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Thorax

ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

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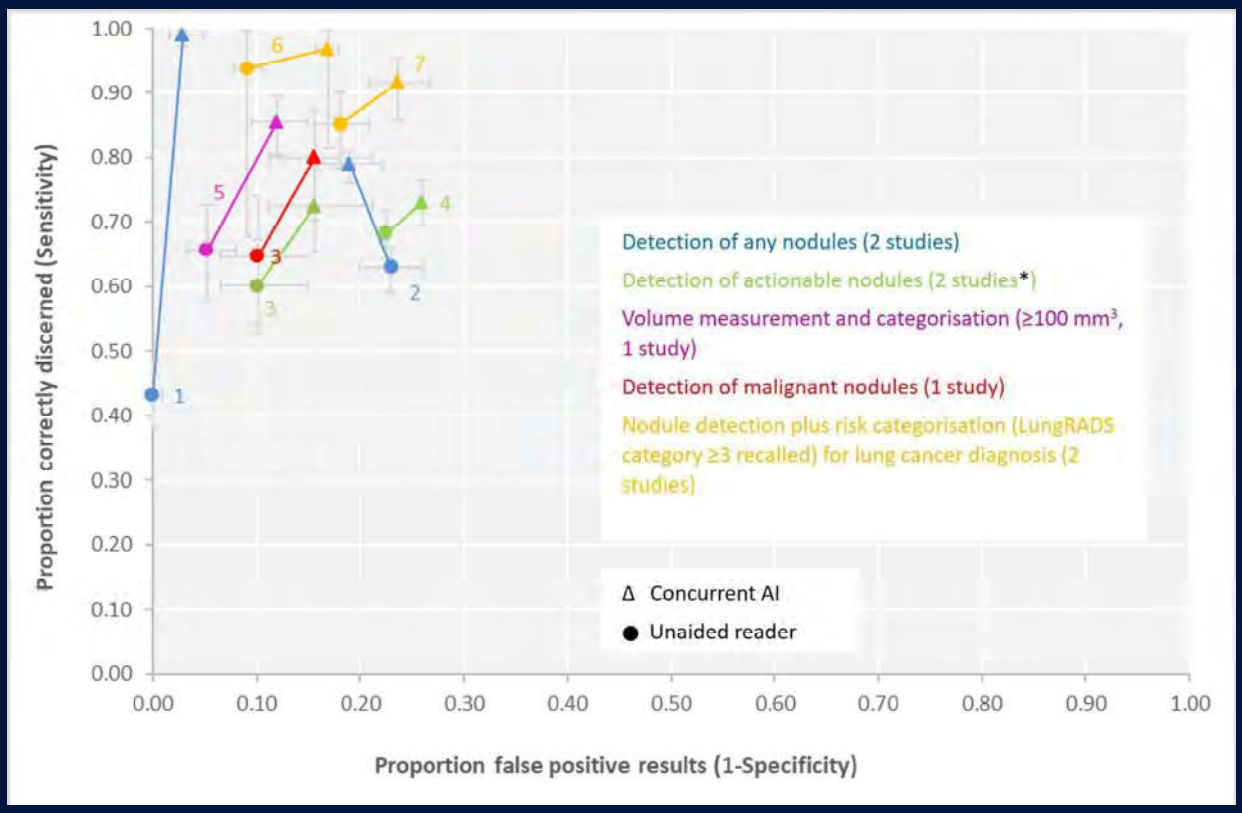

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Dá ritmo à vida[2,3*]

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

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

Zimbus Breezhaler 114 microgramas/46 microgramas/136 microgramas pó para inalação, cápsulas
NOTA: Antes de prescrever consulte o RCM do medicamento. APRESENTAÇÃO: Pó para inalação, cápsula (pó para inalação). Cada cápsula contém 150 microgramas de indacaterol, 50 microgramas de glicopirrónio e 160 microgramas de furoato de mometasona. Cada dose libertada (a dose libertada através do aplicador bocal 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 Breezhaler está indicado como terapêutica de manutenção da asma em doentes adultos não controlados adequadamente com uma associação de um agonista $beta_2$ de ação prolongada e uma dose alta de corticosteroide inalado em regime de manutenção que experimentaram uma ou mais exacerbações da asma no ano anterior. **POSOLOGIA: Adultos:** A dose recomendada é uma cápsula inalada uma vez por dia. A dose máxima recomendada é de 114 µg/46 µg/136 µg uma vez por dia. **Doentes pediátricos (< 18 anos):** Não recomendado em doentes com menos de 18 anos de idade. **Populações especiais: *População idosa:*** Não é necessário ajuste de dose em doentes idosos (65 anos de idade ou mais). ***Compromisso renal:*** Não é necessário ajuste de dose em doentes com compromisso renal ligeiro a moderado. Deve ter-se precaução em doentes com compromisso renal grave ou doença renal terminal que necessitem de diálise. ***Compromisso hepático:*** Não é necessário ajuste de dose em doentes com compromisso hepático ligeiro a moderado. Não existem dados disponíveis sobre a utilização deste medicamento em doentes com compromisso hepático grave, como tal deve ser utilizado nestes doentes apenas se o benefício esperado superar o risco potencial. **Modo de administração:** Apenas para utilização por via inalatória. As cápsulas não podem ser engolidas. Os doentes que não sintam melhorias na sua respiração devem ser questionados se estão a engolir o medicamento em vez de o inalar. As cápsulas têm de ser administradas usando apenas o inalador Zimbus Breezhaler. O tratamento deve ser administrado à mesma hora do dia todos os dias. Pode ser administrado independentemente da hora do dia. Após a inalação, os doentes devem lavar a boca com água sem engolir. Se for omitida uma dose, esta deve ser tomada assim que possível. Os doentes devem ser instruídos a não tomarem mais do que uma dose por dia. As cápsulas de Zimbus Breezhaler devem ser sempre conservadas no blister para proteger da luz e humidade, e só podem ser removidas do blister imediatamente antes da utilização. **CONTRAINDICAÇÕES:** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **ADVERTÊNCIAS/PRECAUÇÕES: ♦ Asma Aguda:** não deve ser utilizado para tratar sintomas agudos de asma, incluindo episódios agudos de broncospasmo, para os quais é necessário um broncodilatador de curta ação. **♦ Hipersensibilidade:** Se ocorrer uma reação de hipersensibilidade, Zimbus Breezhaler deve ser descontinuado imediatamente e deverá ser instituída terapêutica alternativa. **♦ Broncospasmo paradoxal**: Tal como com outra terapêutica inalatória, a administração deste medicamento pode resultar em broncospasmo paradoxal, o qual pode colocar a vida em risco. Se tal ocorrer, o tratamento deve ser interrompido imediatamente e deverá ser instituída terapêutica alternativa. **♦ Efeitos cardiovasculares**: Tal como outros medicamentos contendo agonistas adrenérgicos $beta_2$, 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 tirotoxicose e em doentes com resposta aumentada aos agonistas adrenérgicos $beta_2$. **♦ Hipocaliemia:** Os agonistas adrenérgicos $beta_2$ podem causar uma hipocaliemia significativa em alguns doentes, o que potencialmente pode levar a reações adversas cardiovasculares. Em doentes com asma grave, a hipocaliemia pode ser potenciada pela hipoxia e pela terapêutica concomitante, o que pode aumentar a suscetibilidade a arritmias cardíacas. **♦ Hiperglicemia:** A inalação de doses elevadas de agonistas adrenérgicos $beta_2$ e corticosteroides pode produzir um aumento da glucose plasmática. Nos doentes diabéticos, ao iniciar o tratamento, a glucose 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 m^2), incluindo aqueles com doença renal terminal que necessitam de diálise, deve ser utilizado apenas se o benefício esperado for superior ao risco potencial. **♦ Prevenção de infeções orofaríngeas:** De modo a reduzir o risco de infeção orofaríngea por *candida albicans*, os doentes devem ser aconselhados a lavar a boca ou a gargarejar com água, sem a engolir, ou a lavar os dentes após inalarem a dose prescrita. **♦ Efeitos sistémicos dos corticosteroides:** Podem ocorrer efeitos sistémicos dos corticosteroides inalados, principalmente no caso de doses elevadas prescritas por períodos prolongados. Os efeitos sistémicos possíveis podem incluir: síndrome de Cushing, manifestações Cushingóides, supressão adrenal, atraso do crescimento em crianças e adolescentes, diminuição da densidade mineral óssea, cataratas, glaucoma e, mais raramente, uma série de efeitos psicológicos ou comportamentais incluindo hiperatividade psicomotora, distúrbios do sono, ansiedade, depressão ou agressão (especialmente em crianças). Como tal, é importante que a dose de corticosteroide inalado seja titulada para a dose mais baixa na qual o controlo efetivo da asma é mantido. Podem ser notificados distúrbios visuais com o uso de corticosteroides sistémicos ou tópicos (incluindo intranasais, inalados ou intraoculares). Doentes que apresentem sintomas como visão turva ou outros distúrbios visuais, devem ser considerados para encaminhamento a um oftalmologista para avaliação de possíveis causas dessas perturbações visuais, as quais podem incluir cataratas, glaucoma ou doenças raras como a corioretinopatia central serosa (CRCS), que foram notificadas após o uso de corticosteroides sistémicos ou tópicos. Este medicamento deve ser administrado com precaução em doentes com tuberculose pulmonar ou em doentes com infeções crónicas ou não tratadas. **♦ Gravidez:** Este medicamento deve ser utilizado durante a gravidez apenas se o benefício esperado para o doente justificar o potencial risco para o feto. **♦ Amamentação:** Tem que ser tomada uma decisão sobre a descontinuação da amamentação ou a descontinuação/abstenção da terapêutica, tendo em conta o benefício da amamentação para a criança e o benefício da terapêutica para a mulher. **♦ Trabalho de parto:** Como outros medicamentos contendo agonistas adrenérgicos $beta_2$, o indacaterol pode inibir o trabalho de parto devido a um efeito relaxante no músculo liso uterino. **INTERAÇÕES: ♦ Bloqueadores adrenérgicos beta:** este medicamento não deve ser administrado com bloqueadores adrenérgicos beta (incluindo gotas para os olhos) a menos que existam razões importantes para a sua utilização **♦ Medicamentos conhecidos por prolongarem o intervalo QTc:** este medicamento deve ser administrado com precaução a doentes que estejam a ser tratados com inibidores da monoamina oxidase, antidepressivos tricíclicos ou medicamentos conhecidos por prolongar o intervalo QT. **♦ Tratamento hipocaliémico:** O tratamento hipocaliémico concomitante com derivados da metilxantina, esteróides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocaliémico dos agonistas adrenérgicos b $beta_2$. **♦ Interação com inibidores do CYP3A4 e da glicoproteína P:** A inibição do CYP3A4 e da glicoproteína P (gp-P) não tem impacto na segurança de doses terapêuticas de Zimbus Breezhaler. **♦ Outros antimuscarínicos de ação prolongada e agonistas adrenérgicos $beta_2$ de ação prolongada:** A coadministração deste medicamento com outros medicamentos contendo antagonistas muscarínicos de ação prolongada ou agonistas adrenérgicos $beta_2$ de ação prolongada não foi estudada e não é recomendada. **♦ Cimetidina ou outros inibidores do transporte de catiões orgânicos:** Não é esperada qualquer interação medicamentosa clinicamente relevante. **EFEITOS INDESEJÁVEIS: ♦ Frequentes (≥1% a <10%) e potencialmente graves:** hipersensibilidade. **♦ Muito frequentes:** asma (exacerbação), nasofaringite. **♦ Frequentes (≥1% a <10%):** infeção do trato respiratório superior, candidíase, infeção do trato urinário, cefaleia, taquicardia, dor orofaríngea, tosse, disfonia, gastroenterite, dor musculosquelética. 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. **Escalão de comparticipação:** Escalão B. **Titular da AIM**: Novartis Europharm Limited. **Representante local:** Laboratório Medinfar - Produtos Farmacêuticos, S.A. - Rua Henrique de Paiva Couceiro, Nº 29, Venda Nova, 2700-451 Amadora Informações Essenciais Compatíveis com o Resumo das Características do Medicamento (ZIM_RCM20210422_IEC_v2).

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Editorial

Neste primeiro número do ano de 2025 com uma seleção cuidada de artigos das Revistas *Thorax* e *Archives of Disease in Childhood*, dedicados aos Sócios das Sociedades Científicas de Pneumologia, Alergologia e Imunologia Clínica, Medicina Geral e Familiar e Pediatria, sobressai uma perspetiva do exercício atual da Medicina, com fortes influências derivadas da evolução da Medicina e das tecnologias aplicadas e dos temas que nos têm vindo a preocupar de forma crescente neste primeiro quarto do sec. XX!

A Medicina evolui. O doente encontra-se cada vez mais no centro dos cuidados clínicos, torna-se parceiro e exige novas formas de abordagem. Aumenta a sobrevida, implicando reorganização de cuidados e exigência de ofertas previamente desconhecidas e conhecem-se melhor as doenças raras, sobretudo através de esforços multicêntricos e estudos genéticos. A transição de cuidados, exigindo novos conhecimentos e reorganização de serviços e estruturas funcionais é uma realidade crescente.

Estes conceitos encontram-se descritos nos artigos publicados nas páginas 15, 20, 44 e 76 relatando experiências em crianças com doenças do interstício e fibrose quística, no relato de valorização clínica em crianças com asma e na orientação de doentes crónicos para cuidados paliativos.

As preocupações com os poluentes atmosféricos, *indoor* e *outdoor* justificam a seleção de artigos que nos trazem evidências nesta relação e colocam desafios novos, como os que decorrem de novos conhecimentos da utilização de velhos produtos de consumo de tabaco (pag 29), das implicações da exposição em doentes pulmonares obstrutivos crónicos e da relevância da promoção de estratégias que regulem a exposição diária (pag. 37) e da associação positiva entre exposição a poluição atmosférica e visitas ambu-latórias, a serviços de urgência e internamentos por doença respiratória na criança (pag. 53). Estes artigos sublinham a relevância do conhecimento crescente sobre as influências dos poluentes, a necessidade de incluir estas questões nas consultas clínicas, quer do ponto de vista dos questionários quer das possíveis orientações para a sua evicção. A convergência do mundo moderno com a crescente consciência da necessidade de promover hábitos de vida saudável são tema do artigo "Efeitos do consumo moderado de álcool e hipoxia hipobárica: implicações para o sono dos passageiros, saturação de oxigénio e frequência cardíaca em voos de longa duração".

Tudo bons motivos para leituras neste Inverno em que não para de chover!

Teresa Bandeira

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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 broncospasmo, isto é, como terapêutica de alívio. Asma: Bevespi Aerosphere não deve ser utilizado no tratamento da asma. Broncospasmo paradoxal: Tal como com outra terapêutica inalatória, a administração deste medicamento pode resultar em broncospasmo paradoxal, o qual pode colocar a vida em risco. Se ocorrer broncospasmo paradoxal, o tratamento com o medicamento deve ser interrompido e devem ser considerados outros tratamentos. Efeitos cardiovasculares: Podem ser observados efeitos cardiovasculares, após a administração de antagonistas dos recetores muscarínicos e simpaticomiméticos, incluindo glicopirrónio ou formoterol. Bevespi Aerosphere deve ser utilizado com precaução em doentes com doenças cardiovasculares graves, tais como cardiopatia isquémica, taquiarritmias ou insuficiência cardíaca grave. Recomenda-se também precaução em doentes com tirotoxicose ou com prolongamento do intervalo QTc conhecido ou suspeito. Hipocaliemia: Os agonistas β_2-adrenérgicos podem causar hipocaliemia significativa, o que pode aumentar a suscetibilidade para arritmias cardíacas. A diminuição do potássio sérico é normalmente transitória, não necessitando de suplementação. Em doentes com DPOC grave, a hipocaliemia pode ser potenciada por hipoxia e tratamento concomitante. Hiperglicemia: A inalação de doses elevadas de agonistas β_2-adrenérgicos pode provocar o aumento da glucose plasmática. Atividade anticolinérgica: Devido à sua atividade anticolinérgica, Bevespi Aerosphere deve ser utilizado com precaução em doentes com hiperplasia da próstata sintomática, retenção urinária ou glaucoma de ângulo fechado. Doentes com compromisso renal grave: Como o glicopirrónio é excretado predominantemente por via renal, os doentes com compromisso renal grave (depuração de creatinina <30 ml/min), incluindo aqueles com doença renal em fase terminal com necessidade de diálise, apenas devem ser tratados com Bevespi Aerosphere se o benefício esperado superar o risco potencial. Doentes com compromisso hepático grave: Em doentes com compromisso hepático grave, Bevespi Aerosphere só deve ser utilizado se o benefício esperado superar o risco potencial. Estes doentes devem ser monitorizados para potenciais reações adversas. **Interações medicamentosas e outras formas de interação:** Interações farmacocinéticas: O potencial para interações metabólicas é considerado baixo. Como o glicopirrónio é eliminado principalmente por via renal, podem ocorrer potencialmente interações com medicamentos que afetam os mecanismos de excreção renal. Interações farmacodinâmicas: *Outros antimuscarínicos e simpaticomiméticos*: A coadministração de Bevespi Aerosphere com outros medicamentos contendo anticolinérgicos e/ou agonistas β_2-adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas β_2-adrenérgicos inalados. Não existe evidência clínica de interações quando utilizado concomitantemente com outros medicamentos para a DPOC, incluindo broncodilatadores β_2-adrenérgicos de curta duração de ação, metilxantinas e esteroides orais e inalados. *Hipocaliemia induzida por fármacos*: O tratamento concomitante com derivados da metilxantina, esteroides ou diuréticos não poupadores de potássio pode potenciar o possível efeito hipocaliemico inicial dos agonistas β_2-adrenérgicos, pelo que se recomenda precaução na sua utilização concomitante. *Bloqueadores β-adrenérgicos*: Os bloqueadores β-adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito dos agonistas β_2-adrenérgicos, tal como o formoterol. O uso simultâneo de bloqueadores β-adrenérgicos não seletivos ou seletivos deve ser evitado, a não ser que existam razões determinantes para a sua utilização. Se forem necessários bloqueadores β-adrenérgicos (incluindo colírios), dá-se preferência a bloqueadores β-adrenérgicos cardiosseletivos, embora também estes devam ser administrados com precaução. *Outras interações farmacodinâmicas*: Bevespi Aerosphere deve ser administrado com precaução em doentes que estejam a ser tratados com medicamentos conhecidos por prolongar o intervalo QTc. **Fertilidade, gravidez e aleitamento:** Gravidez: Não existem dados sobre a utilização de Bevespi Aerosphere em mulheres grávidas. Bevespi Aerosphere só deve ser utilizado durante a gravidez se os benefícios esperados superarem os potenciais riscos. Amamentação:

Não é conhecido se o 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, Infeção 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/submissaoram (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**: Tecnimede - 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 comparticipado 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. Hipocaliemia: A hipocaliemia potencialmente grave pode resultar da terapêutica com agonistas-β_2. 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 hipocaliemia também pode ser potencializada pelo tratamento concomitante com outros medicamentos que podem induzir hipocaliemia, tais como derivados de xantinas, esteroides e diuréticos. Hiperglicemia: A inalação de doses elevadas de agonistas β_2-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 dever ser utilizado com precaução em doentes com tirotoxicose. Atividade anticolinérgica: Devido à sua atividade anticolinérgica, este medicamento deve ser utilizado com precaução em doentes com hiperplasia da próstata sintomática, retenção urinária ou glaucoma de ângulo fechado. Os doentes devem ser informados sobre os sinais e sintomas do glaucoma de ângulo fechado e devem ser informados para interromper a utilização deste medicamento e 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 anticolinérgicos. 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 protéase 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 anticolinérgicos e/ou agonistas β_2-adrenérgicos de longa duração de ação não foi estudada e não é recomendada uma vez que poderá potenciar as reações adversas conhecidas dos antagonistas muscarínicos ou dos agonistas β_2-adrenérgicos inalados. 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. *Hipocaliemia induzida por* medicamentos: A hipocaliemia pode aumentar a disposição para arritmias em doentes que são tratados com glicosídeos digitálicos. *Bloqueadores β-adrenérgicos*: Os bloqueadores β-adrenérgicos (incluindo colírios) podem atenuar ou inibir o efeito do formoterol. O uso simultâneo de bloqueadores β-adrenérgicos deve ser evitado, a não ser que o benefício esperado ultrapasse o risco potencial. Se forem necessários bloqueadores β-adrenérgicos, dá-se preferência a bloqueadores β-adrenérgicos cardiosseletivos. *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; Infeção 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 raros*: Sinais ou sintomas de efeitos sistémicos de glucocorticoides, por exemplo supressão suprarrenal; Comportamento anormal. *Desconhecido*: Angioedema; Visão turva; Cataratas; Glaucoma. Pede-se aos profissionais de saúde que notifiquem quaisquer suspeitas de reações adversas através do Sítio da internet: http://www.infarmed.pt/web/infarmed/submissaoram (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**: Tecnimede - 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 comparticipado pelo Escalão B (69% de comparticipação no regime geral e 84% de comparticipação no regime especial). 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ARTIGO ORIGINAL

Testes virais respiratórios para lactentes febris jovens que se apresentam ao atendimento de urgência: uma análise secundária planeada do estudo de coorte observacional prospectivo "Febrile Infants Diagnostic Assessment and Outcome" (FIDO)

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RESUMO

Objetivo Descrever a associação entre os resultados dos testes virais respiratórios e o risco de infecção bacteriana invasiva (IBI) em lactentes febris jovens que se apresentam ao atendimento de urgência.

Desenho do Estudo Uma análise secundária planeada dentro do estudo Febrile Infants Diagnostic Assessment and Outcome (FIDO), um estudo de coorte observacional prospectivo multicêntrico conduzido no Reino Unido e na Irlanda.

Local 35 departamentos de emergência pediátrica e unidades de avaliação no Reino Unido e na Irlanda, entre 6 de julho de 2022 e 31 de agosto de 2023.

Pacientes Lactentes febris com 90 dias ou menos que se apresentam ao atendimento de emergência.

Principais medidas de desfecho Infecção bacteriana invasiva (IBI) (meningite ou bacteremia) entre lactentes febris, submetidos a testes virais respiratórios para o vírus sincicial respiratório (VSR), influenza e SARS-CoV-2.

Resultados 1395 dos 1821 participantes foram submetidos a testes virais respiratórios, dos quais 339 (24,5%) testaram positivo para pelo menos um dos seguintes: SARS-CoV-2, VSR ou influenza. Um total de 45 lactentes (3,2%) foram diagnosticados com IBI. Desses, IBI ocorreu em 40 de 1056 (3,8%) participantes com teste viral negativo e 5 de 339 (1,5%) ocorreram em participantes com teste viral respiratório positivo (p=0,034). Lactentes com 29 dias ou mais e teste viral respiratório positivo tiveram uma taxa significativamente mais baixa de IBI (0,7%) em comparação com aqueles com teste negativo (3,2%) (p=0,015).

Conclusões Lactentes febris jovens com teste viral respiratório positivo para SARS-CoV-2, VSR ou influenza têm menor risco de IBI. Lactentes com mais de 28 dias de idade e teste viral positivo representam o grupo de menor risco.

Número de registro do estudo NCT05259683.

Key messages

What is know about this topic

- ►Febrile infants ≤90 days of age are at considerable risk of invasive bacterial infection (IBI).
- ►The presence of a respiratory virus has been shown to be associated with a lower risk of IBI.
- ►No guidance exists on how to incorporate viral testing into the assessment of febrile infants.

What this study ads

- ►Infants with a positive respiratory viral test have a significantly lower rate of IBI compared with those with a negative respiratory viral test.
- ► Infants over 28 days of age with a positive respiratory viral test have a very low risk of IBI.

How this study might affect research practice or policy

- ►Infants >28 days of age that test positive for SARS-CoV-2, influenza or respiratory syncytial virus on respiratory viral testing may be suitable for management without parenteral antibiotics, lumbar puncture and even blood-based biomarker testing.
- ►Further randomised trials are required to evaluate how the introduction of respiratory viral point-of- care testing can influence outcomes of value to parents and caregivers.

INTRODUCTION

Infants younger than 3 months who develop a fever are at risk of invasive bacterial infection (IBI) such as bacteraemia and meningitis.[1 2] Symptoms are often non-specific in this group, making it difficult, even for experienced clinicians, to assess risk.[1 3] Various clinical decision aids (CDAs) have been developed and validated globally and typically assess risk based on age, clinical appearance and biomarker testing.[1,4–6] None of the international validated CDAs include point-of-care (POC) respiratory viral testing within the diagnostic assessment.[4–6]

The potential role of POC respiratory viral testing within the diagnostic pathway has gained attention in recent years due to the increased availability following the COVID-19 pandemic.[7] The most commonly available POC respiratory viral tests across UK and Irish paediatric emergency departments (EDs) prior to the pandemic were influenza and respiratory syncytial virus (RSV).[8] Multiple studies have reported an association between the detection of a respiratory virus and lower rates of IBI.[2 8–11] Unfortunately, the majority of these studies are retrospective as well as underpowered to determine if respiratory viral testing can identify a subgroup of infants suitable for management without biomarker testing and antibiotics. This has been highlighted by the American Academy of Pediatrics as an important question for future research.[4] If respiratory viral testing could be used to identify a low-risk cohort without the need for blood biomarker testing, then this could reduce the need for painful procedures and shorten the length of stay.

Unlike laboratory-based multiplex respiratory viral test, POC testing can be performed in the emergency care setting with results available within minutes, making POC viral testing an attractive addition to the current diagnostic pathway. The objective of this planned secondary analysis is to describe the association between respiratory viral testing results (specifically for SARS-CoV-2, influenza and RSV) and the risk of IBI.

METHODS

This was a prior planned secondary analysis of data from the Febrile Infant Diagnostic assessment and Outcome (FIDO) study. The FIDO study was a prospective observational cohort study conducted across the paediatric emergency research in the UK and Ireland (PERUKI) network. The protocol for the FIDO study has been published previously and is registered at https://clinicaltrials.gov/ (NCT05259683).[9] This study has been reported in line with Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidance.[10]

Participants

Infants ≤90 days presenting with a fever of ≥38°C recorded in the ED/assessment unit or by anyone within the preceding 24 hours of presentation were eligible for inclusion. Infants whose guardians declined or withdrew consent were excluded from the study. These infants were recruited across 35 PERUKI sites with 1 site in Northern Ireland, 1 in Wales, 1 in Ireland, 2 in Scotland and 30 in England. The sites included a range of both district general hospitals with mixed EDs and tertiary paediatric hospitals. The recruitment period was from 6 July 2022 to 31 August 2023. For this secondary analysis, infants without respiratory viral testing were excluded from the analysis.

Test methods

The index tests evaluated were commercially available, routinely used, respiratory viral test for the following three respiratory viruses; SARS-CoV-2, influenza (included A and B) and RSV. This included both laboratory-based and POC tests. The index test sample was collected at presentation. IBI was defined as a bacterial pathogen identified in either blood or cerebrospinal fluid (CSF) by culture or molecular testing using United Kingdom Accreditation Service (UKAS) accredited National Health Service (NHS) laboratories and accredited laboratory in Children's Health Ireland (CHI). The reference standard test was performed by staff blinded to the clinical data and the suspected diagnosis. As not all infants had blood/CSF cultures or molecular testing, infants were followed up with charts reviews 7 days after discharge to identify any re-presentation with IBI.

Study procedure and data management

Infants were managed according to local practice with respiratory viral testing performed at the discretion of the treating clinician. On arrival to hospital, infants were screened for eligibility by clinical staff. Clinical staff prospectively recorded the initial assessment and clinical findings on a case report form (CRF). These were completed prior to consent discussion as clinical care of these infants should occur without delay. Patients were consented using research without prior consent methodology which has been previously used and reported in the published FIDO study protocol.[9,11] Research Electronic Data Capture (REDCap) tools were used for data capture and management.[12] REDCap is a secure, web-based software platform designed to support data capture for research studies. A secondary CRF was completed by a member of the research team 7 days after discharge to document results of investigations, length of stay, disposition and attendance. Infants with incomplete data for viral testing, reference standard or outcome assessment were excluded from the study.

Data analysis

Descriptive statistics were used to report the demographic characteristics, clinical assessment, vital signs, parenteral antibiotic use, IBI rates, viral testing and disposition. Median and interquartile range (IQR) were used for continuous variables, while frequencies and percentages were used for categorical variables. Demographic characteristics, vital signs, parenteral antibiotic use and IBI rates

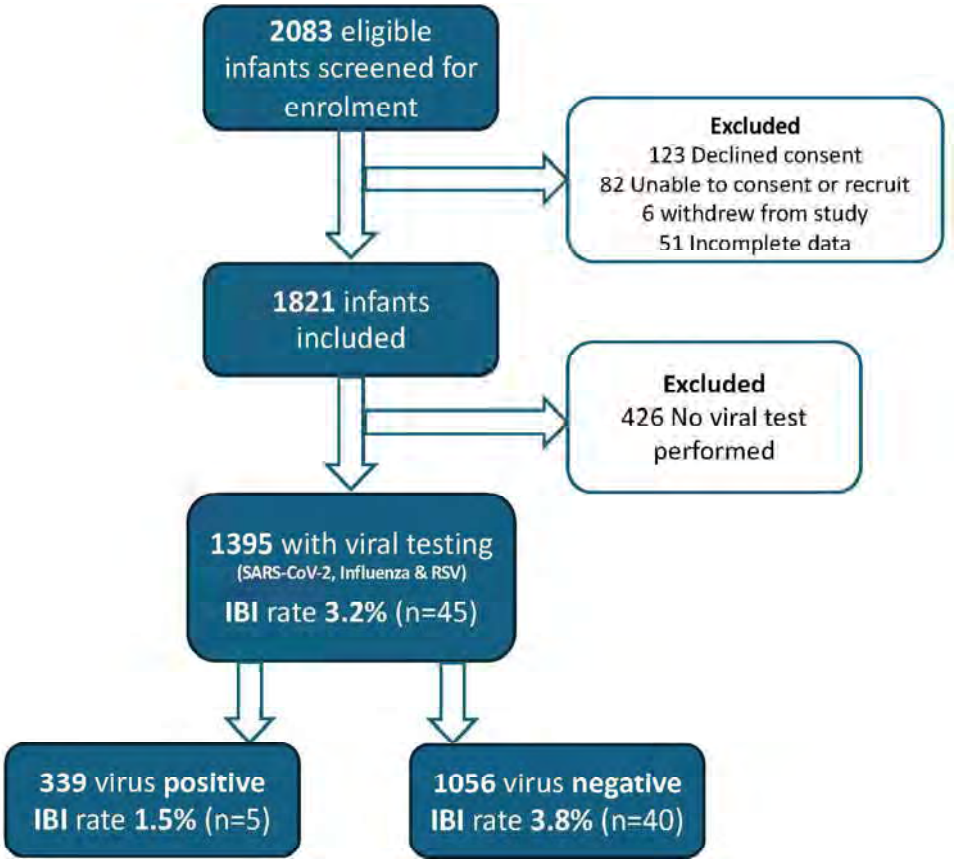

Figure 1 Flowchart of enrollment, viral testing and Invasive Bacterial Infection (IBI) rates. RSV, respiratory syncytial virus.

Table 1 Patient characteristics and IBI rates in infants with and without viral testing

	Total population (n=1821)	Viral testing performed (n=1395)	Viral testing not performed (n=426)	P value
Male gender, n (%)	1108	842 (60)	266 (62)	0.24
Well appearing, n(%)	1058	1065 (76)	352 (83)	0.003
Respiratory symptoms, n (%)	881	694 (50)	187 (44)	0.20
Median age, days (IQR)	46 (30–64)	46 (29–64)	49 (30–65)	0.100
Median temperature, °C (IQR)	38 (37.4–38.4)	38.0 (37.4–38.4)	37.8 (37.1–38.3)	0.001
Median heart rate, BPM (IQR)	167 (152–181)	169 (155–182)	161 (148–177)	<0.001
Median respiratory rate, BPM, (IQR)	47 (40–52)	47 (40–54)	46 (40–52)	0.49
Median CRT, s (IQR)	2 (2)	2 (2)	2 (2)	0.10
Median Oxygen saturations, % (IQR)	99 (97–100)	99 (97–100)	99 (98–100)	0.73
Received antibiotics, n (%)	1401 (77)	1154 (83)	247 (58)	<0.001
IBI, n (%)	67 (3.7)	45 (3.2)	22 (5.2)	0.047

*Vital signs recorded at presentation.
CRT, capillary refill time; IBI, invasive bacterial infection.

were compared in those with and without viral testing performed. IBI rates were compared in the following subgroups: age (≤28 days vs >28 days), respiratory symptoms (cough and coryza) and global assessment (well and unwell appearing). Both 'cough and coryza' and 'general appearance' were distinct elements of the parent study CRF and were not extracted from chart review. Seasonal variation was assessed for viral testing and IBI rates. The classification of the seasons for the year during the study period (2022 and 2023) is as follows: summer is classified as July and August 2022, and June to August 2023; autumn is classified as September to November of 2022; winter is classified as December 2022 to February 2023; and spring is classified as March to May 2023. Continuous variables were analysed using Mann-Whitney U test, and for categorical variables, either a χ^2 or Fisher's exact test was used. Analysis was conducted using IBM statistical package for social sciences (SPSS) V.23, and a p value <0.05 was designated statistically significant.

RESULTS

Of the 1821 FIDO participants, a total of 1395 underwent respiratory viral testing for SARS-CoV-2, influenza or RSV at presentation and 339 out of 1395 (24.3%) had a positive virus test (figure 1). This included 220 participants testing positive for SARS-CoV-2, 70 testing positive for RSV, 72 testing positive for influenza and 23 testing positives to multiple viruses (online supplemental material). All sites performed viral testing, with the overall rate of 1395/1821 (77%) and site variation ranging from 29% to 97% (online supplemental material). Viral testing occurred more frequently in the winter (78%) and spring (79%) compared with autumn (74%) and summer (75%) (p=0.041).

Population comparisons and descriptions

The population undergoing viral testing at presentation was significantly less likely to appear well, with a higher fever at presentation and higher heart rate. Infants undergoing viral testing were significantly more likely to receive parenteral antibiotics and had a lower rate of IBI (table 1).

In the population with viral testing performed, there were 45 cases of IBI overall (3.2%). The IBI rate did not vary between seasons (p=0.614), as shown in figure 2. The most commonly identified bacteria were *Escherichia coli* (22/45, 49%), *Staphylococcus aureus* (7/45, 16%) and Group B *Streptococcus* (5/45, 11%). A full summary of all causes of IBI can be found in the online supplemental material.

IBI and viral testing result

Among the cohort undergoing viral testing with confirmed IBI, 40 out of 1056 (3.8%) occurred in participants with a negative viral test and 5 out of 339 (1.5%) occurred in participants with a positive viral respiratory test (p=0.034). Therefore, of the 45 infants with IBI, 89% had no virus detected and 11% had a virus detected (figure 1).

For participants under 29 days, n=335/1395 (24%), the respiratory viral test result was not associated with any significant change in IBI rate, with 16 out of 299 (5.4%) test negative and 3 out of 36 (8.3%) test positive being diagnosed with IBI, p=0.44 (table 2).

For participants aged 29 days of age and older, n=1060/1395 (76%), the presence of a positive respiratory viral test was associated with a lower rate of IBI (2/303, 0.7%) compared with those participants with a negative test (24/757, 3.2%), p=0.015.

In participants with respiratory symptoms, n=694/1395 (50%), a positive respiratory virus test was not associated with any change in IBI rate with 3 out of 238 (1.3%) testing positive and 10 out of 456 (2.2%) testing negative being diagnosed with IBI, p=0.588.

In participants without respiratory symptoms, n=701/1395 (50%), a positive respiratory virus test was not associated with any change in IBI rate with 2 out of 101 (2.0%) testing positive and 30 out of 600 (5.0%) testing negative being diagnosed with IBI, p=0.30.

For well-appearing participants, n=1065/1395 (76%), the respiratory viral test result was not associated with any change in IBI

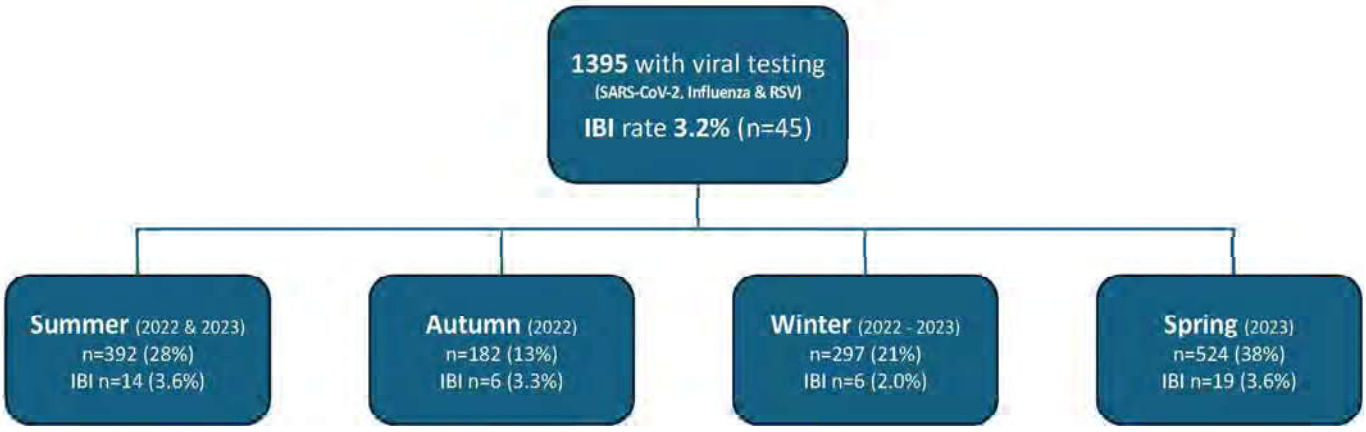

Figure 2 Seasons and invasive bacterial infection (IBI) rate. RSV, respiratory syncytial virus.

Table 2 Summary of results for infants that underwent respiratory viral testing (n=1395)

	Respiratory viral test performed (positive or negative)	Positive respiratory viral test	Negative respiratory viral test	P value
Total sample, n	1395	339	1056	
Invasive bacterial infection, n (%)	45 (3.2%)	5 (1.5%)	40 (3.8%)	0.034
<29 days, n	335	36	299	
Invasive bacterial infection, n (%)	19 (5.7%)	3 (8.3%)	16 (5.4%)	0.44
>28 days and IBI, n	1060	303	757	
Invasive bacterial infection, n (%)	26 (2.5%)	2 (0.7%)	24 (3.2%)	0.015
Respiratory symptoms present, n	694	238	456	
Invasive bacterial infection, n (%)	13 (1.9%)	3 (1.3%)	10 (2.2%)	0.588
Respiratory symptoms absent, n	701	101	600	
Invasive bacterial infection, n (%)	32 (4.6%)	2 (2.0%)	30 (5.0%)	0.30
Well on 'Global Assessment'	1065	248	817	
Invasive bacterial infection, n (%)	22 (2.1%)	3 (1.2%)	19 (2.3%)	0.44
Unwell on 'Global Assessment'	330	91	239	
Invasive bacterial infection, n (%)	23 (7.0%)	2 (2.2%)	21 (8.8%)	0.05

IBI, invasive bacterial infection.

rate with 19 out of 817 (2.3%) testing negative and 3 out of 248 (1.2%) testing positive being diagnosed with IBI, p=0.44.

For unwell-appearing participants, n=330/1395 (24%), the presence of a positive respiratory viral test was associated with a lower rate of IBI (2/91, 2.2%) compared with those participants with a negative test (21/239, 8.8%), p=0.05.

Interpretation

To our knowledge, this is the first study in UK and Ireland to report on the utility of respiratory viral testing in the emergency evaluation of febrile infants. In this large prospective multicentre study conducted across 35 PERUKI sites over 13 months, a total of 1395 infants underwent respiratory viral testing with 339 (24%) testing positive for either SARS-CoV-2, influenza or RSV. Within the tested cohort, there were 45 cases of IBI (3.2%).

The proportion of febrile infants with IBI was significantly lower (1.5%) in those infants with a positive respiratory viral test compared with those with a negative viral test (3.2%), p=0.034. This finding is consistent with several other large multicentre studies conducted in North America that typically report an IBI rate of approximately 1% among febrile infants with a positive respiratory viral test.[2 13 14] Typically, a 1% risk of IBI or higher has been viewed as too high to justify not performing additional investigations such as blood testing and lumbar puncture.[4] It is unclear, however, if combining viral testing results with clinical features could be used to identify a low-risk cohort suitable for assessment without blood biomarker testing.

Sensitivity analysis by age demonstrated that among the younger group (under 29 days) that respiratory viral testing likely has no meaningful role in assessing the risk of IBI with 5.4% of the viral test-positive group also being diagnosed with IBI. In comparison, however, just 2 out of 303 (0.7%) older infants tested positive for a respiratory viral test and were diagnosed with IBI. This was significantly lower than the viral test negative group of the same age (24/757, 3.2%), p=0.015. At 0.7%, the risk of IBI is approaching an acceptable level to justify withholding further investigations and is similar to reported risk of misclassifying an infant as low risk when utilising a number of validated clinical practice guidelines.[5 15 16]

Several observational studies of febrile infants have demonstrated that the presence of respiratory symptoms such as cough and coryza are associated with a lower, but non-negligible, rates of IBI.[17 18] These findings are supported by the observation that 13 out of 694 (1.9%) of those with viral symptoms in this study were diagnosed with IBI. The addition of a positive respiratory viral test in those with respiratory symptoms was not associated with a significantly different risk of IBI (p=0.588), with 1.3% of test-positive and 2.2% of test-negative infants being diagnosed with IBI.

In addition to age and symptomology the global appearance of an infant is universally used to help determine risk of IBI. Unfortunately, assessing wellness in this group is challenging and even with tools, such as the paediatric assessment triangle, the assessment remains highly subjective. A number of studies have demonstrated that clinical appearance alone cannot be used to exclude IBI.[3 19 20] Within our cohort, 1065 out of 1395 (76%) appeared well. For this cohort, the addition of viral testing made no significant difference (p=0.44) to the risk of IBI with 1.2% of well appearing, viral test-positive infants being diagnosed with IBI.

It is evident from these data that the incorporation of viral testing for common respiratory viruses such as SARS-CoV-2, influenza and RSV could be used to identify a cohort of older infants who are at low risk and may be suitable for management without the need for parenteral antibiotics, lumbar puncture or blood-based biomarker testing. Although IBI rates did not vary according to seasons, viral testing varied by season and by site. Similar variation in rates of viral testing per site was reported by Rodgers et al (20%–90%).[21] This highlights the need for unified guidance on the use of viral testing in the care of febrile infants.

Strength and limitation

This study has a number of strengths. It was a large multicentre prospective study involving both district and tertiary hospitals giving a real-world pragmatic view of management of febrile infants and viral testing. A limitation of this study was the small numbers of IBI which is universal to all studies of this type. This study is focused exclusively on IBI, excluding urinary tract infection (UTI), as urinalysis provides an accurate non-invasive diagnostic POC test, a positive UTI does not significantly increase the risk of bacteraemia or meningitis, has lower associated risk of complication or harm and management decisions on admission and route of antimicrobial administration may differ.[22–24]

The parent study was conducted in the UK and Ireland only, the findings may not be generalisable to other settings and populations. The COVID-19 pandemic significantly impacted clinical settings, with a notable rise in viral testing during and after the pandemic. Among the 1821 enrolled subjects, 77% (1395) underwent respiratory viral testing, with 65% of positive tests detecting SARS-CoV-2. Therefore, our findings should be interpreted in the context of a post pandemic era of SARS-CoV-2.

Only 7 sites reported using POC tests, 23 sites used laboratory-based tests, 5 did not report if they used laboratory or POC. The results of this study are not specific to POC testing but reflect overall respiratory viral testing, be that lab-based or POC, for three viruses that are most commonly available as POC in paediatric EDs across the UK and Ireland. To assess the clinical impact of introducing routine respiratory viral POC testing to febrile infant

CDAs, further studies are required with particular focus on implementation.

Summary

The presence of SARS-CoV-2, RSV and influenza positive viral test is associated with low rates of IBI. This was most significant in infants aged 29–90 days. Where rapid POC detection for these viruses is available, a more tailored approach could be applied in febrile infants aged 29–90 days obviating the need for invasive testing and parenteral antibiotics administration. This holds the potential to improve antimicrobial stewardship, patient experience and cost-effectiveness. Infants with positive viral test and urinalysis should be managed in line with guidance for UTI.

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Contributors JE, EU and TW conceived and designed the analysis for the study. TW and EU undertook the statistical analysis for this study. All authors contributed and approved the final version of the manuscript. TW is the guarantor.
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Patient consent for publication Not applicable.
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ARTIGO ORIGINAL

Variabilidade no volume expiratório forçado no primeiro segundo em crianças com asma sintomaticamente bem controlada

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RESUMO

Objetivos A espirometria é utilizada por muitos clínicos para monitorar a asma em crianças, mas pouco se entende sobre sua variabilidade ao longo do tempo. O objetivo deste estudo foi determinar a variabilidade do volume expiratório forçado no primeiro segundo (FEV_1) em crianças com asma sintomaticamente bem controlada, aplicando três métodos diferentes de expressar a mudança no FEV_1 ao longo de intervalos de 3 meses.

Métodos Foram utilizados dados de cinco estudos longitudinais com crianças com asma que mediram o FEV_1 em intervalos de 3 meses ao longo de 6 ou 12 meses. Analisamos as medições emparelhadas de FEV_1 quando os sintomas da asma estavam controlados. A variabilidade do FEV_1% previsto (FEV_1%), do escore z do FEV_1 (FEV_1z) e do score z condicional para a mudança (Zc) no FEV_1 foi expressa como limites de concordância.

Resultados Um total de 881 crianças teve 3338 medições de FEV_1 em ocasiões quando a asma estava controlada; 5184 pares de medições de FEV_1 feitas em intervalos de 3 meses estavam disponíveis. Cada alteração unitária no score z do FEV_1 foi equivalente a um Zc de 1,45 e a uma alteração absoluta no FEV_1% de 11,6%. Os limites de concordância para a alteração no FEV_1% foram de −20 e +21, para a alteração absoluta no FEV_1z foram de −1,7 e +1,7 e para o Zc foram de −2,6 e +2,1. A regressão para a média e a maior variabilidade em crianças mais jovens foram observadas nas comparações de mudança no FEV_1% e FEV_1z, mas não no Zc.

Conclusão Dado os amplos limites de concordância das medições emparelhadas de FEV_1 em crianças sintomaticamente bem controladas, o tratamento da asma deve ser orientado principalmente pelos sintomas e não por uma mudança na espirometria.

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

▶ Guidelines recommend that lung function testing (eg, forced expiratory volume in 1 s, FEV_1) may be a useful objective measurement to support asthma treatment decision-making. There is little understood about how variable FEV_1 measurements are in children with asthma over 3-month periods, that is, a typical interval between clinic visits.

WHAT THIS STUDY ADDS

▶ We describe variation in FEV_1 over 3-month periods in a relatively large number of children with stable asthma. We also describe how change in FEV_1 can be expressed using three different methods, only one of which was not influenced by regression to the mean over time.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

▶ Changes in FEV_1 which are currently considered clinically significant fall within the biological visit-to-visit variability described here. Conditional change score may be superior to other methods of expressing change in FEV_1 in children with asthma.

INTRODUCTION

Asthma is a common chronic condition in childhood and is characterised by chronic airway inflammation which leads to symptoms of cough, wheeze and shortness of breath which relapse and remit over time.[1 2] Asthma guidelines recommend that current asthma symptoms should guide decision-making for asthma treatment.[3–8] Some guidelines also recommend longitudinal measurements of spirometry in children aged over 5 years should be made to help guide decision-making.[4,5,7,8] Only two guidelines, now at least 10 years old, indicate how spirometry should be used to guide asthma treatment in children (ie, treatment should be increased when forced expiratory volume in 1 s (FEV_1) is less than 80% of predicted)[4 5] and one guideline suggests that a change between clinic visits of more than 12% in FEV_1 is excessive[7] but does not say if or how treatment should change.

It remains unclear what magnitude of change in spirometry (eg, FEV_1) is indicative of a clinically significant change in children with asthma. A relative rise of more than 10%[9] or 12%[10] predicted FEV_1 from baseline is considered a positive change after inhaling a bronchodilator within a single test occasion, but this magnitude of change is not necessarily generalisable to repeated FEV_1 measurements made 3–4 months apart for a couple of reasons. First, the time interval between measurements is different (20 min compared with 3–4 months). Second, there is no evidence in children to say by how much FEV_1 changes over 3–4 months; a 12% cut-off[7] is supported by a small study of 47 adult patients where FEV_1 was measured at weekly in-

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tervals over 9–10 weeks.[11] One study reported that the coefficient of variation (CV) in paired measurements of FEV_1 in children was 4.3% for paired values measured within a 2-hour assessment, rising to 8.3% for paired values measured over an interval of 1–4 weeks.12 A second study measured FEV_1 twice daily over 2 weeks and concluded that variability of more than 11.8% in FEV_1 was likely to be clinically relevant.[13] Data on the variability of spirometry indices in children with well-controlled asthma over intervals of months will inform clinical practice and may assist asthma specialists who are known to be uncertain about the role of monitoring asthma by FEV_1 measurements.[14]

The aim of this study was to determine the variability of FEV_1 in children with controlled asthma by applying three different methods of expressing change in FEV_1 over 3-month intervals. We also sought to determine the influence of regression to the mean[15] for each of the three methods of expressing FEV_1 change; regression to the mean is a short-term consequence of the normal variability of FEV_1 which complicates the interpretation of longitudinal FEV_1 measurements.

METHODS

Data

Data from children with a clinical diagnosis of asthma collected in five independent clinical trials were obtained for this secondary data analysis study.[16–20] In each study, prebronchodilator FEV_1 and asthma control status were measured at baseline and approximately 3-month intervals over the course of 6[16] or 12 months,[17–20] resulting in up to five measurements from an individual (0, 3, 6, 9, 12 months). Data from up to four consecutive 3-month periods were analysed and expressed as variability (ie, difference from the mean), rather than reproducibility (ie, the extent to which a test result can be reproduced).

Population details

Fritsch et al[16] undertook a study of 47 children with asthma attending a hospital asthma clinic in Vienna, Austria and collected data (including FENO, asthma symptom score and history of recent exacerbations) at 6-week intervals over 6 months. Petsky et al[17] recruited 63 children from hospital clinics in Australia and Hong Kong, and data were collected on eight occasions over 12 months (1, 2, 3, 4, 6, 8, 10 and 12 months). Szefler et al[18] recruited 546 participants from the community in the USA and collected post-trandomisation information over 46 weeks including at 3 months, 6 months, 8 months and 10 months. Peirsman et al[19] recruited 99 participants with persistent asthma attending hospital asthma clinics across Belgium and collected data at 3-month intervals over 12 months. Turner et al[20] recruited 509 children with asthma from the hospital across the UK and collected data every 3 months over a year. The treatment algorithms in FENO-guided and standard practice arms in each randomised controlled trial (RCT) were different to other RCTs and are summarised in online supplemental table 1.

Spirometry

FEV_1 was measured using spirometry according to the American Thoracic Society/European Respiratory Society standards.[21] Measured FEV_1 values were standardised to per cent predicted ($\%FEV_1$) and z score ($zFEV_1$) using the Global Lung Function Initiative reference equations.[22] A conditional change score (Zc) in FEV_1 was calculated using a formula derived from children without any respiratory condition.[23] Zc adjusts for factors associated with FEV_1 variability, that is, baseline FEV_1, the child's age and time interval between measurements. Additionally, in the absence of data to calculate Zc in children with asthma, Zc was calculated using data from these five populations. Data from each of the 10 pairwise comparisons of FEV_1 measurements were included, that is, 0–3 months, 3–6 months, 6–9 months, 0–6 months, 0–9 months, 0–12 months, 3–9 months, 3–12 months, 6–12 months and 9–12 months. Asthma control was determined with either the Asthma Control Test (ACT, for children aged >12 years),[24] Child ACT (CACT, for children aged 4–11 years)25 or a study-specific questionnaire in two studies.[16 17] For ACT and CACT, control was defined by a score of >19. Visits with missing FEV_1 values and individuals with only a single measurement were excluded from analyses.

Statistical analysis

The mean (with SD), median (with IQR) or proportion (expressed as a percentage) of baseline characteristics for the combined and individual populations were presented. The intraclass correlation coefficient (ICC), a measure of correlation between multiple measurements within the same individual, was calculated for $\%FEV_1$ using a linear mixed effects model with random slope and intercept. The ICC was calculated with and without accounting for the level of asthma control to determine the impact of control on variability (online supplemental table 2). Online supplemental table 3 presents the coefficients for deriving Zc from children with asthma and from a healthy population.[23] Variability for each of the paired comparisons of FEV_1 measurements and an average over the entire pairwise dataset was calculated for the following outcomes:

1. Within-subject CV of $\%FEV_1$, which was calculated as the within-subject SD divided by the individual's mean.
2. Bland-Altman limits of agreement (LoAs) for absolute change in FEV_1.
3. Bland-Altman LoAs for relative change in $\%FEV_1$.
4. Bland-Altman LoAs for absolute change in FEV_1 (relative change in z-scores was not calculated because z-scores are already standardised).
5. 95% prediction limits (mean±1.96×SD) of the Zc derived from a population of children without a chronic respiratory condition.[22]
6. 95% prediction limits (mean±1.96×SD) Zc derived from children with asthma within the present dataset (see online supplemental table 2 for details).

Online supplemental table 2 gives fuller detail of how the variables presented in this paper were derived. All analyses were carried out in R software ((https://www.R-project.org/)).

RESULTS

Study participants

Data were available from 1264 individuals (table 1). There were differences between the cohorts whose data contributed to the overall dataset for age, ethnicity, treatment with long-acting beta-agonist or leukotriene receptor antagonist, proportion controlled at randomisation and median FeNO (table 1). There were also differences across the five populations for FEV_1 z score at baseline and at 12 months but not on the intervening occasions (online supplemental table 4). There were no differences in FEV_1 z score at any time between individuals in separate trial arms (online supplemental table 5).

After excluding data from individuals with only one FEV_1 measurement or missing FEV_1 measurements, and who were uncontrolled on one or more occasions when FEV_1 was measured, there were 881 individuals with a total of 3338 individual measurements and 5184 pairs of measurements (ie, an individual with two measurements gives one pair of measurements, while an individual with three measurements gives three pairs of measurements, etc). Online supplemental figure 1 describes how data for the present analyses were identified from the original 1264 individuals. Of the 881 individuals whose data were analysed, there were 303 (34%) who contributed 5 paired FEV_1 measurements with 242 (27%) contributing 4, 183 (21%) contributing three and 153 (17%) contributing 2 paired measurements. Younger children had fewer controlled visits than older children.

The ICC was 0.81, ie 81% of the variance in $\%FEV_1$ was explained by between-individual differences. The ICC was similar when adjusting for level of asthma control (ICC=0.80) and varied between 0.56 and 0.89 between the five populations contributing data (online supplemental table 4). As uncontrolled asthma did not account for the within-individual variability of $\%FEV_1$, all study visits were used to define the measures of variability.

Variability

The variability of FEV_1 between measurements was consistent across all time intervals for each of the three outcomes (table 2).

Table 1 Characteristics of children recruited in the five trials and whose data contributed to this study

	All children n*=1264	Fritsch *et al*[16] n*=47	Petsky *et al*[17] n*=63	Szefler *et al*[18] n*=546	Peirsman *et al*[19] n*=99	Turner *et al*[20] n*=509
Mean age (SD), years	12.0 (3.2)	11.5 (3.1)	10.0 (3.2)	14.4 (2.1)	10.7 (2.1)	10.1 (2.6)
% male	59 (746)	60 (28)	49 (31)	53 (288)	67 (66)	61 (308)
% white ethnicity	39 (454/1159)	Not stated	0 (0/20)	0	82 (69/84)	76 (385)
% patients with obesity	17 (217/1244)	8 (4)	2 (1)	31 (165/526)	1 (1)	9 (46)
Median dose of inhaled corticosteroids (IQR), micrograms budesonide equivalent	400 (400–1000)	400 (0–800)	400 (250–500)	1000 (400–2000)	320 (200–400)	400 (400–1000)
% prescribed long-acting beta-agonists at randomisation	67 (830/1239)	28 (13)	67 (39/58)	66 (360)	32 (32)	76 (386)
% prescribed leukotriene receptor antagonist at randomisation	36 (465/1239)	38 (18)	10 (6/58)	15 (80)	60 (59)	59 (302)
Mean %FEV_1 at randomisation (SD)	92 (18)	93.5 (15.7)	91 (16)	91 (17)	91 (16)	90 (18)
Mean FEV_1 z score at randomisation (SD)	−0.68 (1.59)	−0.61 (1.28)	−0.07 (1.40)	−0.58 (1.66)	−0.51 (1.34)	−0.91 (1.58)
% controlled at randomisation	65 (781/1206)	49 (23)	72 (41/57)	80 (412/528)	75 (49/65)	50 (256)
Median FeNO at randomisation (IQR) ppb	22 (11–47) n=1211	34 (19–59) n=46	26 (12–48) n=61	20 (11–41)	31 (14–69) n=99	21 (10, 48)

*n=number of children unless stated otherwise.
FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s.

When the analysis was restricted to paired FEV_1 measurements made over only a 3-month interval the results were comparable to paired FEV_1 measurements made over 3, 6, 9 and 12 months intervals (table 2). Each unit change in FEV_1 z score was equivalent to a Zc 1.45 and an absolute change in FEV_1% of 11.6%. The LoAs for a change in %FEV_1 were wide, typically between ±20% for absolute change and ±27% for relative change. Online supplemental figure 2 presents the Bland-Altman plots. The conditional change was similar to an absolute change in zFEV_1; the limits for the conditional change score were wider. When the 687 episodes where asthma was uncontrolled were included in the analysis the variability for all comparisons became slightly wider; the CV for FEV_1 was 6.0 (compared with 5.2) and LoAs for difference in FEV_1% values typically ±21% for absolute change and ±28% for relative change (table 1). Online supplemental table 6 provides full details of the variability when all children were considered and online supplemental figure 3 shows how the 1166 individuals included in the analysis were identified. Conditional change, but not relative change in %FEV_1, absolute change in %FEV_1 or absolute change in FEV_1 mitigated the influence of baseline FEV_1 on subsequent change in FEV_1, also termed regression to the mean (figure 1).

DISCUSSION

In a population of 881 children with controlled asthma symptoms, the LoAs for absolute %FEV_1 were ±~20%, meaning that a child's %FEV_1 would need to rise or fall by at least 20% to be considered outside the limits of a statistically different change. A similar result was seen when children with uncontrolled asthma were included

Table 2 Variability of FEV_1 between each pair of measurements in children

				Limits of agreement				
				Difference between FEV_1 % values			Conditional change in z score	
	Interval (months)	Children (n)	Coefficient of variation for within-subject FEV_1%	Absolute	Relative	Difference between absolute z FEV_1 values	Derived in children with asthma	Derived in children without asthma[22]
Average of all 3-month intervals			5.2	0.1(−18.8,19.0)	0.8(−23.4,25)	0(−1.6,1.6)	−0.2(−2.5,2.1)	−0.2(−2.7,2.4)
Average of all intervals	–	–	5.2	0.3(−20.2,20.8)	1.1(−26.5,28.8)	0.0(−1.7,1.7)	−0.2(−2.6,2.1)	−0.2(−2.7,2.3)
Average of all intervals (all children)	3	1166	6	0.6(−21.6,22.9)	1.7(−27.6,31.1)	0(−1.8,1.9)	−0.2(−2.7,2.2)	−0.2(−2.8,2.3)
Baseline–3 months	3	513	5.3	0.7(−19.6,21.1)	1.7(−25.3,28.7)	0.0(−1.7,1.8)	−0.2(−2.6,2.3)	−0.1(−2.9,2.7)
3–6 months	3	556	5.0	0.0(−19.3,19.4)	0.8(−24.0,25.5)	0.0(−1.6,1.6)	−0.2(−2.6,2.2)	−0.1(−2.8,2.5)
6–9 months	3	546	5.2	−0.2(−19.3,18.9)	0.8(−31.4,33.1)	0.0(−1.6,1.6)	−0.2(−2.5,2.1)	−0.2(−2.7,2.4)
9–12 months	3	540	5.2	0.0(−18.0,18.0)	0.6(−23.4,24.5)	0.0(−1.5,1.5)	−0.2(−2.4,2.0)	−0.2(−2.6,2.3)
Baseline–6 months	6	505	5.2	1.1(−21.5,23.6)	2.2(−27.0,31.4)	0.1(−1.8,2.0)	−0.2(−2.6,2.2)	−0.2(−2.7,2.4)
3–9 months	6	519	5.2	0.0(−20.3,20.4)	1.0(−26.4,28.4)	0.0(−1.7,1.7)	−0.2(−2.5,2.0)	−0.2(−2.5,2.1)
6–12 months	6	541	5.2	−0.2(−19.2,18.8)	0.8(−31.1,32.8)	0.0(−1.6,1.5)	−0.3(−2.4,1.9)	−0.2(−2.4,1.9)
Baseline–9 months	9	477	5.4	0.3(−20.7,21.3)	1.3(−25.5,28.1)	0.0(−1.7,1.7)	−0.3(−2.7,2.0)	−0.3(−2.6,2.0)
3–12 months	9	507	5.1	0.1(−20.0,20.2)	1.0(−25.1,27.0)	0.0(−1.7,1.7)	−0.3(−2.7,2.0)	−0.3(−2.6,2.0)
Baseline–12 months	12	471	5.3	0.4(−19.6,20.4)	1.3(−24.4,27.1)	0.0(−1.7,1.7)	−0.4(−2.8,2.0)	−0.3(−2.6,1.9)

Data are described as mean (95% limits of agreement) using the method of Bland and Altman unless otherwise specified. The limits of agreement indicate the range of values that are observed between two consecutive visit that can be attributed to the biological variability of the test. Each unit change in FEV_1 z score is equivalent to an absolute change in FEV_1% of 11.6 and change score of 1.45.
Results are from children with controlled asthma apart from those on the fourth row (grey).
FEV_1, forced expiratory volume in 1 s.

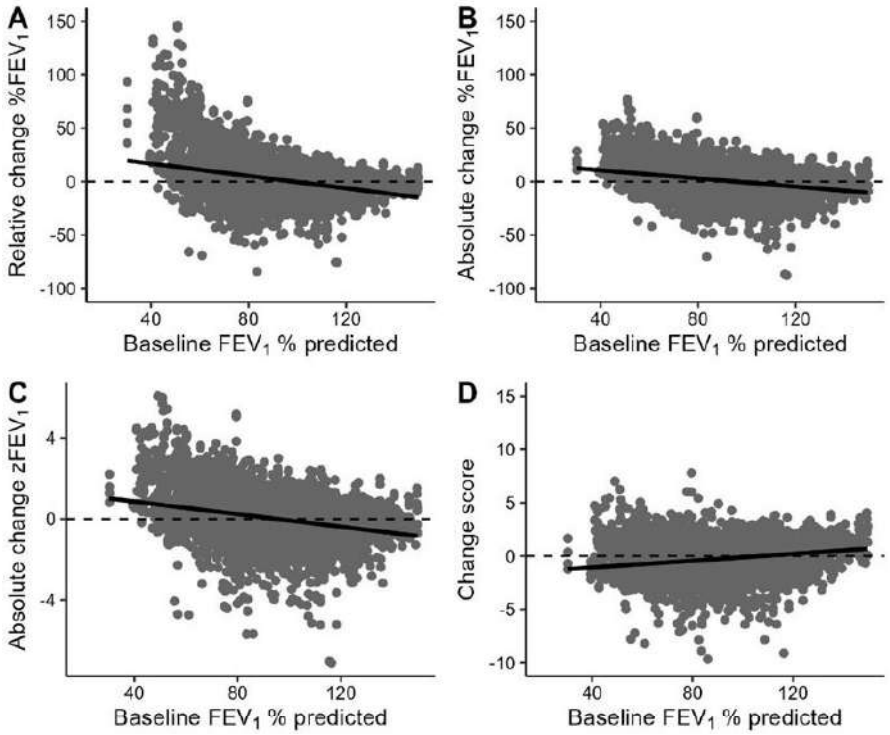

Figure 1 Average change in FEV_1 (variability) between two visits against baseline FEV_1 using (A) relative change in $\%FEV_1$, (B) absolute change in $\%FEV_1$, (C) absolute change in $zFEV_1$, (D) change score derived in health. In all cases, except change score, there is a regression to the mean observed. FEV_1, forced expiratory volume in 1 s.

in the analysis. However, we note that relatively large distribution-based estimates of variability such as the LoAs do not necessarily imply that smaller changes are not clinically relevant.[26] Assuming a ratio of one unit change in FEV_1 z score was equivalent to a change in FEV_1% of 11.6% and a Zc of 1.45, a significant equivalent change in FEV_1 z score (±~1.7) and slightly smaller Zc (±~2.3) were also close to or outside the range which might be expected as within normal variation (±1.96). A benefit of using Zc over the change in FEV_1 z score is that the former is influenced less by age and FEV_1 at first measurement. Collectively, these results support the recommendation asthma treatment should primarily be guided by symptoms,[3–8] and that change in FEV_1 for children with asthma may be best expressed as Zc,[9] and not as a change in $\%FEV_1$ or change in FEV_1 z score. Research is now required to determine what change in Zc is most clinically relevant.

One finding from this study is that it may not be valid to extrapolate results from a bronchodilator response, where an FEV_1% change of 10%[9] or 12%10 is considered clinically relevant, to define a change in FEV_1% over a 3-month interval in children. We demonstrate that an absolute change in FEV_1% of up to 20, or a relative change in FEV_1% of up to 27%, can occur in children whose asthma symptoms are controlled at both measurements. An additional finding of note was that coefficients for Zc in the present population were similar to those for children without asthma, FEV_1 suggesting that the variability between healthy and controlled asthma is similar. In contrast with standardisation of cross-sectional FEV_1 measurements, where there is a large international reference population,[22] there are relatively few studies describing longitudinal change in FEV_1 within populations of children (with or without asthma). Standardisation of longitudinal FEV_1 measurements with a large international reference would allow more meaningful interpretation of longitudinal results.

Our results are mostly consistent with the limited literature describing variation in longitudinal measurements of FEV_1. In a study of 47 adults, Pennock et al[11] report the CV for absolute change in FEV_1 was 13, and that a significant difference would be an absolute change of 20% (ie, CV×1.65). A study of 7885 children with no chronic respiratory condition[23] also reported a CV of 5.2 for FEV1%, identical to the present study. A third study of 232 children aged 7-yeas reported a CV of 4.3% for paired FEV_1 measurements within the same assessment and of 8.3% for paired FEV_1 measurements made over an interval of 1–4 weeks[12]. The higher CV in the study by Strachan[12] compared with the present study may be explained by the former study recruiting younger children who have higher variability in spirometry.

LoAs were reported as the main outcome, and an alternative could have been to report the less conservative variability range, which for FEV_1 was ±8.6% (ie, CV×1.65); this change would notably be smaller that cut-offs currently considered to be clinically relevant.[9 10] We use LoAs since this can be derived for all three outcomes (ie, change in FEV_1%, change in FEV_1 z score and Zc), and therefore, allows direct comparison. An analysis which related change in FEV_1 to clinical outcomes such as loss of asthma control and asthma exacerbation would give useful answers to the question 'what is a clinically significant change in FEV_1'. An additional consideration for future research is that different cut-offs for change may be appropriate for different clinical settings and the pretest probability for example, urgent versus planned assessment.

The conditional change score has been advocated as a method to identify significant change in FEV_1 9 and has been described in healthy children and those with cystic fibrosis.[23] The correlation (r) between repeated FEV_1 measurements and both time and age that were observed in health and stable cystic fibrosis was also observed here in children with controlled asthma (online supplemental table 1), supporting its use as a measure of change in children with asthma. While time did not significantly influence the variability of FEV_1 in this study, the maximum time between measurements was 12 months, whereas the original change score[23] was developed in data of up to 5 years between measurements, for which the influence of time may be more relevant.

Each of the different methods of expressing change in FEV_1 has advantages and disadvantages. Per cent predicted has historically been used to interpret pulmonary function measurements and is familiar to clinicians, patients and families. However, absolute and relative changes in per cent predicted are prone to bias, especially in children with lower lung function; an absolute fall of 10% from a baseline of 100% may be less relevant than a similar fall from a baseline of 70%, and a fall of 100 mL from a baseline of 5 L may

be considered measurement variability but is a 10% fall from a baseline of 1 L. Change in z score avoids the bias of using FEV_1% but exhibits regression to the mean, as we have demonstrated. The conditional change score avoids both bias and regression to the mean, but is not easy to calculate, however manufacturers of pulmonary function devices could imbed this approach into their software and reports.

The study has notable limitations which should be considered when interpreting the data. First, our analysis used more than one pair of FEV_1 measurements from the same individual, and the assumption that paired FEV_1 measurements from the same individual measured over different periods were independent may not be valid. However, using only one paired set of FEV_1 measurements per person would have greatly reduced the amount of data available. Second, we were not able to compare variation between younger and older age groups since the former was less likely to be controlled and thus more likely to be excluded from the analysis; if variation was greater for a younger age group this might be due to a smaller sample size and/or greater inherent variability compared with an older age group. Third, some children may have had an asthma exacerbation between episodes when FEV_1 was measured, and this might have temporarily reduced FEV_1 values; based on a prior analysis of this population[27] we assumed that any change in FEV_1 associated with an exacerbation will have resolved by the time FEV_1 was measured. A fourth limitation of our work is that we did not adjust for multiple testing. Our findings are descriptive and adjustment for multiple testing is not possible, for example, adopting a lower p value. Multiple testing is a particularly relevant consideration for statistical inference, for example, finding false positive results, and our study does not describe significant associations. A further limitation of our analysis is that it has not considered the effect of treatment changing during the period of follow-up. We also assumed that each paired observation was independent for the purposes of these analyses, but it is possible that repeatability may be dependent on an individual (ie, some children may have more variable FEV measures for each of their pairwise comparisons compared with children whose FEV is more stable). Further, the variability pattern within an individual may be an important prognostic indicator.

In summary, our findings demonstrate relatively wide LoAs in paired FEV_1 measurement over time intervals that are relevant to asthma care. The conditional z score for change mitigated bias introduced from baseline FEV_1 and age and may be more appropriate than change in FEV1% or FEV_1z for assessing change in FEV_1 in children with asthma. These data support current guidelines which recommend that asthma treatment should primarily be guided by symptoms and not by change in spirometry.

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ARTIGO ORIGINAL

Epidemiologia da doença pulmonar intersticial infantil em França: a coorte RespiRare

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RESUMO

Introdução As doenças pulmonares intersticiais em crianças (chILD) são doenças pulmonares raras e, na sua maioria, graves. Existem muito poucos dados epidemiológicos disponíveis sobre um conjunto limitado de doentes. O objetivo deste estudo foi avaliar a prevalência e a incidência de chILD em França.

Métodos Realizámos, no âmbito da rede RespiRare, um estudo observacional retrospetivo multicêntrico em doentes com chILD de 2000 a 2022 e uma avaliação prospetiva da incidência de chILD entre fevereiro de 2022 e 2023.

Resultados A chILD foi registada em 790 doentes de 42 centros. Em França, a prevalência estimada para 2022 foi de 44 por milhão de crianças (IC 95% 40,76 a 47,46) e a incidência calculada foi de 4,4 por milhão de crianças (IC 95% 3,44 a 5,56). A idade média do diagnóstico foi de 3 meses, com 16,9% de formas familiares. A biópsia pulmonar e a análise genética foram efetuadas em 23,4% e 76,9%, respetivamente. As etiologias mais frequentes no grupo <2 anos foram a disfunção do metabolismo do surfactante (16,3%) e a hiperplasia das células neuroendócrinas da infância (11,8%). No grupo 2-18 anos, a hemorragia alveolar difusa (12,2%), as doenças do tecido conjuntivo (11,4%), a pneumonite de hipersensibilidade (8,8%) e a sarcoidose (8,8%) foram as mais frequentes. O tratamento incluiu principalmente oxigenoterapia (52%), pulsos de corticosteroides (56%), corticosteroides orais (44%), azitromicina (27,2%), nutrição entérica (26,9%), imunossupressores (20,3%) e hidroxicloroquina (15,9%). A taxa de sobrevivência a 5 anos foi de 57,3% para os doentes diagnosticados antes dos 2 anos e de 86% entre os 2 e os 18 anos.

Conclusão Este estudo epidemiológico sistemático e de grandes dimensões confirma uma incidência e prevalência de chILD mais elevada do que a anteriormente descrita. A fim de desenvolver estudos internacionais, continua a ser necessário envidar esforços para otimizar a recolha de casos e harmonizar as práticas de diagnóstico e de gestão.

Key messages

What is the key question?

▶Childhood interstitial lung diseases (chILD) are rare and mostly severe disorders. Epidemiological studies are incomplete and based on non-systematic reporting systems. The development of clinical trials is needed and requires precise epidemiological data in organised networks

What is the bottom line?

▶The RespiRare network allows to collect chILD data on phenotype and investigations with a high degree of precision. The current study included the highest number of chILD ever reported in a single country and retrospectively and prospectively evaluates the prevalence and incidence of chILD as well as the diagnosis repartition, investigations results, treatment and prognosis.

Why read on?

▶Such study represents a crucial basis for further cohort studies and clinical trials in France and in Europe. It encourages all countries to implement standardised reporting procedures to confirm that chILD is not as rare as initially assumed.

INTRODUCTION

Childhood interstitial lung disease (chILD) is a heterogeneous group of rare lung diseases with common radiological features, namely interstitial signs on chest X-ray or chest CT scan.1 chILD can present throughout life, from birth to adolescence, with wide variations in severity from pauci-symptomatic diseases to end-stage pulmonary fibrosis leading to pulmonary transplantation or death. chILD classifications usually distinguish two age groups: below 2 years and 2–18 years. One of the first classifications was proposed by Deutsch et al and the most commonly used classification is one

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Table 1 Childhood interstitial lung disease reported series

Country/Area	Patients (n)	Period of time (years)	Reported incidence (I) and/or prevalence (P)	Reference
Australia and New Zealand	71	5	NA	Casamento *et al*[8]
	115	10	P: 1.5/million	Saddi *et al*[9]
China	133	5	NA	Tang *et al*[10]
Denmark	884	10	NA	Kornum *et al*[11]
Europe and above	575	NA	NA	Griese *et al*[3]
France	205	4	NA	Nathan *et al*[12]
Germany	56	1	I: 1.32/million/year	Griese et al[13]
Spain	381	2	I: 8.18/million/year P: 46.53/million	Torrent-Vernetta *et al*[14]
UK and Ireland	46	3	P: 3.6/million	Dinwiddie *et al*[15]
	46	1	NA	Laverty *et al*[16]
USA	93	18	NA	Soares *et al*[17]
	256	1	NA	Young *et al*[18]
	683	8	NA	Nevel *et al*[19]
Turkey	416	NA	NA	Nayır-Büyükşahin *et al*[20]

National studies or studies including a large number of centres with a total collection of cases over 40 patients were included in the bibliographic research using the keywords "childhood interstitial lung disease", "interstitial lung disease" and "children", "diffuse parenchymal lung disease" and "children" in PubMed.
NA, non-available data.

of the American Thoracic Society (ATS) classification proposed by Kurland et al in 2013 and the one proposed by Griese et al in Europe in 2018.[2–7]

Based on these classifications, a limited number of patient series of chILD patients have been reported worldwide (table 1) by single centres or large networks.[3 8–20] The reported incidence varied from 1.3 cases/million of children per year in 2009 to 8.2 cases/million of children per year in 2022 and the prevalence from 1.5 cases/million of children in 2017 to 46.5/cases million of children, increasing in recent years, probably because of an improvement of the reporting systems.[9 14 15] In France, a first epidemiological study conducted as part of the Reference Centre for Rare Lung Diseases (RespiRare) in 2012 reported 205 patients over 4 years.[12]

During the past 10 years, the RespiRare network has improved its organisation and case collection. In parallel, a national database for rare diseases has been set up in 2019 (BNDMR, Banque nationale de données maladies rares). Thus, the aim of the present study is to describe the epidemiology of chILD in France in terms

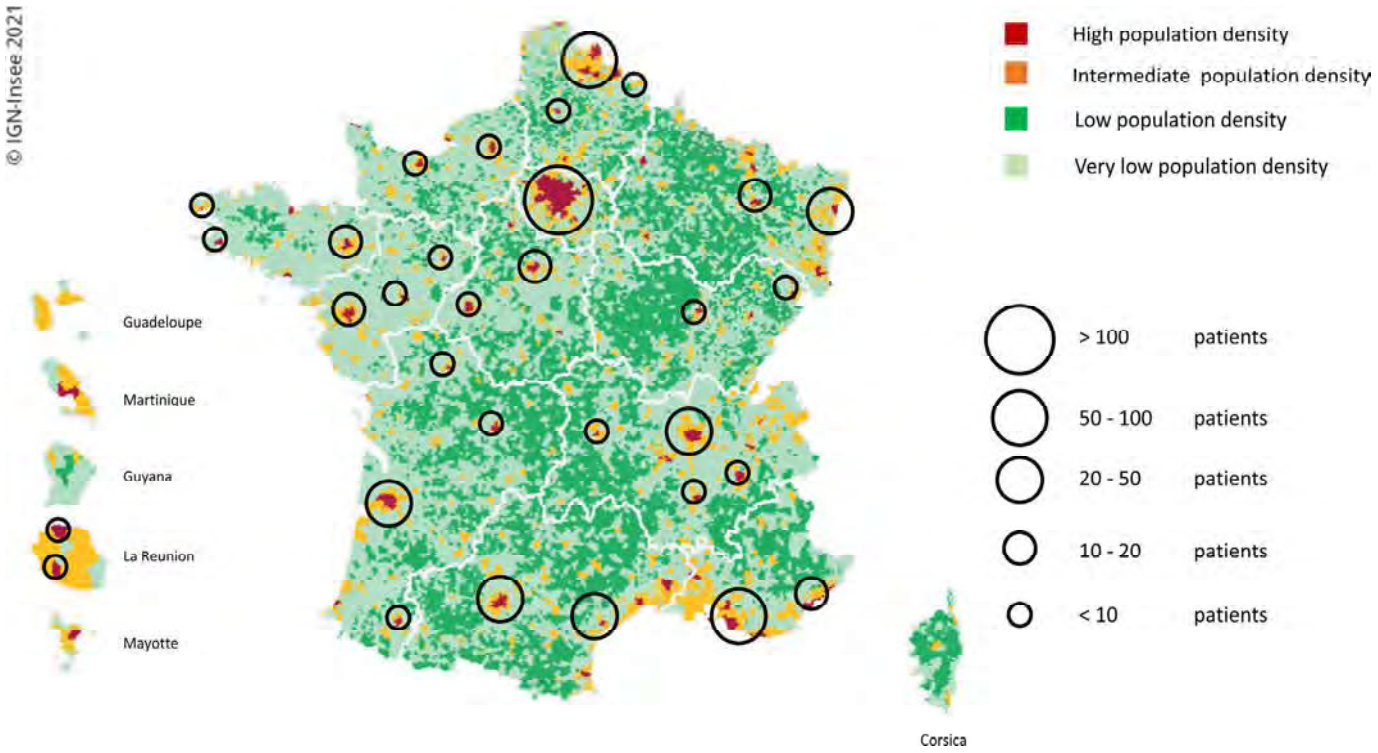

Figure 1 Mapping of the included patients. The RespiRare and collaborating centres who included patients are represented. The larger the circle, the more included patients. The map reflects the population density in France (the highest density of population is represented in red, followed by yellow, light green and dark green). Source: National Institute of Statistics and Economics 2020. Paris area is represented by a single circle (Armand Trousseau hospital n=156, Necker Enfants Malades hospital n=106, Centre Hospitalier Intercommunal de Créteil n=53, Robert Debré hospital n=33, Bichat hospital n=8, Bicètre hospital n=7, Port Royal Hospital n=4, Béclère hospital n=3, Jean Verdier hospital n=1, Saint Denis Hospital n=1), Amiens n=2, Angers n=3, Besançon n=9, Bordeaux n=38, Brest n=4, Caen n=7, Clermont Ferrand n=2, Dijon n=2, Grenoble n=9, La Réunion Island n=15, Lille n=62, Le Mans n=5, Limoges n=2, Lyon n=46, Marseille n=50, Montpellier n=28, Nancy n=10, Nantes n=11, Nice n=20, Nouvelle Calédonie Island n=1, Pau n=1, Polynesia Island n=1, Poitiers n=2, Quimper n=1, Reims n=6, Rennes n=11, Rouen n=4, Saint-Etienne n=1, Strasbourg n=20, Toulouse n=32, Tours n=13.

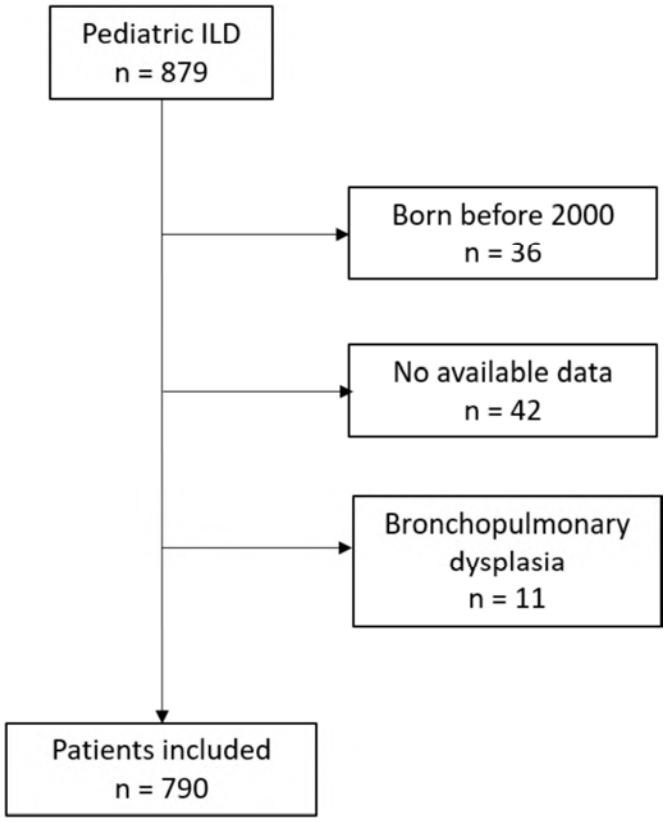

Figure 2 Flow chart. After exclusion of 78 patients who did not meet the inclusion criteria (born before 2000 or without available data) and 11 patients with bronchopulmonary dysplasia, 790 patients were included. ILD, interstitial lung disease.

of prevalence, incidence, respective frequencies of the different aetiologies of ILD, age of onset and mortality.

METHODS

Patients

The study was observational, nationwide, with a retrospective inclusion of the patients between 2000 and February 2022 and a prospective inclusion of the new cases between February 2022 and February 2023. This study was a multicentre study in all the RespiRare centres in France. Patients with ILD born between 2000 and 2022 and aged under 18 years old at diagnosis, were included. The definition of ILD was in line with the ATS Clinical Practice Guideline.[2] The aetiology of the ILD was retrieved from the patient's medical record and was defined by the clinical team in charge of the patient or confirmed by the national chILD multidisciplinary team meeting (MDTm) for those who were alive after the MDTm were implemented in April 2018.[21] Patients with bronchopulmonary dysplasia as well as ILD related to infections secondary to primary immune deficiencies were excluded. However, some diseases that include some dysimmune features, such as auto-inflammatory disorders, remain included in the present study. Additionally, in line with other chILD reports, post-infectious disorders manifesting as ILD such as post-infectious obliterans bronchiolitis with no underlying primary immune deficiencies were not excluded.[2 3 8 9 14 16–19]

Data collection

To ensure exhaustiveness, the patients were identified in a number of ways: through the national online database for rare lung diseases e-Respirare, through patient files discussed at national MDTm for chILD since April 2018. Additionally, direct secured emails were sent to the clinicians of each RespiRare centre to collect unreported cases.[12 21]

In order to prospectively evaluate chILD's incidence, and as recently reported in Spain, the clinicians were contacted again in February 2023, 1 year after the study onset, to collect the data of patients newly diagnosed over 1 year.[14] In parallel, an extraction from the official reporting tool for rare diseases, the BNDMR, was performed.

The following data were collected: age at diagnosis, aetiology of chILD, thoracic CT scans, echocardiography with indirect measurement of pulmonary pressures (a pulmonary hypertension defined as a mean pulmonary arterial pressure >20 mm Hg was suspected by an elevated systolic arterial pressure estimated by a systolic tricuspid regurgitation velocity over 2.5 m/s), genetic analyses, bronchoalveolar lavage (BAL) fluid analysis, histopathological findings, treatments and patient outcome at last follow-up (death, alive or lost to follow-up). Because the study spanned over more than 20 years, genetic analyses were heterogeneous over time. A targeted Sanger sequencing was first proposed when there was a high suspicion of an involved gene, and more largely before 2015; a next generation sequencing (NGS) was first proposed in most cases since then, and an exome sequencing was proposed as a second-intention analysis. The composition of the NGS panels is available as online supplemental table S1. The chILD aetiologies were classified into three main groups: disorders more prevalent in infancy, disorder not specific to infancy and unclassified disorders.[2]

Statistical analyses

The epidemiological information of the overall French paediatric population was extracted from the National Institute for Demographic Studies (Institut National de la Statistique et des Etudes Economiques). The prevalence of chILD in 2022 (number of patients alive with ILD in 2022/number of children alive in France in 2022) and the incidence of chILD between February 2022 and February 2023 (number of new patients with ILD between February 2022 and February 2023/ number of children alive in France in 2022) were calculated. Prevalence and incidence 95% CI were added using the Poisson distribution.

Qualitative/categorical variables are presented as numbers and percentages. Quantitative/continuous variables are presented as median and IQR. χ^2 test was used to compare proportions using Biostat TGV software. For small samples (<5), Fisher's test was used. A p value <0.05 was considered significant. Survival analysis was made using a Kaplan-Meier method and log-rank test on GraphPad Prism software.

RESULTS

All 42 RespiRare centres participated in the study. A total of 879 patients with chILD were reported. Of these, 790 patients were included: 78 patients did not meet the inclusion criteria and 11 patients with bronchopulmonary dysplasia were excluded (figures 1 and 2). In parallel, 473 patients with a chILD diagnosis were retrieved from the BNDMR. This register exists since 2019 and is anonymised, thus, it cannot be ascertained that all of these patients were actually included in the 790 patients of the present RespiRare study. As a comparison, within the 2019–2022 period, 277 patients were included in the RespiRare study.

The following results refer to the number of available data. Demographic information showed the majority of patients were full term (528/642 patients, 82.2%). The median age at diagnosis of ILD was 3 months, IQR (0 years–3.5 years). The sex ratio was 1. A familial ILD was reported in 120/710 (16.9%) of the cases. In February 2022, 665 patients were living with chILD in France. Based on a total number of 15 098 384 alive children in France at the same period, the prevalence of chILD was found to be 44 per millions of children (95% CI 40.76 to 47.46). Between February 2022 and February 2023, 67 new patients with ILD were included, leading to a 2022 chILD computed incidence of 4.4 per millions of children (95% CI 3.44 to 5.56).

chILD aetiologies were classified according to diseases group and the age group (<2 years and 2–18 years) (table 2) and (figure 3). Among all 790 patients, the most frequent diagnoses were inherited surfactant metabolism disorders due to surfactant related genes mutations (n=99, 12.5%), neuroendocrine cell hyperplasia of infancy (NEHI) (n=66, 8.4%), alveolar haemorrhage and pul-

Table 2 Type of ILD according to age

ILD aetiological diagnosis		Total n, (%) (n=790)	<2 years at diagnosis n (%) (n=507, 64.2%)	2–18 years at diagnosis n (%) (n=228, 28.9%)	P value	Unknown age at diagnosis n (%) (n=55)
I Disorders more prevalent in infancy		248 (31.4%)	209 (41.2%)	23 (10.1%)	<0.001	16 (29.1%)
A° Alveolo-capillary dysplasia		18 (2.3%)	16 (3.1%)	0 (0%)	0.004	2 (3.6%)
B° Lung growth abnormalities		19 (2.4%)	13 (2.6%)	6 (2.6%)	0.957	0 (0%)
1) Structural pulmonary changes with chromosomal abnormalities	Trisomy 21	6 (0.8%)	5 (1.0%)	1 (0.4%)		0 (0%)
	Others	11 (1.4%)	7 (1.4%)	4 (1.8%)		0 (0%)
2)Associated with congenital heart disease in children without chromosomal abnormalities		2 (0.3%)	1 (0.2%)	1 (0.4%)		0 (0%)
C° Specific conditions of undefined aetiology: NEHI		66 (8.4%)	60 (11.8%)	2 (0.9%)	<0.001	4 (7.2%)
D° Surfactant metabolism disorders		145 (18.4%)	120 (23.7%)	15 (6.6%)	<0.001	10 18.2%)
1)Surfactant related genes mutations		99 (12.5%)	83 (16.3%)	10 (4.3%)	<0.001	6 (10.9%)
a) SFTPA1, SFTPA2 mutation		5 (0.6%)	0 (0%)	1 (0.4%)		4 (7.2%)
b) SFTPB mutations		10 (1.3%)	10 (10%)	0 (0%)		0 (0%)
c) SFTPC mutation		35 (4.4%)	32 (6.3%)	3 (1.3%)		0 (0%)
d) ABCA3 mutations		32 (4%)	29 (5.7%)	3 (1.3%)		0 (0%)
e) NKX2-1 mutation		17 (2.2%)	12 (2.4%)	3 (1.3%)		2 (3.6%)
2) Pulmonary alveolar proteinosis*		46 (5.8%)	37 (7.3%)	5 (2.2%)	0.006	4 (7.2%)
II° Disorders not specific to infancy		542 (68.6%)	298 (58.8%)	205 (89.9%)	<0.001	39 (70.9%)
A° Disorders of the normal host		122 (15.4%)	51 (10%)	63 (27.6%)	<0.001	8 (14.5%)
1) Infectious and postinfectious process**		46 (5.8%)	34 (6.7%)	11 (4.8%)		1 (1.8%)
2) Alveolar haemorrhage and pulmonary hemosiderosis		49 (6.2%)	17 (3.4%)	28 (12.2%)		4 (7.2%)
3) Hypersensitivity pneumonitis		21 (2.7%)	0 (0%)	20 (8.8%)		1 (1.8%)
4) Eosinophilic pneumonia		6 (0.8%)	0 (0%)	4 (1.8%)		2 (3.6%)
B° Disorders related to systemic disease processes		133 (16.8%)	32 (6.3%)	88 (38.6%)	<0.001	13 (23.6%)
1) Immune-related disorders		23 (2.9%)	9 (1.8%)	11 (4.9%)		3 (5.4%)
2) Connective tissue diseases-associated ILD		30 (3.8%)	1 (0.2%)	26 (11.4%)		3 (5.4%)
3) Vasculitis		23 52.9%)	3 (0.6%)	16 (7%)		4 (7.2%)
4) Interferonopathy		3 (0.4%)	2 (0.4%)	1 (0.4%)		0 (0%)
5) Storage disease and metabolic disease (Gaucher, acid sphingomyelinase deficiency, mucopolysaccharidosis)		22 (2.8%)	14 (2.8%)	7 (3%)		1 (1.8%)
6) Sarcoidosis		23 (2.9%)	2 (0.4%)	20 (8.8%)		1 (1.8%)
7) Pulmonary Langerhans cell histiocytosis		4 (0.5%)	1 (0.2%)	2 (0.9%)		1 (1.9%)
8) Malignant infiltrates		5 (0.6%)	0 (0%)	5 (2.2%)		0 (0%)
C° Disorders post-treatment or transplantation		14 (1.8%)	1 (0.25%)	13 (5.7%)	<0.001	0 (0%)
1) Disorders related to therapeutic intervention		8 (1%)	0 (0%)	8 (3.5%)		0 (0%)
2) Disorders related to transplantation and rejection syndromes		6 (0.8%)	1 (0.2%)	5 (2.2%)		0 (0%)
D° Disorders masquerading as interstitial disease		25 (3.2%)	18 (3.5%)	4 (1.8%)	0.186	3 (5.5%)
1) Primary pulmonary arterial hypertension		6 (0.8%)	6 (1.2%)	0 (0%)		0 (0%)
2) Congestive vasculopathy, including veno-occlusive disease		7 (0.9%)	4 (0.8%)	2 (0.9%)		1 (1.8%)
3) Lymphatic disorders		12 (1.5%)	8 (1.6%)	2 (0.9%)		2 (3.6%)
E° Others causes		10 (1.2%)	4 (0.8%)	6 (2.6%)	0.046	0 (0%)
F° Unclassified		238 (30.1%)	192 (37.9%)	31 (13.6%)	<0.001	15 (27.2%)
1) Idiopathic pulmonary fibrosis		7 (0.9%)	1 (0.2%)	5 (2%)		1 (1.8%)
2) Unknown causes		231 (29.2%)	191 (37.7%)	26 (11.4%)		14 (25.4%)

*Defined by a positive intracellular and extracellular PAS staining on a milky bronchoalveolar lavage. Pulmonary alveolar proteinosis aetiologies includes genetic causes (*MARS, FARSA, FARSB, CSF2RA, CSF2RB*, others), exceptional autoimmune causes in children (anti-GM-CSF antibodies) and unknown causes.
†Online supplemental table S2 provides the results with exclusion of 46 patients with postinfectious obliterans bronchiolitis and exclusion of 85 patients with no available CT scan (not performed or data unavailable). Of 146 patients who did not have an available CT scan, 3 had a postinfectious obliterans bronchiolitis and were already excluded from this table. Of the remaining 143 subjects without CT scan data, 58 were not excluded as ILD was confirmed through alternative approaches: 25 had a lung biopsy ascertaining ILD, 31 had a disorder supporting ILD determined by genetic analysis (ABCA3 (n=9), SFTPB (n=5), SFTPC (n=4), SFTPA1 (n=3), NKX2.1 (n=2)), COPA syndrome (n=1), MARS1 (n=2), Niemann-Pick disease (n=2), chromosomal abnormality (n=3)) and three with diffuse alveolar haemorrhage ascertained on BAL.
BAL, bronchoalveolar lavage; ILD, interstitial lung disease; NEHI, neuroendocrine cell hyperplasia of infancy.

monary hemosiderosis (n=49, 6.2%), infectious and postinfectious processes (n=46, 5.8%), connective tissue disease-associated ILD: dermatomyositis, systemic lupus erythematosus, scleroderma, idiopathic juvenile arthritis, rheumatoid arthritis (n=30, 3.8%), vasculitis (n=23, 2.9%), sarcoidosis (n=23, 2.9%). Finally, the cause of ILD remained unknown in 238/790 patients (30.1%).

In the 507/790 patients (64.2%) diagnosed before 2 years, the most frequent diagnoses were surfactant metabolism disorders in 83 patients (16.3%) and NEHI in 60 patients (11.8%). Among the 228/790 patients (28.9%) diagnosed between 2 and 18 years, the most frequent aetiological diagnoses were alveolar haemorrhage and pulmonary hemosiderosis (n=28, 12.2%), connective tissue diseases-associated ILD (n=26, 11.4%), hypersensitivity pneumonitis (n=20, 8.8%), sarcoidosis (n=20, 8.8%) and vasculitis (n=16, 7%).

A number of investigations were performed during the ILD workup and are reported in table 3: chest CT scan was performed

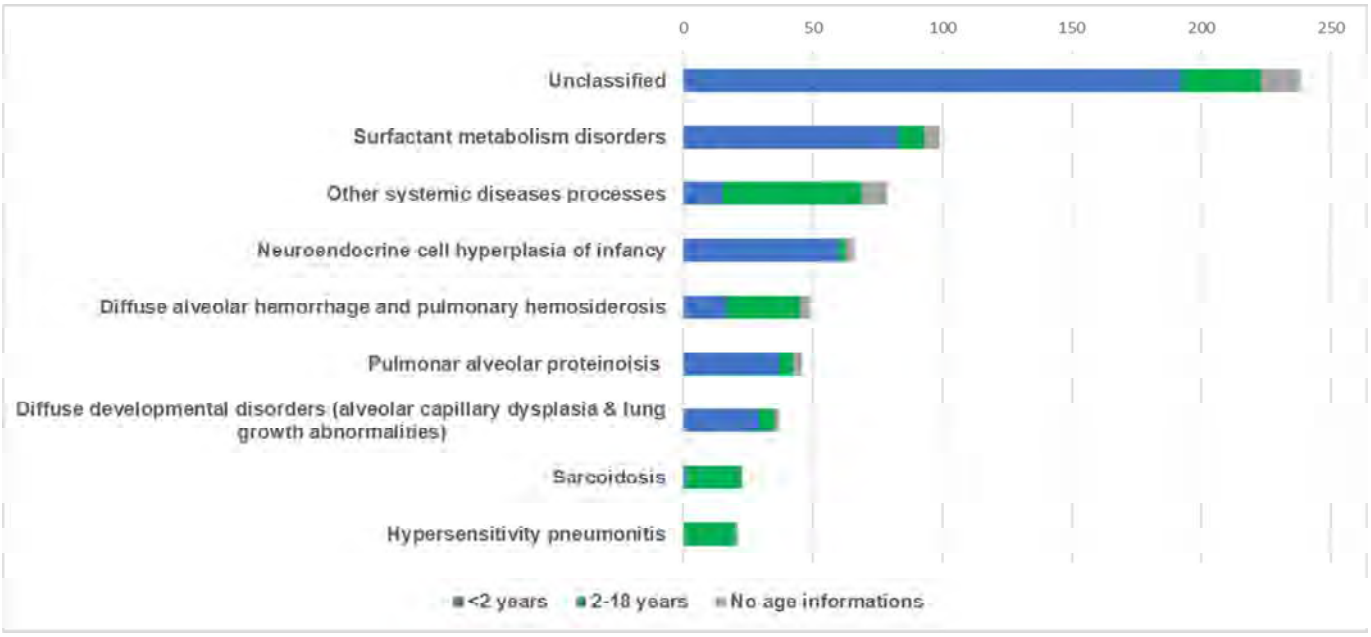

Figure 3 Main aetiological diagnoses of childhood interstitial lung diseases according to age at diagnosis. Number of patients are represented in the different diagnoses according to age at diagnosis (<2 years and 2–18 years).

for almost all the patients (644/711, 90.6%) and showed various patterns, ground glass opacities (GGO) being the most frequent in 391/644 (60.7%) (table 4). The remaining patients were either too unstable to undergo a CT scan (67 patients) or had no available CT scan results (79 patients) despite it was performed. For the patients with no CT scan, the diagnosis of chILD was ascertained by a lung sample analysis in 16 patients and based on the chest radiography only in 51 patients. Genetic analysis was performed in 543/706 patients (76.9%), including targeted Sanger sequencing, NGS panels and exomes, and was positive in 227/543 patients (41.8%), mainly identifying a heterozygous or homozygous surfactant-related gene mutation 120/543 (22.1%), a mutation in a gene involved in pulmonary alveolar proteinosis (PAP) or in auto-inflammatory disorders. After a complete work-up, 161/660 patients (24.4%) underwent a lung biopsy of which 113/161 (70.2%) were before the 2015 European recommendations and 48/161 (29.8%) after 2015. Altogether, 191 patients out of 335 patients alive in 2018–2022 (57%) have been discussed at MDTms since 2018.

As obliterans bronchiolitis is not always considered as ILD, depending on the classifications, online supplemental table S2 provides diagnoses of ILD according to the age, with exclusion of 46 patients with postinfectious obliterans bronchiolitis and 85 patients with no available CT scan (not performed or data unavailable) and no genetic or histology ascertaining the ILD. Among these 85 patients, it is important to notice that available data ascertained a cause of ILD for another 16 patients (2 patients with positive hypersensitivity pneumonitis serology, 1 patient with eosinophilic BAL fluid, 13 patients with systemic diseases). In total, for 69 patients, chILD was ascertained only on chest X-ray and history data.

Most patients received corticosteroids (612/790 patients, 77.5%), administrated as intravenous methylprednisolone pulses and/or oral corticosteroids. Other non-specific treatments included azithromycin, hydroxychloroquine, various immunosuppressive drugs. Interestingly, targeted therapies such as antifibrosing therapies, biotherapies, Jak-inhibitors, methionine and whole lung lavages were also used in specific cases (table 5). Oxygen therapy and enteral nutrition were required in 346/665 patients (52%) and 173/642 (27%) patients (nasogastric tube (50%) or gastrostomy (50%)), respectively. A parenteral nutrition was associated with an enteral nutrition in 17/642 patients (2.7%), and was used alone in 4/643 patients (0.6%). Nine (1.7%) patients aged 2.5–17 years benefited from a lung transplantation (table 6).[22]

Clinical outcome at last follow-up was available in 705/790 patients (89.2%) (table 7). A total of 580/705 patients (82.3%) were alive at last follow-up with a median age of 7 years, IQR (2.6 years–13.7 years). The 5-year survival rate was 57.3% for patients diagnosed before 2 years and 86% for those diagnosed between 2 and 18 years.

Finally, 125/705 patients (17.7%) died at the median age of 6 months, IQR (0.1 years–2.9 years) including two patients after lung transplantation. The Kaplan-Meier curve according to age at diagnosis is provided in figure 4 and showed a reduced survival of the patients who developed chILD before 2 years (log-rank p<0.0001 and log-rank for trend p=0.016).

DISCUSSION

In this largest epidemiological study in chILD in a single country over 23 years, we assessed a prevalence of chILD in 2022 of 44 cases per millions of children and an incidence of chILD between February 2022 and February 2023 of 4.4 cases per millions of children in France. These numbers are much higher than in previous epidemiological studies and similar to the latest Spanish study (table 1).[3 8–19]

Consistently with previous studies, most patients were diagnosed at birth or shortly after birth with a median age at diagnosis of 3 months, IQR (0 year–3.5 years). Below 2 years of age, the most frequent chILD aetiologies were surfactant metabolism disorders (16.3%) and NEHI (11.8%). Between the ages of 2 and 18 years, the most frequent aetiological diagnoses were diffuse alveolar haemorrhage (12.2%), connective tissue diseases-associated ILD (11.4%), hypersensitivity pneumonitis (8.8%), sarcoidosis (8.8%) and vasculitis (7%). In comparison, the 2007 US study based on histological analyses reported fewer surfactant dysfunction disorders (10.9%), a similar number of NEHI and pulmonary glycogenosis (14.5%) and more lung growth abnormalities reflecting impaired alveolarisation (27.9%) in infants. In older patients, the authors found mainly opportunistic infection in immunocompromised host (12.1%) and infections/postinfectious process (10.3%).[6] However, these discrepancies could hardly be compared as this study was based on histological analyses and included immunocompromised host aetiologies. The methodology of the present study was chosen to allow a comparison with the recent Spanish study and found a comparable distribution of the diagnoses, increasing the reliability of both recruitment strategies.

Despite some patients with chILD could have been missed, especially those who presented at birth with a rapid fatal outcome

Table 3 Investigations performed during the diagnostic workout

Investigations	Total number of patients n/n available information (%)	<2 years at diagnosis n/n available information (%)	2–18 years at diagnosis n/n available information (%)	Unknown age at diagnosis n/n available information (%)
CT scan	644/711 (90.6%)	412/644 (64%)	216/644 (33.5%)	16/711 (2.3%)
Bronchoscopy				
Bronchoalveolar lavage	424/685 (61.9%)	257/424 (60.6%)	155/424 (36.6%)	12/424 (2.8%)
Pneumocystis jirovecii research	196/317 (61.8%)	116/196 (59.2%)	76/196 (38.8%)	4/196 (2%)
Pneumocystis jirovecii positive	42/196 (21.4%)	29/42 (61.9%)	12/42 (28.6%)	1/42 (2.4%)
Echocardiography	609/667 (91.3%)	406/609 (66.7%)	189/609 (31%)	14/609 (2.3%)
Suspected pulmonary hypertension	120/609 (19.7%)	85/120 (70.8%)	18/120 (15%)	17/120 (14.2%)
Histology				
Biopsy	161/660 (24.4%)	92/161 (57.1%)	66/161 (41%)	3/161 (1.9%)
Lung biopsy	145/161 (90.1%)			
Other tissue biopsy*	22/161 (13.7%)			
Autopsy	15/660 (2.3%)	14/15 (93.3%)	1/15 (6.7%)	0/15 (0%)
Biopsy and autopsy	2/660 (0.3%)	1/2 (0.5%)	½ (0.5%)	0/2 (0%)
Autoimmunity assessment	518/542 (95.6%)	321/518 (62%)	180/518 (34.7%)	17/518 (3.3%)
At least one positive anti-antibody reaching threshold	131/518 (25.3%)	38/131 (29%)	85/131 (64.9%)	8/131 (6.1%)
Interferon signature	85/637 (13.3%)	35/85 (41.2%)	49/85 (57.7%)	1/85 (1.2%)
Positive	27/75 (36%)	12/27 (44.4%)	15/27 (55.6%)	0/27 (0%)
Genetic analysis	543/706 (76.9%)	417/543 (76.8%)	111/543 (20.4%)	237/543 (43.6%)
Negative	259/543 (47.7%)	203/259 (78.4%)	49/259 (18.9%)	7/259 (2.7%)
Analysis in progress	36/543 (6.6%)	3/36 (8.3%)	3/36 (8.3%)	30/36 (83.3%)
ABCA3	51/543 (9.4%)	45/51 (90.2%)	6/51 (11.8%)	0/51 (0%)
SFTPA1 or SFTPA2	6/543 (1.1%)	2/6 (33.3%)	2/6 (33.3%)	2/6 (33.3%)
SFTPB	10/543 (1.8%)	10/10 (100%)	0/10 (0%)	0/10 (0%)
SFTPC	35/543 (6.4%)	31/35 (88.6%)	4/35 (11.4%)	0/35 (0%)
NKX2.1	18/543 (3.3%)	5/18 (27.8%)	4/18 (22.2%)	9/18 (0%)
MARS†	20/543 (3.7%)	18/20 (90%)	2/20 (10%)	0/20 (0%)
COPA	5/543 (0.9%)	3/5 (60%)	1/5 (20%)	1/5 (0.2%)
FOXF1	10/543 (1.8%)	10/10 (100%)	0/10 (0%)	0/10 (0%)
STING	6/543 (1.1%)	1/6 (16.7%)	5/6 (83.3%)	0/6 (0%)
Other positive genetic diagnosis‡	66/543 (12.1%)	41/66 (62.1%)	23/66 (34.8%)	2/66 (3%)

NA: non-available data.
*Lymph nodes, liver, accessory salivary glands, skin, digestive tract, kidney.
†Most patients with *MARS* variant originate from La Reunion Island and carry the same homozygous variant inherited from a single ancestor according to a founder effect.[35]
‡**Diseases linked with immunodeficiency**: Di George syndrome: 22q11 deletion; Trisomy 21; Ring 20 syndrome; interferonopathy: MORC3 or ACP5, RAG1; lymphocytic granulomatosis: STAT3 GOF; mevalonate kinase deficit: MVK; Mediterranean fever: MEFV; hypocomplementemic urticarial vasculitis: DNASE1L3; RBA; CTLA4; **Developmental disorders**: hereditary pulmonary arterial hypertension: TBX4; veno-occlusive disease: EIF2AK4; lymphangiomatosis: NRAS or RASA1; alpha 1 antitrypsin deficiency: AAT; pulmonary microlithiasis: SLC3A42; **Constitutional disease**: Noonan syndrome: RIT1; Ogden syndrome: NAA10; diastrophic dwarfism: SLC26A2; **Other causes of pulmonary fibrosis**: Hermansky-Puldak syndrome: AP3B1; **Alveolar proteinosis**: FARSA or CSF2RA; **Metabolic and storage diseases**: dibasic protein intolerance: SLC7A7; type 1 mucopolysaccharidosis: IDUA; type A and B Acid sphingomyelinase deficiency: NPC1, NPC2; type 2 and 3 Gaucher disease: GD2, GD3; LCHAD deficiency: HADHA; NFU1 deficiency: NFU1; **Neurological disorder**: syringomyelia phosphodiesterase: SMPD1; Bourneville tuberous sclerosis: TSC2; Charcot-Marie-Tooth disease: YARS; type 1 neurofibromatosis: SPRED1; GJC2 mutation; **Rheumatological disease**: Juvenile idiopathic arthritis: LRBA. To be noted: no patients with Filamin A (FLNA) variant were diagnosed.

such as developmental disorders or surfactant metabolism disorders, it can be supposed that the original use of three different methods of data collection (e-RespiRare, direct contact with clinicians, reports from MDTms), allowed this study to achieve good coverage. This study gathered the information from 42 centres in France enabling data to be collected from a larger number of patients than is reported at European level with non-systematic reporting systems. As France pioneered the collection in rare lung diseases data collection with the launch of the RespiRare network in 2008, a large amount of data was collected for each patient, and a follow-up evaluation was provided.[12] Interestingly, it can be observed in figure 1 that the rate of chILD per centre is consistent with the population density, highlighting a homogeneous ability to diagnose chILD and to collect the data over the national territory. Of note, the national platform for reporting rare diseases (BNDMR) only retrieved 473 chILD since 2019. This system allows to declare cases and to collect a minimum set of data for patients with rare diseases using an ORPHA code. Following informed consent, this register can collect data directly or by systematic transfer from the patient's medical form in a growing number of centres. Although not exhaustive to date, this system will probably be of great benefit in increasing collection of data in rare diseases.

The diagnostic workup showed that genetic testing was used much more frequently than lung biopsy and that it enabled allowing a definitive diagnosis in a greater number of cases (41.8%).23 Mutations in surfactant-related genes were the most commonly reported aetiologies (22.1%), but rarer molecular disorders have also been diagnosed using various NGS panels (67% of the posi-

Table 4 Main lesions among 644 analysed thoracic CT scans

CT scan lesion	Number of patients (percentage)
Ground glass opacities	391 (60.7%)
Nodules or/and micronodules	68 (10.5%)
Cystic formations	66 (10.2%)
Septa thickening	65 (10.1%)
Mediastinal and/or hilar lymphadenopathies	54 (8.4%)
Reticulations	35 (5.4%)
Traction bronchiectasis	33 (5.1%)
Emphysema	34 (5.2%)
'Crazy paving'	13 (2.0%)
Pulmonary fibrosis lesions (honeycombing, etc)	51 (7.9%)

tive results were found through chILD NGS panel, see online supplemental table S1) or whole genome sequencing (table 3). This observation confirms that the indications for lung biopsy are currently decreasing while new biological tests such as the interferon signature, or new molecular techniques are increasing.[24 25] Due to constant improvement of genetic screenings and molecular knowledge of chILD, it seems crucial to store DNA and/or any possible lung tissue material for every patient with chILD or suspicion of chILD without a definitive diagnosis. A molecular analysis should be performed in all cases of chILD, with a whole exome or genome sequencing if first-intention NGS panel is negative. This genetic diagnostic workup has been set-up since 2021 in France where all patients without an identified cause of rare disease through NGS panels can benefit from a whole genome analysis (Plan France Médecine Génomique https://pfmg2025.aviesan.fr/).

This study also highlighted an intriguing finding related to the high rate of positive Pneumocystis jirovecii in chILD patients (42 patients out the 196 researches, 21.4%). Interestingly, the largest group, 13 patients, had an NEHI. At this stage the rational for such observation is not clear but as NEHI pathophysiology remains unclear, a potential role of *P. jirovecii* colonisation needs to be further investigated.

As chILD diagnostic workup remains a long journey, the stepwise approach to an aetiology is increasingly discussed at a national level during the monthly chILD MDTms organised by the RespiFIL network.[21 26] In adults, such MDTms are even considered as the gold standard for ILD diagnosis.[26 27] In children, these meetings has been widely used in the reported population and highlighted the close collaborations that are established between the clinicians, radiologists, geneticists and pathologists involved in chILD.[21 26 28] These meetings are now well organised and easily accessible to all clinicians in France and abroad (www.respiFIL.fr). They are intending to be launched in English language at a European level within the ERS Clinical Research Collaboration (CRC) for chILD (CRC-chILDEU) and the European Reference Networks (ERN)-lung Clinical Patient Management System.

This study confirms that chILD is associated with a high morbidity and disease burden.[29] Half of the patients required oxygen therapy and 27% required enteral nutrition. Most patients received multiple oral or intravenous treatments: corticosteroids were largely used, as well as azithromycin, immunosuppressive drugs and hydroxychloroquine. Their use is mostly based on expert advices while clinical trials are very few owing to high costs and small numbers of included patients.[30–32] To date, very few patients have benefited from targeted treatments, but their number may increase in the coming years with the development of international or even national clinical trials (nintedanib for fibrosing ILD, methionine for MARS1-related PAP, respectively).[33–35] The InPedILD trial is a promising and innovative example that is currently testing nintedanib, which efficacy has been proven in adults, using appropriate dosages in children. Retargeted drugs may also be part of the future chILD treatments of chILD as recently shown with JAK-inhibitors

Table 5 Specific and non-specific therapies used in chILD

Treatment	N (%) among the 790 patients	Indication
Corticosteroids	612 (77.5%)	Non-specific
Methylprednisolone intravenous pulses	343 (43%)	
Oral corticosteroids	269 (34%)	
Long-term azithromycin	182 (23%)	Non-specific
Hydroxychloroquine	105 (13%)	Non-specific
Immunosuppressive drugs (azathioprine, mycophenolate mofetil, ciclosporine, cyclophosphamide, methotrexate, rituximab, sirolimus, tacrolimus, thalidomide)	136 (17%)	Non-specific
Antifibrosing therapies	7 (0.8%)	
Pirfenidone	2 (0.2%)	Undefined fibrosing ILD
Nintedanib	5 (0.6%)	Fibrosing surfactant metabolism disorders
Jak-inhibitors (ruxolitinib, baracitinib, tofacitinib)	22 (2.7%)	SAVI, COPA syndrome, undefined chILD with elevated IFN signature
Biotherapies (tocilizumab, anakinra anti-IL-6; canakinumab anti-IL-1β; inolimomab anti-IL-2; etanercept, infliximab, adalimumab anti-TNF; abatacept anti-TL)		Disorders related to systemic disease processes
Methionine	5 (0.6%)	MARS-related PAP
Whole lung lavages	31 (3.9%)	PAP
Lung transplantation	9 (1.1%)	Cf. table 6

chILD, childhood interstitial lung disease; IFN, interferon; PAP, pulmonary alveolar proteinosis.

Table 6 Patients with chILD who received a lung transplantation

Aetiology of chILD	Age at lung transplantation (years)	Outcome
Obliterans bronchiolitis following BMT	9	Alive at 10 years
	11	Alive at 13 years
Pulmonary fibrosis	11.3	Alive at 16 years
STING-associated vasculopathy of infancy	13.9	Alive at 17 years
	17	Alive at 18 years
Pulmonary alveolar proteinosis	15.2	Alive at 14.5 years
ABCA3 bi-allelic mutations	2.5	Deceased at 2.5 years
Langerhans cell histiocytosis	3.2	Alive at 5 years
	5	Deceased at 5 years

BMT, bone marrow transplantation; chILD, childhood interstitial lung disease.

Table 7 Evolution at the last follow-up

Evolution at the last follow-up	Number of patients/available data (percentage) (IQR)
Alive	580/705 (82.3%)
Median age	7 years (2.56–13.75)
Healed, no treatment	61/513 (11.9%)
Stable without treatment	127/513 (24.8%)
Stable with treatment	284/513 (55.4%)
Worsening	31/513 (6%)
Pulmonary transplantation	7/513 (1.4%)
Deceased	125/705 (17.8%)
Median age	0.5 years (0.08–2.9)
Pulmonary transplantation	2/513 (0.4%)

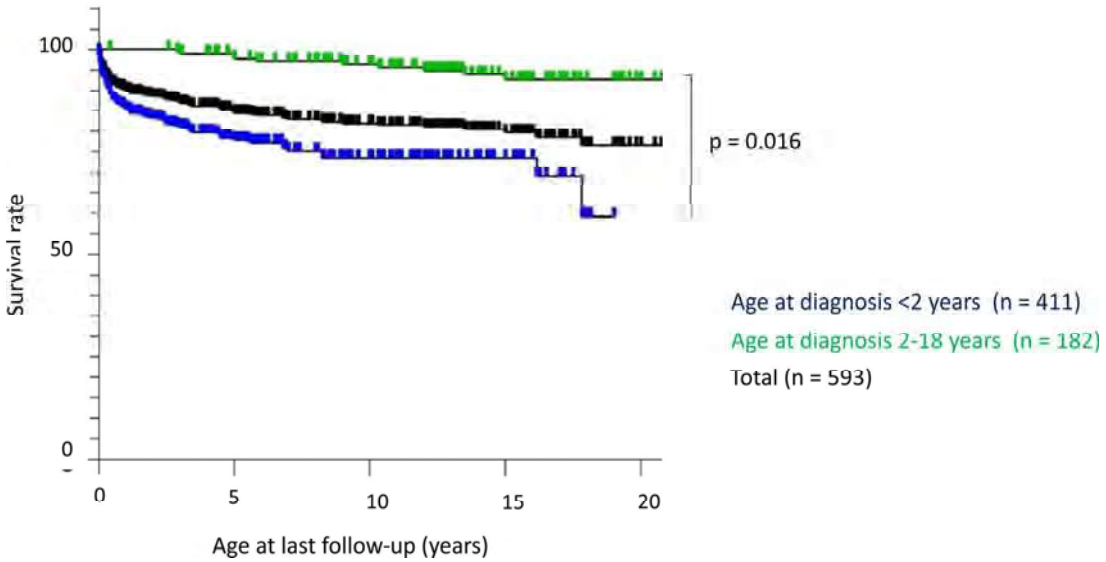

Figure 4 Kaplan-Meier survival curve according to age at diagnosis. Survival rate (%) at the last follow-up (years) according to age at diagnosis (<2 years and 2–18 years). A log-rank test assessed the differences in survival rates.

for auto-inflammatory diseases or CFTR modulators for ABCA3 mutations.[36–38] Even being an optimistic perspective in such rare diseases, large and well-defined patient cohorts are instrumental to the development of such clinical trials. In the meantime, as recently pointed out in chILD, in vitro functional studies of new targeted drugs are probably a more realistic option to be developed.[38]

Therapeutic optimisation and identification of prognosis factors are also required, as prognosis of chILD remains poor with 17.7% of premature death at a median age of 6 months (0.08 years–2.9 years). Very few prospective evaluations of chILD are available. Recently, Cunningham et al provided a 1-year prospective evaluation of 127 young patients (median age 0.9 (IQR 0.3–7.9)) with chILD and found as deleterious prognosis factors an age below 6 months, a SpO2 <94% and developmental/ surfactant disorders (this last group accounting for 20 patients).[39] In line with these results, the present study, the 5-year survival was 57.3% for patients diagnosed before 2 years of age and 86% for patients diagnosed between 2 and 18 years of age, reflecting the poor prognosis of congenital disorders such as diffuse developmental disorders or surfactant metabolism disorders, in particular bi-allelic mutations of SFTPB and ABCA3. Ongoing longitudinal studies will help to confirm these results as, even being large and exhaustive; the median duration of follow-up of this study is limited to 3 years (0.75 years–7 years). The development of transition of care programmes from childhood to adulthood is an interesting perspective for improving the longitudinal quality of the data and assessing patients prognosis over time in terms of survival, development of pulmonary fibrosis, long-term treatment side effects and quality of life.[29 40 41]

The study displays some limitations linked to its retrospective design, which induces a loss of information for some patients and/ or patients lost to follow-up or deceased, especially for neonatal deaths. The expertise of the clinicians of the RespiRare centres reinforces the veracity of their diagnosis. However, the lack of confirmation of the chILD aetiology by the MDTm for a large number of patients still constitute a bias and remains to be improved in the coming years. Another limitation of this study is linked to the ATS classification that was used to compare our results with the 2022 Spanish study.[14] This classification is now 10 years old, and some subcategories could be re-evaluated, in the light of newly identified diseases and with a better harmonisation with adults ILD classifications. Moreover, this classification, like most of chILD classifications, includes disorders such as Trisomy 21 related ILD, or diseases of the distal bronchioles such as postinfectious diseases —obliterans bronchiolitis—or NEHI, whereas some other classifications do not, at least for obliterans bronchiolitis. This choice probably originates from the imaging pattern of obliterans bronchiolitis that may appear as GGO revealing ventilation mosaicism more than ILD. In the present study, online supplemental table S2 excludes obliterans bronchiolitis, without major changes in the remaining chILD frequencies.

Finally, chILD is less rare than previously reported, and remains a group of severe diseases with limited therapeutic options. The next challenge will be to take advantage of well-organised international networks, such as the CRC chILD and the ERN-lung to set-up systematic cohorts and registries—at least for certain chILD aetiologies—to develop and test new therapeutic options and to prepare new classifications including adult ILD diagnoses and new guidelines for the management and transition of care of these patients.

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ARTIGO ORIGINAL

Produtos de tabaco sem ser o cigarro, metilação do gene repressor do receptor aril-hidrocarboneto e desfechos de saúde relacionados ao tabagismo

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RESUMO

Introdução O tabagismo de cigarro leva a alterações na metilação do DNA no gene repressor do receptor aril-hidrocarboneto (AHRR). No entanto, ainda não se sabe se o fumo de cachimbo ou charuto está associado à metilação do AHRR. Avaliamos as associações entre o uso de tabaco não cigarro e a metilação do AHRR e determinamos se a metilação do AHRR estava associada a desfechos de saúde relacionados ao tabagismo.

Métodos Os dados foram agrupados de quatro coortes populacionais que inscreveram participantes entre 1985 e 2002. As exposições ao tabaco foram avaliadas por meio de questionários sobre o tabagismo. A metilação do AHRR cg05575921 foi medida no DNA de leucócitos do sangue periférico. A espirometria e os sintomas respiratórios foram avaliados no momento das medições de metilação e em visitas subsequentes. O status vital foi monitorado usando o National Death Index.

Resultados Entre 8252 adultos (idade média de 56,7±10,3 anos, 58,1% mulheres, 40,6% negros), 4857 (58,9%) participantes usaram cigarros e 634 (7,7%) usaram produtos de tabaco não cigarro. O uso exclusivo de produtos de tabaco não cigarro foi independentemente associado à menor metilação do AHRR (−2,44 unidades, IC 95% −4,42 a −0,45), embora em menor grau do que o uso exclusivo de cigarros (−6,01 unidades, IC 95% −6,01 a −4,10). Entre os participantes que usaram exclusivamente produtos de tabaco não cigarro, a redução da metilação do AHRR foi associada a um maior ônus de sintomas respiratórios (OR 1,60, IC 95% 1,03 a 2,68) e maior mortalidade por todas as causas (log-rank p=0,02).

Conclusão O fumo de cachimbo e charuto foi independentemente associado à menor metilação do AHRR em uma coorte multiétnica de adultos dos EUA. Entre os usuários de produtos de tabaco não cigarro, a menor metilação do AHRR foi associada a desfechos respiratórios adversos e maior mortalidade. A metilação do AHRR pode identificar usuários de tabaco não cigarro com risco aumentado de desfechos adversos de saúde relacionados ao tabagismo.

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

►Cigarette smoking is associated with altered DNA methylation at the aryl-hydrocarbon receptor repressor (AHRR) gene, which in turn is an independent predictor of clinical health outcomes. However, no prior studies have examined the association of pipe or cigar smoking with AHRR methylation, and it remains unknown whether AHRR methylation levels are associated with smoking-related health outcomes among individuals who smoke non-cigarette tobacco products.

WHAT THIS STUDY ADDS

►In the first study to assess how pipe and cigar smoking affect AHRR methylation, the use of non-cigarette tobacco products was independently associated with lower AHRR methylation levels. Among users of non-cigarette tobacco products, lower AHRR methylation was associated with poor respiratory health outcomes and increased all-cause mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

►AHRR methylation appears to be a robust biomarker of pipe and cigar exposure and may help identify users of non-cigarette tobacco products with an increased risk of adverse smoking-related health outcomes. Future research should explore whether clinical applications of AHRR methylation can improve screening and outcomes among users of combustible tobacco products.

INTRODUCTION

Tobacco smoking is the leading cause of preventable disease and death.[1] While the prevalence of cigarette smoking has declined over the past several decades,[2] the landscape of combustible tobacco products has diversified and a wide array of tobacco products has emerged in global markets.[3] In a recent study of tobacco use patterns in adults, pipe and cigar smoking constituted a substantial proportion of tobacco use, and many adults reported regular use of multiple combustible tobacco products.[4] In some parts of the world, the prevalence of pipe and cigar use has increased substantially over the past two decades.[5] Despite the evolution and growing prevalence of non-cigarette tobacco use, few prior studies have examined how pipe and cigar smoking affect human health. Elucidating the health effects of pipe and cigar smoking remains an urgent public health need.

DNA methylation levels in nucleated blood cells may help elucidate the health effects of non-cigarette tobacco use. Cigarette smoking is associated with altered DNA methylation at thousands of CpG sites in nucleated blood cells.[6 7] The CpG site that is most consistently associated with cigarette smoking is the cg05575921 site within the

aryl-hydrocarbon receptor repressor (AHRR) gene.[8] Recent epidemiological studies suggest cg05575921 methylation may identify individuals with increased susceptibility to smoking-related harm, as cigarette-related changes in cg05575921 methylation were associated with an increased risk of lung function impairment, lung cancer and death.[9–11]

While prior research has established the effects of cigarette smoking on AHRR methylation, no prior studies have examined the relation of non-cigarette tobacco use with AHRR methylation. Further, it remains unknown whether AHRR methylation is associated with smoking-related health outcomes among individuals who use non-cigarette tobacco products. We, therefore, aimed to define associations of pipe and cigar smoking with AHRR methylation and to determine whether AHRR methylation is associated with smoking-related health outcomes among pipe and cigar users within a large meta-cohort of US adults.

METHODS

Study population

The National Heart, Lung and Blood Institute (NHLBI) Pooled Cohorts Study[12] harmonised data from four prospective population-based studies that evaluated non-cigarette tobacco use: Atherosclerosis Risk in Communities Study (ARIC)[13]; Coronary Artery Risk Development in Young Adults (CARDIA)[14]; Multi-Ethnic Study of Atherosclerosis (MESA)[15] and Strong Heart Study (SHS).[16] Design features of the cohorts are described in online supplemental table 1. Participants with comprehensive smoking assessments and DNA methylation measurements were included in the analyses.

The NHLBI Pooled Cohorts Study was approved by NHLBI and the institutional review boards of all collaborating institutions. The study complies with the Declaration of Helsinki. All participants provided written informed consent.

Smoking assessments

Comprehensive smoking assessments were performed at the baseline visit in each cohort (online supplemental table 2).[17] Ever use of pipes and cigars was defined based on cohort-specific questionnaires (online supplemental table 3).

AHRR methylation measurements

DNA was extracted from venous blood and treated with bisulfite conversion. DNA methylation profiling was performed in a random subset of participants in ARIC, CARDIA and MESA, and in study participants with available covariate data in SHS. Inclusion criteria for DNA methylation profiling are further described in online supplemental figure 1. Methylation levels were measured using the Illumina Infinium Human Methylation450K BeadChip (Illumina., San Diego, California, USA) in ARIC and MESA and the Methylation EPIC BeadChip (Illumina) in CARDIA and SHS. Each cohort performed quality control, statistical preprocessing, data normalisation and batch correction according to validated protocols.[18 19] DNA methylation measurements produced by the two platforms are proven to be highly correlated, substantiating the application of combined data in population-based research.[20]

Prior research has shown that cg05575921, a CpG site contained in the AHRR gene, is highly associated with cigarette smoking,[6] has promising potential for clinical use[21] and has a methylation set point that is not affected by ethnicity-specific variation.[22] The present study thereby evaluated associations of tobacco use patterns with cg05575921 methylation, which was measured in peripheral blood leucocyte DNA a median of 2.8 years after smoking habits were assessed. AHRR methylation was quantified using methylation M-values and -values. The M-value is the log2 ratio of the amount of methylated probe versus unmethylated probe and was used to derive all reported p values because M-values can be analysed parametrically.[23] The β-value represents per cent methylation (range: 0–1) and was used to derive all reported effect estimates to aid in the biological interpretation of results. Additional details on methylation assays and quality control procedures are reported in online supplemental methods.

Smoking-related health outcomes

Lung function was measured using water-seal, dry-rolling seal or flow-sensing spirometers in accordance with American Thoracic Society guidelines.[12] Spirometry was quality controlled using 2005 criteria.[24] All cohorts measured prebronchodilator forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC). Respiratory symptom questionnaires were used to evaluate the presence of respiratory symptoms including chronic cough, sputum production, wheezing and shortness of breath in ARIC and CARDIA.[25] All-cause mortality was defined as death from any cause. Vital status was ascertained through regular interviews with family members and/or linkage with the National Death Index.[26]

Covariates

Age, sex, race/ethnicity and education were self-reported. Height and weight were measured using standard methods. Medications were self-reported or assessed via medication inventories. Hypertension was defined by blood pressure (≥140/90 mm Hg) or use of antihypertensive medications. Diabetes was self-reported or defined by fasting blood glucose (≥126 mg/dL) or the use of relevant medications. Beyond the exclusion of 50 participants with incomplete smoking assessments, 313 participants (3.7%) were missing data for one or more covariates (online supplemental figure 2).

Statistical analyses

Associations of tobacco use patterns with AHRR methylation were estimated using linear regression. Tobacco use was categorised as never use (reference group), exclusive use of non-cigarette tobacco products, exclusive use of cigarettes or dual use of non-cigarette tobacco products and cigarettes. Three models were used to evaluate associations of tobacco use patterns with AHRR methylation. Model 1 did not adjust for additional parameters. Model 2 adjusted for a priori confounders including age, sex, race/ethnicity, education (high school or less vs some college or more), study cohort and years from smoking assessment to AHRR methylation measurement.[27] Model 3 further adjusted for cigarette smoking status, cigarette pack-years, hypertension, diabetes and body mass index (BMI). Linearity, homoscedasticity and normality were assessed using residual plot analyses. No violations of linearity assumptions were observed. Reported p values are from models evaluating methylation M-values because M-values can be analysed parametrically.[23] Reported effect estimates are from models evaluating methylation -values to aid in the biological interpretation of results.

To determine whether non-cigarette tobacco use further altered AHRR methylation among participants who smoked cigarettes, current and former cigarette smokers were stratified by cigarette smoking pack-years (<5 pack-years, ≥5 and <15 pack-years, ≥15 and <25 pack-years or ≥25 pack-years). Non-cigarette tobacco exposure was categorised as never use (reference group) or ever use. Three different linear regression models were sequentially adjusted for a priori confounders as described above.

To evaluate associations of AHRR methylation with smoking-related health outcomes among participants with distinct tobacco use patterns, participants were stratified by smoking exposures (never use, exclusive non-cigarette tobacco use, exclusive cigarette use or dual non-cigarette tobacco and cigarette use). Within each stratum, associations of AHRR methylation with key clinical outcomes were tested. Linear mixed models were used to test associations of AHRR methylation with lung function. Spirometry assessments collected at the time of DNA methylation assays and in subsequent visits were included in the analyses. Linearity assumptions were confirmed using residual plot analyses. Participants with one spirometry assessment were included in linear mixed models to increase model precision.[11] Unstructured variance–covariance matrices and random intercepts were used to account for within-subject correlation and to optimise model fit.[28] All models were adjusted for a priori confounders including time-varying age, sex, race/ethnicity, education, study cohort, height and years between AHRR methylation assessment and spirometry. Analyses of participants reporting dual use of non-cigarette tobacco products and cigarettes were additionally adjusted for cigarette smoking status and cigarette pack-years. To assess the lon-

Table 1 Baseline characteristics stratified by tobacco use patterns

Cigarette status	Never smoked cigarettes		Smoked cigarettes		
Non-cigarette tobacco status	Never smoked non-cigarette tobacco products	Smoked non-cigarette tobacco products	Never smoked non-cigarette tobacco products	Smoked non-cigarette tobacco products	Total
N	3303	92	4315	542	8252
Age, mean±SD, years	56.2±10.9	59.0±9.2	56.5±9.7	61.4±10.1	56.7±10.3
Male, No. (%)*	920 (27.9)	87 (94.6)	1934 (44.8)	514 (94.8)	3455 (41.9)
Race/ethnicity, No. (%)					
White	973 (29.5)	42 (45.7)	1017 (23.6)	254 (46.9)	2286 (27.7)
Black	1493 (45.2)	40 (43.5)	1614 (37.4)	204 (37.6)	3351 (40.6)
Hispanic/Latino	169 (5.1)	3 (3.2)	183 (4.2)	35 (6.5)	390 (4.7)
American Indian	668 (20.2)	7 (7.6)	1501 (34.8)	49 (9.0)	2225 (27.0)
Education, No. (%)					
Less than high school	364 (11.0)	8 (8.7)	590 (13.7)	69 (12.7)	1031 (12.5)
High school	1250 (37.8)	24 (26.1)	1891 (43.8)	157 (29.0)	3322 (40.2)
Some college	616 (18.7)	9 (9.8)	798 (18.5)	108 (19.9)	1531 (18.6)
College or more	1073 (32.5)	51 (55.4)	1036 (24.0)	208 (38.4)	2368 (28.7)
Non-cigarette tobacco use, No (%)					
Ever pipe use	0 (0.0)	52 (56.5)	0 (0.0)	359 (66.2)	411 (5.0)
Ever cigar use	0 (0.0)	58 (63.0)	0 (0.0)	356 (65.7)	414 (5.0)
Cigarette use, No (%)					
Ever cigarette use	0 (0.0)	0 (0.0)	4315 (100.0)	542 (100.0)	4857 (58.9)
Current cigarette Use	0 (0.0)	0 (0.0)	2013 (46.7)	159 (29.3)	2172 (26.3)
Former cigarette use	0 (0.0)	0 (0.0)	2302 (53.3)	383 (70.7)	2685 (32.6)
Cigarette pack-years, median (IQR)	0 (0.0)	0 (0.0)	13.0 (4.0–29.0)	19.0 (6.6–35.1)	2.0 (0.0–17.6)
Comorbidities					
Hypertension, No. (%)	1663 (50.3)	42 (45.7)	2061 (47.8)	311 (57.4)	4077 (49.4)
Diabetes, No. (%)	769 (23.2)	23 (25.0)	1097 (25.4)	117 (21.6)	2006 (24.3)
BMI, mean±SD, kg/m^2	29.8±6.3	28.4±5.0	29.1±6.0	28.2±4.8	29.2±6.1
Lung function					
FVC, mean±SD, mL	3.26±0.97	4.02±0.80	3.42±0.97	3.98±0.93	3.40±0.98
FEV1, mean±SD, mL	2.53±0.75	3.00±0.60	2.56±0.77	2.90±0.73	2.57±0.76
AHRR β-value, median (IQR)	0.89 (0.85–0.92)	0.85 (0.80–0.89)	0.80 (0.68–0.87)	0.78 (0.67–0.85)	0.85 (0.75–0.90)
Cohort					
ARIC	1576 (47.7)	61 (66.3)	1787 (41.4)	280 (51.7)	3704 (44.9)
CARDIA	577 (17.5)	7 (7.6)	473 (11.0)	33 (6.1)	1090 (13.2)
MESA	482 (14.6)	17 (18.5)	554 (12.8)	180 (33.2)	1233 (14.9)
SHS	668 (20.2)	7 (7.6)	1501 (34.8)	49 (9.0)	2225 (27.0)

*Table shows column percentages.
AHRR, aryl-hydrocarbon receptor repressor; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MESA, Multi-Ethnic Study of Atherosclerosis; SHS, Strong Heart Study.

gitudinal association of AHRR methylation with a rate of change in lung function, the two-way multiplicative interaction term between AHRR methylation level and time from methylation assay to spirometry evaluation was tested. Because non-cigarette tobacco use was more common in male participants, sensitivity analyses were restricted to male participants.

To evaluate associations of AHRR methylation with respiratory symptom burden, participants were stratified by distinct tobacco use patterns. Logistic regression was used to test associations of AHRR methylation with the presence of respiratory symptoms. Models were adjusted for a priori confounders including age, sex, race/ethnicity, education, study cohort, hypertension, diabetes and BMI. Analyses of participants reporting dual use of non-cigarette tobacco products and cigarettes were additionally adjusted for cigarette smoking status and cigarette pack-years.

To evaluate associations of AHRR methylation with all-cause mortality, participants were stratified by distinct tobacco use patterns. Kaplan-Meier curves were used to compare survival for participants in the lowest quartile of AHRR methylation (β value <0.75) to participants in the remaining quartiles of AHRR methylation (β-value ≥0.75). The log-rank test was used to compare survival between the two groups within each stratum. Associations of AHRR methylation with all-cause mortality were also analysed using Cox proportional hazards models. The proportional hazards assumption was confirmed using the scaled Schoenfeld residual test.[29] Models were adjusted for a priori confounders including age, sex, race/ethnicity, education, study cohort, hypertension, diabetes and BMI. Analyses of participants reporting dual use of non-cigarette tobacco products and cigarettes were additionally adjusted for cigarette smoking status and cigarette pack-years. Because non-cigarette tobacco use was more common in male participants, sensitivity analyses were restricted to male participants.

Statistical analyses were performed in R (V.4.0.3) using the lme4 (linear regression models) and survival packages (Cox models). A two-tailed alpha of 0.05 was considered statistically significant for all models.

Table 2 Associations of distinct tobacco use patterns with AHRR methylation

Cigarette status	Non-cigarette tobacco status	N	Model 1*			Model 2†			Model 3‡		
			EE	95% CI	P value	EE	95% CI	P value	EE	95% CI	P value
Never smoked cigarettes	Never smoked non-cigarette tobacco products	3303	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Smoked non-cigarette tobacco products	92	−4.70	−6.87 to −2.52	<0.0001	−1.26	−3.39 to 0.87	0.03§	−2.44	−4.42 to −0.45	0.001
Smoked cigarettes	Never smoked non-cigarette tobacco products	4315	−12.66	−13.61 to −11.71	<0.0001	−9.11	−10.10 to −8.12	<0.0001	−5.05	−6.01 to −4.10	<0.0001
	Smoked non-cigarette tobacco products	542	−11.07	−11.54 to −10.59	<0.0001	−10.59	−11.07 to −10.12	<0.0001	−6.64	−7.14 to −6.14	<0.0001

Table 2 shows associations of distinct tobacco use patterns with AHRR methylation relative to participants who never smoked. Reported p values are from linear regression models evaluating associations of tobacco use patterns with AHRR methylation M-values. Reported effect estimates are from linear regression models evaluating methylation β-values to support biological interpretation. The effect estimates reflect differences in AHRR methylation levels among participants with different tobacco use patterns. Models 1–3 differed by covariate adjustment.
*Model 1: Unadjusted.
†Model 2: Adjusted for age, sex, race/ethnicity, education, study cohort and time between baseline visit and DNA methylation assay.
‡Model 3: Model 2+cigarette smoking status, cigarette smoking pack-years, hypertension, diabetes, BMI.
§In Model 2, exclusive non-cigarette tobacco use was associated with lower methylation M-values (−0.22 units, 95% CI −0.31 to −0.02, p=0.03). Analyses of methylation M-values were used to derive all reported p values because the M-values can be analysed parametrically. The discrepancy between the reported p value and the CI stems from the use of a separate model to derive the effect estimates and confidence intervals. The reported CIs are from models evaluating associations of tobacco use patterns with methylation β-values to aid in the biological interpretation of results. Ultimately, analyses of M-values are used to determine statistical significance.
AHRR, aryl-hydrocarbon receptor repressor; BMI, body mass index; EE, effect estimate.

RESULTS

Baseline characteristics

Among 8252 participants, the mean age was 56.7±10.3 years and 3455 (41.9%) participants were men (table 1). Overall, 3351 (40.6%) participants identified as black, 2286 (27.7%) as white, 2225 (27.0%) as American Indian and 390 (4.7%) as Hispanic/Latino. In total, 634 participants reported use of non-cigarette tobacco products.

AHRR methylation

AHRR methylation was compared among participants reporting distinct tobacco use patterns. Compared with participants who never smoked, exclusive use of non-cigarette tobacco products was associated with lower AHRR β-values in the unadjusted model (table 2). The association remained after adjusting for demographic variables (model 2) and further adjusting for cigarette smoking status, cigarette pack-years and medical comorbidities (model 3). In the fully adjusted model, exclusive use of non-cigarette tobacco products was independently associated with lower AHRR β-values (−2.44 units, 95% CI −4.42 to −0.45) (figure 1).

Compared with participants who never smoked, exclusive use of cigarettes was strongly associated with lower AHRR β-values in all models, including the fully adjusted model (−5.05 units, 95% CI −6.01 to −4.10). Similarly, dual use of non-cigarette tobacco products and cigarettes was strongly associated with lower AHRR β-values in unadjusted and adjusted models. In the fully adjusted model, dual use of non-cigarette tobacco products and cigarettes was strongly associated with lower AHRR β-values (−6.64 units, 95% CI −7.14 to −6.14) compared with participants who never smoked.

To determine whether non-cigarette tobacco use further altered AHRR methylation among participants who smoked cigarettes, participants reporting current or former use of cigarettes were stratified by cigarette smoking pack-years. Among former cigarette smokers, added use of non-cigarette tobacco products was associated with lower AHRR methylation across all strata of smoking pack-years in unadjusted models (online supplemental table 4). However, observed associations were attenuated after adjusting for demographic variables (model 2) and cigarette pack-years and medical comorbidities (model 3). Among participants who reported current cigarettes use, non-cigarette tobacco use was not associated with further changes AHRR methylation (online supplemental table 5).

Respiratory health outcomes

Overall, 4739 (57.4%) participants had one spirometry assessment and 2430 (29.4%) participants had two spirometry assessments measured over a median follow-up of 6.0 years (IQR, 4.1–15.4). Among participants reporting exclusive use of non-cigarette tobacco products, AHRR methylation was not associated with lung function, though the CIs were wide (figure 2). Among participants reporting dual use of non-cigarette tobacco products and cigarettes, a 0.05-unit decrement in AHRR methylation was associated with a 39.05-unit decrement in the FEV_1 (95% CI −59.95 to −18.15) and a 0.75-unit reduction in the FEV_1/FVC (95% CI −1.10 to −0.45) after adjusting for cigarette smoking status and cigarette pack-years

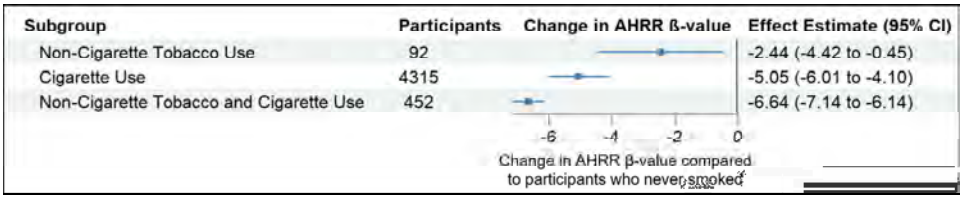

Figure 1 Associations of distinct tobacco use patterns with AHRR methylation. Figure 1 shows associations of different tobacco use patterns with AHRR methylation levels relative to participants who never smoked. Effect estimates are from a single linear regression model evaluating associations of tobacco use patterns with AHRR methylation β-values. Participants who never smoked served as the reference group. The effect estimates reflect differences in AHRR methylation levels among participants with different tobacco use patterns. The fully adjusted regression model was adjusted for age, sex, race/ethnicity, education, study cohort, time between baseline visit and DNA methylation assay, cigarette smoking status, cigarette smoking pack-years, hypertension, diabetes and BMI. HRR, aryl-hydrocarbon receptor repressor; BMI, body mass index.

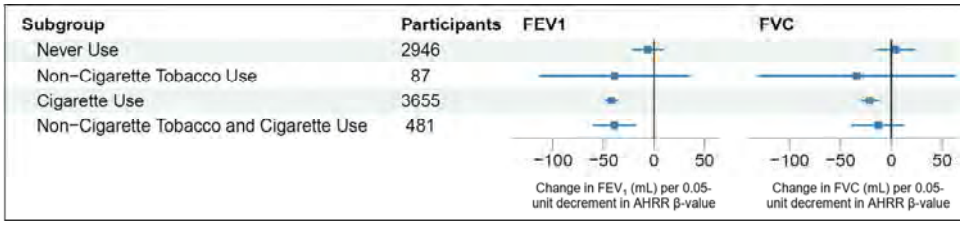

Figure 2 Associations of AHRR methylation with prospective spirometry stratified by tobacco use patterns. Participants were stratified by tobacco use patterns and linear mixed models evaluated associations of AHRR methylation with spirometry. Each row represents a separate regression model. Reported effect estimates are from models evaluating associations of AHRR β-values with lung function to support biological interpretation. The effect estimates reflect differences in lung function per 0.05 decrement in AHRR β-value. All models were adjusted for age, sex, race/ethnicity, education, study cohort, height and time between DNA methylation assay and spirometry. The model analysing lung function among participants reporting dual non-cigarette tobacco use and cigarette use was additionally adjusted for cigarette smoking status and cigarette smoking pack-years. AHRR, aryl-hydrocarbon receptor repressor; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

(online supplemental table 6). AHRR methylation was not associated with accelerated lung function decline, though only 169 dual users had a follow-up spirometry assessment (online supplemental table 7).

Among participants reporting exclusive use of cigarettes, a 0.05-unit decrement in AHRR methylation was associated with a 41.92 mL reduction in FEV_1 (95% CI −48.60 to −35.20), a 21.15 mL reduction in FVC (95% CI −28.95 to −13.40) and a 0.81-unit reduction in FEV_1/FVC (95% CI −0.92 to −0.70). Lower AHRR methylation was also associated with accelerated annual FEV_1/FVC decline (change in FEV_1/FVC per year per 0.05-unit decrement in AHRR β-value: −0.04, 95% CI −0.05 to −0.03). In contrast, among never-smokers, a 0.05-unit decrement in AHRR methylation was only marginally associated with a 0.35-unit reduction in FEV_1/FVC (95% CI −0.55 to −0.10) but was not associated with FEV_1 or FVC. Results were similar in analyses that were restricted to male participants with the exception that AHRR methylation was no longer associated with FEV_1/FVC in never-smokers (online supplemental table 8).

Respiratory symptoms including cough, sputum production, wheezing and dyspnoea were assessed in 4543 (55.1%) participants. Among participants who exclusively used non-cigarette tobacco products, lower AHRR methylation was associated with increased respiratory symptoms (OR per 0.05-unit decrement in AHRR methylation: 1.60, 95% CI 1.03 to 2.68) (figure 3). Similarly, among participants reporting exclusive use of cigarettes, lower AHRR methylation was associated with increased respiratory symptoms (OR 1.17, 95% CI 1.13 to 1.22) (online supplemental table 9). Among participants reporting dual use of non-cigarette tobacco products and cigarettes, reduced AHRR methylation remained strongly associated with respiratory symptom burden (OR 1.14, 95% CI 1.02 to 1.28) after adjusting for cigarette smoking status and cigarette pack-years. In contrast, AHRR methylation was not associated with respiratory symptoms among participants who never smoked.

All-cause mortality

Among 8252 participants, there were 2295 deaths (incidence density rate, 20.4 per 1000 person-years) over a median follow-up of 16.4 years (IQR 10.0–25.0). Among participants who exclusively used non-cigarette tobacco products, those in the lowest AHRR methylation quartile (β-value <0.75) had lower survival compared with participants in the remaining methylation quartiles (β-value ≥0.75) (deaths=29, p=0.018) (figure 4). A similar finding was observed among participants who exclusively smoked cigarettes (deaths=1316, p<0.0001) and among participants who used both non-cigarette tobacco products and cigarettes (deaths=189, p=0.025). Reduced AHRR methylation was not associated with lower survival among participants who never smoked (deaths=761, log-rank p=0.73).

Similar findings were observed in adjusted models. Among participants reporting exclusive of non-cigarette tobacco products, there was a trend towards increased mortality risk among participants with lower AHRR methylation (adjusted HR (aHR) per 0.05-unit decrement in AHRR β-value: 1.32, 95% CI 0.97 to 1.83) (online supplemental table 10). Among participants who exclusively used cigarettes, lower AHRR methylation was associated with increased mortality (aHR per 0.05-unit decrement in AHRR β-value: 1.12, 95% CI 1.10 to 1.15). A similar finding was observed among participants reporting dual use of non-cigarette tobacco products and cigarettes (aHR per 0.05-unit decrement in AHRR β-value: 1.09, 95% CI 1.02 to 1.16) after adjusting for cigarette smoking status and cigarette pack-years (online supplemental figure 3). Among participants who never smoked, AHRR methylation was not associated with mortality risk. Results were similar in analyses restricted to male participants (online supplemental table 11).

DISCUSSION

In the first study to evaluate the relationship of non-cigarette tobacco smoking with DNA methylation, the use of non-cigarette tobacco products was independently associated with lower AHRR methylation, suggesting AHRR methylation may be an informative biomarker of non-cigarette tobacco-related harm. Among users of non-cigarette tobacco products, lower AHRR methylation was associated with poor respiratory health outcomes and increased mortality risk. AHRR methylation may be a reliable biomarker of non-cigarette tobacco exposure and may help identify pipe and

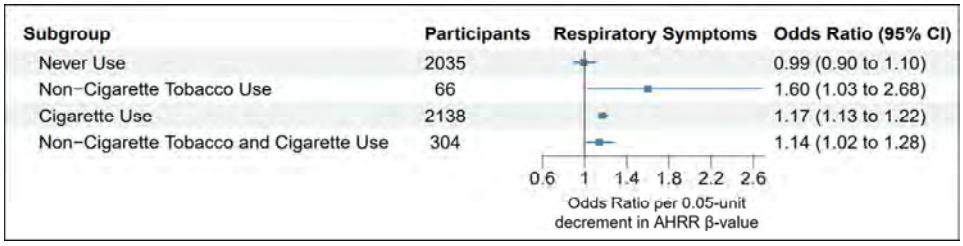

Figure 3 Associations of AHRR methylation with respiratory symptoms stratified by tobacco use patterns. Participants were stratified by tobacco use patterns and logistic regression models evaluated associations of AHRR methylation with presence of respiratory symptoms. Each row represents a separate regression model. Reported effect estimates are from models evaluating associations of AHRR β-values with lung function to support biological interpretation. The ORs reflect odds of having respiratory symptoms per 0.05 decrement in AHRR β-value. All models were adjusted for age, sex, race/ethnicity, education, study cohort, hypertension, diabetes and BMI. The model analysing respiratory symptoms among participants reporting dual non-cigarette tobacco use and cigarette use was additionally adjusted for cigarette smoking status and cigarette smoking pack-years. AHRR, aryl-hydrocarbon receptor repressor; BMI, body mass index.

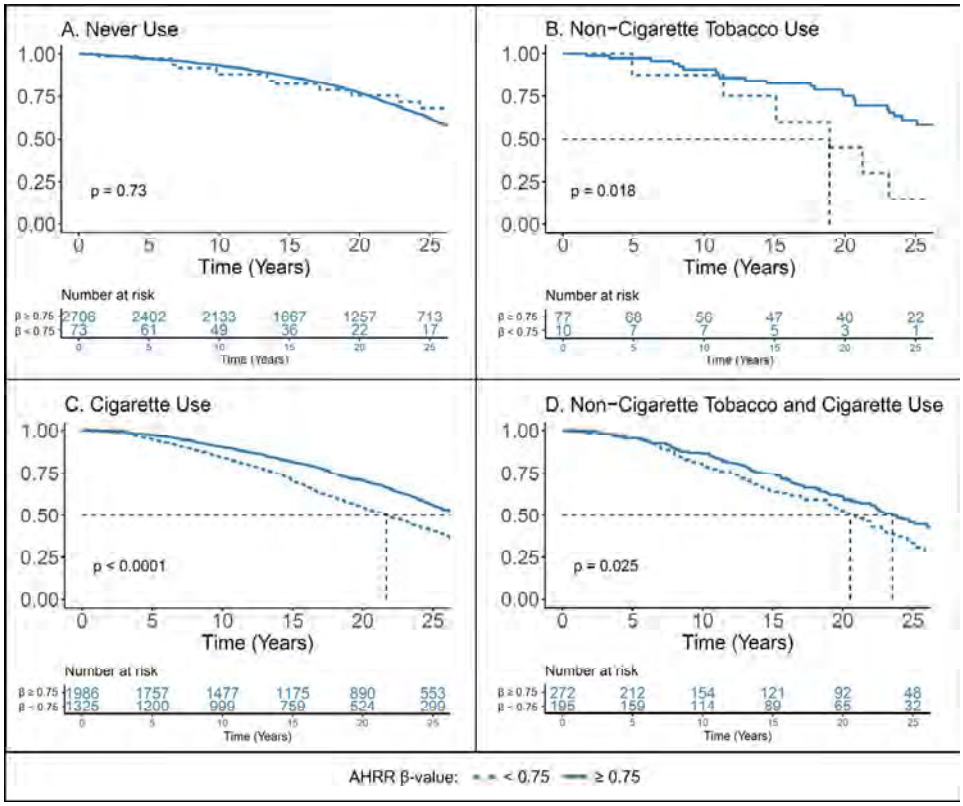

Figure 4 Kaplan-Meier survival estimates for participants with distinct tobacco use patterns stratified by AHRR methylation levels. Participants were stratified by tobacco use patterns. Within each stratum, Kaplan-Meier curves were used to compare survival for participants in the lowest quartile of AHRR methylation (β-value <0.75) to participants in the remaining quartiles of AHRR methylation (β-value ≥0.75). The log-rank test was used to compare survival between the two groups within each stratum. Mortality data were available for 6644 (80.5%) participants. (A) Compares survival estimates for participants who never used tobacco products and AHRR hypomethylation (β-value <0.75) was not associated with mortality risk. (B) Compares survival estimates for participants who exclusively smoked non-cigarette tobacco products and shows AHRR hypomethylation (β-value <0.75) was associated with increased mortality. (C) Compares survival estimates for participants who exclusively smoked cigarettes and shows AHRR hypomethylation (β-value <0.75) was associated with increased mortality. (D) Compares survival estimates for participants who smoked both non-cigarette tobacco products and cigarettes and shows AHRR hypomethylation (β-value <0.75) was associated with increased mortality. AHRR, aryl-hydrocarbon receptor repressor.

cigar users with an increased risk of adverse smoking-related health outcomes.

Use of non-cigarette tobacco products was associated with lower AHRR methylation independently of cigarette smoking. Our results expand on prior studies showing associations of cigarette smoking with AHRR hypomethylation and suggest that altered AHRR methylation is a general effect of combustible

tobacco product consumption.[6] Similar to cigarette smoke, tobacco smoke produced by pipes and cigars may modify DNA methylation through nicotine and carbon monoxide exposure, which downregulates DNA methyltransferase enzymes and alters biological methyl donors.[30] AHRR methylation levels may thereby reflect an individual's true biological 'dose' of tobacco smoke exposure. The variable effects of different tobacco products on AHRR methylation may stem from differences in frequency of use and smoking topography. Daily use is more common among cigarette users than pipe and cigar users,[31] which may explain why cigarette use modified AHRR methylation to a greater extent than non-cigarette tobacco use. Nonetheless, AHRR methylation appeared to be a robust biomarker of non-cigarette tobacco use.

Our findings suggest AHRR methylation may also serve as a viable proxy for smoking-related harm. Toxicants in tobacco smoke interfere with DNA integrity, leading to breaks in DNA strands.[32] DNA breaks recruit DNA methyltransferase enzymes to methylate adjacent CpG sites, which suppresses expression of genetically mutated proteins.[33] However, smoking decreases DNA methyltransferase activity and hinders biological repair mechanisms.[30] AHRR methylation may thereby serve as a proxy for both smoking-related damage and impaired biological repair mechanisms. This is consistent with prior epidemiologic studies showing lower AHRR methylation was associated with accelerated lung function decline.[9,11] The present study expanded on these findings by examining health outcomes among users of non-cigarette tobacco products and showed that reduced AHRR methylation was associated higher burden of respiratory symptoms among users of non-cigarette tobacco products. Lower AHRR methylation was similarly associated with reduced lung function among dual users of non-cigarette tobacco products and cigarettes after adjusting for cigarette smoking status and smoking pack-years. Our findings suggest AHRR methylation is an independent predictor of smoking-related damage that may help identify non-cigarette tobacco users with an increased risk of smoking-related lung injury.

AHRR methylation may also identify individuals with an increased risk of smoking-related mortality. Prior studies showed lower AHRR methylation was associated with increased all-cause mortality in individuals who used cigarettes.[34 35] The present study expanded on these findings by evaluating users of non-cigarette tobacco products and found that reduced AHRR methylation was associated with increased all-cause mortality among participants who used non-cigarette tobacco products. AHRR methylation appeared to capture the biological effects of non-cigarette tobacco use and represented an independent predictor of smoking-related mortality. Ultimately, individuals who smoke non-cigarette tobacco products should be counselled on the adverse health effects associated with consumption of combustible tobacco products and should be closely monitored for smoking-related diseases.[36] Future research should explore whether clinical applications of AHRR methylation can improve screening and outcomes among users of combustible tobacco products.

Strengths of this work include the large, multiethnic population-based sample, use of quality-controlled endpoints and adjustment

for multiple well-characterised confounders. However, the study has several limitations. First, there was a relatively small subset of participants who exclusively used non-cigarette tobacco products, which limited power in stratified analyses. Nonetheless, lower AHRR methylation was consistently associated with adverse smoking-related health outcomes in non-cigarette tobacco users, encouraging further research into the health effects of pipe and cigar use. Second, smoking assessments did not evaluate the intensity or duration of non-cigarette tobacco use. Additional studies are required to determine if non-cigarette tobacco use affects AHRR methylation in a dose-dependent manner. Third, DNA methylation levels were assayed at a median of 2.8 years after tobacco use was assessed. While smoking behaviours between the baseline assessment and DNA methylation assays are unknown, prolonged tobacco exposure is required to generate alterations in DNA methylation and smoking-related changes in DNA methylation persist for a prolonged period even after smoking cessation.[37] Thus, DNA methylation samples obtained several years after smoking assessments may reasonably reflect smoking habits reported at the baseline assessment. Fourth, the use of non-cigarette tobacco products was more common among men, and our results may be most applicable to male populations. However, this is a general limitation of pipe and cigar research as men more frequently use non-cigarette tobacco products.[38] Fifth, non-cigarette tobacco products and use patterns have evolved since these data were collected. The introduction of flavoured non-cigarette tobacco products has been accompanied by more frequent use among younger adults.[39] Future research should evaluate how contemporary products and use patterns affect AHRR methylation and health outcomes. Finally, postbronchodilator spirometry is preferred to measure lung function but was not available in these cohorts. However, prebronchodilator spirometry correlates with postbronchodilator measurements and remains highly predictive of health outcomes in population-based studies.[40]

In conclusion, pipe and cigar smoking were independently associated with lower AHRR methylation in a large population-based sample of adults. Lower AHRR methylation was associated with poor respiratory health outcomes and increased all-cause mortality among participants who used non-cigarette tobacco products. AHRR methylation appears to be an informative biomarker of non-cigarette tobacco exposure and may help identify users of non-cigarette tobacco products with an increased risk of adverse smoking-related health outcomes.

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Contributors CME is the guarantor of the content of the manuscript and takes responsibility for the content of the manuscript, integrity of the data and the accuracy of the data analysis. CME, PB, TRS and ECO contributed to study design. CME performed the data analysis and drafted the manuscript. CME, PB, JEM, SPB, DC, JF, NF, DRJ, LH, RK, YL, LL, PLL, JES, WW, SY, SJL, TRS and ECO revised the manuscript and had final responsibility for the decision to submit for publication.

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Competing interests SPB has had consultancy agreements with Boehringer Ingelheim, Sanofi/Regeneron and IntegrityCE. He has participated in research with Nuvaira Sanofi for which his institution has been remunerated. RK has had consultancy agreements with CVS Caremark, AstraZeneca, GlaxoSmithKline and Boehringer Ingelheim. He has participated in research with AstraZeneca, PneumRx/BTG and Spiration, for which his institution has been remunerated.

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ARTIGO ORIGINAL

Poluição do ar e saúde respiratória em doentes com DPOC: devemos focar em fontes internas ou externas?

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RESUMO

Introdução Embora as associações entre a poluição do ar ambiente e a saúde respiratória em doentes com doença pulmonar obstrutiva crónica (DPOC) sejam bem estudadas, sabe-se pouco sobre a exposição pessoal dos indivíduos à poluição e os efeitos à saúde associados por fonte.

Objetivo Separar a exposição pessoal total medida em poluição gerada internamente e externamente e usar essas métricas aprimoradas em modelos de saúde para estabelecer associações mais confiáveis com exacerbações e sintomas respiratórios.

Métodos Inscrevemos um painel de 76 doentes com DPOC e medimos continuamente sua exposição pessoal a partículas e poluentes gasosos, bem como sua localização, com monitores portáteis por uma média de 134 dias. Recolhemos informações diárias relacionadas à saúde, como sintomas respiratórios, por meio de cartões de diário e do pico de fluxo expiratório (PEF). Modelos de efeitos mistos foram aplicados para quantificar a relação entre a exposição total, gerada internamente e externamente, aos poluentes e a ocorrência de exacerbações, sintomas e PEF.

Resultados A exposição ao dióxido de nitrogénio de fontes internas e externas foi associada a exacerbações e sintomas respiratórios. Observamos um aumento de 33% (22%–45%), 19% (12%–18%) e 12% (5%–20%) nas hipóteses de exacerbação para um aumento no intervalo interquartil (IQR) na exposição total, gerada internamente e externamente, respectivamente. Para o monóxido de carbono, os efeitos na saúde foram principalmente atribuídos à poluição gerada internamente. Embora não tenham sido observadas associações para partículas menores que 2,5 micrómetros ($PM_{2,5}$) com exacerbações da DPOC, as partículas geradas internamente foram associadas a uma diminuição significativa no PEF.

Conclusões A poluição gerada internamente e externamente pode deteriorar a saúde de doentes com DPOC. Os formuladores de políticas, médicos e pacientes com DPOC devem observar a importância de reduzir a exposição igualmente a ambos os tipos de fontes para diminuir o risco de exacerbações.

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

▶Air pollution is known to worsen respiratory health in patients with chronic obstructive pulmonary disease (COPD). Previous studies have supported these associations using ambient air pollution levels and personal exposure data. It is not yet known whether the health impacts differentiate between indoor and outdoor pollution sources.

WHAT THIS STUDY ADDS

▶We studied how indoor-generated and outdoor-generated pollutants affect the respiratory health of patients with COPD independent of each other. Pollution from sources within a patient's home, such as cooking and heating, showed stronger effects on exacerbation than sources from outdoors, with nitrogen dioxide being particularly harmful. Using ambient concentrations as a proxy for exposure, as in the majority of previous studies, can sometimes lead to underestimated health effects.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

▶Understanding the impacts and regulating daily exposure to both indoor and outdoor pollution is vital for patients with COPD, who can take steps to minimise their exposures, and for caregivers who can offer appropriate guidance. Individuals with respiratory conditions should avoid using gas cookers when possible.

INTRODUCTION

Exposure to particulate matter (PM) and gaseous air pollutants is an established risk factor for the worsening respiratory health of chronic obstructive pulmonary disease (COPD) patients.[1] Various metrics have been used for exposure assessment, including ambient concentrations from fixed stations, indoor monitoring at home or personal exposures from portable sensors.[2–4] However, these metrics are influenced to varying degrees by both indoor (eg, cooking) and outdoor (eg, traffic) sources of pollution. For example, the same molecule, indoor-generated nitrogen dioxide (NO_2) is coemitted with a different mixture of chemicals than outdoor-generated NO_2 with potentially different health impacts. This distinction is particularly important for PM, as the chemical composition (and therefore the relative toxicity) depends strongly on the source.

These differences cannot be captured directly with air quality monitors and consequently introduce two main barriers to effective COPD management concerning environmental exposures by patients and practitioners. First, despite the distinct physical and chemical characteristics of the indoor and outdoor air, little is known about potential source-related health effects. Second, the methods to mitigate exposure to individual air pollution sources are very different and, in some cases, conflicting.

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Novel analytical methods are needed to disaggregate the indoor-generated and outdoor-generated components of exposure. Few previous studies have separated indoor-generated (PeIG) and outdoor-generated personal exposures (PeOG),[5 6] and even fewer have assessed the potential health effect differentiation for indoor and outdoor sources.[7 8] Total personal exposure to PM or gases, such as NO_2 or ozone (O_3), as measured by portable monitors has been considered as the 'gold-standard' exposure estimate in epidemiological studies[4] and in assessing measurement error.[9] However, this metric is unable to differentiate the health effects of indoor and outdoor pollution and is not directly comparable with the ambient pollution levels.[10]

Within the 'Characterisation of COPD exacerbations using environmental exposure modelling' (COPE) project, we previously demonstrated that it is feasible to collect personal air pollution measurements for multiple pollutants that have been associated with adverse health effects on patients with COPD,[1] for extended time periods.[11] We found statistically significant associations between total personal exposure to gaseous pollutants and COPD patients' respiratory health but not for PM.[12] However, we did not, at the time, assess whether these associations were driven by indoor-generated or outdoor-generated pollution for gases, or if the lack of association with particles was a consequence of using total personal exposure, masking the effects of specific sources. Identifying and prioritising specific harmful sources of pollution for people's health is crucial for patients, clinicians and policy-makers to improve the quality of life of patients and public health.

In light of these concerns, we present, to our knowledge, the largest respiratory health study to date that separates total personal exposure to $PM_{2.5}$, NO_2, O_3 and carbon monoxide (CO) into indoor-generated and outdoor-generated pollution. We assessed whether the disaggregation leads to refined health estimates compared with widely used exposure metrics in air pollution epidemiology, that is, total personal or ambient exposure estimates. To do that, we associated the acute respiratory health outcomes of 76 patients with COPD with improved exposure metrics extracted from personal and ambient exposure measurements over an average of 134 days each.

METHODS

The COPE study incorporated a large exposure measurement campaign within the Greater London area. Details about the study are available elsewhere.[11 13] Briefly, we followed up 130 ex-smoking patients with COPD from May 2015 to October 2017, and for 76 of whom, we performed the personal exposure source separation; 54 participants who provided data for less than a month or lived primarily outside Greater London were excluded. Baseline information was collected with a general questionnaire on recruitment and training was provided to each participant by a research physiotherapist in the use of a portable peak flow metre (PFM) and diary cards for recording daily respiratory symptoms. No participants were current smokers or held jobs that could be characterised as having significant occupational exposure.

Exposure assessment

A validated personal air quality monitor was used to collect continuous measurements of $PM_{2.5}$, NO_2, CO, O_3 and GPS coordinates at 1 min resolution. The monitors showed good reproducibility and agreement with reference monitor in different microenvironments with mean $R^2>0.8$.[14] Spatial analysis of GPS data was performed to tag each minute of data into 'home', 'other indoor' (other than home) and 'outdoor/transit'.[15] Air pollution concentrations outdoors at each home address were estimated using concurrent measurements from ambient monitoring stations in London, scaled by the London Air Quality Toolkit (LAQT) modelled estimates.[16] Instead of the nearest monitor to each participant's residence, we used a matched monitor approach informed by the LAQT model to better approximate the background residential outdoor air pollution (online supplemental material).

Indoor air quality is affected by outdoor air pollution infiltrating inside, modified by indoor sources, chemical sinks or deposition processes. When participants were at home, the outdoor-generated component of exposure (PeOG) that infiltrated indoors was estimated with an empirical model described previously, which is able to separate out data points unaffected by indoor sources.[17] These separated data points, together with corresponding ambient measurements, were used to calculate an infiltration efficiency for each home, then applied to ambient data to estimated exposure to outdoor sources (PeOG). The indoor-generated component of exposure (PeIG) was then estimated by subtracting PeOG from the total exposure measured with the personal monitors (PeT). When participants were outdoors or in other microenvironments, we assumed no other indoor sources and the measured total personal exposure was regarded as personal exposure from outdoor sources. More details on dataset preparation, matching with ambient data and the partition of indoor-generated and outdoor-generated pollution, can be found in online supplemental material.

Health outcomes

Participants filled in their diary cards every evening, indicating the occurrence of symptoms, medication use and disrupted sleep patterns. A respiratory clinician verified the diary cards and defined an exacerbation as a sustained worsening of symptoms for at least 2 days beyond normal variation. [18] Participants measured their daily peak expiratory flow (PEF) using a PFM at the same time every day.

Statistical analysis

Exposure variables were aggregated to daily means, except for ozone, for which we calculated a daily 8 hours maximum. Mixed-effects logistic regression models were applied with a random intercept per participant for the occurrence of exacerbation and daily symptoms. For PEF, we applied linear random intercept models. Each model was fitted four times, one for each exposure

Table 1 Descriptive statistics for health outcomes and confounders included in the analysis (baseline characteristics and repeated measurements)

Variable	Mean (SD)* or n (%)†
Baseline characteristics (76 participants)	
Sex (females)—n (%)	39 (51.3)
Age—mean (SD)	70.7 (7.8)
Medication use: inhaled corticosteroids (yes)—n (%)	55 (72.4)
Index of Multiple Deprivation Score—mean (SD)	21.1 (12.3)
COPD severity—n (%)	
Mild	12 (15.8)
Moderate	35 (46.1)
Severe	19 (25.0)
Very severe	10 (13.2)
Repeated measurements (10 210 person-days)	
Exacerbation (yes)—n (%)	1363 (13.4)
Breathlessness (yes)—n (%)	1608 (15.8)
Cough (yes)—n (%)	1467 (14.4)
Sleep disturbance (yes)—n (%)	1042 (10.2)
Sputum (yes)—n (%)	710 (7.0)
Wheeze (yes)—n (%)	1146 (11.2)
Peak expiratory flow (L/min)—mean (SD)	236 (105)
Ambient temperature (°C)—mean (SD)	21.1 (2.4)
Time spent outdoors per day (hours)—mean (SD)	1.5 (1.2)
Stayed all day home (yes)—n (%)	5113 (50.1)

*Mean and SD for continuous variables.
†Number of occurrences (n) and percentage across the whole sample/person-days for categorical variables.
COPD, chronic obstructive pulmonary disease.

Table 2 Descriptive statistics for the exposure data included in the analysis (repeated measurements for 76 COPE participants)

Exposure variable		Person-days	Mean (SD)	Min.	25th percentile	Median (IQR)	75th percentile	Max.
NO_2 (ppb)	PeT	10210	7.9 (6.1)	0.3	4.3	6.6 (5.5)	9.7	76.5
	PeIG	10116	4.0 (5.2)	0.0	1.4	2.6 (3.5)	4.9	71.8
	PeOG	10116	4.0 (2.9)	0.2	2.2	3.3 (2.8)	5.0	69.8
	Ambient	9995	16.9 (8.9)	1.0	10.5	15.6 (11.1)	21.5	69.2
$PM_{2.5}$ (µg/m³)	PeT	9636	12.1 (13.8)	0.1	5.3	8.4 (8.7)	14.0	278.2
	PeIG	9375	6.8 (12.2)	0.0	1.7	3.8 (5.9)	7.6	267.9
	PeOG	9369	5.5 (8.2)	0.0	2.1	3.4 (3.8)	6.0	378.4
	Ambient	9609	13.2 (10.7)	2.3	6.7	9.5 (8.7)	15.4	122.0
CO (ppm)	PeT	10209	0.12 (0.10)	0.0	0.1	0.1 (0.08)	0.1	4.1
	PeIG	10174	0.06 (0.06)	0.0	0.0	0.0 (0.06)	0.1	0.9
	PeOG	10174	0.06 (0.06)	0.0	0.0	0.1 (0.03)	0.1	3.5
	Ambient	10137	0.19 (0.13)	0.1	0.1	0.2 (0.09)	0.2	2.0
O_3 (ppb)	PeT	10210	6.4 (4.7)	1.0	3.3	5.2 (4.8)	8.1	57.5
	PeIG	9828	2.8 (3.2)	0.0	1.0	2.0 (2.7)	3.6	54.5
	PeOG	9828	4.4 (3.6)	0.0	2.2	3.5 (3.3)	5.5	51.6
	Ambient	9269	32.8 (13.1)	0.4	25.3	33.8 (15.4)	40.7	95.6

COPD, chronic obstructive pulmonary disease; COPE, characterisation of COPD exacerbations using environmental exposure modelling; PeIG, personal exposure to indoor generated pollution; PeOG, personal exposure to outdoor generated pollution; PeT, total personal exposure.

variable of interest, that is, total, PeIG and PeOG, and ambient concentrations. The associations with total personal exposure have been assessed in our previous publication, but we include them here for comparability with the other exposure metrics. All models were adjusted for a predefined set of potential confounders, including age, sex, COPD severity defined by airflow obstruction using spirometry, medication records and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification,[11] socioeconomic status (SES), medication use on the day, temperature measured from the personal monitor and time trends. For SES, we used the Index of Multiple Deprivation score at postcode level, temperature and time were adjusted using natural spline functions. Potential prolonged effects were investigated by introducing lagged exposures up to day three and the average lag 0–3. Model estimates were reported as per IQR increase in each exposure. The IQR increase provides a plausible exposure increment and assists comparability between epidemiological estimates for exposures of different scale. Exposure–response relationships per 1 unit increase were also quantified (0.1 ppm for CO). STATA V.16 and R V.4.1.2 were used.

RESULTS

Descriptive statistics

We performed the exposure separation on 76 out of 130 participants, with an average/median of 134/150 person-days and a mean age at recruitment of 71 years, of whom 39 (51%) were females, 55 (72%) used inhaled corticosteroids and 29 (38%) had severe or very severe COPD (table 1). For the respiratory outcomes, exacerbation was reported in 13% of the person-days, the rarest symptom was sputum (7%) and the most frequent was breathlessness (16%). The average PEF measurement was 236 L/min. Patients stayed at home all day for 50% of the person-days, and their mean time spent outdoors daily was 1.5 hours. Median time spent in other indoor environments was 0 hours, with a mean (SD) of 0.02 (0.1) hours (results are not shown).

The daily mean (SD) total personal exposures were 7.9 (6.1) ppb for NO_2, 12.1 (13.8) µg/m³ for $PM_{2.5}$, 0.12 (0.10) ppm for CO and 6.4 (4.7) ppb for O_3. The corresponding ambient measurements were considerably higher than total personal exposure for the gaseous pollutants but were similar for $PM_{2.5}$ (table 2). Mean personal exposure from indoor sources was similar to outdoor for NO_2 and CO, higher for $PM_{2.5}$ and lower for O_3. The NO_2 and $PM_{2.5}$ SD were higher for PeIG compared with PeOG.

We observed strong within-person Pearson correlation coefficients (R) between total and indoor-generated personal exposure for all pollutants (R 0.72–0.86), with weaker correlations for outdoor-generated (R 0.51–0.64) for all pollutants except ozone (R 0.73). The correlations between ambient levels of the four pollutants were considerably higher than those between the other exposure metrics (online supplemental material). This indicates that variation in total personal exposure is driven by variation in both indoor and ambient sources. In contrast to what is frequently observed in epidemiological studies using ambient measurements, within-person correlations between pollutants were relatively low. This can be attributed to the high variability of indoor sources operating in different microenvironments compared with outdoors where sources have relatively small variation.

Epidemiological findings

We observed a strong relationship between total personal exposure to NO_2 and COPD exacerbation, with the odds of occurrence increased by 33% (95% CI (22%, 45%)) for an IQR increase in NO_2 (figure 1). This was driven by both indoor (OR 1.19 (1.11, 1.28)) and outdoor (OR 1.12 (1.05, 1.20)) sources. Ambient levels of NO_2 were found to have a smaller association (1.10 (1.01, 1.20)). For CO, we found marginally statistically significant associations for total personal exposure (1.05 (1.01,1.10)), driven by indoor sources (1.06 (1.01, 1.12)). Total personal exposure to ozone had no overall effect on COPD exacerbation (1.00 (0.91, 1.09)), although exposure levels were very low (mean 6.4ppb) in comparison with ambient (32.8ppb), due to its reactivity indoors. Both ambient and indoor-generated ozone had a harmful effect on exacerbations (1.11 (1.01. 1.21) and 1.09 (1.02, 1.16) respectively), while a protective effect of outdoor-generated ozone was observed (0.83 (0.76, 0.91)). This might be attributed to increased ventilation rates that would elevate indoor levels of PeOG O_3. We observed no association with particles for any of the exposure variables under investigation indicating that our previous findings were robust even when using advanced exposure metrics.[12]

We also investigated associations between five individual respiratory symptoms and exposure variables (figure 2). NO_2 was again found to have the highest health effect estimates per IQR increase, with statistically significant estimates observed for all outcomes, except for sleep disturbance. Interestingly, outdoor-generated NO_2 often had higher ORs compared with indoor-generated. Also, PeOG resulted in higher effect estimates compared with using

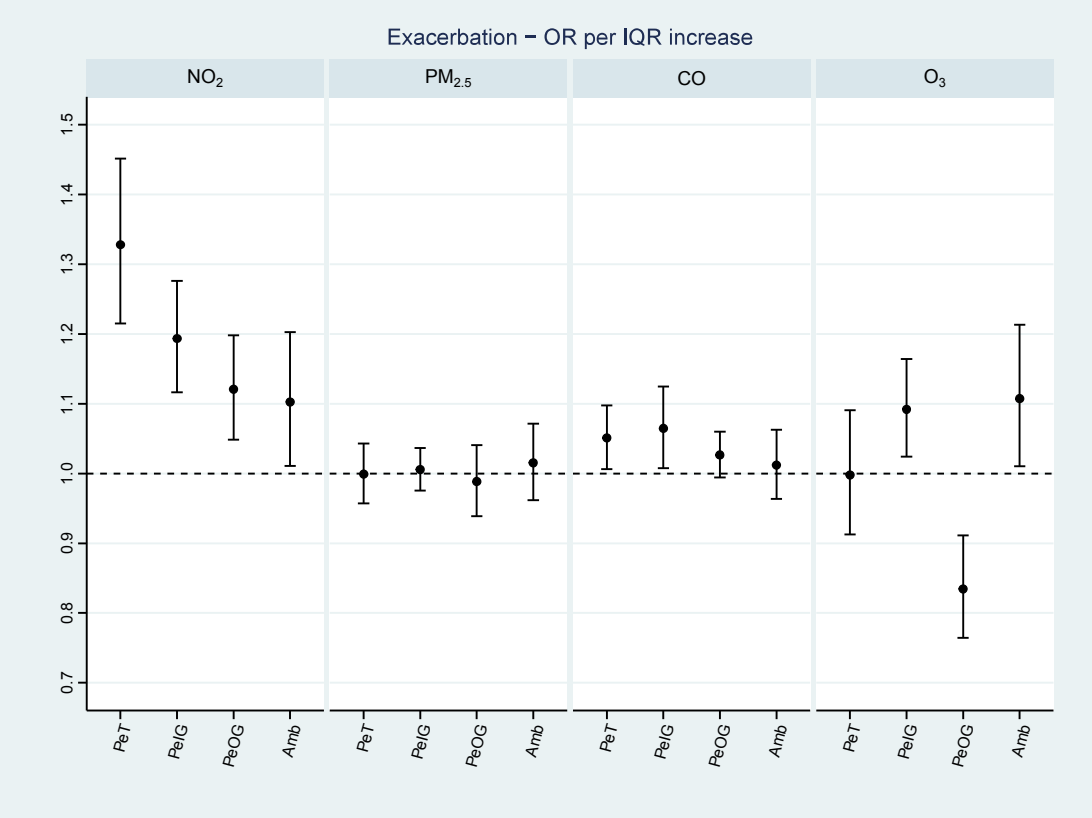

Figure 1 OR with 95% CI for the occurrence of exacerbation associated with an IQR increase on the same day (lag0) for each air pollutant and exposure variable. Random intercept models adjusted for age, sex, COPD severity, Index of Multiple Deprivation Score, inhaled corticosteroids medication use, temperature and time. COPD, chronic obstructive pulmonary disease; NO_2, nitrogen dioxide; PeIG, personal exposure to indoor generated pollution; PeOG, personal exposure to outdoor generated pollution.

ambient concentrations as an exposure proxy for all respiratory symptoms except breathlessness.

CO exposure was statistically significantly associated with all health outcomes except sleep disturbance. In contrast to NO_2, PeIG CO had higher effect estimates than PeOG CO except for wheeze. For O_3, there is no general pattern, as both positive and negative associations were observed but most of them were not statistically significant. Exposure to particles does not seem to have an association with any respiratory symptom.

In general, considerable variation was observed in the estimates of PeIG and PeOG, especially for NO_2 and O_3 (probably because of their higher chemical reactivity) and to a lesser extent for $PM_{2.5}$ and CO. The estimates for total personal exposure seem to additively combine those for indoor-generated and outdoor-generated exposure. We identified cases in which using total personal as the exposure variable expresses the total effects of a pollutant as a chemical, combining the indoor-generated and outdoor-generated personal exposure estimates. However, ozone demonstrated more complex relationships, likely reflecting the strong inverse correlation with NO_2 in ambient air observed in numerous epidemiological studies.[19]

Finally, we explored the relationships between changes in PEF and total personal exposure, PeIG, PeOG and ambient levels of pollution (table 3). Total personal exposure to $PM_{2.5}$ was associated with a decrease in PEF (−0.53 L/min (−0.83, −0.23)), which was mainly driven by PeIG (−0.31 (−0.54, −0.09)). Both effect estimates remained significant for those who spent all day at home. The findings for the gaseous pollutants were not statistically significant, except for a marginal positive association between total NO_2 exposure in all participants (0.58 L/min (0.04, 1.12)) and PeOG NO_2 in those who stayed all day at home (1.74 (0.75, 2.73)).

Sensitivity analysis

The findings remained consistent when we adjusted PeIG for PeOG and vice versa, or for another pollutant from the same source, for example, PeOG $PM_{2.5}$ adjusted for PeOG NO_2 (online supplemental material). Interestingly, the only significant changes were found in the effect estimates of PeIG CO or O_3 when adjusted for PeIG NO_2. For PeIG CO in particular, the adjusted estimate reduced substantially and became not statistically significant. This suggests that the CO estimate may reflect the effects of the pollutant mixture from indoor combustion, rather than pollutant-specific effects, especially if one takes into account the low CO exposures observed in our study. The effect estimates for PeIG O_3 increased when adjusted for PeOG O_3, that is, from 1.09 (1.02, 1.16) to 1.12 (1.05, 1.19).

When we assessed whether there is an effect modification of the air pollution–exacerbation relationship by staying all day at home or not, we found considerably higher regression estimates for those who spent some time outside compared with those who did not for all exposure variables except for ambient ozone (online supplemental material). This was expected for PeOG, but not for PeIG as overall IQRs for the whole population were used as exposure increments. This may imply that people adjust their lifestyle, and, thus, their exposures when they experience an exacerbation or other respiratory symptoms. However, when we assessed the effects of lagged exposures up to 3 days before the occurrence of exacerbation, we found similar and, in many cases, higher effect estimates compared with the same day exposure (online supplemental material). The lag0-3 estimates were even higher indicating prolonged, cumulative effects mainly for gaseous pollutants but also for indoor-generated particles.

We also estimated the associations between all the exposures and outcomes under investigation per 1 unit exposure increment (0.1 ppm for CO), instead of per IQR increase (online supplemental material). The OR for exacerbation occurrence associated with 1 ppb increase in PeT and PeIG were similar, that is, 1.053 (1.036, 1.070) and 1.052 (1.032, 1.072), respectively and slightly higher than PeOG, that is, 1.041 (1.017, 1.066). However, a fixed exposure increase, such as 1 ppb, for different exposure metrics, may not be directly comparable, as one unit increase in total personal exposure might be similar to a fraction of that for PeIG and PeOG.

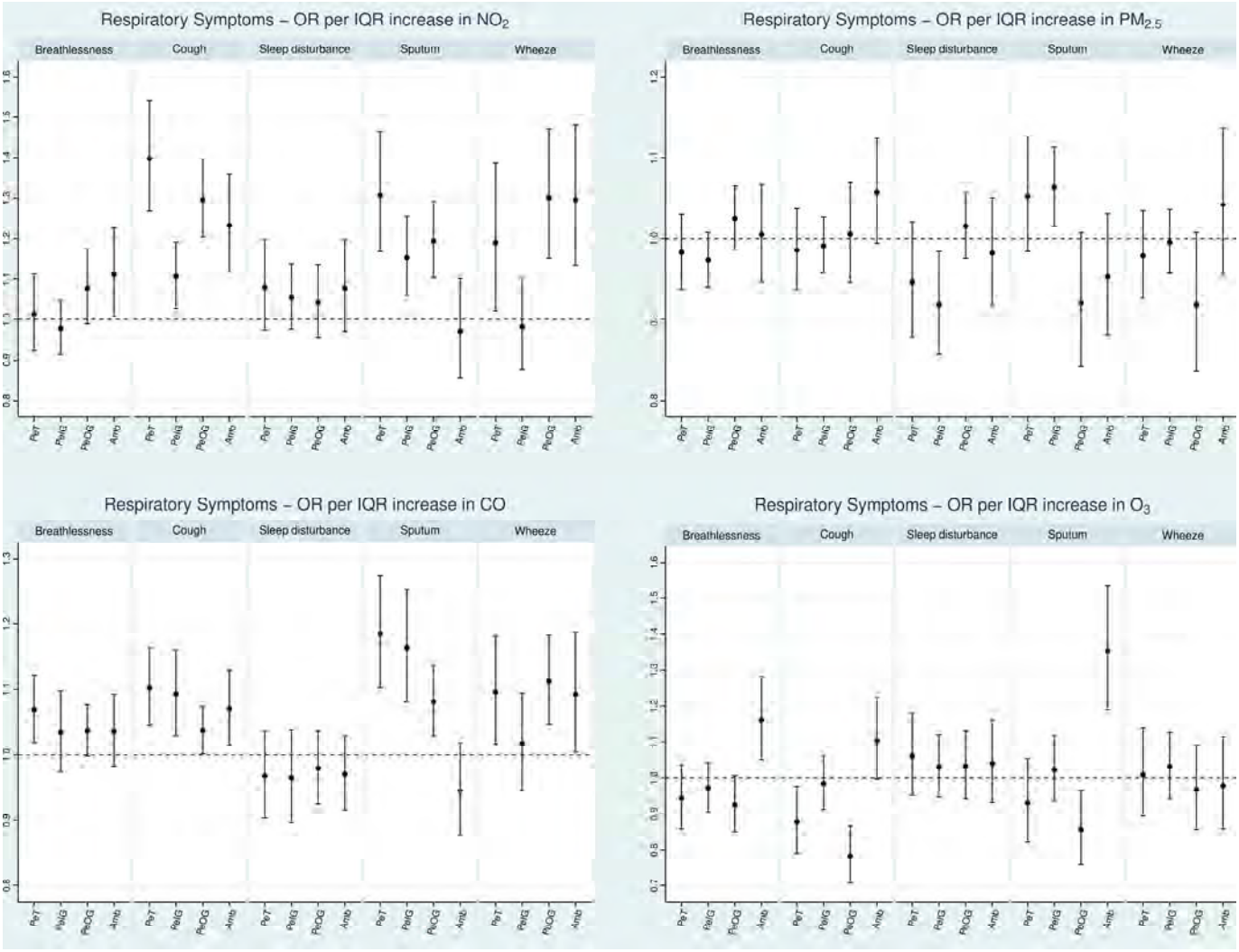

Figure 2 OR with 95% CI for the occurrence of respiratory symptoms associated with an IQR increase on the same day (lag0) for each air pollutant and exposure variable. Random intercept models adjusted for age, sex, COPD severity, Index of Multiple Deprivation rank, inhaled corticosteroids medication use, temperature and time. COPD, chronic obstructive pulmonary disease; NO_2, nitrogen dioxide; PeIG, personal exposure to indoor generated pollution; PeOG, personal exposure to outdoor generated pollution.

DISCUSSION

We investigated associations between personal exposures to multiple pollutants from indoor and outdoor origins with the respiratory health of 76 people with COPD over an extended period (up to 6 months). To our knowledge, this is the first study that assessed the potential differentiation of the acute health effects of personal exposure from different sources on such a large scale. We found higher health effect estimates per IQR increase in the corresponding pollutant for indoor-generated pollution and exacerbation compared with outdoor-generated pollution, although both source types were significant. Using the ambient concentrations which may be an error-prone exposure, resulted in health effect attenuation, especially for NO_2, thus, this pollutant might be more harmful than previously thought. Findings from studies that use this type of exposure metric should be interpreted with caution due to potential measurement error bias towards the null.

Identifying the most harmful sources of pollution in people's personal exposure is important for policy-makers, physicians and patients with COPDs. In most regions, policy-makers currently focus almost entirely on improving ambient pollution levels through specific measures and regulations, but little attention is paid to indoor-generated pollution. However, for patients with COPDs who tend to be older and stay more time indoors, indoor-generated air pollution, either by gas cookers or heaters that are more related to NO_2 exposure, or by smoking and fireplaces that contribute to PM exposure, may be of more importance compared with other population groups. Awareness of the major sources of air pollution allows respiratory physicians to provide personalised environmental medicine to their patients aiming to directly and immediately decrease exacerbations or other symptoms. Not only will this improve COPD patients' health and quality of life, but also it will reduce the burden on the healthcare system with associated health impact reduction and monetary benefits. Raising awareness of the harmful sources of air pollution for patients with COPD can lead to behavioural change that will reduce their exposures and, as a result, improve their respiratory health. While awareness of outdoor sources of air pollution, especially traffic, is improving in many countries, awareness of indoor sources remains low. Our study results show that a focus on indoor combustion sources, such as gas stoves and heaters, and the potential elimination of these sources would have even greater benefits to patients.

We found that the largest effect estimates were linked to indoor generated NO_2, which also displays a larger variability compared with outdoor generated NO_2 exposure. The dominant source of NO_2 indoors is from gas cooking and, to a lesser extent, heating.[20] This finding aligns with established relationships between respiratory health and the use of gas cookers, especially in asthmatics.[21] There is a move in European countries and some US states to legislate against installing gas into new build homes. While this initiative is based on carbon emission reduction, it would also almost entirely remove indoor generated NO_2 and CO from

Table 3 Average change in peak expiratory flow (PEF) and 95% CI associated with an IQR increase on the same day exposure

Pollutant	Exposure variable	Average change in PEF (L/min) per IQR increase (95% CI)		
		All person-days	All-day at home	Not all-day at home
$PM_{2.5}$	PeT	**−0.53 (−0.83, 0.23)**	**−0.56 (−0.94, 0.17)**	**−0.50 (−0.93, −0.06)**
	PeIG	**−0.31 (−0.54, 0.09)**	**−0.43 (−0.70, 0.15)**	−0.04 (−0.41, 0.32)
	PeOG	−0.16 (−0.39, 0.06)	0.051 (−0.60, 0.71)	−0.22 (−0.46, 0.01)
	Ambient	−0.07 (−0.45, 0.30)	0.15 (−0.39, 0.69)	−0.27 (−0.76, 0.23)
NO_2	PeT	**0.58 (0.04, 1.12)**	0.54 (−0.16, 1.25)	0.57 (−0.08, 1.22)
	PeIG	0.14 (−0.24, 0.53)	0.06 (−0.44, 0.55)	0.37 (−0.13, 0.87)
	PeOG	0.37 (−0.09, 0.83)	**1.74 (0.75, 2.73)**	−0.10 (−0.61, 0.41)
	Ambient	0.20 (−0.41, 0.81)	−0.25 (−1.13, 0.63)	0.46 (−0.30, 1.23)
CO	PeT	−0.05 (−0.40, 0.31)	−0.18 (−0.68, 0.33)	0.06 (−0.41, 0.54)
	PeIG	0.14 (−0.28, 0.56)	0.39 (−0.17, 0.94)	−0.00 (−0.60, 0.60)
	PeOG	0.19 (−0.06, 0.45)	0.43 (−0.21, 1.07)	0.10 (−0.17, 0.38)
	Ambient	−0.20 (−0.55, 0.14)	−0.16 (−0.65, 0.32)	−0.24 (−0.69, 0.20)
O_3	PeT	−0.35 (−0.91, 0.21)	−0.45 (−1.16, 0.26)	−0.30 (−1.02, 0.43)
	PeIG	−0.21 (−0.62, 0.21)	−0.17 (−0.70, 0.36)	−0.16 (−0.75, 0.43)
	PeOG	−0.05 (−0.57, 0.47)	−0.73 (−1.75, 0.29)	−0.04 (−0.60, 0.52)
	Ambient	0.31 (−0.28, 0.90)	0.41 (−0.42, 1.23)	0.24 (−0.53, 1.01)

Results were also presented for those who spent all day at home or not. Random intercept models adjusted for age, sex, COPD severity, Index of Multiple Deprivation rank, inhaled corticosteroids medication use, temperature and time. In bold are the statistically significant estimates.
COPD, chronic obstructive pulmonary disease; PeIG, personal exposure to indoor generated pollution; PeOG, personal exposure to outdoor generated pollution; PeT, total personal exposure.

the home environment, leading to potentially significant health gains among patients with COPD and the general population.

Only a small number of studies have tried to separate outdoor-generated and indoor-generated pollution and quantify the associated health effects of each source. Four studies have been identified, although with small sample sizes. Ebelt et al[7] used time-activity data and sulphate measurements as a tracer of PM infiltration, to estimate ambient and non-ambient exposures to PM for 16 patients with COPD (104 person-days).[7] They assessed respiratory and cardiovascular endpoints and found no associations with total and non-ambient personal exposures. They found some statistically significant associations with PeOG which were generally equal to or larger than those for the ambient concentrations. Koenig et al[22] and Allen et al[23] found in the same sample that outdoor-generated particles are associated with increases in airway inflammation (exhaled nitric oxide).[22 23] A more recent study from Ni et al[8] estimated outdoor-originated personal PM exposure and its association with lung function for 33 patients with COPD (170 person-days).[8] They found no association between PEF and either PeOG or ambient concentrations. However, for other lung function measurements, they found higher effect estimates for an IQR increase in ambient levels compared with PeOG, but this might be due to the large difference in scale between PeOG and ambient levels (IQRs of 45.3 and 111 µg/m^3, respectively). We had similar findings for ozone, which is a pollutant that reacts indoors, and thus, PeOG is low, especially compared with ambient concentrations. However, both studies included only a small number person-days (n=104 and 170) in comparison with our study (n=10 184). Additionally, the chemical composition and potential toxicity of indoor-generated PM between countries might be highly heterogeneous due to the diverse sources operating in distant settings.

Our analysis required extensive processing of large volumes of personal measurement data to separate indoor from outdoor sources. Personal or wearable pollution monitoring sensors may not be as accurate as reference monitors.[14] Therefore, reductions in measurement error achieved by using personal assessments of exposure may have been countered by increases in instrument error, but our personal measurements showed good agreement with standard instrumentation in indoor, outdoor and mobile deployments in the UK.[14 15] We also showed that the error introduced from the instrument uncertainty was larger than the error introduced when using ambient measurements as metrics of exposure.[14] Errors might have been introduced most likely in the case of indoor O_3, which might have been insignificant as levels were very low and close to the limit of detection of the sensors. Moreover, further improvements in source identification, such as the inclusion of indoor environments other than the home through location tagging, will add new insight and relevance of application to population subgroups who do not spend such a large proportion of their time at home. For PM specifically, we could not separate the constituents of PM exposure which would have provided further insight on the differentiation of the effects of combustion-derived and non-combustion- derived particles. Future research could use robust source apportionment techniques in exposure assessment to identify exposures to the most toxic components in the PM mixture and indoor volatile organic compounds (VOCs) which is currently almost completely lacking and could enable efficient environmental policy.

Ambient levels of the pollutants were found to be more correlated with each other, compared with any personal exposure variable (total, indoor-generated and outdoor-generated— online supplemental material). This is extremely important for two-pollutant or multipollutant epidemiological modelling through which one can disentangle the independent effects of the pollutants accounting for potential confounding from the other pollutants. High correlations between the exposures create health effect estimates that are unstable and difficult to interpret. Low correlation between personal exposures was probably the reason for not observing large changes in our two-pollutant models, except for O_3 or CO adjusted for NO_2. For O_3, this was expected due to the interlinked formation of these pollutants and its negative correlation with NO_2, but for CO it may be an indicator of the NO_2 effect and their common indoor combustion sources (such as gas cooking). As the levels of CO were very low in comparison with ambient health guidelines, in this study, CO might be a proxy for other coemitted pollutants.

CONCLUSIONS

Regulating day-to-day exposure to both indoor and outdoor sources of gaseous pollution is important to the respiratory

health of patients with COPD in London. There are actions that patients can take to reduce these exposures as well as legislative interventions. Those caring for patients with COPD should be aware of these actions and provide appropriate advice. Those with respiratory conditions should avoid the use of gas cookers where possible.

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Critérios de encaminhamento consensuais para cuidados paliativos para pessoas com doença pulmonar obstrutiva crónica (DPOC)

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RESUMO

Objetivo Pessoas com doença pulmonar obstrutiva crónica (DPOC) avançada têm necessidades substanciais de cuidados paliativos, mas há incertezas sobre a identificação apropriada dos doentes para encaminhamento a cuidados paliativos. Realizamos um estudo Delphi com especialistas internacionais para identificar os critérios de encaminhamento consensuais para cuidados paliativos especializados ambulatoriais para pessoas com DPOC.

Métodos Médicos das áreas de medicina respiratória, cuidados paliativos e cuidados primários de cinco continentes, com expertise em medicina respiratória e cuidados paliativos, classificaram 81 critérios ao longo de três rodadas Delphi. O consenso foi definido a priori como ≥70% de concordância. Um critério foi considerado "principal" se os especialistas concordassem que atender a esse critério sozinho justificaria o encaminhamento para cuidados paliativos.

Resultados As taxas de resposta dos 57 participantes foram de 86% (49), 84% (48) e 91% (52) nas primeiras, segunda e terceira rodadas, respectivamente. Os participantes alcançaram consenso sobre 17 critérios principais para encaminhamento a cuidados paliativos ambulatoriais especializados, categorizados em: (1) "Uso de serviços de saúde e necessidade de terapias respiratórias avançadas" (seis critérios, por exemplo, necessidade de ventilação não invasiva domiciliar); (2) "Presença de sintomas, necessidades psicossociais e de tomada de decisão" (oito critérios, por exemplo, dispneia crónica severa (7-10 em uma escala de 10 pontos)); e (3) "Estimativa prognóstica e estado de desempenho" (três critérios, por exemplo, expectativa de vida estimada pelo médico de 6 meses ou menos).

Conclusões Especialistas internacionais avaliaram 81 critérios potenciais de encaminhamento, alcançando consenso sobre 17 critérios principais para encaminhamento a cuidados paliativos ambulatoriais especializados para pessoas com DPOC. A avaliação da viabilidade desses critérios na prática é necessária para melhorar a entrega padronizada de cuidados paliativos para pessoas com DPOC.

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

▶ Despite significant need for symptom relief and support, referral to palliative care for people with chronic obstructive pulmonary disease is highly variable, and often late, if at all. Uncertainty about when and who to refer underpins much of this variation.

WHAT THIS STUDY ADDS

▶ Collating existing evidence and through iterative assessments, an international panel of 57 leaders and experts in the field have reached consensus on a series of 17 major criteria which, if present, should prompt referral to specialist outpatient palliative care.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

▶ The development of these consensus criteria represents the first step towards improving the standardisation of clinical care, offering an important foundation towards reducing variation in palliative care access, and hence improving equity for people with chronic obstructive pulmonary disease.

INTRODUCTION

Diagnosed in more than 300 million people worldwide, chronic obstructive pulmonary disease (COPD) is currently the third leading cause of death globally.[1 2] People with COPD suffer from significant illness burden through a range of symptoms including dyspnoea (94% of patients), fatigue (71%), xerostomia (60%), cough (56%), worry (51%), as well as functional impairments, social impacts and reduced quality of life.[3 4] Illness burden extends to informal carers who report significant anxiety, frequent exhaustion and unmet needs for support.[5 6] Core tasks of palliative care include attention to all these needs, through the provision of a holistic approach to symptom relief, psychological, social and spiritual support along with support of the person's caregivers.[7] The benefits of palliative care for people with COPD have been recognised for over 20 years,[8 9] and many guidelines make recommendations regarding the importance of palliative care.[10–12] Despite this endorsement, engagement with specialist palliative care (ie, an interdisciplinary team consisting of healthcare professionals with advanced knowledge of palliative medicine and palliative care) by people with COPD and their carers is limited and, when it does occur, is frequently very late in the illness, meaning the potential benefits of early palliative care are not available.[13–15]

A series of factors have been identified as contributing to the lack of early palliative care service delivery including uncertainty about when referral should be made.[16 17] The development of standardised referral criteria for outpatient specialist based palliative care would address this uncertainty and has the potential to reduce variation in care. In cancer care and advanced heart failure, a set of referral criteria for specialist outpatient palliative care, underpinned by a systematic search of the literature

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and agreed to by international consensus, have been developed.[18,19] These criteria have been incorporated into subsequent work[20 21] including the multi-site implementation of early palliative care into routine practice for people diagnosed with cancer.[22 23]

As part of developing similar referral criteria for specialist palliative care for people with COPD, a systematic review[24] demonstrated the most commonly cited factors to prompt referral were hospital use, indicators of poor respiratory status, the presence of physical and emotional symptoms, functional decline, a need for advanced respiratory therapies, and evidence of disease progression.[24] Given the marked heterogeneity of these factors, there is a need to build international consensus around simple, robust referral criteria to facilitate standardisation of practice. The aim of this study was to define consensus criteria for referral to outpatient specialist palliative care for people with COPD through engagement with international experts in respiratory medicine and palliative care.

METHODS

The Delphi methodology involves an iterative process of structured communication towards building consensus with a defined group of experts in the chosen field.[25]

Participants

A Delphi study steering committee of experts caring for people with COPD from Australia, Japan, Taiwan, USA, UK, Sweden and Chile was established, including key international experts in respiratory medicine (n=7), primary care (n=1) and palliative care (n=7 including one allied health). Of note, two steering committee members were dual trained in respiratory and palliative medicine. This steering committee was assembled based on having active research and/or clinical practice in the areas of respiratory palliative care or referral criteria and international representation. This group oversaw all aspects of the study, providing guidance and perspectives throughout.

A Delphi panel of experts with representation from different international regions was assembled, based on the steering committee's recommendations and supplemented with individuals identified as authors of studies from our systematic literature review on referral criteria to palliative care for people with COPD.[24] Expertise and authority in the field were determined using the below-mentioned eligibility criteria (box 1).

Potential participants were contacted by email outlining the study. Those who were eligible and agreed became the study panel and were sent the surveys for all three rounds.

Process

Our Delphi study consisted of three online survey rounds using the Lime Survey (V.3.0) tool,[26] each open for 4 weeks, and spaced approximately 4 weeks apart (figure 1). Weekly email reminders were sent to non-respondents on up to three occasions. Prior to each survey round, the steering committee reviewed the interim findings, and iteratively edited both the referral criteria and the survey presentation. In all the survey rounds, the panel was asked to consider which criteria they would suggest as prompting referral to specialist outpatient palliative care for people with COPD (figure 1).

Round 1

The first Delphi round, conducted from 14 September 2022 to 14 October 2022 consisted of 81 possible criteria collated from our systematic review[24] and edited according to steering committee feedback. These referral criteria were broadly classified into categories to facilitate readability of the online survey questionnaire. The categories were hospital utilisation (n=13 proposed criteria), respiratory therapies (n=7), symptom distress (n=10), exacerbation (n=4), prognosis (n=6), functional impairment (n=9), comorbidities and complications (n=18) and psychosocial factors (n=14). Where gradation of potential criteria was present within a category, this presented an opportunity for panellists to accurately delineate what 'level' should prompt referral. For example, more than two hospital admissions due to complications of COPD in the last 1 month; 3 months; or 6 months. Participants were invited to nominate additional criteria for consideration in subsequent surveys. All panellists' responses were anonymous.

Box 1 Panellists were eligible for participation if they

- ▶Were clinicians (physicians/advanced practice nurses) in active clinical practice with >5 years of post-qualification clinical experience
- ▶ Practised in respiratory/pulmonary medicine, and/or palliative care, and/or primary care/general practice/family medicine with a special interest in care of people living with COPD.
- ▶ Were able to access outpatient specialist palliative care services/clinics.

AND

- ▶ Fulfilled at least ONE of the following criteria:
  - ▶ Board certification in palliative care, respiratory medicine or primary care.
  - ▶ Published in the field of integration of palliative care and COPD in the last 10 years.

COPD, chronic obstructive pulmonary disease.

In this round panellists were also asked to consider how they would define advanced COPD in relation to Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity categories (V.2021),11 modified Medical Research Council dyspnoea score (mMRC), COPD Assessment Test (CAT) scores and frequency of hospitalisation. They were asked personal demographic information including age group, practice setting and specialty.

The majority of questions in the first Delphi round centred on the extent to which panellists agreed with a series of statements based on a 5-point Likert scale ranging from 'strongly agree' to 'strongly disagree'. For each of the criteria, agreement was defined a priori as ≥70% reporting either 'strongly agree' or 'agree', based on the literature which cites agreement levels ranging from 50% to 97%[27] and, specifically methodology adopted in previous similar Delphi studies developing palliative care referral criteria.[18 19]

Round 2

The second Delphi round was conducted between 3 November 2022 and 29 November 2022. Findings from round 1 were synthesised, with re-presentation of only those criteria reaching more than 50% agreement (reporting either 'strongly agree' or 'agree'). Accordingly, the section relating to complications from COVID-19 was removed, and additional criteria suggested by the panel were added including: gradation of breathlessness, steady trajectory of decline (eg, of functional status, symptoms, lung function, weight) and not responding to usual treatment measures (eg, to pulmonary rehabilitation or first-line symptom management).

In this round, 66 criteria were presented for panellists to consider according to importance. Importance referred to whether panellists considered this criterion might be a major factor for referral, meaning that patients who meet this criterion alone would be appropriate for referral to outpatient specialist palliative care, or a minor factor, meaning patients who meet this criterion in combination with at least one other (ie, two or more minor criteria) would be appropriate for referral to outpatient specialist palliative care; or not a criterion at all. For each listed criterion, the panellists were provided with the percentage agreement reached in round 1.

Round 3

The third and final Delphi round, conducted between 9 January 2023 and 8 February 2023 asked panellists to confirm the major criteria that reached ≥70% consensus in the previous round. A total of 17 major criteria were presented and panellists were asked to rate their level of agreement. Again, the percentage agreement reached in the previous round was presented for each criterion.

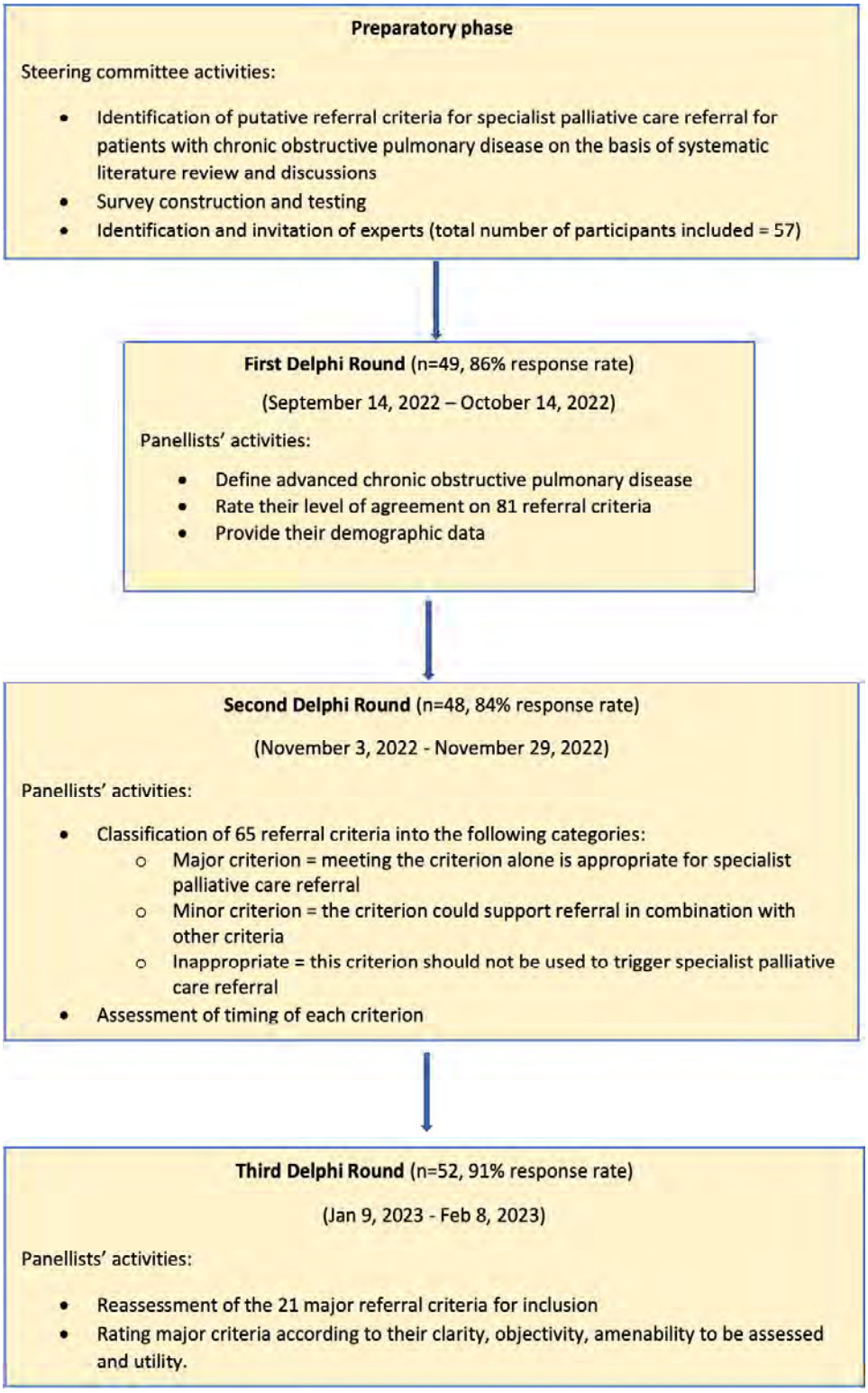

Figure 1 Study flow diagram.

Additional questions were asked about the nature of the criteria—were they considered to be clear, objective and could be readily incorporated into clinical care in the panellists' setting.

Statistical analysis

Data were summarised using descriptive statistics including counts, frequencies and percentages.

RESULTS

Of the 57 international expert panellists identified, 49 (86%), 48 (84%) and 52 (91%) responded in the first, second and third round, respectively. Panellists were from Europe (n=22, 39%), North America (n=14, 25%), Australasia (n=11, 19%), South America (n=5, 9%) and Asia (n=5, 9%). Most were physicians (n=54, 95%), aged over 50 years (n=41, 72%) and almost two-thirds (30/48, 63%) had more than 15 years of clinical practice experience (table 1). Their areas of specialty included respiratory medicine/pulmonology (n=25, 44%), palliative care (n=22, 36%) and primary care (n=5, 9%), while 5 (9%) were dual trained in palliative care and respiratory medicine/pulmonology.

Definition of advanced COPD

In round 1, there was at least 70% agreement across a series of defining characteristics of advanced COPD (table 2).

Table 1 Delphi study expert panellists

Sociodemographics	N (%)
Age group, years	
30–39	5 (9)
40–49	14 (25)
50–59	13 (23)
60–69	22 (39)
>70	3 (5)
Female sex	28 (49%)
Continent	
Asia	5 (9)
Australasia	11 (19)
Europe	22 (39)
North America	14 (25)
South America	5 (9)
Practice setting*	
Tertiary hospital	34
Secondary/community hospital	11
Nursing home or long-term care facility	7
Rehabilitation	4
Home care	17
Outpatient clinic	20
Other	7
Area of Specialty	
Respiratory medicine	25 (44)
Palliative medicine	22 (39)
Respiratory and palliative medicine	5 (9)
Primary care	5 (9)
Discipline	
Physician	54 (95)
Nurse	3 (5)
Years of specialty experience	
6–10	8
11–15	10
16–20	5
>20	24
Expertise*	
Board certified in respiratory medicine, palliative medicine or primary care	54
Publications in the area of specialist palliative care for people with COPD or integration of palliative care and respiratory care in the last 10 years	49
Involvement in national/international guideline on palliative care integration	18

*These categories were not mutually exclusive.
COPD, chronic obstructive pulmonary disease.

Round 1 and round 2 Delphi surveys

In the first Delphi round, the panellists reached consensus (>70% agreement) on 43 of the 81 referral criteria (table 3). Of these 43 criteria, 8 (19%) were psychosocial—decision making based, 7 (16%) related to hospitalisation due to COPD or its complications, 6 (14%) related to comorbidities or complications, 5 (12%) related each to respiratory therapies, symptom distress, prognostic estimates and functional impairment, and 2 (5%) related to exacerbation history.

In the second round, panellists reached consensus on 56 of 65 criteria considered, including 21 major criteria and 34 minor criteria (table 3). Of the 21 major criteria that reached consensus, 5 related to respiratory therapies, 2 to hospitalisations, 6 to prognosis/functional impairment, 3 to psychosocial factors, 4 to symptoms and 1 to comorbidities and complications resulting from COPD.

Table 2 Advanced COPD is defined as any of the following criteria (≥70% agreement)

	% agreement (N=49)
Symptom burden and impact	
GOLD 4 (very severe airflow limitation—FEV_1<30% predicted value)	96 (n=47)
mMRC 3 (breathless after walking a few minutes or 100 yards on the flat)	76 (n=37)
mMRC 4 (too breathless to leave the house/ breathless when dressing/undressing)	96 (n=47)
CAT 21–30 (high impact on life including symptoms/ exacerbations)	88 (n=43)
CAT >30 (very high impact on life including symptoms/ exacerbations)	98 (n=48)
Health service use and need for advanced respiratory therapies	
Repeated hospital admission for COPD or related complications: ≥2 hospitalisations in the past 6 months	96, (n=47)
Repeated hospital admission for COPD or related complications: ≥2 hospitalisations in the past 3 months	98 (n=48)

CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council.

In the third Delphi round, 21 major criteria were re-presented and all reached consensus (table 3). Of note, of the major criteria, four were removed following the third round as they referred to gradation of prognosis or function. For example, referral when physician estimated prognosis as 1 month or 3 months was removed, as agreement had already been reached that referral would occur at an estimated prognosis of 6 months. The final group consisted of 17 major criteria.

Consensus was reached on 34 minor criteria. Four minor criteria were removed as they also referred to a gradation where consensus had already been agreed for referral at an earlier point. Consensus was not reached on eight minor criteria, including: the presence of mild chronic breathlessness, hypercapnia with $PaCO_2$>55 mm Hg, hypoxaemia with PaO_2<60 mm Hg, pulmonary pressure >70 mm Hg and 51–70 mm Hg on transthoracic echocardiogram, body mass index <18 kg/m^2, more than two community managed exacerbations of COPD in the past 6 months, and need for community supports. The final group consisted of 30 minor criteria.

The final major and minor consensus criteria for referral to specialist outpatient palliative care for people with COPD are shown in table 4.

When rated numerically by the panel, the major referral criteria were considered 'clearly stated' (median 9 (IQR 8–10)), 'objective in nature' (median 8 (IQR: 8–9)) and 'can be assessed accurately' (median 8 (IQR 8–10)). They agreed these major referral criteria could be feasibly incorporated into primary or respiratory clinical settings (median 8 (IQR: 7–9)) and may be useful in facilitating specialist outpatient palliative care referral at their institution (median 9 (IQR: 7–9)). Comments made by panellists in the final round highlighted areas for further consideration (box 2).

DISCUSSION

People with COPD and their carers have many palliative care needs that could benefit from timely referral to specialist palliative care in outpatient settings, but they are not receiving such care.[9 28] To address the challenge of identifying which people with COPD may be considered as having advanced disease, agreement was established on the definition of advanced COPD to include those classified as GOLD stage 4, those with mMRC dyspnoea score 3 or greater, those with CAT score 21–30 and those who have had two or more hospitalisations for COPD in the last 6 months. In this

Table 3 Level of agreement (including agree or strongly agree) of putative criteria for specialist palliative care referral for the three Delphi rounds n (%)*

	Round 1 % (N=49)	Round 2 % (N=48)		Round 3 % (N=52)
		Major	Minor	
Hospital utilisation	R=46			
Emergency room (ER) visits for COPD or related complications: ≥2 ER visits within the past 3 months	80 (37)	65 (31)	33 (16)	†
Emergency room (ER) visits for COPD or related complications: ≥2 ER visits within the past 6 months	87 (40)	50 (24)	38 (18)	
Emergency room (ER) visits for COPD or related complications: ≥2 ER visits within the past 12 months	43 (20)	–	–	
Repeated hospital admission for COPD or related complications: ≥2 hospitalisations within the past 3 months	96 (44)	90 (43)	10 (5)	94 (49)
Repeated hospital admission for COPD or related complications: ≥2 hospitalisations within the past 6 months	91 (42)	69 (33)	31 (15)	†
Repeated hospital admission for COPD or related complications: ≥2 hospitalisations within the past 12 months	57 (26)	25 (12)	60 (29)	
Intensive care unit admission for COPD or its complications: ≥2 episodes in the past 12 months	93 (43)	88 (42)	13 (6)	89 (46)
Intensive care unit admission for COPD or its complications: 1 episode in the past 12 months	57 (26)	33 (16)	54 (26)	
Step down unit/high dependency unit admission for COPD or related complications or symptoms: ≥1 admission within the past 3 months	89 (41)	69 (33)	29 (14)	†
Step down unit/high dependency unit admission for COPD or related complications or symptoms: ≥1 admission within the past 6 months	78 (36)	54 (26)	44 (21)	
Step down unit/high dependency unit admission for COPD or related complications or symptoms: ≥1 admission within the past 12 months	48 (22)	–	–	
Recent hospitalisation for COPD or related complications or symptoms with length of acute hospital stay >7 days	43 (20)	–	–	
Recent hospitalisation for COPD or related complications or symptoms with length of acute hospital stay >14 days	65 (30)	38 (18)	46 (22)	
Respiratory therapies				
Use of extracorporeal membrane oxygenation (ECMO): any episode in past 12 months	83 (38)	81 (39)	6 (3)	89 (46)
Non-invasive ventilation (NIV): 1 or more episodes in the past 3 months	89 (41)	85 (41)	15 (7)	†
NIV: 1 or more episodes in the past 6 months	85 (39)	71 (34)	29 (14)	77 (40)
NIV: 1 or more episodes in the past 12 months	63 (29)	27 (13)	67 (32)	
Need for home oxygen/long-term oxygen therapy	57 (26)	21 (10)	58 (28)	
Need for domiciliary NIV	89 (41)	90 (43)	8 (4)	94 (49)
Assessment for lung transplantation	87 (40)	77 (37)	15 (7)	79 (41)
Symptom distress				
Presence of chronic breathlessness (breathlessness that persists despite optimal treatment of the underlying pathophysiology and that results in disability)	80 (35)	60 (29)	35 (17)	
Presence of chronic breathlessness (breathlessness that persists despite optimal treatment of the underlying pathophysiology and that results in disability) SEVERE (7–10 on a 10-point scale)‡	–	92 (44)	6 (3)	100 (52)
Presence of chronic breathlessness (breathlessness that persists despite optimal treatment of the underlying pathophysiology and that results in disability) MODERATE (4–6 on a 10-point scale)‡	–	46 (22)	48 (23)	
Presence of chronic breathlessness (breathlessness that persists despite optimal treatment of the underlying pathophysiology and that results in disability) MILD (1–3 on a 10-point scale)‡	–	8 (4)	54 (26)	
Physical symptoms (eg, pain, dyspnoea, nausea, fatigue): SEVERE (7–10 on a 10-point scale)	98 (43)	88 (42)	13 (6)	94 (49)
Physical symptoms (eg, pain, dyspnoea, nausea, fatigue): MODERATE (4–6 on a 10-point scale)	70 (31)	44 (21)	48 (23)	
Physical symptoms (eg, pain, dyspnoea, nausea, fatigue): MILD (1–3 on a 10-point scale)	16 (7)	–	–	
Emotional symptoms (eg, anxiety, depression): SEVERE (7–10 on a 10-point scale)	91 (40)	75 (36)	25 (13)	81 (42)
Emotional symptoms (eg, anxiety, depression): MODERATE (4–6 on a 10-point scale)	59 (26)	33 (16)	54 (26)	
Emotional symptoms (eg, anxiety, depression): MILD (1–3 on a 10-point scale)	14 (6)	–	–	
Spiritual or existential crisis: (eg, questions of meaning, suffering, life regrets): SEVERE (7–10 on a 10-point scale)	93 (41)	88 (40)	17 (8)	87 (45)
Spiritual or existential crisis: (eg, questions of meaning, suffering, life regrets): MODERATE (4–6 on a 10-point scale)	68 (30)	31 (15)	60 (29)	
Spiritual or existential crisis (eg, questions of meaning, suffering, life regrets): MILD (1–3 on a 10-point scale)	27 (12)	–	–	

Continued

Table 3 Continued

	Round 1 % (N=49)	Round 2 % (N=48)		Round 3 % (N=52)
		Major	Minor	
Comorbidities or complications				
Presence of one or more advanced chronic medical condition in addition to COPD (eg, metastatic cancer, end stage heart failure, end stage renal disease, end stage liver disease, dementia)	83 (35	56 (27)	38 (18)	
Chronic hypercapnia >65 mm Hg	79 (33)	48 (23)	35 (17)	
Hypercapnia >55 mm Hg	60 (25)	21 (10)	48 (23)	
Hypercapnia >45 mm Hg	36 (15)	–	–	
Hypoxaemia <55 mm Hg	71 (30)	29 (14)	48 (23)	
Hypoxaemia <60 mm Hg	50 (21)	17 (7)	52 (25)	
Transthoracic pulmonary pressure on echocardiogram of >70 mm Hg	74 (31)	21 (10)	48 (23)	
Transthoracic pulmonary pressure on echocardiogram of 51–70 mm Hg	60 (25)	10 (5)	46 (22)	
Transthoracic pulmonary pressure on echocardiogram of 30–50 mm Hg	31 (13)	–	–	
Body mass index <18 kg/m^2	64 (27)	10 (11)	46 (24)	
Serum albumin <25 g/L	60 (25)	–	–	
Anaemia < 11.0 g/dL	36 (15)	–	–	–
Presence of cognitive impairment	79 (33)	29 (14)	54 (26)	
Withdrawal/de-escalation of life-prolonging interventions	95 (40)	83 (40)	10 (5)	94 (49)
Comorbidities or complications of COVID-19				
Acute COVID-19 infection managed in community	2 (1)	–	–	
Acute COVID-19 infection requiring hospitalisation and survives with no sequelae	10 (4)	–	–	
Acute COVID-19 infection requiring hospitalisation survives but with long term lung damage	52 (22)	–	–	
Long COVID-19 syndrome	38 (16)	–	–	
Exacerbation of COPD				
Community-managed exacerbation* of COPD: ≥2 in 3 months	80 (35)	42 (20)	44 (21)	
Community-managed exacerbation* of COPD: ≥2 in 6 months	55 (24)	23 (11)	44 (21)	
Community-managed exacerbation* of COPD: ≥2 in 12 months	18 (8)	–	–	
Need for continuous systemic corticosteroids >3 months in the past year	70 (31)	27 (13)	44 (21)	
Time based factors				
BODE index ≥7 (BMI, FEV_1, mMRC+6 min walk distance)	77 (34)	58 (28)	33 (16)	
Treating physician estimated life expectancy of: 1 month or less*	93 (41)	96 (46)	2 (1)	†
Physician estimated life expectancy of: 3 months or less*	93 (41)	90 (43)	8 (4)	†
Physician estimated life expectancy of: 6 months or less*	91 (40)	79 (38)	19 (9)	87 (45)
Physician estimated life expectancy of: 12 months or less*	73 (32)	56 (27)	35 (17)	
Physician estimated life expectancy of: 24 months or less*	36 (16)	–	–	
Functional impairment				
6 min walk test <100 m (ie, distance covered in 6 min is <100 m)	95 (40)	71 (34)	25 (12)	70 (37)
6 min walk test <200 m (ie, distance covered in 6 min is <200 m)	64 (27)	40 (19)	46 (22)	
6 min walk test <300 m (ie, distance covered in 6 min is <300 m)	16 (7)	–	–	
Karnofsky performance status 20 (very ill, urgently requires admission, supportive measures or treatment)	95 (40)	92 (44)	8 (4)	†
Karnofsky performance status 30 (severely disabled, hospital admission indicated but no risk of death)	98 (41)	83 (40)	17 (87)	90 (47)
Karnofsky performance status 40 (disabled, requires special care and help)	86 (36)	56 (27)	44 (21)	†
Karnofsky performance status 50 (requires help often, requires frequent medical care)	60 (25)	13 (6)	79 (38)	
Karnofsky performance status ≥60 (requiring some help, can take care of most personal requirements)	14 (64)	–	–	
Dependent in three or more basic activities of daily living	81 (34)	46 (22)	52 (25)	
Psychosocial factors/decision making				
Severe financial distress	31 (13)	–	–	
Severe family discord	50 (21)	–	–	
Severe informal caregiver distress	83 (35)	71 (34)	29 (14)	79 (41)

Continued

Table 3 Continued

	Round 1 % (N=49)	Round 2 % (N=48)		Round 3 % (N=52)
		Major	Minor	
Severe healthcare professional distress	71 (30)	31 (15)	50 (24)	
Inadequate social support	55 (23)	21 (10)	56 (27)	
Need for additional help at home/community supports	53 (22)	6 (3)	63 (30)	
Request for hastened death/assisted suicide	90 (38)	94 (45)	4 (2)	96 (50)
History of drug or alcohol abuse	45 (19)	–	–	
On chronic opioid therapy (for pain or other symptoms)	52 (22)	17 (8)	60 (29)	
Patient chooses not to pursue life-sustaining treatments such as NIV, hospitalisation including in advanced directives	79 (33)	63 (30)	31 (15)	
Need for assistance with decision making/care planning	88 (37)	50 (24)	48 (23)	
Discussion of treatment preferences	34 (81)	16 (33)	24 (50)	
Hospice referral/discussion	90 (38)	60 (29)	31 (15)	
Patient/family request	95 (40)	75 (36)	23 (11)	94 (49)
Added criteria suggested by panellists				
Steady trajectory of decline (eg, of functional status, symptoms, lung function, weight)	–	48 (23)	50 (24)	
Not responding to usual treatment measures (eg, to pulmonary rehabilitation or first line symptom management)	–	40 (19)	46 (22)	

*Number of respondents per question varied between 42–49 (round 1), 44–48 (round 2), 52 (round 3).
†Not included in final groupings as consensus agreement reached on the criteria which represented a better performance status or an earlier referral point for example, At 6 months rather than 3 or 1 month.
‡Breathlessness was graded following panellist feedback in first round.
BMI, body mass index; BODE, Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ER, emergency room; FEV_1, forced expiratory volume in 1s; mMRC, modified Medical Research Council; NIV, non-invasive ventilation.

study, we also reached agreement on which people with COPD may benefit from referral to specialist outpatient palliative care, presenting seventeen major consensus criteria, each of which could prompt clinicians to consider and enact referral. In addition, a series of 30 minor criteria were agreed on, which, if present in combination with one other minor criterion, should prompt referral. Overall, this study provides the foundations towards standardising referral to specialist palliative care with opportunities to reduce variation in care.

The present consensus criteria closely mirror those triggers for referral to palliative care specialist clinicians suggested in the recent European Respiratory Society Practice Guideline[29] and in the American Thoracic Society and partnering societies' policy statement,[12] including refractory severe breathlessness, need for lung transplantation assessment, intensive care unit admission, unmet physical, psychological, social or spiritual needs and complicated bereavement.[12 29] Above and beyond these triggers, our panellists identified novel criteria, such as caregiver distress, a request for a hastened death/assisted suicide, poor performance status and physician estimate of prognosis of 6 months or less. Of the 17 agreed on major criteria in our study, most related to psychosocial distress (n=8) or health service use (n=6) and some to physician estimate of prognosis/function (n=3). In clinical settings, the method by which the relevant patient groups may be identified will vary based on service structures. This may be more complex when seeking to identify those people where referral to palliative care may be prompted if experiencing two or more minor criteria. Criteria linked to health service use could be anchored to administrative data with the potential to generate prompts for clinicians built into systems of workflow. However, these were not the majority of the criteria. Moreover, as patients move between hospitals and healthcare settings, lack of integration of data systems may hinder people being identified in this way. Additional approaches to identification of those who may benefit should be considered. For the majority of the consensus criteria, successful adoption might rest in how readily an assessment of needs or of function may be built into routine respiratory care. While conducting needs assessments of symptoms and psychological distress is core to most specialist palliative care consultations since these needs are the targets of therapeutic intervention, this is less frequent in respiratory care where other tasks take precedence.[30] This was also highlighted as a challenge to implementation of criteria by the panellists. Strategies towards successful implementation of these criteria into routine clinical practice will form important next steps towards improving the palliative care of people with COPD.

Another challenge centres on the infrastructure and resources required for specialist outpatient palliative care for people with COPD. Internationally, there are differences in how palliative care is organised and who is involved in its delivery. Resourcing was recognised as necessary to undertake the needs assessment which underpinned many of the agreed criteria, but also to support access to outpatient specialist palliative care clinics. Some panellists viewed the underlying assumption of the availability of outpatient specialist palliative care as unrealistic in current systems. Such resource constraints are likely to be even more difficult in low- and middle-income countries, and of note, these countries were not well represented in the panel of experts. Nonetheless, the collation of what is considered best practice into a set of standards is an approach taken by Kruk et al when providing recommendations for the creation of high-quality health systems including in low- and middle-income countries.[31] The authors noted that the gap between existing services and the recommended approach may be daunting, but highlighted the importance of 'aspiration for health systems', with the opportunity for countries 'regardless of [their] starting point, … to get started on the path to high-quality health systems'.[31] The use of guidelines as a tool of advocacy to respond to the gap between current services and international recommendations is well recognised.[32] These internationally agreed criteria may serve a similar purpose for health systems seeking to develop tailored and relevant responses to the needs of people living with COPD.

The question of 'who should deliver specialist outpatient palliative care' is regularly raised, with some suggesting that palliative care should be delivered in conjunction with existing respiratory medicine services.[33] The policy statement by the American Thoracic Society and partnering palliative care organisations recommending palliative care early in the care continuum for patients with serious respiratory illness highlights that primary pallia-

Table 4 Final major and minor criteria

Major criteria	Minor criteria
Health service use and need for advanced respiratory therapies	
≥2 hospitalisations in the past 3 months	≥2 emergency room visits within the past 6 months for COPD or related complications
≥2 intensive care unit episodes in the past 12 months	≥2 hospitalisations within the past 12 months for COPD or related complications
Use of NIV for acute or acute-on-chronic respiratory failure in the past 6 months	1 intensive care unit admission for COPD or its complications in the past 12 months
Need for home NIV	≥1 admission to step down unit/high dependency unit within the past 6 months for COPD or related complications
Assessment for lung transplantation	Acute hospital stay >14 days for COPD or related complications
Any episode of extracorporeal membrane oxygenation (ECMO) use in past 12 months	Use of NIV for acute or acute on chronic respiratory failure in the past 12 months
	Need for home oxygen/long-term oxygen therapy
Presence of symptoms, psychosocial needs, decision making*	
Presence of severe chronic breathlessness (breathlessness that persists despite optimal treatment of the underlying pathophysiology and that results in disability)	Presence of moderate chronic breathlessness (breathlessness that persists despite optimal treatment of the underlying pathophysiology and that results in disability)
Presence of severe physical symptoms (eg, pain, dyspnoea, nausea, fatigue)	Presence of moderate physical symptoms (eg, pain, dyspnoea, nausea, fatigue)
Presence of severe emotional symptoms (eg, anxiety, depression)	Presence of moderate emotional symptoms (eg, anxiety, depression)
Presence of severe spiritual or existential distress: (eg, questions of meaning, suffering, life regrets)	Presence of moderate spiritual or existential distress (eg, questions of meaning, suffering, life regrets)
Severe informal caregiver distress	Severe healthcare professional distress
Request for hastened death/assisted suicide	Inadequate social support
Patient/family request	On chronic opioid therapy (for pain or other symptoms)
Withdrawal/de-escalation of life-prolonging interventions †	Patient chooses not to pursue life-sustaining treatments‡
	Need for assistance with decision making/care planning
	Hospice referral/discussion
Prognostic estimate and performance status	
Treating physician estimated life expectancy of 6 months or less	BODE index ≥7 (BMI, FEV1, mMRC+6 min walk distance)
6 min walk distance <100 m	Physician estimated life expectancy of: 12 months or less
Karnofsky performance status ≤30 *(severely disabled, hospital admission indicated but no risk of death)*	6 min walk test <200 m (ie, distance covered in 6 min is <200 m)
	Karnofsky performance status 50 (*requires help often, requires frequent medical care*)
	Dependent in three or more basic activities of daily living
	Steady trajectory of decline (eg, of functional status, symptoms, lung function, weight)
Comorbidities and exacerbations	
	Presence of one or more advanced chronic medical condition in addition to COPD (eg, metastatic cancer, dementia)
	Chronic hypercapnia >65 mm Hg
	Hypoxaemia <55 mm Hg
	Presence of cognitive impairment
	Community-managed exacerbation of COPD: ≥2 in 3 months
	Need for continuous systemic corticosteroids >3 months in the past year
	Not responding to usual treatment measures (eg, to pulmonary rehabilitation or first line symptom management)

*Where 'severe' is defined as (7–10 on a 10-point scale), and 'moderate' defined as (4–6 on a 10-point scale).
†Typically this would be a decision made in the acute setting and often following a trial of treatment.
‡Typically this would be a patient preference stated in advance and often as part of an advance care plan.
BMI, body mass index; BODE, Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ER, emergency room; FEV_1, forced expiratory volume in 1 s; mMRC, modified Medical Research Council; NIV, non-invasive ventilation.

tive care should be delivered by pulmonary clinicians alongside disease-modifying therapies.[12] People with COPD report looking to their respiratory team for all their care needs.[34] Yet, as already noted, there are multiple, competing tasks that must be addressed in a time limited respiratory consultation. A respiratory clinician must attend to respiratory status, optimal medication, recent and anticipated complications, and management of comorbidities, with plans required for each of these. In delivering palliative care, respiratory clinicians will also be required to explore palliative care needs, fears, family support and future preferences. The time available will usually mean some prioritisation of tasks.[35] For a palliative care physician, review of respiratory status will occur but with the main focus of care being on palliative care needs. The prioritisation of activities will likely differ. The complementary nature of these disciplines working together is evident.

An approach to respiratory palliative care provision whereby a palliative care clinician is embedded in the respiratory clinic has been advocated as providing comprehensive care within existing 'known' systems of care, consistent with patient preferences.[36] Embedding palliative care within the respiratory service aligns with patients' expectations of treatment, ensures both aspects of care (respiratory care and palliative care) are addressed and facilitates

Box 2 Screening for symptomatology and distress as integral to a number of the criteria

Assessment of needs … are not easy to implement in many clinics, but this doesn't mean that we shouldn't prioritise assessing these needs and using these as criteria for referral. It only shows that we need to learn more about assessment of these needs and efficient ways to do that in busy practices.

Resourcing of palliative care was viewed as an impediment to implementation.

I don't think that most of the criteria are realistic as a guideline for referrals to an outpatient palliative care clinic, mostly due to a lack of resources.

General support for the criteria and the study intent, and ways forward for this work.

It is advisable to test the feasibility and utility of such criteria in a multi-centre and international study before applying them in widespread practice. It can be done as two visits over a 12-month period. Our university institution can participate in such a study.

trust between the specialties.[34] This approach readily addresses the recommendations from the American Thoracic Society guidelines that specialist palliative care should be delivered early and concurrent with receipt of respiratory illness-directed therapies.[12] Preliminary data suggest an embedded model is effective, resulting in increased access and participation in advanced care planning compared with historical controls (85% vs 15%) and fewer emergency department presentations.[36] Furthermore, such services have reported high levels of satisfaction through patient reports of improved breathlessness management (96%) and increased confidence managing symptoms (99%).[37]

Limitations

Our multidisciplinary group of expert panellists was all English-speaking, meaning that the views and expertise of those speaking other languages were not represented. Smaller numbers of our panellists were from Asia and South America and none were from the Middle East or Africa. The countries represented were all high income and none of the experts were from low- and middle-income countries. Future studies must purposively and fully sample a more diverse groups of clinicians to understand challenges and possible responses in those countries, including low- and middle-income countries. Our expert panel may not be representative of respiratory palliative care practice internatio ally. Further, the panel was predominantly physicians, with just small numbers of community based or nursing clinicians, and no patient or community representatives were included. While this may impact the diversity of views, the study was focused on those who would be initiating the palliative care referral which, in most health systems, is the physician. Future work should importantly focus on the review of these criteria by people with COPD and their caregivers, with the opportunity to adapt or modify as appropriate.

Importantly, in drawing together this group of international experts, agreement was reached on criteria for referral to outpatient specialist palliative care for patients with COPD, providing a much-needed baseline on which future practice and research can build.

CONCLUSION

This international multidisciplinary Delphi study with representation from five regions of the world propose 17 major and 30 minor consensus criteria for identifying people with COPD who may benefit from specialist outpatient palliative care referral. Responding to the existing practices of infrequent and very late referral to palliative care for people with COPD, the development of these consensus criteria represents the first step towards improving the standardisation of clinical care. Furthermore, it provides the baseline for future clinical trials in the field. Further research is required to understand the views of community members, and of a broader range of clinicians across countries, disciplines and sites of care, as well as the strategies required for implementation of criteria into care, and the impact this may have. Nevertheless, the agreed criteria provide an important foundation towards reducing variation, and hence improving equity in care for people with COPD.

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Correlações entre a poluição do ar ambiente e a prevalência de hospitalizações e visitas a emergências por doenças respiratórias em crianças: uma revisão sistemática

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RESUMO

Objetivo Sabe-se que a exposição à poluição do ar está associada a um risco aumentado de doenças cardiovasculares e respiratórias. Esta revisão teve como objetivo resumir estudos observacionais sobre o impacto da exposição de curto e longo prazo à poluição do ar ambiente na prevalência de hospitalizações e/ou visitas a departamentos de emergência causadas por doenças respiratórias em crianças e adolescentes.

Fontes As bases de dados PubMed, Scopus, Embase e Cochrane Library foram pesquisadas para o período de 2018 a dezembro de 2022, incluindo estudos em qualquer idioma.

Resumo dos achados Um total de 15 estudos publicados entre 2018 e 15 de janeiro de 2022 foi incluído nesta revisão. O $PM_{2,5}$ foi o tipo mais estudado de material particulado. A exposição de curto prazo ao $PM_{2,5}$, PM_{10}, NO_2, SO_2 e O_3, mesmo em concentrações inferiores às diretrizes atuais baseadas na saúde, foi significativamente correlacionada ao aumento do risco de visitas ambulatoriais/hospitalares e hospitalizações por doenças respiratórias em crianças.

Conclusões Nossos achados enfatizam a importância e a urgência do controlo a longo prazo da poluição do ar e das doenças relacionadas à poluição, especialmente entre crianças e adolescentes. Há uma necessidade de pesquisas adicionais que utilizem metodologias mais homogéneas para avaliar as exposições e as medidas de desfecho, a fim de viabilizar revisões sistemáticas com meta-análise.

INTRODUCTION

Air pollutants can be classified into gaseous components, such as ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2), sulphur dioxide (SO_2) and particulate matter (PM).[1] PM can be divided, according to the size of its particles, into inhalable PM (diameter <10 µm (PM_{10})), fine inhalable PM (diameter <2.5 µm ($PM_{2.5}$)) and ultrafine PM (diameter <0.1 µm ($PM_{0.1}$)).[2]

The deposition of PM along the respiratory tract is related to the size, shape and density of its particles.[3] PM with a diameter larger than 10 µm generally accumulates in the upper airways and is filtered by the nose. PM_{10} penetrates the lower airways up to the level of the conducting airways. $PM_{2.5}$ is deposited in the lower airways, accumulating deeper in the terminal bronchioles and alveoli. $PM_{0.1}$ can penetrate the alveoli and even diffuse into the systemic circulation.[4]

Outdoor air pollution or ambient air pollution is the contamination occurring outside a building, whereas indoor occurs inside a building.[5] According to the WHO, nearly the entire global population is exposed to air pollution that exceeds their recommended limits.[6] Exposure to air pollution is known to be associated with an increased risk for cardiovascular and respiratory diseases, even at concentrations lower than the current health-based guidelines.[7] As the 2022 Lancet Commission on Pollution and Health reported, around 9 million deaths occurred in 2019 due to pollution, which accounted for one-sixth of global fatalities. Additionally, they observed that a staggering 92% of pollution-related deaths took place in low-income and middle-income countries.[8]

Children, in particular, are susceptible and vulnerable to the adverse health effects of poor air quality due to their underdeveloped respiratory, metabolic and immune systems.[9] Moreover, they exhibit higher ventilation rates, engage in more mouth breathing and spend more time outdoors playing.[10] Infants and young children who are exposed to air pollution are at risk of experiencing lung damage and have an elevated likelihood of developing conditions such as asthma, pneumonia and chronic obstructive pulmonary disease later in life.[11]

The consequences of exposure to ambient air pollution during early life include respiratory symptoms like coughing, wheezing and shortness of breath. Furthermore, short-term and long-term exposure to air pollution can worsen existing respiratory conditions and increase the risk of respiratory infections.[12] It is well documented that exposure to $PM_{2.5}$, PM_{10}, CO, NO_2, SO_2 and O_3 has a positive and significant association with respiratory disease morbidity and mortality.[13 14]

Despite the significant scale of the issue, the relationship between air pollution and children's health has been largely overlooked in international development and global health agendas. Observational studies have investigated the associations between short-term (eg, hours to days[15]) and long-term (eg, months to years[16]) exposure to ambient air pollutants and respiratory disease outcomes in children. However, few systematic reviews on this topic have been conducted. Researchers report difficulties conducting these studies due to the different methodologies used.[17] A recent systematic review of 33 studies found significantly increased pooled excess risks of outpatient visits for respiratory illnesses among children related to short-term exposure to air pollution.[18] Still, several narrative reviews summarise the potential effects of air pollution on respiratory diseases such as asthma,[17] allergic rhinitis,[17] and respiratory infections.[19]

Furthermore, according to the US Environmental Protection Agency, emergency room visits and hospitalisations for respiratory diseases from exposure to air pollution can be even more severe among people with low income compared with other populations.[20]

This paper aimed to review observational studies on the impact of exposure to ambient air pollution on the prevalence of hospitalisations and emergency department visits (EDVs) caused by respiratory diseases in people ≤18 years old. One of the contributions of this article is the identification of the main environmental pollution variables, confounding factors and statistical models studied and used in correlation studies between respiratory diseases in children and

adolescents and air pollution present in the literature over the last 5 years.

METHODS

This systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[21] (online supplemental file S1) and Meta-analyses Of Observational Studies in Epidemiology Checklist. This review is registered in PROSPERO.

Eligibility criteria

We selected studies that met the following PECOT criteria: participants: people aged ≤18 years; exposure: ambient exposure to PM (eg, $PM_{2.5}$ and PM_{10}) and gaseous pollutants (eg, NO_2, NOX (nitrogen oxides), NO (nitric oxide), SO_2 (sulphur dioxide), CO, O_3); outcome: prevalence of hospitalisations and EDVs caused by respiratory diseases, according to International Classification of Diseases, Tenth Revision (ICD-10) codes J00-J99, and the Ninth Revision (ICD-9) codes 460–519) and type of study: observational studies with a minimum period of 12 consecutive months.

The exclusion criteria were: participants >18 years old; including diseases other than respiratory diseases (eg, cardiorespiratory diseases); indoor air pollution; studies without quantifying the concentration of PM and gaseous pollutants in μg/ m^3; studies without the relative risk (RR) or OR with 95% CI for each 10 μg/m^3 increase in the average concentration of the air pollutant. Studies with disaggregated analytic findings were considered if they provided relevant measures of risk for children and adolescents with respiratory diseases.

Information sources

Pubmed, Scopus, Embase and Cochrane Library databases were searched for the years 2018 to December 2022, including studies in any language. The last search was on 15 January 2023.

Search strategy

Search combined Medical Subject Headings terms for population (eg, child or paediatrics), exposure (eg, 'air pollution' or 'outdoor air pollution' or 'ambient air pollution'), outcome (eg, 'respiratory tract diseases' or 'respiratory diseases' and hospitalisation or 'emergency department visit'). Table 1 presents the search strategies used, including filters and limits.

Selection process

Initial study selection was carried out, simultaneously, by the independent reviewers APdS and CCSG, and a third researcher (JDR) was consulted in cases of disagreement. After searching, the results were uploaded to the Rayyan tool systematic review manager, developed by Qatar Computing Research Institute.

First, a tool available at Rayyan was used to exclude duplicates. Then, another tool was used to select and exclude records that mentioned the following words in the title or abstract: 'systematic review', 'meta-analysis', 'indoor' and 'school'. Second, the reviewers searched the title and abstract of the articles for the following terms: 'air pollution'; 'outdoor air pollution'; 'ambient air pollution'; 'Pediatrics'; 'Child'; 'Respiratory diseases'; 'Respiratory diseases'; 'hospitalisation'.

Subsequently, the full text was read against the inclusion and exclusion criteria previously described.

Finally, the full text of the remaining articles was read, and those that followed the inclusion criteria were selected for review. There was a 4% (12) disagreement rate between the two reviewers, which was resolved by consulting JDR.

Data collection process and data items

Data collection was performed by APdS and confirmed by CCSG, through a Google Document file (online supplemental file S2) containing the following information for each study: authors and year of publication; country and city; study duration time; study design; PM and gaseous pollutants mean/median±SD concentrations observed; age (years) of sample; sample size; ICD-10 and ICD-9 codes used as the outcome; sources for obtaining data related to pollutants and to outcome; control of confounding factors; reported funding source and reported conflicts of interest. The effect measures of each study were collected in a Microsoft Office Excel V.2010 table (online supplemental file S3).

Study risk of bias assessment

Quality assessment of the studies was carried out by two authors. Since we found no specific tool to evaluate the methodological quality of ecological studies, we performed a qualitative evaluation of the quality of the studies, based on what other authors have done,[22] classifying them as low, moderate or high risk of bias, according to criteria previously registered at the review protocol.

Effect measures

For the outcome synthesis, we used the RR or OR with a 95% CI increase in hospitalisation and EDVs for children with respiratory diseases reported for each 10 μg/m^3 increase in the average concentration of the ambient air pollutants.

Synthesis methods

We tabulate the studies' effect measures (online supplemental file S3) according to the exposure characteristics. We grouped the reported outcomes for the same pollutant and synthesised the results found in a forest plot for PM and a table for gaseous pollutants. For the studies that allowed such division, we performed analyses by sex, season and risk of study bias.

Table 1 Full search strategies for all databases consulted in this review

Database	Search strategy
Pubmed	Simple search: ("ambient air pollution" OR "air pollution" OR "outdoor air pollution") AND (child OR children OR pediatrics) AND ("respiratory tract diseases" OR "respiratory diseases") AND (hospitalization OR "emergency department visit") Filter: publication year: 2018-2022
Scopus	advanced search: (TITLE-ABS-KEY ("ambient air pollution") OR TITLE-ABS-KEY ("air pollution") OR TITLE-ABS-KEY ("outdoor air pollution") AND TITLE-ABS-KEY (child) AND TITLE-ABS-KEY ("respiratory tract diseases") OR TITLE-ABS-KEY ("respiratory diseases")) AND TITLE-ABS-KEY ("hospitalization") AND (LIMIT-TO (PUBYEAR, 2023) OR LIMIT-TO (PUBYEAR, 2022) OR LIMIT-TO (PUBYEAR, 2021) OR LIMIT-TO (PUBYEAR, 2020) OR LIMIT-TO (PUBYEAR, 2019) OR LIMIT-TO (PUBYEAR, 2018))
Embase	PICOT search: (('child'/exp OR 'pediatrics'/exp) AND 'respiratory tract disease'/exp OR 'respiratory diseases'/exp) AND ('air pollution'/exp OR 'ambient air pollution'/exp OR 'outdoor air pollution'/exp) AND ('hospitalization'/exp OR 'emergency department visit'/exp) AND ('cross-sectional study'/exp OR 'case control study'/exp OR 'ecological study'/exp OR 'epidemiology'/exp OR 'observational study'/exp) Filter: publication year: 2018-2022
Cochrane Library	Cochrane trials: ("air pollution" or "outdoor air pollution" or "ambient air pollution") and (child or pediatrics) and ("respiratory tract diseases" or "respiratory diseases") in Title Abstract Keyword Filter: publication year: 2018-2022

Reporting bias assessment

Systematic reviews can be compromised by 'non-reporting bias' due to unavailable results of the eligible studies.[23] Thus, we searched for possible sources where study reports and results may be located and we highlighted the non-reported results (eg, effect measures).

RESULTS

Study selection

The initial search identified 355 studies (figure 1—PRISMA flowchart). A total of 54 duplicates were removed. Then, we removed 65 studies by using an automatic tool of Rayyan to select and exclude records that mentioned the words 'systematic review', 'meta-analysis', 'indoor' and 'school' in the title or abstract. The deletion process was verified and approved by humans. After screening the titles and abstracts of the remaining articles, we excluded 138 studies that did not meet our selection criteria. The full texts of the remaining 98 studies were reviewed against the study selection criteria. Of these, 83 studies were excluded. Finally, 15 studies were included in the review.

Study characteristics

The characteristics of the studies included in this review are summarised in a table (online supplemental file S4). Studies originated from around the world with 12 from Asia, one from South America, one from Europe, and one from North America. There were 12 ecological studies and three time-stratified case cross-overs. All included studies were published in English.

Table 2 presents the air pollution and meteorological variables, the variables adopted to control confusion, the statistical models used as well as the statistical tools adopted in the review. Quasi-Poisson Regression with a generalised additive model (GAM) was the most used statistical model (12/15) to estimate the relatio ships between the daily concentration of air pollutants and the search for hospital care.

The studies included in the systematic review used, on average, 4 years of data, and the days of delay in observing the outcome (lag) considered between the studies were, on average, 6 days. Among the confounding variables considered, the most prevalent were other environmental pollutants (14/15), temperature (13/15), relative air humidity (12/15), temporal trend (10/15), days of the week and holidays (10/15), seasons (7/15) and lag (15/15). No studies considered influenza outbreaks, levels of exposure to indoor air pollution, exposure to smoking or socioeconomic factors.

Risk of bias

The quality assessment revealed that two (13,33%) of the included studies presented a high risk of bias, six (40,00%) presented a moderate risk of bias and seven (46,66%) presented a low risk of bias (online supplemental file S5).

Results of individual studies

We assessed respiratory diseases by children and adolescents according to environmental exposure to PM or gaseous pollutants. Online supplemental file S2 reports the details of the respiratory outcomes. No studies were found on the effects of long-term exposure to air pollution on respiratory diseases.

Short-term effects of PM on respiratory diseases

We found that $PM_{2.5}$ was the most extensively studied type of PM. Of the 15 studies included in this review, 14 explored the effects of short-term exposure to $PM_{2.5}$ on respiratory diseases in children. Short-term exposure to $PM_{2.5}$ was significantly associated with hospital admissions (n=5) and outpatient/hospital visits (n=9) for respiratory diseases (n=7), acute lower respiratory infection (ALRI (n=2)), upper respiratory tract infection (URTI (n=3)), bronchiolitis (n=1), pneumonia (n=3), asthma (n=4) and bronchitis (n=3).

We identified 12 studies that reported the effects of short-term exposure to PM_{10}. Short-term exposure to PM_{10} was significantly associated with hospital admissions (n=3) and outpatient/hospital visits (n=4) for respiratory diseases (n=2), ALRI (n=1), URTI (n=3), bronchiolitis (n=1), pneumonia (n=4), asthma (n=3) and bronchitis (n=1).

Figure 2 shows the forest plots for (figure 2A) total daily hospital admissions and EDV due to respiratory diseases associated with exposure to $PM_{2.5}$ (figure 2B) total daily hospital admissions and EDV due to respiratory diseases associated with exposure to

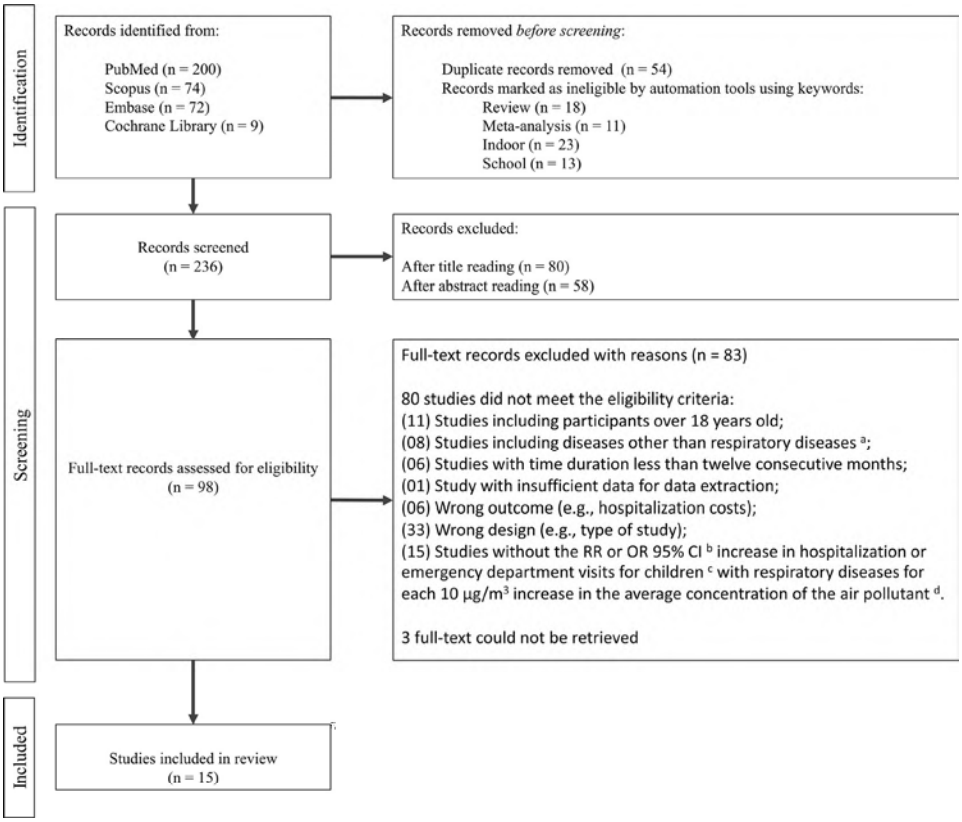

Figure 1 Databases were searched between 2017 and 15 January 2023. Children: person aged 0–18 years old; respiratory disease: according to International Classification of Diseases, Tenth Revision (ICD-10) codes J00-J99 and the Ninth Revision (ICD9) codes 460-519; Air pollutant: PM, $PM_{0,1}$, $PM_{2.5}$, PM_{10}, NO_2, NO_X, NO, SO_2, CO, O_3 or CH_4.

Table 2 Variables considered, statistical models and tools used in the studies included in the review

Author	Environmental pollutants	Control of confounding variables			Statistical model	Tools used
		Environmental pollutants	Meteorological variables	Other variables		
Dong J *et al*	$PM_{2.5}$	$PM_{2.5}$ adjusted for PM_{10}, SO_2 and NO_2	Temperature, Relative humidity	Time trend, Days of the week, Holidays, Seasons, lag	Quasi-Poisson regression with generalised additive model	R Software MGCV package version 3.4.4
Song *et al*[24]	$PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3-8h	Variables adjusted to each other	Temperature, Relative humidity	Time trend, Days of the week, Holidays, Seasons, lag	Quasi-Poisson regression with generalised additive model	Pacote MGCV do software R versão 3.2.1
Liu L *et al*[33]	$PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3-8h, CO	Variables adjusted to each other	Temperature, Atmospheric pressure, Relative humidity, Wind speed	Time trend, Days of the week, Holidays, Seasons, lag	Generalised additive Poisson time series model	SPSS 21.0 Software R Software version 3.6.2
Ma Y *et al*[25]	$PM_{2.5}$, PM_{10}, SO_2, NO_2	Variables adjusted to each other	Temperature, Relative humidity	Time trend, Days of the week, Holidays, lag	Quasi-Poisson regression with generalised additive model	MGCV package of R software version 3.5.2
Li M *et al*[26]	$PM_{2.5}$, PM_{10}, $PM_{10\text{-}2.5}$	$PM_{2.5}$ e PM_{10} adjusted for SO_2, NO_2 and O_3	Temperature, Relative humidity	Time trend, Days of the week, Holidays, Seasons, lag	Quasi-Poisson regression with generalised additive model	MGCV and metafor packages from R software version 3.2.1
He M *et al*[27]	$PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3-8h	Variables adjusted to each other	Temperature, Relative humidity	Time trend, Lag	Quasi-Poisson regression with generalised additive model	MGCV package of R software version 3.6.3
Ibrahim MF *et al*[30]	PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3-8h, CO	Variables adjusted to each other	Temperature, Relative humidity	Time trend, Days of the week, Holidays, lag	Quasi-Poisson generalised linear model with a nonlinear distributed delay model (DLNM)	dlnm packages and splines from R software version 1 February, 5033
Gallo E *et al*[28]	PM_{10}, $PM_{2.5}$, NO_2	Variables adjusted to each other	Temperature, Relative humidity, Atmospheric pressure	Time trend, Holidays, lag	Multivariate conditional logistic regression based on a time-stratified case-crossover design	R statistical software (RCoreTeam, 2020) and dlnm package
Luong LTM *et al*	$PM_{2.5}$	No adjustment	Temperature, Relative humidity	Time trend, Days of the week, Seasonality, lag	Generalised linear models and distributed lag model with the Quasi-Poisson distribution family	tsModel, Epi, dlnm and splines packages from R software version 3.5.3
Liu J *et al*	$PM_{2.5}$	$PM_{2.5}$ adjusted for PM_{10}, SO_2, NO_2, O_3 and CO	Temperature, Relative humidity, Atmospheric pressure	Time trend, Days of the week, Seasonality, lag	Quasi-Poisson regression	Statistical software R version 3.3.2
Carvalho PC *et al*[29]	NO_2, PM_{10}, O_3-8h	NO_2 adjusted for PM_{10} and O_3-8h	Effective temperature (calculated using relative humidity and temperature)	Days of the week, Seasonality, lag	Quasi-Poisson generalised linear model	Stata version 9
Li D *et al*	$PM_{2.5}$, PM_{10}, NO_2, SO_2	Variables adjusted to each other	Temperature, Relative humidity, Precipitation, Wind speed	Days of the week, Holidays, lag	Quasi-Poisson regression with generalised additive model	R software version 3.2.3 gam.check and mgcv packages
Wang X *et al*	PM_1, $PM_{2.5}$, PM_{10}	Variables adjusted for O_3, NO_2 and SO_2	Temperature, Relative humidity, Precipitation, Wind speed	Time trend, Days of the week, Holidays, Seasonality, lag	Nonlinear smoothing function for the regression model and a Poisson model	Statistical software R version 3.6.3
Baek J *et al*[34]	$PM_{2.5}$	Adjusted to O_3-8h	Temperature	None	Conditional logistic regression	Stata version 14 (StataCorp LLC, College Station, TX)
Kuo C-Y *et al*	$PM_{2.5}$, PM_{10}	$PM_{2.5}$ and PM_{10} adjusted for O_3, SO_2 and NO_2	Temperature, Relative humidity	Seasonality, lag	Conditional logistic regression	Statistical software R version 3.3.2

CO, carbon monoxide (ppm); lag, days of delay in observing the outcome; MP_{10}, inhalable particulate matter (µg/m³); $MP_{2.5}$, fine inhalable particles (µg/m³); NO_2, nitrogen dioxide (µg/m³); O_3-8h, ozone (µg/m³) every 8 hours; SO_2, sulphur dioxide (µg/m³).

$PM_{2.5}$ in the sex-stratified analysis (figure 2C) total daily hospital admissions and EDV due to respiratory diseases associated with exposure to PM_{10} (figure 2D) daily hospital admissions and EDV due to respiratory diseases associated with exposure to PM_{10} in the sex-stratified analysis.

Short-term effects of gaseous pollutants

Nine studies explored the effects of gaseous pollutants in respiratory disease hospitalisations and EVDs among children (online supplemental file S6 shows the reported effects of gaseous pollutants on respiratory diseases).

Effects of NO_2 on respiratory diseases

Short-term exposure to NO_2 was significantly associated with outpatient visits for respiratory diseases (n=4), pneumonia (n=2), asthma (n=2), bronchitis (n=3) and URTI (n=2). Two studies found that NO_2 exhibited the highest effects in the transition season.[24 25] Nonetheless, another[26] reported that the impact on hospital visits for pneumonia in the cold season was particularly notable by 7.1% per 10 µg/m³ increase for NO_2 among children aged 0–1 years.

NO_2 showed a slightly higher effect on total respiratory diseases in girls than in boys for the cumulative-day lag effect,[27] higher effect among 0–3 and 0–5-year- old children compared with the older age groups[25 27] and a cumulative effect over the 2 weeks preceding presentations to the emergency department.[28] Another author also identified a later effect of NO_2 in admissions due to acute respiratory infection diseases in children <10 years, with significance at lag 2 up to lag 5 and lag 7 after exposure.[29]

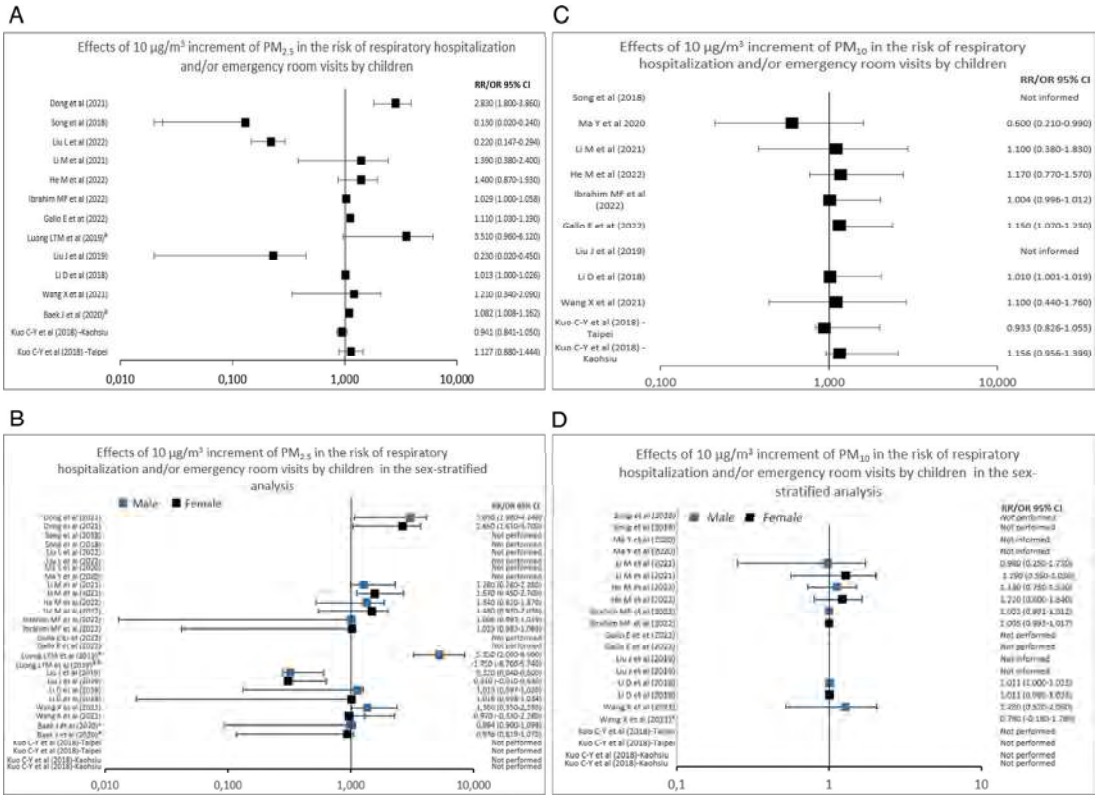

Figure 2 (A) Forest plots for the risks reported by the studies for total daily hospital admissions or outpatient/hospital visits due to respiratory diseases associated with short-term exposure to $PM_{2.5}$ levels. (B) Forest plots for the risks reported by the studies for total daily hospital admissions or outpatient/hospital visits due to respiratory diseases associated with short-term exposure to $PM_{2.5}$ levels in the sex-stratified analysis. (C) Forest plots for the risks reported by the studies for total daily hospital admissions or outpatient/hospital visits due to respiratory diseases associated with short-term exposure to PM_{10} levels (D) Forest plots for the risks reported by the studies for total daily hospital admissions or outpatient/hospital visits due to respiratory diseases associated with short-term exposure to PM_{10} levels in the sex-stratified analysis. OR/RR 95% CI: odds ratio/risk relative with a 95% CI; $PM_{2,5}$: fine inhalable particulate matter with a diameter smaller than 2,5 µm; a represents the studies classified as high risk of bias; b OR/RR 95% CI for female reported by Luong LTM *et al* (2019) was not plotted in the forest plot; Song *et al* (2018), Liu *et al* (2022), Gallo *et al* (2022) and Kuo C-Y *et al* (2018) did not perform the OR/RR 95% CI assessment for the total increase in children's respiratory outpatient visits associated with a 10 µg/m^3 increment of $PM_{2,5}$ concentrations by sex-stratified analysis; Ma Y *et al* (2020) did not report the RR 95% CI assessment for either the total increase in children's respiratory outpatient visits associated with a 10 µg/m_3 increment of $PM_{2,5}$ concentrations by sex-stratified analysis and for the total increase in children's respiratory outpatient visits associated with a 10 µg/m^3 increment of $PM_{2,5}$ concentrations. Song et al (2018) and Li D *et al* (2018) did not inform the OR/RR 95% CI assessment for the total increase in children's respiratory outpatient visits associated with a 10 µg/m^3 increment of PM_{10} concentrations; an OR/RR 95% CI for female reported by Wang X *et al* (2021) was not plotted in the forest plot; Song *et al* (2018), Gallo E *et at* (2022) and Kuo C-Y *et al* (2018) did not perform the OR/RR 95%CI assessment for the total increase in children's respiratory outpatient visits associated with a 10 µg/m^3 increment of PM_{10} concentrations by sex-stratified analysis; Ma Y *et al* (2020) and Liu J *et al* (2019) did not report the RR 95% CI assessment for the total increase in children's respiratory outpatient visits associated with a 10 µg/m^3 increment of PM_{10} concentrations by sex-stratifie.

Effects of SO_2 on respiratory diseases

Short-term exposure to air pollutants SO_2 was significantly associated with total respiratory outpatient visits (n=4), pneumonia (n=3), bronchitis (n=2) and URTI (n=2). SO_2 associations to the increase in children's respiratory outpatient visits were approximately two times higher in the hot season than in the transition season. An increase of 10 µg/m^3 in 2 day average concentrations of SO_2 corresponded to a 0.33% (95% CI 0.10 to 0.56) increase in total respiratory outpatient visits.[24]

SO_2 also showed a late effect on respiratory disease outpatient visits in lag 05, when visits increased by 4.67 (95% CI 1.22 to 8.24) in children aged 0–3 and by 7.95 (95% CI 5.40 to 10.55) in the cold season.[25]

The effect estimates of SO_2 on pneumonia were significantly higher in girls but slightly higher in boys for URTI and bronchitis.[27] One study[30] reported that SO_2 was associated with hospital admissions for respiratory diseases in both boys and girls, but the effect estimates for girls were approximately two times higher than for boys suggesting that girls in Bintulu were more vulnerable and susceptible to ambient air pollution than boys. They also reported that the adverse effects of SO_2 pollution were delayed and reached their peaks after 7 days. Meanwhile, another study[26] only found associations for boys, which were stronger in the cold season among children aged 0–1 years.

Effects of O_3 on respiratory diseases

Short-term

exposure to air pollutants O_3 was significantly associated with hospital outpatient visits for respiratory diseases (n=1), URTI (n=1) and bronchitis (n=1).

The reported associations between O_3 and total respiratory outpatients were positive but non-significant and these associations were higher in the transition season and for children aged 4–6 years old.[24]

The effect estimates of O^3 on URTI and bronchitis were slightly higher in boys than in girls and significantly higher in the 0–5 years age group than in the older groups.[27]

DISCUSSION

Although more than 300 million children around the world are exposed to toxic levels of outdoor air pollution,6 the quality and quantity of scientific studies that relate the functional, structural, static and dynamic impairment of children's lower and upper airways, and that make it possible to understand the prevalence of emergency room visits and hospital admissions due to respiratory diseases related to ambient air pollution, can be considered negligible.

This review synthesised 15 studies and we found that $PM_{2,5}$, PM_{10}, NO_2, SO_2 and O_3 were associated with an increased risk of

outpatient visits, EDVs and hospital admissions due to respiratory symptoms and diseases by children and adolescents.

Most studies were published in Asia (12/15), highlighting the small number of studies in Europe, North America and especially South America. This may be a bias because Asian articles were most strict in terms of including only populations under 19 years of age; hospitalisations and/or emergency visits caused solely by respiratory diseases; study duration greater than 1 year; PM and/or gaseous pollutants measured in μg/m^3; and effect measures in the form of RR or OR, therefore, there may be a selection bias. This highlights the need to carry out studies in a standardised way, to increase the quality and allow comparability between them.

Quasi-Poisson regression with a GAM was the most used statistical model (11/15) to estimate the relationships between the daily concentration of air pollutants and the search for hospital care. Its approach, capable of adapting and versatilely dealing with different non-linear patterns, offers additional flexibility to capture nuances in relationships.[31]

We only found studies on the effects of short-term exposure to air pollution. Factors such as difficulty in collecting data, the need to monitor participants over the years, which makes the study more expensive, and other logistical difficulties, make it difficult to carry out studies on the effects of prolonged exposure to air pollution, which are important for determining the relationship between air quality and human health.[32]

The importance of including confounding variables in the prediction models was also noted, such as the brightness between environmental pollutants, environmental influences, temporary trends, days of the week and holidays, seasons and lag, as these factors affect the proportions of the predicted effects. Studies indicate that the addition of other substances in analyses attenuated or even nullified the measured effects of some substances.[33]

The impacts of air pollution on childhood respiratory diseases varied according to the respiratory disease analysed, age group, sex, season and location of the study. It is noteworthy that the most prevalent diseases, such as asthma, are the most studied. Ambiental exposure to NO_2, O_3, PM_{10} and $PM_{2.5}$ was associated with EDV, within 24 hours,[27] and an increased risk for hospital readmissions for asthma.[34] A systematic review and meta-analysis of 41 studies from low and middle-income countries in Asia found that asthmatic children exposed to PM_{10}, NO_2 and SO_2 may have a poor prognosis, with an increased risk of exacerbation and poor asthma control.[35]

Furthermore, our review demonstrates the differences found in the reported effects between the sexes according to specific respiratory diseases or even between different seasons, which highlights the need to consider these factors.

We found some limitations in the evidence included in this review. First, few studies performed multipollutant evaluations. Since air pollutants are complex mixtures that exist in the environment, a single pollutant may not be the best model to evaluate the impact of air pollution on people's health. Also, none of the studies controlled for influenza outbreaks, exposure to smoking or socioeconomic factors as confounding factors.

This systematic review has some limitations. First, grey literature was not included. Second, due to the high heterogeneity among the studies found, we were unable to carry out a systematic review with meta-analysis. Third, other confounding factors such as indoor air quality and socioeconomic factors were not considered.

However, this review found consistent evidence of a significant association between short-term exposure to ambient air pollution and the risk of hospitalisations and EDVs caused by respiratory diseases in children. Our findings contribute supplementary information to the current evidence, emphasising the urgency of long-term control of air pollution and pollution-related diseases, especially among children. There is a need for further research employing exposure assessment methodologies such as personal exposure monitoring and long-term trend analysis, as well as better control of confounding factors.

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Software usando inteligência artificial para detecção de nódulos e cancro em exames de tomografia computadorizada (TC) para rastreamento de cancro do pulmão: revisão sistemática dos estudos de precisão de testes

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RESUMO

Objetivos Examinar a precisão e o impacto da assistência de software de inteligência artificial (IA) no rastreamento de cancro do pulmão utilizando TC.

Métodos Foi realizada uma revisão sistemática de softwares baseados em IA com marcação CE para detecção e análise automatizada de nódulos no rastreamento de cancro do pulmão por TC. Diversas bases de dados, incluindo Medline, Embase e Cochrane CENTRAL, foram pesquisadas de 2012 até março de 2023. Foram incluídas pesquisas primárias que reportaram a precisão dos testes ou o impacto no tempo de leitura ou na gestão clínica. O QUADAS-2 e o QUADAS-C foram usados para avaliar o risco de viés. Realizamos uma síntese narrativa.

Resultados Onze estudos avaliando seis softwares diferentes baseados em IA e reportando sobre 19.770 doentes foram elegíveis. Todos apresentaram alto risco de viés, com várias preocupações sobre a aplicabilidade. Comparado com a leitura sem auxílio, a leitura assistida por IA foi mais rápida e, geralmente, melhorou a sensibilidade (+5% a +20% para detectar/categorizar nódulos acionáveis; +3% a +15% para detectar/categorizar nódulos malignos), com menor especificidade (−7% a −3% para detectar/categorizar corretamente pessoas sem nódulos acionáveis; −8% a −6% para detectar/categorizar corretamente pessoas sem nódulos malignos). A assistência por IA tendia a aumentar a proporção de nódulos alocados para categorias de risco mais altas. Assumindo uma prevalência de cancro de 0,5%, esses resultados se traduziriam em 150 a 750 cancros adicionais detectados por milhão de pessoas que participam do rastreamento, mas levariam a 59.700 a 79.600 pessoas que participam do rastreamento sem cancro recebendo vigilância de TC desnecessária.

Conclusões A assistência de IA no rastreamento de cancro de pulmão pode melhorar a sensibilidade, mas aumenta o número de resultados falso-positivos e a vigilância desnecessária. Pesquisas futuras precisam aumentar a especificidade da leitura assistida por IA e minimizar o risco de viés e preocupações sobre aplicabilidade por meio de um melhor desenho dos estudos.

Número de registo do PROSPERO CRD42021298449.

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Artificial intelligence (AI)-based software is increasingly used to assist the detection and measurement of pulmonary nodules as part of lung cancer screening, but its impact on test accuracy and clinical management has not been comprehensively critiqued and summarised.

WHAT THIS STUDY ADDS

- AI assistance in lung cancer screening tends to increase sensitivity (detecting more cancers) but at the cost of reduced specificity (resulting in significant additional surveillance of nodules, which would never develop into cancer).
- Evidence was mostly from retrospective studies conducted in research settings with high risk of bias and applicability concerns.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Adoption of AI software and further research should focus on improving the specificity of AI assistance and prospective collection of evidence from in-practice settings using robust study design.

INTRODUCTION

Early detection, assessment, monitoring and timely intervention of pulmonary nodules are the key approach to reducing lung cancer morbidity and mortality. Lung cancer screening programmes have been established in several countries including the USA, Croatia, Czech Republic and Taiwan following growing evidence demonstrating survival benefits.[1 2] In September 2022, the UK National Screening Committee recommended targeted lung cancer screening using low-dose CT for people aged 55–74 identified as being at high risk of lung cancer.[3]

Recommendations for nodule management differ across guidelines internationally,[4] but most rely on measuring the diameter or the volume of the nodule to help determine next steps. Many individuals with nodules are placed under regular CT surveillance to assess whether the nodule is growing. Obtaining an accurate manual measurement of nodules can be challenging; nodules present in a wide range of different shapes and sizes. There is evidence of substantial inter-reader and intra-reader variability, and that variability increases the more complex the nodule morphology is.[5] In the recently published Dutch–Belgian lung cancer screening trial (NELSON), 9.2% of the CT scans were indeterminate (ie, showed either a solid nodule with a volume of 50–500 mm^3,

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pleural-based solid nodules with a minimal diameter of 5–10 mm or a solid nodule with a non-solid component with a mean diameter of ≥8 mm).[6] All these individuals required a repeat CT scan in 3 months to calculate volume-doubling time. As the proportion of people with nodules detected on CT scans is high, the accurate measurement and appropriate management of nodules have significant implications for radiologist time and potential patient anxiety.

Computer-aided detection (CAD) systems for assisting radiologists in reading CT scans, which rely on predefined rules, thresholds and patterns, have been available for many years. They were used in the NELSON trial,[6] the UKLS trial,[7] the Multicentric Italian Lung Detection trial[8] and the ongoing Yorkshire Lung Screening Trial.[9] Different types of software using modern forms of artificial intelligence (AI) capable of automatically detecting and measuring pulmonary nodules have become available and could potentially reduce the screening workload and reading time for radiologists. These operate differently to traditional CAD systems; they do not rely on predefined rules and instead learn task-relevant features and generate algorithms from raw input data.

We aimed to examine the accuracy of CE-marked (compliant with relevant European Union regulations), AI-based software use for automated detection and analysis of pulmonary nodules in chest CT scans as part of lung cancer screening. As secondary outcomes, we analysed the reading time and the provided information on the impact of AI assistance on Lung CT Screening Reporting & Data System (Lung-RADS) categorisation.

METHODS

Protocol and registration

This systematic review is an update of part of a diagnostic technology assessment for the National Institute for Health and Care Excellence.[10] The protocol for the original systematic review was registered with PROSPERO. This paper is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for diagnostic test accuracy studies.[11]

Data sources

We conducted literature searches on 17–19 January 2022 and updated these on 6 March 2023. The search strategy was based on three themes: lung cancer/nodules, AI and computer tomography/mass screening/early detection of cancer. Databases searched were MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane CENTRAL, Health Technology Assessment (HTA) database (CRD), International HTA database (INAHTA), Science Citation Index Expanded (Web of Science), Conference Proceedings—Science (Web of Science). Endnote V.20 was used to identify and remove duplicate results.

We searched or reviewed websites of selected conference proceedings, health technology assessment organisations, device manufacturers and devices@FDA between 24 January and 16 February 2022. Forward citation tracking from key publications of included studies was also undertaken in May 2022, using Science Citation Index (Web of Science) and Google Scholar. Details of the search strategies are provided in online supplemental material 1. Reference lists of included studies and recent, relevant systematic reviews identified via the database searches were checked.

Study selection

Two reviewers independently reviewed titles and abstracts of all retrieved records and all potentially eligible full-text publications against inclusion criteria. Disagreements were resolved by consensus or discussion with a third reviewer. Studies were eligible for inclusion if they reported test accuracy of AI-based software for automated detection and analysis of lung nodules from CT images performed for lung cancer screening or secondary outcomes relating to the impact on clinical management and practical implications. We included all AI-based software which had (or was anticipated to have) an appropriate regulatory approval (CE mark) across the UK and the EU by December 2021 and was near-market— that is, with anticipated availability for commercial use by 2023. The reference standard for lung nodule presence/absence was experienced radiologist reading. Lung cancer presence was confirmed by histological analysis of lung biopsy or health record review; lung cancer absence was confirmed by CT surveillance (imaging follow-up) without significant nodule growth or follow-up without lung cancer diagnosis. Eligible outcomes included test accuracy for nodule detection and/or risk categorisation based on size (any nodules, actionable nodules and malignant nodules, respectively), impact on clinical management and practical implications. Eligible study designs were test accuracy studies, randomised controlled trials, cohort studies, historically controlled trials, before–after studies and retrospective multireader multicase (MRMC) studies. We included peer-reviewed papers; conference abstracts and manufacturer data were only included if they were related to an eligible peer-reviewed full-text paper and reported additional outcome data.

We excluded studies using PET-CT scan images, lung phantom images or where less than 90% were CT images taken for lung cancer screening. We excluded studies if traditional CAD systems without deep learning were used, or they had no relevant test accuracy or clinical management outcomes, and non-human studies along with letters, editorials and communications unless they reported outcome data not reported elsewhere, in which case they were handled in the same way as conference abstracts. We excluded articles not available in English or published before 2012.

Data extraction and quality assessment

Detailed information related to study design, sampling of patients or CT scan images, AI-based software, reference standard and test accuracy outcomes was collected from each included study. Data allowing construction of 2×2 tables were extracted where possible, to calculate sensitivity and specificity. The unit of analyses (per person or per nodule) and features of detected/missed nodules were noted. Comparative data on the potential or actual impact of AI assistance on clinical management (eg, risk categorisation of lung nodules according to clinical guidelines based on measured nodule sizes) and time required by readers to interpret and report findings of the CT scans were also collected.

One reviewer extracted data into a predesigned electronic data collection form (online supplemental material 2). Data extraction sheets were checked by a second reviewer. Any disagreements were resolved through discussion, with the inclusion of a third reviewer when required. Study quality was assessed independently by two reviewers using QUADAS-212 combined with the QUADAS-C tool for comparative studies,13 tailored to the review question (online supplemental material 3). Assessment of applicability was based on a UK/EU frame of reference. Disagreements were resolved through consensus, with the inclusion of a third reviewer if required.

Data analysis

We focused on comparisons between trained human readers (radiologists or other trained healthcare professionals) assisted by AI-based software and those undertaking unassisted reading of CT scan images as this reflects current use of the technology in clinical practice. Supplementary evidence from other comparisons (ie, performance of stand-alone software vs unassisted reading) or non-comparative test accuracy studies (ie, AI-assisted reading or stand-alone software vs reference standard) were also reported where available. We calculated sensitivities and specificities in paired forest plots for the detection of any nodules, actionable nodules and malignant nodules. Where data allowed, we plotted our findings in receiver operating characteristic (ROC) space. Given the substantial heterogeneity in study populations, technologies, reader specialty and experiences, reference standards, test accuracy outcomes used and other study design features, no meta-analysis was carried out and findings are summarised narratively. Secondary outcomes such as reading time and impact on Lung-RADS ratings were summarised narratively.

RESULTS

Study selection

We retrieved 6330 unique results in January 2022, of which 4886 were published since 2012. Nine records were judged to be relevant,[14–22] and two records were identified from other sources.[23 24] Update sear-

ches in March 2023 yielded an additional 1687 results, only one was identified as potentially eligible[25] but was subsequently excluded. Eleven studies were, therefore, included (see online supplemental material 4 for full PRISMA flow diagram). Reasons for exclusions at full-text level are listed in online supplemental material 5.

Study characteristics

Characteristics of included studies are presented in table 1.[14–24] They comprised 19 770 screened participants. There is potential for overlap as some studies may have sampled the same patients while using the same databases. Two studies used data from the Korean Lung Cancer Screening Project[15 16] and four studies used US National Lung Screening Trial (NLST) data.[18–20 22] Three studies were conducted in the USA.[14 18 20] Two studies reported data from the same screening programme in South Korea.[15 16] One study was conducted in each of the UK,[23] Taiwan[17] and China.[21] Two studies conducted in the Netherlands and Denmark22 and in South Korea,[19] respectively, utilised CT scan images from the US NLST. The remaining reader study was conducted in the Netherlands using ultralow-dose CT images from Russia.[24] Eight studies adopted an MRMC design.[17–24] Two of these used unaided reading originally carried out as part of clinical practice for the comparators.[21 23] Four studies sampled consecutive

Table 1 Characteristics of included studies

Study, country, software, time period for CT scan	Design, setting, sampling method and sample size	Index test and comparator(s) *	Reader details/reading conditions	Reference standard	Reported outcomes
Chamberlin *et al* USA AI-Rad Companion, prototype VA10A (Siemens Healthineers) January 2018–July 2019[14]	Retrospective test accuracy study (non-comparative). Random sample from 1 US centre; 117 LDCT scans.	(A) Stand-alone AI	NA	**Nodules**: Consensus of two expert radiologists	**Accuracy for detecting nodules >6 mm (per person and per nodule analysis)**
Hall *et al* UK Veolity, version 1.2 (MeVis) Date unclear: LSUT November 2015–July 2017[23]	Retrospective test accuracy study and MRMC study (fully paired). Consecutive sample from UK-based LSUT; 735 LDCT scans.	(C) Concurrent AI (E) Original unaided reader	(C) MRMC: Two radiographers without prior experience in thoracic CT reporting. (E) Clinical practice (LSUT): Five radiologists with 5–28 years of experience in thoracic imaging (5% double reading).	**Clinically significant nodules**: Original radiologist reading or consensus of two independent radiologists after reviewing discrepant readings between study radiographers and original radiologists. **Cancer**: NR	**Accuracy for detecting clinically significant lung nodules ≥5 mm; accuracy for detecting malignant nodules;** reading time
Hsu *et al* Taiwan ClearRead CT, market version (Riverain Technologies) January–December 2017[17]	MRMC study (fully paired). Consecutive cases with nodules ≤10 mm or no nodules from one hospital in Taiwan; 150† CT images (57 LDCT from lung cancer screening).	(B) Second-read AI (C) Concurrent AI (D) Unaided reader	MRMC: Three residents in radiology and three experienced chest radiologists. Two reading sessions with 8-week washout period: first unaided reading followed by second-read AI, then concurrent AI; images in random order.	**Nodules**: Consensus of two thoracic radiologists with >15 years of experience	**Accuracy for detecting any nodules (stratified by seniority of readers)**
Hwang *et al* South Korea AVIEW Lungscreen (Coreline Soft) April 2017–March 2018[15]	Before-and-after study (unpaired). Consecutive participants from K-LUCAS (11–14 institutions): 1821 participants (before); 4666 participants (after).	(C) Concurrent AI (E) Original unaided reader	Clinical practice: attending thoracic radiologists from 14 institutions (unpaired design)	**Cancer**: Review of medical records	**Accuracy of detecting and categorising actionable nodules to detect lung cancer (Lung-RADS category ≥3)**
Hwang *et al* South Korea AVIEW Lungscreen (Coreline Soft) April 2017–December 2018[16]	Retrospective analysis of prospective cohort study (non-comparative). 10 424 consecutive participants from K-LUCAS (14 institutions)	(C) Concurrent AI	Clinical practice: 25 radiologists from 14 institutions with 5–38 years of experience; no comparator.	**Cancer**: Review of medical records; lung cancer diagnosed within 1 year (primary outcome) or any time after LDCT (secondary outcome)	**Accuracy of detecting and categorising actionable nodules to detect lung cancer (Lung-RADS category ≥3)**
Jacobs *et al* USA/Denmark/ Netherlands Veolity, version 1.5 (MeVis) August 2002–August 2004[22]	MRMC study (fully paired). Random sample from NLST (baseline and round 1), 40 cases from each Lung-RADS category; 160 LDCT scans.	(C) Concurrent AI (D) Unaided reader	MRMC: Three radiologists with >5 years of experience and four radiology residents. Two reading sessions with ≥2 weeks washout period: Half with AI support and half unaided per session; images in random order.	NA	Shift in Lung-RADS categorisation; Reading time
Lancaster *et al* Russia/Netherlands AVIEW LCS, version 1.0.34 (Coreline Soft) February 2017–2018[24]	MRMC study (fully paired). Nodule-enriched: ≥1 solid nodule, no lung cancer diagnosed within 2 years from MLCS baseline scan; 283 ultra-LDCT scans.	(A) Stand-alone AI (C) Concurrent AI (D) Unaided reader	(C) MRMC: Three thoracic radiologists with >7 years of experience in lung cancer screening. (D) MRMC: Two different thoracic radiologists with >7 years of experience in lung cancer screening (using other semi-automated volume measurement software).	**Nodules**: Independent consensus of three experienced radiologists and one IT technologist	**Accuracy of nodule volume measurement and categorisation (<100 mm^3, ≥100 mm^3)**

Continued

Table 1 Continued

Study, country, software, time period for CT scan	Design, setting, sampling method and sample size	Index test and comparator(s) *	Reader details/reading conditions	Reference standard	Reported outcomes
Lo *et al* USA ClearRead CT (first generation, pre-market) (Riverain Technologies) Date unclear: NLST screened from August 2002 to September 2007[18]	MRMC study (fully paired). Nodule-enriched: 2 normal cases for each case with nodules from NLST and 2 US hospitals; 324 LDCT scans.	(A) Stand-alone AI (C) Concurrent AI (D) Unaided reader	MRMC: 12 general radiologists with 6–26 years of experience. Two reading sessions with a minimum interval of 37 days (mean, 57 days): first unaided; then AI-assisted.	**Actionable nodules**: Consensus of three expert thoracic radiologist assisted by corresponding NLST or source documentation. **Cancer**: Histological findings (presence) or long-term follow-up (absence).	**Accuracy for detecting actionable nodules; accuracy for detecting malignant nodules;** reading time
Park *et al* USA/South Korea VUNO Med-LungCT AI, v.1.0.1 (VUNO) Date unclear: NLST baseline screen from August 2002[19]	MRMC study (fully paired). Nodule-enriched from NLST baseline screens; 200 LDCT scans.	(A) Stand-alone AI (C) Concurrent AI (D) Unaided reader	MRMC: One radiology resident and four radiologists with 1–20 years of experience. Two reading sessions with 6-week washout period: first unaided, then AI-assisted; images in random order.	**Cancer**: NR (Lung cancer diagnosed within 1 year in the NLST)	**Accuracy of detecting and categorising actionable nodules to detect lung cancer (Lung-RADS category ≥3)** Change in Lung-RADS category
Singh *et al* USA ClearRead CT, market version (Riverain Technologies) Date unclear: NLST screened from August 2002 to September 2007[20]	MRMC study (fully paired). Nodule-enriched: 100 with SSNs and 23 without SSNs from NLST; 123 LDCT scans.	(A) Stand-alone AI (C) Concurrent AI (vessel suppression only) (D) Unaided reader	MRMC: Two radiologists with 5 and 10 years of thoracic CT experience; sequential interpretation of unprocessed CT images alone, then vessel-suppressed images without washout period.	**Sub-solid nodules**: Consensus of two experienced thoracic radiologists (11 and 27 years of experience) with adjudication of conflicts by a third radiologist	**Accuracy for detecting sub-solid nodules ≥6 mm;** Change in Lung-RADS category
Zhang *et al* China InferRead CT Lung, market version (Infervision) November to December 2019[21]	Retrospective test accuracy study and MRMC study (fully paired). Consecutive sample from one hospital in China; 860 LDCT scans.	(C) Concurrent AI (MRMC study) (E) Original unaided reader (clinical practice)	(C) MRMC: One resident with 5 years of experience with supervision by one radiologist with 20 years of experience. (E) Clinical practice: One resident drafted report with supervision by radiologist (14 residents and 15 radiologists).	**Nodules**: Consensus of two radiologists with 20 and 31 years of experience	**Accuracy for detecting any nodules (stratified by types and sizes of nodules)**

*Index test and comparators: (A) Stand-alone AI: analysis of CT scan image by AI-based software without human input; (B) Second-read AI: CT scan image was first reviewed by an unaided human reader, then was re-interpreted after analysis by AI-based software was shown; (C) Concurrent AI: CT scan image was reviewed by a human reader assisted by concurrent display of analysis by AI-based software; (D) Unaided reader: CT scan image was reviewed by a human reader without assisted by AI-based software; (E) Original unaided reader: CT scan image was interpreted by a human reader as part of clinical practice, and therefore the reader was different from the human reader who interpret the CT scan image in the reader study.
†The study included mixed populations. Only those who underwent CT scans for screening were included in this systematic review.
AI, artificial intelligence; K-LUCAS, Korean Lung Cancer Screening; LDCT, low-dose CT; LSUT, Lung Screen Uptake Trial; Lung-RADS, Lung CT Screening Reporting & Data System; MLCS, Moscow Lung Cancer Screening; MRMC, multi-reader, multi-case study; NA, not applicable; NLST, National Lung Screening Trial.

patients,[15 16 21 23] and six used nodule-enriched samples,[17–20 22 24] while the remaining study adopted random sampling.[14]

Six different AI-based software programs were used in the studies: AI-Rad Companion (Siemens Healthineers),[14] AVIEW Lungscreen (Coreline Soft),[15 16 24] ClearRead (Riverain Technologies),[17 18,20] InferRead CT Lung (Infervision),[21] VUNO Med LungCT AI (VUNO)[19] and Veolity (MeVis).[22 23]

Risk of bias and applicability

The evidence is of low quality. There were problems in most studies in almost all domains in terms of risk of bias and applicability, given the design and operationalisation of the studies and our UK/EU frame of reference (table 2 and online supplemental material 6). Risk of bias according to QUADAS-C was considered 'high' in three or more domains in five of the eight comparative studies.[17 18 20 23] 24 These issues included no consecutive or random sampling, test set laboratory studies in which radiologist behaviour is known to differ from clinical practice,[26] unpaired design (before/after study or different radiologists with and without AI) and/or suboptimal or biased reference standard.

Test accuracy

AI-assisted reading versus unaided reading

Eight studies reported on AI-assisted reading, where AI-based software was used concurrently (seven studies[15 18–21 23 24]) or in addition sequentially (also referred to as 'second-read AI')[17] to re-interpret images.

One study (described later) compared AI assisted radiographers (without prior experience in thoracic CT reporting) with unaided, experienced radiologists.[23] Across all remaining seven studies, the addition of concurrent AI to trained radiologists increased sensitivity and decreased specificity compared with unaided, trained radiologists. Two studies reported detection of actionable nodules (range: +5% to +13% for sensitivity; −3% to −6% for specificity)[18 20] and one for detecting malignant nodules (+15% for sensitivity, −6% for specificity).[18] Two studies reported detection of lung cancer through Lung-RADS category ≥3 (range, +3% to +7% for sensitivity; −8% to −6% for specificity),[15 19] see figure 1 and online supplemental material 7. Concurrent AI-assistance also increased sensitivity (+20%) and decreased specificity (−7%) in nodule measurement and categorisation using a volume cut-off of 100 mm^3.[24] For detection of nodules of any size, including nodules too small to be considered clinically actionable, radiologists' sensitivity was increased with concurrent AI use (range, +16% to +56%), with an unclear impact on specificity (range, −3% to +4%).[17 21] One of these studies[17] evaluated both concurrent AI and second-read AI and found very similar sensitivity (79% vs 80%) and specificity (81% vs 82%), see online supplemental material 7 and 8.

For illustrative purposes (ie, the examples given here are plausible but hypothetical, given that test accuracy often changes as the scre-

Table 2 Limitations of the included studies

Reference and country	Applicability concerns regarding European screening population	Design concerns	Laboratory effect[26]	Applicability concerns to European screening LDCT reading practice	Applicability concerns—actionable nodule definition	Bias in reference standard	Nodule detection or measurement only	Accuracy reported per nodule only
Chamberlin *et al*, USA[14]	**Yes—** 1 US centre; 55–80 years. Excluded images rejected by software due to slice thickness >3 mm or poor image quality.	**Yes—** Non-comparative (A)	(A) NA	**Yes—** Stand-alone AI	**Yes—** >6 mm	**Nodules: Yes—** <3 experienced chest radiologist; not blinded to index test	**Yes—** Detection of actionable nodules	**No**
Hall *et al*, UK[23]	**No**	**Yes—** Fully paired CT images but not the same readers with and without AI.	(C) **Yes—** MRMC	**Yes—** (C) Two inexperienced radiographers. (E) 5% double reading.	**No**	**Nodules: Yes—** Original radiologist report (E) plus radiologist review of scans with additional nodules detected by (C).	**Yes—** Detection of actionable nodules. Detection of malignant nodules ((C) only).	**No**
			(E) **No**			**Cancer: Unclear—** Cancers detected either from baseline scan or nodule surveillance.		
Hsu *et al*, Taiwan[17]	**Yes—** One centre in Taiwan; 31/57 never smoked. Selected cases with nodule≤1 cm or no nodules. Exclusion of cases with severe pulmonary fibrosis, diffuse bronchiectasis, extensive inflammatory consolidation, pneumothorax, and massive pleural effusion. 2.5 mm slice thickness.	**No**	(A) NA	**Yes—** (A) Stand-alone AI. (B) (C) (D) Three residents in radiology; three experienced chest radiologists.	**Yes—** No size cut-off used.	**Nodules: Yes—** <3 experienced chest radiologists; not blinded to index test.	**Yes—** Detection of any nodules.	**Yes—** Per-nodule sensitivity; per-person specificity.
			(B) (C) (D) **Yes—** MRMC					
Hwang *et al*, South Korea[15]	**Yes—** 11 (before) and 14 (after) institutions in Korea (K-LUCAS). Only 145/6,487 (2.2%) women.	**Yes—** (A) Non-comparative. (C) (E) Unpaired non-randomised; not the same readers with and without AI.	(A) NA	(A) **Yes—** Stand-alone AI.	(A) **Yes—** No size cut-off used.	**Nodules: Yes—** Single radiologist with second-read AI. **Cancer: Yes—** Medical record review.	(A) **Yes—** Nodule detection (any, actionable, malignant).	(A) **Yes—**Per-nodule sensitivity.
			(C) (E) **No**	(C) (E) **No**	(C) (E) **No**		(C) (E) **No**	(C) (E) **No**
Hwang *et al*, South Korea[33]	**Yes—** 14 institutions in Korea (K-LUCAS). Only 283/10,424 (2.7%) women.	**Yes—** Non-comparative (C)	**No**	**No**	**No**	**Cancer: Yes—** Medical record review.	**No**	**No**
Jacobs *et al*, NL, USA, Denmark[22]	**Yes –** US NLST (baseline and round 1). Nodule-enriched; Lung-RADS ≥3 120/160 (75%). Slice thickness 1.0 to 3.2 mm.	**No**	(C) (D) **Yes—** MRMC	**Yes—** Three radiologists with >5 year of experience and four radiology residents (fifth year).	**No**	**NA**	**NA**	**NA**
Lancaster *et al*, NL, Russia[24]	**Yes—** Ultra-LDCT (≤1 mSv); 50–80 years. Selected participants who had ≥1 solid nodule and did not develop lung cancer in following 2 years.	**Yes—** Not the same readers with and without AI.	(A) NA	(A) **Yes—** Stand-alone AI	**No**	**Nodule size and categorisation: Yes—** 2/4 consensus panel readers involved in index test.	**Yes—** Nodule measurement and risk category.	**No**
			(C) (D) **Yes—** MRMC	(C) (D) **No**				

Continued

Table 2 Continued

Reference and country	Applicability concerns regarding European screening population	Design concerns	Laboratory effect[26]	Applicability concerns to European screening LDCT reading practice	Applicability concerns—actionable nodule definition	Bias in reference standard	Nodule detection or measurement only	Accuracy reported per nodule only
Lo *et al*, USA[18]	**Yes—** US NLST and 2 US hospitals; nodule-enriched (1:2); 3/178 nodules ≥3 mm.	**No**	(A) NA (C) (D) **Yes—** MRMC	**Yes—** (A) Stand-alone AI. (C) (D) 12 general radiologists.	**No**	**Nodules: No** **Cancer: No**	**Yes—** Detection of nodules (actionable, malignant).	**Yes—** Per-nodule sensitivity; per-person specificity.
Park *et al*, South Korea, USA[19]	**Yes –** US NLST; Nodule and cancer-enriched: Prevalence of Lung-RADS≥3 127/200 (64%); lung cancer prevalence 31/200 (16%).	**No**	(A) NA (C) (D) **Yes—** MRMC	**Yes—** (A) Stand-alone AI. (C) (D) 1 of 5 readers was a fourth-year radiology resident.	**No**	**Cancer: Unclear—** Same-year positive cancer diagnosis (not stated how diagnosed).	**No**	**No**
Singh *et al*, USA[20]	**Yes—** US NLST; enriched for sub-solid nodules: prevalence of sub-solid nodules 100/123 (81%).	**No**	(A) NA (C) (D) **Yes—** MRMC	(A) **Yes—** Stand-alone AI. (C) **Unclear—** AI for vessel suppression. (D) **No**	**No**	**Nodules: No**	**Yes—** Detection of actionable nodules.	**Yes—** Per-nodule sensitivity; Per-person specificity.
Zhang *et al* China[21]	**Yes—** One hospital in China (part of NELCIN-B3); general population aged 45–74 years.	**Yes—** Not the same readers with and without AI.	(C) **Yes—** MRMC (E) **No**	**Yes—** (C) One resident supervised by 1 radiologist; (E) 1 of 14 residents supervised by 1 of 15 radiologists.	**Yes—** No size cut-off.	**Nodules: Yes—** <3 experienced chest radiologists; not blinded to index test.	**Yes—** Detection of any nodules.	**No**
Legend	**No =** Random or consecutive screening LDCT images from heavy current or former smokers aged 50–75 years[34] living in Europe; no inappropriate exclusions; ≤2 mm slice thickness.	**No =** Comparative, fully paired design; same readers with and without AI.	**No =** CT images assessed in clinical practice.	**No =** Single reading by experienced chest radiologist with (C) or without AI support (D) or (E).	**No =** In agreement with BTS[35], Lung-RADS[36] or EUPS[37] guidelines.	**No =** Nodules: ≥3 blinded, experienced chest radiologists. Cancer: Histopathology after biopsy/excision or 2-year follow-up without cancer diagnosis.	**No =** Accuracy of detection + risk categorisation + recall for lung cancer diagnosis.	**No =** Per-person sensitivity and specificity.

Index test and comparators: (A) Stand-alone AI: Analysis of CT scan image by AI-based software without human input; (B) Second-read AI: CT scan image first reviewed by an unaided human reader, then re-interpreted after analysis by AI-based software was shown; (C) Concurrent AI: CT scan image reviewed by a human reader assisted by concurrent display of analysis by AI-based software; (D) Unaided reader: CT scan image reviewed by a human reader without AI-based software assistance; (E) Original unaided reader: CT scan image interpreted by a human reader as part of clinical practice; different to the human reader who interpreted the CT scan image in the reader study.
AI, artificial intelligence; BTS, British Thoracic Society; Categ, categorisation; EUPS, European Position Statement; K-LUCAS, Korean Lung Cancer Screening Project; LDCT, low-dose CT; LSUT, Lung Screen Uptake Trial; Lung-RADS, Lung CT Screening Reporting & Data System; MRMC, multi-reader, multi-case study; NA, not applicable; NELCIN-B3, Netherlands-China Big-3 disease screening; NL, Netherlands; NLST, National Lung Screening Trial.

ened population and disease prevalence varies, and the data were based on individual studies that used different AI software), if the changes in sensitivity and specificity for the detection of malignant nodules with concurrent AI assistance was in the range of those observed in the large screening programme reported by Hwang et al[15] or in the MRMC study by Lo et al,[18] and if the prevalence of lung cancer among the screening population was similar to that observed in the NELSON trial (ie, 0.5%),6 AI assistance would allow an additional 150–750 people attending screening with cancers to be detected but an additional 59 700 to 79 600 people attending screening without cancer would be placed on CT surveillance and/or further investigations per million people screened (equivalent to a reduction in positive predictive value of screening from 5% to 3%[15] or from 3% to 2%, respectively[18]; online supplemental material 9).

Impact on Lung-RADS categorisation

Three MRMC studies provided comparative data on the impact of AI assistance on Lung-RADS categorisation of nodules.[19 20 22] The proportion of actionable nodules identified (Lung-RADS categories 3–4) was higher when images were assessed with AI assistance in all three studies (66% vs 53%,22 34.2% vs 28.5%,[19] 55% vs 50%[20]). However, no reference standards were used, so it is not possible to know whether the additional actionable nodules were malignant.

Impact on CT scan reading time

Three comparative MRMC studies reported on the impact of AI assistance on reading times.[18 22 23] Reading times were significantly faster with AI assistance compared with unaided readers: median 86 (IQR 51–141) seconds vs 160 (IQR 96–245) seconds (p<0.001)[22] and mean 98.0 seconds vs 132.3 seconds per case (p<0.01)[18] for radiologists, and median 3 (IQR 2–5) and 5 (IQR 4–8) min for radiographers using AI in a laboratory (ie, non-clinical) setting vs 10 (IQR 5–15) min for radiologists (unassisted reading in clinical practice).[23]

Other methods of using AI (stand-alone AI and supporting less experienced staff)

Studies have also investigated other ways of using AI (comparing stand-alone AI with no human input to unaided radiologists or used AI to support less trained staff) or used non-comparative evidence (eg, AI-assisted reading or unaided reading compared with a reference standard). These are presented in online supplemental material 8.

Across studies and outcomes, stand-alone AI was associated with the highest sensitivity (range 58%–100%) but lowest specificity (62%–82%) when compared with AI-assisted radiologist reading (sensitivity 71%–99%, specificity 74%–97%) and/or unaided radiologist reading (sensitivity 43%–94%, specificity 63%–97%) (online supplemental material 8).[18–20 24]

One study investigated whether AI assistance would support radiographers to match the accuracy of radiologists.[23] Experienced radiologists were more sensitive (91% vs 71%) and specific (97% vs 92%) for detecting and categorising actionable nodules than AI-assisted reading by radiographers (without prior experience in thoracic CT reporting) (online supplemental material 8). Further decisions of experienced, unaided radiologists (made during clinical practice) were consistent with British Thoracic Society guidance 71.6% of the time, while the decisions of two radiographers with AI assistance in a laboratory setting were consistent with the guidance 39.7% and 60.7% of the time, respectively.

DISCUSSION

Summary of clinical context

Targeted lung cancer screening programmes are being set up in many countries due to strong randomised controlled trial (RCT) evidence that screening leads to a reduction in lung cancer-specific mortality. This will, however, place enormous pressure on already over-stretched healthcare systems, particularly in terms of scanner capacity and radiologist time. Different types of software using AI-derived algorithms have become available and could potentially

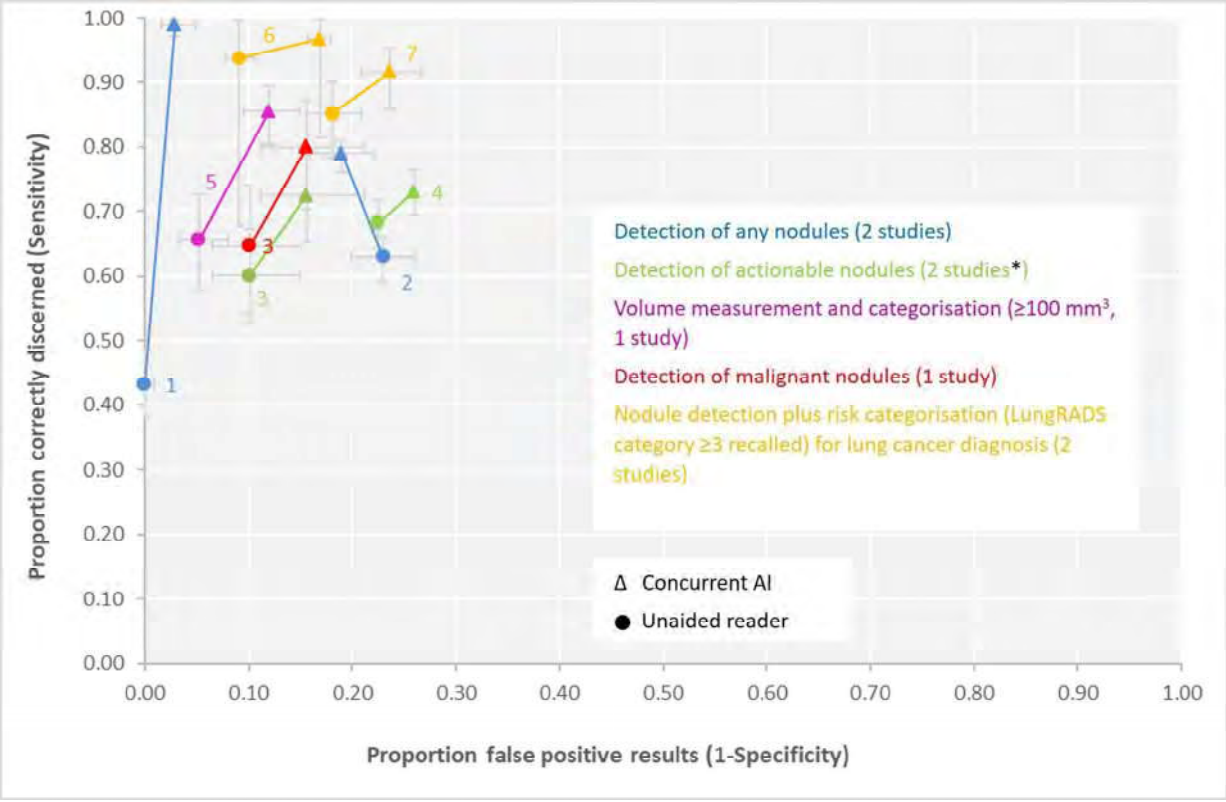

Figure 1 Accuracy of readers (nodule detection; nodule categorisation based on volume measurement; or nodule detection plus risk categorisation and recall decision for lung cancer diagnosis) both with and without concurrent AI use (seven studies with comparative data). Estimates connected with a line are from the same study. [1] Zhang *et al*[21]; [2] Hsu *et al*[17]; [3] Lo *et al*[18]; [4] Singh *et al*[20]; [5] Lancaster *et al*[24]; [6] Hwang *et al*[15]; [7] Park *et al*.[19] *Data from Hall *et al*[23] are not presented as the study compared AI-assisted reading by radiographers against unaided radiologists, which differed in nature from the other studies. AI, artificial intelligence; Lung-RADS, Lung CT Screening Reporting & Data System.

reduce the screening workload and reading time for radiologists. These AI-based software, however, also have the potential to cause patient harm or create further workload for radiologists, and evidence is required to determine their performance in a screening context. Here, we have reported the results of a systematic review, synthesising the available evidence on the accuracy, reading time and impact on clinical management.

Statement of principal findings

Our searches yielded 6573 publications, from which 11 heterogeneous studies, reporting on nearly 20 000 patients from six different countries and using six different AI-based software systems were included. All 11 studies were at high risk of bias with multiple applicability concerns. We used a narrative approach to summarise our results, finding that AI-assisted reading was faster and generally improved sensitivity (range: +5% to +20% for detecting/categorising actionable nodules; +3% to +15% for detecting/categorising malignant nodules), with lower specificity (range: −7% to −3% for correctly detecting/categorising people without actionable nodules; −8% to −6% for correctly detecting/categorising people without malignant nodules) compared with unaided reading. AI assistance tended to increase the proportion of nodules allocated to higher risk categories. If these findings were replicated in a population of a million people attending screening, the impact of AI would be an extra 150–750 cancers detected at the cost of 59 700–79 600 people receiving unnecessary surveillance, reducing positive predictive value.

Strengths and limitations

Our searches were extensive but limited by date (January 2012–March 2023). The 2012 cut-off was introduced after discussion with experts who considered that our definition of AI would not include systems introduced or tested prior to that date. Our searches are also limited to studies published in the English language although this is unlikely to have biased our findings.[27 28] We aimed to include all AI-based software, which had (or was anticipated to have) appropriate regulatory marking (CE mark) across the UK and the EU, with anticipated availability for commercial use by 2023. However, our searches were inclusive, and we were unlikely to have omitted significant studies from our research because of this inclusion criterion.

QUADAS-2 was used independently by two reviewers[12] combined with the QUADAS-C tool for comparative studies,[13] which we tailored to the review question to assess risk of bias and applicability. Almost all the studies fell short in key elements of quality, including patient selection, definition of reference standard, index test and flow and timing. The studies we identified were extremely heterogeneous using six different AI-based software systems and from at least six different countries, where the epidemiology of lung cancer, training of radiologists and experience of use of CT screening for lung cancer differ substantially. Therefore, we undertook a narrative review and plotted our findings in ROC space, however if it was possible, meta-analysis would allow for more precise estimates of the accuracy of the addition of AI-based software to CT lung cancer screening. We acknowledge that the potential benefit of AI assistance (150–750 additional lung cancers detected in a screened population of a million people) will depend on the prevalence of lung cancer in the cohort and as such is not generalisable to other populations at higher or lower risk. In addition, software derived from AI potentially allows continuous improvement of performance through learning from expanding sources of data. Although the various softwares evaluated in our review did not involve learning from data in real time, companies may refine their software by retraining their AI models with new datasets and then update the AI-derived algorithms used in the software periodically. Published evaluations on the performance of AI-based software in screening are, therefore, only a snapshot and could be outdated by the time when they are published, and our findings might not completely reflect systems that are currently available. The AI software that we evaluated only processed and utilised data from CT scan images to enhance nodule segmentation, detection and measurement that underpin current practice based on contemporary guidelines. Use of AI software to combine and interrogate additional morphological data from scan images (radiomics) along with a wide range of demographic, histological, proteomic and genomic data for prediction of nodules that are malignant is an area of very active research. These advances could fundamentally change clinical practice in the future. Nevertheless, it is crucial that any claims of improvement in risk stratification and cancer detection with AI software are supported by robust evidence generated from studies with strong designs that address risk of bias and applicability concerns that we highlighted.

Strengths and weaknesses versus other studies

We identified 12 previous systematic reviews on the accuracy of AI for lung nodule/cancer detection and/or malignancy risk prediction in medical images. Nine of these were non-comparative and focused on stand-alone AI performance of algorithms that were not commercially available, so were not informative for our review question (references are reported in online supplemental material 10). One rapid review[29] was comparative but focused on the accuracy of AI-based software for the classification of lung nodules into benign or malignant, a software function that was not included in our review.

Two reviews[30 31] did cover our question but were broader and did not separately report on the screening population or on commercially available software. Li et al[31] evaluated the impact of AI on physicians' performance in detecting various thoracic pathologies on CT and chest X-ray. The review by Ewals et al.[30] was more relevant but covered not only the screening population but also the oncologic, symptomatic or mixed populations as well as software that was not commercially available. Of our 11 included papers, only one[20] was identified in the review by Li et al[31] and three[17 18 21] in the review by Ewals et al.[30] Despite the broader population in the review by Ewals et al, they found a similar pattern of increased sensitivity and reduced specificity with AI use. However, Li et al found that, across all pathologies and both image types, both sensitivity and specificity generally improved when using AI-based devices. In concordance with our review, a faster reading time was reported with concurrent AI use in both previous reviews.[30 31]

CONCLUSIONS AND IMPLICATIONS FOR CLINICIANS AND POLICYMAKERS

Our systematic review demonstrates that, when used in population-based lung cancer screening programmes, assistance of AI-based software can increase sensitivity, but at the expense of a reduction in specificity, that is, an increase in false-positive findings. The lung checks in the NHS England Targeted Lung Health Checks programme are already supported by AI,[32] and removing AI-based software from existing screening programmes is not a practical policy option. However, the limited available evidence suggests that there is significant scope for improvement in the AI-based software, particularly in specificity. This is particularly important to consider as the screening programme is rolled out in the UK, given the potential increase in false-positive findings and the resulting additional workload for radiologists and anxiety for patients. Furthermore, care must be taken that AI-based software does not contribute to changing disease definitions or referral thresholds as the limited evidence base suggests its measurements and categorisations are more cautious and biased towards greater referral. Finally, more research is needed particularly in clinical settings and around the impact of AI assistance on medical staff with less training. Prospective, comparative, test accuracy studies that measure accuracy of the whole testing pathway with AI assistance integrated in clinical practice and compare it with the accuracy of the pathway without AI assistance are needed.

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ARTIGO ORIGINAL

Efeitos do consumo moderado de álcool e hipoxia hipobárica: implicações para o sono dos passageiros, saturação de oxigénio e frequência cardíaca em voos de longa duração

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RESUMO

Contexto Passageiros em voos de longa duração frequentemente consomem álcool. O sono durante o voo agrava a queda na saturação de oxigénio no sangue (SpO_2) causada pela diminuição da pressão parcial de oxigênio na cabine. Investigamos a influência combinada do álcool e da hipoxia hipobárica no sono, SpO_2 e na frequência cardíaca.

Métodos Dois grupos de indivíduos saudáveis passaram duas noites com uma oportunidade de sono de 4 horas (00:00–04:00 horas) no laboratório de sono (n=23; 53 m acima do nível do mar) ou na câmara de altitude (n=17; 753 hPa correspondendo a 2438 m acima do nível do mar, condição hipobárica). Os participantes consumiram álcool antes de uma das noites (concentração média±erro padrão da concentração de álcool no sangue 0,043±0,003%). A ordem das noites foi contra-balanceada. Duas noites de recuperação de 8 horas (23:00–07:00 horas) foram programadas entre as condições. Polissonografia, SpO_2 e frequência cardíaca foram registrados.

Resultados A exposição combinada ao álcool e à condição hipobárica reduziu a SpO_2 para uma mediana (percentil 25/75) de 85,32% (82,86/85,93) e aumentou a frequência cardíaca para uma mediana (percentil 25/75) de 87,73 bpm (85,89/93,86) durante o sono, em comparação com 88,07% (86,50/88,49) e 72,90 bpm (70,90/78,17), respectivamente, na condição hipobárica sem álcool, 94,97% (94,59/95,33) e 76,97 bpm (65,17/79,52), respectivamente, na condição com álcool e 95,88% (95,72/96,36) e 63,74 bpm (55,55/70,98), respectivamente, na condição sem álcool do grupo do laboratório de sono (todos p<0,0001). Sob a exposição combinada, a SpO_2 foi de 201,18 min (188,08/214,42) abaixo do limiar clínico de hipoxia de 90% de SpO_2, em comparação com 173,28 min (133,25/199,03) na condição hipobárica e 0 min (0/0) em ambas as condições do laboratório de sono. O sono profundo (N3) foi reduzido para 46,50 min (39,00/57,00) sob a exposição combinada, em comparação com ambas as condições do laboratório de sono (álcool: 84,00 min (62,25/92,75); sem álcool: 67,50 min (58,50/87,75); ambos p<0,003).

Conclusões A combinação de álcool e hipoxia hipobárica durante o voo reduziu a qualidade do sono, desafiou o sistema cardiovascular e levou a uma duração prolongada da hipoxemia (SpO_2 <90%).

Key messages

What is the key question?

►To stay in a hypobaric environment is known to decrease oxygen saturation and increase heart rate. Aeroplane passengers with cardiopulmonary diseases have an increased risk of aggravation of symptoms due to the decreased cabin pressure at cruising altitude, which is amplified during sleep. Alcohol, which is often consumed on board, has similar effects, but hypobaric hypoxia-induced changes are usually more pronounced.

What is the bottom line?

►This study is the first to investigate the combined impact of hypobaric hypoxia and alcohol during sleep. Effects on oxygen saturation and heart rate were supra-additive. Young and healthy individuals experienced prolonged and clinically relevant desaturations.

Why read on?

►We show that the on-board consumption of alcohol is an underestimated health risk that could be easily avoided. Practitioners, passengers and crew should be informed about the potential risks, and it may be beneficial to consider altering regulations to restrict the access to alcoholic beverages on board aeroplanes.

INTRODUCTION

The number of long-haul flights has been increasing for many years. While in 2002 about one billion air travellers per year were estimated,[1] in 2018 the number had quadrupled.[2] The environmental conditions during flight might pose health risks for passengers, especially those with respiratory diseases.[3] To increase passenger safety, the minimal cabin pressure on commercial flights is equivalent to 2438 m (753 hPa) as prescribed by international regulations,[1] which is defined as the lower limit of moderate altitude.[4–7] Atmospheric pressure decreases exponentially with altitude due to the diminishing mass of the overlying air column and decreasing gravitational force. This leads to a decline in arterial oxygen partial pressure (PaO_2), which falls to approximately 73 hPa at 2438 m, a level that corresponds to a blood oxygen saturation (SpO_2 = proportion of oxygen-saturated haemoglobin) of approximately 90% in healthy persons.[5,6] Due to the sigmoid shape of the oxygen binding curve, a further reduction of PaO_2 below 73 hPa results in a more pronounced drop in SpO_2 per linear drop in PaO_2 [8] and is defined as hypobaric hypoxia.[9] Acclimatisation in the mountains can reduce the negative effects of the reduced atmospheric pressure on SpO_2.[10–12] However, such an acclimatisation cannot be achieved during a long-haul flight.

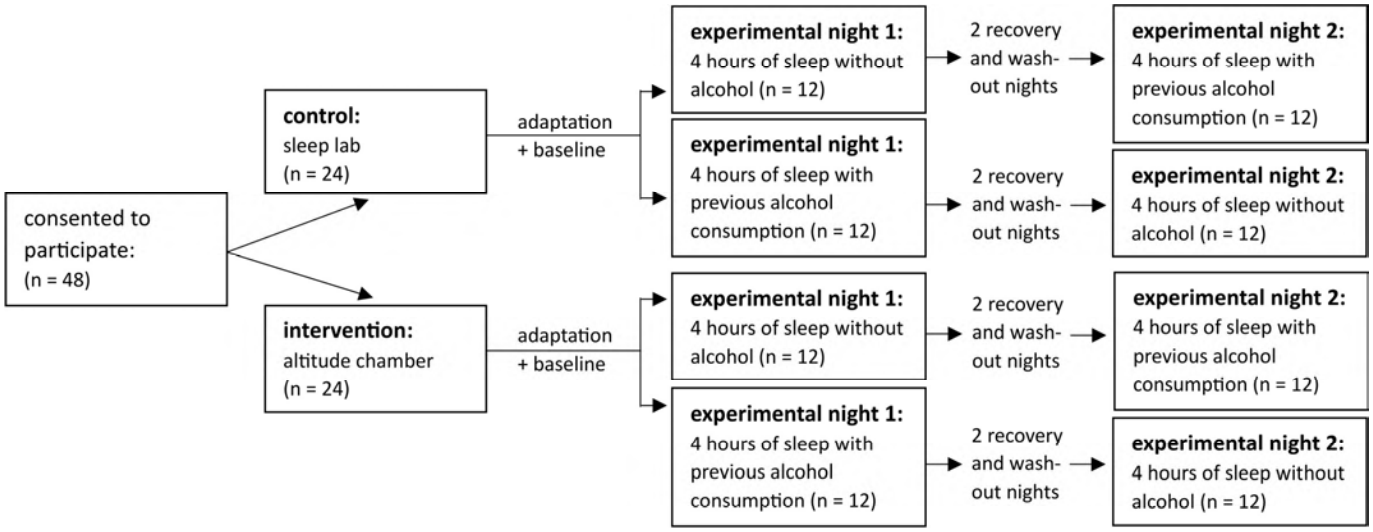

Figure 1 Study flow.

Offering free alcoholic beverages to passengers during long-haul flights is so common that surveys were conducted to see whether passengers would prefer to book non-alcoholic flights.[13] It is therefore important to understand the implications of a combination of alcohol consumption and sleep during long-haul flights.

Alcohol acts as a potent somnogen which leads to a reduced sleep onset latency and rapid eye movement (REM) sleep duration[14–18] and may result in cognitive impairment, difficulties in concentration and memory disorder.[19] The alcohol-induced systemic vasodilatation increases heart rate during sleep.[20] Hypobaric hypoxia leads to a shortened N3 and REM sleep duration and decreased SpO2 during sleep while the heart rate is increased.[21] We hypothesised that the combination of alcohol and hypobaric conditions would exacerbate the changes in sleep observed under single exposure conditions.

METHODS

Participants

Forty-eight participants aged 18–40 years were randomly assigned to two groups stratified by age, gender and body mass index (for further details see online supplemental method). Applicants with physical, psychological, intrinsic sleep or circadian disorders were excluded from participation in this study based on the results of questionnaires, medical history, physical examination, blood and urine tests and electrocardiography.

Laboratory procedures

The study was performed at the Institute of Aerospace Medicine of the German Aerospace Centre in Cologne. The protocol described in this paper was a segment of a larger research project that investigated a range of related research goals (see online supplemental method).[22] This paper presents data of two experimental nights in which sleep opportunities lasted 4 hours (00:00–04:00 hours). One of the experimental nights was preceded by alcohol exposure in the evening.

The Control Group slept under conditions of normobaric normoxia in the sleep laboratory (53 m altitude) whereas the InFlight Group slept in a simulated crew-rest compartment in the altitude chamber where the pressure was decreased to 753 hPa, simulating the minimal pressure inside an aeroplane cabin at cruising altitude. In addition, realistic noise as inside a plane (70 dB(A) recorded during a flight from Cologne to Kairo) was generated.

The following two groups and conditions were compared:

Control Group: (a) one night without alcohol consumption in normobaric conditions at sea level (Control NonAlc) and (b) one night with previous alcohol consumption in normobaric conditions at sea level (Control Alc).

InFlight Group: (a) one night without alcohol consumption in hypobaric conditions (InFlight NonAlc) and (b) one night with previous alcohol consumption in hypobaric conditions (InFlight Alc). The flowchart in figure 1 provides details of study flow.

Alcohol administration

The individual amount of alcohol needed to achieve the target value of 0.06% blood alcohol concentration (BAC) was selected with reference to the usual BAC limits for driving in Western Europe (0.05%) and the USA (0.08%) and was calculated according to the modified Widmark formula of Watson et al.[23] This is equivalent to drinking two cans of beer (5%) or two glasses of wine (175 mL, 12%). At 23:15 hours the participants drank the calculated amount of pure vodka (on average 114.5 mL). Due to individual variability in resorption and absorption rates, the average BAC of the subjects measured at 23:45 hours was 0.043±0.003%. The next morning at 06:00 hours the BAC was 0.0±0.0% in both groups. All mentioned BACs were calculated from the measured breath alcohol concentrations (with Dräger Alcotest 6810) according to Pavlic et al.[24]

During the nights polysomnography, SpO_2 and heart rate were monitored continuously.

Polysomnography

Polysomnography was recorded according to the international 10–20 system (electroencephalography (EEG): C3, F3, O1, and C4, F4, O2, referenced to A2 and A1, respectively, electro-oculography, submental electromyography) as previously described.[7] One trained technician scored sleep stages and EEG arousals according to conventional criteria.[25] Heart rate was recorded with one-lead electrocardiography.

We derived the following dependent variables: total sleep time (TST), sleep efficiency (SE; TST/time in bed×100), sleep onset latency (SOL) defined as the first occurrence of any sleep stage deeper than N1 (ie, N2, N3, or REM), duration spent in sleep stages N1–3 and REM, wake after sleep onset (WASO; ie, wake duration between sleep onset and end of time in bed), number of sleep stage

Table 1 Participant demographics and blood alcohol concentration (alcohol condition)

	Control Group	InFlight Group	P value (Wilcoxon)
Sample size	n=23	n=17	
Sex (% male)	61	47	0.3967
Age (years)	26.4±1.2	26.4±1.2	0.8274
BMI (kg/m^2)	24.3±0.6	23.5±0.6	0.3510
Usual alcohol intake (g/week)	24.4±4.15	39.6±8.2	0.2202
Heart rate, resting (bpm)	67.4±2.6	65.4±2.8	0.6153
Blood alcohol concentration (%)	0.042±0.003	0.043±0.005	0.7954

Values are shown as mean±SE.
bpm, beats per min

Table 2 Descriptive statistics and mixed ANOVA results: polysomnography and heart rate

Condition	Normal sleep	Alcohol	Hypobaric hypoxia	Combination of alcohol and hypobaric hypoxia	Mixed ANOVA		
Group	Control Group (Control NonAlc)	Control Group (Control Alc)	InFlight Group (InFlight NonAlc)	InFlight Group (InFlight Alc)	Condition	Group	Interaction Condition × Group
	Median (25th/75th percentile)	Median (25th/75th percentile)	Median (25th/75th percentile)	Median (25th/75th percentile)	P value	P value	P value
Polysomnography							
TST (min)	213.00 (211.25/216.75)	218.00 (209.75/221.75)	214.00 (194.00/217.50)	212.50 (199.00/222.00)	0.3972	**0.0117**	0.8725
SE (%)	88.75 (88.02/90.31)	90.83 (87.40/92.40)	89.17 (80.83/90.63)	88.54 (82.92/92.50)	0.3972	**0.0082**	0.8725
SOL (min)	22.50 (13.75/25.00)	16.00 (10.50/22.75)	19.00 (13.50/23.50)	12.50 (10.50/20.50)	**0.0060**	0.7180	0.4366
N1 (min)	9.50 (5.50/13.00)	**6.00 (3.50/9.00)**	7.00 (5.50/10.00)	6.50 (4.00/14.00)	0.0714	0.0870	0.0869
N2 (min)	88.00 (78.75/103.00)	99.00 (87.75/113.50)	**116.00 (105.00/132.00)**	**138.00 (116.00/150.50)**	**0.0017**	**<0.0001**	0.6193
N3 (min)	67.50 (58.50/87.75)	84.00 (62.25/92.75)	51.00 (47.50/66.00)	**46.50 (39.00/57.00)**	0.7250	**0.0002**	**0.0369**
REM (min)	37.00 (32.50/51.00)	**32.50 (23.75/36.75)**	**22.00 (20.00/31.00)**	**14.50 (9.50/19.50)**	**<0.0001**	**<0.0001**	0.7523
WASO (min)	5.50 (3.00/7.50)	5.50 (3.25/9.50)	**9.00 (5.00/20.50)**	**10.50 (6.50/20.50)**	0.2624	**0.0018**	0.7672
SSW per h TST (number)	12.86 (9.88/14.63)	10.54 (9.03/13.07)	10.69 (8.88/14.21)	13.47 (12.13/14.09)	0.9147	0.6036	0.0842
Arousals per h TST (number)	4.79 (3.14/7.22)	5.15 (4.49/6.40)	4.64 (3.29/5.50)	5.58 (4.73/6.99)	**0.0424**	0.2410	0.0746
Heart rate							
TST (bpm)	63.74 (55.55/70.98)	**76.97 (65.17/79.52)**	**72.90 (70.90/78.17)**	**87.73 (85.89/93.86)**	**<0.0001**	**<0.0001**	**0.002**
N1 (bpm)	62.99 (58.74/70.89)	**77.46 (67.82/81.49)**	**72.96 (71.04/79.41)**	**90.79 (88.04/94.25)**	**<0.0001**	**<0.0001**	**0.0088**
N2 (bpm)	61.99 (54.47/69.74)	**75.90 (64.31/78.70)**	**75.79 (71.93/81.20)**	**87.46 (85.14/93.46)**	**<0.0001**	**<0.0001**	0.3102
N3 (bpm)	63.50 (55.41/72.05)	**77.42 (65.75/81.39)**	**72.48 (71.04/79.88)**	**89.06 (85.85/94.38)**	**<0.0001**	**<0.0001**	**0.0425**
REM (bpm)	66.74 (59.33/71.12)	**75.65 (68.68/80.43)**	**77.02 (74.73/80.61)**	**90.89 (86.95/94.63)**	**<0.0001**	**<0.0001**	**0.0068**

Sleep was restricted to 4 hours from 0:00 hours to 04:00 hours in all conditions.
Results of mixed ANOVAs with the main factors condition, group and the interaction between condition and group and post hoc Tukey–Kramer adjustment ($\alpha<0.05$). Significant ANOVA results and significant differences compared to normal sleep are printed bold. Mixed ANOVAs for polysomnography were adjusted for baseline sleep in the sleep laboratory as covariate.
22 datasets of the Control Group and 17 datasets of the InFlight Group were taken into account (see online supplemental method).
Arousals per h TST, number of arousals per hour TST; N1–3 and REM, sleep stages; SE, sleep efficiency (ie, percent TST of complete time spent in bed); SOL, sleep onset latency; SSW per h TST, number of sleep stage changes per hour TST; TST, total sleep time; WASO, wake after sleep onset.

Table 3 Descriptive statistics: oxygen saturation

Condition	Normal sleep	Alcohol	Hypobaric hypoxia	Combination of alcohol and hypobaric hypoxia
Group	Control Group (Control NonAlc)	Control Group (Control Alc)	InFlight Group (InFlight NonAlc)	InFlight Group (InFlight Alc)
	Median (25th/75th percentile)	Median (25th/75th percentile)	Median (25th/75th percentile)	Median (25th/75th percentile)
Oxygen saturation				
TST (%)	95.88 (95.72/96.36)	**94.97 (94.59/95.33)**	**88.07 (86.50/88.49)**	**85.32 (82.86/85.93)**
N1 (%)	96.27 (96.04/96.97)	**95.52 (95.08/95.93)**	**87.72 (86.37/89.01)**	**85.83 (83.02/86.47)**
N2 (%)	95.83 (95.50/96.39)	**94.89 (94.59/95.36)**	**88.26 (86.68/88.60)**	**85.51 (83.04/86.18)**
N3 (%)	95.77 (95.33/96.47)	**94.80 (94.45/95.19)**	**87.27 (86.14/89.00)**	**84.84 (82.18/85.88)**
REM (%)	96.54 (95.78/96.88)	**95.50 (94.63/95.88)**	**88.15 (87.03/88.77)**	**84.74 (83.63/85.81)**
Oxygen saturation <90%				
TST (min)	0.00 (0.00/0.00)	0.00 (0.00/0.00)	**173.28 (133.25/199.03)**	**201.18 (188.08/214.42)**
N1 (min)	0.00 (0.00/0.00)	0.00 (0.00/0.00)	**4.08 (2.60/6.49)**	**6.98 (3.90/12.16)**
N2 (min)	0.00 (0.00/0.00)	0.00 (0.00/0.00)	**30.21 (19.27/51.00)**	**132.68 (119.74/147.93)**
N3 (min)	0.00 (0.00/0.00)	0.00 (0.00/0.00)	**51.00 (32.72/56.50)**	**46.32 (37.20/52.11)**
REM (min)	0.00 (0.00/0.00)	0.00 (0.00/0.00)	**17.08 (9.56/20.26)**	**14.50 (9.75/21.25)**

Sleep was restricted to 4 hours from 00:00 hours to 04:00 hours in all conditions. Significant differences compared to normal sleep are printed bold.
22 datasets of the Control Group and 14 datasets of the InFlight Group were taken into account (see online supplemental method).
N1–3 and REM, sleep stages; TST, time sleep time.

changes (per hour TST) and number of arousals (per hour TST). Mean heart rates were calculated per TST, N1–3 and REM.

Blood oxygen saturation (SpO_2)

A finger tip sensor was part of the sleep recording device (PD3, DLR) and used to measure SpO_2. From these data, average SpO_2 values were calculated per TST, N1–3 and REM as dependent variables. A further finger tip sensor (PalmSAT 2500 Series, Nonin) provided continuous online monitoring during sleep periods, ensuring the safety of the participants in the altitude chamber.

Statistical analysis

We analysed the single and combined effects of alcohol and hypobaric conditions on dependent variables using SAS version 9.4. In mixed ANOVAs with the main factors condition (alcohol, no alcohol), group (Control Group, InFlight Group) and the interaction between condition and group, we analysed dependent variables of sleep and heart rate. Individual baseline parameters of sleep in the sleep laboratory were included as covariates in the sleep analyses. Post hoc pairwise comparisons were adjusted for multiple testing according to the Tukey–Kramer test. An exploratory inclusion of sex, age and BAC into analyses did not impact the interaction results. In order to achieve a normal distribution, some parameters were transformed prior to analysis (TST, SE, N3, WASO, number of arousals). Normal distribution of residuals was assessed using Kolmogorov–Smirnov tests and Q–Q plots. The significance level was $\alpha<0.05$. SpO_2 and SpO_2<90% measured during TST and sleep stages (N1–3, REM) within and between groups were analysed with paired Wilcoxon signed rank tests and unpaired Wilcoxon rank sum tests as no normal distribution of residuals could be achieved. Bonferroni adjustment for multiple comparisons was applied and the significance level set to 0.0083 (0.05/6). The time period during sleep with SpO_2<90% was of special interest as this threshold is used as a definition of hypoxia in clinical guidelines.[26] If not otherwise mentioned, values are given as median (25th/75th percentile).

RESULTS

The demographic data of the participants did not differ between the groups (table 1).

Tables 2 and 3 provide an overview of the results.

Effects of moderate alcohol consumption

Comparing the alcohol and non-alcohol conditions of the Control Group, the following isolated effects of alcohol under normobaric conditions on sleep (figure 2), SpO_2 and heart rate (figure 3, online supplemental figures 1, 2) were observed: N1 (p=0.0448) and REM (p=0.0053) durations were shorter, SpO_2 during sleep was reduced (TST, N1–3, REM: p<0.0001) and heart rate accelerated (TST, N1–3, REM; p<0.0001) under alcohol exposure. During TST the median SpO_2 remained above the hypoxia threshold of 90%.

Effects of hypobaric inflight conditions

Comparing the non-alcohol condition between groups, a shorter REM (p=0.0005), longer N2 duration (p<0.0001) and longer WASO (p=0.0471) were observed in the InFlight Group. SE (p=0.0165, adjusted p=0.0822), N1 (p=0.0179, adjusted p=0.0886) and N3 duration (p=0.0133, adjusted p=0.0678) only changed on trend-niveau, but TST (p=0.0223, adjusted p=0.1059) and number of arousals (p=0.0448, adjusted p=0.1903) were not significantly different after adjustment.

In the InFlight Group, SpO_2 during sleep was reduced (TST, N1–3, REM; p<0.0001) and resulted in SpO_2 <90% in 81% of TST(figure 4). Heart rate was accelerated (TST, N1–3, REM; p<0.002).

Combined effects of alcohol and hypobaric conditions

In comparison to the normobaric, non-alcohol condition of the Control Group, N3 (p=0.0029) and REM (p<0.0001) duration decreased, N1 duration showed a decreased trend (p=0.0791) and N2 duration (p<0.0001) and WASO (p=0.0071) increased in the alcohol condition of the InFlight Group.

SpO_2 during sleep in the alcohol condition of the InFlight Group was reduced (TST, N1–3, REM; p<0.0001) and time spent with SpO_2<90% was prolonged (TST, N1–3 REM; p<0.0001). SpO_2 during TST fell from 95.88% (95.72/96.36) in the non-alcohol condition of the Control Group to 85.32% (82.86/85.93) under the combined exposure to alcohol and hypobaric conditions. Heart rate was accelerated (TST, N1–3, REM; p<0.0001).

What does alcohol add to the effects of hypobaric conditions?

The effect of alcohol in addition to that of the hypobaric environment can be quantified when comparing the alcohol and non-alcohol conditions of the InFlight Group. Alcohol led to a shortened REM (p=0.0467), a trend to longer N2 duration (p=0.0641), a trend to shorter SOL (p=0.0827), decreased SpO_2 (TST, N1–3, REM; all p<0.0002) and increased heart rate (TST, N1–3, REM; p<0.0001) (figures 2 and 3). SpO_2 during TST fell further from 88.07% (86.50/88.49) without alcohol to 85.32% (82.86/85.93) with alcohol in the InFlight Group (figure 4). During N3 and REM

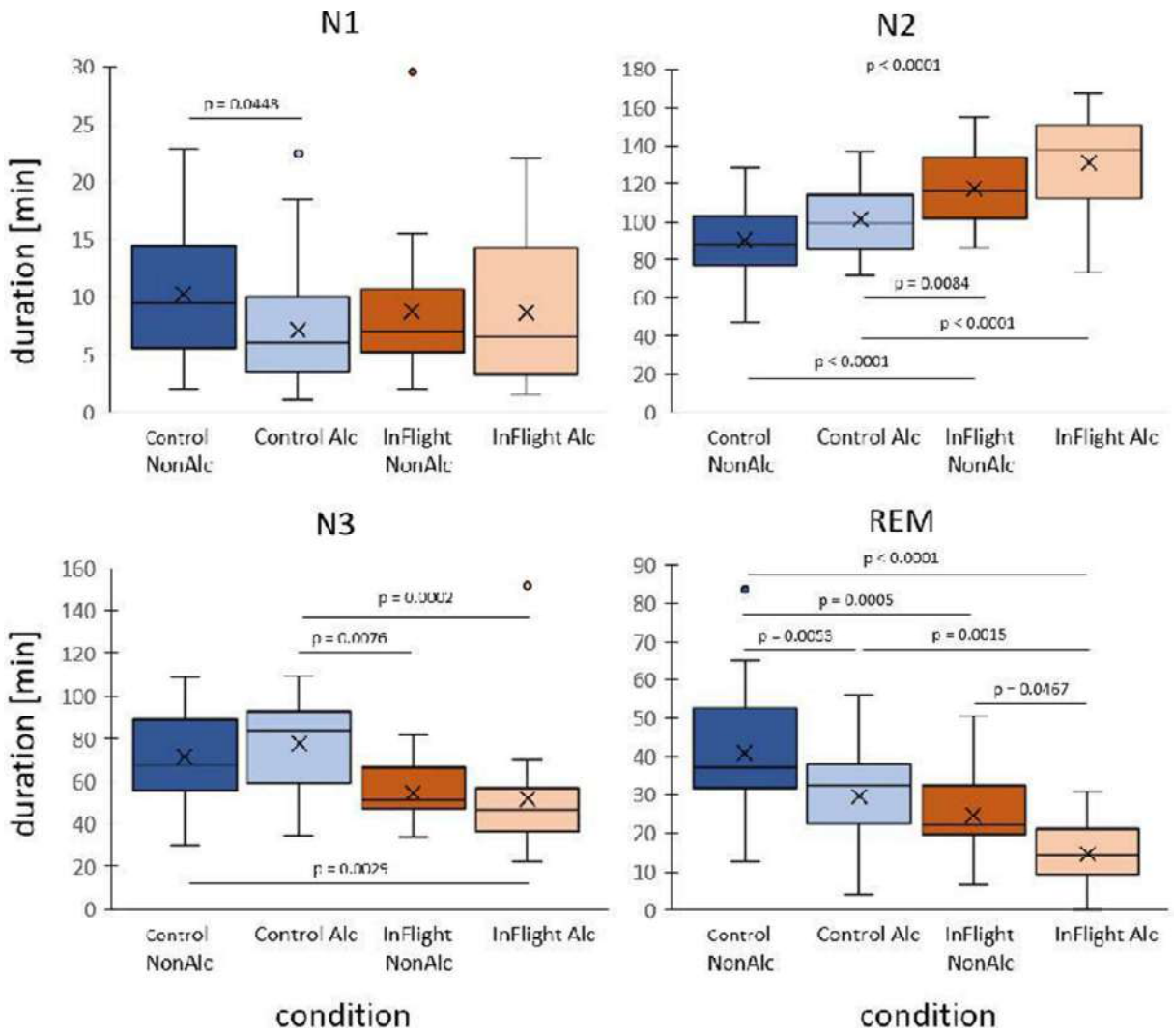

Figure 2 Duration of sleep stages (N1–3, REM) under two conditions (non-alcohol and alcohol) in the Control Group and InFlight Group. Mixed ANOVAs with the main factors condition, group and the interaction between condition and group and post-hoc Tukey–Kramer adjustment ($\alpha<0.05$) for polysomnography. Mixed ANOVAs were adjusted for baseline sleep in the sleep laboratory as covariate. Data are from two independent groups recorded during 4-hour sleep episodes (00:00–04:00 hours) in an altitude chamber at a simulated flight level (ie, atmospheric pressure corresponding to 2438 m above sea level; n=17) and in the sleep laboratory (53 m; n=22). Box plots include mean values expressed as "X". Whiskers represent 1.5× IQR.

sleep, even lower SpO_2 values were registered after previous alcohol consumption (84.84% (82.18/85.88); 84.74% (83.63/85.81)). During TST, time spent with SpO_2 <90% (p=0.0034) was 201.18 min (188.08/214.42) under the combined condition compared with 173.28 min (133.25/199.03) in the non-alcohol condition InFlight. Heart rate increased to 87.73 bpm (85.89/93.86) under the combined condition compared with 72.90 (70.90/78.17) in the non-alcohol condition InFlight. To quantify the strength of the alcohol-induced effects on SpO_2 and heart rate, a delta was calculated for each subject as the difference between conditions and compared between groups. The alcohol-induced reduction in SpO_2 (TST, N1–3, REM; p<0.0004) and increase in heart rate (TST, N1, N3, REM; p<0.03) was higher in the InFlight Group (TST SpO_2: 3.02 (2.28/3.74), TST heart rate: 13.94 (17.11/11.60)) than in the Control Group (TST SpO_2: 0.85 (0.56/1.41), TST heart rate: 9.96 (12.73/7.33)). In combination, hypobaric hypoxia and alcohol had a supra-additive effect on SpO_2 and heart rate.

What does the hypobaric condition add to the alcohol effect?

By comparing the alcohol conditions between the groups, the additional influence of hypobaric hypoxia was quantified. Sleep architecture under alcohol plus hypobaric conditions was characterised by a shortened REM (p=0.0015) and N3 duration (p=0.0002), while N2 duration (p<0.0001) was prolonged (figure 2). Participants spent more time awake (WASO, p=0.0223). SpO_2 (figure 3) was lower (TST, N1–3, REM; p<0.0001). Participants in the InFlight Group spent 95% of TST at a SpO_2 <90% in the alcohol condition compared with 0% in the Control Group in the alcohol condition (p<0.0001; figure 4). During sleep in the alcohol conditions, heart rate was higher in the InFlight Group compared with the Control Group (TST, N1–3, REM; p<0.0001).

DISCUSSION

Passengers frequently drink alcoholic beverages during a long-haul flight and fall asleep afterwards. Understanding the interacting effects of alcohol and sleep at altitude is therefore highly relevant. Such research provides insights for both passengers and healthcare professionals, facilitating the development of recommendations and guidelines for avoiding medical emergencies on board. The aim of this paper was to study the impact of moderate alcohol consumption and hypobaric conditions on sleep structure, SpO_2 and heart rate, with a special focus on the interacting effects of both conditions. An InFlight Group in a pressure chamber at a simulated altitude of 2438 m and a Control Group in the sleep laboratory were compared under two conditions of 4 hours of sleep: (1) sober and (2) with prior moderate alcohol consumption leading to a BAC of 0.04±0.003% just before going to sleep.

The combined impact of alcohol and hypobaric conditions led to an altered sleep architecture with shorter REM and N3 duration, prolonged N2 duration and increased WASO. During TST,

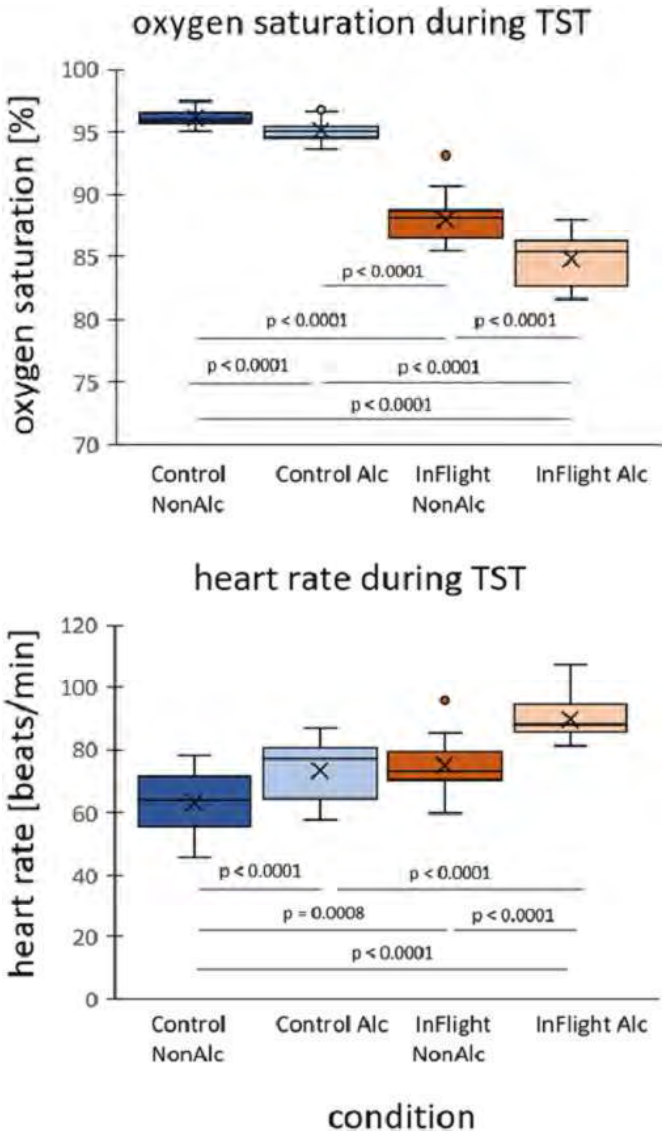

Figure 3 Top: Oxygen saturation under non-alcohol and alcohol conditions in the Control Group and InFlight Group. Paired and unpaired Wilcoxon tests were calculated and Bonferroni adjusted (α=0.05/6=0.0083). Data are from two independent groups recorded during 4-hour sleep episodes (00:00–04:00 hours) in an altitude chamber at a simulated flight level (ie, atmospheric pressure corresponding to 2438 m above sea level; n=14) and in the sleep laboratory (53 m; n=22). Box plots include mean values expressed as "X". Whiskers represent 1.5× IQR. Bottom: Heart rate under non-alcohol and alcohol conditions in the Control Group and InFlight Group. Mixed ANOVAs were performed with the main factors condition, group and the interaction between condition and group and post-hoc Tukey–Kramer adjustment (α<0.05). Data are from two independent groups recorded during 4-hour sleep episodes (00:00–04:00 hours) in an altitude chamber at simulated flight level (ie, atmospheric pressure corresponding to 2438 m above sea level; n=14) and in the sleep laboratory (53 m; n=22). Box plots include mean values expressed as "X". Whiskers represent 1.5× IQR. TST, total sleep time.

SpO_2 decreased to a median of 85% which was accompanied by a compensatory increase in heart rate to a median of 88 bpm. Participants' SpO_2 was in total 95% of TST below the clinical hypoxia threshold of 90%. Together these results indicate that, even in young and healthy individuals, the combination of alcohol intake with sleeping under hypobaric conditions poses a considerable strain on the cardiac system and might lead to exacerbation of symptoms in patients with cardiac or pulmonary diseases. Cardiovascular symptoms have a prevalence of 7% of inflight medical emergencies, with cardiac arrest causing 58% of aircraft diversions.[27] The risk of venous thromboembolism is lower in comparison, with one out of 6000 affected per flight of >4 hours.[28] It has been shown that desaturations below the hypoxia threshold were associated with worse postoperative patient outcome[29] and increased mortality risk for emergency admissions.[30] Thus, elderly people and/or people with pre-existing conditions are in danger of clinically relevant desaturations due to impaired ability for compensation, resulting in greater hypoxaemia.[5 6 31] We have previously identified sleep as a potential exacerbating factor that reduces the ability to compensate for the decreased oxygen partial pressure in the atmosphere.[7] Likewise, a study in a hypobaric chamber simulating a 20-hour flight with healthy participants not acclimatised to altitude showed that SpO_2 was lower during sleep in a coach-class aeroplane seat compared with being awake, and that even lower SpO_2 levels are to be expected in older passengers than in younger passengers.[4]

In agreement with our findings on the impact of hypobaric conditions on SpO_2 (median SpO_2 of 88% during TST), a reduction in SpO_2 levels from 93.8% to 84% has been reported in response to simulated (normobaric hypoxia) and real (hypobaric hypoxia) altitude of 2000–3000 m.[12 21 32 33] Hoshikawa et al simulated an altitude of 2000 m under conditions of normobaric hypoxia with 16.4% oxygen. As in our study, the duration of N3 and REM sleep was shortened, SpO_2 decreased (89.6% vs 95.4%) and heart rate increased (55.6 bpm vs 51.3 bpm) compared with normobaric normoxia.[21] The strikingly lower heart rate under both test conditions compared with our study can be explained by the fact that only medium and long distance runners were included in the study. Latshang et al reported a reduction in slow wave sleep (NREM stages 3 and 4) and a decreased SpO_2 during sleep at 2590 m compared with 490 m.[10] As N3 and REM sleep are considered important for the recuperative value of sleep,[19] sleeping at altitude is less recuperative and refreshing and might impair cognitive functioning.

The single exposure to moderate alcohol intake just before bedtime in our study reduced median N1 and REM duration by 3.5 min and 4.5 min, respectively. A variety of potential effects of alcohol consumption on sleep (including no effects) have been reported.[18] In line with our findings, moderate, high and intoxicating doses of alcohol have been reported to reduce the duration of REM sleep.[17 34] Thakkar et al, however, stated that alcohol before bedtime irrespective of the dose shortens SOL and increases slow-wave sleep.[14] Alcohol facilitates sleep by a rapid increase in cerebral adenosine receptor availability,[16] which explains why alcohol is often used as a self-prescribed sleep aid. Accordingly, reduced SOL has been found frequently[16 18] and deemed to be the most robust effect of alcohol on sleep.[17] Alcohol has also been reported to increase N2 duration.[34] In our study SOL seemed shorter and N2 longer under the influence of alcohol, but the effects were non-significant.

Alcohol intake also decreased SpO_2 by 1% to a median of 95% during TST and increased heart rate by 13 bpm to a median of 77 bpm compared with normobaric normoxic conditions without alcohol. In this case, the decrease in SpO2 is unlikely to account for the acceleration in heart frequency. Under normoxic conditions a SpO_2 range from 96% to 98% has been defined as normal.[12] During sleep an average SpO_2 of 96.5±1.5% has been reported in healthy participants,[35] confirming the slight decrease from normal due to alcohol in our study as well as in other studies.[18 20 36] De Zambotti et al reported a dose-dependent impact of alcohol consumption just before retiring on heart rate during sleep.[37] A plausible mechanism is that alcohol induces peripheral systemic vasodilation which triggers the baroreceptor reflex resulting in an increased heart rate.[20]

With different statistical comparisons, we tried to disentangle the additional and potentially synergistic impact that either alcohol had on top of hypobaric conditions or that hypobaric conditions had on top of alcohol intake. The additional exposure to alcohol primarily reduced REM duration further by 7.5 min compared with the hypobaric condition alone and showed a trend to shorten SOL and to prolong N2. It further decreased SpO_2 by 3% and led

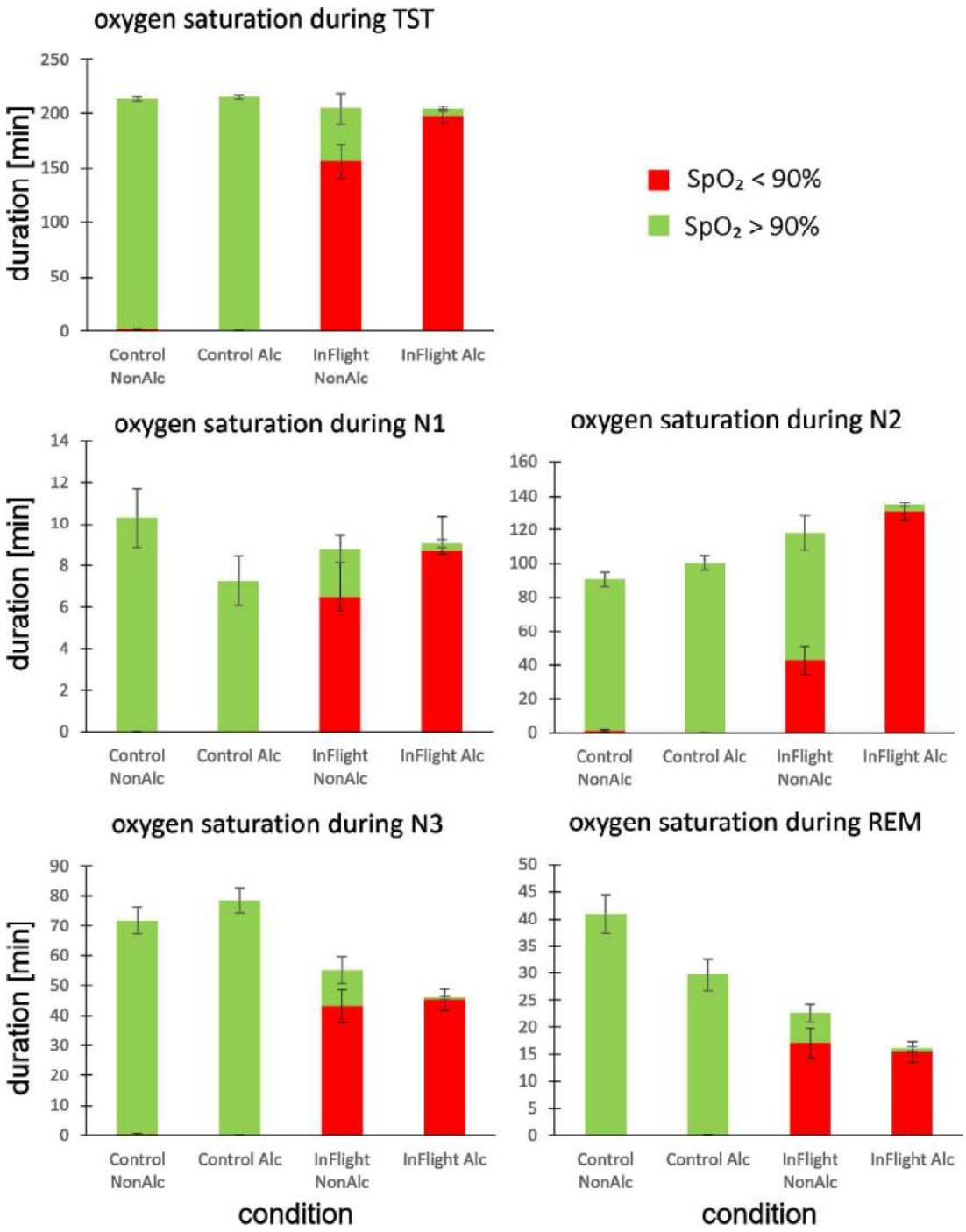

Figure 4 Comparison of blood oxygenation between non-alcohol and alcohol conditions in the Control Group and InFlight Group. Data are from two independent groups recorded during 4-hour sleep episodes (00:00–04:00 hours) in an altitude chamber at simulated flight level (ie, atmospheric pressure corresponding to 2438 m above sea level; n=14) and in the sleep laboratory (53 m; n=22). Mean±SE duration during sleep that participants spent with an oxygen saturation >90% and <90% (hypoxic state). N1–3, REM, sleep stages; TST, total sleep time.

to an increase in the heart rate by 15 bpm. Comparing the change induced by alcohol intake (as the difference between both conditions) between the groups showed that alcohol also added a decrease in N3 duration to the hypoxia effect. Together these results fit well with the alterations that have been observed in response to alcohol intake alone, as discussed above. The additional exposure to the hypobaric condition reduced REM duration by 18 min, decreased N3 duration by 38 min, increased N2 duration, and WASO compared with alcohol exposure alone. It decreased SpO_2 and increased heart rate during TST by 10% and 11 bpm, respectively. Therefore, alcohol and hypobaric conditions have synergistic effects but the hypobaric condition contributes more to the observed changes than alcohol.

The results of this study refer only to a sleep duration of 4 hours, which limits the transferability to other sleep durations. However, the sleep duration was chosen to reflect realistic inflight sleep opportunities. Participants slept in supine positions, which resembles the situation of passengers travelling first and business class. Sleeping in a sitting position has been reported to impair sleep efficiency and REM duration.[38] Following the notion that hypobaric hypoxia is aggravated by sleep, passengers travelling in economy class might be affected to a lesser extent by the exposure to alcohol and hypobaric conditions. The free access of first and business class passengers to alcoholic beverages might increase the risk.

The sample examined in our study was of limited size and does not represent the average population. We derived the presented results from a subpart of a larger study,[22] so the absence of an a priori power calculation is a limitation. However, our findings are strong and robust and in line with existing literature. Even in these young and healthy subjects, critical oxygen desaturations below

90% were registered. In elderly and chronically ill people, the combined effects of alcohol consumption and hypobaric conditions on sleep architecture, SpO_2 and heart rate might be considerably stronger. Therefore, studying participants with stable treated respiratory disease is of wider public interest and is realistically feasible as it has already been done.[39] Barometric pressure was only one of several systematic differences between the sleeping environments. Factors such as personal comfort (real bed vs bunk bed as well as altitude chamber vs sleep laboratory) or ambient noise (quiet vs realistic inflight cabin noise) might have affected the outcome. Even though we provided two nights of recovery between conditions, carryover effects cannot be completely ruled out.

CONCLUSION

We conclude that the combined influence of alcohol and reduced atmospheric pressure has a supra-additive effect and even young and healthy participants suffered from clinically relevant desaturations (SpO_2 <90%) and heart rate accelerations during sleep. Since sleep quality was compromised, inflight sleep cannot be considered as fully recuperative. This is even more true for passengers travelling first and business class because they have the possibility to sleep in a horizontal position. Our findings support the recommendations of the BTS Clinical Statement on Air Travel to avoid alcohol in the 12 hours preceding and during air travel when suffering from obstructive sleep apnea syndrome or obesity hypoventilation syndrome.[3] Moreover, public awareness of this topic should be raised through patient charities, public campaigns and written health advice of airlines. Technical and economic constraints make it unlikely that an increase in cabin pressure will be implemented by airlines.[6]

STATEMENT OF SIGNIFICANCE

Passengers frequently consume alcoholic beverages during long-haul flights before falling asleep. Despite this being a routinely occurring situation, the combined impact of moderate alcohol consumption and inflight hypobaric conditions on sleep, blood oxygen saturation (SpO_2) and heart rate is unknown. In young and healthy adults we found a decrease in SpO2 to a median of 85% during sleep under the combined exposure that was accompanied by an increase in heart rate and disturbed sleep. Higher doses of alcohol could amplify these observed effects, potentially escalating the risk of health complications and medical emergencies during flight, especially among older individuals and those with pre-existing medical conditions. Our findings strongly suggest that the inflight consumption of alcoholic beverages should be restricted.

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Transição da fibrose quística dos cuidados pediátricos para os cuidados de adultos: resultados de uma investigação internacional

A transição é o movimento planeado e intencional dos doentes dos cuidados pediátricos para os cuidados de adultos[1]. Nos últimos cinco décadas, houve muitos avanços no tratamento da fibrose quística (FQ). As mortes na população pediátrica são agora raras, com apenas seis relatadas no Reino Unido em 2021 (população total n=10.908)[2]. Portanto, espera-se que a maioria dos afetados faça a transição para os cuidados de adultos, sendo assim, há uma necessidade de que as equipas de FQ tenham processos de transição robustos.

Uma investigação foi disseminada para equipas de FQ em conferências internacionais de FQ ao longo de um período de 18 meses. Para estabelecer um consenso, procurámos informações sobre aspectos chave da transição. Os participantes incluíram enfermeiros, fisioterapeutas, nutricionistas, psicólogos, assistentes sociais e médicos especializados em FQ pediátrica/adulta. Houve múltiplas respostas para cada pergunta. As respostas foram n=34/40, representando equipas multidisciplinares (EMT) de 16 países (Europa do Norte, Leste e Ocidental, América do Norte e do Sul, África do Sul e Australásia).

Na pergunta sobre a idade em que as discussões sobre transição foram introduzidas, a maioria dos respondentes (38%) relatou que isso ocorreu entre 14 e 15 anos, enquanto 32% indicaram entre 16 e 18 anos. Houve maior concordância quanto à idade da transição, com 71% relatando a transição aos 18 anos. No entanto, internacionalmente há variação, já que a transição normalmente ocorre aos 16-17 anos no Reino Unido[3] e aos 18-21 anos nos Estados Unidos.[4] A maioria das equipas de FQ realiza reuniões conjuntas de transição pediátrica/adulta (74%). Apenas 24% utilizam um caminho de transição que foi formalmente acordado pelas equipes adultas e pediátricas que regularmente fazem a transição de pacientes entre seus serviços, ou um programa de transição como o 'Ready Steady Go'.[5] Os respondentes decidiram o que constituía um processo formal dentro de seus serviços. Fatores como geografia e distância entre os centros podem afetar o processo de transição em alguns países, por exemplo, nos EUA e no Canadá, onde os doentes podem precisar viajar grandes distâncias entre as clínicas adulta e pediátrica.[4]

Box 1 Survey responses

At what age do you start discussing transition to adult services?
- ⇒ <10 years: 24% (n=8).
- ⇒ 14 years–15 years: 38% (n=13).
- ⇒ 16 years–18 years: 32% (n=11).

At what age do patients transition into the adult service, are parents/carers involved?
- ⇒ Transition age: 18 years, 71% (n=24).
- ⇒ Parental involvement: 100%.

Transition communication between adult and paediatric teams
- ⇒ Joint paediatric and adult multidisciplinary team: 74% (n=25).
- ⇒ Email: 59% (n=20).
- ⇒ Telephone: 47% (n=16).
- ⇒ Referral letter: 53% (n=18).

Do you have a formal transition programme?
- ⇒ Yes: 24% (n=8).
- ⇒ Transition key worker: 53% (n=18).
- ⇒ Co-ordinator:
  - ⇒Social worker: 76% (n=26).
  - ⇒Physiotherapist: 62% (n=21).
  - ⇒Consultant: 53% (n=18).

Do you monitor disengagement?
- ⇒ Monitor disengagement: 76% (n=26).
  - ⇒Cystic fibrosis nurse: 56% (n=19).
  - ⇒Physiotherapist: 50% (n=17).

A monitorização do desengajamento no momento da transição é importante, pois é reconhecido que os adolescentes têm maior probabilidade de se afastar das equipas de saúde durante esse período. O desengajamento foi monitorizado por 76% dos respondentes, com enfermeiros e fisioterapeutas especializados em FQ desempenhando o papel de forma igualitária (caixa 1). A preparação precoce dos jovens e de seus pais/cuidadores é fundamental para uma transição bem-sucedida, com muitos serviços de FQ iniciando as conversas aos 14 anos. A comunicação compartilhada e o trabalho conjunto entre as equipas pediátricas e de adultos foram reconhecidos como fatores-chave para o sucesso de uma boa transição.[4] As reuniões conjuntas entre pediatria e de adultos são comuns, com a maioria dos participantes relatando que as realizam regularmente. A consistência é fundamental para um programa compartilhado, e parcerias fortes entre as equipas pediátricas e de adultos podem mitigar as limitações de recursos e determinar a entrega dos serviços. Esta pesquisa reflete as opiniões dos profissionais que trabalham em serviços de FQ internacionalmente, embora os autores tenham se esforçado para obter respostas da maioria dos países onde os serviços de FQ estão presentes, algumas áreas onde a FQ é menos prevalente não estão representadas, incluindo o Oriente Médio, Ásia Central e Sudeste Asiático. Isso pode ser considerado uma limitação deste trabalho. Em resumo, os resultados da pesquisa demonstram que há um amplo consenso sobre as práticas de transição da FQ ao redor do mundo (tabela 1).

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Table 1 Consensus CF transition recommendations

Age at first transition discussion	Discussions introducing transition concepts often begin before the age of 10 years but commonly from 14 years onwards.
Age at transition	Most young people will have transitioned to adult services at or by 18 years.
Parents/carers involvement in the process	Parents/carers should always be part of transition planning.
Communication between paediatric and adult CF multidisciplinary teams	Regular communication and a shared, structured transition programme between paediatric and adult CF services is essential.
Co-ordination	Transition should be coordinated by a named transition key worker or co-ordinator.
Monitoring	Monitoring disengagement at the time of transition is important so that young people are not lost to follow-up.
Resources and education programmes	Basic, practical information about the adult CF service should be provided including: ► Location of the service. ► Clinic schedules and frequency of reviews. ► Provision for urgent review. ► Location and layout of the ward and facilities available. ► Contact details for the team. Formal education programmes designed to develop autonomy and knowledge should be available.

CF, cystic fibrosis.