

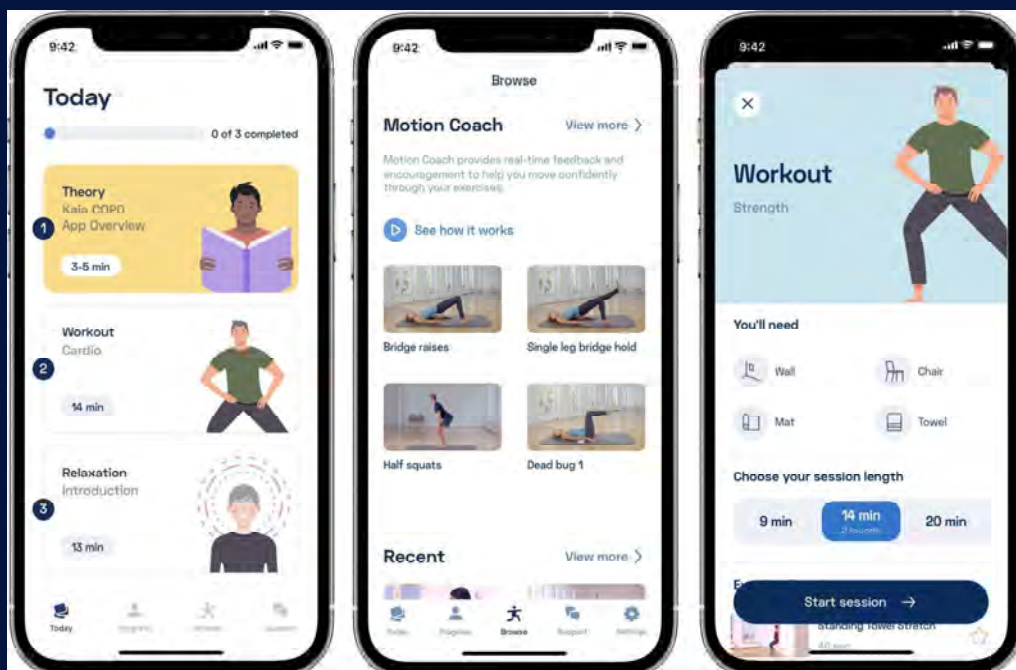
Thorax

ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

com artigos do

ARCHIVES OF
DISEASE IN
CHILDHOOD

Edição Portuguesa





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

1 vez dia¹

**Zimbus®
breezhaler®**

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

**NOVA
ASSOCIAÇÃO
LABA/LAMA
/ICS¹**

Dá ritmo à vida^{2,3}

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

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

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

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



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Editorial

Com o verão a chegar, estamos de novo com os nossos leitores para apresentar mais um número com artigos selecionados das revistas Thorax e Archives of Disease in Childhood.

Nesta edição da Revista, chamamos a sua atenção para alguns artigos.

O primeiro é um artigo de revisão cujo objetivo foi avaliar a segurança do uso de curto prazo do salbutamol inalado em crianças com menos de dois anos com sibilância aguda. As principais conclusões são que o salbutamol inalado pode ser usado com segurança em crianças com menos de dois anos com sibilância aguda, sendo que a administração através de um inalador pressurizado pode ser potencialmente mais segura do que a formulação nebulizada, nenhuma das formulações tendo sido associada a efeitos adversos graves.

O segundo artigo, “Eficácia dos centros de asma pediátricos: um estudo clínico piloto”, apresenta um estudo piloto incluindo crianças e jovens entre 4 e 17 anos encaminhados para o centro com asma não controlada ou após uma crise de asma, com o objetivo de investigar a viabilidade e eficácia desses centros, fornecendo avaliações pós-crise, educação sobre asma, testes diagnósticos de função pulmonar e otimização do tratamento. Após avaliar 312 crianças e jovens, o estudo concluiu que os centros de asma pediátricos são um modelo viável de atendimento para proporcionar avaliações pós-crise asmática e identificar doentes de alto risco que necessitam de tratamento adicional, tendo a espirometria, a prova de reversibilidade ao broncodilatador e a avaliação do FeNO permitido a confirmação diagnóstica numa proporção significativa das situações.

No artigo seguinte, “Síndrome da apneia obstrutiva do sono e risco futuro de demência entre indivíduos acompanhados na prática clínica geral do Reino Unido”, os autores tiveram como objetivo determinar o risco de demência em indivíduos com e sem apneia obstrutiva do sono (SAOS). Os dados foram extraídos dos registos eletrónicos de 2,3 milhões de adultos (≥ 18 anos) do Clinical Practice Research Datalink, um banco de dados nacionalmente representativo de registos eletrónicos de cuidados de saúde primários no Reino Unido. A principal conclusão foi que o SAOS está associada a maiores riscos de demência por todas as causas e algumas de suas subcategorias, sendo necessários mais estudos para avaliar os benefícios clínicos da triagem para comprometimento cognitivo em pessoas com SAOS e para determinar melhor o impacto do CPAP no declínio cognitivo e no risco de demência.

Por último, no artigo “Disponibilidade, custo e acessibilidade de medicamentos essenciais para a cessação do tabagismo em países de baixo e médio rendimento: um estudo transversal”, foram recolhidos dados transversais sobre medicamentos para a cessação tabágica em farmácias, unidades de saúde e armazéns centrais de medicamentos em 60 países de baixo e médio rendimento (LMIC), tendo-se verificado que os medicamentos apresentavam uma disponibilidade variável, grandes intervalos de preços e eram essencialmente inacessíveis, sendo considerado fundamental garantir o acesso a esses medicamentos para reduzir o consumo de tabaco e as doenças associadas. São igualmente necessárias estratégias para integrar os serviços de cessação tabágica nos sistemas de saúde, a fim de alcançar as metas dos Objetivos de Desenvolvimento Sustentável.

Uma vez que estamos a entrar em época de férias para muitas pessoas, desejamos a todos um excelente repouso e prometemos regressar em breve com novas sugestões de artigos.

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

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

Informações essenciais compatíveis com o Resumo das Características do Medicamento

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

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ARTIGO ORIGINAL

Segurança do salbutamol em crianças menores de 2 anos com sibilância aguda: uma meta-análise de ensaios clínicos randomizados

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RESUMO

Objetivo: Avaliar a segurança do uso de curto prazo do salbutamol inalado em crianças com menos de 2 anos com sibilância aguda.

Fontes de dados Foram pesquisadas bases de dados eletrônicas (PubMed, Trip, MEDLINE) e a Biblioteca Cochrane para estudos publicados até outubro de 2022.

Seleção do estudo A pesquisa foi restrita a ensaios clínicos randomizados publicados em inglês sobre a segurança do salbutamol inalado em crianças com menos de 2 anos com sibilância.

Extração e síntese de dados A estratégia de pesquisa na literatura resultou em 3532 referências. A meta-análise foi conduzida de acordo com as diretrizes PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Principais desfechos e medidas A incidência de reações adversas associadas à administração de salbutamol inalado em comparação com placebo.

Resultados Foram incluídos 24 estudos. Em 7 estudos envolvendo 597 doentes, o salbutamol inalado foi comparado com controles, e não foi encontrada diferença estatisticamente significativa na incidência de reações adversas entre os dois grupos (OR 2,12, IC 95% 0,69 a 6,51; $p=0,19$). A administração de salbutamol por nebulização foi associada a um aumento na incidência de reações adversas (OR 6,76, IC 95% 2,01 a 22,71; $p=0,002$). Nenhum dos estudos relatou efeitos colaterais cardíacos graves que exigissem retirada do estudo após a administração de salbutamol. Apenas um estudo relatou um efeito colateral não cardíaco significativo (tremores severos) que exigiu interrupção da terapia.

Conclusões O salbutamol inalado pode ser usado com segurança em crianças com menos de 2 anos com sibilância aguda, sendo que a administração via inalador de dose medida pode ser potencialmente mais segura do que a formulação nebulizada. Nenhuma das formulações foi associada a efeitos adversos graves.

INTRODUCTION

Inhaled short-acting beta-agonists are routinely used to treat bronchospasm with salbutamol as the drug of choice due to its bronchodilator effect, rapid onset of action and ease of administration.¹ The inhaled route of salbutamol administration, whether nebulised or using a metered-dose inhaler (MDI) with or without a spacer (MDI-S), produces faster bronchodilation than the oral route and fewer adverse effects (ADRs) than both the oral and intravenous routes.² Inhaled salbutamol is recommended for the treatment of acute asthma in children and for the treatment of wheezing disorders in preschool children even from 1 year of age.^{2–5} On the other hand, the role of bronchodilators in bronchiolitis, which typically affects children younger than 2 years, is controversial.^{1,6} In the past, a therapeutic attempt with salbutamol was very common in children older than 6 months with a family

Key messages

What is known about this topic

► Salbutamol is commonly used in children presenting with acute wheezing but recently there have been concerns about its safety in children under the age of 2. The aim of this study is to evaluate the safety of inhaled salbutamol in children under the age of 2 with wheezing disorders.

What this study adds

► In this meta-analysis, none of the analysed studies reported severe cardiac side effects following salbutamol administration. Salbutamol administration via nebulisation was associated with an increased incidence of adverse reactions compared with the metered-dose inhaler.

How this study might affect research practice or policy

► Inhaled salbutamol can be safely used in children under 2 years of age with administration via a metered-dose inhaler being potentially safer than a nebulised formulation.

history of atopy or asthma⁷ but this practice is no longer recommended.^{1,6} Concerns have been raised regarding the safety and tolerability of salbutamol use in children under 2 years of age, considering that it may be inappropriate to extrapolate the safety data of older children to infants younger than 2 years old due to unique physiological mechanisms that can affect pharmacokinetics and dynamics.^{8–10}

For safety reasons, the Food and Drug Administration in the USA and the European Medicines Agency in Europe only approve nebulised salbutamol for children over the age of 2 and MDI salbutamol for children over the age of 4. However, there are few large-sample studies specifically addressing the safety of inhaled salbutamol in children under 2 years of age and the current literature lacks consensus and definitive guidelines for its use in this population. Therefore, this systematic review with meta-analysis aims to systematically review and critically evaluate existing randomised controlled trials (RCTs) on the safety profile of inhaled salbutamol in children under 2 years of age to provide clinicians with evidence-based guidance when considering the use of this drug in this paediatric population.

Table 1 Summary of included studies. Quality assessed using the Cochrane tool for randomised controlled trial*

Reference (first author and year)	Country	Study design	Data collection date/enrolment period	Patients' age (months)	Total n of patients	Intervention and control group	Quality assessment
Anil, 2010 ²⁰	Turkey	RCT. Double blind.	Nov 2005–March 2006	1.5–24	186	Group 1: 1.5 mg epinephrine+0.9% NaCl two times a day (n=38). Group 2: 1.5 mg epinephrine+3% NaCl two times a day (n=39). Group 3: 2.5 mg NEB salbutamol+0.9% NaCl two times a day (n=36). Group 4: 2.5 mg NEB salbutamol+3% NaCl two times a day (n=36). Group 5: 0.9% NaCl (n=37).	Some concerns
Bertrand, 2001 ¹⁷	Chile	RCT. Double blind.	May 1994–Sept 1994	1–12	30	Intervention: NEB salbutamol 2.5 mg every 2–4 hours (n=14). Control: NEB epinephrine 0.5 mg every 2–4 hours (n=16).	Some concerns
Cengizlier, 1997 ²⁷	Japan	RCT. No blinding.	NA	6–24	31	Intervention 1: MDI-S (coffee cup) salbutamol two puffs (100 µg=1 puff) every 3 hours (n=12). Intervention 2: Oral salbutamol 0.1 mg/kg per dose, four times a day (n=11). Control: No bronchodilator (n=8).	High risk
Delgado, 2003 ¹⁵	USA	RCT. Double blind.	Aug 1995–Dec 1996	2–24	168	Intervention: MDI-S salbutamol three puffs (90 µg per puff) followed by NEB 0.9% NaCl (n=83). Control: MDI-S placebo followed by NEB salbutamol 0.15 mg/kg (n=85).	High risk
Dobson, 1998 ²⁹	USA	RCT. Double blind.	Dec 1995–March 1996	0–24	52	Intervention: NEB salbutamol 1.25 mg for <10 kg, 2.5 mg for >10 kg every 2 hours in the first 24 hours, then every 4 hours for 48 hours (n=23). Control: NEB 0.9% NaCl (n=29).	Some concerns
Gadomski, 1994 ⁴¹	Egypt	RCT. Double blind.	Feb 1990–Dec 1992	0–18	64	Intervention: NEB salbutamol 0.15 mg/kg two times a day. Control: NEB NaCl. Intervention 2: Oral salbutamol 0.15 mg/kg per dose, once. Control 2: Oral placebo.	Some concerns
Gadomski, 1994 ³⁰	USA	RCT. Double blind.	NA	0–15	93	Intervention 1: NEB salbutamol 0.15 mg/kg two times a day (n=22). Control 1: NEB 0.9% NaCl two times a day (n=22). Intervention 2: Oral salbutamol 0.15 mg/kg (n=19). Control 2: Oral NaCl (n=24).	Some concerns
Hedrick, 2009 ³¹	USA	RCT. Double blind.	NA	0–24	86	Intervention 1: MDI-S salbutamol 90 µg 3/day for 4 weeks (n=29). Control 1: Placebo 3/day for 4 weeks (n=28). Intervention 2: MDI-S salbutamol 180 µg 3/day for 4 weeks (n=29). Control 2: Placebo 3/day for 4 weeks (n=28).	Some concerns
Ho, 1991 ²⁸	Australia	RCT. Double blind. Cross over.	NA	3 weeks–6 months	21	Intervention: NEB salbutamol followed by 0.9% NaCl (n=13). Control: NEB 0.9% NaCl followed by salbutamol (n=8).	High risk
John, 2006 ¹⁹	India	RCT. No blinding.	Feb 2003–Aug 2004	2–24	30	Intervention: NEB salbutamol 0.15 mg/kg for three times in 1 hour and then hourly (n=15). Control: NEB epinephrine 1:1000 (0.5 mL/kg max 2.5 mL) for three times in 1 hour, then hourly (n=15).	Some concerns
John, 2010 ¹⁸	India	RCT. No blinding.	May 2006–May 2008	2–60	60	Intervention: NEB salbutamol 0.15 mg/kg for three times (n=30). Control: NEB epinephrine (1:1000, 0.5 mL/kg) for three times (n=30).	Some concerns
Kaashmiri, 2010 ³⁷	USA	RCT. Double blind, parallel group.	NA	0–24	87	Intervention: MDI-S salbutamol 180 µg (n=43). Control: MDI-S salbutamol 360 µg (n=44).	Some concerns
Klassen, 1991 ³⁹	Canada	RCT. Double blind.	Nov 1988–April 1990	1–21	83	Intervention: NEB salbutamol 0.10 mg/kg two times a day (n=42). Control: NEB 0.9% NaCl two times a day (n=41).	Some concerns
Kose, 2014 ²⁶	Turkey	RCT. Double blind.	Oct 2012–March 2013	1–24	56	Group 1: NEB salbutamol 0.15 mg/kg (n=18). Group 2: NEB MgSO ₄ 150 mg (n=19). Group 3: NEB salbutamol+MgSO ₄ (n=19).	Some concerns
Langley, 2005 ²¹	Canada	RCT. Double blind.	Nov 1999–April 2002	1.5–24	62	Intervention: NEB salbutamol 0.75 mg <6 kg, 1.25 6–10 kg, 1.5 >10 mg every 1–4 hours (n=31). Control: NEB 2.25% epinephrine 0.5 mL every 1–4 hours (n=31).	Some concerns

Continued

Table 1 Continued

Reference (first author and year)	Country	Study design	Data collection date/enrolment period	Patients' age (months)	Total n of patients	Intervention and control group	Quality assessment
Luo, 2010 ³⁸	China	RCT. Double blind.	Nov 2007–Feb 2008	0–24	93	Intervention: NEB salbutamol 2.5 mg+4 mL 3% NaCl every 8 hours (n=50). Control: NEB salbutamol 2.5 mg+4 mL 0.9% NaCl every 8 hours (n=43).	Some concerns
Mull, 2004 ²²	USA	RCT. Double blind.	Three consecutive winters (1998–2000)	0–12	66	Intervention: NEB salbutamol 0.15 mg/kg for three times (n=32). Control: NEB epinephrine 0.9 mg/kg for three times (n=34).	Some concerns
Reijonen, 1995 ²³	Finland	RCT. Double blind.	Jan 1992–2 Nov 1993	1–24	100	Group 1: Epinephrine 0.9 mg/kg followed by 0.9% NaCl (n=24). Group 2: Salbutamol 0.15 mg/kg followed by 0.9% NaCl (n=27). Group 3: 0.9% NaCl followed by epinephrine 0.9 mg/kg (n=24). Group 4: 0.9% NaCl followed by salbutamol 0.15 mg/kg (n=25).	Some concerns
Rubilar, 2000 ¹⁶	Chile	RCT. Single blind.	June 1999–Nov 1999	1–24	123	Intervention: MDI salbutamol two puffs (100 µg=1 puff) for five doses (n=62). Control: NEB salbutamol 0.25 mg/kg for three doses (n=61).	High risk
Schuh, 1990 ⁴²	Canada	RCT. Double blind.	Dec 1988–April 1989	1.5–24	40	Intervention: NEB salbutamol 0.15 mg/kg/dose for three times (n=21). Control: 0.9% NaCl solution two doses+one salbutamol dose (n=19).	Some concerns
Schweich, 1992 ⁴³	USA	RCT. Double blind.	Nov 1989–March 1990	0–24	25	Intervention: NEB salbutamol 0.15 mg/kg two times a day (n=13). Control: 0.9% NaCl two times a day (n=12).	Some concerns
Uysalol, 2017 ³²	Turkey	RCT. Double blind.	Oct 2011–April 2012	2–24	378	Intervention 1: NEB salbutamol 0.15 mg/kg (n=72). Control 1: NEB 3% NaCl (n=77). Intervention 2: NEB salbutamol 0.15 mg/kg (n=72). Control 3: NEB 0.9% NaCl (n=79).	Some concerns
Wang, 1992 ²⁴	Canada	RCT. Double blind.	4 Jan 1988–June 1989	2–24	62	Group 1: NEB salbutamol 0.15 mg/kg/dose+ipratropium bromide (125 µg if <6 months, 250 µg if >6 months). Repeat every 4 hours until discharge, max 3 days (n=17). Group 2: NEB salbutamol+0.9% NaCl (n=14). Group 3: NEB 0.9% NaCl+ipratropium (n=15). Group 4: NEB 0.9% NaCl (n=16).	High risk
Yuksel, 2001 ²⁵	Turkey	RCT. Double blind.	NA	0–24	29	Intervention: NEB salbutamol 0.15 mg/kg, three doses (n=13). Control: NEB salbutamol 0.075 mg/kg+ipratropium bromide (250 µg/dose) four doses (n=16).	High risk

*NA is reported when no information was stated in the article.

†

‡

MDI, metred-dose inhaler; MDI-S, metred-dose inhaler+spacer; MgSO₄, magnesium sulfate; NaCl, sodium chloride; NEB, nebulised; RCT, randomised controlled trial.

METHODS

Literature search

This systematic review with meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.¹¹ Electronic databases, including PubMed, Trip, MEDLINE and the Cochrane Library, were searched to identify relevant studies published up to October 2022. The string used to perform the search is provided in the online supplemental material. This systematic review was registered on the International Prospective Register of Systematic Reviews (ID: CRD42020172441) (<https://www.crd.york.ac.uk/prosperto/>).

The search was restricted to RCTs published in English that involved infants under 2 years old with wheezing (including infants with bronchiolitis) treated with inhaled salbutamol in any clinical setting. In the included studies, inhaled salbutamol was administered via various routes, namely MDI-S and nebulisation. The comparison was with a placebo with other treatments or with different administration methods.

The primary outcome was the incidence of ADRs associated with inhaled salbutamol versus placebo. The secondary outcomes were a description of the frequency and type of ADR associated with inhaled salbutamol administration.

Two reviewers (ME and CS) independently screened titles and abstracts to identify potentially eligible studies. The same authors assessed the available full texts of potentially relevant studies for inclusion and consulted the references of previously published primary and secondary papers to manually search for additional relevant papers.¹² Any disagreement regarding systematic review eligibility and inclusion was resolved through discussion and consensus between the two readers. If consensus could not be reached, the opinion of a third author (CDB), who served as a 'blind' arbiter, was sought. Investigators and corresponding authors were contacted to obtain additional information about studies with incomplete data.

Data extraction, descriptive analysis and meta-analysis

We used the same methodology for data extraction, performed independently by three reviewers (ME, CS and CDB) under the supervision of a fourth author (LP). The following outcomes were evaluated in descriptive analysis, when available: Incidence of ADRs, ADR type and description, ADR that necessitated drug withdrawal. We then conducted a meta-analysis of studies comparing inhaled salbutamol with placebo and reporting the total incidence of ADRs. We also performed a sensitivity analysis, excluding patients who received hypertonic saline 3% either with

	D1	D2	D3	D4	D5	Overall
Anil et al. 2010	+	+	+	+	?	?
Bertrand et al. 2001	?	+	+	+	?	?
Cengizlier et al. 1997	+	+	+	+	?	+
Delgado et al. 2003	+	+	+	+	?	+
Dobson et al. 1998	?	+	+	+	?	?
Gadomski et al. 1994	+	+	+	+	?	?
Gadomski et al. Ped Pharm and Ther 1994	+	+	+	+	?	?
Hedrick et al. 2009	?	+	+	+	?	?
Ho et al. 1991	+	+	+	+	?	+
John et al. 2006	+	+	+	+	?	?
John et al. 2010	+	?	+	+	?	?
Kaashimiri et al. 2010	+	+	+	+	?	?
Klassen et al. 1991	+	+	+	+	?	?
Kose et al. 2014	+	+	+	+	?	?
Langley et al. 2005	+	+	+	+	?	?
Luo et al. 2010	?	+	+	+	?	?
Mull et al. 2004	+	+	+	+	?	?
Reijonen et al. 1995	+	+	+	+	?	?
Rubilar et al. 2000	+	?	+	+	?	+
Schuh et al. 1990	+	+	+	+	?	?
Schweich et al. 1992	+	+	+	+	?	?
Uysalol et al. 2017	+	+	+	+	?	?
Wang et al. 2000	+	+	+	+	?	+
Yukselet al. 2001	+	+	+	+	?	+

Figure 1 Quality assessment of all the included studies assessment was performed using V.2 of the Cochrane risk-of-bias tool for randomised trials. Green indicates a 'low' risk of bias, yellow indicates 'some concerns', and red indicates a 'high' risk of bias. D1 indicates the evaluation domain for the randomisation process; D2 denotes deviation from intended interventions; D3 represents missing outcome data; D4 refers to measurement of the outcome; and D5 is the selection of reported results.

salbutamol or control, as well as studies in which salbutamol was administered via an MDI. The meta-analysis was conducted using RevMan V.5.4 (<https://revman.cochrane.org>). We analysed statistical heterogeneity to determine the feasibility of summing the results of the different studies deemed eligible for the meta-analysis. We assessed heterogeneity by calculating the I^2 statistic which represents the percentage of variance in effect estimates attributable to heterogeneity as opposed to sampling bias (chance). A I^2 statistic >40% indicated significant heterogeneity. When the number of studies was <5 or the studies were substantially heterogeneous, we used a random-effects model in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.¹³ We opted for forest plots to graphically show effect estimates with 95% CIs for individual trials and pooled results.

Quality assessment

Two authors (CS and CDB) assessed quality independently under the supervision of a third author (ME). We used V.2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2) to assess the quality of the included RCTs. The Cochrane tool is organised into a fixed set of bias domains: Randomisation process, deviation from intended interventions, missing outcome data, measurement of the outcome and selection of reported results. Within each domain, a series of questions (signalling questions) are de-

signed to elicit information regarding trial features relevant to the risk of bias. Each bias judgement domain is generated by an algorithm based on answers to the signalling questions. Each judgement contributes to the overall assessment of each RCT which can be 'low' or 'high' risk of bias or 'some concerns'.¹⁴

RESULTS

Literature search

The literature search strategy yielded a total of 3532 references, including 2765 from PubMed and 767 from other sources (429 from Trip, 228 from MEDLINE, 102 from the Cochrane Library and 8 from a manual search). As shown in the online supplemental figure 1, the number of potentially relevant papers identified by full titles after removing duplicates was 598 and after examining the full text, 467 were excluded because they did not meet inclusion criteria. Of the 131 papers evaluated for inclusion in the quantitative synthesis, 35 were excluded because they did not include children aged <2 years and 28 because they were either reviews or meta-analyses. Also excluded were 19 retrospective studies, 13 prospective observational studies and 6 publications in which salbutamol was not used as a treatment for wheezing or bronchiolitis. Moreover, 6 studies that included infants younger than 2 years but did not report data specific to this population were also excluded. A total of 24 records were included and a detailed description of each study is provided in table 1. 13 trials were conducted in the emergency department, 10 on hospitalised children and 1 in an ambulatory setting. Salbutamol was administered through nebulisation in 21 studies, through MDI-S in 5 studies and in 2 studies, both routes of administration were reported. The latter two studies were the only ones to compare nebulised versus MDI-S salbutamol administration.^{15–16} Dosing schedule differed in the included works ranging from one administration per day to hourly administration, as detailed in table 1. Seven studies compared salbutamol to epinephrine,^{17–23} two to ipratropium bromide^{24,25} and one to magnesium sulfate.²⁶ In eight studies, multiple comparison groups with different drugs, salbutamol dosages and additional treatments, such as hypertonic saline 3%, were present. A detailed description of the trial design, groups and exclusion criteria can be found in table 1 and online supplemental table 1.

Table 1 and figure 1 present the results of a quality assessment of the included studies as described in the Methods section. Based on the RoB 2 assessment, six studies^{15–16–24–25–27–28} were deemed to have a high risk of bias while the remaining studies were classified as having 'some concerns'.^{20–24}

Meta-analysis on total ADRs

The meta-analysis included seven studies in which total ADR outcomes were reported as frequencies in the experimental (salbutamol) and control groups. A comparison was made between salbutamol and controls consisting of placebo in six studies (one with MDI-S placebo, four with inhaled saline and one with inhaled saline or 3% hypertonic),^{20–24–29–32} or no treatment in one study.²⁷ Comparisons between salbutamol and other drugs were not included in the meta-analysis.

In seven studies involving eight cohorts,^{20–24–27–29–32} inhaled salbutamol with or without hypertonic saline 3% was compared with controls with or without hypertonic saline 3% for a total of 597 patients: 273 and 324 in the salbutamol and control groups, respectively. There was no statistically significant difference in the incidence of ADRs between the two groups (19.0% in the salbutamol group vs 13.3% in the control group) with an OR of 2.12 (95% CI 0.69 to 6.51; $p=0.19$). The level of heterogeneity between studies was high, reaching 57% (figure 2).

Excluding patients that received hypertonic saline 3% with salbutamol or control, eight cohorts were included,^{20–24–27–29–32} with 237 patients in the salbutamol group and 247 in the control group. Even in this instance, there was no difference in the incidence of ADRs between the two groups (21.9% vs 17.4%) with an OR of 1.50 (95% CI 0.80 to 2.81; $p=0.20$). Heterogeneity was marginally lower at 38% (online supplemental figure 2).

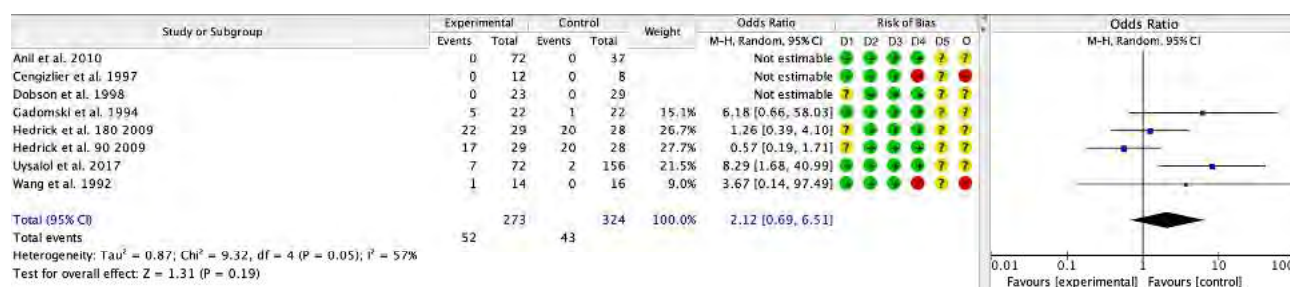


Figure 2 Incidence of total adverse drug reaction between inhaled salbutamol with or without hypertonic saline 3% versus controls with or without hypertonic saline 3%.

Trials in which salbutamol was administered through an MDI were then removed from the quantitative synthesis. In the remaining five studies^{20 24 29 30 32} in which only nebulised salbutamol was administered, a total of 463 patients were enrolled with 203 and 260 in the salbutamol and control groups, respectively. Salbutamol delivery through nebulisation was associated with an increased incidence of ADRs (6.4% vs 1.2%) with an OR of 6.76 (95% CI 2.01 to 22.71; $p=0.002$). There was no heterogeneity between studies (0%) (figure 3).

ADRs descriptive analysis

Descriptive analysis on ADRs types associated with salbutamol administration in the 24 included studies are summarised in table 2 and described in detail in the online supplemental text. In all the included studies, none reported severe cardiac side effects that necessitated withdrawal from the study following salbutamol administration through nebulisation or MDI. Only one study using nebulised salbutamol reported a significant non-cardiac side effect (severe tremulousness) that necessitated withdrawal from therapy²⁴ (online supplemental text).

DISCUSSION

The use of salbutamol in children under 2 years of age is controversial and has been the subject of extensive debate for over 20 years. Notably, despite the existence of a few small studies, there is a dearth of large studies specifically addressing the safety of inhaled salbutamol in this population and, therefore, the current literature has failed to express a definitive consensus.

This study tries to fill this gap and represents, to the best of our knowledge, the first comprehensive analysis of RCTs evaluating the short term safety profile of inhaled salbutamol in children under 2 years of age. The quantitative analysis revealed no clinically significant increase in the incidence of ADRs between inhaled salbutamol and placebo. However, an increase in ADRs was observed when only nebulised salbutamol was considered. The clinical significance of these data may be mitigated by the observation that, among the 203 patients in the intervention group, only one significant severe ADR necessitating withdrawal from the study was reported. Consequently, MDI-S administration of salbutamol appears safer than nebulisation. This is consistent with the findings of Cates et al, who demonstrated that MDI-S is not only safer but also more effective than nebulisation in adults and in children older than the age of 2.³³ Similarly, equivalent, if not better, outcomes have been reported in younger children

using MDI-S as opposed to nebulisers for the administration of inhaled salbutamol.^{15 34 35}

A meta-analysis reported that children younger than 5 years of age with moderate-to-severe wheezing exacerbations had lower hospital admission rates (OR 0.42, 95% CI 0.24 to 0.72) when using MDI-S as opposed to a nebuliser.³⁶ Similarly, a randomised study of children younger than 24 months ($n=123$) with mild-to-moderate wheezing demonstrated that the use of an MDI-S resulted in faster symptom resolution and statistically significant improvement at 1 hour (OR 3.9, 95% CI 1.5 to 10.4).¹⁶

This meta-analysis has some limitations. The majority of studies did not aim to directly assess salbutamol ADRs or at least this was not the primary objective. Only eight studies included an evaluation of ADRs as one of their principal objectives.^{19 21 29,31,32,37–39} The main objectives of the included studies can be found in table 1. Second, the studies that assessed ADRs only looked for specific ADRs and typically do not report ADRs if they are not deemed clinically relevant. These concerns are reflected in the high proportion of studies presenting a 'high' risk of bias in the domain of outcome measurements (figure 1). In fact, most authors looked for cardiovascular effects such as tachycardia and changes in blood pressure as well as tremors whereas only a few authors looked for facial blanching or pallor, loss of deep tendon reflexes, nausea and vomiting, potassium and glucose levels (table 2). However, we believe that these limitations do not have a significant impact on the findings presented here because, in all the studies, patients were periodically fully evaluated by healthcare professionals (nurses or doctors) who would have noticed and reported other side effects, especially if clinically significant. Another limitation of our study is that tachyarrhythmias were evaluated differently across studies. The majority of studies evaluated heart rate via peripheral pulse assessment or pulse oximeter; however, a few authors used electrocardiographic monitoring to assess heart rhythm.^{28 31 37} Furthermore, most authors reported the mean heart rate whereas others only reported the number of patients who developed tachycardia after arbitrary cut-offs were established (eg, HR >200 bpm, used by Anil et al²⁰) which were not always specified. It should be noted that the average heart rate increase reported in most of the studies was only 5% or 8–9 bpm. Moreover, none of the studies reported a clinically significant increase in heart rate with the use of inhaled salbutamol. Thus, this slight increase in the heart rate can be considered an expected effect.



Figure 3 Incidence of total adverse drug reaction between nebulised salbutamol with or without hypertonic saline 3% versus controls with or without hypertonic saline 3%.

Table 2 Main adverse drug reactions in salbutamol and placebo group classified in cardiac and non-cardiac side effects

	Cardiovascular ADRs, n		Other ADRs, n				
	Tachycardia; (changes in HR from baseline)	Arrhythmias (including QT prolongation) and changes in BP	Tremor	Fever/fever pallor	Vomit and abnormal K or glucose levels	Irritability/agitation/adrenergic stimulation, loss of deep tendon reflex	Nasopharyngeal symptoms and facial blanching
Anil <i>et al</i> ²⁰	NEB salbutamol+0.9% NaCl	0/36; (142±16.2 vs 138.4±22 bpm)	0/36				
	NEB salbutamol+3% NaCl	0/36; (140.5±11.2 vs 135±14 bpm)	0/36				
	NEB 0.9% NaCl	0/37; (139.2±14.6 vs 136.5±7 bpm)	0/37				
Bertrand <i>et al</i> ¹⁷		Changes in BP					
NEB salbutamol	(146±4 bpm vs 153±2.9 bpm)	0/14	0/14				
Cengizlier <i>et al</i> ²¹	MDI+spacer salbutamol	0/12; (4.7±6.8 bpm change)					
	No bronchodilator	0/8; (2.6±1.8 bpm change)					
Delgado <i>et al</i> ¹⁵					Vomit		
NEB salbutamol	5.8% increase				9.40%		
MDI+spacer salbutamol	1% increase				13.20%		
Dobson <i>et al</i> ²⁹		Arrhythmias					
NEB salbutamol	0/23	0/23					
NEB 0.9% NaCl	0/29	0/29					
Gadomski <i>et al</i> ⁴¹							
NEB salbutamol	(2±16 bpm change)						
NEB 0.9% NaCl	(−4±24 bpm change)						
Gadomski <i>et al</i> ³⁰							
NEB salbutamol	(11±18 bpm change)						
NEB 0.9% NaCl	(2±28 bpm change)						
Hedrick <i>et al</i> ³¹		No clinically relevant differences in ECG findings and BP		Fever	Abnormal K or glucose levels		
MDI+spacer salbutamol 90 mg	2/29			2/29 (7%)	0	0	
MDI+spacer salbutamol 180 mg	5/29			7/29 (24%)			
Placebo	2/28			3/28 (11%)			
Ho <i>et al</i> ²⁸		Arrhythmias					↓SaO2
NEB salbutamol followed by 0.9% NaCl	0/13	0/13					11/13
NEB 0.9% NaCl followed by salbutamol	0/8	0/8					8/8
John <i>et al</i> ¹⁹		Arrhythmias				Facial blanching	
NEB salbutamol	0/15 (8.93±2.89 bpm change)	0/15	0/15		0/15		
John <i>et al</i> ¹⁸							
NEB salbutamol	(9.63±2.58 bpm change)						
Kaashmiri <i>et al</i> ³⁷		Arrhythmias—changes in BP		Fever/fever	Abnormal K or glucose levels	Nasopharyngeal symptoms	Bronchial hyperactivity
MDI+spacer salbutamol 180 mcg	12/43	13/43–0/43		1/43	0/43	2/43	0/43
MDI+spacer salbutamol 360 mcg	19/44	3/44–0/44		1/44	0/44	0/44	1/44

Continued

Table 2 Continued

	Cardiovascular ADRs, n		Other ADRs, n					
	Tachycardia; (changes in HR from baseline)	Arrhythmias (including QT prolongation) and changes in BP	Tremor	Fever/fever and pallor	Vomit and abnormal K or glucose levels	Irritability/agitation/adrenergic stimulation, loss of deep tendon reflex	Nasopharyngeal symptoms and facial blanching	Bronchial hyperactivity and ↓SaO2
Klassen <i>et al</i> ¹⁹								
NEB salbutamol	(159±16 vs 150±16 bpm)							
NEB 0.9% NaCl	(152±16 vs 146±16 bpm)							
Kose <i>et al</i> ¹⁶								
NEB salbutamol	0/18	Arrhythmias and changes in BP				Loss of deep tendon reflex		
Langley <i>et al</i> ²¹		0/18				0/18		
NEB salbutamol			6/31	Pallor	Vomit			
Mull <i>et al</i> ²²				6/31	8/31			
NEB salbutamol				Pallor	Vomit			
			0/32	0/32	5/32			
Reijonen <i>et al</i> ²³								
NEB salbutamol followed by 0.9% NaCl								
NEB 0.9% NaCl followed by salbutamol	(Mean HR increased at 15 at 30' after salbutamol, but not significant)							
Rubilar <i>et al</i> ¹⁶								
MDI salbutamol			1/62					
NEB salbutamol			3/61					
Schuh <i>et al</i> ⁴²								
NEB salbutamol	0/21; (7.8±2.7 bpm change)	Arrhythmias						
NEB 0.9% NaCl	0/19; (−6.8±3.8 bpm change)	0/21	0/21			0/21		
Schweich <i>et al</i> ⁴³		0/19	0/19			0/19		
NEB salbutamol	(−13 bpm change)							
NEB 0.9% NaCl	(−15 bpm change)							
Uysalol <i>et al</i> ³²								
NEB 0.9% NaCl								
NEB salbutamol								
NEB 3% NaCl								
Wang <i>et al</i> ⁴⁴								
NEB salbutamol			1/14					
NEB 0.9% NaCl			0/16					
Yuksel <i>et al</i> ²⁵								
NEB salbutamol	Non-statistically significant increased HR (119±21.6 vs 128±4.1)	Significantly increased QTc max and QTcd						
In studies in which the comparison was not made with placebo, only the salbutamol group is reported. ADR, adverse drug reaction; BP, blood pressure; HR, heart rate; K, potassium; MDI, metered dose inhaler; NaCl, sodium chloride; NEB, nebulised; SaO2, oxvaen saturation.								

In studies in which the comparison was not made with placebo, only the salbutamol group is reported.

ADR, adverse drug reaction; BP, blood pressure; HR, heart rate; K, potassium; MDI, metered dose inhaler; NaCl, sodium chloride; NEB, nebulised; SaO₂, oxygen saturation.

This meta-analysis only considered salbutamol short-term effects. However, there is considerable debate also on the regular and excessive use of beta-2 agonists which may lead to beta-receptor downregulation with consequently rebound hyperresponsiveness, decreased bronchodilator response and increased airway inflammation, especially when used without inhaled corticosteroids.⁴⁰ The included studies are dated, having been conducted and published between 1988 and 2017. However, the low heterogeneity regarding the total incidence of ADRs observed in most of the comparisons conducted in the meta-analysis and the fact that no gross difference was found in the data reported by year may support the validity of the present results.

In the future, larger studies should be designed to specifically assess the safety of salbutamol in children younger than 2 years of age, clearly stating the evaluated ADRs, defining in advance which ADRs are considered clinically significant and highlighting the most severe ones necessitating drug discontinuation. Moreover, addressing the different safety profiles between nebulised salbutamol and MDI and MDI-S salbutamol could also have a profound impact on clinical practice.

In conclusion, this meta-analysis has shown that salbutamol can be used safely for short term use in children under 2 years of age with acute wheezing, with MDI-S preferred. Although there was an increase in ADRs with nebulised salbutamol, it is reassuring that severe ADRs have only rarely been reported suggesting that nebulised salbutamol can also be used safely, when clinically indicated.

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ARTIGO ORIGINAL

Eficácia dos centros de asma pediátricos: um estudo clínico piloto

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RESUMO

Contexto Crianças e jovens (CYP) com asma no Reino Unido apresentam um risco mais elevado de desfechos negativos em comparação com outros países europeus de alto rendimento, devido a fatores como acesso limitado a revisões de asma de alta qualidade, testes diagnósticos e avaliações inconsistentes após ataques asmáticos. O Leicester Integrated Care Board financiou o primeiro centro piloto de asma no Reino Unido para CYP, com o objetivo de investigar a viabilidade e eficácia desses centros, fornecendo avaliações pós- crise, educação sobre asma, testes diagnósticos de função pulmonar e otimização do tratamento.

Métodos Estudo clínico piloto incluindo CYP entre 4 e 17 anos encaminhados para o centro com asma não controlada ou após um ataque asmático, entre novembro de 2021 e abril de 2022. Os CYP receberam uma avaliação clínica estruturada, incluindo investigações diagnósticas de primeira linha do National Institute for Health and Care Excellence (NICE), como espirometria, reversibilidade ao broncodilatador (BDR) e fração de óxido nítrico exalado (FeNO).

Resultados Dos 312 CYP encaminhados (idade média de 8,6±3,2 anos; 42% mulheres), 266 (85,3%) compareceram à consulta. O tempo mediano entre o encaminhamento e a revisão foi de 2 dias (IQR 1–3). Três CYP (1,1%) estavam gravemente doentes na revisão e precisaram de tratamento hospitalar adicional. Entre os 231 CYP que completaram os testes de primeira linha, a asma foi confirmada em 73 (31,6%) com base nos critérios diagnósticos do NICE para CYP. 22% das crianças com espirometria basal normal apresentaram ≥12% de BDR.

Conclusão Os centros de asma pediátricos são um modelo viável de atendimento para fornecer avaliações pós- crise asmática e identificar doentes de alto risco que necessitam de tratamento adicional. Os testes de espirometria, BDR e FeNO permitiram a confirmação diagnóstica em uma proporção significativa de CYP.

INTRODUCTION

The UK children and young people (CYP) experience high rates of severe asthma attacks and asthma deaths compared with other high income European countries.^{1–3} The 2014 UK National Review of Asthma Deaths (NRAD) highlighted that the vast majority of CYP asthma deaths are avoidable.⁴ The reasons for poor outcomes in CYP with asthma are multifactorial but include poor access to high-quality asthma reviews,^{4–6} a lack of access to first-line objective lung function tests recommended by the National Institute for Health and Care Excellence (NICE)⁷ and recent European guidelines^{8–10} and reviews after severe asthma attacks.¹¹

The lack of access to first-line lung function tests, spirometry, bronchodilator reversibility (BDR) and fraction of exhaled nitric oxide (FeNO) tests frequently results in asthma misdiagnosis including under diagnosis in CYP.^{12–13} CYP with undiagnosed asthma are at significant risk of severe asthma attacks¹⁴ in addition to poorer health-related quality of life.¹²

The best model of care for UK CYP with asthma has not been determined. The UK CYP Transfor-

Key messages

What is known about this topic

- UK asthma outcomes in children and young people (CYP) are worse than in other high-income European countries.
- The National Review of Asthma Deaths in 2014 highlighted improvements needed in asthma care and postattack asthma reviews within 2 working days were subsequently recommended by the UK National Institute for Health and Care Excellence (NICE).
- These postattack reviews are frequently not performed.

What this study adds

- We show that postattack reviews including lung function testing highlights a small but significant group of children with an ongoing severe asthma attack and low lung function that are at risk of a poor outcome.
- We also show that performing NICE recommended first-line asthma diagnostic tests in this setting confirm the diagnosis in a higher proportion than in unselected children in primary care with possible asthma.

How this study might affect research practice or policy

- We show that asthma hubs performing postattack reviews are feasible and attended by a high proportion of families and CYP. Asthma hubs may be suitable for large parts of the UK for postattack reviews and to facilitate diagnosis using objective tests. Further research is needed to study medium to long-term outcomes following an asthma hub review.

mation Programme is committed to improving asthma outcomes.¹¹ The programme recommends the creation of asthma hubs to address access to objective tests. Such hubs require careful evaluation to ensure they achieve their objectives, are cost-effective and acceptable to families.¹¹ The current NICE asthma quality standards also recommend asthma reviews within 2 working days in CYP from 5 years and adults after a severe asthma attack.¹⁵

The Leicester, Leicestershire and Rutland (LLR) Integrated Care Board funded what to our knowledge is the first UK pilot paediatric asthma hub in 2021/2022 and the aim of this study was to evaluate feasibility, acceptability to families, diagnostic effectiveness and ability to identify high-risk CYP with unresolved acute attacks.

METHODS

Study design: real-life clinical pilot study

Participants

CYP aged 5-to-17 years with doctor-diagnosed acute wheezing or asthma treated at University Hospitals of Leicester NHS Trust (UHL) emergency department (ED) or as inpatient between 30 November 2021 and 11 April 2022 were eligible for referred to the hub. Three children aged 4 years were also referred and their data are included. The ED at UHL serves the entire LLR region, which based on the latest Office for National Statistics Census data accounts for a population of more than 70 000 children.¹⁶ Leicester City primary care practices were also eligible to refer children with either (1) uncontrolled asthma or (2) following an asthma attack treated in primary care. The index of multiple deprivation (IMD) was obtained from the¹⁷ English Indices of Deprivation 2019 issued by the UK Ministry of Housing, Communities and Local Government¹⁷ and distance between CYP home and asthma hub was obtained using FreeMapTools.¹⁸

Referral process

Patient details including carer contact information were sent by the attending medical team to the paediatric administration team who contacted families to book appointments. Eight appointments were available each working day. The primary care referral process was set up using the Pathway Referral Implementation System.

Pilot asthma hub procedures

The hub was based in a large primary care practice close to the centre of Leicester, providing easy access and free parking.

A paediatric consultant or specialist asthma nurse staffed the hub on a rotational basis. Peripheral oxygen saturations using pulse oximeter were recorded. CYP were then invited to perform FeNO testing (Niox Vero, Circassia, Oxford, UK) following American Thoracic Society (ATS) guidelines¹⁹ using the 10 s mode in older children and the 6 s paediatric mode where the 10 s mode was unsuccessful. Thereafter, spirometry testing (Microlab 3500, Becton Dickinson, New Jersey) and BDR (10–15 min after 400 µg of inhaled salbutamol administered via spacer) were performed according to European Respiratory Society (ERS)/ATS standards.²⁰

Spirometry was considered abnormal if FEV₁ or FEV₁/FVC or both were below the lower limit of normal using Global Lung Initiative data.²¹ Inhaler technique was checked for all CYP and a written personalised asthma action plan was completed. Written communication with treatment recommendations was sent to the CYP's General Practitioner (GP).

Two clinic rooms were available to allow 45 min to disinfect rooms between patients due to the COVID-19 pandemic at the time. A System Integrated Air Sterilisation Unit (AirScrubber) ASU 6000 mobile unit (Mansfield Pollard, Bradford, UK) was used for 30 min with an additional 15 min to clean surfaces. A list of resources needed to perform hub asthma reviews is shown in table 1.

Asthma control tests

Asthma control test (ACT)²² for children aged ≥12 years, and the childhood ACT²³ for children aged 4–11 years were used to assess asthma control. A score of ≥20 in either questionnaire denotes good asthma control in the previous 4 weeks.

Feasibility outcomes

We assessed the feasibility of the asthma hub based on four parameters: (1) ability to see patients within 2 working days (rapid access) as per NICE quality standards,¹⁵ (2) proportion of referred CYP who attended, (3) success of lung function testing, (4) time needed to conduct the reviews.

Effectiveness outcomes

We evaluated the number of acutely unwell CYP needing further-emergency care and the proportion of children given a diagnosis of asthma as per NICE guidelines.⁷

Table 1 List of resources needed to run a paediatric asthma hub

Space	One room minimum; two rooms if disinfection of room needed between patients.
Staff	One staff member needed to run the hub, additional staff needed if covering holidays or sick days or to provide advice or support as well as interpretation of test if required.
Equipment:	Training needs: National bundle of care for CYP with asthma eLearning tier 3 training.
Spirometer x 1	ARTP certificate spirometry performance (essential) and interpretation (desirable).
FeNO equipment x 1 including test sensors	
Pulse oximeter	
Consumables:	
Filters for spirometer	
FeNO filters	
Spacers	
Placebo training inhalers	
Drugs:	Staff could be a nurse prescriber, or they would need access to a prescriber. Having the hub situated in a healthcare facility (GP or hospital setting) is ideal.
Salbutamol for BDR testing when CYP do not bring their own and for emergency bronchodilation.	
Access to oral corticosteroids	
Access to oxygen	
List of resources and additional information for each resource required to run a paediatric asthma hub. ARTP, Association for Respiratory Technology & Physiology; BDR, bronchodilator reversibility; CYP, children and young people; GP, General Practitioner.	

Data analysis

Data were extracted prospectively from the asthma hub review record sheet and entered into a Microsoft excel database. Continuous variables were presented as mean (±SD) and medians (ranges). χ^2 tests were used for count data. An independent sample t-test was used to compare means for parametric data. Cohen's kappa coefficients were calculated to measure the agreement between the diagnostic measurements. All statistical analyses were conducted using IBM SPSS Statistics for Windows V.28.0 (Armonk, New York: IBM Corp). All statistical tests were performed at an alpha=5% level.

RESULTS

Participants

Of 312 CYP referred, 266 patients (85.3%) attended. Two hundred and thirty-three (74.7%) were referred from (UHL) and 76 (24.4%) from primary care. The referral source was missing for three patients. The median time from referral to clinic appointment was 2 working days (IQR 1–3). The mean time taken to review a child was 50 min (SD 17.2). A total of 142 (53.4%) CYP were already prescribed regular asthma preventer treatment at the time of their appointment. The baseline demographic characteristics of participants are shown in table 2.

Forty-six CYP (14.7%; mean age 8.8 years) did not attend their appointment (56.5% men; 45.7% white; 6.5% black; 28.3% Asian; 10.9% 'mixed' and 8.7% from another ethnic background). No significant difference in sex (p=0.82) or ethnicity (p=0.69) was detected compared with attendees. In addition, we found no significant difference in the IMD Decile (p=0.92), the distance between CYP home and asthma hub (p=0.47) between attendees and non-attendees. Of 42 families living >10 miles from the hub, 34 (81%) attended their appointment.

Table 2 Baseline characteristics of 266 children and young people who attended their asthma hub appointment

Mean age in years (SD)	8.5 (3.3)
Number of males (%)	155 (58.2)
Ethnicity	
White, n (%)	130 (48.9)
Black, n (%)	13 (4.9)
Asian, n (%)	86 (32.3)
Mixed ethnicity, n (%)	19 (7.1)
Other	18 (6.8)
Median distance from clinic (IQR)	2.7 (1.8–4.2)
Median Index of Multiple Deprivation Decile (IQR)	4 (2–8)
Clinical assessment of children attending the hub (n=266)	
In respiratory distress at the time of appointment, n (%)	22 (8.3)
Audible wheeze, n (%)	13 (4.9)
Median baseline O ₂ (IQR)	97% (96–98)
Median number of attacks ever (IQR)	4 (2–10)
Median number of attacks in the past year (IQR)	1 (1–3)
Median number of OCS in the past year (IQR)	1 (0–1.75)
Median number of A&E visits ever (IQR)	2 (1–4)
Median number of A&E visits in the past year (IQR)	1 (1–2)
Median (C)ACT score	16 (13–20)
Baseline lung function results	
Median FeNO in ppb (IQR) (n=125)	20 (11–44)
Mean baseline FEV ₁ predicted (%) (SD) (n=241)	86.7 (15.4)
Mean baseline FEV ₁ z-score (SD)	−0.8 (1.3)
Mean baseline FVC predicted (%) (SD)	91.3 (16.0)
Mean baseline FVC z-score (SD)	−0.5 (1.4)
Mean baseline FEV ₁ /FVC (%) (SD)	84.6 (8.8)
Mean baseline FEV ₁ /FVC z-score (SD)	−0.5 (1.3)
Abnormal FEV ₁ n (%)	66 (27.4)
Abnormal FEV ₁ /FVC n (%)	58 (24.0)
Abnormal FEV ₁ and FEV ₁ /FVC n (%)	26 (10.8)
Characteristics, clinical assessment, and lung function results of the 266 patients who attended their asthma hub appointment.	
ACT, asthma control test; A&E, Accident & Emergency; FEV ₁ , forced expiratory volume in one second; FVC, forced vital capacity; GP, General Practitioner; OCS, oral corticosteroids.	

Identification of high-risk patients with ongoing severe asthma attack

Twenty-two (8.3%) CYPs were deemed to be in respiratory distress by the attending healthcare practitioner and three children (1.1%) were sent back to the ED due to ongoing acute asthma and peripheral oxygen saturation <94%. Two CYP were subsequently readmitted to hospital, and one received further asthma emergency treatment. 138 CYP (51.9%) had been prescribed oral corticosteroids (OCS) prior to their review, of these nine (6.5%) were still on OCS at the time of their review. 135 out of 138 (97.8%) of the CYP who had been prescribed OCS before their appointment were referred from the hospital. Thirteen patients (4.9%) were prescribed further systemic corticosteroids and advised to have a review with their GP within 7 days. The median (C)ACT score for attendees was 16 (IQR 13–20).

First-line asthma diagnostic tests

Spirometry

Usable spirometry data were obtained from 241 out of 266 (90.6%) CYP. Of the 241 CYP with acceptable spirometry, 66 (27.3%) had abnormal baseline spirometry (table 2). Of these 40 (60%) had low FEV₁ only, 58 (87.9%) had low FEV₁/FVC and 26 (39.4%) had low FEV₁ and FEV₁/FVC.

Fraction of exhaled nitric oxide

One hundred and twenty-five CYP out of 266 (46.9%) achieved acceptable FeNO measurements. FeNO was obtained in 45 of 155

children aged 4–8 years (29.0%) and in 80 of 111 CYP aged 9–17 years (72.1%). The median FeNO was 20 ppb (IQR 11–44 ppb). Fifty CYP (40%) had a FeNO measurement ≥25 ppb and in 37 CYP (29.6%), FeNO was ≥35 ppb. Scatterplots of first-line asthma diagnostic tests stratified by age are presented in figure 1.

Asthma diagnosis

Two hundred and thirty-one (96%) CYP achieving baseline spirometry also performed postbronchodilator spirometry. Mean BDR was 8.8% (SD 10.8). Of the 231 CYP with acceptable post-bronchodilator spirometry, 73 (31.6%) had BDR ≥12%. These CYP represent 27.4% of all CYP who attended the asthma hub and in whom asthma could be confirmed in a single visit. Fifty-two of these (71.2%) were newly diagnosed with asthma. Of the 52 newly diagnosed CYP, 26 (50%) were already on ICS treatment at the time of their appointment. Thirty-eight of 175 (21.7%) CYP with normal spirometry had a BDR ≥12%. We found no agreement between positive FeNO measurements and positive BDR measurements. Measurements of agreement between the different diagnostic tests are shown in table 3.

Comparison between GP and hospital referrals

We stratified success rate and outcome of diagnostic tests of CYP based on referral by their GP or the hospital as shown in table 4.

DISCUSSION

To our knowledge, we report feasibility and effectiveness data for the first one-stop rapid access paediatric asthma hub in England. Just over 8% of CYP reviewed shortly after receiving hospital treatment for a severe asthma attack were deemed to be in ongoing severe respiratory distress requiring further acute asthma treatment. Our pilot study highlights the importance of postattack reviews.¹⁵ In addition, usable spirometry results were obtained from over 90% of CYP, and asthma confirmed using NICE diagnostic criteria in 27% of CYP who attended.

Strengths and limitations

A large and representative number of CYP reflecting the demographics of Leicester and Leicestershire were reviewed during the pilot. Nearly all patients treated at UHL with severe wheezing were referred to the hub and seen within 2 working days. The success of the hub was facilitated by being staffed by dedicated specialist nurses and/or doctors with training in the management of childhood asthma and the success rate at obtaining acceptable spirometry and FeNO results were high.

The hub was located close to the city centre, approximately 1 mile from UHL, with easy access and free parking. The postattack reviews were attended by 85% of CYP referred. Attendance rates were not different between poorer and more affluent families as assessed by IMD or by distance to the asthma hub, suggesting that the service could be replicated in many other areas of the country.

A small but significant number of CYP were found to have unresolved acute severe asthma at review and three had to be sent back to the children's ED, resulting in two readmissions to hospital. These CYP must be considered high risk for adverse outcomes as caregivers may be wrongly reassured by the discharge from hospital that their child's asthma has been adequately treated. We do not know how many families would have either returned to hospital by themselves or sought further advice from their GP; however, it is important to note that the NRAD report showed that people who died from asthma were likely to have recently been discharged from hospital following an asthma attack.⁴

The average review time was 50 min, this encompassed the total contact time including 15 min of waiting time post-SABA, asthma education, completion of a personalised written asthma action plan and checking of inhaler technique. This was longer than the average GP appointment but similar to appointment times reported in the NICE feasibility project,²⁴ which was deemed cost-effective despite not including asthma education, inhaler technique checks or reviews of the action plan.²⁵ The level of specialist staff support-

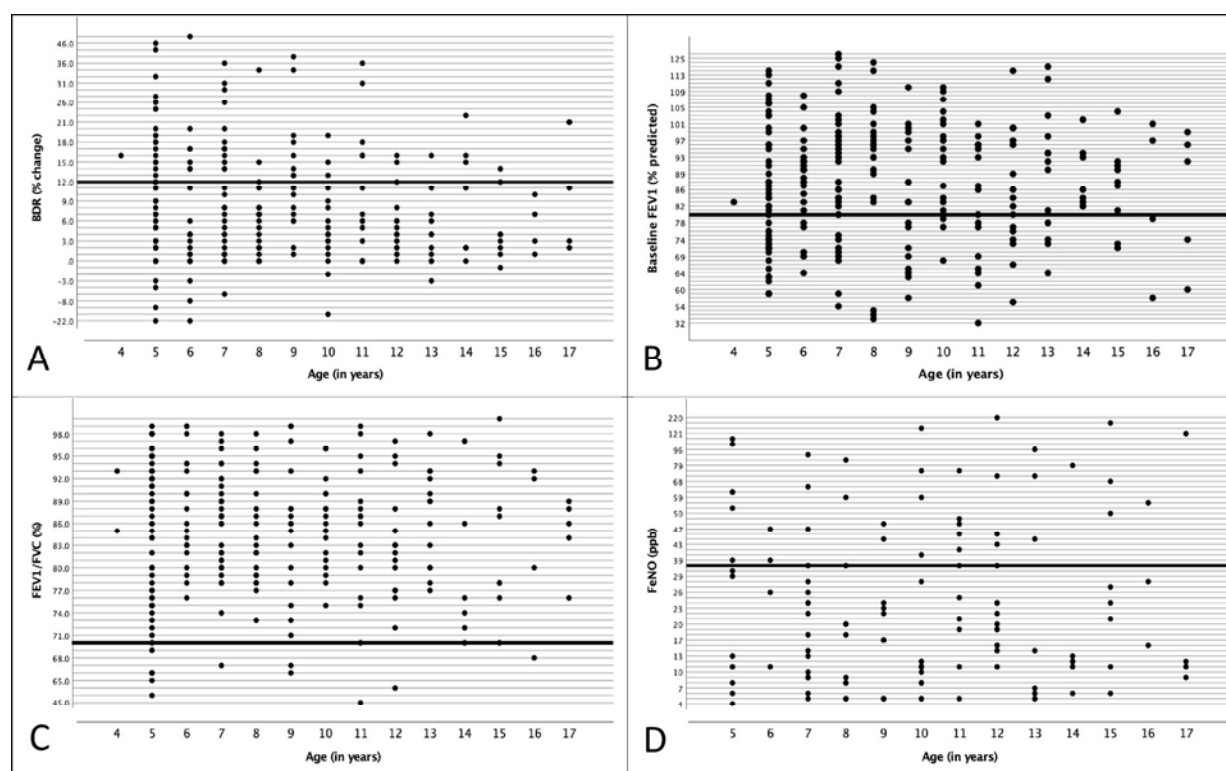


Figure 1 (A) Scatterplot demonstrating the spread of post-bronchodilator percentage change by age. A reference line is included at 12% to indicate the cut-off for asthma diagnosis as per National Institute for Health and Care Excellence (NICE) guidelines. (B) Scatterplot demonstrating the baseline forced expiratory volume in one second (FEV_1) by age, FEV_1 results are reported as percentage predicted. A reference line is included at 80% to indicate abnormal spirometry. (C) Scatterplot of the ratio of forced expiratory volume in one second to the forced vital capacity (FEV_1/FVC) by age. The ratio is presented as a percentage. A reference line is included at 70% to indicate abnormal spirometry as per NICE guidance. (D) Scatterplot of fractional exhaled nitric oxide (FeNO) results (in particles per billion) by age. A reference line is included at 35 particles per billion to indicate the cut-off for asthma diagnosis as per NICE guidelines.

ing the pilot hub and the time taken to conduct the review would not be available in primary care, highlighting the potential role of asthma hubs to provide detailed high-quality asthma reviews with appropriately trained staff.

Over 90% of CYP attending managed to perform acceptable spirometry. Of those, 24% had ongoing obstructed spirometry. In addition, over 30% of the 231 CYP who managed acceptable spirometry pre-SABA and post-SABA had $BDR \geq 12\%$. These children had asthma confirmed by NICE guidelines. It is noteworthy that 22% of CYP with normal baseline spirometry showed a $BDR \geq 12\%$ supporting ERS guidance⁸ to consider BDR in symptomatic children under investigation for asthma even when baseline spirometry is normal. It is likely that diagnostic yield would have been higher still if children had been tested as soon as possible in the ED. It is important to stress that asthma cannot be excluded on the basis of one-off inconclusive first-line tests. Moreover, patients were not told to withhold SABA usage before

their asthma hub review for safety reasons, this was a pragmatic study of children with poor asthma control or those following a recent asthma attack. It is likely that, the proportion of children where a diagnosis could be confirmed with positive BDR would have been higher if we had held SABA for at least 4 hours prior to review. Additionally, despite the majority of CYP prescribed OCS having been referred from the hospital, we found that median FeNO levels were higher in the hospital cohort compared with CYP referred from primary care.

Table 4 Comparison of lung function test results between GP and hospital referrals

	GP (n=67)	Hospital (n=199)	P value
Median FeNO (IQR)	18 (8.75–36)	22 (11–47)	0.13
Mean FEV_1 % predicted (SD)	91.4 (13.2)	85.1 (16.9)	0.006
Mean FEV_1 z-score (SD)	−0.44 (1.19)	−0.98 (1.28)	0.003
Mean FVC % predicted (SD)	94.1 (12.8)	90.4 (16.9)	0.12
Mean FVC z-score (SD)	−0.27 (1.13)	−0.61 (1.41)	0.07
Mean FEV_1/FVC (SD)	87.1 (8.0)	84.1 (9.0)	0.02
Mean FEV_1/FVC z-score (SD)	−0.30 (1.25)	−0.62 (1.24)	0.07
Acceptable baseline spirometry, n (%)	61 (91.0)	179 (89.9)	0.59
Acceptable post-bronchodilator spirometry, n(%)	59 (88.1)	172 (86.4)	0.51
Acceptable FeNO measurements, n (%)	38 (56.7)	87 (43.7)	0.48
Abnormal FEV_1/FVC , n (%)	9 (13.4)	49 (24.6)	0.05
Abnormal BDR, n (%)	22 (32.8)	51 (25.6)	0.11
Abnormal FeNO, n(%)	11 (16.4)	26 (13.1)	0.43

Lung function tests from patients referred from GP and hospital were compared and p values were calculated using an independent t-test for parametric data and a Mann-Whitney U test for non-parametric continuous data. χ^2 test was used for categorical data. BDR, bronchodilator reversibility; FEV_1 , forced expiratory volume in one second; FVC, forced vital capacity.

Table 3 Measurement of agreement between first-line asthma diagnostic tests

	Agreement on positive asthma diagnosis	Kappa
BDR vs FEV_1 z-score	27.0%	0.32
BDR vs FEV_1/FVC z-score	30.9%	0.14
FEV_1 z-score vs FEV_1/FVC z-score	25.9%	0.23
FeNO vs BDR	32.5%	−0.09
FeNO vs FEV_1 z-score	28.9%	0.07
FeNO vs FEV_1/FVC z-score	20.2%	−0.04

Measurement of agreement using Cohen's Kappa Coefficient between positive BDR spirometry $\geq 12\%$, abnormal baseline spirometry (below lower limit of normal) and FeNO (≥ 35 ppb) as per NICE guidelines. BDR, bronchodilator reversibility; FEV_1 , forced expiratory volume in one second; FVC, forced vital capacity; NICE, National Institute for Health and Care Excellence.

Our study highlights that diagnosing asthma using currently available objective tests can be difficult and timing of the testing is critical to the success rate of first-line tests (spirometry, BDR and FeNO). The best approach to diagnostic testing is yet to be determined. The success rate during a single appointment in our study, however, was higher than in any other previously reported study. Ideally, children would be tested following presentation with an asthma attack in the ED or at the GP. This is, however currently rarely available.

There were fewer referrals from primary care directly for objective lung function testing despite an easy direct online referral process advertised to practices via newsletters and direct communication from the Integrated Care Board likely reflecting service pressures in UK primary care, resulting in a longer lead-in time for uptake of new services available to GPs.

Of children referred directly from primary care with symptoms of asthma and tested within 2 working days, 37% were confirmed asthmatic following a single visit. These numbers are considerably higher than those reported in the NICE7 asthma guidelines feasibility study and our group's previous cohort study of asthmatic children managed in primary care,¹⁴ where the diagnosis was confirmed in less than 20% of patients tested. Our data confirm that the timing of asthma diagnostic investigations matter and diagnostic tests are most helpful when patients present with respiratory symptoms and before starting treatment where safe to do so.

Recent discussion around postattack management has focused on the recommendation of 'as needed salbutamol'.²⁶ The evidence is largely based on studies using readmission to hospital as the primary outcome and lung function is rarely measured. Our study highlights the importance of postattack reviews combined with monitoring of lung function as some children may be receiving inadequate treatment following hospital discharge, especially as symptoms of breathlessness perceived by the patient correlate poorly with airway obstruction.²⁷

FeNO testing is more challenging than spirometry in a real-world clinical setting, especially in children 8 years and younger as shown in previous studies,^{14,28} and despite the use of the 6 s mode. Readings were obtained in only one-third of CYP aged 5–8 years, however, measurements were successful in 60% of children aged 9–16 years. This highlights the need for better technology in the younger age-group.²⁸

This is particularly pertinent given the recently published draft NICE/BTS/SIGN guideline²⁹ that recommend diagnosing asthma in children with FeNO ≥ 35 ppb as a single test. Only 46.9%, less than half of the CYP who attended the review, managed a FeNO measurement. In 37 CYP (13.9% of all those who attended), the FeNO value was ≥ 35 ppb. Using the draft guideline recommendations, this would have confirmed the diagnosis in an additional 28 (10.5%) children who had an FeNO ≥ 35 ppb and BDR $< 12\%$.

We found poor agreement between FeNO and BDR. This is not surprising as they measure different aspects of asthma pathophysiology, namely airway inflammation and bronchial lability.

Moreover, CYP in our particular setting will have been exposed to recent systemic corticosteroids affecting FeNO levels and most will have received SABA treatment postattack, sometimes shortly before hub attendance affecting BDR. Low baseline FEV₁, large BDR, significant airway obstruction and high FeNO levels were evident in CYP of all ages.

We did not have access to patient electronic follow-up data because this would have required informed consent from each general practice from which patients were registered. We do not know, therefore, whether patients were appropriately added to practice asthma registers and whether the hub was effective at reducing future asthma attacks. This also precluded a health economic assessment. Moreover, we were unable to discuss adherence to preventer medication or SABA overuse as a result. This information is important and should be sought in future studies, especially as adherence to preventer medication is poor in the paediatric population.³⁰

In conclusion, we found that rapid referral paediatric asthma hubs providing 2 working days follow-up after treatment for an acute severe asthma attack are feasible and effective at identifying high-risk patients with ongoing acute severe asthma. The availability of spirometry, BDR and FeNO testing was effective at confirming a diagnosis of asthma in a large proportion of CYP who attended the hub. The findings from our study are relevant to sup-

port the need for postattack reviews and help inform the design and implementation of asthma hubs in the UK.

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ARTIGO ORIGINAL

Life's Essential 8 e os riscos de mortalidade e morbidade cardiovascular em indivíduos com PRISm e suas associações com trajetórias de transição do PRISm

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RESUMO

Contexto Embora a morbilidade e mortalidade sejam reportadamente aumentadas em indivíduos com espirometria comprometida com razão preservada (PRISm), pouco se sabe sobre como otimizar a saúde relacionada ao PRISm.

Objetivos O Life's Essential 8 (LE8) está associado à mortalidade e morbidade cardiovascular em indivíduos com PRISm e às trajetórias de transição do PRISm?

Métodos Foram incluídos participantes com PRISm (n=31 943) com dados completos sobre LE8 e 23 179 indivíduos com duas medições espirométricas do UK Biobank. O LE8 foi criado com oito componentes de saúde, gerando uma pontuação de 0 a 100. Modelos de riscos proporcionais de Cox foram utilizados para avaliar associações do LE8 com morbidade cardiovascular e mortalidade por todas as causas, cardiovascular e respiratória. Modelos de regressão logística multinomial foram conduzidos para avaliar associações entre LE8 e trajetórias de transição do PRISm.

Resultados Entre os participantes com PRISm, 3113 (9,75%), 25 254 (79,06%) e 3576 (11,19%) foram categorizados como pontuação alta (LE8≥80), moderada (50≤LE8<80) e baixa (LE8<50), respetivamente. Comparado ao grupo de LE8 alto, o grupo de LE8 baixo demonstrou maiores riscos de doença cardiovascular (HR: 2,702, IC 95% 2,391 a 3,054) e mortalidade por todas as causas (2,496, 2,082 a 2,993), cardiovascular (4,165, 2,672 a 6,493) e respiratória (4,103, 1,866 a 9,020). Indivíduos com pontuação baixa no LE8 (vs LE8 alto) tiveram maiores probabilidades de transição da espirometria normal para PRISm (OR: 2,238, IC 95% 1,638 a 3,057) e menores probabilidades de transição de PRISm para espirometria normal (OR: 0,506, IC 95% 0,339 a 0,757).

Conclusão Uma pontuação mais baixa no LE8 foi associada a riscos aumentados de morbidade cardiovascular e mortalidade por todas as causas, cardiovascular e respiratória em PRISm. Uma pontuação mais baixa no LE8 também esteve relacionada a uma maior probabilidade de desenvolvimento de PRISm e menor probabilidade de recuperação do PRISm.

INTRODUCTION

Preserved ratio impaired spirometry (PRISm), also referred to as restrictive spirometry pattern or unclassified spirometry, defined as a forced expiratory volume in 1 s (FEV₁) less than 80% predicted and a preserved FEV₁/forced vital capacity (FVC) ratio, is a newly identified spirometry pattern affecting 6.6%–17.6% of the general population.^{1–5} An increasing number of recent studies have suggested that this subpopulation is at increased risks of cardiovascular and respiratory morbidity and mortality.^{4–11} Furthermore, evidence has shown that individuals with PRISm could go on to de-

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Life's Essential 8 (LE8) has been demonstrated to be associated with a wide variety of cardiovascular and non-cardiovascular outcomes in the general population. However, it remains unclear whether it is associated with mortality and cardiovascular morbidity in individuals with preserved ratio impaired spirometry (PRISm) and with transition trajectories of PRISm.

WHAT THIS STUDY ADDS

► A lower LE8 score was associated with higher risks of cardiovascular disease and all-cause, cardiovascular and respiratory mortality in individuals with PRISm.
► Participants with lower LE8 scores also had higher odds to transition from normal spirometry to PRISm and lower odds to transition from PRISm to normal spirometry.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► Our study supports the important value of the LE8 metric to identify individuals at high risk for cardiovascular disease and mortality among people with PRISm. More importantly, analyses of transition trajectories of PRISm support an intervention study to validate whether improving health-related behaviours and factors could result in improvement of pulmonary function and persistence (or not) of PRISm over time.

velop chronic obstructive pulmonary disease or revert to normal spirometry,^{12–15} which indicates that PRISm might be a promising intervention target. Considering the notable morbidity and mortality associated with PRISm, identification of modifiable factors that could predict and/or counteract adverse outcomes in individuals with PRISm and even promote reversion of PRISm to normal spirometry is of great significance.

In 2022, the American Heart Association (AHA) introduced the Life's Essential 8 (LE8) metric, including four health behaviours and four health factors, to evaluate cardiovascular health (CVH).¹⁶ This new construct has been demonstrated to be powerful in the prediction of all-cause mortality,^{17,18} cardiovascular morbidity¹⁷ and mortality,¹⁹ and a wide variety of non-cardiovascular outcomes^{20,21} in the general population. However, disparities in CVH may exist across a wide range of subpopulations,¹⁶ and evidence derived from the overall population might not be applicable to specific populations and settings. Thus, the AHA further proposes that there is need for assessment of the new CVH scoring algorithm in diverse subpopulations to extend its application.¹⁶ Considering the inherent link between CVH and pulmonary disease,^{22,23} we speculate that the LE8 metric also holds great potential in the identification of individuals at high risk for morbidity and mortality among those with PRISm. To our knowledge, no prospective studies have evaluated the associations of LE8 with health outcomes in people with PRISm. In addition, prior evidence has indicated that smoking, physical activity, body mass index (BMI) and hypertension, which are ingredients of the composite LE8 index, are associated with persistence or development of PRISm.^{1,9,15} Given the potentially transitory nature of PRISm,^{12–15} it is therefore also reasonable to hypothesise that the LE8 metric will be related to incidence and resolution of PRISm.

To test our hypotheses, we first investigated whether LE8 was associated with various cardiovascular morbidity and all-cause, cardiovascular and respiratory mortality in participants with PRISm, and then explored how the baseline LE8 score was correlated with different transition trajectories of PRISm.

MATERIAL AND METHODS

Study population

The UK Biobank represents a large and detailed prospective study with over 500 000 participants aged 37–73 years (99.5% aged 40–69

years) recruited between 2006 and 2010.²⁴ The baseline assessment collected data concerning sociodemographic, dietary, lifestyle, reproductive and environmental factors, along with a series of physical measurements and biological sample assays.²⁵

In this study, participants who met any of the following criteria at baseline were excluded: (1) withdrew from the survey, (2) had missing data on FVC or FEV₁, and (3) had missing values on LE8 components. In total, 31 943 individuals with PRISm were included for mortality analyses. We additionally excluded individuals with cardiovascular disease (CVD) (n=14 513) at baseline when CVD was considered as the outcome. For analyses of transition trajectories of PRISm, we excluded participants without two spirometry measurements, leaving 2201 individuals with PRISm and 20 978 individuals with normal spirometry at baseline for further analyses. The detailed flow chart of participant selection is presented in figure 1.

Assessment of spirometry

Spirometry in the UK Biobank was carried out before bronchodilator administration using a Vitalograph Pneumotrac 6800 at baseline and participants were asked to record two to three blows (lasting for at least 6 s) within a period of about 6 min by trained medical technicians and nurses.²⁶ The computer compared the reproducibility of the first two blows, and if acceptable (defined as a <5% difference), the third blow was not required. The maximum measurements recorded were used for subsequent analyses. Among participants with spirometry measurement at baseline, some were invited back to take a repeat survey with spirometry if they resided close to an assessment centre. A total of 43 130 individuals were re-examined for spirometry between 2014 and 2020. The original value was divided by the predicted value to calculate FVC (% predicted) and FEV₁ (% predicted). We defined three spirometry groups based on the spirometry at baseline: PRISm was defined as having an FEV₁/FVC ratio $\geq$ the lower limit of normal (LLN) and an FEV₁ <80% predicted, obstructive spirometry was defined as an

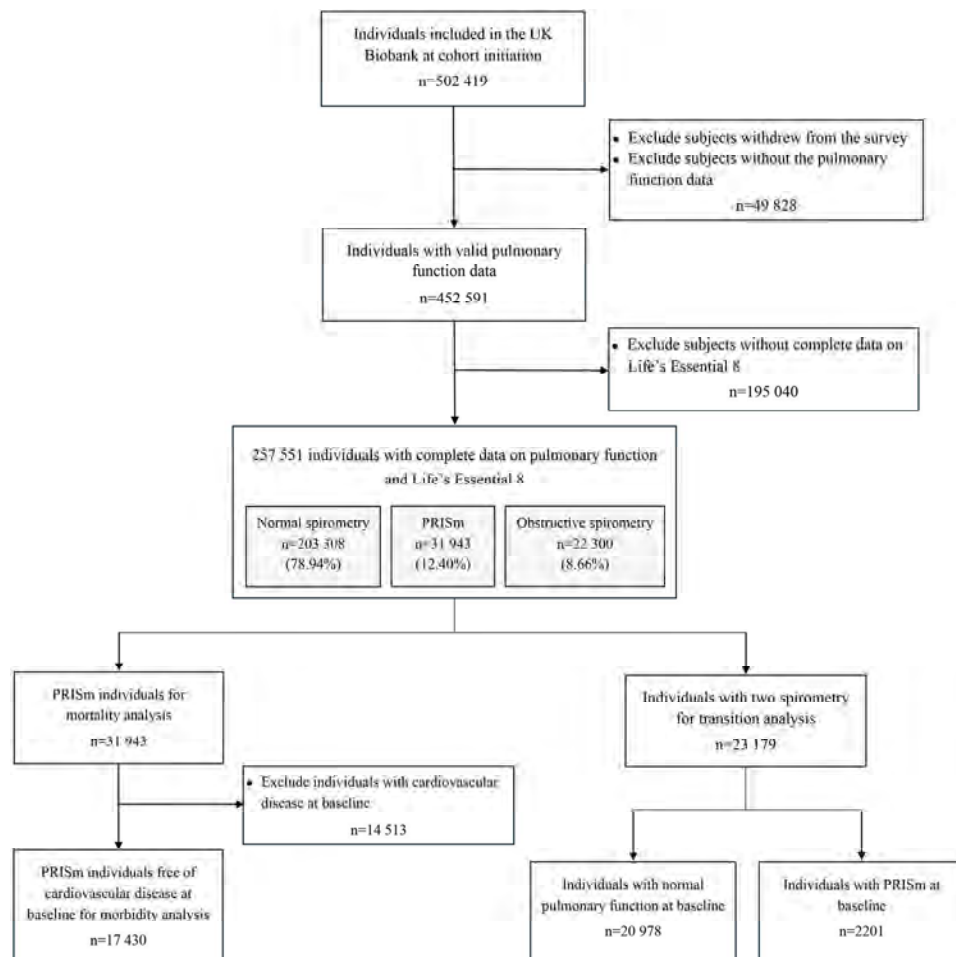


Figure 1 Flow chart of participants selection. PRISm, preserved ratio impaired spirometry.

FEV₁/FVC ratio <LLN, and normal spirometry was defined as an FEV₁/FVC ratio ≥LLN and an FEV₁ ≥80% predicted.⁹ Additionally, participants with normal or PRISm spirometry category at baseline who had undergone spirometry twice were further categorised into six groups based on their subsequent spirometry outcomes (online supplemental figure 1).

Definition of LE8

Eight health-related components, including four health behaviours and four health factors, were used to calculate the LE8 score, that is (1) diet, (2) physical activity, (3) tobacco/nicotine exposure, (4) sleep, (5) BMI, (6) blood glucose, (7) non-high-density lipoprotein (non-HDL) cholesterol and (8) blood pressure.¹⁶ The information on dietary intake, physical activity (minutes of moderate or vigorous physical activity per week), tobacco/nicotine exposure (combustible tobacco use and secondhand smoke exposure) and sleep (sleep duration) were collected during the interview process. A recent definition of ideal intake of dietary components for CVH was used to evaluate dietary quality for each participant.²⁷ BMI was calculated as weight in kilograms divided by standing height in metres squared. Laboratory tests, including fasting blood glucose, total cholesterol and HDL cholesterol, were measured using autoanalyser (Hitachi 747, Hitachi, Tokyo, Japan). Glycated haemoglobin was measured by high-performance liquid chromatography. Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol. Blood pressure was measured twice and average levels of systolic and diastolic blood pressure were used in this study. The detailed definitions and scoring for each component of LE8 are provided in online supplemental table 1 and 2. Each of the eight CVH components ranged from 0 to 100 points, and the overall CVH score was calculated as the mean of the eight components, thus also ranging from 0 to 100 points, with a higher score representing better CVH. According to the AHA's recommendation, we categorised overall CVH into three levels, that is, low (LE8<50), moderate (50≤LE8<80) and high (LE8≥80).

Outcomes

Follow-up outcomes in this study included incident CVDs and all-cause, cardiovascular and respiratory mortality.

Occurrences of CVDs were identified using data based on death register, primary care, hospital admission and to a less extent on self-reported data. In this study, we defined coronary heart disease (CHD, codes I20–I25), stroke (codes I60–I64 and I69) and CVDs (codes I00–I99) by International Classification of Diseases, 10th Revision, codes (ICD-10). The survival time for participants was from the date of completion of the spirometry measurement to the date of occurrence of the outcome, date of death, loss to follow-up or the last date of follow-up (December 2022), whichever came first.

Date and underlying (primary) cause of death were obtained from death certificates held by the National Health Service (NHS) for participants from England and Wales, and for participants from the NHS Central Register, Scotland. We defined cardiovascular and respiratory mortality using the ICD-10 codes: I00–I99 for cardiovascular death and J00–J99 for respiratory death. If respondents had complete information in death time, the survival time was calculated as the interval between the date of completion of the spirometry measurement and the exact date on which the end event occurred. For those who had survived during the follow-up period, the follow-up time was survival time. Participants were followed up until death or December 2022.

Covariates

Sociodemographic covariates included age, sex, race (classified as white, mixed, Asian/Asian British, black/black British and others), education status (classified into five different levels: College or University degree, National Vocational Qualification or Higher National Diploma or Higher National Certificate or equivalent, Other professional qualifications, Advanced levels/Advanced Subsidiary levels or equivalent, Ordinary levels/General Certificates of Secondary Education or equivalent/Certificate of Secondary Education or equivalent, None of the above), household income (classified as

greater than £100 000, £52 000 to £100 000, £31 000 to £51 999, £18 000 to £30 999, less than £18 000) and Townsend deprivation index. Townsend deprivation index was derived from participants' postcodes and assigned a score based on socioeconomic status through the quartiles of the indices. Details of these covariates can be found in the online UK Biobank showcase (<http://biobank.ndph.ox.ac.uk/showcase>).

Statistical analysis

The predicted value of FEV₁ and FVC was calculated according to the GLI-2012 (Global Lung Initiative equation), using the RSpino package in R (V.4.3.1). Baseline characteristics of participants were described as mean±SD for continuous variables and frequency (percentage) for categorical variables.

The Kaplan-Meier curves of each outcome of interest stratified by spirometry pattern are shown in online supplemental figure 2. Cox proportional hazards models were used to estimate HRs and 95% CIs for the prospective associations of LE8 with CVD, CHD, stroke and all-cause, cardiovascular and respiratory mortality in participants with PRISm. Taking the high level of the LE8 score as the reference, we ran a total of three different models: model 1 was unadjusted; model 2 was adjusted for age and sex; model 3 was further adjusted for ethnicity, education status, household income and Townsend score. The proportional hazards assumption was checked using Schoenfeld residuals.

Moreover, we divided participants with normal spirometry at baseline into three groups based on follow-up spirometry: normal spirometry to normal spirometry, normal spirometry to PRISm and normal spirometry to obstructive spirometry. Likewise, individuals with PRISm were classified into three groups: PRISm to PRISm, PRISm to normal spirometry and PRISm to obstructive spirometry. Multinomial logistic regression models were used to examine the associations of the LE8 score with these transition trajectories of spirometry. ORs and 95% CIs were calculated to measure the associations between LE8 and transition trajectories. We conducted three different models with the same covariates as those used in association analyses of morbidity and mortality.

We performed the following sensitivity and subgroup analyses to test the robustness of our findings. First, we excluded events that occurred within the first 2 years of follow-up. Second, we repeated the mortality analyses after excluding individuals with CVD at baseline. Third, we repeated the analyses using the fixed ratio definition for PRISm (FEV₁/FVC ≥0.70 and FEV₁ <80% predicted). Fourth, considering death as a competing risk event, the Fine-Gray model was conducted to examine the associations of LE8 with cardiovascular morbidity. Fifth, we repeated the analyses by quartiles of LE8. Sixth, we examined the associations of each component in LE8 with all-cause, cardiovascular and respiratory mortality, cardiovascular morbidity and transition trajectories of spirometry. Seventh, potential interaction effects were tested by adding interaction terms between the LE8 index and covariates (age, sex, Townsend score, education status, household income and FVC) in the model. Thereafter, stratified subgroup analyses were also performed.

Statistical analyses were performed using SAS V.9.4 (SAS Institute) and R software (V.4.3.1). All statistical tests were two sided, and p value of <0.05 was considered statistically significant.

RESULTS

Study population characteristics

Of 31 943 participants with PRISm (16 161 women (50.59%), 15 782 men (49.41%)) included in this study, 3113 (9.75%), 25 254 (79.06%) and 3576 (11.19%) participants were categorised into high LE8 score, moderate LE8 score and low LE8 score groups, respectively. Participants with low LE8 were older, had higher deprivation index, lower levels of education attainment and annual household income, were less likely to be women (table 1), and had higher prevalence of common comorbidities than those with high LE8 (online supplemental table 3). The baseline characteristics of other subpopulations in this study are presented by CVH levels in online supplemental tables 4–6.

Table 1 Baseline characteristics of the PRISm group

	Total	High LE8	Moderate LE8	Low LE8
No. of participants	31 943	3113	25 254	3576
Male sex	15 782 (49.41)	850 (27.30)	12 697 (50.28)	2235 (62.50)
Age, y	56.94±8.09	52.78±8.34	57.37±7.99	57.54±7.54
Ethnicity				
White	28 956 (90.65)	2823 (90.68)	22 836 (90.43)	3297 (92.20)
Mixed	132 (0.41)	3 (0.10)	112 (0.44)	17 (0.48)
Asian or Asian British	1789 (5.60)	193 (6.20)	1447 (5.73)	149 (4.17)
Black or black British	553 (1.73)	35 (1.12)	453 (1.79)	65 (1.82)
Other	434 (1.36)	54 (1.73)	342 (1.35)	38 (1.06)
Townsend score				
I (least deprived)	7959 (24.92)	864 (27.75)	6461 (25.58)	634 (17.73)
II	7955 (24.90)	802 (25.76)	6403 (25.35)	750 (20.97)
III	7991 (25.02)	773 (24.83)	6260 (24.79)	958 (26.79)
IV	7998 (25.04)	668 (21.46)	6102 (24.16)	1228 (34.34)
Education status				
College or university degree	9948 (31.14)	1430 (45.94)	7774 (30.78)	744 (20.81)
NVQ or HND or HNC or equivalent	2248 (7.04)	122 (3.92)	1838 (7.28)	288 (8.05)
Other professional qualifications	1736 (5.43)	135 (4.34)	1411 (5.59)	190 (5.31)
A levels/AS levels or equivalent	3616 (11.32)	419 (13.46)	2828 (11.20)	369 (10.32)
Ordinary levels/GCSEs or equivalent/CSEs or equivalent	8597 (26.91)	766 (24.61)	6859 (27.16)	972 (27.18)
None of the above	5532 (17.32)	228 (7.32)	4325 (17.13)	979 (27.38)
Income per year				
Greater than £100 000	1374 (4.30)	224 (7.20)	1057 (4.19)	93 (2.60)
£52 000 to £100 000	5310 (16.62)	732 (23.51)	4149 (16.43)	429 (12.00)
£31 000 to £51 999	7027 (22.00)	784 (25.18)	5583 (22.11)	660 (18.46)
£18 000 to £30 999	7253 (22.71)	643 (20.66)	5843 (23.14)	767 (21.45)
Less than £18 000	7059 (22.10)	390 (12.53)	5484 (21.72)	1185 (33.14)
Life Essential 8 points				
Total	64.63±11.94	84.45±3.67	65.23±7.77	43.18±5.63
Diet points	37.88±17.61	46.60±17.27	37.88±17.25	30.32±16.92
Physical activity points	80.67±37.83	98.82±7.46	85.34±33.43	31.88±44.95
Smoking points	74.51±33.70	93.05±16.28	76.30±31.87	45.75±39.87
Sleep health points	88.34±19.50	95.90±10.82	89.26±18.37	75.29±26.17
Body mass index points	61.86±30.49	91.33±15.22	61.91±28.99	35.85±27.10
Blood lipids points	47.62±28.85	73.55±26.38	46.14±27.45	35.52±27.60
Blood glucose points	86.06±23.54	98.13±9.17	87.23±22.45	67.28±28.78
Blood pressure points	40.13±31.31	78.22±25.56	37.78±29.30	23.54±23.34
FVC, % predicted	75.14±9.67	76.08±9.51	75.21±9.66	73.79±9.72
FEV1, % predicted	71.56±8.19	72.32±7.98	71.62±8.14	70.46±8.60
FEV1 to FVC ratio, %	75.26±5.48	75.84±5.20	75.20±5.49	75.23±5.57

Data were presented as frequency (%) or mean ± SD.

A levels, advanced levels; AS levels, advanced subsidiary levels; CSE, Certificate of Secondary Education; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GCSE, General Certificate of Secondary Education; HNC, Higher National Certificate; HND, Higher National Diploma; LE8, Life's Essential 8; NVQ, National Vocational Qualification; PRISm, preserved ratio impaired spirometry.

Associations of LE8 with incident CVD and all-cause, cardiovascular and respiratory mortality in the individuals with PRISm

Results from Cox proportional hazards models showed that compared with participants with high LE8 score, those with moderate LE8 score had higher risks of incident CVD, CHD and stroke, with respective HRs (95% CIs) of 1.706 (1.545 to 1.884), 2.123 (1.625 to 2.773) and 1.896 (1.213 to 2.962). The corresponding HRs (95% CIs) for low LE8 score versus high LE8 score were 2.702 (2.391 to 3.054), 4.603 (3.427 to 6.183) and 3.011 (1.795 to 5.053), respectively. When evaluating the LE8 index as a continuous variable, HRs (95% CI) for every 10-point decrease in LE8 score were 1.280 (1.252 to 1.309) for CVD, 1.411 (1.344 to 1.481) for CHD and 1.286 (1.178 to 1.405) for stroke (figure 2). Figure 3 shows that after multivariate adjustment, a lower

LE8 score was associated with higher risks of all-cause mortality (moderate LE8 vs high LE8: HR 1.358, 95% CI 1.147 to 1.608; low LE8 vs high LE8: 2.496, 2.082 to 2.993), cardiovascular mortality (moderate LE8 vs high LE8: 1.910, 1.245 to 2.928; low LE8 vs high LE8: 4.165, 2.672 to 6.493) and respiratory mortality (moderate LE8 vs high LE8: 1.862, 0.872 to 3.977; low LE8 vs high LE8: 4.103, 1.866 to 9.020), respectively. Each 10-point reduction of the LE8 score was associated with a 29.1% increased risk of all-cause mortality (HR: 1.291, 95% CI 1.254 to 1.329), a 42.4% higher risk of cardiovascular mortality (HR: 1.424, 95% CI 1.343 to 1.509), and a 38.7% elevated risk of respiratory mortality (HR: 1.387, 95% CI 1.250 to 1.538).

Associations of LE8 with transition trajectories of PRISm

The majority of those with normal spirometry at baseline had normal spirometry in follow-up (n=18 982), while smaller numbers

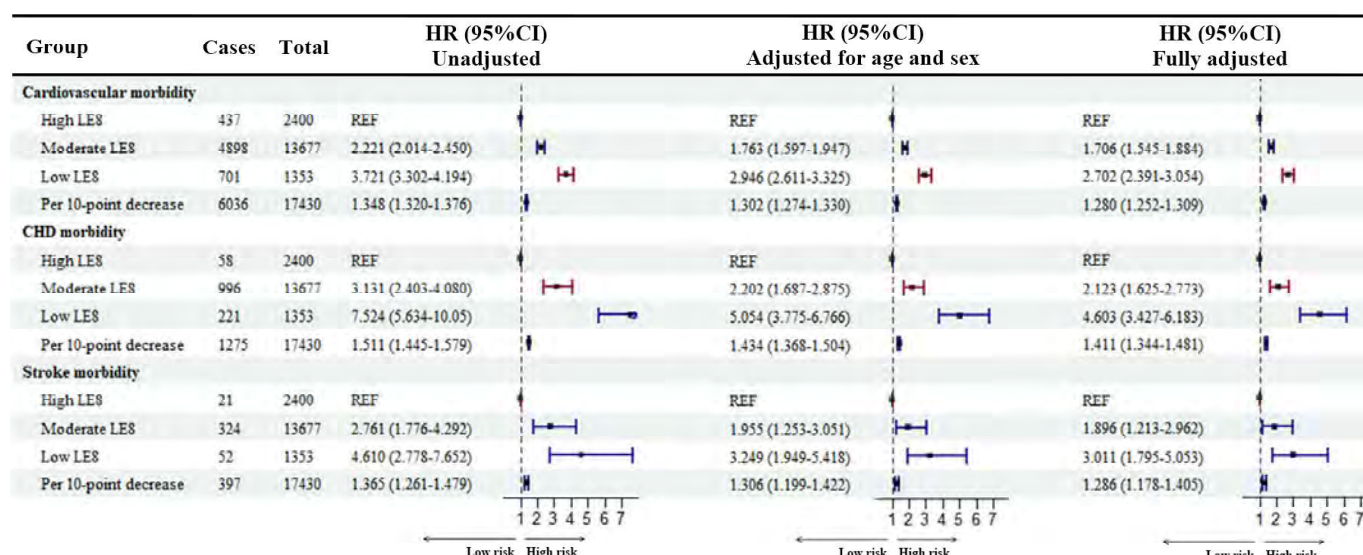


Figure 2 Associations between the Life's Essential 8 (LE8) score and cardiovascular morbidity in individuals with preserved ratio impaired spirometry (PRISm). Models were adjusted for age, sex, ethnicity, education status, household income and Townsend score.

transitioned from normal spirometry to PRISm ($n=1099$) or to obstructive spirometry ($n=897$). The results from multinomial logistic regression analyses showed that compared with participants in the normal spirometry to normal spirometry group, those with a lower LE8 score at baseline had increased likelihood to transition from normal spirometry to PRISm, with OR (95% CI) being 1.297 (1.091 to 1.542) for moderate LE8 versus high LE8 and 2.238 (1.638 to 3.057) for low LE8 versus high LE8. Each 10-point decrement in the LE8 score was associated with a 21.3% increased risk of transitioning from normal spirometry to PRISm (OR: 1.213, 95% CI 1.144 to 1.287). In contrast, the association between the LE8 score and the transition from normal spirometry to obstructive spirometry was not significant (OR 0.929, 95% CI 0.783 to 1.101 for moderate LE8 vs high LE8; 0.789, 0.508 to 1.224 for low LE8 vs high LE8; 1.001, 0.937 to 1.071 per 10-point decrement). Detailed results are provided in table 2.

Among those with PRISm at baseline, many either demonstrated PRISm at follow-up ($n=1026$) or transitioned to normal spirometry ($n=1047$), while a smaller number transitioned from PRISm to obstructive spirometry ($n=128$). With the PRISm to PRISm group as the reference, participants with a lower LE8 score had reduced odds to transition from PRISm to normal spirometry than those with higher LE8 score; the fully adjusted ORs (95% CIs) were 0.874

(0.675 to 1.131) for moderate LE8 versus high LE8 and 0.506 (0.339 to 0.757) for low LE8 versus high LE8. On assessing the LE8 score as a continuous metric, a 10-point lower LE8 score was associated with a 10.1% lower likelihood of PRISm to normal transition (OR: 0.899, 95% CI 0.832 to 0.972). By contrast, the adjusted ORs (95% CIs) for the transition from PRISm to obstructive spirometry were 1.123 (0.621 to 2.032) for moderate LE8 versus high LE8 and 0.574 (0.220 to 1.496) for low LE8 versus high LE8. There was also no significant association with the transition from PRISm to obstructive spirometry (OR: 0.903, 95% CI 0.763 to 1.068, per 10-point decrement) when the LE8 index was analysed as a continuous variable. Detailed results are provided in table 3.

Sensitivity and subgroup analyses

We observed similar inverse associations between the LE8 score and cardiovascular morbidity and all-cause, cardiovascular and respiratory mortality within further sensitivity analyses, including excluding cases that occurred within 2 years of follow-up (online supplemental table 7), excluding individuals with CVDs at baseline in the mortality analysis (online supplemental table 8), using the fixed ratio to define obstructive spirometry ($FEV_1/FVC < 0.70$) versus PRISm (online supplemental tables 9–11), using the Fine-Gray model (online supplemental table 12) and categorising participants

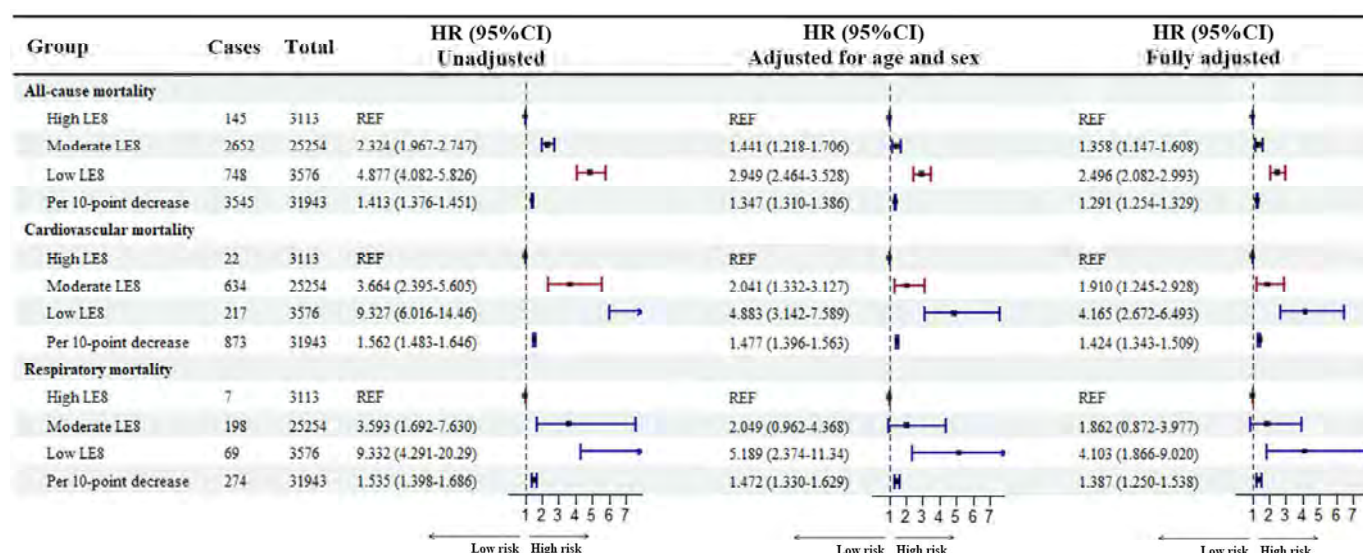


Figure 3 Associations between the Life's Essential 8 (LE8) score and all-cause, cardiovascular and respiratory mortality in individuals with preserved ratio impaired spirometry (PRISm). Models were adjusted for age, sex, ethnicity, education status, household income and Townsend score.

Table 2 Associations of the Life's Essential 8 score with different transition trajectories of spirometry in individuals with normal spirometry

	Normal to normal*	Normal to PRISm	OR (95% CI)	Normal to obstructive	OR (95% CI)
	N _{case} /N _{total}	N _{case} /N _{total}		N _{case} /N _{total}	
Unadjusted					
High LE8	3907/4271	172/4271	REF	192/4271	REF
Moderate LE8	14 488/16 035	866/16 035	1.358 (1.148 to 1.605)	681/16 035	0.956 (0.812 to 1.127)
Low LE8	587/672	61/672	2.361 (1.741 to 3.202)	24/672	0.832 (0.540 to 1.283)
Per 10-point decrease	18 982/20 978	1099/20 978	1.221 (1.155 to 1.292)	897/20 978	1.009 (0.947 to 1.076)
Adjusted for age and sex					
High LE8	3907/4271	172/4271	REF	192/4271	REF
Moderate LE8	14 488/16 035	866/16035	1.332 (1.122 to 1.582)	681/16 035	0.959 (0.809 to 1.136)
Low LE8	587/672	61/672	2.344 (1.722 to 3.191)	24/672	0.861 (0.557 to 1.332)
Per 10-point decrease	18 982/20 978	1099/20 978	1.223 (1.154 to 1.296)	897/20 978	1.018 (0.953 to 1.088)
Fully adjusted†					
High LE8	3907/4271	172/4271	REF	192/4271	REF
Moderate LE8	14 488/16 035	866/16 035	1.297 (1.091 to 1.542)	681/16 035	0.929 (0.783 to 1.101)
Low LE8	587/672	61/672	2.238 (1.638 to 3.057)	24/672	0.789 (0.508 to 1.224)
Per 10-point decrease	18 982/20 978	1099/20 978	1.213 (1.144 to 1.287)	897/20 978	1.001 (0.937 to 1.071)
*Multinomial logistic regression models were conducted with the Normal to Normal group as the reference					
†Adjusted for age, sex, ethnicity, education status, household income and Townsend score.					
LE8. Life's Essential 8: PRISm. preserved ratio impaired spirometry.					

*Multinomial logistic regression models were conducted with the Normal to Normal group as the reference

†Adjusted for age, sex, ethnicity, education status, household income and Townsend score.

LE8, Life's Essential 8; PRISm, preserved ratio impaired spirometry.

by quartiles of LE8 (online supplemental tables 13–15). For transition analyses, in sensitivity analysis using the fixed ratio definition, there were notably lower odds of transition from PRISm to obstructive spirometry in the low LE8 versus high LE8 groups (online supplemental table 11). When we evaluated each LE8 component, we found that most LE8 components were associated with various mortality and cardiovascular morbidity (online supplemental tables 16 and 17).

Among individual components of LE8, tobacco exposure, BMI and blood glucose were associated with transition from normal spirometry to PRISm, while tobacco exposure and diet measured on a continuous scale were inversely associated with transition from PRISm to normal spirometry (online supplemental tables 18 and 19). Furthermore, we assessed potential interactions between LE8

and various demographic and socioeconomic variables (online supplemental tables 20–23). We found more pronounced associations of low LE8 with cardiovascular morbidity and all-cause mortality in those below 60 years old and low LE8 with cardiovascular mortality in those who had higher FVC (all p for interaction <0.05).

DISCUSSION

In this prospective cohort, lower levels of LE8 were associated, in a graded manner, with higher risks of cardiovascular morbidity and all-cause, cardiovascular and respiratory mortality in individuals with PRISm. Moreover, participants with lower LE8 levels were found to have elevated likelihood to transition from normal spirometry to PRISm and decreased likelihood to transition from PRISm to normal spirometry.

Table 3 Associations of the Life's Essential 8 (LE8) score with different transition trajectories of spirometry in individuals with PRISm

	PRISm to PRISm*	PRISm to normal	OR (95% CI)	PRISm to obstructive	OR (95% CI)
	N _{case} /N _{total}	N _{case} /N _{total}		N _{case} /N _{total}	
Unadjusted					
High LE8	140/325	170/325	REF	15/325	REF
Moderate LE8	785/1705	814/1705	0.854 (0.669 to 1.090)	106/1705	1.260 (0.713 to 2.228)
Low LE8	101/171	63/171	0.514 (0.349 to 0.756)	7/171	0.647 (0.255 to 1.644)
Per 10-point decrease	1026/2201	1047/2201	0.906 (0.842 to 0.975)	128/2201	0.940 (0.804 to 1.100)
Adjusted for age and sex					
High LE8	140/325	170/325	REF	15/325	REF
Moderate LE8	785/1705	814/1705	0.860 (0.668 to 1.108)	106/1705	1.162 (0.647 to 2.087)
Low LE8	101/171	63/171	0.509 (0.343 to 0.755)	7/171	0.615 (0.238 to 1.587)
Per 10-point decrease	1026/2201	1047/2201	0.901 (0.835 to 0.973)	128/2201	0.926 (0.785 to 1.092)
Fully adjusted†					
High LE8	140/325	170/325	REF	15/325	REF
Moderate LE8	785/1705	814/1705	0.874 (0.675 to 1.131)	106/1705	1.123 (0.621 to 2.032)
Low LE8	101/171	63/171	0.506 (0.339 to 0.757)	7/171	0.574 (0.220 to 1.496)
Per 10-point decrease	1026/2201	1047/2201	0.899 (0.832 to 0.972)	128/2201	0.903 (0.763 to 1.068)
*Multinomial logistic regression models were conducted with the PRISm to PRISm group as the reference.					
†Adjusted for age, sex, ethnicity, education status, household income and Townsend score.					
PRISm, preserved ratio impaired spirometry.					

*Multinomial logistic regression models were conducted with the PRISm to PRISm group as the reference.

†Adjusted for age, sex, ethnicity, education status, household income and Townsend score.

PRISm, preserved ratio impaired spirometry.

This study, for the first time, investigated the associations of LE8 with cardiovascular morbidity and all-cause, cardiovascular and respiratory mortality in participants with PRISm. The relationship between PRISm and a variety of adverse health outcomes,^{1 4 6–11} particularly cardiovascular morbidity and mortality,^{4 7 10 11} has been previously reported. Using data from the UK Biobank, Higbee et al¹ found that PRISm was associated with increased risks of CVD, diabetes, asthma and all-cause mortality. Of note, Li et al¹¹ demonstrated that participants with PRISm had elevated risks of macrovascular, microvascular complications and mortality in individuals with type 2 diabetes, supporting the potential inherent link between PRISm and CVH. LE8, released by the AHA, is a comprehensive CVH metric that encompasses the key modifiable factors necessary for a fulfilling and balanced life. Previous studies have also shown that individuals with a higher LE8 score had significantly decreased risks of a wide variety of adverse outcomes, including a 0.53-fold to 0.86-fold lower risk of all-cause mortality^{28–30} and 0.26-fold to 0.82-fold lower risks of cardiovascular mortality,^{17 28–31} heart failure³² and chronic kidney disease^{33 34} in the general population. The AHA has called for further assessment of the LE8 score in diverse subpopulations.¹⁶ For example, a recent study demonstrated inverse associations between high LE8 score (LE8 score ≥ 80 vs LE8 score ≤ 49) and incident macrovascular (HR: 0.20, 95% CI 0.05 to 0.79) and microvascular (HR: 0.24, 95% CI 0.06 to 0.98) diseases among participants with type 2 diabetes.³⁵ Zhang et al³⁶ showed that high LE8 score was inversely associated with incident atherosclerotic CVD in patients with cancer (HR_{Tertile 3 vs Tertile 1}: 0.54, 95% CI 0.39 to 0.75). Considering the potential link between PRISm and CVH,¹¹ our current findings extended existing studies by demonstrating that in participants with PRISm, a high-risk subpopulation for CVD and mortality,^{6–9} lower LE8 scores were associated with increased risks of cardiovascular morbidity and all-cause, cardiovascular and respiratory mortality, which supports the utility of monitoring and screening LE8 in individuals with PRISm. With LE8 as an easy-to-access and yet powerful tool, we can identify individuals at higher risk and take care to modify individual risk factors, thereby preventing adverse outcomes in individuals with PRISm to the greatest extent possible.

The potential for deterioration or improvement of spirometry has gained considerable interest in prior research.^{12 14 15} Wan et al¹⁴ demonstrated that individuals with PRISm are members of an unstable group, with frequent significant transitions to both obstruction and normal spirometry over time. Furthermore, previous studies have identified the susceptibility of the transition from PRISm to normal spirometry,^{12 14 37} especially in individuals with mild PRISm.⁶ Therefore, it is important to mention that our study provided inspiring insights into the associations of LE8 with diverse transition trajectories of spirometry. Our findings revealed that a lower LE8 score was associated with increased likelihood of transitioning from normal spirometry to PRISm and reduced odds of reverting from PRISm to normal spirometry, which indicates the potential value of LE8 as an intervention target to promote reversion of PRISm to normal spirometry. Considering the frequency of adverse outcomes in relation to PRISm,^{4 6–11} adhering to an ideal LE8 score may play an important role in achieving normal spirometry and optimising prognosis of PRISm. The fact that LE8 and PRISm can be measured and monitored through routine health examinations supports the usability and convenience of the intervention strategies. Altogether, our results support a potential CVH-based intervention study in individuals with PRISm to see if improving health-related behaviours and factors could result in improvement in pulmonary function over time.

We also observed an interesting phenomenon that participants with lower LE8 levels tended to have decreased odds of transitioning from PRISm to obstructive spirometry in a sensitivity analysis using a fixed ratio of FEV₁/FVC rather than the LLN criteria. However, we found that in this transition group, participants with low LE8 score tended to have numerically greater declines in FEV₁ and especially FVC than those with high or moderate LE8 score, suggesting worsening of lung function overall, while about half of participants with high LE8 score even improved their FVC during follow-up (on-

line supplemental table 24). Furthermore, those with low LE8 score continued to have significantly elevated respiratory mortality (HR: 3.904, 95% CI 1.533 to 9.942) when PRISm was defined using the fixed ratio criteria, suggesting that the finding of lower odds of transition to obstructive spirometry may be an epiphenomenon in this context. We speculate that at least some participants with moderate or high LE8 scores in this transition group may represent individuals who developed a reduced FEV₁/FVC ratio due to a relative improvement in the FVC on follow-up. Literature on obstructive spirometry suggests that the criterion for obstructive spirometry, when defined as an FEV₁/FVC ratio below 0.7, may lead to overestimation of obstructive spirometry in older individuals.^{9 12 38 39} In the present study, the use of FEV₁/FVC $\geq$ LLN to define PRISm should represent an optimal option, since approximately half of the individuals included were over 60 years old at baseline. Taken together, the finding that a lower LE8 score may reduce the odds of transition from PRISm to obstructive spirometry using the fixed ratio definition should be interpreted with caution; further studies with larger sample sizes are needed to validate these hypotheses.

One of the main strengths of our study lies in it being the first assessment of LE8 scores in relation to a range of adverse outcomes in individuals with PRISm. Most importantly, we are the first to explore the relationship between LE8, an important measure of CVH, and subsequent PRISm trajectories. Other strengths of our study contained a large sample size, a prospective study design, a long follow-up duration and professional spirometry. However, several limitations should also be mentioned. First, due to data availability, we could not account for potential changes of LE8 score during follow-up. Second, since information on e-cigarettes was not available in UK Biobank, we might slightly overestimate the LE8 score in this study. Third, although our study employs a prospective design, considering its observational nature, future research is still warranted to determine the causal relationship. If validated in randomised controlled trials, LE8 could have far-reaching implications for interventions aimed at reversal of PRISm to normal spirometry. Fourth, due to data availability, only a subset of individuals was included in the transition trajectory analyses. Although baseline characteristics were statistically different between the included population and the whole population (online supplemental tables 25 and 26), most differences were not large from a clinical perspective, and we have adjusted for these potential influencing factors in multivariate analyses. Fifth, the participants from the UK Biobank are generally of British or Irish ancestry, and hence our findings may not be fully generalisable to individuals with other ethnic backgrounds. Further studies are needed to explore the associations among individuals with different ethnic backgrounds. Finally, other limitations included recall bias in self-reported data, residual confounding due to unmeasured confounders, and the use of a modified diet score due to the unavailability of metrics recommended by the AHA.

CONCLUSION

This prospective study revealed that in individuals with PRISm, having a lower LE8 score was associated with considerably increased risks of cardiovascular morbidity and all-cause, cardiovascular and respiratory mortality. These findings suggest that screening and monitoring LE8 in individuals with PRISm could have far-reaching benefits for the prevention of adverse outcomes. In addition, our study uncovered the associations between the LE8 score and the occurrence and reversal of PRISm, indicating a potential intervention target for maintaining or improving pulmonary function. Future studies are warranted to determine the causal nature of these associations and to gain a more profound understanding of the role of LE8 in pulmonary health and intervention.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The UKB study was approved by the Northwest Multi-Centre Research Ethics Committee (REC reference: 11/NW/03820), and all participants signed informed consent forms. Participants gave informed consent to participate in the study before taking part.

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ARTIGO ORIGINAL

Síndrome da apneia obstrutiva do sono e risco futuro de demência entre indivíduos acompanhados na prática clínica geral do Reino Unido

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RESUMO

Contexto: A síndrome da apneia obstrutiva do sono (OSAS) tem sido reconhecida como um potencial fator de risco para o declínio cognitivo, mas a sua relação precisa com a demência ainda é incerta. Este estudo teve como objetivo determinar o risco de demência em indivíduos com e sem OSAS.

Métodos Os dados foram extraídos de 2,3 milhões de adultos (≥18 anos) do Clinical Practice Research Datalink (2000–2022), um banco de dados nacionalmente representativo de registros eletrônicos de saúde primária no Reino Unido. Foram aferidos por resultados de propensão 193 600 indivíduos com OSAS e 536 701 indivíduos sem OSAS. Modelos de regressão de riscos proporcionais de Cox foram aplicados para quantificar o risco de desenvolver demência por todas as causas, demência vascular e doença de Alzheimer entre indivíduos com e sem OSAS.

Resultados Com um seguimento mediano de 4,0 anos (IQR 1,8–7,5), 2802 e 6211 indivíduos desenvolveram demência por todas as causas nos grupos com e sem OSAS, respetivamente, correspondendo a taxas de incidência bruta de 2,47 e 2,34 por 1000 pessoas-ano. A presença de OSAS foi associada a maiores riscos de demência por todas as causas (HR ajustado (aHR) 1,12, IC 95% 1,07 a 1,17), demência vascular (1,29, IC 95% 1,19 a 1,41) e risco inalterado de doença de Alzheimer (1,07, IC 95% 0,99 a 1,16). Indivíduos com OSAS que receberam tratamento com pressão positiva contínua nas vias aéreas (CPAP) apresentaram um risco semelhante de demência por todas as causas em comparação com seus pares aferidos (0,99, IC 95% 0,74 a 1,32).

Conclusão A OSAS está associada a maiores riscos de demência por todas as causas e algumas de suas subcategorias. São necessárias mais investigações para avaliar os benefícios clínicos da triagem para comprometimento cognitivo em pessoas com OSAS e para determinar melhor o impacto do CPAP no declínio cognitivo e no risco de demência.

INTRODUCTION

Dementia is a syndrome that leads to deterioration in cognitive function mainly in older people and is currently the seventh leading cause of death globally affecting more than 55 million people.¹ In 2019, approximately 25.3 million disability-adjusted life-years were attributed to Alzheimer's disease and other dementias, with future prevalence projected to increase as populations age.² This represents a huge public health challenge for societies and health systems.^{1,3} About 40% of cases of dementia can be attributed to known modifiable risk factors, such as high body mass index (BMI), high fasting plasma glucose, tobacco use and consumption of sugar-sweetened beverages.² Further work is needed to identify and mitigate other modifiable risk factors causally associated with the future risk of dementia.

Obstructive sleep apnoea syndrome (OSAS) is defined as the coexistence of excessive daytime sleepi-

Key messages

What is the key question?

- Individuals with obstructive sleep apnoea syndrome (OSAS) are at a higher risk of cognitive decline, including impairments in memory, attention, executive function and overall cognitive abilities.
- However, the association of OSAS with dementia remains uncertain.
- A small number of studies with significant methodological limitations have primarily focused on specific subpopulations of OSAS, limiting the generalisability of findings.

What is the bottom line?

- We found that the presence of OSAS is associated with an increased risk of all-cause dementia, specifically vascular dementia.
- This finding persisted across age and weight subgroups, but not among women.
- Notably, among individuals with OSAS who received continuous positive airway pressure (CPAP) treatment, no elevated risk of all-cause dementia was observed.

Why read on?

- This work suggests that OSAS may be an important independent and modifiable risk factor for dementia.
- Patients with OSAS should be counselled about this risk and receive access to cognitive assessments to screen for dementia.
- This risk may potentially be ameliorated by CPAP, which could form part of a preventative strategy to reduce the risk of dementia onset in people with OSAS.

ness with obstructive sleep apnoea (OSA), which is irregular nocturnal breathing secondary to partial or complete upper airway collapse during sleep, resulting in oxygen desaturation.⁴ The prevalence of OSAS is estimated to vary from 3% to 7%,⁵ which is likely to increase with the global rise in obesity.⁶ OSAS has been recognised as an independent risk factor for a number of chronic conditions, including hypertension,⁷ cardiovascular disease⁸ and stroke.⁹ OSAS can potentially be treated by addressing modifiable risk factors, such as obesity, smoking and alcohol use, and by use of continuous positive airway pressure (CPAP) or intraoral devices.¹⁰

Emerging evidence suggests that OSAS may be associated with an increased risk of dementia.

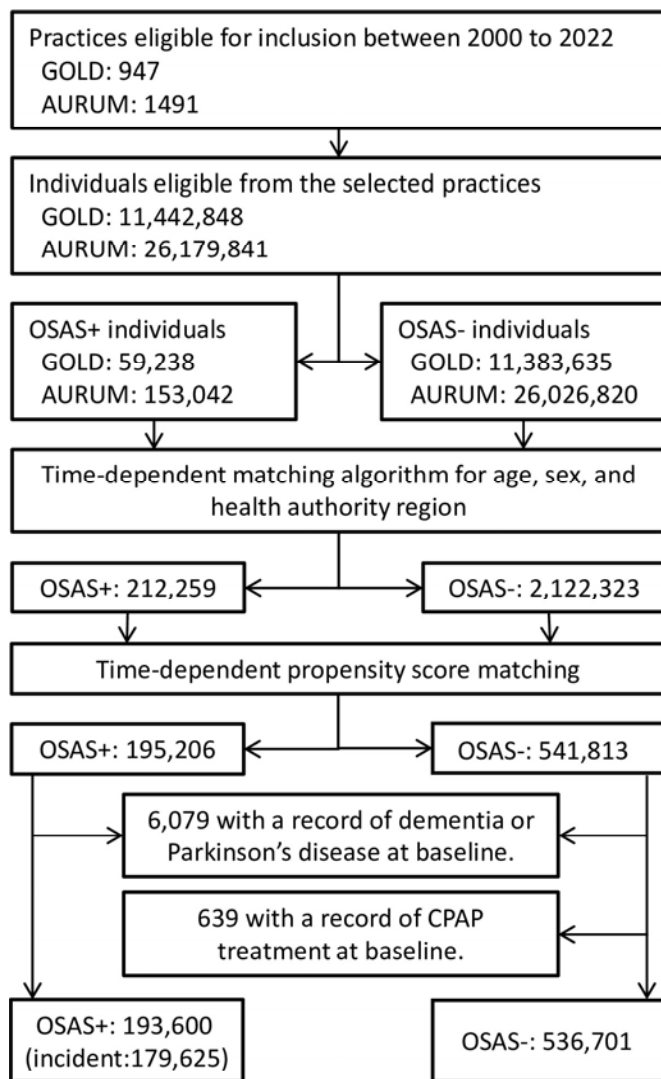


Figure 1 Flow chart. CPAP, continuous positive airway pressure; OSAS, obstructive sleep apnoea syndrome.

A systematic review and meta-analysis of observational studies showed that individuals with sleep-disordered breathing were 26% more likely to develop cognitive impairment than those without.¹¹ A neuroimaging study of 83 middle-aged to older adults with evidence of cognitive impairment showed an association between oxygen desaturation and reduced temporal lobe cortical thickness.¹² This suggests how OSA may contribute to neurodegeneration in older adults.

A recent meta-analysis found an association between sleep apnoea and the risk of dementia and its subtypes.¹³ It included six cohort studies (all-cause dementia: four studies with 190 187 individuals, vascular dementia: two studies with 188 222 individuals, and Alzheimer's disease: five studies with 1 241 193 individuals), the results of which were largely dominated by one study with only older male veterans ($n=179\,738$) and another with only older adults that did not control for obesity ($n=1\,035\,536$, age ≥ 66 years).^{14–15} Three further meta-analyses identified a number of cohort studies showing an association between sleep-disordered breathing and cognitive impairment and dementia.^{16–18} Most of the included studies, however, used self-reported measures of OSAS, most were cross-sectional, and many had small sample sizes.

There is therefore a need for large-scale high-quality population-based studies to investigate the associations between OSAS and the risk of dementia and its subtypes (mainly Alzheimer's disease and vascular dementia), and whether any such associations are modified by CPAP. The objective of this epidemiological study was to investigate the association between OSAS and the incidence of dementia and its most common subtypes, and to

evaluate whether any observed associations could be mitigated by the use of CPAP.

METHODS

Study design

This was an open cohort study using electronic health record data to estimate the risk of developing dementia and its most common subtypes (Alzheimer's disease and vascular dementia) among individuals with OSAS compared with propensity score-matched individuals without OSAS.

Data source

The data for this study were derived from the Clinical Practice Research Datalink (CPRD) GOLD and CPRD Aurum databases, which receive data from computerised primary care records covering approximately 16.8 million active participants from general practices that use Vision/EMIS Web electronic medical records software across the UK in 2022.¹⁹ Information relating to symptoms, examinations, investigations and diagnoses is recorded as Read codes and SNOMED-CT codes in CPRD GOLD and CPRD Aurum (online supplemental tables 1–4), respectively.²⁰ To improve data quality, general practices were eligible to be included in this study from the later of 12 months after the installation of Vision/EMIS Web software and 12 months after reporting acceptable mortality rates.²¹ Data from CPRD GOLD and CPRD Aurum were merged for this analysis.

Population

Adults aged 18 years and above and registered between 1 January 2000 and 31 December 2022 were eligible for inclusion. Individuals with Parkinson's disease or dementia at baseline were excluded. All eligible individuals with a diagnosis of OSAS (prevalent or incident) constituted the exposed cohort, while those without OSAS were eligible for the unexposed cohort. Individuals with a record of CPAP treatment at baseline in the unexposed cohort were further excluded.

Outcomes

The primary outcome was all-cause dementia, as defined by relevant clinical (Read/SNOMED-CT) codes (online supplemental table 2). The secondary outcomes were the two main subtypes of dementia, Alzheimer's disease and vascular dementia (online supplemental tables 3,4).

Follow-up period

The index date for exposed individuals was the latest of the following events: (1) date of OSAS diagnosis; (2) 12 months after registration date; (3) 12 months after achieving acceptable mortality reporting; or (4) 12 months usage of electronic medical records. In the subcohort restricted to exposed individuals with a new diagnosis of OSAS (incident cases) and their corresponding matched counterparts, the index date for exposed individuals was the first diagnosis date of OSAS. All eligible individuals were followed up until the earliest of any censoring event (patient left the dataset or transferred out of practice, death, study end date, most recent practice data upload or an outcome event).

Covariates

Covariates that may influence the outcomes were selected based on biological plausibility and previous literature (online supplemental table 5). The covariate included within this study were (1) socio-demographic characteristics: age, sex, ethnic group, Townsend index (a measure of socioeconomic deprivation) and index year; (2) behavioural risk factors: BMI, smoking status (smoker, ex-smoker and non-smoker) and drinking status (drinker, ex-drinker and non-drinker); (3) comorbidities: atrial fibrillation, hypertension, type 1 diabetes, type 2 diabetes, heart failure, myocardial infarction, ischaemic heart disease, stroke or transient ischaemic attack, peripheral vascular disease, chronic kidney disease (stage 3 to 5), chronic liver disease, rheumatoid arthritis, osteoarthritis, gout,

Table 1 Baseline demographic characteristics, behavioural risk factors and medications of individuals with OSAS and propensity score-matched individuals without OSAS

	OSAS+ (n=193 600)	OSAS– (n=536 701)	SMD*
<i>Demographic characteristics</i>			
Mean age, years (SD)	53.01 (13.15)	53.17 (12.95)	0.012
Age categories, years			0.025
<40	32 645 (16.9)	85 773 (16.0)	
40 to <65	124 600 (64.4)	350 489 (65.3)	
≥65	36 355 (18.8)	100 439 (18.7)	
Male	140 126 (72.4)	398 143 (74.2)	0.041
Mean BMI, kg/m ² (SD)	33.67 (7.57)	31.39 (6.52)	0.321
BMI categories, kg/m ²			0.359
<25	16 134 (8.3)	62 119 (11.6)	
25 to <30	44 387 (22.9)	147 788 (27.5)	
30 to <35	50 389 (26.0)	139 143 (25.9)	
35 to <40	35 109 (18.1)	73 351 (13.7)	
≥40	32 847 (17.0)	43 379 (8.1)	
Missing	14 734 (7.6)	70 921 (13.2)	
Ethnicity			0.043
White	116 947 (60.4)	331 334 (61.7)	
South Asian	8800 (4.5)	26 929 (5.0)	
Black	7295 (3.8)	19 831 (3.7)	
Mixed race	1297 (0.7)	3836 (0.7)	
Others	2302 (1.2)	6072 (1.1)	
Missing	56 959 (29.4)	148 699 (27.7)	
Townsend			0.042
1st (least deprived)	35 931 (18.6)	105 194 (19.6)	
2nd	37 626 (19.4)	107 935 (20.1)	
3rd	38 437 (19.9)	106 997 (19.9)	
4th	40 883 (21.1)	110 743 (20.6)	
5th (most deprived)	40 648 (21.0)	105 637 (19.7)	
Missing	88 (0.0)	188 (0.0)	
<i>Behavioural risk factors</i>			
Smoker status			0.045
Never smoked	48 788 (25.2)	132 647 (24.7)	
Ex-smoker	52 408 (27.1)	138 296 (25.8)	
Smoker	34 162 (17.6)	93 610 (17.4)	
Missing	58 242 (30.1)	172 148 (32.1)	
Drinking status			0.056
Non-drinker	9644 (5.0)	22 233 (4.1)	
Ex-drinker	4874 (2.5)	11 742 (2.2)	
Drinker	112 043 (57.9)	306 653 (57.1)	
Missing	67 039 (34.6)	196 073 (36.5)	
<i>Medications/treatments</i>			
Metformin	26 527 (13.7)	59 321 (11.1)	0.081
Other glucose-lowering drugs	19 283 (10.0)	43 930 (8.2)	0.062
Lipid-lowering drugs	67 090 (34.7)	171 283 (31.9)	0.058
ARB/ACE	67 926 (35.1)	167 906 (31.3)	0.081
Other antihypertensive drugs	83 272 (43.0)	207 224 (38.6)	0.090

Continued

Table 1 Continued

	OSAS+ (n=193 600)	OSAS– (n=536 701)	SMD*
Anticoagulants	13 865 (7.2)	31 204 (5.8)	0.055
Antiplatelets	45 674 (23.6)	113 464 (21.1)	0.059
CPAP	6624 (3.4)	0 (0.0)	NA
Data are presented as mean±SD or n (%).			
Data were presented for the first imputed matched cohort.			
* Matched on age, sex, BMI, ethnicity, Townsend, smoking status, drinking status, type 1 diabetes, type 2 diabetes, hypertension, atrial fibrillation, heart failure, myocardial infarction, stroke or transient ischaemic attack, peripheral vascular disease, hypothyroidism, hyperthyroidism, chronic kidney disease, chronic liver disease, rheumatoid arthritis, osteoarthritis, gout, multiple sclerosis, depression, anxiety, deafness/hearing loss, age-related macular degeneration, cataracts, glaucoma, B ₁₂ deficiency, metformin, other glucose-lowering drugs, lipid-lowering drugs, ARB/ACE, other antihypertensive drugs, anticoagulants, antiplatelets, HbA1c categories, eGFR categories, systolic BP, diastolic BP, total cholesterol categories, HDL-cholesterol categories, LDL-cholesterol categories, triglycerides categories and data source (GOLD/Aurum).			
ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CPAP, continuous positive airway pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable; OSAS, obstructive sleep apnoea syndrome; SMD, standardised mean difference.			

hypothyroidism, hyperthyroidism, multiple sclerosis, age-related macular degeneration, cataract, glaucoma, deafness/hearing loss, B12 deficiency, depression and anxiety; (4) biomarkers: haemoglobin A1c (HbA1c), estimated glomerular filtration rate, systolic and diastolic blood pressures, and lipid profile; (5) medications: glucose-lowering agents, lipid-lowering drugs, antihypertensive drugs, anticoagulants and antiplatelets. All covariates were identified on or before the index date. All prescriptions and conditions mentioned above were identified by relevant clinical (Read/SNOMED-CT) codes. Missingness of variables with over 20% missing were classed as a separate missing category. Multiple imputation using chained equations with predictive mean matching was used for continuous variables with missingness less than 20% (BMI and systolic and diastolic blood pressures), with 20 simulated complete datasets being created,²² under the assumption of values being missing at random.

Propensity score matching

Data were initially extracted for the study using the Data Extraction for Epidemiological Research (DExTER) tool using a time-dependent exact matching algorithm (matching ratio=1:10) for age (±5 years), sex and health authority region to save computational power.²³ After multiple imputations, time-conditional propensity score matching was applied as the exposure model in each simulated complete dataset. Propensity scores for the presence of OSAS were estimated using a logistic regression model including a set of covariates described in the Covariates section. Continuous variables with imputed values were used to generate propensity scores. To ensure positivity (having adequate variation in the treatment of interest within confounder strata), propensity scores were truncated and only participants with propensity scores that lay on the common support with a calliper width of 0.2 were eligible for matching. For each patient with OSAS, up to four individuals without OSAS were randomly selected by propensity score using the nearest neighbour algorithm. Unexposed individuals matched to the OSAS individuals were assigned the same index date to mitigate immortal time bias.²⁴

Analysis

The baseline covariates were summarised for individuals with OSAS and matched individuals without OSAS using standard descriptive statistics. Categorical variables were presented as fre-

Table 2 Baseline comorbidities and metabolic characteristics of individuals with OSAS and propensity score-matched individuals without OSAS

	OSAS+ (n=193 600)	OSAS– (n=536 701)	SMD*
Comorbidities			
Hypertension	70 544 (36.4)	178 392 (33.2)	0.067
Ischaemic heart disease	19 997 (10.3)	49 641 (9.2)	0.036
Heart failure	8937 (4.6)	17 613 (3.3)	0.069
Myocardial infraction	7790 (4.0)	20 182 (3.8)	0.014
Stroke or transient ischaemic attack	8755 (4.5)	21 998 (4.1)	0.021
Peripheral vascular disease	2495 (1.3)	6378 (1.2)	0.009
Atrial fibrillation	10 410 (5.4)	23 297 (4.3)	0.048
Type 1 diabetes	2280 (1.2)	5747 (1.1)	0.010
Type 2 diabetes	30 547 (15.8)	70 116 (13.1)	0.077
Rheumatoid arthritis	2402 (1.2)	6027 (1.1)	0.011
Osteoarthritis	40 365 (20.8)	101 108 (18.8)	0.050
Gout	14 017 (7.2)	35 606 (6.6)	0.024
Multiple sclerosis	688 (0.4)	1876 (0.3)	0.001
Hypothyroidism	12 543 (6.5)	29 435 (5.5)	0.042
Hyperthyroidism	2445 (1.3)	6116 (1.1)	0.011
Chronic kidney disease (stages 3–5)	10 013 (5.2)	24 738 (4.6)	0.026
Chronic liver disease	8078 (4.2)	18 471 (3.4)	0.038
Depression	101 644 (52.5)	255 395 (47.6)	0.098
Anxiety	39 200 (20.2)	97 794 (18.2)	0.051
Deafness/hearing loss	25 419 (13.1)	64 870 (12.1)	0.031
Age-related macular degeneration	1318 (0.7)	3418 (0.6)	0.005
Cataracts	8740 (4.5)	22 970 (4.3)	0.011
Glaucoma	3298 (1.7)	8854 (1.6)	0.004
B ₁₂ deficiency	6191 (3.2)	14 540 (2.7)	0.029
Metabolic characteristics			
HbA1c (%)			0.086
<5.7	12 469 (6.4)	32 310 (6.0)	
5.7 to <6.5	15 591 (8.1)	36 561 (6.8)	
6.5 to <7.5	8328 (4.3)	18 942 (3.5)	
≥7.5	9783 (5.1)	22 045 (4.1)	
Missing	147 429 (76.2)	426 843 (79.5)	
eGFR (mL/min/1.73 m ²)			0.081
<30	373 (0.2)	771 (0.1)	
30 to <60	3750 (1.9)	8365 (1.6)	
60 to <90	24 468 (12.6)	57 739 (10.8)	
≥90	8966 (4.6)	20 750 (3.9)	
Missing	156 043 (80.6)	449 076 (83.7)	
Systolic BP (mm Hg)			0.164
<140	126 461 (65.3)	341 979 (63.7)	
≥140	61 329 (31.7)	160 086 (29.8)	
Missing	5810 (3.0)	34 636 (6.5)	
Diastolic BP (mm Hg)			0.169
<90	152 806 (78.9)	417 528 (77.8)	

Continued

Table 2 Continued

	OSAS+ (n=193 600)	OSAS– (n=536 701)	SMD*
≥90	34 946 (18.1)	84 411 (15.7)	
Missing	5848 (3.0)	34 762 (6.5)	
Total cholesterol (mmol/L)			0.060
<5.2	82 038 (42.4)	214 497 (40.0)	
5.2 to <6.1	36 351 (18.8)	100 262 (18.7)	
≥6.1	23 901 (12.3)	66 612 (12.4)	
Missing	51 310 (26.5)	155 330 (28.9)	
HDL-cholesterol (mmol/L)			0.068
<1.53	113 649 (58.7)	296 975 (55.3)	
≥1.53	22 280 (11.5)	67 368 (12.6)	
Missing	57 671 (29.8)	172 358 (32.1)	
LDL-cholesterol (mmol/L)			0.052
<2.6	38 050 (19.7)	97 263 (18.1)	
2.6 to <3.4	30 535 (15.8)	81 368 (15.2)	
3.4 to <4.2	21 529 (11.1)	58 684 (10.9)	
4.2 to <4.9	8355 (4.3)	23 057 (4.3)	
≥4.9	3363 (1.7)	9147 (1.7)	
Missing	91 768 (47.4)	267 182 (49.8)	
Triglycerides (mmol/L)			0.069
<1.69	66 558 (34.4)	187 143 (34.9)	
1.69 to <2.26	27 723 (14.3)	71 322 (13.3)	
2.26 to <5.63	32 365 (16.7)	80 252 (15.0)	
≥5.63	2204 (1.1)	5236 (1.0)	
Missing	64 750 (33.4)	192 748 (35.9)	

Data are presented as mean±SD or n (%).

Data were presented for the first imputed matched cohort.

*Matched on age, sex, BMI, ethnicity, Townsend, smoking status, drinking status, type 1 diabetes, type 2 diabetes, hypertension, atrial fibrillation, heart failure, myocardial infraction, stroke or transient ischaemic attack, peripheral vascular disease, hypothyroidism, hyperthyroidism, chronic kidney disease, chronic liver disease, rheumatoid arthritis, osteoarthritis, gout, multiple sclerosis, depression, anxiety, deafness/hearing loss, age-related macular degeneration, cataracts, glaucoma, B₁₂ deficiency, metformin, other glucose-lowering drugs, lipid-lowering drugs, ARB/ACE, other antihypertensive drugs, anticoagulants, antiplatelets, HbA1c categories, eGFR categories, systolic BP, diastolic BP, total cholesterol categories, HDL-cholesterol categories, LDL-cholesterol categories, triglycerides categories and data source (GOLD/Aurum).

BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin A1c; HDL-cholesterol, high-density lipoprotein-cholesterol; LDL-cholesterol, low-density lipoprotein-cholesterol; OSAS, obstructive sleep apnoea syndrome.

quencies and percentages and continuous variables as means and SD. Crude incidence rates per 1000 person-years of dementia, Alzheimer's disease and vascular dementia were calculated for individuals with OSAS and their corresponding matched individuals without OSAS using a Poisson regression model.

Competing risk Cox proportional hazards regression models were used to calculate crude and adjusted HRs together with their corresponding 95% CIs. Death during the follow-up period was treated as a competing event for all outcome events. Schoenfeld residual test was applied to assess the assumption of proportionality in the Cox proportional hazards model. All covariates listed in the above section were included in the Cox models and missingness was treated as a separate category. After matching, each of the imputed propensity score-matched datasets were independently

Table 3 Incidence of all-cause and cause-specific dementia among individuals with OSAS and propensity score–matched individuals without OSAS

Outcomes	All-cause dementia		Vascular dementia		Alzheimer's disease	
	OSAS+	OSAS–	OSAS+	OSAS–	OSAS+	OSAS–
Total number of participants	193 600	536 701	193 600	536 701	193 600	536 701
Outcome events, n (%)	2802	6211	898	1627	920	2219
Person-years	1 135 023	2 658 037	1 140 686	2 670 415	1 140 543	2 668 488
Incident rate (per 1000 person-years, 95% CI)	2.47 (2.38–2.56)	2.34 (2.28–2.40)	0.79 (0.74–0.84)	0.61 (0.58–0.64)	0.81 (0.76–0.86)	0.83 (0.80–0.87)
Unadjusted HR (95% CI)	1.00 (0.96, 1.05)		1.20 (1.11, 1.30)		0.95 (0.88, 1.02)	
Adjusted HR (95% CI)†	1.12 (1.07, 1.17)		1.29 (1.19, 1.41)		1.07 (0.99, 1.16)	
Adjusted HR (95% CI)‡	1.12 (1.07, 1.18)		1.28 (1.17, 1.40)		1.09 (1.01, 1.18)	

*Data were presented for the first multiple imputed matched cohort.
†Adjusted HR estimated from a competing Cox proportional hazards model adjusting for the following covariates: index year, age, sex, BMI categories, ethnicity, Townsend, smoking status, drinking status, type 1 diabetes, type 2 diabetes, hypertension, atrial fibrillation, heart failure, myocardial infarction, stroke or transient ischaemic attack, peripheral vascular disease, hypothyroidism, hyperthyroidism, chronic kidney disease, chronic liver disease, rheumatoid arthritis, osteoarthritis, gout, multiple sclerosis, depression, anxiety, deafness/hearing loss, age-related macular degeneration, cataracts, glaucoma, B₁₂ deficiency, metformin, other glucose-lowering drugs, lipid-lowering drugs, angiotensin-receptor blocker/ angiotensin-converting enzyme inhibitors, other antihypertensive drugs, anticoagulants, antiplatelets, haemoglobin A1c (HbA1c) categories, estimated glomerular filtration rate (eGFR) categories, systolic blood pressure categories, diastolic blood pressure categories, total cholesterol categories, high-density lipoprotein-cholesterol categories, low-density lipoprotein-cholesterol categories, triglycerides categories and data source (GOLD/Aurum).
‡Sensitivity analysis limiting the study participants to individuals with an incident diagnosis of OSAS and their corresponding matched individuals without OSAS.
BMI, body mass index; CPAP, continuous positive airway pressure; NA, not applicable; OSAS, obstructive sleep apnoea syndrome.

analysed using the same methods and the results combined to produce estimates and CIs that incorporate missing-data uncertainty, using Rubin rules.

To limit the possibility of survival bias, sensitivity analyses were performed restricted to exposed individuals with a new diagnosis of OSAS during the study period (incident cases) and their corresponding matched individuals without OSAS. To delineate the effect of OSAS on all-cause dementia in specific subgroups, subgroup analyses were conducted stratified by age, sex, obesity status and the presence of CPAP treatment at baseline. For subgroup analyses of age, sex and obesity status, individuals with OSAS and their matched counterparts in the same subgroup were used for analyses.

Given that our cohort extended over a 22-year period, we modelled the HR according to year of cohort entry year as continuous variables by using restricted cubic splines to examine whether a potential period effect on the findings was present.

All analyses were performed in R V4.3.0 (The R Foundation for Statistical Computing). 95% CIs were constructed using a two-sided alpha of 0.05.

RESULTS
Participant characteristics

The study included 193 600 individuals with OSAS (incident OSAS: 179 625) and 536 701 propensity score–matched individuals without OSAS (figure 1, tables 1 and 2). The age, sex, ethnicity, socioeconomic status, and smoking and drinking status of both groups were similar. Mean BMI values were 33.7 (SD 7.6) in individuals with OSAS and 31.4 (SD 6.5) in individuals without OSAS. In general, comorbidities were slightly more prevalent among individuals with OSAS than matched individuals without OSAS.

All-cause dementia

About 2802 of 193 600 individuals with OSAS over 1 135 023 person-years developed all-cause dementia during the study period, giving a crude incidence rate of 2.47 per 1000 person-years (table 3). Then, 6211 of 536 701 matched individuals without OSAS developed all-cause dementia over 2 658 037 person-years, giving a crude incidence rate of 2.34 per 1000 person-years. The relative hazard of developing all-cause dementia was similar between individuals with OSAS and matched individuals without OSAS before adjustment (crude HR 1.00, 95% CI 0.96 to 1.05; figure 2). After adjusting for all covariates, HRs were estimated to be 12% higher in individuals with OSAS (adjusted HR 1.12, 95% CI 1.07 to 1.17), which was close to the results of the sensitivity analysis when limited to individuals with incident OSAS and their matched counterparts (adjusted HR 1.12, 95% CI 1.07 to 1.18).

Figure 3 presented the results of subgroup analyses stratified by age, sex, BMI categories and the presence of CPAP treatment. The effect of OSAS on incident dementia persisted among most subgroups, but not females (adjusted HR 1.05, 95% CI 0.93 to 1.18). When stratifying by those treated with CPAP versus those untreated (compared with their corresponding matched individuals without OSAS), the effect disappeared in the CPAP-treated group (adjusted HR 0.99, 95% CI 0.74 to 1.32) while remaining statistically significant in the untreated group (adjusted HR 1.12, 95% CI 1.07 to 1.18).

Vascular dementia

Out of 193 600 individuals with OSAS, 898 were recorded as having developed vascular dementia over 1 140 686 person-years of follow-up, giving a crude incidence rate of 0.79 per 1000 person-years (table 3). About 1627 of 536 701 matched individuals without OSAS developed vascular dementia over 2 670 415 person-years, with an incidence rate of 0.61 per 1000 person-years. After adjustment for covariates, individuals with OSAS still had a significantly higher hazard of developing vascular dementia compared with their matched individuals without OSAS (adjusted HR 1.29, 95% CI 1.19 to 1.41; Figure 2, table 3).

Alzheimer's disease

About 920 of 193 600 individuals with OSAS and 2219 of 536 701 matched individuals without OSAS developed Alzheimer's disease during the follow-up period, corresponding to crude incidence rates of 0.81 and 0.83 per 1000 person-years, respectively. After adjustment, the difference was not statistically significant between individuals with prevalent or incident OSAS and those without OSAS (adjusted HR 1.07, 95% CI 0.99 to 1.16). However, a small but statistically significant increased risk of developing Alzheimer's disease was observed in individuals with incident OSAS, compared with their unexposed counterparts (adjusted HR 1.09, 95% CI 1.01 to 1.18, table 3).

Restricted cubic splines analyses showed that differences in the relative risk of outcome events between those with and without OSAS remained constant over the cohort entry year (online supplemental figure 1).

DISCUSSION

We found that individuals with prevalent or incident OSAS had significantly increased risks of developing all-cause dementia and vascular dementia, but not Alzheimer's disease, compared with their matched counterparts without OSAS. The enhanced risk of all-cause dementia remained present in different age and BMI groups, but not in females and those treated with CPAP.

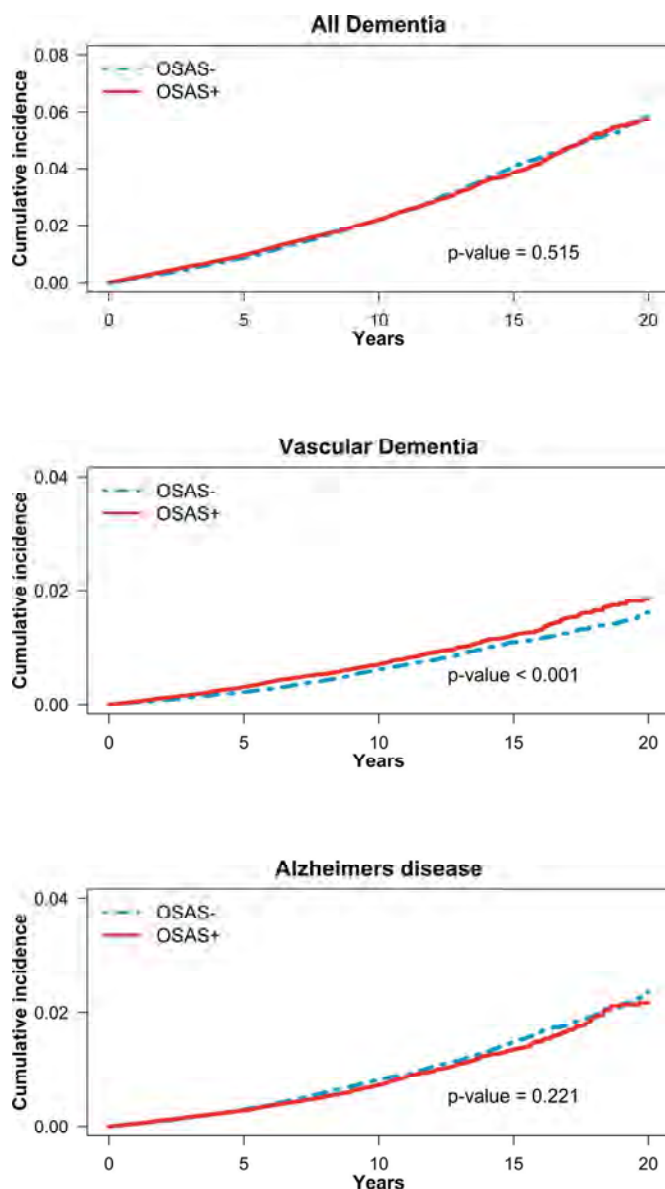


Figure 2 Cumulative hazard of all-cause, Alzheimer's and vascular dementia among individuals with obstructive sleep apnoea syndrome (OSAS) and propensity score-matched individuals without OSAS.

Our results are largely consistent with previous large-scale studies but with slightly smaller effect estimates. This may partly be due to the minimised confounding between the groups with and without OSAS by propensity score matching, which included the vast majority of key confounding factors. It may be also because of the relatively high BMI values (mean BMI 33.7 kg/m² in those OSAS and 31.4 kg/m² in those without) of participants, as obesity was recognised a well-known risk factor for dementia,²⁵ compared with other studies.

Similar to the results of our subgroup analysis for males, a study in the USA using data derived from 179 738 male veterans found individuals with sleep apnoea (n=7010) had increased risk of all-cause dementia (adjusted HR 1.23, 95% CI 1.14 to 1.33), vascular dementia (adjusted HR 1.18, 95% CI 0.99 to 1.42) and Alzheimer's disease (adjusted HR 1.20, 95% CI 1.01 to 1.42), compared with those without sleep apnoea.¹⁴ The significant imbalance in characteristics between the groups in this study, especially obesity (35% vs 15.4%) and comorbidities, may have contributed to the higher effect estimates in that study as compared with our findings.

In our study, we identified that women with OSAS had no increase in risk of all-cause dementia. This may be due to a greater degree of underdiagnosis of OSAS in women, leading to a bias towards the null.²⁶ However, we also observed that the association

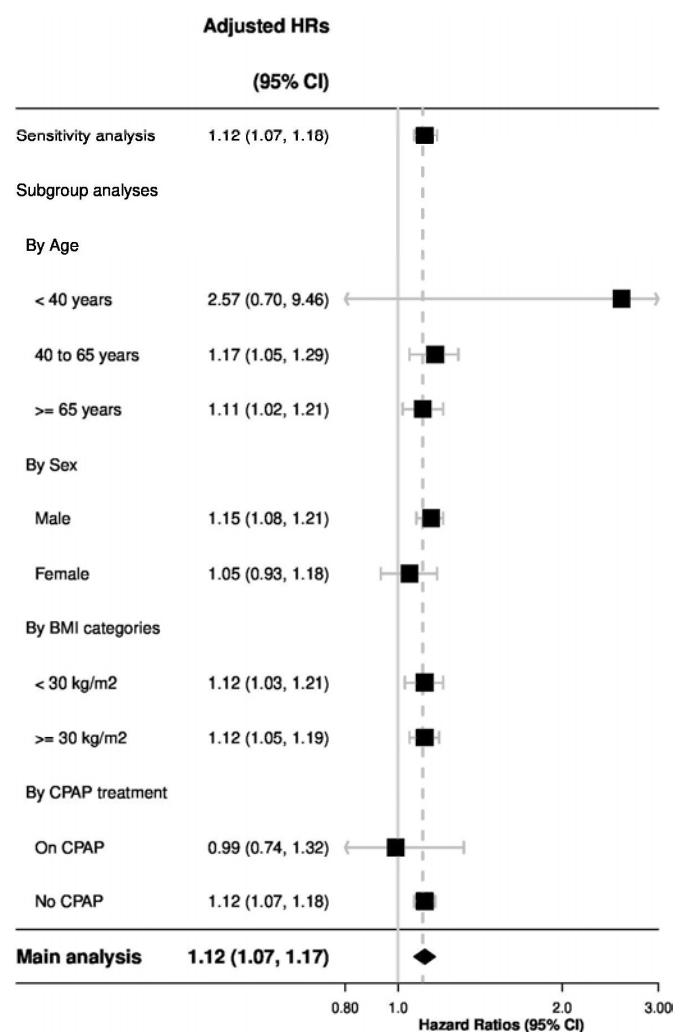


Figure 3 The association of obstructive sleep apnoea syndrome (OSAS) with all-cause dementia stratified by age, sex, body mass index (BMI) categories, and the presence of continuous positive airway pressure (CPAP) treatment.

with dementia appears stronger for vascular dementia. Men are at greater risk of developing vascular dementia than women,²⁷ while the association is inverted for Alzheimer's disease, and so if OSAS causes dementia through vascular mechanisms, OSAS may pose a greater risk to men for developing dementia. Further research is needed to confirm both causative mechanisms and the associations reported, as other studies have observed conflicting relationships between OSAS and dementia in women.²⁸

Evidence suggests the pathophysiological process behind increased rates of dementia in individuals with OSAS is most strongly related to repeated episodes of hypoxia during sleep rather than sleep deprivation itself.¹⁴ A prospective study of brain autopsies in Honolulu found that the longer men spent with hypoxia during sleep, the greater the number of microinfarcts found in the brain at autopsy.²⁹ This may explain our finding that OSAS appears to predict a higher risk of developing vascular dementia, and this may well be exacerbated by cardiovascular comorbidities.

Another US-based study using administrative claims data from a million older adults (mean age 76 years) observed an increased risk of developing Alzheimer's disease (adjusted HR 1.25, 95% CI 1.21 to 1.29) in participants with OSAS, compared with those without OSAS.¹⁵ However, this also found an increased risk in the predefined negative control outcome (renal colic, adjusted HR 1.24, 95% CI 1.11 to 1.39). A limitation of this study is that it did not control for BMI, which is critically important for the disease progress of both OSAS and all types of dementia.^{30 31}

Another potential explanation for the subtle difference in risk of Alzheimer's disease we observed between those with and without

OSAS is that we did not account for OSAS severity, which is typically not recorded in primary care electronic health records. A recent meta-analysis included 8 studies of about 800 participants showing that Alzheimer's disease-related biomarkers in cerebrospinal fluid, including amyloid β 42, T-tau and P-tau, were not different between patients with OSAS and their controls.³² However, elevated blood T-tau, P tau and amyloid β 40, as well as decreased cerebrospinal fluid amyloid β 42, were observed only in individuals with moderate to severe OSAS, as compared with the controls.

Our results found that those receiving CPAP had a similar risk of all-cause dementia as their matched controls, while those not receiving CPAP had an elevated risk to their matched controls. This subgroup of individuals who received CPAP may also represent those with more severe disease. However, they only constituted 3.4% of those diagnosed with OSAS in our cohort, so caution is needed in interpreting these findings. These results were partly confirmed by previous literature, although in among small studies. In a systematic review published in 2022, 9 out of 11 studies reported a protective effect of PAP therapy on mild cognitive impairment and Alzheimer's disease incidence in adults with OSAS.³³ Similarly, Pollicina et al performed a comprehensive review of English language articles over 20 years and found that 10 out of 14 articles reported neurocognitive performance improvements in patients with OSAS after CPAP therapy.³⁴

Our study included a large sample size and adjusted for many important confounding factors that are known to be associated with both OSAS and an increased risk of dementia. However, the study has several limitations. Although we were able to adjust for several clinically relevant covariates, there was limited data on the severity of OSAS in CPRD GOLD and Aurum.

There is likely to be a degree of under-recognition and thus misclassification of OSAS in primary care as those presenting for care are likely to be relatively more symptomatic. An estimated 23.5 million (80%) of the 29.4 million adults with OSAS in the USA remain undiagnosed, resulting in an annual economic burden of \$149.6 billion.³⁵ Our result may therefore not be representative of all individuals with the condition, but rather reflect risks in individuals who access primary care services and are successfully diagnosed with OSAS. Furthermore, the diagnosis of OSAS was not standardised due to differences in the methods currently employed by different sleep clinics (oximetry vs polygraphy vs polysomnography) and cut-off criteria of Apnea Hypopnea Index or oxygen desaturation index, which is a common problem existing in large-scale population-based studies using electronic health records. Test results from secondary care were not available in this primary care dataset, and so we could not standardise cut offs or account for possible mechanisms such as nocturnal hypoxaemia. Meanwhile, patients with OSAS may have more frequent interactions with healthcare professionals, potentially leading to detection bias. Although we controlled for relevant comorbidities at baseline, residual confounding related to differential diagnostic practices may still exist. Lastly, while multiple imputation was applied, it is worth acknowledging that its assumption of missing at random may not be fully satisfied.

Individuals with OSAS appear to be at increased risk of developing all-cause and vascular dementia. These individuals are likely to benefit from more intensive primary cardiovascular prevention (eg, management of hypertension, hypercholesterolaemia and smoking cessation) to reduce dementia risk, particularly for vascular dementia. They may also benefit from screening for dementia due to the observed increased risk. It is currently unclear whether CPAP or other interventions for OSAS modifies this increased risk, but our data support the hypothesis that it may. Further prospective studies are needed to assess whether CPAP improves the risks and outcomes from all-cause and vascular dementia in these individuals.

CONCLUSIONS

OSAS is associated with increased risks of all-cause dementia and vascular dementia, but not Alzheimer's disease. Further cohort

studies are needed to confirm this association. Further research is needed to assess whether enhanced cardiovascular risk prevention and CPAP modify this increased risk and whether screening for dementia is beneficial in these individuals.

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ARTIGO ORIGINAL

Reabilitação pulmonar baseada em aplicação móvel na DPOC: um ensaio clínico randomizado multicêntrico

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RESUMO

Contexto A reabilitação pulmonar (RP) é um elemento essencial na gestão da doença pulmonar obstrutiva crónica (DPOC). No entanto, o acesso a programas convencionais de RP presenciais é limitado.

Métodos Este ensaio clínico randomizado multicêntrico recrutou doentes com DPOC de 18 locais na Alemanha e Suíça, com o objetivo de avaliar o impacto de 12 semanas de uma aplicação móvel (grupo de intervenção, GI) na qualidade de vida, medida pelo Teste de Avaliação da DPOC (CAT), e na capacidade de exercício, avaliada pelo teste de sentar-levantar de 1 minuto (1MSTST), em comparação com um grupo de controlo (GC) que recebeu cuidados padrão melhorados.

Resultados Foram incluídos 278 doentes no estudo, com idade mediana de 65 anos (IQR 60–70) e volume expiratório forçado em 1 segundo de 48% previsto (IQR 37–60). Na análise por intenção de tratar na semana 12, o CAT melhorou em média –4 pontos no GI versus –3 pontos no GC (diferença: 0 pontos, IC 95%: –1, 2; $p=0,7$); o 1MSTST melhorou em 1 vs 2 repetições, respetivamente (diferença: 1 repetição, IC 95%: 0, 2; $p=0,12$). Num subgrupo do GI, com doentes agrupados por adesão à aplicação (≥ 3 dias/semana durante $\geq 75\%$ das semanas), os utilizadores aderentes (40,4%) melhoraram o 1MSTST em comparação com os não aderentes, com mediana de 2 repetições (IC 95%: 1, 3; $p=0,006$). O uso da aplicação não levantou preocupações de segurança.

Conclusões A RP baseada em aplicação móvel melhorou os resultados na DPOC em comparação com a linha de base, e os utilizadores aderentes melhoraram mais a capacidade de exercício em comparação com os não aderentes. Embora não tenha sido estatisticamente significativa em comparação com os cuidados padrão melhorados, este estudo pode apoiar o uso desta aplicação na gestão da DPOC e aborda o desafio do acesso a intervenções de RP.

Registro do ensaio clínico: DRKS 00024390.

INTRODUCTION

Pulmonary rehabilitation (PR) is an essential part of the management of chronic obstructive pulmonary disease (COPD), comprising exercise training, education and behaviour modification. The evidence for traditional face-to-face PR in COPD is compelling, with beneficial effects on exercise capacity, muscle function, quality of life and symptoms.^{1,2} However, such programmes are limited by access, capacity and uptake,^{3–5} being used by fewer than 2% of eligible patients with COPD.⁶ Tele-PR has been proposed as an alternative strategy in COPD,^{7,8} although the term ‘tele-PR’ encompasses different models, including videoconferences, webpages or mobile apps, with varying telephone support and monitoring.^{9–11} A Cochrane review comparing tele-PR with conventional centre-based PR or no rehabilitation found that tele-PR generated similar outcomes to

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Pulmonary rehabilitation (PR) is widely recognised as a cornerstone in managing chronic obstructive pulmonary disease (COPD). It offers significant benefits in terms of exercise capacity, quality of life and symptom control. However, traditional face-to-face PR programmes have limitations such as limited access, capacity constraints and low uptake rates. Tele-PR has emerged as a potential solution, encompassing various modalities such as videoconferencing, webpages or mobile applications. Although some studies have shown comparable outcomes between tele-PR and centre-based PR, the follow-up effects of tele-PR, particularly application-based application approaches, remain underexplored.

WHAT THIS STUDY ADDS

► This multicentre randomised controlled trial aims to investigate the effectiveness of a fully automated, interactive smartphone application in improving symptoms and physical function in COPD. Unlike previous studies, which primarily focused on tele-PR via videoconferencing or web-based platforms, this trial specifically examines the impact of an application-based intervention. The application includes customised exercise training, educational material and breathing/relaxation sessions, making it a comprehensive self-management tool for patients with COPD. This study enhances the existing literature by addressing the gap in knowledge regarding the effectiveness of application-based PR in COPD management, through the use of rigorous methodology and a large sample size across multiple centres.

centre-based PR in terms of exercise capacity and quality of life, and was superior to no rehabilitation.¹² However, the varying approaches, limited number of study participants, and few studies including post-intervention follow-up, mean that identifying the long-term effects of tele-PR is

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► The study's findings provide valuable insights into the role of mobile applications in COPD management and PR. Although the overall analysis did not show statistically significant differences between the application-using group and the enhanced standard of care group, the study highlights the potential benefits of application-based interventions, particularly for adherent users. Adherent application users showed improved exercise capacity, suggesting that the application could be a promising alternative for patients facing barriers to accessing centre-based rehabilitation (especially compared with the real-life situation where patients with COPD receive less support than in the enhanced standard of care group). Furthermore, the high patient satisfaction and safety profile of the Kaia COPD application highlight its potential as a viable option for addressing the challenges of access and adherence in PR interventions. These findings could guide future research directions, clinical guidelines and healthcare policies to enhance COPD management through innovative digital health solutions.

challenging. In particular, of the 15 tele-PR studies included in the Cochrane analysis, only one used an app-based approach. Given the minimal prior data, we conducted a trial to investigate the effectiveness of a fully automated, interactive, mobile app in improving symptoms and physical function in patients with COPD.

METHODS

Study design and participants

This multicentre randomised controlled trial (RCT) was conducted across 18 study centres in Germany and Switzerland, comprising six medical practices, five hospitals, five research institutions and two PR centres (Online supplemental e-table 1).

Participants were aged ≥ 40 years, diagnosed with COPD, with post-bronchodilator forced expiratory volume in 1 s $\geq 30\%$ predicted, COPD Assessment Test (CAT) total score ≥ 20 , and receiving stable maintenance COPD treatment (ie, with no treatment changes in the 4 weeks prior to entry). Additionally, they had a good understanding of German and were able to comprehend

the study materials, assessments and smartphone apps in general. Patients with physical, cognitive or safety-related problems hindering their ability to participate, receiving long-term oxygen therapy at >3 L/min, or regularly using non-invasive ventilation were ineligible, as were those enrolled in another clinical trial involving an investigational medication/device within 30 days prior to enrolment, with prior experience of a COPD self-management app or web-based programme, or who intended to participate in a conventional PR programme during the study. The trial was registered with the German Clinical Trials Register (registered: 26 May 2021), and was conducted according to Good Clinical Practice and the Declaration of Helsinki.

Study procedure

The study intervention duration was 12 weeks, with additional follow-up after a total of 24 weeks. After enrolment, patients were randomised 1:1 using block randomisation (block size four) to an intervention group (IVG) receiving the app or a control group (CTG). A randomisation list was generated for each site, with treatment assignment concealed from the statistician during the final analysis (although not study staff and participants, due to the nature of the intervention). All participants were provided with a study smartphone, to protect patient privacy by not using personal smartphones, and entered patient-reported outcomes data on a website via this smartphone, with data securely transmitted directly to the electronic case report form (eCRF) as electronic patient-reported outcomes (ePROs).

Intervention group

The study intervention was the multimodal personalised therapy app 'Kaia COPD' (Kaia Health Software, Munich, Germany). This consists of three therapy modules that are components of PR to promote self-management: individualised exercise training; educational content; and breathing/relaxation sessions (figure 1). The app dashboard presented participants with a daily choice of all three modules and encouraged them to complete one, two or all three at a convenient time, preferably daily. The use and completion of each module were automatically tracked by the app, with a weekly usage report provided to study sites. Inactive participants (<3 days of app usage per week) were contacted by study staff and were motivated to use the app.

The core component of the app, the exercise training programme, required minimal equipment (eg, a mat, chair, water bottles as weights or a resistance band). Exercise sessions lasted approximately 15–20 min, were completed in an unsupervised manner

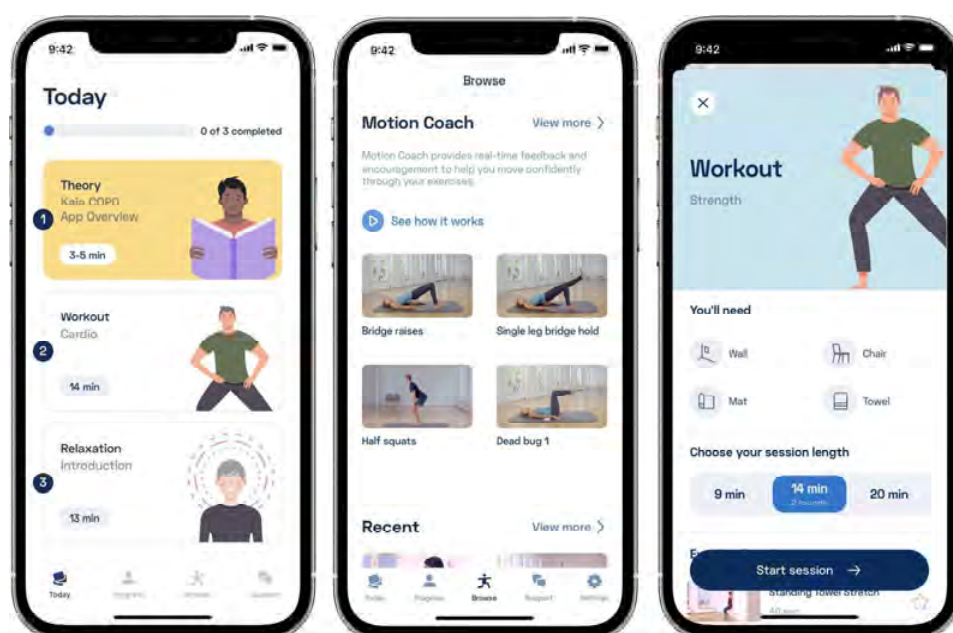


Figure 1 Screenshots of the fully automated mobile Kaia COPD application and its three modules: a digital exercise programme delivered by video instructions, a self-management programme (including relaxation and breathing exercises) delivered by audio instructions and a patient education programme. (Figure provided courtesy of Kaia Health). COPD, chronic obstructive pulmonary disease.

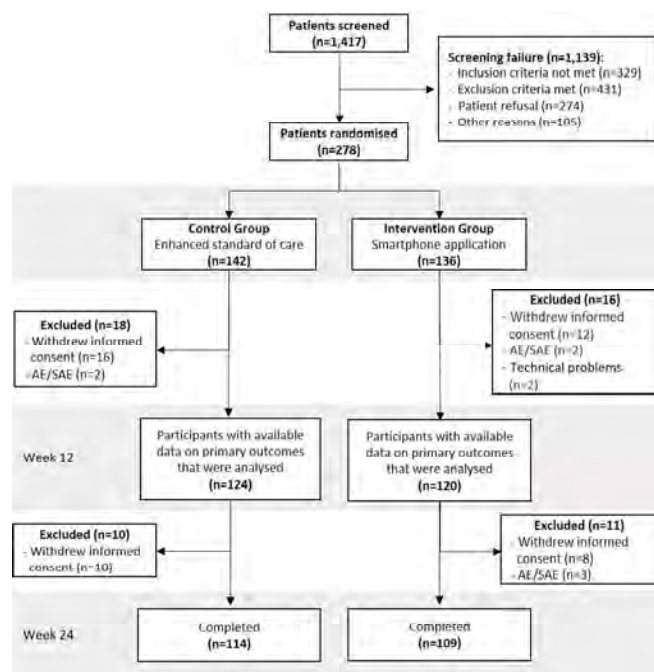


Figure 2 Participant flow through the study. AE, adverse event; SAE, severe AE.

and consisted of exercises focusing on muscle strengthening, balance and mobility, with visual and verbal instructions provided by video tutorials and a countdown timer. A standard exercise session consisted of an automatic selection of five exercises out of a pool of 64, with each exercise completed one to three times. After each session, patients rated the perceived difficulty on a five-point scale (very easy to very hard). An algorithm then automatically increased or decreased the difficulty for the next training session according to the patients' ratings, adapting the duration, intensity and exercise type to patients' individual needs.

The educational content was based on the internationally validated 'Living Well with COPD' patient guideline¹³ supplemented with videos on correct inhaler use. The breathing/relaxation sessions included audio instructions on relaxation and/or breathing techniques, such as mindfulness or progressive muscle relaxation.

Control group

Patients allocated to the CTG received the 'Living Well with COPD' booklet containing disease management information and exercise instructions, and used a study smartphone to report outcomes, but did not have access to the app. At the request of the lead ethics committee, this group received additional support beyond the standard care to reduce potential psychological bias. This included education and encouragement to exercise, and a paper-based exercise diary. The CTG therefore received an 'enhanced standard of care' rather than the usual care originally planned. Both CTG and IVG participants received telephone calls every 2 weeks from study staff to monitor for adverse events or other safety concerns. These calls did not include additional encouragement to exercise for intervention group participants, as their exercise guidance was fully integrated into the app content.

OUTCOMES

The prespecified co-primary outcomes were differences between IVG and CTG at 12 weeks in terms of health status (assessed by CAT) and exercise capacity (measured by 1-minute sit-to-stand test (1MSTST) repetitions). The 1MSTST tests were performed remotely via a video appointment between the participant and the study site staff.¹⁴ Outcome assessors were not blinded to group allocation (as all outcomes except the 1MSTST were collected digitally via an email link).

Secondary ePROs at baseline, and after 12 and 24 weeks included levels of anxiety and depression (Hospital Anxiety and Depression

Table 1 Demographic and baseline disease characteristics (intention-to-treat population)

	Control group (n=142)	Intervention group (n=136)	P value
Age, years	64 (59–70)	66 (60–72)	0.166
Sex			0.628
Female	72 (50.7)	65 (47.8)	
Male	70 (49.3)	71 (52.2)	
BMI, kg/m ²	26.4 (22.9–31.2)	25.5 (22.6–29.4)	0.083
COPD GOLD			0.999
I	5 (4.2)	4 (3.4)	
II	51 (42.9)	50 (42.7)	
III	63 (52.9)	63 (53.8)	
Smoking status			0.030
Current smoker	53 (37.3)	34 (25.2)	
Former smoker	89 (62.7)	102 (74.8)	
Mean smoking pack years	45 (35–54)	39 (25–49)	0.282
Age at COPD diagnosis	55 (49–61)	55 (50–62)	0.353
Comorbidities			
Cardiovascular	87 (61.3)	89 (66.4)	0.374
Orthopaedic	56 (39.4)	61 (45.2)	0.333
Metabolic	49 (34.5)	46 (34.3)	0.975
Psychological	33 (23.2)	32 (23.9)	0.900
Cerebrovascular	14 (10.0)	14 (10.4)	0.903
Treatment			
LABA	125 (88.0)	126 (92.6)	0.194
LAMA	127 (89.4)	124 (91.2)	0.624
ICS	86 (60.6)	86 (63.2)	0.647
LTOT	27 (19)	27 (20)	0.836
FEV ₁ , L	1.38 (1.03–1.77)	1.23 (1.04–1.66)	0.327
FEV ₁ , % predicted	48 (40–61)	48 (36–57)	0.222
FEV ₁ /FVC	0.52 (0.45–0.58)	0.50 (0.44–0.57)	0.135
COPD Assessment Test total score	23 (21–26)	23 (21–26)	0.617
1-minute sit-to-stand test repetitions	18 (14–22)	17 (13–22)	0.196
Patients with at least one acute COPD exacerbation during the previous 12 months, n (%)	45 (31.6)	50 (36.8)	0.371

All continuous variables are median (IQR) and are compared via Mann-Whitney U test. All categorical variables are the absolute number (percentage), and are compared using χ^2 test.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β_2 -receptor agonist; LAMA, long-acting muscarinic antagonist; LTOT, long-term oxygen therapy.

Scale (HADS)), health-related quality of life and disease burden (Veterans RAND 12-item health survey (VR-12)), patient engagement in healthcare (Patient Activation Measure 13 (PAM-13)), healthcare resource utilisation, adverse events, CAT and 1MSTST at 24 weeks and app satisfaction and helpfulness (IVG only). Further details on these endpoints are in the Online supplement.

As an exploratory outcome, the effect of the intervention on the incidence of mild, moderate or severe COPD exacerbations (Global Initiative of Chronic Obstructive Lung Disease 2022 definition¹⁵) was assessed (during telephone calls every two weeks in both groups to ask about the occurrence of any adverse events and any changes in medication).

Table 2 The COPD Assessment Test total score and 1-minute sit-to-stand test at baseline, and change from baseline at 12 (co-primary outcomes) and 24 weeks (follow-up)

	Intention-to-treat population (including all patients)		Per-protocol population (including only adherent application users in the IVG)	
	Control group (n=142)	Intervention group (n=136)	Intervention group vs control group differences	Intervention group vs control group differences
COPD Assessment Test total score				
Baseline	23 (21 to 26)	23 (21 to 26)	23 (21 to 25)	22 (20 to 25)
Week 12, change from baseline	−3 (−8 to 0)	−4 (−8 to −1)	−3 (−8 to 0) p=0.697	−4 (−8 to −2) 1 (−1 to 3) p=0.409
Week 24, change from baseline	−3.5 (−8 to 1)	−4 (−9 to −1)	−3 (−8 to 1) p=0.074	−4 (−9 to −2) 2 (−0 to 4) p=0.075
1-minute sit-to-stand test, repetitions				
Baseline	18 (14 to 22)	17 (13 to 22)	18 (24 to 23)	18 (13 to 22)
Week 12, change from baseline	2 (0 to 6)	1 (−1 to 4)	2 (0 to 6) p=0.120	3 (0 to 4) 0 (−2 to 2) p=0.901
Week 24, change from baseline	4 (0 to 7)	3 (0 to 6)	4 (0 to 7) p=0.485	3 (1 to 6.5) 0 (−2 to 1) p=0.709
COPD, chronic obstructive pulmonary disease; IVG, intervention group.				

Sample size and statistical analyses

Based on a two-tailed t-test with 80% power, assuming a mean difference of 2.5±6.0 points in CAT total score,¹⁶ 111 patients per group would be required. For the 1MSTST, assuming a minimally important difference of 3±6 repetitions,¹⁷ 78 patients per arm would be required. Considering both primary endpoints with an initial alpha of 0.025, the CAT score calculation with the higher patient number determined the final sample size of 278 participants, including an expected 25% dropout rate.

Normality was tested using the Shapiro-Wilk test with histograms and qq-plots. Between-group comparisons were conducted using t-tests or Mann-Whitney U test for continuous variables and χ^2 test or Fisher's exact test for non-continuous variables, with median differences calculated using the Hodges-Lehmann estimator. A p value of 0.05 was considered statistically significant, with the co-primary endpoints adjusted for multiple testing using Bonferroni's method. Statistical analyses were performed using R (V4.3.1) with R studio (2023.09.1+494, Foundation for Statistical Computing, Vienna, Austria).

The intention-to-treat (ITT) population included all randomised patients, regardless of their eligibility status after randomisation or adherence. The per-protocol (PP) population consisted of all randomised patients who adhered to the study protocol, completed all relevant procedures at baseline and week 12, and had data available at week 12 for at least one co-primary endpoint. The IVG PP population included only participants who met a predefined app adherence threshold (completion of the exercise programme≥3 days/week for≥75% of the weeks from baseline to week 12, based on app usage data). Subgroup analyses were also prespecified on the co-primary endpoints, with patients grouped by this adherence threshold.

Handling of missing data

Full case analysis is presented for ITT and PP analysis. As a sensitivity analysis, missing data was imputed using a jump-to-reference approach with 2000 bootstrap samples.

RESULTS

Between May 2021 and May 2023, 1417 patients were screened, with 278 randomised (figure 2; baseline demographics are in table 1). A total of 124 and 120 patients in the IVG and CTG, respectively, completed the primary intervention phase (week 12), with 109 and 114, respectively, completing week 24. The PP IVG population consisted of 46 patients (40.4%); 68 patients were excluded on the basis of adherence.

Primary endpoints

In the ITT population, between-group comparisons showed no statistically significant difference in improvement from baseline in the CAT total score at week 12, with a median change of −4 points (IQR −8 to −1; p<0.001) in the IVG and −3 points (IQR −8 to 0; p<0.001) in the CTG (table 2). For the 1MSTST, there were also no significant between-group differences in improvement from baseline at week 12. Within-group changes in the ITT and PP population showed significant improvements from baseline in both CAT total scores and 1MSTST repetitions in both groups.

Furthermore, in a subgroup analysis of the IVG, with participants grouped by adherence, although CAT total score did not differ significantly between adherent and non-adherent patients, there was a greater improvement from baseline for 1MSTST in adherent patients, resulting in 2 (0 to 8) more repetitions in favour of the IVG (p=0.006; figure 3). There was also a significant correlation (p=0.016, online supplemental e-figure 1) between the number of active app training days and improvement in 1MSTST from baseline to week 12 in adherent versus non-adherent app users. There were no significant differences in baseline characteristics between adherent and non-adherent app users (online supplemental e-table 2).

Secondary endpoints

For the secondary endpoints, there were no differences between IVG and CTG (ITT population) at weeks 12 or 24 (online supplemental

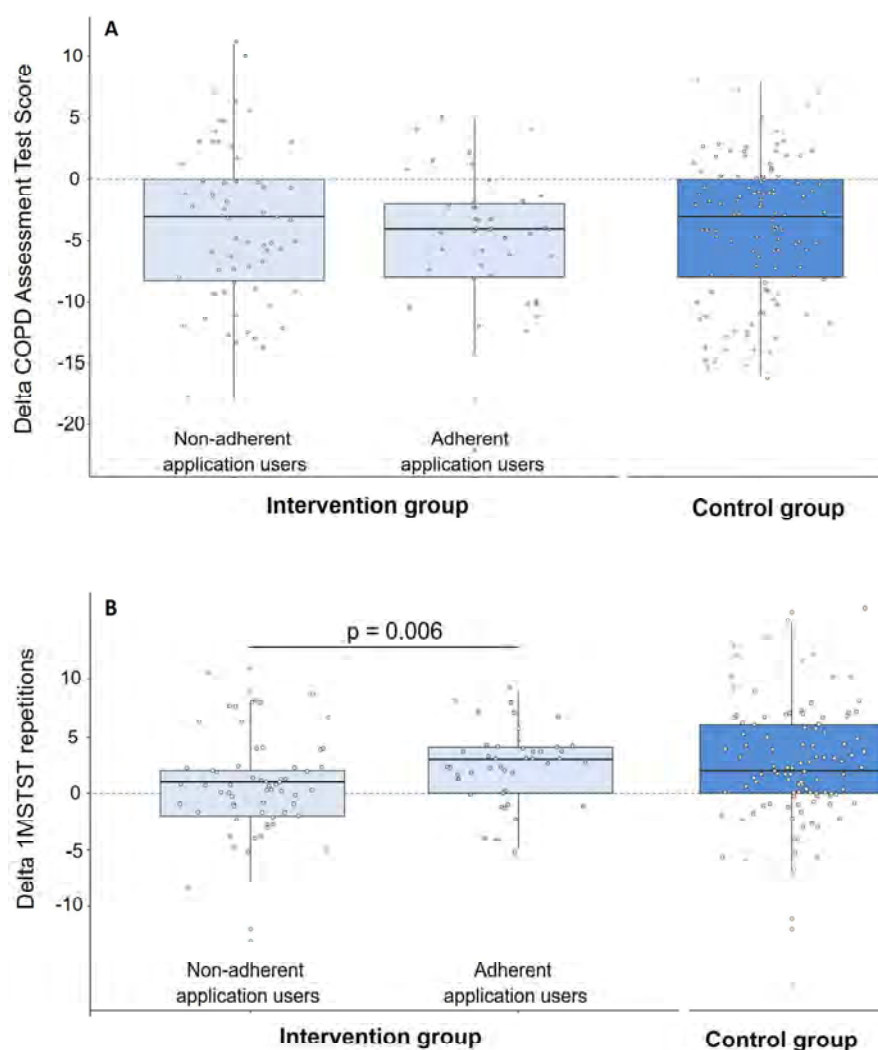


Figure 3 Changes in COPD Assessment Test score (A) and changes in 1-minute sit-to-stand test (1MSTST) repetitions (B) from baseline to week 12 between adherent application users ($\geq 75\%$ adherent training weeks, $n=46$) and non-adherent application users ($<75\%$ adherent training weeks, $n=68$) in the intervention group and the control group ($n=122$). COPD, chronic obstructive pulmonary disease.

e-tables 3 and 4). In the PP population, there were IVG versus CTG differences at week 12 for VR-12 (physical and mental components), PAM-13 and HADS (total score and depression), and at week 24 for PAM-13 and HADS anxiety (online supplemental e-table 3), although the group differences were not statistically significant when expressed as change from baseline (table 3). There were also trends to lower healthcare utilisation in the IVG than the CTG, although again with no statistically significant differences (online supplemental e-table 5). From baseline to 12 weeks, 25.7% of IVG and 30.4% of CTG reported regular participation in outpatient exercise programmes or physiotherapy. On average, 40.4% of patients in the IVG used the app adherently, with consistent use of the physical exercise module for the duration of follow-up (online supplemental e-figure 2 and e-table 6).

Exploratory outcomes

At baseline, the proportion of patients having at least one exacerbation in the previous 12 months in the IVG (36.8%, $n=50$) was similar to the CTG (31.6%, $n=45$) ($p=0.4$). During the 24-week study period, fewer patients in the IVG experienced an exacerbation than the CTG (ITT: 20.5% vs 30.2%, $p=0.086$; PP: 26.1% vs 32.0%, $p=0.582$). Furthermore, the total number of exacerbations was lower in the IVG (ITT: 34 vs 52; PP: 16 vs 48) (figure 4).

Application adherence and satisfaction

During the first 12 weeks, 46 patients (40.4%) were adherent app users. Of these, the majority ($n=31$, 72.1%) remained adherent throughout the follow-up period. Patient satisfaction with the app

was very high. In the ITT population, at week 12, 93.6% of patients in the IVG indicated they would recommend the app to another patient (at week 24 follow-up: 94.1%). Furthermore, at week 12, 93.6% of patients were satisfied or very satisfied with the app (at week 24: 94.0%).

Adverse events

During the intervention period, 56 patients (41.2%) reported an adverse event in the IVG, compared with 58 (40.8%) in the CTG, with no difference between groups ($p>0.9$; online supplemental e-table 7). Over the subsequent follow-up period, a further 38 (27.9%) and 31 (21.8%) patients, respectively, reported an adverse event ($p=0.2$). None of these adverse events were directly related to the intervention.

DISCUSSION

In this large, multicentre, RCT, there were improvements from baseline in the co-primary endpoints of CAT and 1MSTST in both the IVG and CTG over both the 12-week main study period and the subsequent follow-up, with between-group differences not statistically significant. Similarly, between-group differences in the secondary endpoints were not statistically significant. However, in the PP population (which excluded patients from the IVG who were not adherent to the app), improvements from baseline during the 12-week intervention period were consistently numerically greater in the IVG than the CTG. Furthermore, in a subgroup analysis of the IVG, there was a significantly greater improvement in 1MSTST in favour of adherent app users compared with non-adherent app

Table 3 Between-group results in the per-protocol population (ie, including only adherent application users in the intervention group) for changes from baseline in secondary endpoints at weeks 12 and 24

	Control group (n=122)	Intervention group (n=46)	Intervention group vs control group differences
Veterans RAND 12-Item health survey: physical component score			
Baseline	32.3 (27.2 to 37.5)	33.4 (29.3 to 40.7)	
Week 12, change from baseline	0.3 (−2.7 to 6.1)	1.3 (−2.8 to 6.3)	0 (−3 to 2); p=0.764
Week 24, change from baseline	1.9 (−2.7 to 5.8)	1.7 (−2.2 to 4.8)	0 (−3 to 2); p=0.778
Veterans RAND 12-Item health survey: mental component score			
Baseline	47.1 (38.3 to 54.3)	52.2 (38.9 to 59.4)	
Week 12, change from baseline	−2.5 (−7.2 to 3.5)	−0.1 (−4.0 to 2.7)	−2 (−5 to 1); p=0.209
Week 24, change from baseline	−0.9 (−7.2 to 4.8)	0.1 (−6.1 to 3.7)	−1 (−4 to 3); p=0.719
Patient Activation Measure 13			
Baseline	42 (39 to 45)	44 (40 to 47)	
Week 12, change from baseline	0 (−3 to 2)	1 (−1 to 3)	−1 (−2 to 0); p=0.169
Week 24, change from baseline	0 (−2 to 3)	2 (−1 to 4)	−1 (−3 to 0); p=0.152
Hospital Anxiety and Depression Scale: total score			
Baseline	11 (8 to 16)	9 (6 to 16)	
Week 12, change from baseline	1 (−2 to 4)	−1 (−5 to 1)	2 (0 to 4); p=0.043
Week 24, change from baseline	0 (−3 to 4)	0 (−3.5 to 3)	1 (−1 to 3); p=0.546
Hospital Anxiety and Depression Scale: anxiety			
Baseline	5 (3 to 8)	5 (3 to 7)	
Week 12, change from baseline	0 (−1 to 2)	0 (−3 to 1)	1 (−0 to 2); p=0.111
Week 24, change from baseline	0 (−2 to 2)	0 (−2 to 2)	0 (−1 to 2); p=0.424
Hospital Anxiety and Depression Scale: depression			
Baseline	6 (4 to 8)	4 (2 to 7)	
Week 12, change from baseline	0 (−2 to 2)	−1 (−2 to 1)	1 (−0 to 2); p=0.056
Week 24, change from baseline	0 (−2 to 2)	0 (−1 to 1.5)	0 (−1 to 1); p=0.634

All continuous variables are shown with median (IQR) and were compared via Mann-Whitney U test.

users, with an improvement of two repetitions ($p=0.006$). Adherent app users in the IVG (ie, the PP population) also needed numerically fewer healthcare resources and had fewer exacerbations than the CTG. Importantly, adherence to app usage over 12 weeks in the ITT population was 40%, substantially higher than the 22% adherence in a previous mobile PR app study.¹⁸

The lack of statistically significant differences between groups for the co-primary endpoints needs to be considered in the context of the CTG receiving ‘enhanced standard of care’. The conventional standard of care in a PR study typically results in either no improvement or a deterioration in CAT or 1MSTST.^{19–20} In the present study, the CTG received phone calls with encouragement to exercise every 2 weeks. Such phone calls from healthcare professionals can significantly increase daily training duration in patients with COPD.²¹ Furthermore, the CTG was provided the ‘Living Well with COPD’ booklet,¹³ which has been shown to enhance the quality of life, reduce exacerbation rates and healthcare usage, and increase the 1MSTST by three repetitions.^{22–23} These interventions presumably benefitted the CTG, limiting the potential for further improvement in the IVG. A previous RCT in 166 participants with moderate-to-very severe COPD investigated a monitoring and self-management app called EDGE.²⁴ This study also found no difference in COPD-specific health outcomes over 12 months compared with an ‘enhanced standard of care’ (who received the same information on leaflets, but without digital monitoring).

In general, only a few mobile exercise or PR applications have been investigated in COPD. In an observational trial, Yonchuk et al concluded that their application (Respercise) could be easily deployed, and improved the 5-repetition sit-to-stand test by 2.2 s after 13 weeks.²⁵ However, that application primarily focuses on daily step goals, and includes a limited selection of four strength training exercises. myCOPD, application developed by the UK National Health Service, is designed to aid individuals with COPD by

providing education, self-monitoring and self-management functions. In an RCT involving 60 patients with mild-to-moderate COPD, CAT total score improved by −1.27 points ($p=0.44$) after 12 weeks in application users compared with usual care.¹⁸ Furthermore, the mobile PR application efil breath was evaluated in a Korean RCT that included physical activity monitoring, exercise training and education in patients with COPD.²⁶ A total of 85 participants were randomly assigned to either application-based PR or usual care. Application-based PR resulted in a non-significant improvement from the baseline of −2.7 points in the CAT total score over 12 weeks. The CAT improvements in both of these studies are considerably smaller than the change from baseline in the IVG in the current study (−4 points).

Application-based coaching interventions can increase physical activity levels in patients with COPD.²⁷ The application used in the current study has also been evaluated as a PR maintenance intervention in COPD²⁸; combined with a physical activity tracker, activity levels were preserved and disease burden was reduced compared with the control group 6 months after a comprehensive 3-week inpatient PR. In the current study, the focus of the intervention has shifted to examining the effects of the application’s content—exercise, education and breathing exercises—on improving exercise capacity and quality of life, without including physical activity monitoring or counselling.

While fully automated apps and video-based interventions offer advantages in terms of accessibility, consistency, staff burden and cost-effectiveness, videoconference-based interventions provide human interaction, individualised guidance and flexibility. Achieving the best possible outcome may require a combination of both, striking a balance between automated services and the human touch. Importantly, digital PR apps that either complement or replace some aspects of usual care offer an opportunity for more convenient, cost-effective care.²⁹

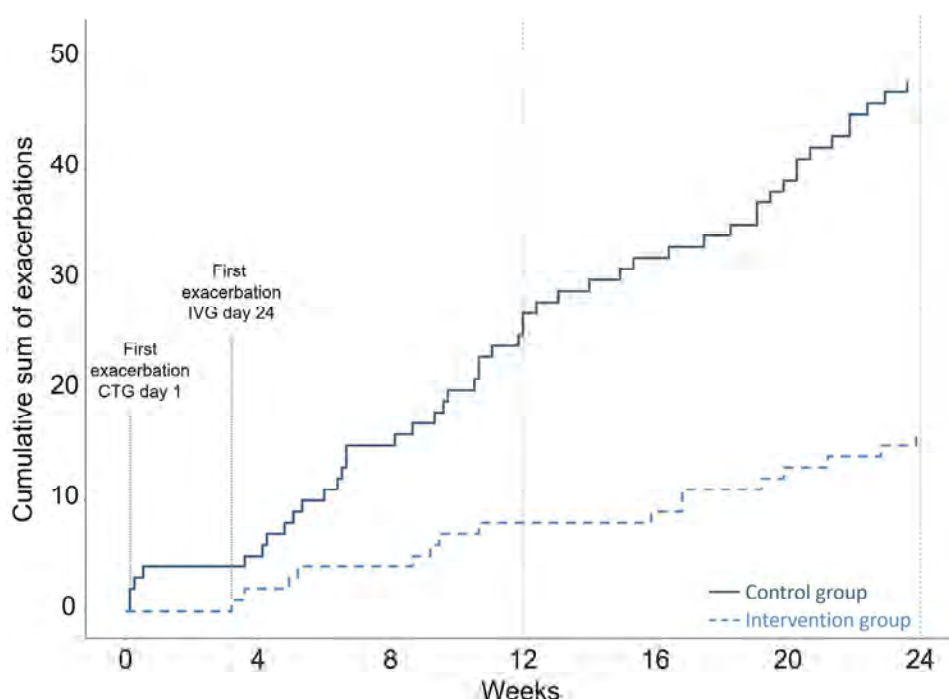


Figure 4 This Kaplan-Meier plot shows the cumulative sum of exacerbations in the per-protocol population over 24 weeks (control group: 48 acute exacerbations and 16 acute exacerbations in the intervention group). The difference was not statistically significant. The first exacerbation occurred on day 1 in the control group (CTG) and on day 24 in the intervention group (IVG); HR (95% CI) IVG 0.83 (0.41, 1.69) (post-hoc analysis).

The study has some limitations. First, due to the nature of the intervention patients were not blinded. Second, COPD maintenance therapy during the study was not restricted. Third, as discussed above, the CTG received 'enhanced standard of care' differing from typical daily care. Fourth, the app-based exercise programme did not include an aerobic training component, which may have diminished the greater benefits of the app. Finally, the study excluded patients with very severe COPD who may require greater supervision due to their disease severity. As strengths, the current study is noteworthy for its robust design, multisite nature and recruitment of the largest sample size thus far studied for a digital PR app. In addition, several clinical outcomes highly relevant to COPD management were assessed.

Conclusions

This RCT did not show statistically significant differences in the primary outcome between the app-using group and the enhanced standard of care group. However, some benefits were observed in adherent app users, including an improvement in exercise capacity compared with non-adherent users, and no safety issues were identified with app use. These findings suggest that the Kaia COPD app may offer a benefit in the management of COPD. However, we recommend further studies to substantiate these observations and to examine the role of the app compared with conventional usual care.

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the manuscript (no award/grant number available). However, data monitoring and data analysis were performed by independent study research associates and a statistician. This separation of roles was implemented to maintain objectivity, transparency and scientific integrity throughout the research process.

Competing interests RG has received speaker fees from AstraZeneca, Chiesi and GlaxoSmithKline and has attended advisory boards from AstraZeneca and Chiesi. MS has nothing to disclose. AS and AP are employees of Kaia Health Software (Munich, Germany) and hold a Virtual Options Program from Kaia Health Software. DK has nothing to disclose. JJ has received speakers fee from CSL Behring. TS has nothing to disclose. BU received payment from Kaia Health Software for statistical analysis of this manuscript. CFV has received institutional grants from the German Ministry of Education and Science (BMBF), AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, GlaxoSmithKline, Grifols and Novartis. Consulting fees from Aerogen, AstraZeneca, Boehringer Ingelheim, CSL Behring, Chiesi, GlaxoSmithKline, Insmmed, Menarini, Novartis, Nuvaaira, Sanofi. Speakers fees from Aerogen, AstraZeneca, Boehringer Ingelheim, CSL Behring, Chiesi, GlaxoSmithKline, Insmmed, Menarini, Novartis, Nuvaaira and Sanofi. ARK has received institutional grants from the Bavarian Ministry of Health. Consulting fees from AstraZeneca, Boehringer Ingelheim, CSL Behring, Chiesi, GlaxoSmithKline, Menarini, Pfizer, PulmonX, and Sanofi. Speakers fees from AstraZeneca, Boehringer Ingelheim, CSL Behring, Chiesi, GlaxoSmithKline, Menarini and Sanofi.

Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. De-identified individual participant data and a data dictionary defining each field in the set can be made available to others on approval of a written request to the corresponding author. The request will be evaluated by a committee formed by a subset of coauthors to determine the research value. A data-sharing agreement will be needed. The full study protocol will be available on request from the study author.

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ARTIGO ORIGINAL

Efeitos de curto prazo da reabilitação pulmonar domiciliar durante agudizações da DPOC geridas em regime ambulatorial: um ensaio clínico randomizado

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RESUMO

Contexto: Existe incerteza sobre os efeitos benéficos da reabilitação pulmonar (RP) durante agudizações da doença pulmonar obstrutiva crónica (DPOC). Este estudo explorou os efeitos de curto prazo e o impacto autorrelatado de um programa de RP domiciliar para pessoas com agudizações da DPOC geridas em regime ambulatorial.

Métodos: Foi realizado um ensaio clínico randomizado de métodos mistos em pessoas com agudizações da DPOC geridas em regime ambulatorial. Os participantes foram aleatoriamente atribuídos ao grupo de controlo (GC, ou seja, cuidados habituais) ou ao grupo experimental (GE, ou seja, cuidados habituais e RP domiciliar de 3 semanas) dentro de 48 horas após o diagnóstico (linha de base). As avaliações foram realizadas na linha de base e após 3 semanas (pós-intervenção). O teste de avaliação da DPOC (CAT) foi o desfecho primário. Os desfechos secundários incluíram medidas de sintomas e capacidade funcional. Após a RP, foram realizadas entrevistas. As análises foram conduzidas utilizando análise de variância mista (não) paramétrica, análise temática dedutiva e integração narrativa através de exposições conjuntas.

Resultados: Foram incluídos 50 participantes com agudizações da DPOC geridas em regime ambulatorial (78% homens, 70±11 anos, volume expiratório forçado no primeiro segundo 47,4±16,4% previsto). Foram observadas melhorias significativamente maiores no GE em comparação com o GC para o CAT (GE Δ–12,5±7,2 vs GC Δ–5,9±7,2, $p=0,002$) e 12 de 13 outros desfechos secundários. Foi identificado um impacto positivo autorrelatado da RP nos sintomas, controlo da vida diária, saúde, estado mental e autonomia. Nenhum evento adverso foi relatado.

Conclusões: Um programa de RP domiciliar de 3 semanas é seguro, significativo e mais eficaz do que apenas a medicação padrão na melhoria dos sintomas, capacidade funcional e estado de saúde, desfechos frequentemente associados a um mau prognóstico. Isso destaca o papel da RP na melhoria do processo de recuperação durante agudizações da DPOC geridas em regime ambulatorial, podendo contribuir para um melhor prognóstico nesses indivíduos.

Registo do ensaio clínico: NCT03751670.

INTRODUCTION

The clinical trajectory of chronic obstructive pulmonary disease (COPD) is frequently punctuated by exacerbations (ECOPD), which are defined as events characterised by increased dyspnoea and/or cough and sputum that worsens over less than 14 days, and can be managed in an inpatient (severe ECOPD) or outpatient (mild to moderate ECOPD) setting.¹ These events have a negative impact on health status and disease progression, leading to worsening of symptoms, accelerated lung function decline, impaired muscle strength, exercise performance, physical activity levels and quality of life, which often do not fully recover.^{1,2} Moreover, ECOPD increase individuals' susceptibility for fur-

Key messages

WHAT IS ALREADY KNOWN ON THIS TOPIC

► Pulmonary rehabilitation (PR) is a cornerstone intervention for the management of people with stable chronic obstructive pulmonary disease (COPD) (evidence level A) and has beneficial effects in patients following hospitalisation for exacerbation of COPD (ECOPD) (evidence level B).

WHAT THIS STUDY ADDS

► A 3-week home-based PR programme delivered concurrently with pharmacotherapy for people undergoing outpatient management of ECOPD (ie, ECOPD that do not require hospitalisation, representing more than 80% of all ECOPD) is safe, more effective than just pharmacological treatment, and results in positive short-term effects and self-perceived impact on symptoms, physical activity, activities of daily living, functional capacity and health status.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

► This is the first randomised controlled trial exploring the role of PR delivered concurrently with pharmacotherapy for people with outpatient-managed ECOPD. Our study provides a significant contribution for healthcare professionals to improve the care of people with outpatient-managed ECOPD, with a safe and patient-meaningful intervention. The PR programme implemented in this study can be translated readily into clinical practice.

ther exacerbations, other acute events, hospitalisations and death.¹ The goals of treatment for ECOPD are, therefore, to minimise the negative impact of these events and prevent their recurrence.¹

Pulmonary rehabilitation (PR) is a cornerstone intervention for the management of people with stable COPD, which has shown to (1) improve exercise capacity, muscle strength and health-related quality of life, (2) reduce symptoms, hospitalisations and unscheduled healthcare visits, and (3) en-

hance self-management and self-efficacy.^{1,3} These are common and persistent treatable traits presented by people with ECOPD, hence, given the benefits of PR in these traits, it seems logical to also consider PR as a management strategy for ECOPD. In fact, the current Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline shows an evidence level B for PR after hospitalisation for ECOPD;¹ however, studies focused on people with ECOPD who do not need hospital admission are lacking.⁴ These outpatient-managed ECOPD represent more than 80% of all exacerbations and have a huge negative impact on people's lives; yet, they are treated with pharmacotherapy alone.^{1,5} Our previous pilot study showed promising results of PR in the management of people with outpatient-managed ECOPD on symptoms, vital signs, quadriceps muscle strength and impact of the disease,⁶ but randomised controlled trials with larger samples are warranted.

This study explored the short-term effects and self-reported impact of a home-based PR programme among people with outpatient-managed ECOPD. We hypothesise that by adding PR to the current usual care (pharmacotherapy) for people with outpatient-managed ECOPD, we will improve symptoms and impact of the disease, preserve or enhance functional status and have a positive self-perceived impact.

MATERIAL AND METHODS

Study design and ethics

A randomised controlled trial (NCT03751670) with a convergent mixed-methods design (QUAN+QUAL) was conducted among people with outpatient-managed ECOPD between October 2019 and February 2023. Participants were randomly assigned to the control (CG, ie, usual care) or experimental (EG, ie, usual care plus PR) groups during the initial visit, prior to the collection of any baseline measures, in an 1:1 ratio, using sealed opaque envelopes. These envelopes were prepared before starting the recruitment process by using a web-based sequence generator (<https://www.graphpad.com/quickcalcs/randomize1.cfm>). The nature of the intervention and limited staff precluded blinding of participants, treating physiotherapists and assessors.

Approval for this study was obtained from the ethical committees of Centro Hospitalar do Baixo Vouga (15.23.2020), Centro Hospitalar Universitário de Santo António (2020.023: 018-DEFI/ 019-CE), Centro Hospitalar Vila Nova de Gaia/ Espinho (127/2019-1), Unidade Local de Saúde de Matosinhos (73/CE/JAS) and Unidade Investigação em Ciências da Saúde: Enfermagem (P618-10/ 2019). All participants provided written informed consent before any data collection. This study is reported according to the consolidated standards of reporting trials (CONSORT), consolidated criteria for reporting qualitative research (COREQ) and good reporting of a mixed methods study (GRAMMS) guidelines.⁷⁻⁹

Participants

People with outpatient-managed ECOPD were consecutively recruited, via their treating physicians, from the Pulmonology and Emergency departments of hospitals in the North and Centre regions of Portugal (more details in the online supplemental material). The inclusion criteria were: (1) previous diagnosis of COPD according to the GOLD criteria (confirmed by spirometry)¹⁰; (2) current diagnosis of ECOPD, defined as an acute worsening of respiratory symptoms that resulted in additional therapy (ie, any escalation of the COPD treatment, such as, intensification or change of the bronchodilator regime, antibiotics, oral corticosteroids)¹⁰; (3) included within 48 hours of the ECOPD diagnosis; and (4) able to provide informed consent. Exclusion criteria included: (1) need for hospitalisation to manage the current ECOPD; (2) history of an acute cardiac or respiratory condition in the previous month; (3) unstable cardiovascular disease; (4) presence of musculoskeletal or neuromuscular impairments that precluded the ability to perform the assessments or intervention; (5) signs of cognitive impairment; (6) current neoplasia; and (7) any therapeutic intervention in addition to usual care.

Interventions

The usual care intervention consisted of conventional medical treatment (ie, pharmacotherapy and medical advice). The home-based PR programme was delivered in fully supervised sessions, on an 1:1 basis, and consisted of two sessions per week (approximately 60 min/session), for 3 weeks, composed of exercise training, breathing control and retraining, airway clearance techniques, education and psychosocial support.^{4,6} Exercise training included step training and strength training focused on the upper limbs, lower limbs and trunk, performed with free weights or individuals' own bodyweight, either in a sitting or standing position, depending on their condition. Education and psychosocial support was delivered in every session through talks/coaching, flyers and the demonstration of practical strategies. Sessions were delivered by physiotherapists with experience in respiratory interventions (AM or CD) following a standard protocol, which is described in detail in the online supplemental material according to the Consensus on Exercise Reporting Template (CERT) guidelines.¹¹ A multidisciplinary team composed by physicians, nurses, social workers, psychologists and nutritionists was available to provide additional support, according to participants' needs, and contributed to the education and psychosocial support component of this intervention. Patients in both groups received a verbal general encouragement to be physically active.

Data collection

Participants were assessed at home, by trained physiotherapists (AM or CD), within 48 hours of the diagnosis of ECOPD (baseline) and 3 weeks after (post).

Sociodemographic (age, sex), anthropometric (height and weight to compute body mass index (BMI)) and general clinical data (smoking habits, self-reported number of exacerbations and hospitalisations in the past year, medication and comorbidities (self-reported and from medical records), use of long-term oxygen therapy and non-invasive ventilation) were collected. The severity of comorbid diseases was recorded and scored according to the Charlson comorbidity index (CCI).¹² The most recent lung function assessment and GOLD classification (ie, grade and group)¹ were retrieved from the medical file. At post assessment, the number of self-reported ECOPD-related unscheduled healthcare visits during the 3-week study time were retrieved.

The primary outcome was the impact of the disease assessed with the COPD assessment test (CAT). This outcome measure presents robust measurement properties during ECOPD and is recommended by the GOLD.¹ The CAT total score ranges from 0 to 40, with higher scores indicating higher impact. Minimal clinically important differences (MCID) of 2–3 points for hospitalisation due to ECOPD and 3 weeks PR have been reported.¹³

Secondary patient-reported outcome measures included the brief physical activity assessment tool for physical activity level,¹⁴ the modified Medical Research Council dyspnoea questionnaire for activity-related dyspnoea,¹ the London chest activity of daily living for dyspnoea during activities of daily living,¹⁵ the cough and sputum assessment questionnaire (CASA-Q) for symptoms of cough and sputum and their impact,¹⁶ and the functional assessment of chronic illness therapy–fatigue and checklist individual strength–fatigue (eight items) for symptoms of fatigue.¹⁷

Secondary outcomes related to functional capacity were hand-grip strength measured on the dominant side with a hand dynamometer (Jamar 12–0241 Lite, Fabrication Enterprises, White Plains, New York),¹⁸ biceps and quadriceps isometric muscle strength measured on the dominant side with a handheld dynamometer (microFET2, Hoggan Health, The best Salt Lake City, Utah),¹⁹ the short physical performance battery (ie, standing balance, 4 m gait speed, 5-repetitions sit-to-stand test),²⁰ the 1 min sit-to-stand test (1-minSTS)²¹ and the Chester step test (CST).²²

At the postassessment, short, semistructured, individual face-to-face interviews were conducted with the EG aiming to explore their perspectives and self-reported impact of the PR programme. A semistructured interview guide with open-ended questions (see

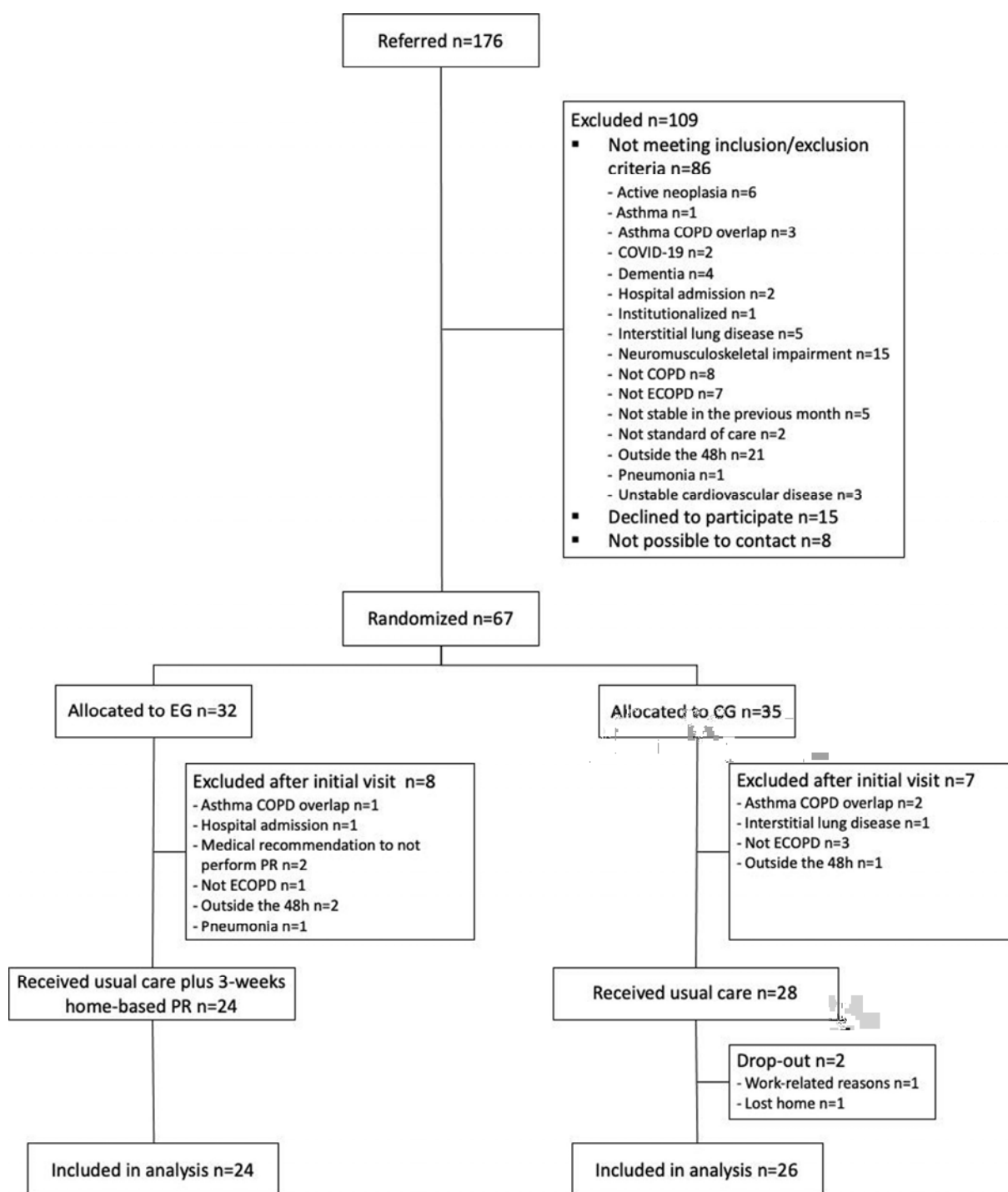


Figure 1 Consolidated standards of reporting trials (CONSORT) flow diagram of participants through the study. COPD, chronic obstructive pulmonary disease; ECOPD, exacerbation of COPD; PR, pulmonary rehabilitation.

online supplemental material) was developed informed by the literature, previous experience of the team and an experienced qualitative researcher. It was used to ensure that the topics under investigation were covered in a consistent manner but allowing flexibility. Interviews were audio recorded (Olympus digital voice recorder WS-750m) and transcribed verbatim. All interviews were anonymised by assigning pseudonyms to participants. Details on research team and reflexivity, and on rigour and trustworthiness, are provided in online supplemental file.

Data analysis

A sample size calculation was performed based on the estimated partial η^2 for the mixed analysis of variance (ANOVA) of the primary outcome (CAT) obtained in a previous pilot study.⁶ Assuming a 30%–35% dropout rate,²³ it was estimated that 50 patients

with outpatient-managed ECOPD would be needed to detect a moderate effect ($f=0.30$)⁶ with 80% power, at the 5% significance level.

The quantitative data were analysed per protocol since only two dropouts (CG) occurred (less than 10% missing data). Descriptive statistics were used to describe the sample and the normality of data was explored with the Kolmogorov-Smirnov test. Comparisons within (ie, baseline vs post) and between groups and group×time interaction were explored with parametric and non-parametric mixed ANOVAs, accordingly. Group×time interactions were further explored using analysis of covariance (ANCOVA) to control for age, sex, BMI, smoking status and comorbidities (CCI total score). Statistical analyses were performed using IBM SPSS Statistics V.28.0 (IBM Corporation, Armonk, New York) and RStudio V.2022.12.0 (Posit PBC, Boston, Massachusetts). The level

Table 1 Sociodemographic, anthropometric and general clinical characteristics of participants with an exacerbation of chronic obstructive pulmonary disease (n=50)

	Experimental group (n=24)	Control group (n=26)
Sex (male), n (%)	22 (91.7%)	17 (65.4%)
Age, years	72.5±9.8	67.1±11.1
Body mass index, kg/m ²	24.9±4.6	25±4
Lung function (stable)		
FEV ₁ , %predicted	48.7±15.3	46.4±17.5
FVC, %predicted	70.1±15.3	69.7±17.3
GOLD grade (stable), n (%)		
1	2 (8.3%)	0 (0%)
2	8 (33.3%)	10 (38.5%)
3	10 (41.7%)	11 (42.3%)
4	4 (16.7%)	5 (19.2%)
GOLD group (stable), n (%)		
A	3 (18.8%)	2 (13.3%)
B	6 (37.5%)	6 (40%)
E	7 (43.8%)	7 (46.7%)
Smoking status		
Never smoker	2 (8.3%)	2 (7.7%)
Current smoker	5 (20.8%)	13 (50%)
Former smoker	17 (70.8%)	11 (42.3%)
Pack-years	52.8±42.1	42.3±29.2
N° hospitalisations last year	0 (0; 0.5)	0 (0; 1)
N° hospitalisations due to ECOPD last year	0 (0; 0.5)	0 (0; 0)
N° ECOPD last year	1 (0; 1)	2 (1; 3)
Long-term oxygen therapy	2 (8.3%)	6 (23.1%)
Non-invasive ventilation	2 (8.3%)	5 (19.2%)
Charlson comorbidity index, total score	4.5 (4; 5)	4 (3; 5)
Comorbidities, n (%)		
Diabetes	5 (20.8%)	4 (15.4%)
Dyslipidaemia	12 (50%)	8 (30.8%)
Controlled arterial hypertension	15 (62.5%)	13 (50%)
Arrhythmia	4 (16.7%)	5 (19.2%)
Peripheral vascular disease	4 (16.7%)	5 (19.2%)
Heart failure	3 (12.5%)	1 (3.8%)
Other cardiovascular disease	7 (29.2%)	12 (46.2%)
Anxiety	2 (8.3%)	5 (19.2%)
Depression	2 (8.3%)	4 (15.4%)
Medication (stable), n (%)		
SABA	5 (20.8%)	6 (23.1%)
SAMA	4 (16.7%)	3 (11.5%)
LABA	2 (8.3%)	0 (0%)
LAMA	7 (29.2%)	3 (11.5%)
ICS	4 (16.7%)	3 (11.5%)
LABA+LAMA	10 (41.7%)	12 (46.2%)
Triple therapy	3 (12.5%)	7 (26.9%)
Medication (ECOPD), n (%)		
SABA	11 (45.8%)	16 (61.5%)

Continued

Table 1 Continued

	Experimental group (n=24)	Control group (n=26)
SAMA	10 (41.7%)	14 (53.8%)
Antibiotic	13 (54.2%)	16 (61.5%)
Oral corticosteroid	17 (70.8%)	19 (73.1%)
Mucolytic	7 (29.2%)	9 (34.6%)

Data are presented as mean±SD, median [first quartile; third quartile] or number (percentage), unless stated otherwise.
ECOPD, exacerbation of chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting beta2-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta2-agonist; SAMA, short-acting muscarinic antagonist.

of significance was set at 0.05. Data are presented as mean±SD, mean (95% CI), median (IQR) or number (percentage).

Qualitative data were analysed using deductive thematic analysis since there were preconceived themes expected to be found (ie, impact of the PR programme, opinions regarding the PR programme), which the research team wished to investigate while still maintaining flexibility to allow for generation of new themes.²⁴ The six-step procedure of Braun and Clarke was followed.²⁴ First, two

Table 2 Baseline characteristics (primary and secondary outcomes) of participants with an exacerbation of chronic obstructive pulmonary disease (n=50)

	Experimental group (n=24)	Control group (n=26)
BPAAT, total score	0 (0; 0)	0 (0; 0)
mMRC, grade	3 (2; 3)	2 (2; 3)
CAT, total score	23.1±7.1	23.2±7.1
LCADL, total score	23 (17.5; 39)	24.5 (19; 39)
LCADL, % score	45.2 (35.9; 57.3)	39.3 (31.4; 56)
FACIT-F, total score	30 (22; 34)	25 (21; 34)
CASA-Q, score		
Cough symptoms	37.8±28.8	47.4±29.3
Cough impact	44.5±23.1	52.3±29.5
Sputum symptoms	29.2 (8.3; 58.3)	29.2 (16.7; 66.7)
Sputum impact	56.4±29.8	52.1±30.5
CIS-8, total score	44.5 (39; 50.5)	46 (38; 52)
Handgrip strength, kg	23.3±10.1	25.2±10.5
Handgrip strength, %pred	71.1±27.2	79.3±25
Biceps muscle strength, kgf	15±4.3	16.9±5
Biceps muscle strength, %pred	65.2±17.1	81.4±20.3
Quadriceps muscle strength, kgf	22±6	23.4±7.3
Quadriceps muscle strength, %pred	67±15.7	72±22.4
5-repetitions sit-to-stand test, s	12.4 (11; 17.3)	11.3 (7.7; 17.1)
SPPB, total score	9 (7.5; 10)	9 (8; 11)
1 min sit-to-stand test, repetitions	17.3±6	17.9±9.4
1 min sit-to-stand test, %pred	50 (41.4; 66.2)	49.3 (35.3; 64)
Chester step test, n° of steps	14 (6.5; 31.5)	30 (16; 42)

Data are presented as mean±SD or median [first quartile; third quartile], unless stated otherwise.

BPAAT, Brief Physical Activity Assessment Tool; CASA-Q, Cough and Sputum Assessment Questionnaire; CAT, COPD Assessment Test; CIS-8, Checklist Individual Strength 8-Items Questionnaire; COPD, chronic obstructive pulmonary disease; FACIT-F, Functional Assessment of Chronic Illness Therapy—Fatigue Scale; LCADL, London Chest Activity of Daily Living Scale; mMRC, modified Medical Research Council dyspnoea questionnaire; SPPB, short physical performance battery.

Table 3 Effects of a 3-week home-based pulmonary rehabilitation programme during exacerbations of chronic obstructive pulmonary disease (n=50)

	Experimental group (n=24)	Control group (n=26)	Group×Time interaction
	Mean Δ (95% CI)	Mean Δ (95% CI)	
BPAAT, total score	3.5 (2.7; 4.3)*	−0.4 (−1.2; 0.3)	<0.001
mMRC, grade	−0.5 (−0.8; −0.3)*	0 (−0.3; 0.3)	0.006
CAT, total score	−12.5 (−15.4; −9.5)*	−5.8 (−8.7; −3)*	0.002
LCADL, total score	−5.4 (−8.1; −2.7)*	0.1 (−2.5; 2.7)	0.006
LCADL, % score	−9.1 (−13.1; −5.2)*	0 (−3.8; 3.9)	0.001
FACIT-F, total score	11.2 (8.3; 14.1)*	3.4 (0.6; 6.2)	0.001
CASA-Q, score			
Cough symptoms	46.7 (33.4; 60)*	23.1 (10.3; 35.9)*	0.006
Cough impact	43.8 (32.2; 55.4)*	23.7 (12.5; 34.8)*	0.047
Sputum symptoms	46.5 (32.3; 60.8)*	31.1 (17.4; 44.8)*	0.081
Sputum impact	36.6 (23.6; 49.5)*	28.7 (16.2; 41.1)*	0.948
CIS-8, total score	−11.8 (−15.8; −7.8)*	−4.3 (−8.2; −0.5)	0.003
Handgrip strength, kg	2.1 (0.9; 3.3)*	−0.5 (−1.8; 0.7)	0.003
Handgrip strength, %pred	6.9 (3; 10.7)*	−1.4 (−5.4; 2.6)	0.004
Biceps muscle strength, kgf	2.3 (1.1; 3.5)*	−0.1 (−1.2; 1.1)	0.004
Biceps muscle strength, %pred	10.4 (5; 15.8)*	−0.5 (−6.1; 5)	0.006
Quadriceps muscle strength, kgf	3.9 (2; 5.9)*	−0.4 (−1.7; 0.9)	<0.001
Quadriceps muscle strength, %pred	12.4 (6.5; 18.2)*	−1.3 (−5.3; 2.8)	<0.001
5-repetitions sit-to-stand test, s	−2.6 (−5.1; −0.2)*	−0.4 (−2.7; 1.8)	0.002
SPPB, total score	1.4 (0.8; 2)*	0.6 (−0.1; 1.2)	0.049
1 min sit-to-stand test, repetitions	4.4 (2.5; 6.3)*	2 (0.3; 3.8)	0.061
1 min sit-to-stand test, %pred	13.7 (7.8; 19.7)*	7.1 (0.8; 13.4)	0.086
Chester step test, n° of steps	23.4 (6.2; 40.5)*	11.6 (1; 22.3)*	0.047
N° ECOPD-related unscheduled healthcare visits (at Post)	0 (0; 0)	0 (0; 2)	0.025†

Data are presented as mean (95% CI), unless stated otherwise. Bold denotes a significant group×time interaction. Mean Δ, mean change post-baseline.
 *Significant time effect (baseline vs post).
 †P value from Mann-Whitney U test.

BPAAT, Brief Physical Activity Assessment Tool; CASA-Q, Cough and Sputum Assessment Questionnaire; CAT, COPD Assessment Test; CIS-8, Checklist Individual Strength 8-Items Questionnaire; ECOPD, exacerbation of chronic obstructive pulmonary disease; FACIT-F, Functional Assessment of Chronic Illness Therapy—Fatigue Scale; LCADL, London Chest Activity of Daily Living Scale; mMRC, modified Medical Research Council dyspnoea questionnaire; SPPB, short physical performance battery.

researchers (AM and CP) familiarised themselves with the data by reading and rereading the transcriptions before starting the coding process; independently organised units of text under each code, creating additional codes if new issues were identified and organised the codes in themes and subthemes by combining the codes with similar or related ideas. Then, the research team reviewed the data coded under each theme/subtheme, contributed to the appropriate naming and definition of the themes and produced the report. The initial themes and subthemes found independently were compared between researchers (AM and CP) and, in case of disagreement, consensus was reached by discussion. Analysis of the transcripts was conducted using the Web Qualitative Data Analysis (WebQDA, Oliveira de Azeméis, Portugal) software. Representative quotes were included to support the interpretation of the identified themes and subthemes.

Quantitative and qualitative data were first analysed separately, in a parallel process, and afterwards merged for integration of both methods in the final interpretation of the results, using a narrative integration with contiguous approach and integration through joint displays.

RESULTS

One-hundred and seventy-six people were referred for participation in the study. From these, 67 were randomised to either the EG or the CG and 50 participants with outpatient-managed ECOPD (78% men, 70±11 years, forced expiratory volume in one second 47.4±16.4% pred) were included in the analysis (figure 1). An inaccurate or unconfirmed diagnosis of COPD or ECOPD was found in 36 of the referred individuals.

Participants' baseline characteristics are summarised in tables 1 and 2. They all experienced a moderate ECOPD, according to GOLD classification.¹ Twenty-two participants in the EG completed the full PR programme (ie, 6/6 sessions, 100% adherence), 1 completed 5/6 sessions and 1 completed 4/6 sessions. No adverse events were reported. One participant in the EG did not perform the interview due to hearing difficulties.

Significantly greater improvements were found in the EG compared with the CG for the CAT (EG Δ −12.5 (−15.4; −9.5) vs CG Δ −5.8 (−8.7; −3), p=0.002) and all secondary outcome measures, besides the CASA-Q sputum scores and the 1-min-STS (table 3). After correcting the analysis for age, sex, BMI, smoking status and CCI total score, all differences remained significant (p<0.05) except for the CASA-Q scores, 1-minSTS %predicted and CST.

At postassessment, the EG presented significant improvements in all outcome measures, while the CG only improved on the CAT, CASA-Q and CST. During the study period, a smaller number of ECOPD-related unscheduled healthcare visits were observed in the EG (0 (0; 0)) compared with the CG (0 (0; 2)) (p=0.025).

From the qualitative interviews, three main themes were identified: impact of the PR programme, thoughts about the PR programme, and (lack of) motivation to continue the PR programme (table 4). The full list of themes, subthemes and interview quotations are found in online supplemental material.

Participants described an overall positive impact of the PR programme, with a specific positive impact on symptoms, control of daily life, health, mental status and empowerment:

I am more stable regarding my problems of breathing, shortness of breath, everything. I felt a difference in my symptoms for better, for better. For what I could not do, God forbid!

Feedback on the design and setting of the programme, the exercises and support materials used and the support received from healthcare professionals was also positive. Although most participants valued the home-based setting, one participant would appreciate a setting with more equipment available. Participants also mentioned the need for a longer PR programme. No suggestions of improvements for the PR programme were given. Education and breathing techniques were components highly valued by participants to support them in regaining control:

The main thing was to know the breathing techniques. If I would know that before, I would have done it long ago. There was no need of feeling as bad as I was feeling, right. That was a really important thing. (...) The breathing was the main thing. Now I do it, I do it. And with the acapella also and so. In the morning and at night. (...) This was the main thing, to have clean lungs.

Conflicting ideas concerning motivation to continue the PR programme emerged, with some participants feeling they are able to continue the programme alone, while others acknowledged the importance of continuing PR but do not feel able to do it by themselves:

Table 4 Qualitative themes and subthemes with supporting illustrative quotes of participants with an exacerbation of chronic obstructive pulmonary disease included in the experimental group, at the end of the 3-week home-based pulmonary rehabilitation programme

Theme	Subtheme	Illustrative quote
Impact of the PR programme	Overall impact	<i>I think everything improved. I feel better in everything (...) I can say, considering how I was, I can even say that I am almost at 100%. Comparing with how I was, how I was feeling lately... To my day-to-day, I am better, of course (...)</i>
	Symptoms relief	<i>I feel much, much better in comparison with the first day. I had a lot of cough, shortness of breath, and I felt really bad, I didn't feel well at all. I couldn't sleep. Now, at the end of the PR programme, I feel good, I am already able to do the exercises and I don't feel so tired, I am able to breathe much better. (...) I used to have more difficulties sleeping. There was also the cough, but now it is gone.</i>
	Regaining control of daily life	<i>I improved in all activities, in everything. (...) Before I couldn't walk much, now I can walk a lot. Now I am able to sweep the stairs up and down. And I know how to... yeah, I am now able to do a lot of things that I couldn't do before.</i>
	Health recovery	<i>I felt more stable. I felt with more... more, with a bit more health.</i>
	Overcoming isolation, stress and fears	<i>Therefore, the impact this programme have is that I feel more protected because I know what is going on with me and what I will need to do to not get worse. (...) The impact that it had I think it is more mental, more psychological, because I am better informed (...)</i>
	Feeling empowered	<i>Now I got clarified regarding the breathing control. I already have a self-control, minimum, but I already have it. I know that any effort I make, I can sit and control my breathing and it will relieve me faster.</i>
Thoughts about the PR programme	Design and setting	<i>For me everything was positive. (...) All the programme, it was adequate and positive. (...) Hmm, I think there is nothing to change (...) Everything I did was normal.</i>
	Exercises and support materials	<i>The leaflets are good. Everything was easy to understand, both from reading and from talking with you. The language was easy to understand. (...) The leaflets I think they are all very explicit in what we need to do.</i>
	Education and breathing techniques to regain control	<i>I think this is a good programme, that in fact everyone who has this health problem should do, because it teaches you, you learn a lot, how to deal with the disease, how to improve your physical condition, basic knowledge and really important for this type of disease, and I think that it was really good. (...) Because it taught me new information regarding exercise, and many other things, and it taught me a lot.</i>
	Need for a longer programme	<i>Ah if I could have the programme during more time it would be better. I would do more sessions because it is for my own good. Because when someone sees that it is for our own good, we ask for more.</i>
	Support from health professionals	<i>Having a physiotherapist taking care of us, at least one or two times per week, I think it is really good for us.</i>
(Lack of) Motivation to continue the PR programme	I can do it alone	<i>To do the exercises at home alone it is really easy! Easy. I do it really easily. I already did some exercises. And I am going to continue doing them. It is for my own good. I have to continue doing them.</i>
	I can't do it alone	<i>If I am here alone, I can't do anything. (...) To exercise alone is nothing, nothing. I lack the will to do it. If someone is motivating you, then you will do it.</i>

PR, pulmonary rehabilitation.

It was important to keep doing it to feel the difference in my conditioning. To feel the difference in my conditioning, to see if I would decide to start moving alone, walk around outside. But I am not seeing it happen. (...) I just lack the will. I lack the will.

The integration of the quantitative and qualitative results through a joint display is shown in figure 2. Findings from both types of data are confirmatory of each other, that is, positive short-term effects of the PR programme on physical activity, symptoms, activities of daily living, functional capacity and health status, and a positive self-perceived impact in the same domains.

DISCUSSION

This study showed that a 3-week home-based PR programme in people with outpatient-managed ECOPD is safe and more effective than pharmacological treatment alone in reducing impact of the disease, improving symptoms, physical activity levels and functional capacity and reducing ECOPD-related unscheduled healthcare utilisation. Moreover, a positive self-perceived impact of PR was found on symptoms, control of daily life, health, mental status and empowerment.

In line with previous literature,^{2 25} individuals receiving just pharmacological treatment presented some recovery, however this was limited to the CAT, CASA-Q and CST. It is known that ECOPD are heterogeneous events in terms of presentation and trajectory of recovery, with different parameters taking different times to recover and often persistent impairments being sustained.^{2 26 27} Hence, pharmacological treatment is likely insufficient for individuals to achieve (full) recovery.

High impact of the disease measured with the CAT has been linked to hospital readmission, ECOPD recurrence and mortality

up to 6 months after hospitalisation for ECOPD, hence, poor prognosis.²⁸ Moreover, an association between change in the CAT score and change in systemic inflammation following ECOPD has been shown,²⁹ with low levels of recovery in the CAT (≤ 4 points) being associated with treatment failure.³⁰ In this study, PR resulted in a good level of improvement in the CAT, which was two times superior to the improvement obtained with pharmacological treatment alone and exceeded the available MCID13 by four to sixfold. This result emphasises the important role of PR in the recovery process of people with outpatient-managed ECOPD, potentially contributing to a better prognosis in these individuals.

Significant improvements after PR were also found in symptoms, physical activity levels and functional capacity, always at least twofold greater than the CG. In fact, the 3-week home-based PR programme led to improvements similar or up to sixfold superior to the available MCID for 6–12-week PR in stable COPD.^{31–33} These improvements are particularly important due to the known relationship between worse symptoms, physical activity and functional capacity with higher risk of ECOPD, hospitalisations and mortality.^{34 35} Nevertheless, the short programme duration and lack of follow-up assessments hinder the possibility of exploring potential long-term effects of PR on these outcomes. Phone call follow-ups are being conducted to assess any potential role of PR in the prognosis of these individuals.

People with outpatient-managed ECOPD have mentioned symptoms as their main concern during ECOPD and, thus, symptom relief as one of their main needs.⁵ Limitations in activities of daily living and negative psychological, emotional, social and physiological impacts have also been reported, along with the need to be able to walk.⁵ By leading to a positive self-perceived impact on symptoms, activities of daily living, functional capacity

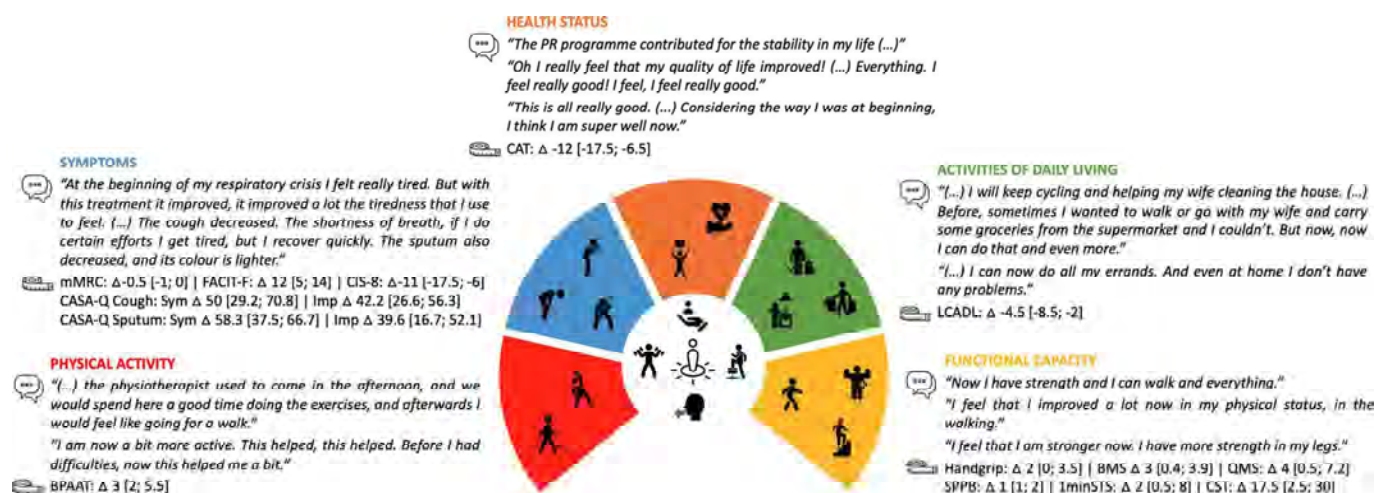


Figure 2 Joint display presenting the integration of quantitative and qualitative data. Data are presented as median change [first quartile; third quartile] and represent the results obtained in the experimental group. 1-minSTS, 1 min sit-to-stand test; BMS, biceps muscle strength; BPAAT, Brief Physical Activity Assessment Tool; CASA-Q, Cough and Sputum Assessment Questionnaire; CAT, COPD Assessment Test; CIS-8, Checklist Individual Strength 8-Items Questionnaire; CST, Chester Step Test; FACIT-F, Functional Assessment of Chronic Illness Therapy—Fatigue Scale; Imp, impact subscore; LCADL, London Chest Activity of Daily Living Scale; mMRC, modified Medical Research Council dyspnoea questionnaire; PR, pulmonary rehabilitation; QMS, quadriceps muscle strength; SPPB, short physical performance battery; Sym, symptoms subscore.

city, mental and health status, this home-based PR programme was able to target the main needs of these individuals, showing that PR is not only safe but also meaningful for people with outpatient-managed ECOPD.

Participants mentioned the need for a longer PR programme and, despite the positive impact found on empowerment, not all individuals felt able to continue the PR programme alone after its completion. This home-based PR programme might, therefore, be seen as a rapid access programme to provide a bridge between the exacerbation period and the enrolment in a conventional stable PR programme.³⁶ In fact, these individuals are likely to be good candidates for referral to conventional PR as some of the commonly reported barriers to adherence (eg, lack of perceived benefits, comorbidities and disabilities, perception of being too unwell to do it)³⁷ are already overcome. Primary care centres were mentioned as a potential setting to continue PR due to their proximity to people's homes.

Finally, participants highlighted the importance of education and breathing techniques to help them regaining control of daily life, reinforcing previous findings that PR programmes for people with ECOPD should include exercise training, breathing techniques and education and psychosocial support.⁴⁵

Methodological considerations

This study has some strengths and limitations that need to be acknowledged. First, to our knowledge, this is the first randomised controlled trial exploring the role of PR in the recovery process of people being actively managed as outpatients for ECOPD. A major strength of this study is its mixed-methods design. Using both quantitative and qualitative data allowed a more comprehensive understanding of the role of PR, while maximising the strengths and minimising the weaknesses of each type of data. Moreover, findings from both types of data were confirmatory of each other, which increased results' credibility. The most well-established guidelines to report quantitative (CONSORT), qualitative (COREQ) and mixed-methods studies (GRAMMS) and exercise interventions (CERT) were followed. The PR programme was delivered always by the same two physiotherapists (AM and CD) and followed a structured and detailed intervention protocol (online supplemental material), which ensured consistency and reproducibility among participants. The nature of the intervention makes it impossible to blind participants and those delivering PR, hence, psychological and placebo effects cannot be excluded and are not possible to quantify. Nevertheless, PR led to considerable improvements in all outcome measures, always superior to the CG, thus it

is likely that a true physiological effect contributed to the observed improvements. Moreover, similar benefits with short interventions have been found in hospitalised patients with ECOPD³⁸ and critically ill patients with COPD in intensive care.³⁹ Another limitation is the lack of blinding of assessors, which may introduce bias to the results. Nevertheless, patient-reported outcomes were completed by the participants themselves, without direct input from the assessors, and the measures of functional capacity followed standardised protocols that do not place subjective requirements on the assessor. The interviews were mostly conducted by the treating physiotherapist, which might also introduce bias; however, a semistructured interview guide with open-ended questions was used to ensure that the topics were covered in a consistent manner, without inducing predefined responses. Our population was mostly composed by men which might limit the generalisation of our findings to all people with COPD, especially women. Additionally, our sample includes a low percentage of individuals from GOLD grade 4 and on long-term oxygen therapy or non-invasive ventilation, hence it is uncertain whether the benefits of this short-term PR programme would be as substantial in individuals with more severe disease. Finally, the interviews were conducted in Portuguese, thus, the translation process might have influenced the findings, particularly regarding the use of colloquial expressions or proverbs. We believe to have minimised this limitation by having a bilingual speaker revising the main themes, quotes and conclusions.

Implications for future practice and research

Our study provides a significant contribution for healthcare professionals to improve the care of people with outpatient-managed ECOPD, with a safe and patient-meaningful intervention. We envision the broad implementation of our PR programme by real-world primary care healthcare professionals, both in primary care centres and individuals' homes (depending on individual needs and barriers to participation in PR), to further explore the evidence of PR in people with outpatient-managed ECOPD and increase access and awareness to this key intervention. Although primary care has been recognised as the most inclusive, equitable and cost-effective setting by the WHO,⁴⁰ and the PR protocol developed is possible to be used even in low resources, some implementation challenges are expected in different health systems. First, the establishment of a direct PR referral pathway from both the emergency department and primary care providers is recommended, which requires training and increased awareness for PR among these physicians, and might require the reconfiguration of

the health system. The broad implementation of PR can impose some challenges in sites with limited or less experienced staff, resulting in access disparities and the need of hiring and/or training more healthcare professionals. Lack or limited insurance coverage can also be problematic in some health systems, hence new specific reimbursement policies might be required. Further adequately designed multicentric pragmatic randomised controlled trials are needed to build up the evidence of PR in people with outpatient-managed ECOPD, and implementation trials and a cost-effectiveness analysis are warranted. These could strengthen the work with policymakers and other relevant stakeholders to advocate for integration and coverage of PR in this context.

Moreover, by improving the recovery process of people with outpatient-managed ECOPD, PR showed potential to contribute to a better prognosis in these individuals. Longitudinal studies exploring the mid-term and long-term effects of PR in people with outpatient-managed ECOPD are now needed. Approximately 20% of the individuals referred to this study had an inaccurate diagnosis of COPD/ECOPD, thus, the diagnostic criteria for COPD/ECOPD must be implemented with more rigour. Finally, the benefits obtained with this PR programme could only be compared with MCID established for PR in stable COPD. Specific MCID for PR in ECOPD are needed to better understand the clinical significance of these findings.

CONCLUSIONS

A 3-week home-based PR programme in people with outpatient-managed ECOPD is safe, more effective than just pharmacological treatment, and results in positive short-term effects and self-perceived impact on symptoms, physical activity, activities of daily living, functional capacity and health status, outcomes often associated with poor prognosis. This highlights the role of PR in improving the recovery process during outpatient-managed ECOPD and, in turn, in potentially contributing to a better prognosis in these individuals. A longitudinal study, exploring the mid-term and long-term effects of this PR programme, is being conducted to verify this hypothesis.

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Competing interests None declared.

Patient consent for publication Not applicable.

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Disponibilidade, custo e acessibilidade de medicamentos essenciais para a cessação do tabagismo em países de baixo e médio rendimento: um estudo transversal

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RESUMO

A cessação do tabagismo é mais eficaz quando apoiada por medicamentos. Os dados sobre a disponibilidade, custo e acessibilidade desses tratamentos em países de baixo e médio rendimento (LMIC) são limitados. Foram recolhidos dados transversais sobre medicamentos para cessação do tabagismo em farmácias, unidades de saúde e armazéns centrais de medicamentos em 60 LMIC (2022–2023). Os medicamentos apresentaram disponibilidade variável, grandes variações de preço e foram essencialmente inacessíveis. Garantir o acesso a esses medicamentos é fundamental para reduzir o consumo de tabaco e as doenças associadas. São necessárias estratégias para integrar os serviços de cessação do tabagismo nos sistemas de saúde, a fim de alcançar as metas dos Objetivos de Desenvolvimento Sustentável.

INTRODUCTION

The WHO Sustainable Development Goals (SDG) target a reduction in tobacco consumption by 30% by 2025, as part of the strategy to reduce premature deaths from non-communicable disease by a third by 2030.¹ The WHO MPOWER measures outline ways to reduce tobacco consumption, including ‘offering help to quit’.² Over 80% of tobacco smokers live in low-income and middle-income countries (LMIC),³ and smoking cessation medications should be accessible and affordable to all.⁴

Smoking cessation medications including nicotine gums, transdermal patches, bupropion and varenicline tablets have been on the WHO ‘Model List of Essential Medicines’ (EML) since 2009, based on their efficacy, cost-effectiveness and safety.⁵ Evidence on the availability, cost and affordability of these treatments in LMIC is limited. This study provides high-quality data describing the current accessibility of these medications in LMIC.

METHODS

Healthcare professionals in LMIC completed a survey on the availability and cost of smoking cessation medications from three facility types: a pharmacy, healthcare facility (HCF) and central medicine store (CMS, online supplemental appendix). Collaborators were recruited through professional networks and snowballing. Supply for 1 month’s treatment was based on average cigarette consumption of 10/day.⁶ Prices for 1 month’s treatment were compared. A medicine was considered affordable if 1 month’s treatment cost less than 1 day’s wage of the lowest paid government worker, defined by local minimum wage.⁷ Global varenicline supply was interrupted in 2021, so it was not explored in this study.⁸ This survey was nested in the Thorax-published study on the accessibility of chronic respiratory disease medicines (online supplemental appendix).⁹

RESULTS

Data were reported from 60 countries, representing 84% of the global LMIC population. Information from pharmacies, HCFs and CMSs was available from 57, 56 and 46 countries, respectively. Most pharmacies were private (51/60), and more HCFs were public (45/60). There were 18 low-income (LIC), 24 low-middle-income, 17 upper-middle-income (UMIC) countries; Venezuela was unclassified (online supplemental appendix). Africa was the best-represented region with 26/60 countries.

Nicotine gum

Nicotine gum was available in 20/57 pharmacies, 5/56 HCFs and 4/46 CMSs. Doses ranged from 2 to 4 mg (table 1, figure 1, online supplemental appendix). Price was provided by 19/20 pharmacies, 5/5 HCFs and 2/4 CMSs. The median (IQR) cost was US\$96 (US\$65.13–123.98), US\$61.94 (US\$55.88–89.05) and US\$65.72 (US\$11.44–120.00) in pharmacies, HCFs and CMSs, respectively. It was unaffordable from all facilities that provided price information (figure 1, online supplemental appendix).

Nicotine patch

Nicotine transdermal patches were available in 13/57 pharmacies, 6/56 HCFs and 5/46 CMSs (table 1, online supplemental appendix). Doses ranged from 1 to 21 mg. Price was provided by 13 pharmacies, five HCFs and three CMSs. The median (IQR) cost was US\$62.09 (US\$51.54–100.90), US\$68.61 (US\$43.80–307.31) and US\$43.72 (US\$12.00–124.29) in pharmacies, HCFs and CMSs, respectively. It was affordable in one pharmacy (China) (figure 1, online supplemental appendix).

Bupropion tablets

Bupropion 150 mg tablets were available in 2/57 pharmacies, 2/56 HCFs and 2/46 CMSs. Two pharmacies and two HCFs gave price information. The median (IQR) cost of tablets was US\$143.89 (US\$–151.15) and US\$25.10 (US\$24.26–25.94) in pharmacies and HCFs, respectively. Bupropion was unaffordable from all facilities that provided price information (table 1, figure 1, online supplemental appendix).

DISCUSSION

This survey provides up-to-date, high-quality data on the availability, cost and affordability of smoking cessation medications globally and is the largest cross-sectional study on this topic in LMIC to date. Data came from a variety of income levels and 16 out of 20 of the most populous LMIC.

WHO EML medications for smoking cessation were not widely available and were largely unaf-

Table 1 Comparisons of availability, cost and affordability of WHO EML medicines for smoking cessation in LMIC

Smoking cessation medications				
Facility	Survey measurement	Nicotine gum (2 mg, 4 mg)	Nicotine transdermal patch (15–30 mg/16 hours; 7–21 mg/24 hours)	Bupropion tablets (150 mg)
Pharmacy	Availability	20/57	13/57	2/57
	Median cost (IQR, US\$)	96 (65.13–123.98)	62.09 (51.54–100.90)	143.89 (129.38–158.40)*
	Median DOW (IQR)	10.35 (5.74–51.07)	5.84 (3.16–40.03)	31.76 (6.37–57.16)*
HCF	Availability	5/56	6/56	2/56
	Median cost (IQR, US\$)	61.94 (55.88–89.05)	68.61 (43.80–307.31)	25.10 (23.42–26.78)*
	Median DOW (IQR)	3.81 (3.26–7.70)	27.78 (3.01–60.53)	1.38 (1.32–1.43)*
CMS	Availability	4/46	5/46	1/46
	Median cost (IQR, US\$)	65.72 (11.44–120.00)	43.72 (12.00–124.29)	NIA

Cost: Supply for one month's treatment was guided by average daily cigarette consumption in LMIC of 10 cigarettes/day. One month's supply of nicotine gums was 10 gums/day, 30 transdermal patches (1 patch/day) and for bupropion 60 tablets/month based on average maintenance dose. Affordability was not calculated for CMSs as their prices were wholesale prices.

*IQR could not be calculated due to missing information on price so results given as median (minimum-maximum).

CMS, central medicine store; DOW, days of work required to pay for 1 month's treatment; HCF, healthcare facility; LMIC, low-income and middle-income countries; NIA, no information available.

fordable for those living in LMIC. The most available form was nicotine gum, and the least available was bupropion. All pharmacotherapies were more available in UMIC (online supplemental appendix, table 2). Our data showed wide variability in price. Medicines were more available in pharmacies but more expensive (table 1), which is likely to be an accessibility barrier.

Table 2 Availability of WHO EML medications for smoking cessation by World Bank country income level

Medication	Availability	Low-income country (n=18)	Low-middle-income country (n=24)	Upper-middle-income country (n=17)
Nicotine gum (2 mg, 4 mg)	Pharmacy	5	5	10
	HCF	0	1	4
	CMS	0	1	3
Nicotine transdermal patch (15–30 mg/16 hours; 7–21 mg/24 hours)	Pharmacy	3	2	8
	HCF	0	3	4
	CMS	0	2	3
Bupropion tablets (150 mg)	Pharmacy	0	1	1
	HCF	0	0	2
	CMS	0	0	2

Pharmacies n=57 LMIC, HCF n=56 LMIC, CMS n=46 LMIC. Venezuela was not classified.

CMS, central medicine store; HCF, healthcare facility; LMIC, low-income and middle-income countries.

Results showed that these medications were mostly unaffordable, especially as treatment typically lasts at least 3 months. From our data, the median cost for 1 month of cigarettes is US\$12.27(IQR US\$7.71–21.23) (online supplemental appendix), cheaper than the cost of any medication to support smoking cessation (table 1). The latest WHO report suggests that LMIC needs to raise taxes and prices of cigarettes.¹⁰ Our data show the importance of coordinated implementation of the MPOWER measures as 'offering to help quit' is economically undermined if cigarettes remain more affordable than treatment.

The strengths of the study were the wide range of included LMIC and the actual determination of availability and cost by health professionals. There were some limitations including sampling bias towards urban, large centres. Participants were asked to enter the cheapest price of gum, patch and tablet per facility, so there could be more price variety and higher median costs. Information on

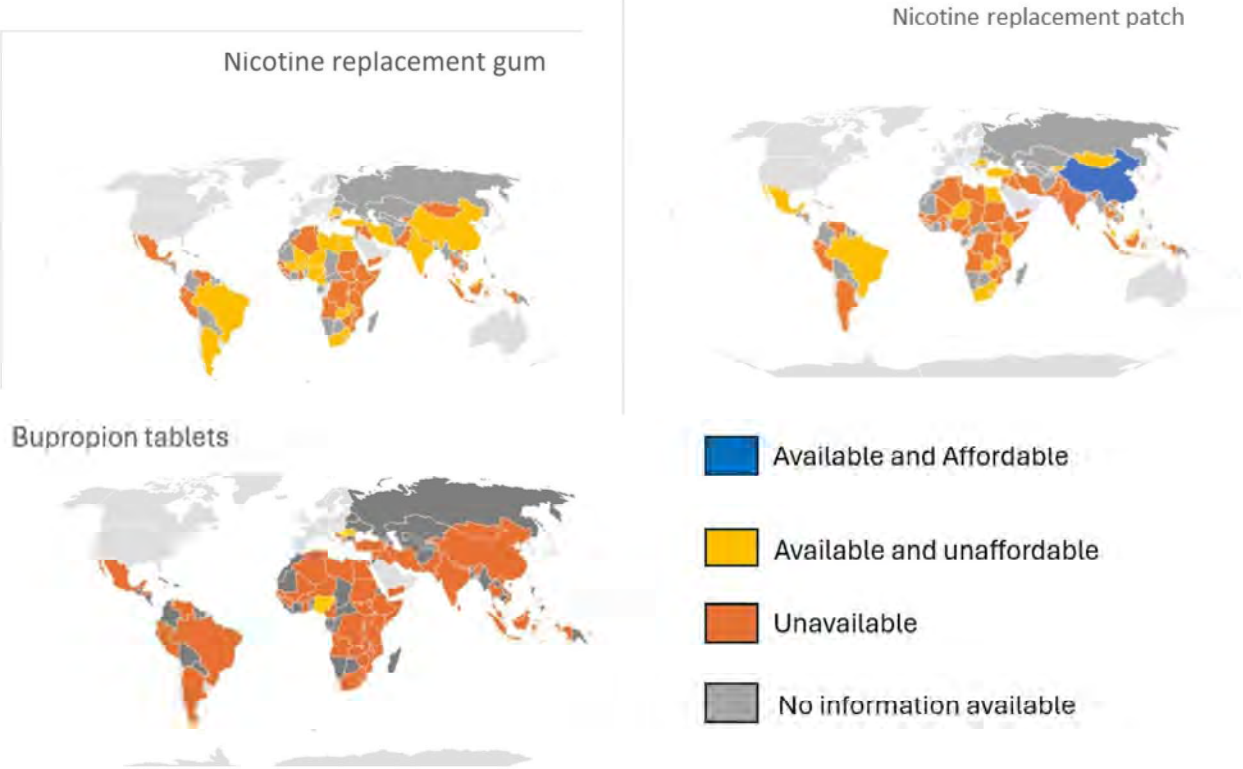


Figure 1 Availability and affordability of nicotine gum, nicotine patches and bupropion by region.

prices of tablets from HCFs and CMSs was limited and some facilities had missing data. Since data collection, there has been an update to the WHO EML in July 2023, which now includes other forms of nicotine replacement therapy; lozenges and oral spray.

CONCLUSION

Everyone globally should have the best support in stopping smoking, but without medications chances of successful smoking cessation are reduced. Our data can be used to inform smoking cessation programmes in LMIC, and combining this with other strategies will be key in achieving the greatest success for the individuals, as well as global targets in disease reduction.

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Papel dos corticosteroides orais no tratamento da sibilância aguda em crianças em idade pré-escolar

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No Reino Unido (UK), a sibilância pré-escolar é geralmente definida como ocorrendo em crianças entre 1 e 5 anos de idade. Estudos de prevalência indicam que um terço das crianças experimenta pelo menos um episódio de sibilância antes dos 3 anos, aumentando para metade de todas as crianças aos 6 anos.¹ Esses episódios agudos representam um grande impacto na saúde pública, causando morbidade significativa, estresse parental e redução da produtividade, com custos anuais de saúde no Reino Unido superiores a £53 milhões.^{2,3}

A natureza multifatorial da sibilância pré-escolar aguda (APSW) faz com que, na realidade, seja um termo abrangente, englobando vários fenótipos em vez de uma entidade única.¹ Em 2008, a Força-Tarefa da Sociedade Respiratória Europeia recomendou a classificação dos fenótipos clínicos em sibilância viral episódica (EVW) ou sibilância de múltiplos gatilhos (MTW).⁴ A EVW é mais comum, geralmente associada a infecções respiratórias virais e sintomas mínimos entre episódios,⁴ enquanto crianças com MTW são mais frequentemente atópicas, podem ter histórico familiar de asma, apresentam sintomas entre episódios e têm maior probabilidade de desenvolver asma.⁵ No entanto, há debate significativo sobre a utilidade dessa terminologia, pois a classificação não leva em conta a gravidade ou frequência da sibilância, e muitas crianças apresentam sobreposição fenotípica.⁵⁻⁷ Além disso, há evidências limitadas de que esses fenótipos preveem padrões de sibilância a longo prazo ou resposta terapêutica.⁷

Abordagens de tratamento As estratégias de gestão da APSW não são específicas para fenótipos e muitas vezes são extrapoladas de algoritmos desenvolvidos para crianças mais velhas com asma.^{8,9} As diretrizes do *National Institute for Health and Care Excellence* (NICE), bem como as diretrizes conjuntas da *British Thoracic Society* e da *Scottish Intercollegiate Guidelines Network*, abordam a gestão da asma aguda e da sibilância em crianças.^{8,9} Em crianças com sintomas graves que requerem hospitalização, os corticosteroides orais (OCS) são recomendados como parte da escalada do

cuidado.⁹ No entanto, em crianças pré-escolares com sibilância leve a moderada, as diretrizes atuais não são claras quanto à prescrição de OCS. As diretrizes do Reino Unido sugerem que os OCS devem ser considerados em casos de diagnóstico existente ou suspeito de asma subjacente, mas recomendam cautela em crianças mais novas que não se enquadram nessa categoria.⁸

Determinar se uma criança pré-escolar tem asma subjacente é extremamente difícil no contexto agudo, pois não há uma definição universalmente aceita ou teste diagnóstico para asma, e o diagnóstico depende fortemente do histórico clínico e da resposta a um tratamento preventivo experimental.¹⁰ Além disso, crianças mais novas com APSW são difíceis de distinguir daquelas com bronquiolite. Embora a bronquiolite seja mais comum entre 3 e 6 meses de idade, as diretrizes do NICE incluem lactentes até 2 anos.¹¹ As evidências atuais, incluindo uma meta-análise de Cochrane, não apoiam o benefício clínico dos OCS na gestão da bronquiolite por vírus sincicial respiratório (RSV).^{11,12} No entanto, evidências emergentes sugerem heterogeneidade dentro da bronquiolite, e pode haver fenótipos responsivos a corticosteroides.

Uso de OCS na APSW Dadas essas dificuldades, o uso de OCS na APSW continua sendo um tema de debate, com variação significativa na prática clínica entre os departamentos de emergência pediátrica do Reino Unido.

Ensaio clínico randomizados (RCTs) que examinaram o impacto dos OCS na APSW produziram resultados conflitantes. Uma meta-análise de 2016, que incluiu 11 estudos sobre APSW, não demonstrou eficácia geral dos OCS em comparação com placebo na redução de hospitalizações, necessidade de corticosteroides sistêmicos adicionais, duração da hospitalização ou atendimentos não programados no serviço de emergência (razão de risco: 0,73; IC 95% 0,35 a 1,52).¹³ No entanto, foi observada heterogeneidade significativa entre os estudos, e uma análise estratificada para o ambiente de emergência encontrou que crianças que receberam OCS tiveram menor risco de hospitalização e menor necessidade de corticosteroides sistêmicos adicionais.¹³ Os autores concluíram que mais estudos são necessários.

O maior ensaio clínico randomizado (RCT) incluído na meta-análise de 2016, conduzido por Panickar *et al*, não encontrou diferença significativa entre corticosteroides orais (OCS) com prednisolona por 5 dias e placebo no desfecho primário de duração

da hospitalização (13,9 horas vs. 11,0 horas) ou nos desfechos secundários (pontuação PRAM aos 4, 12 e 24 horas, uso de salbutamol e pontuação de sintomas aos 7 dias) em crianças de 10 meses a 6 anos com sibilância leve a moderada.¹⁴

As principais críticas a este estudo incluem um possível “efeito teto”, ou seja, um grande número de crianças incluídas apresentava sintomas leves (pontuação PRAM média de 4,3 em 12), tornando menos provável que mostrassem benefício do tratamento. Além disso, uma proporção substancial dos participantes tinha menos de 2 anos (idade média de 26 meses), o que pode refletir a inclusão de um maior número de crianças com bronquiolite por vírus sincicial respiratório (RSV), a causa mais comum de infecção do trato respiratório inferior (LRTI) em crianças menores de 2 anos.

Dois outros grandes RCTs sobre o uso de OCS na APSW foram publicados posteriormente. O estudo de Foster *et al* incluiu 605 crianças australianas de 24 a 72 meses com APSW e demonstrou uma redução significativa na mediana da duração da hospitalização (diferença de 170 minutos) em crianças que receberam prednisolona (1 mg/kg/dia por 3 dias) *versus* placebo.¹⁵ Em claro contraste com Panickar *et al*, crianças menores de 2 anos foram excluídas, e uma proporção maior de crianças apresentou sibilância moderada a grave. Com uma idade média de 41 meses, esta população estudada representa melhor a faixa etária pré-escolar, em vez de um grupo predominantemente afetado por bronquiolite.

O estudo foi criticado por uma mudança *pós-hoc* no plano de análise, de não inferioridade para superioridade, bem como pela alteração do desfecho primário, de duração da estadia no serviço de emergência (ED) e duração total da hospitalização, para um desfecho combinado de duração total da hospitalização.¹⁶ No entanto, os autores refutaram essas críticas, destacando que a duração total da hospitalização foi pré-especificada como um dos dois desfechos primários, e que todas as análises estatísticas foram realizadas antes da revelação dos dados.¹⁷

Mais recentemente, Wallace *et al* conduziram um RCT em 477 crianças da Nova Zelândia, com idades entre 24 e 59 meses, com APSW. Este estudo negativo não conseguiu demonstrar um desfecho primário estatisticamente significativo entre prednisolona (2 mg/kg/dia por 3 dias) e placebo na alteração da pontuação de sintomas respiratórios (PRAM) em 24 horas (diferença média -0,39, IC 95% -0,84 a 0,06, $p=0,09$).³ Além disso, não houve diferença entre os grupos em relação ao tempo necessário para retomar atividades habituais ou às taxas de retorno ao hospital dentro de 7 dias.³

No entanto, foram observadas melhorias significativas em vários desfechos secundários, incluindo pontuação PRAM absoluta mais baixa aos 4 e 24 horas (ambos $p=0,01$) no grupo prednisolona. São necessários mais estudos para validar prospectivamente

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esses desfechos secundários e determinar se existem subgrupos que possam beneficiar dos OCS.³

Resultados variáveis dos RCTs disponíveis Os resultados variáveis dos ensaios clínicos randomizados (RCTs) provavelmente refletem diferenças no desenho dos estudos, particularmente idade dos participantes, gravidade da doença, medidas de desfecho primário e definição dos fenótipos de APSW. As intervenções estudadas também variaram consideravelmente, incluindo diferentes medicamentos esteroides, doses e durações de tratamento, refletindo a variação na prescrição de esteroides na prática clínica. De fato, estabelecer medidas padronizadas de desfecho tem sido um desafio, com os RCTs mencionados estudando diferentes desfechos primários.^{3,14,15}

Além disso, estabelecer consenso sobre um desfecho clinicamente relevante é debatido e varia entre médicos, crianças e seus cuidadores.¹⁸ Se a redução da duração da hospitalização (LOS) for considerada um desfecho prioritário, quanto de redução justifica a prescrição de OCS ainda não está claro. Notavelmente, Panickar *et al* relataram negativamente uma estadia 16% mais curta (114 min) no grupo OCS, semelhante à redução de 18% (170 min) relatada positivamente no grupo OCS de Foster *et al*. Uma revisão sistemática recentemente publicada também buscou avaliar a eficácia dos OCS para APSW por meio de uma meta-análise de dados individuais dos participantes.¹⁹ A análise de dados de quatro estudos (1360 doentes) demonstrou que a duração da hospitalização foi significativamente reduzida no grupo OCS (diferença média de 3,1 horas na sibilância moderada a grave e 2,23 horas na sibilância leve).¹⁹ As opiniões sobre se uma redução de 3,1 horas na hospitalização é suficientemente benéfica para compensar os possíveis efeitos colaterais dos OCS variam. Alguns podem considerar essa duração uma troca inadequada, enquanto outros, como médicos de emergência, podem considerá-la uma redução valiosa e importante. São necessários mais estudos para avaliar as opiniões de cuidadores e médicos sobre essa questão.

O papel da etiologia viral na APSW na literatura, sugere que um subgrupo de APSW pode se beneficiar dos OCS. Há evidências emergentes de que a etiologia viral pode desempenhar um papel importante na identificação desse subgrupo. As estimativas da etiologia viral na APSW variam amplamente, de aproximadamente 30% a 90%, e uma revisão sistemática recente identificou os vírus mais frequentemente implicados como rinovírus (RV) (35,6%) e vírus sincicial respiratório (RSV) (31,0%).²⁰ O RV é a causa mais comum de sibilância em crianças e, comparado a outros vírus, está mais frequentemente associado a episódios recor-

rentes de sibilância suficientemente graves para necessitar de atendimento hospitalar.² A infecção por RSV, além de sua associação com bronquiolite, está sendo cada vez mais reconhecida como uma causa significativa de infecção respiratória aguda (LRTI) em crianças pré-escolares mais velhas, com 33 milhões de LRTIs associadas ao RSV globalmente em crianças menores de 5 anos em 2019.¹²

Até o momento, a maioria dos RCTs sobre OCS na APSW não realizou testes de vírus respiratórios, dificultando a avaliação do impacto da etiologia viral na eficácia dos OCS. Como mencionado anteriormente, a inclusão de crianças menores de 24 meses é uma limitação chave do RCT de Panickar *et al*, dado que a bronquiolite induzida por RSV, a causa mais comum de LRTI em menores de 2 anos, não responde à terapia com OCS. Foster *et al*, que relataram benefícios com OCS, descreveram testes virais em 531 participantes do estudo, dos quais 65% tinham pelo menos um vírus detectado.²¹ A análise de subgrupos por tipo de vírus demonstrou tendências de melhora no desfecho primário para prednisolona versus placebo na etiologia viral não-RSV, mas o estudo não teve poder estatístico suficiente para demonstrar significância.

Infecção bacteriana e coinfeção também podem desempenhar um papel importante. Isso foi avaliado por meio de amostras de lavagem broncoalveolar eletiva em crianças pré-escolares entre episódios de sibilância aguda, mas mais pesquisas são necessárias para avaliar o papel da infecção bacteriana no contexto agudo.

Conclusão, até o momento, os RCTs falharam em fornecer evidências robustas para esclarecer a prática clínica. São necessários ensaios clínicos que avaliem o uso de OCS em fenótipos específicos de sibilância (que se espera que respondam) e APSW causada pelos dois vírus desencadeantes mais comuns (RSV e RV) para compreender melhor essa questão complexa. Isso pode exigir processos inovadores para caracterizar rapidamente os fenótipos de APSW no contexto de emergência, a fim de superar a abordagem “tamanho único”. O uso de testes adicionais, como testes rápidos de patógenos respiratórios virais/bacterianos, testes rápidos de eosinofilia (sangue ou nasal), fração de óxido nítrico exalado e breath-omics, merece consideração em trabalhos futuros. No entanto, essas ferramentas ainda não foram validadas para avaliação da APSW no contexto agudo, e muitas provavelmente serão impraticáveis para implementação em um ambiente de emergência movimentado.

Dado o impacto substancial da APSW e os potenciais efeitos negativos dos OCS na saúde infantil, mais esclarecimentos são urgentemente necessários.

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Cigarros eletrônicos: quem sabe melhor, a OMS?

Ross John Langley,¹ Elif Dagli,² Andrew Bush³

Todos estão familiarizados com os efeitos devastadores do tabagismo, que afetam especialmente as famílias de baixa renda. No século XX, a indústria global do tabaco utilizou diversas táticas de marketing, muitas vezes direcionadas a grupos específicos, incluindo crianças e jovens (CYP). Essas estratégias incluíram publicidade estratégica na mídia, patrocínios (incluindo grandes eventos desportivos) e colocação de produtos em filmes. Vergonhosamente, médicos também participaram dessas campanhas publicitárias. Regulamentações sobre publicidade, tributação, restrições ao uso público e mudanças na opinião social reduziram significativamente o uso do tabaco e melhoraram os resultados de saúde.

No entanto, a indústria do tabaco contra-atacou com os cigarros eletrônicos. Especialmente em Inglaterra, alega-se repetidamente que esses dispositivos são a chave para acabar com a dependência do tabaco e que são 95% mais seguros do que os cigarros tradicionais. Embora haja espaço para a redução de danos, os cigarros eletrônicos são realmente a solução? A Sociedade Respiratória Europeia (ERS) rejeita firmemente essa ideia.¹ Além disso, a redução de danos deve abranger toda a comunidade, não apenas os fumadores. Crianças e jovens estão cada vez mais vulneráveis devido às estratégias de marketing² atuais. Preocupantemente, um em cada seis vapores confiscados de crianças em idade escolar contém a droga Spice. Sem dúvida, a indústria do tabaco alegaria que não tem responsabilidade, mas não pode escapar às consequências de seus dispositivos chegarem às mãos das crianças.

Surpreendentemente, o *Royal College of Physicians* publicou um documento sobre redução de danos sem envolver pediatras respiratórios.³ Este artigo destaca o comportamento enganoso recente da indústria do tabaco, estudos emergentes que levantam preocupações sobre segurança, novas diretrizes da OMS e da ERS, e a nova legislação proposta no Reino Unido. Uma investigação recente⁴ revelou que as estratégias de marketing e os conselhos de segurança foram influenciados pela mesma indústria que criou o manual de marketing do tabaco no século passado. Fabricantes de tabaco financiaram pesquisas que minimizam os riscos do *vaping* entre jovens, posteriormente citadas como evidência em consul-

tas governamentais. Eventos de cessação do tabagismo *pró-vaping* (onde cessação do tabagismo significa trocar para cigarros eletrônicos, não abstinência de nicotina!) foram financiados pela indústria do tabaco e frequentados por médicos britânicos.⁵

O fabricante de cigarros eletrônicos JUUL pagou quase meio bilhão de dólares para resolver processos de vários estados dos EUA sobre publicidade ilegal direcionada a menores. Os fantoches podem ter mudado, mas o mestre continua o mesmo. A transparência na indústria dos cigarros eletrônicos continua sendo uma contradição. Assim como ocorreu com o tabaco no século XX, as empresas parecem tentar ocultar, manipular ou negar preocupações sobre os riscos à saúde dos cigarros eletrônicos.

Os cigarros eletrônicos são realmente mais seguros que o tabaco? Existem duas razões pelas quais os efeitos adversos podem não ser detectados: primeiro porque não existem e segunda, porque não foram investigados suficientemente ou no lugar certo.

Filosoficamente, apenas a falta de segurança pode ser provada, não a segurança. Isso precisa ser enfatizado, pois muitos aderiram à ideia de que os cigarros eletrônicos são seguros. Por exemplo, um estudo concluiu que “o uso regular de cigarros eletrônicos ou adesivos de nicotina por gestantes fumadoras não parece estar associado a efeitos adversos”,⁶ apesar dos efeitos bem conhecidos da nicotina no desenvolvimento pulmonar. A nicotina é uma substância viciante com toxicidade multiorgânica ao longo da vida. O princípio da precaução não deve ser descartado.

Estudos recentes demonstraram que centenas de compostos são produzidos quando os líquidos dos cigarros eletrônicos são aquecidos, incluindo tributílofosfina,⁷ um químico industrial perigoso. Além disso, o *vaping* foi associado a alterações no transcriptoma do tecido pulmonar,⁸ mudanças epigenéticas semelhantes às observadas no cancro de pulmão, e alterações na expressão proteica das vias respiratórias que se sobrepõem às características da asma eosinofílica e neutrofílica.⁹ O *vaping* tem múltiplos efeitos adversos em indivíduos com asma. A toxicidade aguda do *vaping* é muito maior do que a do tabaco, causando lesões pulmonares induzidas por cigarros eletrônicos, sem equivalente no tabaco tradicional. Diante desses factos, como podemos afirmar com confiança que os cigarros eletrônicos são seguros a longo prazo?

A OMS publicou recentemente um quadro de “segurança em primeiro lugar” baseado em dados mundiais e independentes para auxiliar o desenvolvimento de políticas sobre cigarros eletrônicos.¹⁰ O Reino Unido seria bem aconselhado a adotar este quadro global

posição, em vez de ser um caso atípico internacional. Ou toda a gente está errada, ou a indústria está a fazer o Reino Unido de parvo. As mensagens da OMS são claras (caixa 1), apesar de, infelizmente, a *Food and Drug Administration* ter aprovado a publicidade de vaporizadores de mentol para a cessação tabágica.¹¹ A *British Pediatric Respiratory Society* publicou também recentemente um documento de posição, que está estreitamente alinhado com as declarações da OMS e de outras sociedades internacionais. É também de esperar que o *Royal College of Paediatrics and Child Health* adote formalmente esta declaração.

Pode haver luz na escuridão. O Reino Unido propõe proibir os cigarros eletrônicos descartáveis “o mais rápido possível”,¹² mas com um período de transição de pelo menos 6 meses para que as empresas possam adaptar-se. Adaptar-se a quê? Encontrar formas de contornar as regulamentações? O mesmo relatório afirma que “estamos a reforçar a regulamentação dos sabores de vape, das embalagens e da forma como são exibidos nas lojas” e que “para combater as vendas a menores, os agentes de fiscalização terão o poder de emitir multas imediatas quando detectarem a venda de tabaco e vapores a crianças na Inglaterra e no País de Gales”. As escolas serão alvo de medidas—precisam de ter uma “política”, aquela tática antiga e desgastada usada para empurrar um problema para o futuro. Quem conhece a linguagem governamental perceberá imediatamente a preocupante falta de detalhes.

Falar em reforçar a regulamentação dos sabores é estranho, porque como se reforça algo que não existe? Prepare-se para uma reação bem financiada e bem direcionada da indústria do tabaco, e fique atento aos detalhes, onde o perigo e a indústria estarão à espreita. Já estamos a ver publicações que destacam quantos adultos serão afetados pela proibição, como se isso fosse relevante.

Caixa 1 – Recomendações da OMS

- ▶ Proibir explicitamente os sabores, incluindo mentol e análogos sintéticos de mentol.
- ▶ Limitar a concentração de nicotina.
- ▶ Aumentar a tributação.
- ▶ Os países devem continuar a promover medidas de cessação do tabagismo utilizando apenas métodos comprovados e não seguir uma estratégia que permita a comercialização dos cigarros eletrônicos como produtos de consumo.
- ▶ Se os cigarros eletrônicos forem usados como auxiliares na cessação do tabagismo, devem ser regulamentados como medicamentos.

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No entanto, as medidas recentemente propostas devem ser acolhidas com entusiasmo, e o novo governo deve ser responsabilizado por essas promessas. O plano de aumentar progressivamente a idade mínima para compra de tabaco também é bem-vindo, desde que seja efetivamente aplicado. Mas isso não é suficiente. Apelamos ao governo para que assine o quadro da OMS sobre cigarros eletrônicos e o implemente imediatamente.

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