1.32), p=0.25, vs 0.41 (SD 0.74), p=0.45; nasal blockage—0.81 (SD 1.11), p=0.21, vs 0.58 (SD 1.01), p=0.115; and rhinorrhoea—0.63 (SD 0.72), p=0.44, vs 0.70 (SD 0.72), p=0.77.	Inclusion if positive skin prick test to five common allergens in the local community (dust mite, cat, fungi, wheat and peanut). But no pollens tested for. Only the group that ingested honey showed a significant improvement in individual AR symptoms. The improvement persisted for a month after the cessation of the treatment. No paediatric patients.
Rajan <i>et al</i> ³	36 patients, aged range of 20–72 years randomised to local honey, or national honey (cases) or corn syrup with synthetic honey flavouring (control). Invited through public announcements/advertisements.	Double blinded RCT (1b)	44 parameters (11 symptoms × 4 periods of the allergy season). Symptom scores tracked—subjectively graded 0 to 3. For each symptoms study groups ranked by the mean number of symptomatic days reported, the group with least number ranked 1, the next 2, etc.	Placebo group did better than the two honey study groups for 19 parameters, the local honey for 18, and supermarket honey for seven parameters. No difference in patients with/without aeroallergen skin prick positivity.	13 patients dropped out from the study, attributed almost exclusively to an inability to tolerate the extreme sweetness of the regimen: 6 allocated to placebo, 5 to national and 2 local honey group. No paediatric patients included.
AR, allergic rhinitis; BPH, birch pollen-impregnated honey; RCT, randomised controlled trial; RH, regular honey; SD, standard difference.					



Identificámos muito poucos estudos em crianças que avaliassem se o mel, sob várias formas, poderia melhorar os sintomas em doentes com febre dos fenos quando ingerido.

Todos os estudos avaliaram a eficácia do mel local não pasteurizado medindo os sintomas subjetivamente através de pontuações ou escalas de sintomas (resultado primário) e avaliando a utilização de medicamentos adicionais para a alergia (resultado secundário). Em cada estudo, foi utilizado um placebo de xarope de milho com sabor a mel. Em dois dos três estudos, os pacientes também receberam medicação anti-histamínica juntamente com o regime de mel.^{1,2}

Dois estudos sugerem que o mel pode servir como terapia complementar para a RA.^{1,2} Saarinen et al demonstraram que a ingestão de mel proporcionou um controlo significativamente melhor dos sintomas do que o tratamento apenas com medicação convencional, mas não se verificaram diferenças estatisticamente significativas entre a utilização de um mel de pólen de bétula local não pasteurizado e o mel normal sem qualquer pólen de bétula ou amieiro.¹

Asha'ari et al afirmaram que a ingestão de mel local em doses elevadas melhorava os sintomas gerais da RA.² No entanto, o estudo utilizou doses muito elevadas, sugerindo que os benefícios positivos para a saúde só são alegadamente alcançados se forem consumidos entre 50-80 g por ingestão: a sua dose de 1 g de mel por quilograma de peso corporal excederia grosseiramente a quantidade máxima diária de açúcar recomendada pelo sistema nacional de saúde inglês, que é de 19 g para crianças dos 4-6 anos, 24 g para crianças dos 7-10 anos e 30 g para adultos.⁶

O estudo de Rajan et al não demonstrou qualquer diferença significativa nos sintomas de RA com a ingestão de mel local.³

No entanto, a dose de 1 colher de sopa (aproximadamente 21 g) foi suficiente para levar 13 dos 36 participantes a desistir por não conseguirem tolerar a doçura.

As limitações dos estudos incluídos nesta revisão incluem o viés de relato das pontuações subjetivas dos sintomas e a necessidade de replicação de estudos de maior dimensão com um maior número de participantes.

Outra limitação inclui a variação das etnias presentes nestes estudos, que tiveram lugar na Malásia, Finlândia e EUA, respetivamente.¹⁻³ Isto pode dificultar a comparação com a população do Reino Unido devido a especificidades no tipo de pólen prevalente, no nível de exposição ao pólen e na dieta local.

Em conclusão, não existem provas substanciais que apoiem a utilização de mel local não pasteurizado para reduzir os sintomas ou a necessidade de medicação em crianças e jovens com RA.

Clinical bottom lines

- ⇒ Large doses of honey may reduce symptom scores in allergic rhinitis in adult patients. (Grade D)
- ⇒ The sugar load of ingested 'doses' of honey potentially required as an immunotherapy are well in excess of the recommended dietary intakes. (Grade B)
- ⇒ Local honey dosing is not recommended as an adjunct for allergic rhinitis control in children. (Grade D)

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REFERÊNCIAS

- 1 Saarinen K, Juntunen J, Haahtela T. Birch pollen honey for birch pollen allergy: a randomized controlled pilot study. *Int Arch Allergy Immunol* 2011;155:160–6.
- 2 Asha'ari ZA, Ahmad MZ, Jihan WS, et al. Ingestion of honey improves the symptoms of allergic rhinitis: evidence from a randomized placebo-controlled trial in the East coast of Peninsular Malaysia. *Ann Saudi Med* 2013;33:469–75.
- 3 Rajan TV, Tennen H, Lindquist RL, et al. Effect of ingestion of honey on symptoms of rhinoconjunctivitis. *Ann Allergy Asthma Immunol* 2002;88:198–203.
- 4 Scadding GK, Kariyawasam HH, Scadding G, et al. BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (revised edition 2017; first edition 2007). *Clin Exp Allergy* 2017;47:856–89.
- 5 Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases a WHO position paper. *J Allergy Clin Immunol* 1998;102:558–62.
- 6 NHS. Sugar: the facts. 2020. Available: <https://www.nhs.uk/live-well/eat-well/foodtypes/how-does-sugar-in-our-diet-affect-our-health/> [Accessed 20 Sep 2022].