

Thorax

ORIGINALITY, RIGOUR & EXCELLENCE IN RESPIRATORY MEDICINE

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ARCHIVES OF
DISEASE IN
CHILDHOOD

Edição Portuguesa



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1 INALAÇÃO¹



1 VEZ AO DIA¹



1 DISPOSITIVO¹

+171mL
($p < 0,001$)

MELHORIA SUPERIOR E CLINICAMENTE SIGNIFICATIVA DA FUNÇÃO PULMONAR vs. BUD/FOR Turbohaler²

-34%
($p < 0,001$)

REDUÇÃO SIGNIFICATIVA DA TAXA ANUAL DE EXACERBAÇÕES POR DPOC, ASSOCIADAS A HOSPITALIZAÇÕES vs. LAMA/LABA³

-42%
($p = 0,01$)

REDUÇÃO SIGNIFICATIVA DA MORTALIDADE POR TODAS AS CAUSAS (on-treatment) vs. LAMA/LABA^{3*}



Não foram registados novos dados de segurança relativos ao uso da associação entre um ICS, um LAMA e um LABA.³

ELEBRATO
FUROATO DE FLUTICASONA | UMECLIDÍNIO | VILANTEROL | ELLIPTA
ELE RESPIRA

Referências: 1. RCM Elebrato Ellipta, novembro 2021; 2. Lipson DA et al. Am J Respir Crit Care Med 2017; 196:438–446; 3. Lipson DA et al. N Engl J Med 2018 378:1671–1680.
BUD: Budesonida; DPOC: Doença pulmonar obstrutiva crónica; FOR: Formoterol; ICS: Corticosteroide inalado; LABA: Agonista β_2 de longa duração de ação; LAMA: Antagonista muscarínico de longa duração de ação.

*A mortalidade por todas as causas foi um endpoint exploratório do estudo IMPACT. Aqui, estão apresentados os dados on-treatment. Os eventos on-treatment são os que ocorreram desde o início de tratamento e até 7 dias após o seu término.

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NOME DO MEDICAMENTO Elebrato Ellipta **COMPOSIÇÃO QUALITATIVA E QUANTITATIVA** Cada inalação disponibiliza uma dose administrada de 92 microgramas de furoato de fluticasona, 65 microgramas de brometo de umecliclínio equivalente a 55 microgramas de umecliclínio e 22 microgramas de vilanterol (como trifenateato). Isto corresponde a um recipiente unido de 100 microgramas de furoato de fluticasona, 74,2 microgramas de brometo de umecliclínio equivalente a 62,5 microgramas de umecliclínio e 25 microgramas de vilanterol (como trifenateato). Excipiente com efeito conhecido: cada dose administrada contém aproximadamente 25 mg de lactose mono-hidratada. **FORMA FARMACÉUTICA** Pó para inalação em recipiente unido. **INDICAÇÕES TERAPÉUTICAS** Tratamento de manutenção em doentes adultos com doença pulmonar obstrutiva crónica (DPOC) moderada a grave, que não estejam adequadamente tratados com uma associação de um corticosteroide para inalação e um agonista beta-2 de longa duração de ação ou uma associação de um agonista beta-2 de longa duração de ação e um antagonista muscarínico de longa duração de ação (ver RCM para informação sobre efeitos sobre o controlo dos sintomas e prevenção das exacerbações). **POSOLÓGIA E MODO DE ADMINISTRAÇÃO** **Adultos** A dose máxima recomendada é uma inalação 1x/dia, à mesma hora em cada dia. **Doentes idosos, Compromisso renal e Compromisso hepático** Não é necessário ajustar a posologia. Utilizar com precaução em doentes com compromisso hepático moderado a grave. **População pediátrica** A utilização não é relevante na população pediátrica (<18 anos) para a indicação de DPOC. Modo de administração Via inalatória. **CONTRAINDICAÇÕES** Hipersensibilidade às substâncias ativas ou a qualquer um dos excipientes. **EFEITOS INDESEJÁVEIS** As reações adversas mais frequentemente notificadas foram nasofaringite, cefaleia e infeção das vias respiratórias superiores. **Infeções e infestações** Frequentes Pneumonia, infeção das vias respiratórias superiores, bronquite, faringite, rinite, sinusite, gripe, nasofaringite, candidíase da boca e da garganta e infeção do trato urinário **Pouco frequentes** Infeção viral das vias respiratórias superiores **Doenças do sistema imunitário** Raras Reações de hipersensibilidade, incluindo anafilaxia, angioedema, urticária e erupção cutânea **Doenças do sistema nervoso** Frequentes Cefaleia **Pouco frequentes** Disgeusia **Afeções oculares** **Pouco frequentes** Visão turva, Glaucoma, Dor ocular **Raros** Tensão intraocular aumentada **Cardiopatias** **Pouco frequentes** Taquiarritmia supraventricular, taquicardia e fibrilhação auricular **Doenças respiratórias, torácicas e do mediastino** Frequentes Tosse e dor orofaríngea **Pouco frequentes** Disfonia **Doenças gastrointestinais** Frequentes Obstipação **Pouco frequentes** Boca seca **Afeções musculoesqueléticas e dos tecidos conjuntivos** Frequentes Artralgia e dor de costas **Pouco frequentes** Fraturas **TITULAR DA AIM** GlaxoSmithKline Trading Services Limited, 12 Riverwalk, Citywest Business Campus, Dublin 24, Irlanda **DATA DA REVISÃO DO TEXTO** novembro 2021 **APRESENTAÇÃO:** Elebrato Ellipta 92 mcg+55 mcg+22mcg, 30 doses. **Regime de Comparticipação:** Escalão B. Regime Geral 69%; Regime Especial 84%. Está disponível informação pormenorizada sobre este medicamento no sítio da internet da Agência Europeia de Medicamentos <http://www.ema.europa.eu/>. Consultar o RCM completo para informação detalhada. Medicamento sujeito a receita médica. Para mais informações e em caso de suspeita de um acontecimento adverso ou de outra informação de segurança, contactar o departamento médico da GlaxoSmithKline - +351 214129500. Para mais informações contactar o representante local do titular da AIM: Bial-Portela & C³, S.A., -A Av. da Siderurgia Nacional, 4745-457 S.Mamede do Coronado; NIF: 500220913. As Marcas Registradas são propriedade ou licenças das empresas do grupo GSK. ©2022 empresas do grupo GSK ou sob licença. DMgMA_PT211220

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Editorial

Estamos a chegar ao período de férias que, para muitos colegas, constitui finalmente a possibilidade de descansar um pouco na companhia das suas famílias e amigos. Infelizmente, as notícias do dia-a-dia não são nada animadoras. Já não chegava a crise económica e social pós-pandémica, a horrível guerra na Ucrânia com milhares de mortos e feridos e a devastação de cidades inteiras, gerando uma vaga de refugiados sem precedente na Europa deste século, o seu impacto brutal na economia Mundial, a ameaça de fome em vários países de baixo rendimento devido ao agravamento dos preços dos cereais, temos agora mais uma desnecessária, mas já recorrente, crise nos serviços de urgência da rede pública. Isto é apenas a ponta do iceberg de problemas estruturais do SNS que continuam por resolver.

Entretanto, estamos de regresso com um novo número da edição em língua Portuguesa de artigos seleccionados das revistas *Thorax* e *Archives of Disease in Childhood*.

Bem a propósito da situação mundial atual, mas agora a nível ambiental, recomendamos o editorial que relaciona a crise climática com uma idêntica crise de direitos das crianças, afirmando: “Todas as crianças têm direito a ar puro, água potável, saneamento, alimentação acessível e nutritiva e abrigo. No entanto, milhões de crianças no Reino Unido e a nível global não têm acesso a estes elementos críticos para a saúde - uma situação que será agravada pelas alterações climáticas.” Os autores concluem que “esta crise climática é a maior ameaça à saúde que a humanidade enfrenta e é uma crise de direitos da criança. Combater as alterações climáticas requer medidas ousadas e urgentes para proteger as gerações de crianças atuais e futuras”.

Na mesma linha, os autores do artigo “Apelo a medidas de emergência para limitar o aumento da temperatura global, restaurar a biodiversidade e proteger a saúde” sugerem que os países que criaram desproporcionadamente a crise ambiental devem fazer mais para apoiar os países de baixo e médio rendimento para a construção de sociedades mais limpas, mais saudáveis e mais resilientes.

Tendo como objetivo dar um pequeno contributo para o debate sobre as possíveis vantagens e limitações do pagamento por desempenho, assunto muito atual no debate sobre a reavaliação e revisão do modelo retributivo dos profissionais da Unidades de Saúde Familiar, sugere-se a leitura do artigo com o título “O pagamento por desempenho melhora os resultados dos pacientes admitidos por agudização aguda de DPOC?”. Este artigo refere-se ao pagamento por desempenho a nível hospitalar, assunto que tem estado igualmente presente nos debates sobre a promoção e compensação de atividades nos serviços hospitalares do SNS. Segundo os autores, o preenchimento dos critérios combinados da COPD BPT não parece estar associado a uma redução da mortalidade ou a um novo internamento a 30 dias. No entanto, a revisão especializada foi associada a uma redução da mortalidade hospitalar. Esta análise questiona se o modelo de pagamento por desempenho contribui de facto para melhorar a mortalidade ou os novos internamentos.

Na secção de “controvérsias e desafios” pode ler-se um interessante artigo sobre o “Passado, presente e futuro da oxigenoterapia conservadora nos cuidados críticos”.

Para terminar esta curta seleção de artigos sugiro a leitura de uma “Comunicação curta” sobre a “aceitabilidade de intervenções de higiene, cobertura facial e distanciamento social para prevenir exacerbações em pessoas que vivem com doenças das vias aéreas”.

Esperamos que esta seleção vos agrade e desejamos uma boa leitura.

Jaime Correia de Sousa

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INFORMAÇÕES ESSENCIAIS COMPATÍVEIS COM RESUMO DAS CARACTERÍSTICAS DO MEDICAMENTO

A crise climática também é uma crise de direitos das crianças

Haytham Ali,¹ Alison Firth,² Alison Leaf,³ Cinthu Vivehananthan,⁴ Dhurgshaarna Shanmugavadivel,⁵ Ekundayo Ajayi-Obe,⁶ Jay Halbert,⁷ Jenny Harper Gow,⁸ Mia Thomas,⁹ Paula de Sousa,¹⁰ Tony Waterston,¹¹ Bernadette O'Hare¹²

O *Royal College of Paediatrics and Child Health* (RCPCH) publicou recentemente uma nova posição sobre a crise climática antes da Conferência das Nações Unidas sobre Alterações Climáticas de 2021 em Glasgow (a 26ª Conferência das Partes ou COP26).¹ A declaração visa recordar o direito que as crianças têm à saúde, incluindo aos cuidados de saúde e a outros direitos económicos e sociais fundamentais. Uma abordagem baseada nos direitos da criança assenta numa abordagem dos direitos humanos, mas inclui as necessidades específicas das crianças. Além disso, muitos acordos internacionais, como a Agenda para o Desenvolvimento Sustentável de 2030 e o Acordo de Paris, afirmam os compromissos dos países com uma abordagem ao desenvolvimento e às medidas climáticas baseada nos direitos humanos. Logo, os impactos negativos das alterações climáticas nas crianças desencadeiam obrigações entre os responsáveis, tanto para a mitigação como para a adaptação.²

A declaração da posição do RCPCH diz:

Todas as crianças têm direito a ar puro, água potável, saneamento, alimentação acessível e nutritiva e abrigo. No entanto, milhões de crianças no Reino Unido e a nível global não têm acesso a estes elementos críticos para a saúde - uma situação que será agravada pelas alterações climáticas.

A poluição atmosférica terá impacto em quase todas as crianças em qualquer parte do mundo. Quase todas as crianças

do mundo respiram ar de má qualidade e, em 2016, 300 000 crianças com menos de 5 anos de idade morreram devido à poluição do ar ambiente, e mais 400 000 morreram como resultado da poluição do ar das suas casas.¹ As crianças respiram mais rapidamente e, por isso, inalam mais substâncias tóxicas transportadas pelo ar em proporção ao seu peso, numa altura em que os seus órgãos ainda se estão a formar. A exposição a poluentes atmosféricos durante a gravidez e a infância pode ter efeitos nocivos e irreversíveis sobre o desenvolvimento dos pulmões e outros órgãos e sobre potenciais problemas de saúde em idade adulta.^{1,3}

Milhões de crianças não dispõem atualmente de acesso aos serviços críticos necessários para satisfazer as suas necessidades básicas. As alterações climáticas irão degradar ainda mais estes direitos. Além disso, na sua esmagadora maioria, estas crianças vivem nas regiões do mundo que menos contribuíram para a crise climática e nos países com menos recursos para prestar os serviços críticos de que têm direito, muito menos para adaptar os serviços atuais às alterações climáticas. Na verdade, muitas crianças estão atualmente expostas à escassez de água relacionada com as alterações climáticas, ondas de calor, doenças transmitidas por vetores e inundações.³ Até 2030, poderá haver mais 77000-131000 mortes entre crianças com menos de 5 anos como consequência de subnutrição provocada pelas alterações climáticas. Além disso, até 2040, uma em cada quatro crianças viverá em zonas de stress hídrico extremamente elevado.¹

AS VOZES DAS CRIANÇAS

Num vácuo de liderança global, crianças e jovens de todo o mundo assumiram a luta e exigiram medidas aos seus governos a uma escala inspiradora e sem precedentes. Estão a utilizar todas as ferramentas à sua disposição, incluindo manifestações, ativismo online e vias legais, para encontrar soluções para uma crise que os irá afetar mais do que os adultos simplesmente porque têm toda a sua vida pela frente. Por exemplo, em 2020, seis crianças e jovens de Portugal levaram 33 países ao Tribunal Europeu dos Direitos do Homem (TEDH). Pretendem que o TEDH tome uma decisão juridicamente vinculativa que obrigue os governos a tomar medidas urgentes sobre as alterações climáticas.⁴ Numa decisão histórica de 2021, como resposta a uma petição histórica relacionada com o clima, apresentada por 16 crianças e jovens, o Comité dos Direitos da Criança das Nações Unidas concluiu que os países

são responsáveis pelo impacto prejudicial das suas emissões de carbono sobre os direitos das crianças nos seus países e além fronteiras.

Adicionalmente, um membro do Comité declarou que "a natureza coletiva das causas das alterações climáticas não deve absolver um Estado da sua responsabilidade individual".⁵ Contudo, apesar desta decisão encorajadora, o Comité explicou numa carta aberta às crianças e jovens que o caso era inadmissível porque os procedimentos de queixa exigem que todos os casos sejam primeiramente apresentados aos tribunais nacionais.⁶

NECESSIDADE DE UMA AÇÃO URGENTE E COLETIVA

O RCPCH reconhece que as alterações climáticas constituem uma ameaça existencial para a saúde e o bem-estar das crianças e dos jovens. Portanto, em outubro de 2020, o RCPCH juntou-se às alianças de saúde e académicas nacionais para declarar uma emergência climática e ecológica que requer ações de colaboração aceleradas. Impulsionado por pediatras e estagiários de pediatria e apoiado por um painel de especialistas em saúde infantil e pela direção da faculdade, foi formado em 2021 o RCPCH *Climate Change Working Group*. O COP26 apresentou uma oportunidade para apoiar as crianças do mundo na sua busca para salvar o seu futuro dos impactos das alterações climáticas. À medida que avançamos, o RCPCH junta-se aos profissionais de saúde de todo o mundo para apelar aos líderes de cada país para que tornem a saúde humana central em todas as ações de mitigação e adaptação às alterações climáticas para proteger as gerações atuais e futuras de crianças e jovens. Os países que mais contribuíram para as alterações climáticas precisam de fazer investimentos significativos para a mitigação e adaptação naquelas regiões do mundo que menos contribuíram. Em particular, o colégio quer que os líderes se empenhem nas seguintes três áreas:¹

1. Apoio e proteção das crianças. Apelamos a que a saúde infantil seja um tema central em todas as decisões políticas relativas às alterações climáticas. Reconhecendo que a crise climática é uma crise de direitos da criança, os governos devem mobilizar e atribuir o máximo de recursos disponíveis para proteger esses direitos e incluir uma avaliação de risco dos direitos da criança como parte de todas as decisões políticas em matéria de clima.

2. Mitigação para reduzir as emissões decorrentes das alterações climáticas. Apelamos a todos os países para que deem prioridade a uma transição rápida e justa em relação aos combustíveis fósseis. As crianças e os jovens são especialmente vulneráveis aos impactos da poluição atmosférica e a exposição a uma má qualidade do ar tem implicações ao longo da vida para o potencial de um indivíduo. Os governos devem reforçar as metas para acabar com a utilização de combustíveis fósseis em todos

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os setores como parte da sua transição para fontes de energia renováveis limpas, incluindo a cessação imediata de toda a exploração e subsídios de combustíveis fósseis.

3. Adaptação para proteger as gerações atuais e futuras de crianças dos impactos das alterações climáticas. Apelamos ao investimento direto em serviços de saúde e educação resistentes às alterações climáticas, com baixo teor de carbono e sustentáveis. Crescer num ambiente limpo e seguro é um direito de todas as crianças e o investimento urgente em água limpa, saneamento e boas práticas de higiene deve ser uma prioridade para a prosperidade das crianças. É fundamental que as crianças possam continuar a frequentar a escola e a ter acesso a serviços de saúde apesar dos riscos crescentes apresentados pelas alterações climáticas. Além disso, como membro da *UK Health Alliance on Climate Change*, juntamo-nos a outros organismos profissionais do Reino Unido para apoiar as seguintes recomendações⁷:

► Todos os países devem atingir emissões líquidas zero até 2040, com os países com emissões elevadas de carbono a efetuarem cortes superiores aos países com baixas emissões.

► Países com a maior responsabilidade pelas emissões de carbono (na sua maioria países de elevado rendimento) para transferir fundos para os países mais vulneráveis aos impactos da crise climática, permitindo-lhes adaptar-se e preparar-se.

► Fim de todos os subsídios aos combustíveis fósseis (protegendo ao mesmo tempo os vulneráveis que podem estar injustamente em desvantagem), juntamente

com um investimento massivo em energias renováveis e armazenamento, infraestruturas verdes e empregos verdes.

► Todas as empresas de combustíveis fósseis passarão a ter emissões líquidas zero até 2040.

► Todos os serviços de saúde passarão a emissões líquidas zero o mais cedo possível e antes de 2040.

CONCLUSÃO

Esta crise climática é a maior ameaça à saúde que a humanidade enfrenta e é uma crise de direitos da criança. Combater as alterações climáticas requer medidas ousadas e urgentes para proteger as gerações atuais e futuras de crianças. A COP26 tem sido uma oportunidade crucial para avaliar, reafirmar e reforçar os atuais compromissos assumidos pela comunidade internacional em matéria de alterações climáticas. Além de converter promessas em medidas urgentes para mitigar as alterações climáticas, é necessária uma solidariedade global na adaptação, incluindo o financiamento. Dados os atuais riscos ambientais que muitas crianças enfrentam, os defensores da saúde infantil devem estar ao lado das crianças e dos jovens para exigir uma ação urgente sobre as alterações climáticas.

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Apelo a medidas de emergência para limitar o aumento da temperatura global, restaurar a biodiversidade e proteger a saúde

Lukoye Atwoli,¹ Abdullah H Baqui,² Thomas Benfield,³ Raffaella Bosurgi,⁴ Fiona Godlee,⁵ Stephen Hancocks,⁶ Richard Horton,⁷ Laurie Laybourn-Langton,⁸ Carlos Augusto Monteiro,⁹ Ian Norman,¹⁰ Kirsten Patrick,¹¹ Nigel Praities,¹² Marcel GM Olde Rikkert,¹³ Eric J Rubin,¹⁴ Peush Sahni,¹⁵ Richard Smith,⁸ Nicholas J Talley,¹⁶ Sue Turale,¹⁷ Damián Vázquez¹⁸

As nações ricas devem fazer muito mais e muito mais depressa.

A Assembleia Geral das Nações Unidas, em setembro de 2021, reunirá os países num momento crítico para a mobilização de uma ação coletiva para enfrentar a crise ambiental global. Reunir-se-ão novamente na cimeira sobre biodiversidade em Kunming, China, e na conferência sobre o clima (Conferência das Partes (COP)26) em Glasgow, Reino Unido. Antes destas reuniões cruciais, nós - os editores das revistas de saúde de todo o mundo - apelamos a uma ação urgente para manter o aumento médio da temperatura global abaixo de 1,5°C, travar a destruição da natureza e proteger a saúde. A saúde já está a ser prejudicada pelo aumento da temperatura global e pela destruição do mundo natural, um problema para o qual os profissionais de saúde têm vindo a chamar a atenção há décadas.¹

A ciência não tem dúvidas; um aumento global de 1,5°C acima da média pré-industrial e a contínua perda de biodiversidade representam um risco catastrófico para a saúde que será impossível de inverter.^{2,3} Apesar da necessária preocupação mundial com a COVID-19, não podemos esperar que a pandemia termine para reduzir rapidamente as emissões. Refletindo sobre a gravidade do momento, este editorial aparece em revistas de saúde de todo o mun-

do. Estamos unidos no reconhecimento de que só mudanças fundamentais e equitativas nas sociedades inverterão a nossa trajetória atual. Os riscos para a saúde dos aumentos acima de 1,5°C estão agora bem estabelecidos.² De facto, nenhum aumento de temperatura é "seguro". Nos últimos 20 anos, a mortalidade atribuída ao calor entre pessoas com mais de 65 anos aumentou em mais de 50%.⁴ As temperaturas mais elevadas trouxeram um aumento da desidratação e perda da função renal, doenças dermatológicas, infeções tropicais, efeitos adversos para a saúde mental, complicações na gravidez, alergias e morbilidade e mortalidade cardiovascular e pulmonar.^{5,6}

Os danos afetam desproporcionadamente os mais vulneráveis, incluindo crianças, populações mais idosas, minorias étnicas, comunidades mais pobres e aqueles com problemas de saúde subjacentes.^{2,4} O aquecimento global está também a contribuir para o declínio do potencial de rendimento global das principais culturas, caindo 1,8%-5,6% desde 1981; isto, juntamente com os efeitos de condições meteorológicas extremas e do esgotamento do solo, está a dificultar os esforços para reduzir a subnutrição.⁴ Ecossistemas prósperos são essenciais para a saúde humana e a destruição generalizada da natureza, incluindo habitats e espécies, está a degradar a segurança hídrica e alimentar e a aumentar a probabilidade de pandemias.^{3,7,8} As consequências da crise ambiental recaem desproporcionadamente sobre os países e comunidades que menos contribuíram para o problema e que são menos capazes de mitigar os danos. No entanto, nenhum país, por mais rico que seja, se pode proteger destes impactos.

Permitir que as consequências recaiam desproporcionadamente sobre os mais vulneráveis irá gerar mais conflitos, insegurança alimentar, deslocação forçada e doenças zoonóticas, com graves implicações para todos os países e comunidades. Tal como com a pandemia da COVID-19, somos globalmente tão fortes como o nosso membro mais fraco. Subidas acima de 1,5°C aumentam a hipótese de atingir pontos de viragem em sistemas naturais que poderiam prender o mundo a um estado extremamente instável. Isto prejudicaria seriamente a nossa capacidade de mitigar os danos e de prevenir alterações ambientais catastróficas e incontroláveis.^{9,10}

OS OBJETIVOS GLOBAIS NÃO SÃO SUFICIENTES

Felizmente, muitos governos, instituições financeiras e empresas estão a estabelecer metas para atingir emissões líquidas zero, incluindo metas para 2030. O custo das energias renováveis está a descer rapidamente. Muitos países estão a tentar proteger pelo menos 30% das terras e oceanos do mundo até 2030.¹¹ Estas promessas não são suficientes. As metas são fáceis de estabelecer e difíceis de alcançar. Ainda não são compatíveis com planos credíveis a curto e longo prazo para acelerar tecnologias mais limpas e transformar sociedades. Os planos de redução de emissões não incorporam adequadamente as questões sanitárias.¹² Cresce a preocupação de que os aumentos de temperatura acima de 1,5°C começam a ser vistos como inevitáveis, ou mesmo aceitáveis, pelos membros poderosos da comunidade global.¹³ No que respeita às estratégias atuais para reduzir as emissões a zero até meados do século, é pouco provável que o mundo venha a adquirir uma grande capacidade para remover da atmosfera os gases com efeito de estufa.^{14,15}

Esta ação insuficiente significa que é provável que os aumentos de temperatura sejam bem superiores a 2°C,¹⁶ um resultado catastrófico para a saúde e estabilidade ambiental. Essencialmente, a destruição da natureza não tem paridade de estima com o elemento climático da crise e todos os objetivos globais para restaurar a perda de biodiversidade até 2020 foram perdidos.¹⁷ Esta é uma crise ambiental global.¹⁸ Os profissionais de saúde estão unidos aos cientistas ambientais, empresas e muitos outros ao rejeitarem que este resultado é inevitável. Podemos e devemos fazer mais agora - em Glasgow e Kunming - e nos anos imediatos que se seguem. Juntamo-nos aos profissionais de saúde de todo o mundo que já apoiaram pedidos para uma ação rápida.^{1,19} A equidade deve estar no centro da resposta global. Contribuir com uma quota-parte justa para o esforço global significa que os compromissos de redução devem ser responsáveis pela contribuição cumulativa e histórica de cada país para as emissões, bem como pelas suas atuais emissões e capacidade de resposta.

Os países mais ricos terão de reduzir as emissões mais rapidamente, fazendo reduções até 2030 para além das atualmente propostas^{20,21} e atingindo emissões líquidas zero antes de 2050. São necessárias metas e ações de emergência semelhantes para a perda da biodiversidade e para a destruição generalizada do mundo natural. Para atingir estas metas, os governos devem fazer mudanças fundamentais na forma como as nossas sociedades e economias estão organizadas e como vivemos. A atual estratégia de encorajar os mercados a optarem por tecnologias mais limpas não é suficiente. Os governos devem intervir para apoiar a reformulação dos sistemas de transporte, cidades, produção e distribuição de alimentos, mercados de investimentos fi-

¹East African Medical Journal, Nairobi, Kenya

²Journal of Health, Population and Nutrition, Baltimore, Maryland, USA

³Danish Medical Journal, Copenhagen, Denmark

⁴PLOS Medicine, Cambridge, UK

⁵The BMJ, London, UK

⁶British Dental Journal, London, UK

⁷The Lancet, London, UK

⁸UK Health Alliance on Climate Change, London, UK

⁹Revista de Saúde Pública, São Paulo, Brazil

¹⁰International Journal of Nursing Studies, London, UK

¹¹CMAJ, Ottawa, Ontario, Canada

¹²Pharmaceutical Journal, London, UK

¹³Dutch Journal of Medicine, Nijmegen, The Netherlands

¹⁴NEJM, Boston, Massachusetts, USA

¹⁵National Medical Journal of India, New Delhi, India

¹⁶Medical Journal of Australia, Newcastle, New South Wales, Australia

¹⁷International Nursing Review, Geneva, Switzerland

¹⁸Pan American Journal of Public Health, Washington, DC, USA

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nanceiros, sistemas de saúde e muito mais. É necessária uma coordenação global para garantir que a corrida às tecnologias mais limpas não se faça à custa de mais destruição ambiental e exploração humana. Muitos governos enfrentaram a ameaça da pandemia COVID-19 com um financiamento sem precedentes.

A crise ambiental exige uma resposta de emergência semelhante. Será necessário um enorme investimento, para além do que está a ser considerado ou entregue em qualquer parte do mundo. Mas tais investimentos produzirão enormes resultados positivos em termos de saúde e económicos. Estes incluem empregos de alta qualidade, redução da poluição atmosférica, aumento da atividade física e melhoria da habitação e da alimentação. Uma melhor qualidade do ar, por si só, permitiria obter benefícios de saúde que facilmente compensariam os custos globais da redução de emissões.²² Estas medidas também melhorarão os determinantes sociais e económicos da saúde, cujo estado precário poderá ter tornado as populações mais vulneráveis à pandemia da COVID-19.²³ Mas as mudanças não podem ser conseguidas através de um regresso a políticas de austeridade lesivas ou com a continuação das grandes desigualdades a nível de poder e riqueza não só dentro dos próprios países como entre os diferentes países.

A COOPERAÇÃO DEPENDE DE UM MAIOR ESFORÇO DAS NAÇÕES RICAS

Os países que criaram desproporcionadamente a crise ambiental devem fazer mais para apoiar os países de baixo e médio rendimento para a construção de sociedades mais limpas, mais saudáveis e mais resilientes. Os países de elevado rendimento devem cumprir e ir além do seu compromisso excepcional de contribuir com 100 mil milhões de dólares por ano, compensando qualquer carência em 2020 e aumentando as contribuições para 2025 e mais além. O financiamento deve ser dividido igualmente entre mitigação e adaptação, incluindo a melhoria da resiliência dos sistemas de saúde. O financiamento deve ser feito através de concessões, em vez de empréstimos, melhorando as capacidades locais e habilitando verdadeiramente as comunidades, e isto deve ser acompanhado pelo perdão de grandes dívidas, que constroem a atu-

ação de tantos países de baixo rendimento. O financiamento adicional deve ser mobilizado para compensar as perdas e danos inevitáveis causados pelas consequências da crise ambiental. Como profissionais de saúde, devemos fazer tudo o que estiver ao nosso alcance para ajudar a transição para um mundo mais sustentável, justo, resiliente e saudável. Para além de agirmos no sentido de reduzir os danos da crise ambiental, devemos contribuir proativamente para a prevenção global de novos danos e para a ação sobre as causas profundas da crise. Devemos responsabilizar os líderes mundiais e continuar a educar os outros sobre os riscos sanitários da crise. Temos de unir forças para alcançar sistemas de saúde sustentáveis antes de 2040, reconhecendo que isto implicará uma mudança na prática clínica. As instituições de saúde já desinvestiram mais de 42 mil milhões de dólares de ativos de combustíveis fósseis. Outras devem juntar-se a elas.⁴ A maior ameaça à saúde pública global é o fracasso contínuo dos líderes mundiais em manter o aumento da temperatura global abaixo de 1,5°C e em recuperar a natureza. É necessário empreender mudanças urgentes, em toda a sociedade, que conduzam a um mundo mais justo e saudável. Nós, como editores de revistas de saúde, apelamos aos governos e outros líderes a agir, marcando 2021 como o ano em que o mundo finalmente muda o seu rumo.

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Competing interests FG serves on the executive committee for the UK Health Alliance on Climate Change and is a trustee of the Eden Project. RS is the chair of Patients Know Best, has stock in UnitedHealth Group, has done consultancy work for Oxford Pharmagenesis and is chair of the Lancet Commission on the Value of Death.

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Patient consent for publication Not required.

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Nova diabetes de tipo 1 em crianças finlandesas durante a pandemia de COVID-19

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RESUMO

Contexto As infecções virais podem desencadear diabetes de tipo 1 (DT1) e relatórios recentes sugerem um aumento da incidência de DT1 e/ou cetoacidose diabética (CAD) pediátrica durante a pandemia de COVID-19.

Objetivo Estudar se o número de crianças admitidas na unidade de cuidados intensivos pediátricos (UCI) por CAD devido a um aumento de casos de novo aparecimento de DT1 durante a pandemia COVID-19 e se a infecção por SARS-CoV-2 exerceu alguma influência.

Métodos Este estudo de coorte retrospectivo inclui dois conjuntos de dados: (1) crianças admitidas na UCI devido a novo aparecimento de DT1 e (2) crianças diagnosticadas com novo aparecimento de DT1 e incluídas no Registo Finlandês de Diabetes Pediátrica no Hospital Universitário de Helsinquia entre 1 de abril e 31 de outubro no período de 2016–2020. Comparámos a incidência, número e características das crianças com DT1 recém-diagnosticada entre os períodos pré-pandémico e pandémico.

Resultados O número de crianças admitidas na UCIP devido a novo aparecimento de DT1 aumentou de uma média de 6,25 admissões no período entre 2016–2019 para 20 admissões em 2020 (rácio de taxa de incidência [IRR] 3,24 [95% IC 1,80 a 5,83]; $p=0,0001$). Em média, foram registadas 57,75 crianças no RFDP em 2016–2019, em comparação com 84 em 2020 (IRR 1,45; 95% IC 1,13 a 1,86; $p=0,004$). 33 das crianças diagnosticadas em 2020 foram analisadas para anticorpos SARS-CoV-2 e todas estiveram negativas.

Conclusões Durante a pandemia, mais crianças com DT1 apresentaram CAD grave no diagnóstico. Isto não foi uma consequência da infecção por SARS-CoV-2. Provavelmente, resultou de atrasos no diagnóstico na sequência de alterações no comportamento dos pais e na acessibilidade aos cuidados de saúde.

RESUMO

An increase in the number of children with newly diagnosed type 1 diabetes (T1D) has been reported during the COVID-19 pandemic,¹ and several reports from regions heavily impacted by the pandemic suggest that more children with new-onset T1D now present with severe diabetic ketoacidosis (DKA).^{1–6} Lacking epidemiological studies, it is unclear whether there is a true increase in the T1D incidence, or rather an exacerbation of the disease presentation. Furthermore, the mechanisms of a potential association between COVID-19 and new-onset T1D are unknown.^{7,8}

Finland has the highest incidence of T1D in the world,⁹ whereas the number of paediatric COVID-19 cases remained low during the first wave of the COVID-19 pandemic.^{10,11} Nevertheless, strict infection control measures affecting children were put in place from mid-March 2020: schools were closed, elective healthcare appointments cancelled or changed to eHealth outpatient visits and families advised to avoid unnecessary contacts.

Despite a low local COVID-19 infection rate, also we noticed that more children were admitted to the paediatric intensive care unit (PICU), Helsinki University Hospital (HUS) for newly diagnosed

What is already known on this topic?

- During the COVID-19 pandemic, an increased incidence and a more severe clinical presentation of type 1 diabetes in children have been reported.
- It is unclear whether the observed changes in the incidence and/or clinical presentation of type 1 diabetes are directly associated with SARS-CoV-2 infection.

What this study adds?

- During the pandemic, there was an increase in the number of children admitted to paediatric intensive care unit due to new-onset type 1 diabetes with severe ketoacidosis.
- A smaller increase in the incidence of new-onset type 1 diabetes diagnoses was observed.
- As no SARS-CoV-2 antibodies were detected in these children, indirect effects of the pandemic are more plausible causes for an altered presentation of new-onset type 1 diabetes.

T1D from May 2020 onward. We set out to assess whether the occurrence of T1D had increased, or the disease presentation at diagnosis worsened, conceivably due to delays in seeking or receiving medical attention. Furthermore, as the COVID-19 might function as a trigger of the manifestation of T1D,¹² we analysed SARS-CoV-2 antibodies in children with newly diagnosed T1D. As the baseline seroprevalence of SARS-CoV-2 antibodies in the region was only 0.6%,¹⁰ we hypothesised that this approach would enable us to infer whether the observed increase in new T1D cases or DKA at diagnosis was directly associated with preceding SARS-CoV-2 infection.

METHODS

Study design

This retrospective cohort study consists of two datasets of children newly diagnosed with T1D during 1 April–31 October 2020 (*the pandemic period*) and corresponding periods (1 April–31 October) in 2016–2019 (*the prepandemic periods*). The first dataset includes all children admitted to the PICU in The New Children's Hospital, HUS for new-onset T1D with severe DKA. The second dataset comprises all children prospectively enrolled to the Finnish Paediatric Diabetes Registry (FPDR) from the HUS district. In addition, serum samples for

SARS-CoV-2 antibody testing were available from a subset of children enrolled in the registry cohort during the pandemic period.

This work was supported by the Public Health Agency of Canada through the CPSP and a grant from Paediatric Consultants, Hospital for Sick Children.

Setting

The study was conducted in the HUH district (total population 2 188 253, paediatric population 369 807 (31 December 2019)) in Finland (population 5 525 292, paediatric population 872 996 (31 December 2019)),¹³ which is a Nordic welfare state with universal healthcare for residents. Private or outpatient care for new-onset T1D for children is not available in Finland. The New Children's Hospital is the only provider of PICU care in the HUH district. Thus, the incidence of severe DKA in this population can be calculated from the number of patients treated in the HUH. During the pandemic, the PICU admission criteria did not change. Our PICU was not used to treat adults with COVID-19 or any other new patient groups.

Participants

With the consent of the patient and/or the caregiver, Finnish children and adolescents with newly diagnosed T1D may participate in the FPDR. This includes prospectively collecting structured data on patient history, clinical presentation, including biochemistry and serology at diagnosis, details about in-hospital care¹⁴ and storage of biological samples including serum. In 2016–2019, approximately 90% of newly diagnosed T1D children were registered, and 72% consented to donate a serum sample. Thus, the number of registered patients reflects the incidence of T1D in children in the area.

For the PICU cohort, we reviewed records of all newly diagnosed T1D children ≤15 years, treated in the HUH PICU during the pandemic period (1 April–31 October 2020), and those from the corresponding prepandemic periods 2016–2019, from the PICU electronic patient record (Clinisoft, GE). In the registry

cohort, we reviewed records of all newly diagnosed children from the HUH district registered in the FPDR during the corresponding pandemic and prepandemic periods.

Data collection and definitions

We collected patient characteristics, duration of symptoms, the length of stay and biochemical findings on presentation (tables 1 and 2). As markers of severity of DKA, we recorded blood pH, plasma osmolality, β-hydroxybutyrate and glucose concentration in the PICU cohort, and pH and glucose concentration in the registry cohort. As markers of a possible diagnostic delay, we included the duration of symptoms before diagnosis, and the glycosylated haemoglobin value at diagnosis.

Details of SARS-CoV-2 antibody tests,^{15–18} other laboratory tests and patient selection for PICU admission are included in the online supplemental data file.

Statistical methods

We compared the pandemic study period (1 April–31 October 2020) to corresponding time periods in the four preceding years (2016–2019) to evaluate possible pre-existing trends and to account for seasonal variation in the occurrence of T1D. As the observational periods were 7 months each year, we scaled the yearly population sizes to 7-month person-times in order to calculate and compare incidences in both cohorts between prepandemic and pandemic periods. Incidences were calculated based on the size of the paediatric population (children aged ≤15 years) at risk separately for each year.

We compared continuous and ordinal variables with the Mann-Whitney U test and categorical variables with the Fisher's test. A p value <0.05 was considered statistically significant.

Ethical aspects

Written informed consent was obtained from the participants and/or caregivers in the registry. The patients in the PICU cohort were not contacted for the purposes of the study.

Table 1 Characteristics and laboratory values of the children admitted to the PICU in the Helsinki University Hospital for newly diagnosed type 1 diabetes during the pandemic period 1 April to 31 October 2020, and the corresponding periods in 2016–2019

	Prepandemic period 2016–2019 (n=25)	Pandemic period 2020 (n=25)	P value
Number of patients per study period, n	6.25*	20	
Incidence, per 100 000 person-years (95% CI)	2.89 (1.95–4.27)	9.35 (6.03–14.49)	0.0001
Age, median (IQR), years	9.5 (6.2–11.4)	10.0 (8.1–12.3)	0.42
Female sex, n (%)	10 (40)	9 (45)	0.77
Previously healthy, n (%)†	20 (83)	15 (75)	0.71
Duration of symptoms, n (%)			
<7 days	5 (20)	2 (10)	0.09
7–13 days	8 (32)	5 (25)	
14–20 days	7 (28)	2 (10)	
21–27 days	0	3 (15)	
≥28 days	5 (20)	8 (40)	
Altered level of consciousness, n (%)	7 (28)	4 (20)	0.73
Severe DKA (blood pH <7.10), n (%)	19 (76)	15 (75)	1.00
Laboratory values			
pH, median (IQR)	7.05 (6.97–7.10)	7.02 (6.91–7.13)	0.37
β-hydroxybutyric acid, median (IQR), mmol/L	6.2 (5.4–7.2)	8.0 (8.0–8.0)	0.004
Glucose, median (IQR), mmol/L	33.5 (25.0–37.3)	24.0 (22.2–34.8)	0.05
HbA1C, median (IQR), mmol/mol	112 (97–130)	116 (106–130)	0.42
HbA1C, median (IQR), %	12.4 (11.0–14.0)	12.8 (11.8–14.0)	0.42
Osmolarity, median (IQR), mmol/kg	320 (310–351)	329 (314–346)	0.78

*Mean number of patients per study period during prepandemic study periods 2016–2019.

†No underlying chronic medical conditions requiring medication or ongoing medical attention present at the time of T1D diagnosis.

HbA1C; glycated haemoglobin; DKA, diabetic ketoacidosis; PICU, paediatric intensive care unit; T1D, type 1 diabetes.

Table 2 Characteristics and laboratory values of children registered to the Finnish Paediatric Diabetes Registry in the Helsinki University Hospital district during the pandemic period (1 April–31 October 2020) and during corresponding prepandemic periods in 2016–2019

	Prepandemic periods 2016–2019 (n=231)	Pandemic period 2020 (n=84)	P value
Number of patients per period, n	57.75*	84	
Incidence, per 100 000 person-years (95% CI)	38.68 (34.00 to 44.00)	56.00 (45.22 to 69.34)	0.004
Age, median (IQR), years	8.0 (4.0–11.9)	8.2 (4.4–11.2)	0.53
Female sex, n (%)	103 (45)	36 (43)	0.80
Previously healthy, n (%)†	215 (93)	74 (88)	0.17
Duration of symptoms, n (%)			
less than 7 days	39 (18)	18 (22)	0.29
7–13 days	70 (32)	24 (30)	
14–20 days	34 (15)	14 (18)	
21–27 days	28 (13)	12 (15)	
28 days or more	51 (23)	12 (15)	
Admitted to PICU, n (%)	15 (6)	16 (19)	0.002
Severe DKA (blood pH <7.10), n (%)	20 (9)	13 (16)	0.10
Laboratory values			
pH, median (IQR)	7.36 (7.25–7.39)	7.36 (7.18–7.39)	0.34
β-hydroxybutyric acid, median (IQR), mmol/L	3.1 (0.7–6.0)	4.5 (0.9–6.1)	0.23
Glucose, median (IQR), mmol/L	25.8 (18.9–34.3)	23.4 (18.0–29.9)	0.04
HbA1C, median (IQR), mmol/mol	104 (84–129)	103.0 (82–119)	0.46
HbA1C, median (IQR), %	11.7 (9.9–14)	11.6 (9.7–13.0)	0.46

*Mean number of patients per study period during prepandemic study periods 2016–2019.

†No underlying chronic medical conditions requiring medication or ongoing medical attention present at the time of T1D diagnosis.

DKA, diabetic ketoacidosis; HbA1C, glycated haemoglobin; PICU, paediatric intensive care unit; T1D, type 1 diabetes.

RESULTS

During the pandemic period 1 April–31 October 2020, 20 children with newly diagnosed T1DM were admitted to the PICU, as compared with four to nine (mean 6.25) children during the corresponding prepandemic periods in 2016–2019. The incidence of PICU admission due to new-onset T1D increased from 2.89/100 000 person years (PY) in 2016–2019 to 9.35/100 000 PY in 2020 with an incidence rate ratio (IRR) of 3.24 (95% CI 1.80 to 5.83); $p < 0.001$ (figure 1, table 1, online supplemental table 1). The increase was not explained by a pre-existing trend (figure 1) or a lower admission threshold, as the severity of acidosis and hyperosmolarity were equal in all periods (table 1). During the pandemic period, 11/20 (55%) of the children admitted to PICU had been symptomatic for at least 3 weeks, as compared with 5/25 (20%) during prepandemic periods, but the difference was not statistically significant ($p = 0.087$, table 1, online supplemental figure 1). SARS-CoV-2 RT-PCR test from nasopharyngeal swab was performed in 7/20 (35%) of the PICU patients. All tests were negative. Four

tests had been ordered as infection control measures, and three because symptoms of DKA had been mistaken for symptoms of acute infection but without a medical visit. In a tachypnoeic child with DKA, COVID-19 had been tested twice. Another child with abdominal pain had not been allowed to book a medical appointment without a negative test.

During the pandemic period, 84 children with newly diagnosed T1D from the HUH district were registered to the FPDR, as compared with 53–62 (mean 57.75) children each year in the prepandemic periods 2016–2019. The incidence of children registered to FPDR increased from 38.7/100 000 PY in 2016–2019 to 56.0/100 000 PY in 2020 with an IRR of 1.45 (95% CI 1.13 to 1.86); $p = 0.004$ (figure 1, table 2, online supplemental table 2).

Monthly numbers of children with newly diagnosed T1D admitted to the PICU and of those registered to the FPDR during the prepandemic and pandemic periods are shown in figure 2.

A serum sample was available from 33 children in the FPDR during the pandemic period. The median time from diagnosis to

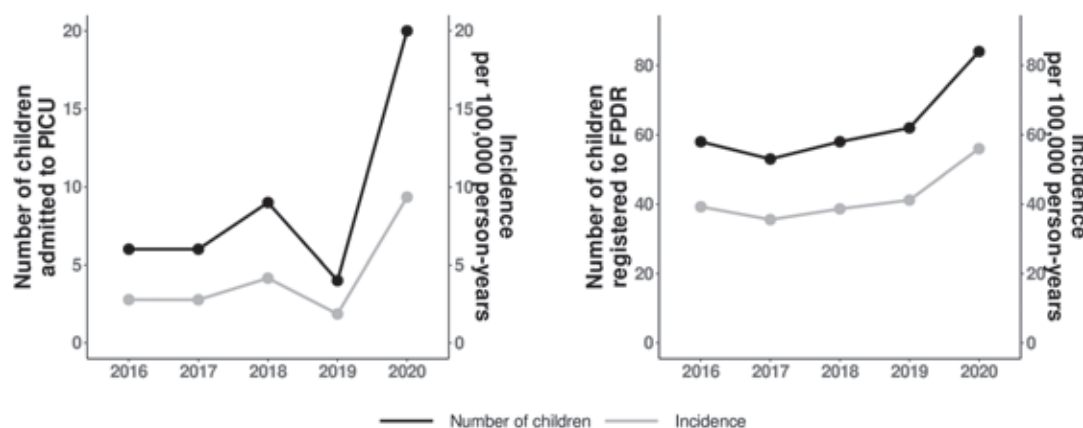


Figure 1 Number (y-axis left) and incidence (y-axis right) of children admitted to PICU (A) or registered in the Finnish Paediatric Diabetes Registry (B) with newly diagnosed type 1 diabetes between 1 April and 31 October each year 2016–2020 (x-axis). PICU, paediatric intensive care unit.

serum sample collection was 7 days (IQR 5–10 days). All samples were first tested for SARS-CoV-2 spike IgG antibodies using ELISA and 32/33 were negative. One sample with a weak positive result in ELISA was further tested with a microneutralisation assay and no neutralising antibodies were detected.

DISCUSSION

In this retrospective cohort of children with newly diagnosed T1D during the COVID-19 pandemic, we noticed a significant increase in the number of children requiring PICU care for severe ketoacidosis. The number of children registered to FPDR with newly diagnosed T1D also increased, but this smaller increase was unlikely to explain the increase in PICU admissions. None of the children tested had SARS-CoV-2 antibodies, suggesting that SARS-CoV-2 infection was not the primary trigger for more severe presentation of T1D or for the increase in children diagnosed with T1D.

Our findings are in line with recent Italian, German, UK and Australian studies reporting an increased incidence of DKA in children with new-onset T1D during the COVID-19 pandemic^{1 3 4 6} and a recent report from UK¹ suggesting that also the incidence of paediatric T1D had increased. In contrast, a German study reported no increase in the incidence of T1D.¹⁹ All the published studies except for one²⁰ found that the clinical presentation of T1D had changed. In the absence of population-based studies over a longer period, a worsened clinical presentation at diagnosis may create false impression of increasing incidence of T1D. However, the increase we observed in the total number of children with new-onset T1D is surprising, as the incidence of T1D in Finnish children has been declining since 2010.²¹ A longer follow-up is needed to confirm the change in the T1D incidence. Furthermore, we cannot exclude the possibility that the pandemic could have influenced the participation or recruitment to the FPDR.

As T1D may be triggered by viral infections in susceptible individuals, the potential association of SARS-CoV-2 with either increasing incidence of T1D or more severe disease presentation needs to be addressed. Studies on cell cultures, animal and organoid models have indicated that the primary SARS-CoV-2 entry receptor ACE2 and viral entry coreceptors transmembrane serine protease 2 (TMPRSS2) and neuropilin-1 (NRP1) are expressed in pancreatic beta cells.^{22–25} Human stem cell derived beta cells were also permissive to SARS-CoV-2 infection.²³ However, in a recent study combining data from multiple transcriptomic datasets and human pancreatic tissue sections, ACE2 and TMPRSS2 expression was detected in pancreatic microvasculature and ductal cells but not in beta cells, suggesting that ACE2 mediated direct beta cell cytotoxicity due to SARS-CoV-2 is unlikely.²⁶

Among children with newly diagnosed T1D in UK, SARS-CoV-2 was detected by PCR in 2/21 and SARS-CoV-2 antibodies in 3/16 children tested.¹ Without a control group or a population-based approach, it is difficult to interpret these results. As we noticed a similar change in the presentation of T1D in a population less affected by the pandemic and with no detectable SARS-CoV-2 antibodies in any of the newly diagnosed children, it seems likely that the virus plays no direct role in the increased incidence or more severe presentation of T1D in children. As long-term consequences of SARS-CoV-2 infection remain to be seen and not all patients infected with SARS-CoV-2 develop antibodies,²⁷ long-scale population-based studies are needed to confirm these findings.

Delays in the diagnostic process of T1D are likely to explain the increase in the number of children with DKA, as many of the children admitted to the PICU had been symptomatic for longer than the patients in previous years. Several patients with DKA had been tested for COVID-19 without a medical examination, as they presented with tachypnoea, fatigue or abdominal pain. Thus, in our setting, the delayed diagnosis did not result from medical care providers mistaking the symptoms of T1D for COVID-19.²⁸ Instead, more complex associations, influencing the threshold of families to seek medical attention and the accessibility of health services, seem to have been involved.

The pandemic and the infection control measures abruptly changed practices in child healthcare, and the behaviour of

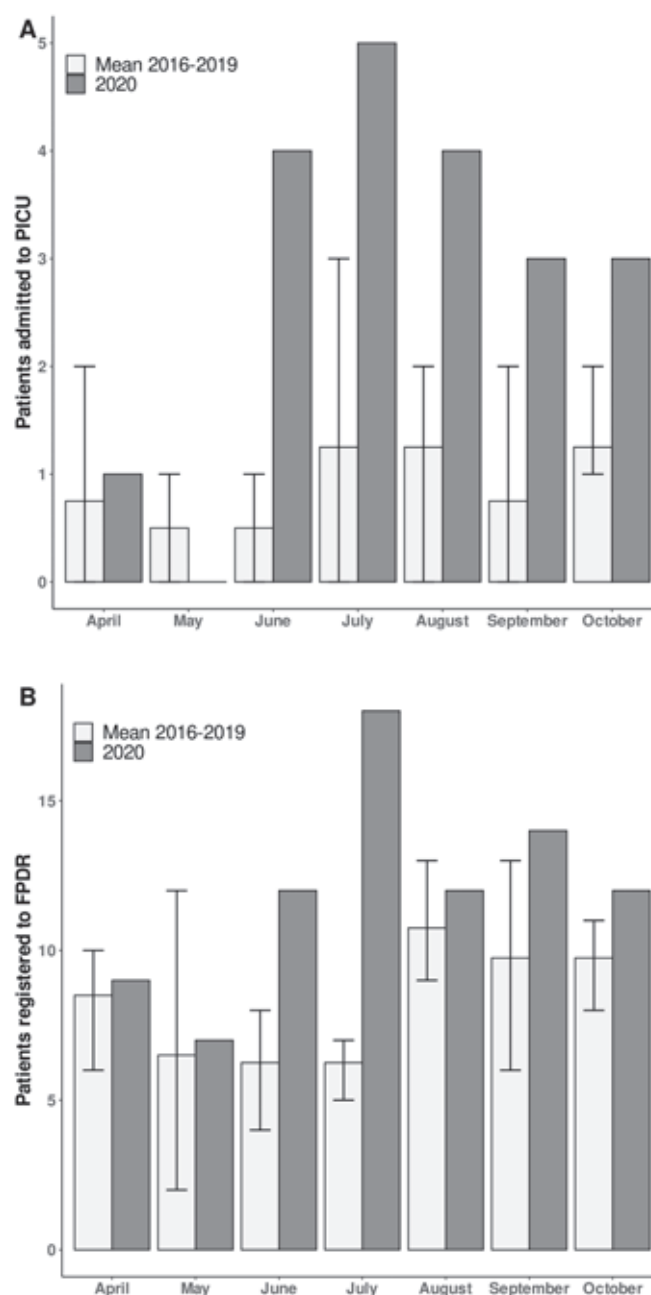


Figure 2 Monthly number of patients (y-axis) admitted to PICU (A) or registered in the Finnish Paediatric Diabetes Registry (B) with newly diagnosed type 1 diabetes during the pandemic period 1 April–31 October 2020 (dark grey) and mean of corresponding pre-pandemic periods in 2016–2019 (light grey). Error bars represent ranges. PICU, paediatric intensive care unit.

families with children. In regions with high COVID-19 infection rates, with seroprevalence rates above 5% early in the pandemic,²⁹ the infection control measures led to severe delays in the diagnosis and treatment of critically ill children.^{3 6 30 31} Alarming, our results show the same phenomenon in a setting with low COVID-19 incidence. With a 0.6% seropositivity¹⁰ and 2.7% positivity of COVID-19 in children with acute infections in the emergency department (ED),¹¹ the capacity of our healthcare system was not overburdened. On the contrary, our paediatric ED visits decreased by 45% after the start of the pandemic.³² Instead, social distancing measures, prioritisation of COVID-19 infection control in healthcare and, possibly, unfounded parental fears of their child contracting COVID-19 seem to have needlessly impaired the functioning of the healthcare system.

In the future waves of the pandemic, guidance to the public promoting social distancing and staying home must be balanced against the risks of such advice and practices to families with

children. Public awareness of the symptoms of paediatric critical illness should be increased. Also, healthcare providers must learn to prioritise their functions so that patients at risk for critical illness are not missed. Otherwise, children continue to be at risk of becoming collateral damage of infection control measures designed to protect adults. The actual impact of control measures should be evaluated for all subpopulations and the measures reasonably targeted in order to avoid causing unnecessary harm.

Our study is limited by its single-centre setting. However, as all children with new-onset T1D are cared in the same healthcare system including a single PICU, we covered all children requiring intensive care in the region. Furthermore, the study was conducted in the largest metropolitan area of the country with the highest incidence of childhood T1D in the world. This allowed us to analyse a significant number of cases despite the single centre design. Although serum samples were not available from all patients, none had SARS-CoV-2 antibodies detected. As the population seroprevalence is low, it is highly unlikely that more samples would have altered the conclusions. Last, as the FPDR is based on voluntary participation and the follow-up period was limited, larger, population-based studies with longer follow-up are needed to confirm the increased incidence of T1D observed in our study. The strengths of the study include prospectively collected clinical data from the FPDR and structured review of medical records from a single PICU. Furthermore, prospectively collected serum samples allowed us to analyse the presence of SARS-CoV-2 antibodies uniformly at the time of T1D diagnosis.

CONCLUSIONS

As compared with previous years, more children with newly diagnosed T1D presented with severe ketoacidosis in 2020. This change took place in a setting of low incidence of COVID-19 infections in the paediatric population and without detectable SARS-CoV-2 antibodies in children with newly diagnosed T1D. The total number of children with new-onset T1D in the same area also increased but not sufficiently to explain the increase in DKA.

The higher incidence of DKA is unlikely a direct consequence of COVID-19 infection. Instead, it may stem from changes in the functionality of the healthcare system, the availability of healthcare services and from parental fears over contracting COVID-19. These changes may have created barriers in the accessibility of the healthcare, leading to a delayed diagnosis and aggravated presentation of T1D.

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Risco e impacto da tosse crônica em indivíduos obesos da população em geral

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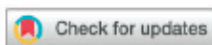
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RESUMO

Contexto Os indivíduos obesos podem estar em maior risco de tosse crônica. Investigamos o risco e o impacto da tosse crônica em indivíduos obesos da população em geral.

Métodos Registámos a tosse crônica, índice de massa corporal (IMC) e outras condições clínicas relacionadas em 44 554 adultos do Estudo Geral da População de Copenhaga. Foram excluídos os indivíduos com asma e/ou doença pulmonar obstrutiva crônica (n=10 977). O IMC foi dividido em: peso baixo (IMC <18,5 kg/m²), peso normal (18,5–24,9 kg/m²), excesso de peso (25,0–29,9 kg/m²), obeso (30,0–34,9 kg/m²) e gravemente obeso (≥35,0 kg/m²).

Resultados Entre 33 577 adultos da população em geral, 27 829 (83%) não eram obesos e 5748 (17%) eram obesos. Em comparação com indivíduos com peso normal, os OR ajustados a multivariáveis para risco de tosse crônica foram de 1,4 (95% IC 1,2 a 1,6) em excesso de peso, 1,9 (95% IC 1,7 a 2,2) em obesos e 2,6 (95% IC 2,1 a 3,2) em indivíduos gravemente obesos. As análises de mediação demonstraram que a tosse crônica devido à obesidade foi até 23% mediada pela doença de refluxo gastroesofágico (DRGE). Outros mediadores incluíram baixo consumo de vegetais com 10% e exposição profissional com 8%. Entre os indivíduos obesos, aqueles com tosse crônica *versus* sem tosse crônica apresentaram piores sintomas respiratórios e uma maior frequência de comorbidades, como DRGE, diabetes, maior utilização de cuidados de saúde, menor função pulmonar e maior inflamação sanguínea (todos p<0,05).

Conclusão Existe uma relação dose-resposta entre o IMC e a tosse crônica e o risco de tosse crônica é duas a três vezes superior em indivíduos obesos da população em geral. Este risco acrescido foi parcialmente mediado pela DRGE, baixa ingestão de vegetais e exposição profissional, o que suporta que podem existir benefícios na melhoria de alguns destes fatores em indivíduos obesos com tosse crônica.

INTRODUCTION

Chronic cough is defined as a cough lasting for >8 weeks and affects roughly 4%–10% of the adult general population.^{1,2} Although chronic cough has been viewed as a symptom of common respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), it is nowadays classified as a disease in its own entity.^{3–5} Indeed, chronic cough can severely affect daily life through fatigue, muscle pain, nausea, incontinence, sleep disturbance, low mood and sadness, and reduced social activities.^{3,5,6} Most risk factors for chronic cough in the general population are modifiable or treatable.¹

Obesity is another common condition and an important risk factor for diabetes and cardiovascular disease.⁷ Obesity also seems to play a role in asthma and COPD.^{8,9} A higher prevalence of chronic cough has been reported among obese individuals.^{10,11} It has, therefore, been hypothesised that obesity could be involved in chronic cough development and severity, and further studies have been warranted to explore this interesting relationship.¹²

Key messages

What is the key question?

► To what extent does obesity impact risk and severity of chronic cough in the general population?

What is the bottom line?

► Chronic cough risk is twofold to threefold higher in obese individuals in the general population. This increased risk was partly mediated by gastro-oesophageal reflux disease, low vegetable intake and occupational exposure.

Why read on?

► This analysis provides novel information on obesity and chronic cough risk in the general population. To our knowledge, the study is the largest on the topic using a random sample of the adult population.

In the present study, we investigated the risk and impact of chronic cough in obese individuals from the general population. For this purpose, we used information on 44 554 adults from the Copenhagen General Population Study (CGPS). First, we investigated a potential dose–response relationship between body mass index (BMI) and risk of chronic cough. Second, we performed mediation analysis to assess how much of this excess risk of chronic cough is mediated through obesity-related comorbidities. Third, we investigated disease severity in obese individuals with chronic cough.

MATERIALS AND METHODS

Study design and population

The CGPS is a Danish population-based prospective cohort study initiated in 2003 with ongoing enrolment. All individuals in Denmark are assigned a unique identification number at birth/immigration and recorded in the national Danish Civil Registration System. By using this unique number, individuals aged 20–100 years are randomly selected and invited from the national Danish Civil Registration System to reflect the adult Danish population. All participants completed a comprehensive questionnaire, underwent a physical examination and gave blood for biochemical analyses.¹ Questionnaires were reviewed at the day of attendance by a healthcare professional together with the participant.

Chronic cough and obesity

Chronic cough was defined as an affirmative response to the question: ‘Do you have a cough lasting for more than 8 weeks?’ in accordance with the clinical recommendations from the American College of Chest Physicians, the British Thoracic Society, and the European

Respiratory Society.^{1 3–5 13} A subset of individuals with chronic cough completed the Leicester Cough Questionnaire (LCQ), a validated health-related quality of life questionnaire specifically developed for patients with chronic cough^{1 14}; reduced scores in the LCQ are associated with greater impairment in cough related quality of life.

BMI was calculated as measured weight divided by measured height squared (kg/m^2). Individuals were divided into five groups based on the WHO classification: underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$), normal weight ($18.5\text{--}24.9 \text{ kg/m}^2$), overweight ($25.0\text{--}29.9 \text{ kg/m}^2$), obese ($30.0\text{--}34.9 \text{ kg/m}^2$) and severely obese ($\geq 35.0 \text{ kg/m}^2$).

Clinical outcomes and other relevant information

Prebronchodilator forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were measured as described previously.¹⁵ COPD was defined as $\text{FEV}_1/\text{FVC} < 0.70$ excluding individuals with asthma.¹⁶ Asthma was defined as an affirmative response to the question: 'Do you have asthma?'.¹⁷ Individuals with asthma and/or COPD were excluded ($n=10\,977$), as chronic cough is a common symptom in these diseases (figure 1). Smoking status was defined as never, former or current smoking. Cumulative tobacco consumption was calculated in pack-years based on information on age at smoking initiation and cessation, duration of tobacco consumption, and amount of consumed tobacco in form of number of daily consumed cigarettes, cheroots and cigars and grams of weekly consumed pipe tobacco: a pack-year was defined as 20 cigarettes or equivalent smoked daily for a year. Dyspnoea was shortness of breath during different levels of activity, at night-time and/or while seated/at rest. Wheezing was whistling or wheezing while breathing. Sputum production was phlegm from the lungs in the morning and/or during the day for as long as three consecutive months each year. Chronic non-productive cough was defined as chronic cough without sputum production, while chronic productive cough was defined as chronic cough with sputum production. Information on health-care utilisations was self-reported and available for a subset of individuals.

Hypertension was defined as systolic blood pressure $\geq 140 \text{ mm Hg}$, diastolic blood pressure $\geq 90 \text{ mm Hg}$ and/or use of antihypertensive medication. Gastro-oesophageal reflux disease (GERD) was defined as an affirmative response to the question 'Do you experience episodes of acid reflux?', use of antireflux medication and/or an official doctor diagnosis according to the national Danish Patient Registry (International Classification of Diseases (ICD)-10: K21). Diabetes was based on self-report, nonfasting plasma glucose $> 11 \text{ mmol/L}$ or use of antidiabetic medication. Blood eosinophilia was defined as blood eosinophil counts $\geq 300 \text{ cells}/\mu\text{L}$. Hay fever was defined as an affirmative response to the question 'Do you have hay fever?'. Allergy was defined if

participants reported asthma, hay fever or eczema as a reaction to food, medication, grass, flower, animal hair or other allergens. Upper airway cough syndrome, sometimes known as postnasal drip syndrome, was defined as having an official doctor diagnosis of different chronic inflammatory diseases affecting the upper airways according to the national Danish Patient Registry (ICD-8: 502–505 and ICD-10: J30–J34), as recommended from the American College of Chest Physicians.¹⁸ Bronchiectasis was defined as having an official doctor diagnosis according to the national Danish Patient Registry (ICD-8: 518 and ICD-10: J47). Occupational exposure and passive smoking were self-reported. Physical activity was reported according to hours per week and degree of activity in leisure-time. Level of education was reported as years attending school and income as annual household income. Intake of vegetables was reported as number of intakes per day and/or week.

Statistical analyses

Statistical analysis was performed using STATA/SE V.12.1 for Windows (StataCorp), and a two-tailed $p < 0.05$ was considered significant. Wilcoxon rank-sum, Pearson's χ^2 , Fisher's exact test and Student's t-test were used for group comparisons. Cuzick's non-parametric trend-test was used to assess for trend across ordered groups. Logistic regression model adjusting for age, sex and smoking status were used to assess risk of chronic cough. Potential risk factors related to chronic cough through obesity such as GERD, smoking, hypertension, diabetes, blood eosinophilia, hay fever, allergy, bronchiectasis, upper airway cough syndrome, female sex, occupational exposure, low income and low vegetable intake were included one by one as single mediators in mediation analyses (online supplemental figure S1). The beta coefficients were inspected with regard to statistical significance of the effect of the exposure (obesity) on the intermediate variable (the mediator), the effect of the mediator on the outcome (chronic cough), and their combined effect calculated from multiplying the beta coefficients.¹⁹ Significant mediators from the one by one analysis of mediation in the study population were all included in a multiple mediation analysis from which insignificant interactions were excluded. Final estimates of the proportion of excess risk mediated in the multiple mediator models were calculated using the following equation:

$$\text{Excess risk mediated} = \frac{\text{Total indirect effect}}{\text{Direct effect} + \text{Total indirect effect}}$$

The total indirect effect is the sum of all multiplied pairs of beta coefficients ($(\sum_{i=1}^n \beta_{i1} \times \beta_{i2})$), while the direct effect is the effect that the exposure (obesity) has on the outcome (chronic cough).

We validated the results from the mediation analysis using a method for decomposing total effects from logit models into direct and indirect effects²⁰ in order to use these for computing the proportion of mediation in one by one as well as multiple

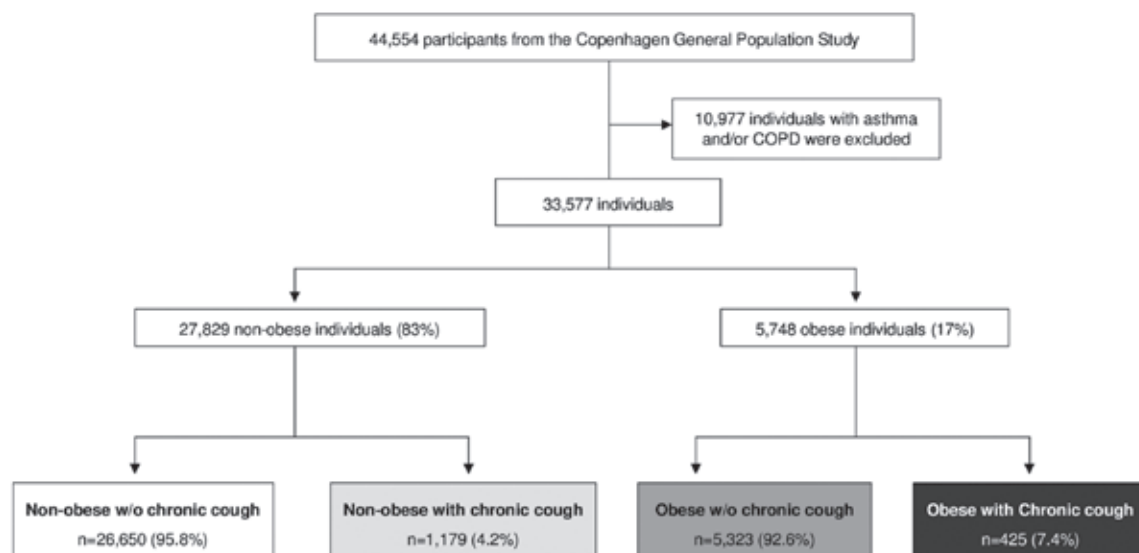


Figure 1 Flow chart. COPD, chronic obstructive pulmonary disease.

mediation results. This additional analysis showed similar results to those presented using the products of beta coefficients method.

For analyses stratified according to smoking status, the significant mediators from the one by one mediation analysis of the total population, were included in a new one by one analysis and reported, regardless of significance, while only significant mediators were included in multiple mediation analyses from which total excess risk mediated was calculated, as described above. Sensitivity analyses of mediation was performed by reintroducing individuals with asthma and/or COPD and rerunning the mediation analyses.

RESULTS

Among 33 577 individuals without asthma and/or COPD in the CGPS, 5748 (17%) were obese (BMI ≥ 30 kg/m²), of whom 425 (7.4%) had chronic cough (figure 1). Among the remaining 27 829 non-obese individuals, 1179 (4.2%) had chronic cough. Obese individuals with chronic cough vs without were more likely older, had lower lung function and were more often physically inactive (table 1). Furthermore, these individuals were more often current smokers with higher cumulative tobacco consumption and had more often occupational exposure to dusts and/or fumes. Similar differences could be observed when comparing non-obese individuals with vs without chronic cough. Among individuals with chronic cough, 26% were obese (425 individuals) compared with 17% (5323 individuals) in individuals without chronic cough.

Obesity and risk of chronic cough

The prevalence of chronic cough in the general population was stepwise increased with increasing BMI (figure 2). The prevalence of chronic cough was 9.0% in severely obese, 6.9% in obese, 5.0% in overweight, 3.5% in normal weight and 4.6% in underweight individuals. A similar pattern could be observed in current smokers and non-smokers, ranging from 19% to 5.7% in current smokers and 7.8% to 3.1% in non-smokers (figure 2). Correspondingly, risk of chronic cough was stepwise increased with increasing BMI in the general population (figure 3). Compared with normal weight individuals, adjusted OR for chronic cough was 2.6 (95% CI 2.1 to 3.2) in severely obese, 1.9 (95% CI 1.7 to 2.2) in obese and 1.4 (95% CI 1.2 to 1.6) in overweight

individuals. Similar results were seen for current smokers and non-smokers (figure 3) and in subgroup analyses where chronic cough was stratified into non-productive and productive chronic cough (online supplemental figure S2). Impaired cough related quality of life (lower LCQ scores) was not significantly associated with increasing BMI in individuals with chronic cough (online supplemental figure S3).

Obesity and chronic cough complications

Among obese individuals in the general population, those with chronic cough vs those without had more often accompanying respiratory symptoms, including dyspnoea, night-time dyspnoea, wheezing and sputum production (figure 4). Similar differences could be observed when comparing non-obese individuals with chronic cough versus those without chronic cough.

Among obese individuals, those with chronic cough vs those without had more often GERD, diabetes, blood eosinophilia, bronchiectasis and higher levels of high-sensitive C reactive protein, fibrinogen, leucocytes, neutrophils and eosinophils in blood (table 2). Similar differences could be observed when comparing non-obese individuals with versus without chronic cough but also included more frequent hypertension and upper airway cough syndrome. Number of visits to the general practitioner and emergency department and number of hospitalisation days in the past 12 months increased with presence of obesity and chronic cough (online supplemental figure S4).

Mediators of chronic cough from obesity

In mediation analysis, GERD in obese vs non-obese individuals mediated 23% of the increased risk of chronic cough in the general population (figure 5). Corresponding values were 10% for low vegetable intake, 8% for occupational exposure, 7% for hypertension, 3% for smoking, 3% for low income and 2% for blood eosinophilia. After excluding hypertension, the six other variables could explain 38% of the increased risk for chronic cough in obese individuals in a multifactorial analysis.

Among current smokers, GERD in obese versus non-obese individuals mediated 16% of the increased risk of chronic cough (figure 5). Corresponding values were 6% for low vegetable intake and 4% for low income. After excluding low income, 21% of the increased risk for chronic cough in obese smokers were

Table 1 General characteristics of individuals with obesity and chronic cough

	Non-obese w/o chronic cough n=26 650	Non-obese with chronic cough n=1179	Obese w/o chronic cough n=5323	Obese with chronic cough n=425
Age (years)	57 (49–67)	62 (53–71)***	60 (51–69)*** †††	63 (53–71)*** ††
Female (%)	15 012 (56)	677 (57)	2759 (52)*** †††	239 (56)
BMI	24.8±2.8	25.3±2.8***	33.5±3.5*** †††	33.9±3.5*** ††† †
FEV ₁ % predicted	103.2±13.6	99.7±15.2***	97.7±14.5*** †††	93.7±15.4*** ††† †††
FVC % predicted	105.1±13.3	101.4±14.3***	98.7±14.5*** †††	95±14.8*** ††† †††
FEV ₁ /FVC	0.774 (0.743–0.807)	0.767 (0.735–0.801)***	0.782 (0.750–0.814)*** †††	0.773 (0.741–0.808)† †††
Low education (%)	3617 (14)	244 (21)***	1313 (25)*** ††	108 (25)*** †
Low income (%)	1879 (7)	132 (11)***	598 (11)***	58 (14)***
Occupational exposure to dusts/fumes (%)	1690 (6)	159 (13)***	643 (12)***	73 (17)*** ††
Passive smoking (%)	1647 (6)	129 (11)***	557 (10)***	57 (13)***
Physically inactive (%)	855 (3)	58 (5)**	527 (10)*** †††	57 (13)*** ††† †
Never-smokers (%)	13 579 (51)	493 (42)***	2401 (45)*** †	151 (36)*** † †††
Former smokers (%)	10 658 (40)	451 (38)	2414 (45)*** †††	182 (43)
Current smokers (%)	2244 (8)	235 (20)***	484 (9)†††	92 (22)*** †††
Cumulative tobacco consumption (pack-years)	10 (4–21)	15 (6–30)***	17 (8–30)***	22 (9–38)*** ††† †††

Data are presented as median with 25 and 75 percentiles, numbers (%), or mean±SD.

P<0.01, *P<0.001 versus non-obese individuals without chronic cough calculated with the Wilcoxon rank-sum test, Pearson χ^2 test or Student's t-test.

†P<0.05, ††P<0.01, †††P<0.001 versus non-obese individuals with chronic cough calculated with the Wilcoxon rank-sum test, Pearson χ^2 test or Student's t-test.

‡P<0.05, ‡‡P<0.01, ‡‡‡P<0.001 versus obese individuals without chronic cough calculated with the Wilcoxon rank-sum test, Pearson χ^2 test, or Student's t-test.

BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

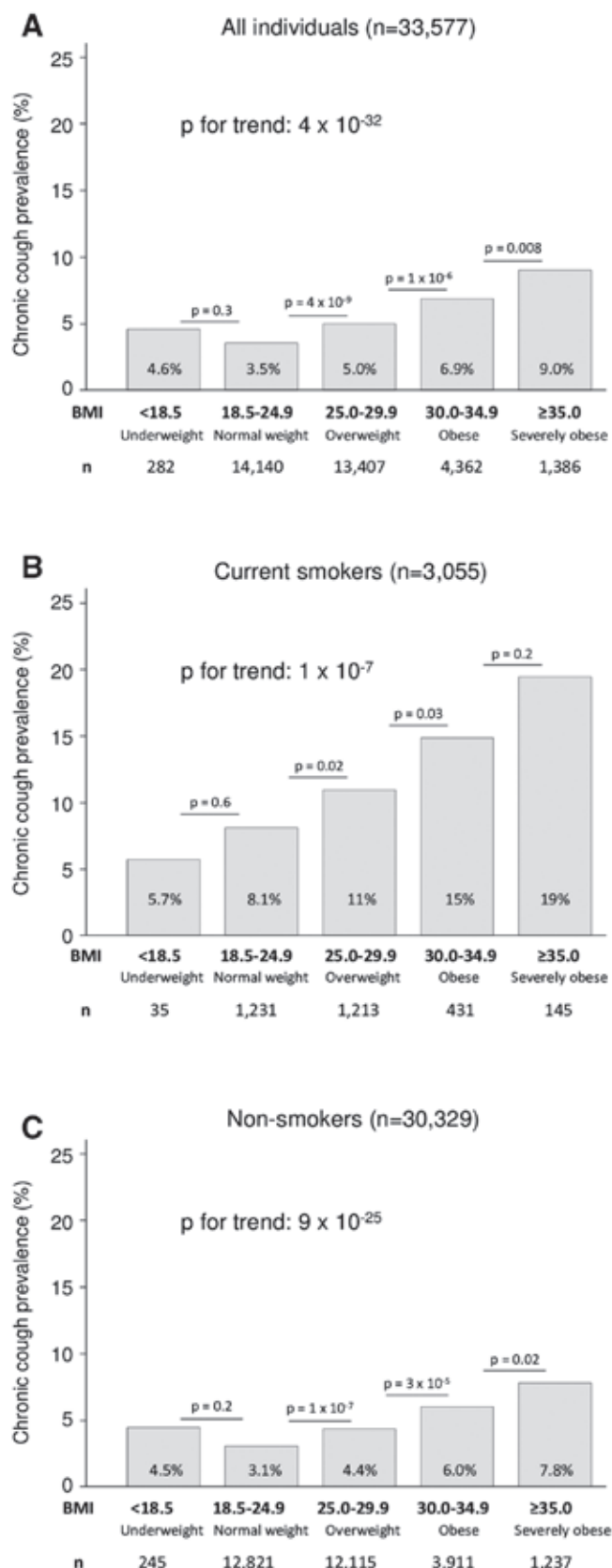


Figure 2 Prevalence of chronic cough according to BMI. P values obtained from Pearson's χ^2 test. BMI, body mass index.

mediated through GERD and low vegetable intake. Among non-smokers, GERD in obese versus non-obese individuals mediated 25% of the increased risk of chronic cough (figure 5). Corresponding values were 11% for hypertension, 10% for low vegetable intake, 9% for occupational exposure, 2% for low income, 2% for blood eosinophilia and 2% for smoking (only relevant for former smokers). After excluding low income and smoking, these five variables could explain 45% of the increased risk for chronic cough in obese non-smokers.

When individuals with asthma and/or COPD were included and were used as mediators in the analysis, 41% of the increased risk for chronic cough in obesity was being mediated through GERD, asthma, low vegetable intake, occupational exposure, low income, blood eosinophilia, smoking and COPD.

DISCUSSION

This study describes the relationships between chronic cough and obesity in a large population-based cohort, providing by far the most convincing evidence to date for a link between obesity and chronic cough. The main finding is of a dose-response relationship between obesity and prevalence of chronic cough, present irrespective of smoking status. Chronic cough risk was up to threefold higher in obese individuals independent from age, sex, smoking, asthma and COPD. Furthermore, we found that the risk of chronic cough associated with obesity was partly mediated through GERD, low vegetable intake and occupational exposures, supporting that there may be benefit to gain by ameliorating some of these factors in obese individuals with chronic cough.

The study also revealed that among obese individuals, those with chronic cough versus those without had worse accompanying respiratory symptoms, more often comorbidities including GERD and diabetes, greater healthcare utilizations, lower lung function and higher levels of markers of inflammation in blood. This indicates that chronic cough in obese individuals is associated with more severe pulmonary involvement independent from common respiratory diseases like asthma and COPD. This could be related to other unidentified chronic respiratory diseases (other than asthma and COPD) in the obese patients with chronic cough; however, we are unaware of any results suggesting that this is the case. We suggest that the phenotype is examined in further detail, for example, with regard to pulmonary inflammation, airway remodelling and response to therapy.

Consistent with our finding of a dose-response relationship between BMI and chronic cough risk, previous reports have also observed a positive association of obesity with coughing or chronic cough.^{6 10-12 21} Recently, Zeiger *et al* found that adults with specialist-diagnosed chronic cough more often had obesity compared with matched controls (25% vs 19%).⁶ Arinze *et al* by defining chronic cough as coughing nearly daily for three consecutive months or more the past 2 years found an elevated OR for obesity of 1.3 in the Rotterdam Study.²¹ Ford *et al* found a similar elevated OR of 1.7 for obesity in individuals with cough from primary care.¹⁰ Morales-Estrella *et al* found that cough was more often of greater severity in patients with higher BMI.¹¹

Our mediation analysis showed that the three intermediate variables that explained the highest excess risk of chronic cough from obesity in the general population were GERD with 23%, low vegetable intake with 10%, and occupational exposure to dust/fumes with 8%. Both in overall and in stratified analyses, other mediators of importance were hypertension, smoking, low income and blood eosinophilia. When individuals with asthma and COPD were included in the analyses, the three intermediate variables that explained the highest excess risk of chronic cough from obesity were GERD, asthma and low vegetable intake, followed by occupational exposure, low income, blood eosinophilia, smoking and COPD. Female sex did not have association with chronic cough in line with previous results from our cohort study.¹

GERD has been an established risk factor for chronic cough in obese individuals for many years.²² Mechanistically, elevated intra-abdominal and intragastric pressures in obese individuals facilitate movement of gastric juice from the stomach to the oesophagus causing increased cough reflex.²³ Current guidelines on chronic cough due to GERD recommend diet modification to promote weight loss in overweight or obese adult patients, head-of-bed elevation and avoiding meals within 3 hours of bedtime, and in patients reporting heartburn and regurgitation, proton-pump inhibitors, H₂-receptor antagonists, alginate or antacid therapy.^{3 24}

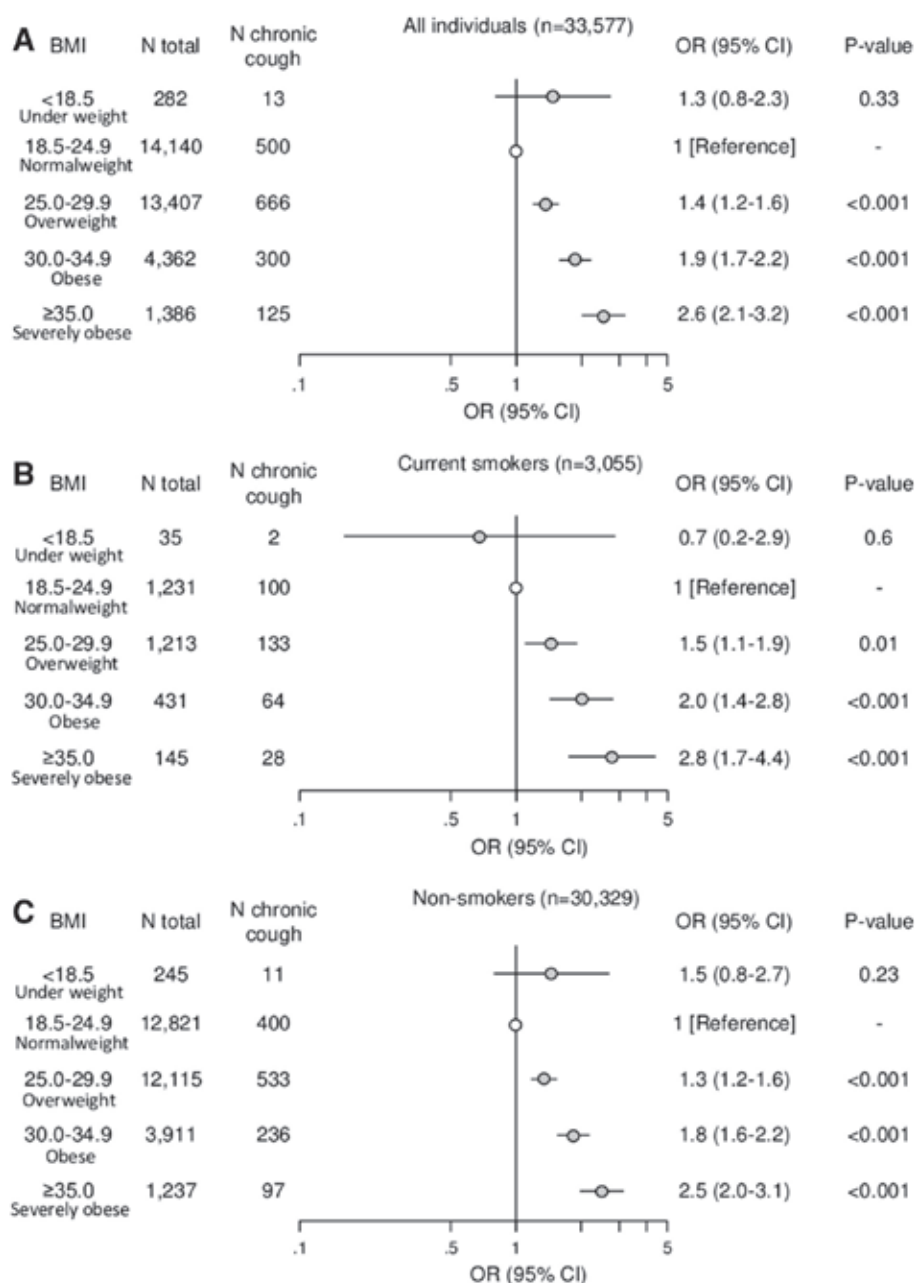


Figure 3 Risk of chronic cough according to BMI. OR with 95 CIs obtained from logistic regression models, multivariable adjusted for age and sex. P values obtained from Wald's test. BMI, body mass index.

In line with our results for vegetable intake, previous studies indicate an inverse relationship between dietary fibres and coughing/chronic cough.^{1 25-29} Mechanistically, consumption of more high-fat diet by obese individuals has been suggested to play a role in GERD, and thereby chronic cough, by decreasing gastric emptying, reducing the oesophageal sphincter-pressure, and increasing the number of episodes of transient lower oesophageal sphincter relaxation.³⁰ Smith *et al* demonstrated that low calorie and fat intake and weight loss were associated with reduced cough symptoms in patients with obesity and cough due to airway reflux.²⁶ Butler *et al* revealed dietary fibres may reduce development of cough with phlegm in the general population,²⁸ and Omenaas *et al* found that dietary vitamin C intake was inversely associated with cough in young smokers.²⁵

Environmental and occupational exposure to noxious gasses or particles has been suggested as a risk factor for chronic cough in previous reports,^{1 27} and guidelines recommend that such exposures should be considered and reduced if present.^{4 31} We speculate that obese individuals could have increased susceptibility to chronic cough from occupational exposures, due to higher minute ventilation which may result in higher deposition of particles in their lungs compared with normal weight individuals.³²⁻³⁴ This

may, with time, be further amplified due to lung function impairments associated with obesity.^{33 35} Other factors not included in the study for example, shear (mechanical) stresses on the airway in the obese individuals may also be important mediators of increased chronic cough risk in obese individuals in the population. Occupational exposure, poor diet, GERD and other analysed factors together explained only up to 38% of the excess risk of chronic cough conferred by obesity in the study.

Our study showed that obese individuals with chronic cough in the general population had more severe disease in terms of worse additional respiratory symptoms and comorbidities, and lower lung function. Although results for LCQ score did not reach statistical significance, there was a trend towards lower scores with increasing BMI in individuals with chronic cough. This non-significant trend in LCQ score could be due to reduced statistical power for this particular analysis. However, the obese patients were also more likely to be smokers, and less active, and it could be that these patients did not find coughing impacts much on their quality of life. Morales-Estrella *et al*¹¹ demonstrated greater cough severity with increasing BMI using a visual analogue scale, while our results for cough-related quality of life assessed only one component of cough severity. Together the data may support that obese patients

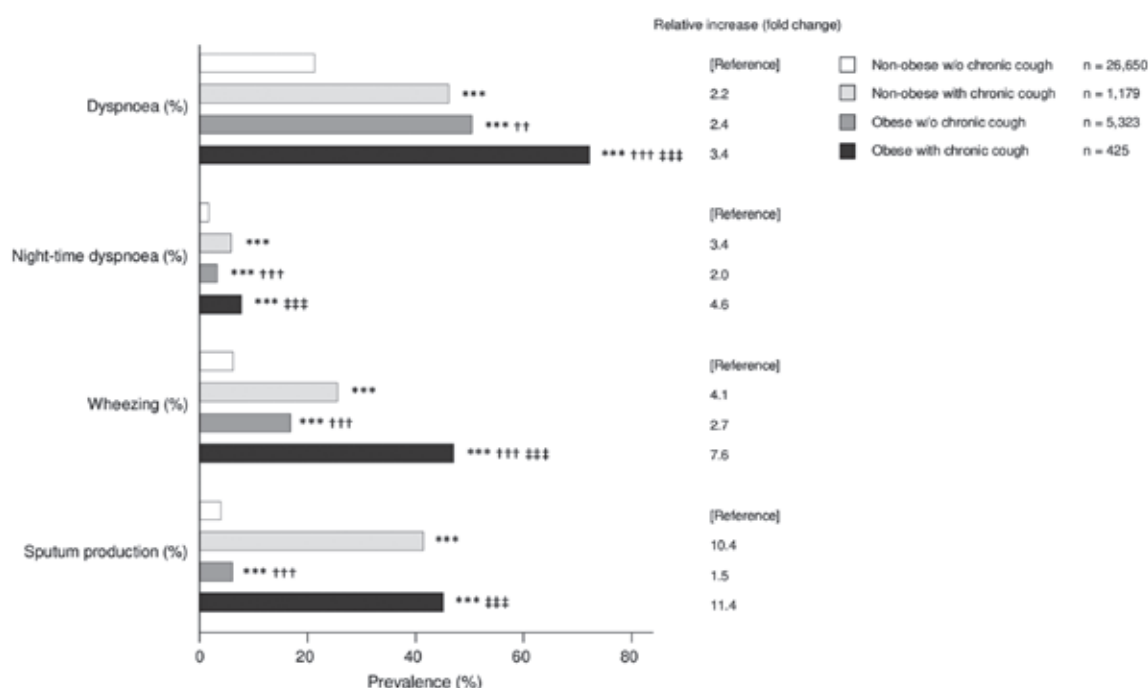


Figure 4 Accompanying respiratory symptoms in individuals with obesity and chronic cough. *** $P < 0.001$ for comparison with individuals without obesity or chronic cough. †† $P < 0.01$, ††† $P < 0.001$ for comparison with individuals without obesity but with chronic cough. ††† $P < 0.001$ for comparison with individuals with obesity but without chronic cough. P values obtained from Pearson's χ^2 test.

with chronic cough had a more severe disease phenotype or that they were more likely to have an underlying lung disease other than asthma and COPD given the reductions in lung function and increased healthcare utilisations.

Strengths of the present study include a large sample from the general population, and the collection of endpoints without prior knowledge of the participant's disease or risk factor status. A potential limitation is the cross-sectional study design, which cannot determine if the association between BMI and chronic cough risk is causal. Consequently, the risk estimates in the mediation analysis could potentially be confounded by other risk factors for chronic cough correlated with the intermediate variables; however, reverse causation or unmeasured confounding seem unlikely as obesity and the associated intermediate variables have previously been

described as risk factors for chronic cough, and since we observed an independent dose-response relationship. Some of the individuals with the most severe types of obesity and chronic cough may not have attended the physical examination and participated in the study. This could theoretically tend to bias the results towards the null hypothesis and lead us to underestimate the associations between individuals with obesity and chronic cough and the investigated clinical outcomes. Generalisability of our results may be limited as 99.9% of the individuals studied were of white Caucasian descent; however, this also makes our results less dependent on influences caused by ethnic differences. That said, we are not aware of results which would suggest that our findings are not relevant to individuals of all races. Finally, we used self-reported GERD and hypertension medication exposures. However, a recent

Table 2 Comorbidities and inflammatory biomarkers in blood in individuals with obesity and chronic cough

	Non-obese w/o chronic cough n=26 650	Non-obese with chronic cough n=1179	Obese w/o chronic cough n=5323	Obese with chronic cough n=425
Hypertension (%)	14347 (54)	721 (61) ***	4130 (78) *** †††	320 (75) *** †††
GERD (%)	3440 (13)	342 (29) ***	1389 (26) ***	169 (40) *** ††† †††
Diabetes (%)	787 (3)	70 (6) ***	612 (11) *** †††	82 (19) *** ††† †††
Upper airway cough syndrome (%)	1294 (5)	81 (7) **	290 (5)	27 (6)
Blood eosinophilia (%)	533 (2)	35 (3) *	132 (3) *	18 (4) ** †
Bronchiectasis (%)	55 (0)	24 (2) ***	14 (0) †††	7 (2) *** †††
Allergy (%)	6936 (26)	334 (28)	1382 (26)	122 (29)
Hay fever (%)	5674 (21)	269 (23)	1112 (21)	99 (23)
Hs-CRP—mg/dL	0.9 (0.5–1.7)	1.3 (0.7–2.5) ***	2.2 (1.2–3.9) *** †††	2.6 (1.4–5.4) *** ††† †††
Fibrinogen— μ mol/L	10.4 $\pm$ 2.0	11.2 $\pm$ 2.3 ***	11.8 $\pm$ 2.2 *** †††	12.2 $\pm$ 2.2 *** ††† †††
Leucocytes $\times 10^9/L$	6.7 $\pm$ 2.4	7.1 $\pm$ 2.1 ***	7.5 $\pm$ 2.1 *** †††	7.7 $\pm$ 1.9 *** ††† †
Neutrophils $\times 10^9/L$	3.9 $\pm$ 1.2	4.2 $\pm$ 1.3 ***	4.4 $\pm$ 1.3 *** †††	4.5 $\pm$ 1.4 *** ††† ††
Eosinophils $\times 10^9/L$	0.14 (0.10–0.21)	0.16 (0.10–0.23) **	0.17 (0.11–0.24) *** †††	0.19 (0.11–0.27) *** ††† ††
IgE—IU/mL	15 (4–44)	14 (4–40)	19 (6–57) *** †††	18 (5–50)

Data are presented as numbers (%), median with 25 and 75 percentiles or mean $\pm$ SD.

* $P < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for comparison with non-obese individuals without chronic cough.

††† $P < 0.001$ for comparison with non-obese individuals with chronic cough.

† $P < 0.05$, †† $p < 0.01$, ††† $p < 0.001$ for comparison with obese individuals without chronic cough.

GERD, gastro-oesophageal reflux disease;

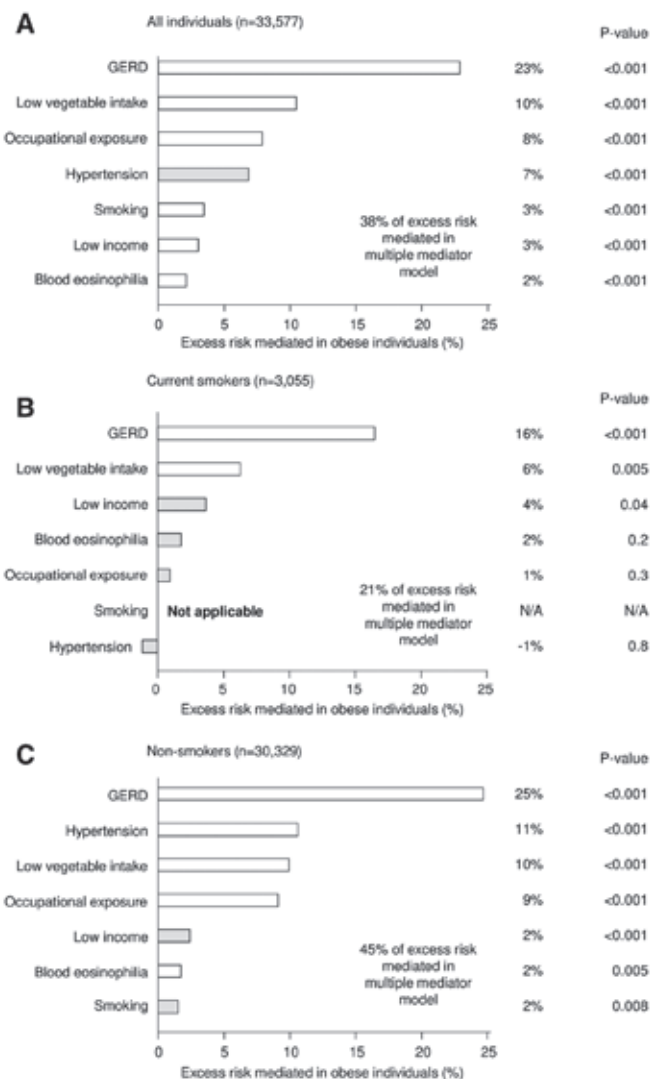


Figure 5 Mediated excess risk of chronic cough in individuals with obesity. Mediators were identified in all 33 577 individuals using the product of coefficients method in a logistic regression model. P values are for significance of the mediated effect (axb) in univariate analysis. Grey bars indicate non-significance in the multiple adjusted analysis with $p \geq 0.05$. GERD, gastro-oesophageal reflux disease; N/A, not available.

Danish study found similar or better estimates of medicine exposure by self-report vs the National prescription registry for acid related disorder drugs (75% vs 80%, excl. over-the-counter drugs) and for cardiovascular drugs (92% vs 42%).³⁶

In conclusion, there was dose-response relationship between BMI and chronic cough, and chronic cough risk was up to twofold to threefold higher in obese individuals from the general population. The increased risk was partly mediated by GERD, low vegetable intake and occupational exposures, suggesting that there may be benefit to gain by ameliorating some of these factors in obese individuals with chronic cough.

Correction notice This article has been corrected since it was published Online First. Changes have been made to table 1 footnote, figure 4 legend and a minor change has been made to an in-text citation.

Contributors EML, YC, BGN, PL and MD contributed to the study concept and design. EML, YC, BGN, PL and MD collected, analysed or interpreted the data. EML wrote the draft manuscript and did the statistical analyses. EML, YC, BGN, PL and MD revised the manuscript for important intellectual content.

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Competing interests YC reports personal fees from AstraZeneca, Boehringer Ingelheim and Sanofi Genzyme outside the submitted work. PL reports grants from AstraZeneca and GlaxoSmithKline and personal fees from Boehringer Ingelheim, AstraZeneca, Novartis, and GlaxoSmithKline outside the submitted work. EML, BGN and MD have nothing to disclose.

Patient consent for publication Not required.

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Data availability statement Data are available upon reasonable request. Summarised data and scripts for analyses are available according Danish law.

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ARTIGO ORIGINAL

A função pulmonar, os basófilos e eosinófilos periféricos e nas vias respiratórias estão associados a endotipos farmacogenômicos moleculares de resposta aos esteroides na asma grave

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RESUMO

Introdução A asma é uma doença complexa de expressão/gravidade heterogênea. Existe um interesse crescente em definir endotipos da asma consistentemente associados a diferentes respostas terapêuticas, concentrando-se na inflamação de tipo 2 (Th2) como um mecanismo patológico fundamental. Os endotipos atuais da asma definem-se principalmente por critérios clínicos/laboratoriais. Cada endotipo é provavelmente caracterizado por mecanismos moleculares distintos que identificam terapias ótimas.

Métodos Aplicamos uma análise não supervisionada (sem critérios clínicos a priori) dos componentes principais dos dados transcriptômicos de sequenciamento de ARN de células de expetoração das vias respiratórias de 19 asmáticos do Programa de Investigação de Asma Grave no início do estudo e entre as 6-8 semanas de seguimento após uma dose de 40 mg de corticosteroides intramusculares. Investigamos os componentes principais PC1, PC3 para associação com 55 variáveis clínicas.

Resultado PC3 foi associado a características clínicas basais Th2, incluindo eosinofilia no sangue (*rank-sum* $p=0,0082$) e nas vias aéreas (*rank-sum* $p=0,0024$), alteração do FEV₁ (Kendall tau-b $R=-0,333$ (-0,592 a -0,012)) e seguimento do FEV₁ como resposta ao albuterol (Kendall tau-b $R=0,392$ (0,079 a 0,634)). PC1 com basofilia sanguínea (*rank-sum* $p=0,0191$). O top 5% dos genes que contribuem para PC1, PC3 foram enriquecidos para diferentes ontologias do sistema imunitário/inflamação, sugerindo distintos *clusters* específicos por indivíduo de resposta transcriptômica aos corticosteroides. A associação de PC3 com a alteração no FEV₁ foi reproduzida *in silico* num conjunto de dados independentes e comparáveis de 14 sujeitos (início do estudo, 8 semanas após inalação diária de corticosteroides (ICS)) referentes a microARNoma de células epiteliais das vias aéreas.

Conclusões Os PC transcriptômicos desta metodologia não supervisionada definem endotipos farmacogenômicos moleculares que podem produzir uma nova biologia subjacente a diferentes respostas específicas ao tratamento da asma com corticosteroides e um cuidado otimizado e personalizado da asma. Os genes que mais contribuem para estes PC podem sugerir novos objetivos terapêuticos.

INTRODUCTION

Asthma is a common complex disease with heterogeneity in both expression and severity. Multiple studies have addressed clinically based endotypes of asthma.¹⁻⁸ Despite heterogeneity in asthma study populations and their defining clinical features/criteria, some universally recognised common clinical subgroups have emerged. These include mild atopic asthma originating in childhood, atopic asthma with lower lung function, and medication-resistant exacerbation-prone asthma. Clinical endotypes have also been consistently associated with different responses to therapy.⁹

Key messages

What is the key question?

► Can we discover asthma endotypes using transcriptomic data alone before/after corticosteroid treatment in asthmatic airway cells that are clinically relevant to disease typing and therapeutic response?

What is the bottom line?

► In a population of 19 mainly severe asthmatic adults, we show that their sputum airway cell transcriptomic changes 6–8 weeks after a single systemic corticosteroid treatment can be used (without any a priori clinical/laboratory criteria) to define molecular pharmacogenomic endotypes that are associated with type 2 inflammation asthma clinical features and changes in lung function.

Why read on?

► This methodology is readily adaptable to similar study designs of corticosteroid treatment response in asthma. The top contributing genes to these endotypes may yield novel biology of corticosteroid treatment response and new therapeutic targets.

With the advent of next generation biologics for the treatment of severe asthma, endotyping efforts have focused on identifying type-2 airway inflammation (Th2) asthma.¹⁰⁻¹⁴ Currently, asthma endotypes have been defined primarily by clinical laboratory or biomarkers criteria.⁹ For example, the Th2 clinical features include fractional exhaled nitric oxide (FeNO) >25 ppb, peripheral blood eosinophil count >300 (or >150, 2 cut-offs considered separately) cells/μL, and sputum eosinophils >2%. There has been no reported molecular clustering in asthma without these *a priori* clinical criteria.¹⁵⁻¹⁶ A common theme is that each endotype is likely characterised by distinct molecular mechanisms that may identify optimal therapies for targeting the endotype.¹⁻²⁻⁵⁻⁶⁻¹⁷ Indeed, several studies have reported distinct transcriptomic differences that appear to correlate with clinical subgroups.⁷⁻¹⁸⁻¹⁹

The aim of this study is to extend the concept of molecular endotype identification in asthma in novel directions through RNA-sequencing (RNA-seq) of sputum airway cells derived from a subset of 19 asthmatic subjects in the Severe Asthma Research Program (SARP, Wake Forest

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University centre) at baseline before (baseline), and 6–8 weeks after (follow-up) administration of a 40 mg dose of intramuscular corticosteroid (CS).¹⁵ We used the unsupervised principal components (PCs)^{20–22} of transcriptomic changes following systemic CS treatment to define distinct molecular pharmacogenomic endotypes, derived independently of any *a priori* clinical criteria and evaluated these endotypes for their association with clinical features (focusing on Th2 ones) and clinical response outcomes.

METHODS

Study population and biological samples

The study population consisted of 19 subjects from the National Heart, Lung and Blood Institute Severe Asthma Research Program 3 (SARP 3, Wake Forest University centre Institutional Review Board IRB00021507) ClinicalTrials.gov identifier NCT01750411. Twelve subjects in this longitudinal cohort have severe asthma and seven have non-severe (mild to moderate) asthma. All subjects underwent extensive phenotyping²³ including an induced phenotype where each subject had systemic CS responsiveness characterised before ('baseline'), and 6–8 weeks after ('follow-up') the administration of a 40 mg dose of intramuscular CS triamcinolone acetonide.¹⁵ Sputum was obtained at both baseline and follow-up using standardised SARP protocols.^{24–26} Thirty-eight transcriptome profile samples of subject sputum cells total were obtained using RNA-seq: 19 subjects×2 timepoints.

RNA-seq and data analysis

Expanded in online supplemental methods M1. Briefly, unsupervised principal component analysis (PCA) was applied on the subject-wise sample difference (follow-up minus baseline) column vectors of expression of 16944 robustly detected genes to identify the dominant directions of sample variation in transcriptome space called PCs20 21 focusing on PC1–3. Sample PC coordinates were tested for association with the 55 core clinical variables, online supplemental table S1. Gene ontology (GO) enrichment analysis was performed on the top 5% contributing genes of each PC. All data used in this study will be publicly available on NCBI GEO GSE184433.

RESULTS

The 19 SARP subjects in this study are listed on online supplemental table S2 with select clinical variables at baseline, and their change (follow-up minus baseline) 6–8 weeks after a 40 mg dose of intramuscular CS. Sputum cell samples were obtained at baseline and follow-up, and the 19×2 sputum sample transcriptome profile were obtained using RNA-seq and analysed. Figure 1 outlines the analysis workflow and key results on these transcriptomic data with select clinical variables, and on a comparable independent set of airway epithelial cells (N=14 subjects) microRNAome dataset GSE34466²⁷ on NCBI GEO to assess generalisability of our strategy and results in silico.

Sputum cell transcriptomic PC1 and PC3 sample coordinate dichotomies are associated with Th2 clinical features

We applied PCA on the CS treatment sample difference/change (follow-up minus baseline, paired) column vectors of 16944 genes for all 19 subjects. Without using any clinical variables, PCA identifies the directions of dominant global variance among the 19 subjects in this 16 944-gene dimensional sputum cell transcriptome space. PC1–3 accounted for 28.93%, 19.95% and 11.93% of the global transcriptomic variance, respectively. We plotted the 19 subjects in PC1–3 space, and visual inspection suggests transcriptomic clusters within quadrants of PC1/PC3 space, figure 2A–B.

We dichotomised PC1 and PC3 coordinates at 0, respectively, to define transcriptomic endotypes, and we checked whether these dichotomies/endotypes were associated with CS treatment response in particular Th2 clinical features (eg, FeNO, sputum eosinophil %) and lung function change, table 1.

PC1 dichotomy was significantly associated with baseline blood basophil count ($p=0.0191$, Wilcoxon rank-sum). PC3 dichotomy was significantly associated with baseline blood eosinophil count ($p=0.0082$), baseline ($p=0.0024$) and change ($p=0.0181$) in sputum

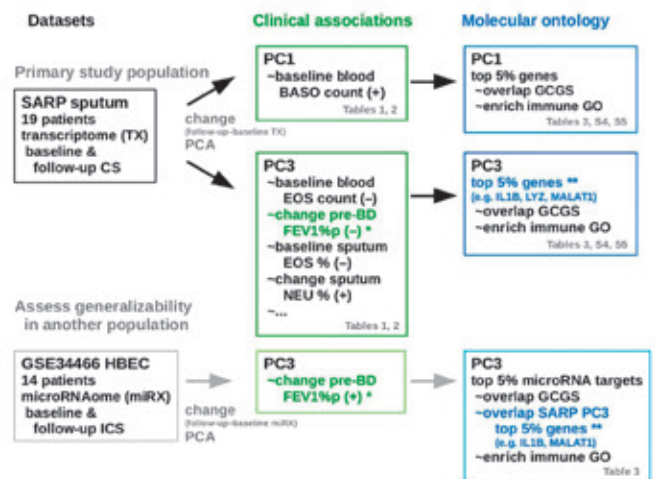


Figure 1 Outline of the analysis workflow and key results from the primary study population of 19-subject sputum transcriptome dataset with select clinical variables from the Severe Asthma Research Program, and on a comparable independent 14-subject airway epithelial cells (HBEC) microRNAome dataset GSE34466 on NCBI GEO for assessing the generalisability of the strategy and results in silico. CS, corticosteroid; BASO, basophils; EOS, eosinophils; GCGS, glucocorticoid gene set; GO, Gene ontology; HBEC, human bronchial epithelial cells; NEU, neutrophils; PC#, principal component #; PCA, principal component analysis; SARP, Severe Asthma Research Program.

eosinophil %. Thus, the molecular endotypes of CS treatment response defined by PC1 and PC3 dichotomies are directly associated with baseline blood basophilia (PC1), baseline blood eosinophilia (PC3), and baseline/change in sputum/airway eosinophilia (PC3). We also noted there were no significant associations with FeNO or pre-bronchodilator (BD) FEV₁ percent predicted (%p). PC2 dichotomised at 0 was not associated with any clinical variables here.

Sputum cell transcriptomic PC1 and PC3 sample coordinates associated with baseline blood basophil and eosinophil counts respectively

Next, to increase the power of our transcriptomic endotype analysis, we treated the subject PC1–3 coordinates as continuous variables (not dichotomised as above), and we checked whether these coordinates were associated with 55 core clinical variables, online supplemental table S1). We highlight select clinical variable associations for investigation in table 2 focusing on Th2 clinical features. In addition, we investigated these associations within the 12/19 severe asthma sub-population.

PC1 was significantly associated with baseline blood basophil count (Kendall tau-b correlation $R=0.340$ (0.020 to 0.597) 95% CI). PC2 was not associated with any clinical variables here. PC3 with baseline blood eosinophil count ($R=-0.457$ (–0.680 to –0.158)) and baseline sputum eosinophil % ($R=-0.367$ (–0.627 to –0.051)), figure 2C–D. PC1 and PC3 were not associated with baseline/follow-up/change in FeNO. Within the 12/19 severe asthma sub-population, the baseline blood basophil (PC1) and eosinophil (PC3) associations were not significant, but the baseline sputum eosinophil % (PC3) became greater ($R=-0.509$ (–0.769 to –0.102)).

Focusing on the PC1 versus baseline blood basophil count, and PC3 versus baseline blood eosinophil count associations, we used ROC curve analyses to assess the diagnostic performance of PC1 and PC3 as binary classifiers of high versus not high baseline blood basophil and eosinophil counts respectively, as the PC discrimination threshold is varied, figure 3A–B. We consider a subject to have a high blood basophil count if their blood basophil count >10 cells/μL. For blood eosinophil count, we considered two cut-offs: >300 cells/μL yielding just 4/19 (21%) high blood eosinophil subjects, and >150 cells/μL yielding 12/19 (63%) high blood eosinophil subjects. The areas under receiver operator characteristic curve (AUCCH) values of 0.883 (PC1 vs blood basophil), and 0.900, 0.815 (PC3 vs blood eosinophil at >300, >150 cells/μL cut-offs) indicate

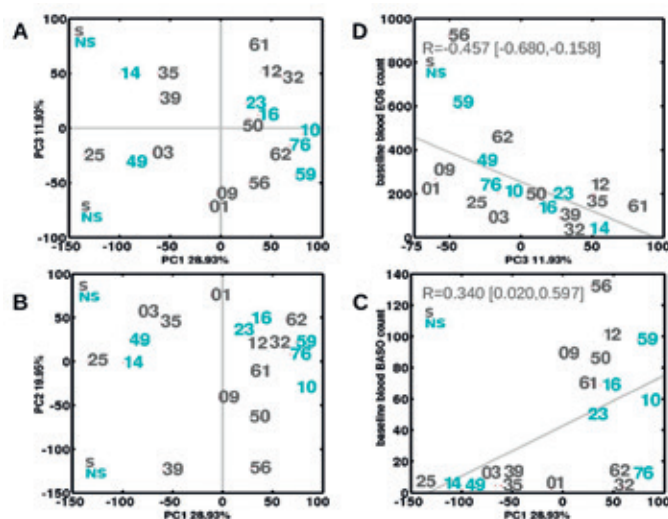


Figure 2 (A, B) Principal component (PC) analysis of corticosteroid induced transcriptomic change (follow-up minus baseline) sample coordinates in the PC1–3 planes. (C) PC1 sample coordinate versus baseline blood basophil count. (D) PC3 sample coordinate versus baseline blood eosinophil count. Each subject is indicated by their unique 2-digit identifier, 7/19 non-severe asthmatics are in cyan. The PC1 and PC3 dichotomy line at 0 is drawn in (A, B). The linear regression line is drawn in (C, D) and the Kendall tau-b correlation and 95% CI are indicated.

the CS treatment response PCs to be robust predictors of high baseline blood basophil and eosinophil counts, respectively.

Sputum cell transcriptomic PC3 sample coordinates sputum macrophage and neutrophil % following CS treatment

While the primary focus in our work here is Th2 clinical feature associations of PC1/3, we noted that PC3 was significantly associated with baseline/follow-up/change in sputum neutrophil % (Kendall tau-b $R=0.556$ (0.284 to 0.745)), and change in sputum macrophage % ($R=-0.485$ (−0.699 to −0.193)), table 2, figure 4C–D. Change in sputum neutrophil and macrophage % associations remain significant within the 12/19 severe asthma subpopulation. Blood neutrophil count is not associated with PC1–3.

sputum cell transcriptomic PC3 sample coordinates associated with change in pre-BD FEV_1 following CS treatment

A notable result when the subject PC3 coordinates is treated as a continuous variable (not dichotomised at 0) is that PC3 is significantly associated with two lung function measurements following CS, table 2, figure 4A–B, namely change in pre-BD FEV_1 %p (Kendall tau-b $R=-0.333$ (−0.592 to −0.012)), follow-up BD response ($R=0.392$ (0.079 to 0.634)). Within the 12/19 severe asthma subpopulation both associations became greater, and interestingly PC1 is now significantly associated with baseline ($R=0.485$ (0.071 to 0.756)) and follow-up ($R=0.576$ (0.195 to 0.806)) BD response.

Focusing on the change in pre-BD FEV_1 %p with PC3, we used a ROC curve analysis to assess the diagnostic performance of PC3 for discriminating lung function improvement. We consider a subject to have improved lung function if their change in pre-BD FEV_1 %p following CS is >0 . In this mainly severe asthmatic population (12/19 severe), just 2/19 had $>10\%$ increase in pre-BD FEV_1 %p and 8/19 had >0 . The AUCCH value of 0.864 indicate PC3 to be a robust predictor of lung function improvement following CS treatment, figure 3D. That is, PC-defined molecular endotypes resulting from CS treatment response can be used to as a pharmacogenomics predictor of clinical response.

In contrast to a supervised analysis, no baseline/follow-up Th2 clinical features were significantly associated with BD response or with change in pre-BD FEV_1 %p, table 2, online supplemental table S3. We did note that change in FeNO was associated with change in pre-BD FEV_1 %p.

Top contributing genes to sputum cell transcriptomic PC1 and PC3 enriched for immune system and inflammation GOs

We regard the top 5% PC loading coefficient magnitude genes as the top contributing genes driving variation along each respective PC coordinate axis. There are ~847/16 944 (~5%) such genes ranked by loading coefficient magnitude per PC after adjusting for ties and repeat genes. We investigated their GO enrichments separately. In contrast to a supervised analysis, we similarly investigated the top 5% genes rank correlated (magnitude) with Th2 clinical features: baseline blood basophil/eosinophil counts and FeNO, and change in FeNO.

First, we found strong overlap between top 5% PC1 genes (OR 4.07 (3.22 to 5.13) Fisher exact 95% CI) and top 5% PC3 genes (OR 3.73 (2.94 to 4.73)) with our previously reported glucocorticoid gene set (GCGS),²⁸ table 3. In contrast, the supervised top 5% Th2 clinical features correlated gene overlaps with GCGS were not significant or had smaller ORs. Also notable is that the top PC1 and PC3 gene sets strongly overlapped (OR 70.28 (59.02 to 83.70)), whereas the supervised top Th2 clinical features correlated gene sets overlaps were less strong (ORs range 0.22–6.29), table 4.

We separated the top 5% PC1 and PC3 contributing genes by loading coefficient sign prior to GO enrichment analysis, focused on the 10% highest enrichment scoring significant GO clusters, and summarised their keywords, table 5. For PC1 and PC3, we found significant and repeated enrichments of immune system and inflammation related ontologies among the top 10% scoring clusters. Interestingly, steroid metabolism ontologies are found in PC1 positive GO cluster 23, PC3 positive GO cluster 12 and PC3 negative GO cluster 100, data not shown. In contrast, the supervised top 5% Th2 clinical features correlated genes (except change in FeNO) had lesser enrichments for immune system and inflammation related GO clusters, online supplemental table S4.

Airway epithelial cells microRNAome PC3 sample coordinates associated with change in pre-BD FEV_1 following 8-week inhaled CS regimen

To assess the generalisability of our findings in silico, we applied the above unsupervised analysis on an comparable independent microRNA dataset GSE34466²⁷ on NCBI GEO of 862-microRNA profiles of airway epithelial cells from bronchoscopic brushing of 14 steroid-naïve (6 weeks before enrolment) asthma subjects at baseline before, and after an 8-week inhaled CS 200 µg two times a day, with pre-BD FEV_1 measurements at both timepoints, figure 1. In contrast to the mainly severe asthmatic SARP study population where just 2/19 had $>10\%$ and 8/19 had $>0\%$ increase in pre-BD FEV_1 %p, in this population 4/14 had $>10\%$ and 8/14 had $>0\%$ increase in pre-BD FEV_1 %p.

First, we applied PCA on the 14-subject 8 weeks minus baseline sample difference column vectors of 862 microRNAs with PC1–3 accounting for 38.64%, 14.71% and 12.13% of the global microRNAome variance respectively, as we had done with the SARP transcriptome data above. Second, we found PC3 to be associated with change (8 weeks minus baseline) in pre-BD FEV_1 %p (Kendall tau-b $R=0.389$ (0.001 to 0.675)). We highlight the positive correlation ($R=0.389$) of pre-BD FEV_1 %p with the GSE34466 microRNAome PC3, in contrast to the negative correlation ($R=-0.333$) of pre-BD FEV_1 %p with the SARP transcriptome PC3 above. Finally, we identified 405 functionally validated target genes (miRTarBase July 15 2019²⁹) of the top 5% PC3 contributing microRNAs by their PC3 loading coefficient magnitude and found significant overlaps with our earlier top 5% PC3 contributing genes (OR 3.65 (2.73 to 4.89), data not shown), and with our previously reported GCGS (OR 5.63 (4.19 to 7.57)), table 3.

DISCUSSION

We identified molecular pharmacogenomic endotypes to an induced phenotype of response to systemic CSs in mainly severe asthmatic subjects using unsupervised PCA of a subject's sputum airway cell transcriptomic changes.^{15 16} We used resulting the PC1 and PC3 coordinates (figure 2) to define endotypes in two ways: dichotomised at the 0 coordinate point (binary variable) and as is

Table 1 Select clinical variables (asthma severity, sex, age, body mass index (BMI), pre-bronchodilator (BD) FEV1% predicted) and Th2 clinical feature associations of two molecular endotypes of corticosteroid treatment response defined by corticosteroid induced sputum cell transcriptomic change (=follow up minus baseline) in PC1 and PC3 sample coordinates, respectively, dichotomised at 0 from the 19-subject Severe Asthma Research Program study

Clinical variables	Ratio // median (IQR)		OR (95% CI)// ranksum p	Ratio // median (IQR)		OR(95% CI)// ranksum p
	PC1 <0	PC1 ≥0		PC3 <0	PC3 ≥0	
# Not severe: severe asthma	2:6	5:6	0.400 (0.055 to 2.933)	4:6	3:6	1.333 (0.204 to 8.708)
# Female: male	6:2	10:1	0.300 (0.022 to 4.060)	8:2	8:1	0.500 (0.037 to 6.684)
Age (years, baseline)	43.43 (41.64–50.40)	45.81 (38.80–52.29)	0.8404	50.40 (45.08–54.47)	41.77 (39.22–43.18)	0.0350*
BMI (baseline)	32.28 (25.76–44.97)	33.41 (32.32–39.98)	0.5448	33.38 (31.32–35.42)	32.66 (30.88–42.61)	0.9048
Baseline blood basophil count (cells/ul)	4 (3–5)	69 (16–95)	0.0191*	5 (4–89)	50 (4–74)	0.9506
Baseline blood eosinophil count (cells/ul)	162 (90–244)	200 (148–394)	0.4073	244 (180–456)	140 (68–188)	0.0082*
Baseline blood neutrophil count (cells/ul)	4025 (2921–5963)	4554 (3968–5752)	0.3950	4295 (3640–5874)	4554 (3725–6057)	0.8421
FeNO (ppb) baseline	17.5 (7.0–37.5)	29.0 (16.3–39.8)	0.3942	32.5 (20.0–38.0)	14.0 (7.0–36.5)	0.3143
Follow-up	14.5 (9.0–27.5)	29.0 (24.3–39.8)	0.0786	27.0 (20.0–32.0)	24.0 (8.5–36.3)	0.6448
Change	–3.0 (–10.0 to 1.5)	–2.0 (–6.3 to 10.5)	0.4785	–4.5 (–7.0 to 2.0)	–1.0 (–6.0 to 4.8)	0.5350
Change, #<0 : #≥0	5 : 2	7 : 4	0.952 (0.144 to 6.281)	7 : 3	5 : 4	1.867 (0.283 to 12.310)
Sputum eosinophil % baseline	0.70 (0.30–1.85)	0.20 (0.00–0.65)	0.1604	1.20 (0.40–2.00)	0.00 (0.00–0.20)	0.0024*
Follow-up	0.50 (0.30–1.10)	0.20 (0.00–0.43)	0.1171	0.40 (0.20–1.00)	0.20 (0.00–0.73)	0.2252
Change	–0.30 (–0.55 to 0.10)	–0.20 (–0.45 to 0.15)	0.6132	–0.45 (–1.50 to 0.20)	0.00 (–0.20 to 0.40)	0.0181*
Change, #<0 : #≥0	6:2	8:3	1.125 (0.141 to 8.995)	9:1	5:4	7.200 (0.622 to 83.342)
Pre-BD FEV1% predicted baseline	70.39 (57.55–86.41)	78.07 (70.71–89.94)	0.3950	78.45 (59.77–86.87)	72.33 (67.42–85.47)	0.9048
Follow-up	70.67 (58.44–84.36)	80.32 (59.27–87.41)	0.5999	82.20 (57.08–87.51)	75.25 (61.80–82.90)	0.7802
Change	–0.17 (–2.05 to 1.89)	–3.43 (–8.38 to 2.03)	0.3101	0.51 (–2.80 to 2.25)	–3.43 (–7.39 to 0.28)	0.2428
Change, #<0 : #≥0	4:4	7:4	0.571 (0.090 to 3.641)	4:6	7:2	0.190 (0.025 to 1.432)

For continuous-valued clinical variables, the median (IQR) and 2-sided Wilcoxon rank-sum p value are shown. For binary-valued clinical variables (eg, asthma severity, change in pre-BD FEV1% predicted dichotomised at 0), the ratios, ORs and Fisher exact test (95% CI) are shown.

*indicates significance at $p < 0.05$.

(continuous variable). Respectively, we investigated PC1 and PC3 separately for associations with a set of 55 clinical variables, focusing on Th2 clinical features. We used the top 5% genes contributing to these PCs to uncover biologically and clinically meaningful treatment response genes and ontologies. Crucially, the molecular endotypes defined in this fashion were associated with clinical response to CS. Namely, PC3 is associated with treatment-related change in pre-BD FEV1 and follow-up BD response (table 2). While the molecular endotypes were also related to baseline Th2 status, with PC1 associated with baseline blood basophils, and PC3 with baseline blood and sputum eosinophils (tables 1–2, figures 2–3), none of these baseline Th2 clinical features were themselves associated with clinical response to CS (online supplemental table S3). Within the 12/19 severe asthma subpopulation, the baseline blood basophil (PC1) and eosinophil (PC3) associations were diminished, PC3 associations with sputum eosinophil % and change in pre-BD FEV1 and follow-up BD response became greater. The differences between the molecular treatment response endotypes and Th2 status is further emphasised through different biologies represented by ontology enrichment analysis of top loading (contributing) genes from the PC-defined endotypes (table 5) versus the top correlated genes with any Th2 clinical feature (online supplemental table S4). Finally, we demonstrated that the molecular endotypes are generalisable at the level of the airway epithelial cell, in an independent inhaled CS treatment cohort analysis of microRNA data. Overall, molecular treatment endotypes appear to be more representative of CS induced changes in biology and more specific predictors of clinical CS treatment response.

Underscoring the Th2 biologic significance of our findings, the endotype defined by positive PC1 coordinates mainly has subjects with baseline peripheral blood basophilia, figure 3A. Basophils are underappreciated mediators of Th2 immune response that are increasingly recognised as mediators of thymic stromal lymphopoietin induced Th2 inflammation.^{30–31} In contrast, the endotype defined by negative PC3 coordinates has subjects with the classic Th2 phenotype of blood and sputum eosinophilia,^{32–33} figure 3B–C. This emphasises the role that Th2 status may play in response to CS³⁴ and supports Th2 status as a key underlying feature of our molecular endotypes. From a clinical response perspective, as the PC3 coordinates increased, there was a significant decrease in lung function change following CS administration, figure 4B. Given that blood/sputum eosinophils were not found to be associated with lung function change, the PC3 molecular endotype contains features that represent a more comprehensive biological picture of treatment response than blood/sputum eosinophils alone. This is consistent with previous work suggesting that molecular features might be superior to clinical characteristics in predicting response to CS in severe asthma from children in SARP.³⁵ The top 5% PC1 and PC3 contributing genes were enriched for CS signalling indicated by their significant enrichment for our previously reported GCGS²⁸ table 3. Thus, these mainly severe asthmatic subjects appear to cluster into at least two distinct types of clinically and biologically relevant molecular responses to CS treatment.

We previously applied unsupervised PCA to identify top 5% PC contributing genes to be associated with human fetal lung

Table 2 Select clinical variable associations of sputum cell transcriptomic change PC1 and PC3 sample coordinates and severity (binary) variable in the Severe Asthma Research Program study using Kendall tau-b correlation where * indicates significance where 0 lies outside the respective 95% CI

Variables tested for association	Kendall tau-b correl R (95% CI)				
	PC1 28.93%	PC3 11.93%	Severe	PC1 28.93% (in 12/19 severe)	PC3 11.93% (in 12/19 severe)
PC1 28.93%	–	0.018 (–0.307 to 0.338)	–0.184 (–0.478 to 0.148)	–	0.212 (–0.238 to 0.587)
PC3 11.93%	0.018 (–0.307 to 0.338)	–	0.000 (–0.323 to 0.323)	0.212 (–0.238 to 0.587)	–
Severe	–0.184 (–0.478 to 0.148)	0.000 (–0.323 to 0.323)	–	–	–
Sex	–0.022 (–0.342 to 0.303)	0.066 (–0.262 to 0.381)	–0.031 (–0.351 to 0.294)	0.275 (–0.174 to 0.630)	0.110 (–0.334 to 0.514)
Age baseline	0.088 (–0.242 to 0.399)	–0.404 (–0.642 to 0.093)*	–0.367 (–0.617 to 0.051)*	–0.273 (–0.628 to 0.176)	–0.394 (–0.704 to 0.042)
BMI baseline	0.146 (–0.185 to 0.448)	–0.018 (–0.338 to 0.307)	0.033 (–0.292 to 0.352)	0.152 (–0.296 to 0.545)	0.091 (–0.351 to 0.500)
Baseline blood BASO count	0.340 (0.020 to 0.597)*	0.000 (–0.323 to 0.323)	0.025 (–0.300 to 0.345)	0.152 (–0.296 to 0.545)	0.152 (–0.296 to 0.545)
Baseline blood EOS count	0.199 (–0.132 to 0.490)	–0.457 (–0.680 to 0.158)*	–0.050 (–0.367 to 0.277)	0.198 (–0.251 to 0.578)	–0.290 (–0.639 to 0.158)
Baseline blood neutrophil count	0.193 (–0.138 to 0.485)	0.053 (–0.275 to 0.369)	0.367 (0.051 to 0.617)*	0.061 (–0.378 to 0.477)	0.242 (–0.208 to 0.608)
FeNO baseline	0.047 (–0.280 to 0.364)	–0.177 (–0.473 to 0.154)	–0.370 (–0.619 to 0.054)*	0.109 (–0.336 to 0.513)	–0.233 (–0.601 to 0.218)
Follow-up	0.219 (–0.112 to 0.506)	–0.041 (–0.359 to 0.285)	–0.211 (–0.500 to 0.120)	0.264 (–0.186 to 0.622)	–0.047 (–0.466 to 0.390)
Change	0.212 (–0.118 to 0.501)	0.083 (–0.247 to 0.395)	0.438 (0.134 to 0.666)*	0.321 (–0.125 to 0.659)	0.229 (–0.221 to 0.599)
Sputum EOS % baseline	–0.068 (–0.383 to 0.260)	–0.367 (–0.617 to 0.051)*	0.098 (–0.232 to 0.407)	–0.127 (–0.527 to 0.319)	–0.509 (–0.769 to 0.102)*
Follow-up	–0.237 (–0.520 to 0.092)	–0.275 (–0.549 to 0.053)	–0.125 (–0.430 to 0.206)	–0.259 (–0.619 to 0.191)	–0.323 (–0.660 to 0.122)
Change	–0.042 (–0.360 to 0.285)	0.294 (–0.032 to 0.563)	–0.094 (–0.404 to 0.236)	0.016 (–0.416 to 0.441)	0.362 (–0.078 to 0.685)
Sputum macrophage % baseline	–0.029 (–0.349 to 0.296)	0.228 (–0.102 to 0.513)	–0.067 (–0.381 to 0.261)	–0.030 (–0.453 to 0.403)	0.333 (–0.111 to 0.667)
Follow-up	–0.129 (–0.434 to 0.202)	–0.199 (–0.490 to 0.132)	–0.385 (–0.629 to 0.071)*	–0.290 (–0.639 to 0.158)	–0.168 (–0.556 to 0.281)
Change	–0.064 (–0.379 to 0.264)	–0.485 (–0.699 to 0.193)*	–0.050 (–0.367 to 0.277)	–0.061 (–0.477 to 0.378)	–0.545 (–0.789 to 0.153)*
Sputum neutrophil % baseline	0.018 (–0.307 to 0.338)	–0.333 (–0.592 to 0.012)*	–0.150 (–0.451 to 0.181)	–0.121 (–0.523 to 0.324)	–0.303 (–0.647 to 0.144)
Follow-up	0.053 (–0.275 to 0.369)	0.333 (0.012 to 0.592)*	0.217 (–0.114 to 0.504)	0.182 (–0.268 to 0.566)	0.303 (–0.144 to 0.647)
Change	0.181 (–0.150 to 0.476)	0.556 (0.284 to 0.745)*	0.067 (–0.261 to 0.381)	0.273 (–0.176 to 0.628)	0.455 (0.032 to 0.739)*
Pre-BD FEV ₁ %p baseline	–0.064 (–0.379 to 0.264)	0.053 (–0.275 to 0.369)	–0.100 (–0.409 to 0.230)	–0.091 (–0.500 to 0.351)	0.152 (–0.296 to 0.545)
Follow-up	–0.135 (–0.438 to 0.197)	–0.088 (–0.399 to 0.242)	–0.284 (–0.555 to 0.043)	–0.242 (–0.608 to 0.208)	–0.061 (–0.477 to 0.378)
Change	–0.146 (–0.448 to 0.185)	–0.333 (–0.592 to 0.012)*	–0.334 (–0.593 to 0.013)*	–0.273 (–0.628 to 0.176)	–0.455 (–0.739 to 0.032)*
BD response baseline	–0.018 (–0.338 to 0.307)	0.029 (–0.296 to 0.349)	0.100 (–0.230 to 0.409)	0.485 (0.071 to 0.756)*	0.000 (–0.429 to 0.429)
Follow-up		0.392 (0.079 to 0.634)*	0.000 (–0.323 to 0.323)	0.576 (0.195 to 0.806)*	0.515 (0.111 to 0.773)*
Change	0.135 (–0.197 to 0.438)				
Change	0.146 (–0.185 to 0.448)	0.146 (–0.185 to 0.448)	–0.067 (–0.381 to 0.261)	0.121 (–0.324 to 0.523)	0.364 (–0.077 to 0.685)

There associations were also studied within the 12/19 severe asthma subpopulation.

*Indicates statistical significance.

BD, bronchodilator; BMI, body mass index.

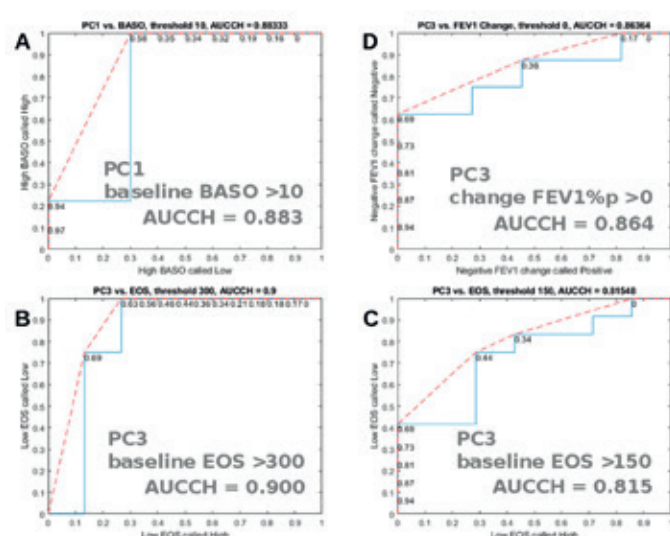


Figure 3 Areas under receiver operator characteristic curve (AUCCH) analyses for: (A) PC1 sample coordinate and baseline blood basophil count >10 cells/μL. (B) PC3 sample coordinate and baseline blood eosinophil (EOS) count >300 cells/μL. (C) PC3 sample coordinate and baseline blood EOS count >150 cells/μL. (D) PC3 sample coordinate and change in pre-BD FEV₁ % predicted >0.

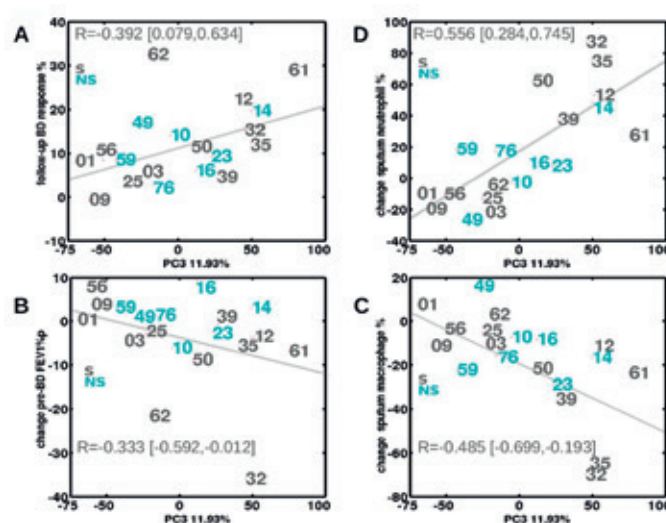


Figure 4 (A) PC3 sample coordinate versus follow-up bronchodilator response. (B) PC3 sample coordinate versus change in pre-bronchodilator FEV₁ % predicted. (C) PC3 sample coordinate versus change in sputum macrophage %. (D) PC3 sample coordinate versus change in sputum neutrophil %. Each subject is indicated by their unique 2-digit identifier, 7/19 non severe asthmatics are in cyan. The linear regression line is drawn in each and the Kendall tau-b correlation and 95% CI are indicated.

Table 3 Overlaps between previously reported glucocorticoid gene set (GCGS) with the top 5% PC1 and PC3 contributing genes (unsupervised), the top 5% Th2 clinical feature rank correlated genes (supervised) from Severe Asthma Research Program, and target genes of the top 5% PC3 contributing microRNAs (unsupervised) from GSE34466

GCGS overlap with each test variable	PC1 28.93%	PC3 11.93%	Baseline blood baso	Baseline blood eos	Baseline FeNO	Change FeNO	GSE34466 PC3	Test variable	GCGS
# genes in overlap	15 598	15 592	15 531	15 542	15 544	15 556	16 040	No	No
	484	490	553	545	545	526	522	No	Yes
	753	759	820	809	807	795	311	Yes	No
	95	89	26	34	34	53	57	Yes	Yes
OR(95% CI)	4.07 (3.22 to 5.13)*	3.73 (2.94 to 4.73)*	0.89(0.60 to 1.33)	1.20(0.84 to 1.71)	1.20(0.84 to 1.71)	1.97 (1.47 to 2.64)*	5.63 (4.19 to 7.57)*		

The number of overlapping genes, ORs and Fisher exact test 95% CI are indicated.

*Indicates statistical significance.

development in the context of embryonic gestational age, vitamin D signalling and CS response.^{20 21 36} While those analyses were aimed at expanding basic understanding of lung development biology, our current study suggests that molecular subgroups resulting from such unsupervised analysis may also reflect distinct biologic mechanisms in response to CS treatment. The method may be generally applied to classifying and predicting CS treatment response. In contrast to supervised analyses using clinical variables, unsupervised PCA (and more generally surrogate variable analysis SVA²²) has two distinct advantages. First, a gene's contribution is not limited to a single PC as shown by the strong overlap between top PC1 and PC3 contributing genes, table 4. Indeed this might reflect the interactome being the basis of a systems biology model, or pleiotropy in general. Second, we can systematically identify and prioritise the top N contributing genes per PC to clarify both individual genes and their ontologies that underlie the endotypic subgroups. We highlight the effectiveness of our method by contrasting it with supervised analysis using the top 5% Th2 clinical features (ie, blood and sputum eosinophilia, high FeNO) correlated genes which ultimately had fewer overlapping genes with each other (table 4) and lesser enrichment for GCGS (table 3), immune system and inflammation related ontologies (online supplemental table S4) suggesting less biologic certainty for prominent involvement of these processes.

Our work complements current clinical cluster analyses. A recent SARP analysis focused on CS response in severe asthmatics¹⁸ suggested four potential CS response clusters, with the cluster associated with the greatest CS response demonstrating the highest levels of blood eosinophils. Another current SARP-3 analysis²⁶ identified differences in pre-BD and post-BD lung function longitudinal trajectories between subjects stratified into four groups by baseline sputum eosinophil % high/low+neutrophil%

high/low. While our subset analysis does not have sufficient sample size to assess the presence of such clinical clusters, the association of blood eosinophils and sputum neutrophils with PC3 supports a possible overlap of a portion of the clinical endotype with molecular features. Nonetheless, given the deficiencies of supervised analysis to fully capture meaningful ontological associations, it is also likely that molecular endotyping can independently yield additional novel biology when used as an independent metric, as supported by our ontology enrichment analysis. Others and we previously cited the advantage of molecular endotyping for predicting therapeutic response in asthma.³⁷ Fitzpatrick *et al*³⁵ noted that clinical features were of limited use for predicting triamcinolone response, whereas systemic mRNA expression of inflammatory cytokines and chemokines related to interleukin (IL)-2, IL-10 and tumour necrosis factor signalling pathways, including, AIMP1, CCR2, IL10RB, and IL5, strongly differentiated children who failed to achieve control with triamcinolone treatment. Our analysis also includes prediction of response using molecular features that were not noted using clinical biomarkers alone,^{15 16} but in the context of molecular endotypes generated by genome-wide RNA-seq CS response data.

Several studies have described gene expression signatures that may predict CS responsiveness in asthma.^{35 38} However, these have generally focused on circulating blood cells rather than airway cells, and on baseline differential gene expression differences between predefined responding and non-responding subject populations. Moreover, their prior expression analyses focused on panels of preselected candidate genes. In contrast, our molecular endotyping of each subject is based on whole transcriptomic change in sputum cells following CS treatment. Our model has the unique advantage of capturing dynamic changes inherent in transcriptional response to CS treatment that is agnostic to clinical

Table 4 Overlaps between gene sets from the 19-subject Severe Asthma Research Program study: the top 5% PC1 and PC3 contributing genes (unsupervised), and the top 5% Th2 phenotypes rank correlated genes (supervised)

Top 5% gene overlaps	PC3 11.93%	Baseline blood baso	Baseline blood eos	Baseline FeNO	Change FeNO	# gene overlap
PC1 28.93%	510	62	36	23	109	
	70.28*	1.54*	0.84	0.52*	3.06*	OR
	(59.02 to 83.70)*	(1.18 to 2.01)*	(0.60 to 1.18)	(0.34 to 0.79)*	(2.47 to 3.79)*	(95% CI)
PC3 11.93%		47	74	36	82	
		1.12	1.90*	0.84	2.14*	
		(0.83 to 1.52)	(1.48 to 2.44)*	(0.60 to 1.18)	(1.69 to 2.72)*	
Baseline blood baso			73	53	9	
			1.88*	1.30	0.20*	
			(1.46 to 2.41)*	(0.97 to 1.73)	(0.10 to 0.38)*	
Baseline blood eos				84	10	
				2.24*	0.22*	
				(1.77 to 2.84)*	(0.12 to 0.41)*	
Change FeNO					180	
					6.29*	
					(5.24 to 7.54)*	

The number of overlapping genes, ORs and Fisher exact test 95% CI are indicated.

*indicates statistical significance.

Table 5 Top 10% significant gene ontology (GO) clusters and their keywords for the top 5% PC1 and PC3 negative and positive contributing genes from the 19-subject Severe Asthma Research Program study

	PC1		PC3	
# genes top 5% negative (N)	378		371	
# GO clusters (N)	93		70	
# genes top 5% positive (P)	470		477	
# GO clusters (P)	90		117	
Top 10% GO cluster order (N)	Score	Keyword	Score	Keyword
1	13.92	lysosome	13.67	ribosome, RNA processing
2	12.64	cell adhesion	6.88	lysosome
3	9.14	glycosylation	5.24	cell-cell adhesion
4	5.19	host-virus interaction	2.59	phosphatidylinositol binding, retromer
5	3.93	chaperone, endoplasmic reticulum	2.56	innate immunity
6	3.72	cell adhesion	2.33	annexin
7	3.66	ATP-binding	2.23	NAD, oxidation-reduction
8	3.45	actin-binding, spectrin		
9	3.36	antigen processing and presentation, asthma, MHC class II		
Top 10% GO cluster order (P)	Score	Keyword	Score	Keyword
1	25.36	immunity	16.50	cell-cell adhesion
2	12.41	response to virus	11.54	innate immunity
3	7.68	ribosome, RNA processing	8.19	cell membrane
4	3.66	antigen processing and presentation, MHC class I	4.73	virus receptor activity
5	2.88	infection	3.77	antigen processing and presentation, asthma, interferon, MHC class I, MHC class II
6	2.75	NF-kappa B signalling	3.74	ATP-binding
7	2.42	interferon	3.65	GTP-binding
8	2.39	chemotaxis, cytokine	3.65	chemotaxis, cytokine
9	2.12	Ig-binding	3.55	SH3 domain
10			3.53	glycosylation, transmembrane
11			3.28	lysosome

outcomes/features a priori and gene/molecular preselection biases, and yet our resulting molecular endotypes were found to be associated with clinical variables at baseline and follow-up. Interestingly, 3 genes* from a 6-gene baseline sputum gene expression signature (CLC, CPA3, DNASE1L3, IL1B*, ALPL*, CXCR2*)^{39,40} reported to discriminate inflammatory phenotypes of asthma and predict ICS treatment response are among the top 5% genes contributing to PC1 and PC3 with IL1B ranked 2, online supplemental table S5, Berthon *et al*⁴⁰ noted the 3 genes to be neutrophil markers and PC3 was significantly associated with baseline/follow-up/change in sputum neutrophils, table 2, figure 4D.

The small sample size of our study is an important multifaceted issue. Clinically, severe asthma is heterogeneous and sample size limits our ability to fully characterise this heterogeneity.

With regards to generalising the pre-BD FEV₁%p association to other asthma populations, we addressed this technically in silico in a comparable independent microRNA dataset GSE34466²⁷ (cf. Result 6) where we found the resulting microRNAome change PC3 to be associated with change in pre-BD FEV₁%p with an opposite signed correlation. This is intriguing considering that expression of microRNAs and their target genes are generally understood to be inversely correlated. Also, MALAT1 (ranked 6 in PC3, and a target of a top 5% GSE34466 microRNAome PC3 hsa-miR-429, online supplemental table S5) is one of five key long non-coding RNAs in an asthma-associated competing endogenous network targeted by eight potential new drugs.⁴¹ Despite sample size, we achieved potentially meaningful clinical endotypes. It is notable that neutrophils, eosinophils and basophils (peripheral blood/sputum inflammatory cells clinically known to be associated with asthma severity) are relevant to transcriptomic endotyping for steroid response thus suggesting that a simple Th2 versus non-Th2 dichotomy may be insufficient to describe response to inhaled steroids in severe asthma.

CONCLUSIONS

Our analysis of sputum airway cell RNA-seq data in well-characterised mainly severe asthmatics identified distinct molecular pharmacogenomic endotypes in response to an induced phenotype with systemic CSs. Since CSs remain a mainstay of therapy for most asthmatics with persistent symptoms, these endotypes may clarify biological differences underlying the heterogeneity in CS treatment response, and provide an objective useful model for predicting treatment response and developing novel therapies. Our analysis suggest that unsupervised PCA/SVA can be used to objectively define testable (across multiple datasets and populations) molecular endotypes that may yield novel biology underlying different responses to CS therapy in asthma, identify potential new therapeutic targets, and improve the identification of subjects most likely to respond to CSs alone versus those who may benefit from a biologic added to their CS regimen leading to optimal personalised asthma care. Potentially such molecular endotyping could be applied as a diagnostic test using sputum induction and rapid gene expression measurements designed to delineate therapy specific responses in asthma.

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ARTIGO ORIGINAL

O pagamento por desempenho melhora os resultados dos pacientes admitidos por agudização aguda de DPOC?

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RESUMO

Contexto A *COPD Best Practice Tariff* (BPT) (Tarifa por Melhores práticas de DPOC) é um esquema de pagamento por desempenho existente em Inglaterra que incentiva a revisão por um especialista de cuidados respiratórios no prazo de 24 horas após internamento e o preenchimento de uma lista de elementos de cuidados essenciais antes da alta, conhecido como *discharge bundle* (organograma de alta), para pacientes admitidos por agudização aguda de DPOC (AECOPD, do inglês *acute exacerbation of COPD*). Investigamos se os dois elementos da COPD BPT estavam associados a uma mortalidade inferior a 30 dias e à readmissão de pessoas com alta após agudização aguda de DPOC.

Métodos Estudo longitudinal dos dados recolhidos a nível nacional contendo detalhes das admissões por agudização aguda de DPOC em Inglaterra e no País de Gales entre 01 de fevereiro de 2017 e 13 de setembro de 2017. Os dados foram ligados aos dados nacionais sobre internamentos e mortalidade. Utilizou-se uma regressão logística de efeitos mistos, com uma interceção aleatória para o hospital para ajustar o agrupamento de pacientes, de forma a determinar a relação entre os critérios de COPD BPT (combinados e separados) e a mortalidade e novo internamento a 30 dias. Os modelos foram ajustados para idade, sexo, estatuto socioeconômico, duração da hospitalização, estado tabágico, índice de comorbidade de Charlson, doença mental e necessidade de oxigênio ou ventilação não invasiva durante o internamento.

Resultados Foram incluídos 28 345 pacientes que tiveram alta hospitalar após agudização aguda de DPOC. 37% dos internamentos estavam em conformidade com os dois critérios COPD BPT. Não foi observada qualquer associação entre os internamentos conformes a BPT e a mortalidade a 30 dias (OR: 1,09 (95% IC 0,92 a 1,29)) ou novos internamentos (OR: 0,96 (95% CI 0,90 a 1,02)). Não foi observada qualquer associação entre qualquer um dos elementos individuais da COPD BPT e a mortalidade ou novos internamentos a 30 dias. Contudo, uma revisão especializada em qualquer momento durante a admissão foi associada a uma menor mortalidade hospitalar (OR: 0,69 (95% IC: 0,58 a 0,81)).

Conclusão O preenchimento dos critérios combinados da COPD BPT não parece estar associado a uma redução da mortalidade ou novo internamento a 30 dias. No entanto, a revisão especializada foi associada a uma redução da mortalidade hospitalar. Embora seja difícil argumentar que os *discharge bundles* não melhoram os cuidados, esta análise questiona se o modelo de pagamento por desempenho melhora a mortalidade ou os novos internamentos.

BACKGROUND

COPD is the third leading cause of death worldwide¹ and an estimated 1.2 million people in the UK have a diagnosis of COPD.² Many patients with COPD experience episodes of worsening in their symptoms termed an acute exacerbation of COPD (AECOPD), which in the most severe cases require hospitalisation. COPD exacerbations account for approximately 3% of US hospital admissions per year,³ and in England, there are over 100 000 hospital admissions annually due to AECOPD,⁴ each one costing the National Health Service an average of £1868.⁵

Pay-for-performance incentives exist in several countries and for several diseases.^{6–8} In England, optimal care of AECOPD admissions has been incentivised

Key messages

What is the key question?

► Is the combination of specialist review within 24 hours and discharge care bundle incentivised by the English COPD Best Practice Tariff (BPT) pay-for-performance scheme associated with improved mortality and readmission in acute exacerbation of COPD (AECOPD) admissions?

What is the bottom line?

► The combination of specialist review within 24 hours and a discharge care bundle as incentivised by the English COPD BPT pay-for-performance scheme did not appear associated with 30-day mortality or readmission in AECOPD admissions; however, respiratory specialist review was associated with decreased inpatient mortality.

Why read on?

► This is the first study to use a large national audit to investigate the impact of the combination of specialist review and discharge care bundles as incentivised by the English COPD BPT pay-for-performance scheme on readmission and mortality in AECOPD admissions.

since 2017 through the COPD Best Practice Tariff (BPT), which encourages best practice by paying care providers an additional amount for AECOPD admissions that are (1) reviewed by a respiratory specialist within 24 hours of the admission and (2) receive a discharge care bundle before the patient leaves hospital. A care bundle is a collection of evidence-based interventions.⁹ For example, the British Thoracic Society (BTS) COPD Discharge Care Bundle comprises: (1) review medication and check inhaler technique, (2) provide a self-management plan and emergency drug pack where appropriate, (3) offer support to achieve smoking cessation, (4) assess and refer for pulmonary rehabilitation and (5) arrange follow-up.¹⁰ The aim of the BTS COPD discharge bundle is to improve patient self-management and postdischarge care in order to reduce COPD readmissions.

Achievement of the COPD BPT is assessed at the hospital level, based on admissions recorded in the UK National Asthma and COPD Audit Programme (NACAP), such that if 60% of audited patients with a primary diagnosis of AECOPD receive the two components of the COPD BPT (specialist review and discharge bundle), the hospital will receive an additional payment for all AECOPD admissions managed. If the 60% target is not met, the hospital will not receive



the additional payment for any of the AECOPD admissions it managed and will instead be reimbursed at the standard rate.^{11–14} However, approximately 40% of hospitals in England have negotiated an alternative system of reimbursement for admissions meaning that the COPD BPT does not apply to them.

Review by a multidisciplinary respiratory specialist improves the quality of care received by patients¹⁵ and may lead to a reduction in mortality and length of hospital stay.^{14,16} There is also weak evidence that discharge bundles reduce readmissions.¹⁷ However, data suggest that discharge bundles are not always effectively implemented.¹⁸ Data from the 2014 COPD audit showed that only 57% of AECOPD admissions were reviewed by a respiratory specialist¹⁵ and only 69% of providers used discharge bundles.¹⁹ The COPD BPT aims to increase receipt of these two items of care for AECOPD admissions.¹³

There are few studies on the effectiveness of pay-for-performance in secondary care settings and no study to date has investigated whether implementing the two COPD BPT criteria together improves AECOPD admission outcomes. Therefore, in this analysis of national audit data, we aimed to determine whether people admitted with AECOPD who receive both COPD BPT criteria have fewer readmissions and lower mortality than those who do not receive the COPD BPT. Specifically, we want to determine whether the combination of specialist review and discharge bundle that the COPD BPT seeks to incentivise improves individual patient outcomes, rather than whether the 60% target used by the COPD BPT improves patient outcomes at the hospital level. Therefore, we examine outcomes at the patient level in all hospitals rather than comparing outcomes between eligible hospitals that met the 60% target versus those that did not. If we were instead to compare trusts that met and did not meet the 60% target in an ecological-type analysis, there would be admissions that both did and did not meet the BPT criteria in both the $\geq 60\%$ and $< 60\%$ groups. This would make it harder to determine whether the BPT criteria were truly having an impact on patient outcomes.

METHODS

Database/population

The NACAP reports care received by patients admitted to hospitals in England and Wales with AECOPD. From 2017, audit data collection has been continual. All acute hospitals in England and Wales were eligible to participate (Scotland joined in 2018), and of 197 eligible hospitals, 182 (92%) participated in data collection. The first report on these prospective data was published in 2018 including analysis for patients admitted from 01 February 2017 and discharged by 13 September 2017. Further details of the audit methodology and results can be found in the published report²⁰ and a paper describing the longitudinal evolution of national COPD audit in the UK.²¹

In 2019, a follow-up with longer term outcomes—30-day and 90-day mortality and readmission—of the admissions included in the original 2017 audit report was published. All included patients had details of their admission linked with mortality data from the UK Office for National Statistics (ONS)²² and admissions data from England's Hospital Episode Statistics (HES) Admitted Patient Care (APC) database²³ or Wales' Patient Episode Database for Wales (PEDW).²⁴ After data cleaning to remove patients aged < 35 years and admissions with an impossible chronology, the data set was limited to the first admission for each patient in the audit period. This left a data set of 30 294 patients. This data set was used to conduct our analysis; further details are found in the audit outcomes report.²⁵

Variables

The primary exposure in this study was conforming to the COPD BPT. An admission was considered to have conformed to the BPT if a patient received a respiratory specialist review ≤ 24 hours after admission and a COPD discharge bundle before discharge. The nature of discharge bundle was left to individual hospitals. Admissions where the patient was not reviewed by a respiratory specialist were included in the same category as admissions that received a respiratory specialist review > 24 hours after admission. The two components of the COPD BPT (specialist review within 24 hours and discharge bundle) were also examined separately in secondary analyses.

Patients who died during their admission or self-discharged were excluded from analyses as these patients are unlikely to have been able to receive a discharge bundle and it would be unfair to include these admissions in our assessment of conformation to the COPD BPT.

The outcomes examined in this study were 30-day mortality and readmissions. The patient was considered to have died within 30 days of admission if there was an ONS death record < 30 days after their admission date (as inpatient deaths were excluded this means that our definition of 30-day mortality represents a variable period after discharge dependent on the length of stay). The data received by us only contained 30-day mortality in a binary format (yes/no patient died within 30 days of admission); therefore, we are unable to calculate 30-day postdischarge mortality. The patient was considered to have been readmitted within 30 days of discharge if there was a HES APC or PEDW admission record for any emergency hospital admission < 30 days after discharge.

Potential confounders used in the analysis were age, sex, socioeconomic status, oxygen needed during admission, noninvasive ventilation (NIV) administered during admission, length of stay, smoking status, Charlson comorbidity index and a history of mental illness. Respiratory specialist review was included as an additional confounder in analyses of the COPD discharge bundle as we hypothesised that individuals who had received a specialist review were more likely to receive a discharge bundle. Detailed definitions of confounders are found in online supplemental methods and online supplemental tables S1 and S2.

Statistical analysis

Data management and statistical analyses were performed using Stata V.15 (StataCorp, College Station, Texas). Data were first summarised using means and proportions where appropriate. In our primary analysis to investigate association between an admission conforming to the COPD BPT (receiving specialist review within 24 hours and receiving a discharge bundle) and 30-day mortality (from admission) and 30-day readmission (from discharge), we used mixed-effects logistic regression (xtlogit command, 're' option) with a random intercept for hospital to account for clustering of patients within hospitals. ORs and 95% CIs were generated for each outcome. After univariate analysis, regression models were adjusted by including the potential confounders described above as covariates in the model.

Secondary analyses were performed using specialist review within 24 hours and receipt of a discharge bundle as the independent variables in place of conformation to the BPT to test the individual components of the BPT. Additionally, we further tested the components of the specialist review variable: patients who either did or did not have a specialist review, and for patients who did have a review, those who had one in ≤ 24 hours and those who had one in > 24 hours.

Missing data were minimal for variables included in regression models and where data were missing, complete case analysis was used. OR graphs were generated using coefplot.²⁶

Sensitivity analyses

We repeated the discharge bundle analysis excluding 'not clear' responses to the 'Has a BTS, or equivalent, discharge bundle been completed for this admission?' question to determine if there was a strengthening of the effect of a discharge bundle on the outcomes if it was known for certain whether a patient received a bundle or not. We repeated the specialist review analyses using the full audit cohort (including patients who died as an inpatient or self-discharged) to determine whether specialist review was associated with mortality in the full 30-day period from admission or inpatient mortality. Additionally, we repeated the analysis using 90-day mortality and 90-day readmissions as the outcomes to examine if the benefits of the COPD BPT were not detectable until sufficient time had passed for all elements of the discharge bundle to be completed (such as smoking cessation and pulmonary rehabilitation). We also ran the analysis without Welsh hospitals, as these are not eligible to participate in the BPT, to see if there was any change in outcomes. Finally, we examined if there was any difference in patient outcomes between hospitals that met the 60% target for BPT conforming admissions and hospitals that did not meet the target.

RESULTS

After exclusion of patients who self-discharged (n=465 (0.5%)) died during admission (n=1213 (4.0%)) and had 'other' as the response for whether they received a discharge bundle (n=571 (1.9%)), the final analysed cohort in this study comprised 28 345 patients (first admission in audit period only) from 181 hospitals.

COPD BPT conforming admissions

Thirty-seven per cent of admissions conformed to the BPT (received specialist review within 24 hours and a discharge bundle) (table 1). BPT conforming admissions, compared with admissions not meeting BPT, were more frequently prescribed oxygen (60.9% vs 51.3%), had more NIV administered (11.4% vs 7.6%), had fewer hospital stays of 0–1 days (24.5% vs 27.4%), more patients with smoking status recorded (95.6% vs 87.7%), more patients with a Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation (DECAF) score (measure of AECOPD severity²⁷) recorded (26.5% vs 6.4%) and more patients with spirometry results available (46.0% vs 32.9%).

In mixed-effects logistic regression analysis, no significant difference in 30-day mortality (OR: 1.09 (95% CI 0.92 to 1.29)) and 30-day readmission (OR: 0.96 (95% CI 0.90 to 1.02)) was found between admissions that conformed to the BPT and admissions that did not conform (figure 1 and online supplemental table S3).

The COPD BPT individual components

Respiratory specialist review

Fifty-three per cent of admissions were reviewed by a respiratory specialist within 24 hours (online supplemental table S4). Twenty-four per cent of patients did not receive a respiratory specialist review at all (online supplemental table S5). Of the 76% of patients who did receive a review, 69% were within 24 hours of admission, meaning that 31% of reviewed patients had to wait more than 24 hours for a review (online supplemental table S6). A detailed description of the differences between the exposure groups for each of the respiratory specialist review exposures is found in online supplemental results.

In mixed-effects logistic regression analysis, no significant difference in 30-day mortality or 30-day readmission was observed between admissions that were reviewed by a respiratory specialist within 24 hours and those that were not reviewed or reviewed in >24 hours (figure 2A and online supplemental table S7). No significant difference in 30-day mortality or 30-day readmission was observed between patients who did and patients who did not receive a specialist review (figure 2B and online supplemental table S8) and no significant difference was found in either outcome between patients who received a review within 24 hours and those who received a review in >24 hours (figure 2C and online supplemental table S9).

COPD discharge care bundle

Fifty-four per cent of admissions received a discharge bundle (online supplemental table S10). A detailed description of the differences between admissions that did and did not receive a discharge bundle is found in online supplemental results. In mixed-effects logistic regression analysis, no significant difference in 30-day mortality or 30-day readmission was observed between admissions that received a discharge bundle and those that did not receive a discharge bundle (figure 2D and online supplemental table S11).

Sensitivity analysis

Repeating the discharge bundle analysis without 'not clear' responses made no material difference to the odds of 30-day mortality and readmission (data available on request).

Repeating the specialist review analyses including patients who died during their admission (summary statistics by each specialist review exposure definition are shown in online supplemental tables S12–S14) and therefore, examining mortality in the full 30-day period following admission, did result in changes to the odds of 30-day mortality. However, the only statistically significant result was found for patients who received a specialist review at any time, who had 18% lower odds (OR: 0.82 (95% CI 0.72 to 0.94)) of 30-day death than patients who did not receive a specialist review (figure 3 and online supplemental table S15). Limiting mortality to inpatient mortality only, the effect of specialist review was even stronger with patients who received a specialist review at any time during

Table 1 Demographics and outcomes for people discharged from hospital following acute exacerbation of COPD whose admissions did conform to the COPD Best Practice Tariff (BPT) (receipt of a respiratory specialist review within 24 hours of admission and a discharge bundle) and those whose admissions did not conform to the COPD BPT, N=28 345

	Admission conformed to COPD BPT N=10 530 n (%)	Admission did not conform to COPD BPT N=17 815 n (%)
Age (years)		
Mean (SD)	71.5 (10.3)	72.5 (11.0)
Gender		
Male	4895 (46.5%)	8343 (46.8%)
Female	5635 (53.5%)	9472 (53.2%)
Quintile of IMD/WIMD		
1 (most deprived)	3485 (33.1%)	5768 (32.4%)
2	2509 (23.8%)	4254 (23.9%)
3	1894 (18.0%)	3337 (18.7%)
4	1492 (14.2%)	2510 (14.1%)
5 (least deprived)	1058 (10.1%)	1778 (10.0%)
No data	92 (0.9%)	168 (0.9%)
Oxygen prescription		
Not needed	1773 (16.8%)	3579 (20.1%)
Not prescribed	2341 (22.2%)	5098 (28.6%)
Prescribed	6416 (60.9%)	9138 (51.3%)
NIV administered	1201 (11.4%)	1354 (7.6%)
Length of stay quintile		
0–1 day	2581 (24.5%)	4875 (27.4%)
2–3 days	2581 (24.5%)	4290 (24.1%)
4–5 days	1770 (16.8%)	2878 (16.2%)
6–8 days	1685 (16.0%)	2471 (13.9%)
9+ days	1913 (18.2%)	3301 (18.5%)
Smoking status		
Never smoked	256 (2.4%)	732 (4.1%)
Ex-smoker	6236 (59.2%)	9559 (53.7%)
Current smoker	3586 (34.1%)	5335 (30.0%)
Not recorded	452 (4.3%)	2189 (12.3%)
Charlson comorbidity index		
1	5330 (50.6%)	8305 (46.6%)
2	2598 (24.7%)	4510 (25.3%)
3	1383 (13.1%)	2457 (13.8%)
4	662 (6.3%)	1267 (7.1%)
5	313 (3.0%)	670 (3.8%)
6	107 (1.0%)	273 (1.5%)
7+	137 (1.3%)	333 (1.9%)
Mental health diagnoses		
No mental illness	8309 (78.9%)	14 347 (80.5%)
Mild/moderate mental illness	1547 (14.7%)	2366 (13.3%)
Severe mental illness	674 (6.4%)	1102 (6.2%)
DECAF score		
Low risk (0–1)	1650 (15.7%)	568 (3.2%)
Intermediate risk (2)	677 (6.4%)	330 (1.9%)
High risk (3–6)	468 (4.4%)	237 (1.3%)
No data	7735 (73.5%)	16 680 (93.6%)

Continued

Table 1 Continued

	Admission conformed to COPD BPT	Admission did not conform to COPD BPT
	N=10 530	N=17 815
	n (%)	n (%)
Spirometry: FEV ₁ /FVC ratio		
≥0.7	507 (4.8%)	866 (4.9%)
<0.7	4253 (40.4%)	4884 (27.4%)
Invalid (<0.2 or >1.0)	83 (0.8%)	115 (0.7%)
No data	5687 (54.0%)	11 950 (67.1%)
Outcomes		
Patient died within 30 days of admission	285 (2.7%)	461 (2.6%)
Patient readmitted within 30 days of discharge	2659 (25.3%)	4577 (25.7%)

BPT, best practice tariff; COPD, chronic obstructive pulmonary disease; DECAF, Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; IMD, English Index of Multiple Deprivation; NIV, non-invasive ventilation; WIMD, Welsh Index of Multiple Deprivation.

admission having 31% lower odds (OR: 0.69 (95% CI 0.58 to 0.81)) of inpatient death (figure 3 and online supplemental table S15).

When using 90-day mortality and 90-day readmission as study outcomes, review within 24 hours of admission was significantly associated with 90-day mortality, with patients reviewed within 24 hours having 16% greater odds of dying within 90 days (OR: 1.16 (95% CI 1.05 to 1.28)) (online supplemental table S7). Patients who were reviewed by a respiratory specialist also had 20% higher odds (OR: 1.20 (95% CI 1.06 to 1.36)) of dying within 90 days than patients who were not reviewed by a respiratory specialist (online supplemental table S8), and patients who were reviewed within 24 hours had 13% higher odds (OR: 1.13 (95% CI 1.01 to 1.26)) of dying within 90 days than patients who were reviewed in >24 hours (online supplemental table S9). There was no material difference in mortality or readmissions at 90 days compared with 30 days for patients who received a discharge bundle (online supplemental table S11).

In the analysis using only English hospitals, there was no material difference in 30-day outcome results; however, there were some changes in significance for 90-day outcome results. Patients had 12% lower odds (OR: 0.88 (95% CI 0.79 to 0.98)) of death within 90 days if they received a discharge bundle and patients who received a specialist review within 24 hours (relative to those who received a review in >24 hours) were no longer significantly likely (OR: 1.11 (95% CI 0.99 to 1.24)) to die within 90 days of admission (online supplemental table S16).

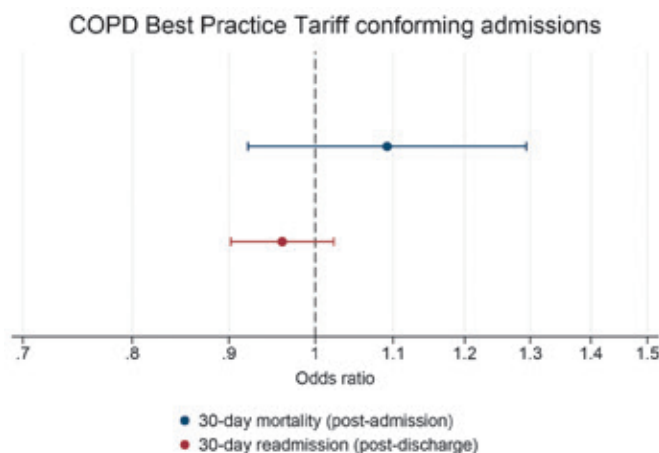


Figure 1 Forest plot of adjusted ORs and 95% CIs for 30-day post-admission mortality and 30-day post-discharge readmission for people discharged from hospital following acute exacerbation of COPD whose admissions conformed to the COPD Best Practice Tariff (BPT) relative to those whose admissions did not conform to the COPD BPT. Values <1 favour conforming to the BPT; values >1 favour not conforming to the BPT.

In the analysis comparing hospitals where ≥60% of admissions conformed to the COPD BPT and hospitals where <60% of admissions conformed, we did not find a significant difference in outcomes between the two groups (online supplemental table S17).

DISCUSSION

In this study, we did not find an association between the combination of the two criteria (specialist review within 24 hours and receipt of a discharge bundle) of the English COPD BPT pay-for-performance scheme and a reduction in 30-day (postadmission) mortality or 30-day (postdischarge) readmissions among people discharged from hospital following AECOPD. While the BPT was not designed to reduce mortality or readmission rates specifically, rather the intention was to promote better quality patient care, it might be anticipated that better patient care should in turn lead to better outcomes of readmission and mortality. In further analysis, when individually examining the two COPD BPT components, we also did not find an association between being reviewed by a respiratory specialist within 24 hours or receiving a discharge bundle and 30-day mortality or readmissions. However, when we included patients who died as an inpatient, we found that having a specialist review at any time during the admission was associated with 18% lower odds of 30-day mortality and 31% lower odds of inpatient mortality. This suggests that specialist review at any point during an admission is beneficial for inpatient mortality but does not improve mortality after discharge. When repeating the analysis using 90-day outcomes, patients who were reviewed by a specialist within 24 hours of admission had greater odds of dying within 90 days than those who were not reviewed or were reviewed after 24 hours. The most likely explanation for this is that there is important confounding from admission severity that we have not been able to adjust for and that, appropriately, the sicker patients are being reviewed in priority to those who are less unwell. In fact, given that patients seen by a respiratory specialist were more frequently prescribed oxygen and required NIV, respiratory specialist review may simply be a proxy for admission severity.

While it is difficult to argue that discharge bundles do not increase best-practice care, this analysis raises concern that while the right boxes are being ticked in the audit, there is not always effective intervention. We can measure conformance to the BPT, but we cannot measure the quality of the delivery of its components. For example, the bundle component of inhaler technique check will not provide any benefit if the inhaler is used poorly by the patient and optimal use is not then demonstrated and confirmed by the medical team, with a switch to an alternative device as appropriate. It is possible that some hospitals or members of the multiprofessional team may consider a bundle complete if just a few of the items have been completed, while others may complete all bundle items without realising and state that a bundle has not been completed. For example, results from the most recent COPD audit²⁸ show that 74% of admissions were described as having received a discharge bundle, yet the patient was assessed for suitability for pulmonary rehabilitation in only 56% of admissions. We performed a sensitivity analysis, limiting our analysis to just English hospitals to exclude hospitals ineligible to participate in the BPT in case recording of data was better in those participating in the BPT. However, other than a possible suggestion that a discharge bundle was beneficial for 90-day mortality, no material difference was found. One possible reason for not seeing a benefit from the COPD BPT could be that benefits from some of the bundle items, such as smoking cessation and pulmonary rehabilitation, are not seen until after a longer period than 30 days, or the benefits are manifest in other ways (such as improved quality of life) that are not captured by readmission or mortality outcomes. It may also be possible that there is an indirect beneficial effect of the COPD BPT in the form of increased financial investment in respiratory teams as part of the focus to meet the BPT requirements. This may have helped to improve quality of care in COPD admissions. These are important aspects that this analysis cannot address and deserve further study.

While there have not been any previous studies of the COPD BPT pay-for-performance scheme, studies of the COPD BPT components have been completed. A systematic review¹⁷ of COPD discharge bundles found that they did not significantly improve

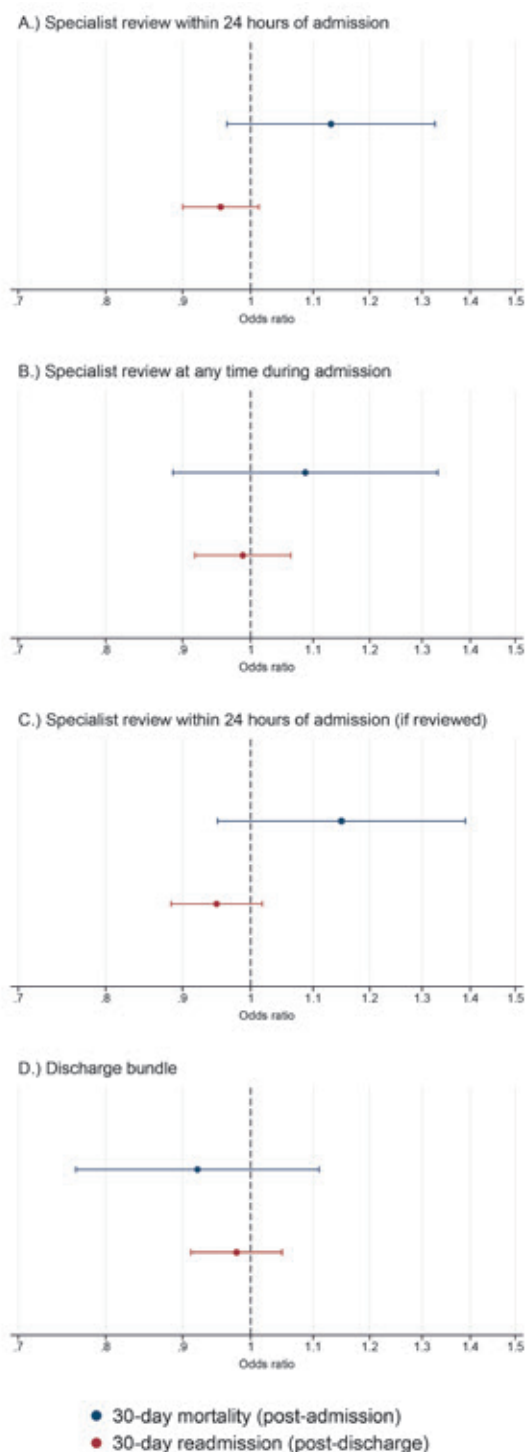


Figure 2 Forest plot of adjusted ORs and 95% CIs for 30-day post-admission mortality and 30-day post-discharge readmission for people discharged from hospital following acute exacerbation of COPD who: (A) received a respiratory specialist review within 24 hours of admission relative to those who did not receive a review or received a review in >24 hours of admission; (B) received a respiratory specialist review at any time during admission relative to those who did not receive a respiratory specialist review at any point during admission; (C) received a respiratory specialist review in ≤24 hours of admission relative to those who received a respiratory specialist review in >24 hours of admission; (D) received a discharge bundle relative to those who did not receive a discharge bundle. Values <1 favour the intervention; values >1 favour not receiving the intervention.

mortality or quality of life and only weak evidence for a reduction in readmissions. A more recent literature review²⁹ concluded that it was inconclusive if COPD admission or discharge care bundles reduced readmissions, and that further study was required. A recent UK study¹⁸ found no evidence that COPD care bundles reduced

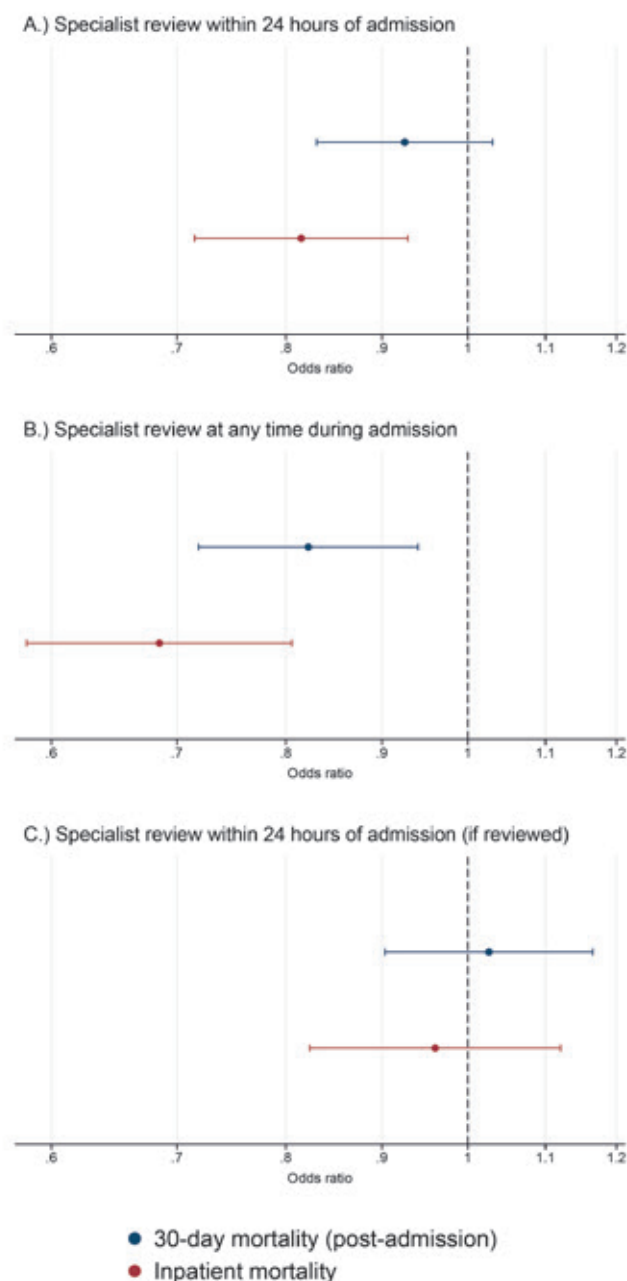


Figure 3 Forest plot of adjusted ORs and 95% CIs for 30-day post-admission mortality and inpatient mortality for patients admitted to hospital with acute exacerbation of COPD (ie, the full audit cohort including patients who died as an inpatient or self-discharged) who: (A) received a respiratory specialist review within 24 hours of admission relative to those who did not receive a review or received a review in >24 hours of admission; (B) received a respiratory specialist review at any time during admission relative to those who did not receive a respiratory specialist review at any point during admission; (C) received a respiratory specialist review in ≤24 hours of admission relative to those who received a respiratory specialist review in >24 hours of admission. Values <1 favour the intervention; values >1 favour not receiving the intervention.

28-day readmission, although emergency department attendances did reduce after care bundles were implemented in hospitals. It was also found that not all items of the admission and discharge bundles were reliably completed. A recent French study³⁰ also concluded that a COPD discharge care bundle had no impact on 28-day AECOPD readmission or mortality. However, one recent US study³¹ found that all-cause readmissions reduced after implementing a COPD care bundle. It is worth noting that all these bundle studies have comparatively small numbers of included patients and generally compare outcomes at a population-level rather than the patient-level as

we have done in this study. No formal assessment of publication bias was conducted in the literature reviews^{17–29} due to the limited number of published randomised controlled trials and it is possible there is resultant publication bias.

Timely receipt of respiratory specialist input in AECOPD admissions has not been as extensively studied as COPD discharge bundles; however, a study in North East England³² found that after implementing a model that ensured respiratory specialists were available 24 hours a day, 7 days a week, 30-day mortality decreased. An increase in 90-day (but not 30-day) readmissions was also observed. Again, this study compared population-level figures at two time points, which could explain differences from our study.

Although there are no prior studies of the COPD BPT, studies have examined the impact of the hip fracture BPT on patient outcomes. The hip fracture BPT is another pay-for-performance scheme in England, similar to the COPD BPT, that aims to improve care quality for hip fractures. Oakley *et al*³³ compared admissions before and after the introduction of the hip fracture BPT, BPT compliant and BPT noncompliant admissions. They found that the hip fracture BPT did not lead to any improvements at the organisational level (pre-BPT vs post-BPT), however, at the patient-level, mortality was significantly reduced (BPT vs non-BPT admissions). Survival analysis also found a significant long-term survival benefit for BPT conforming admissions. Whitaker *et al*³⁴ similarly found that 1-year survival was significantly better in BPT conforming admissions. Metcalfe *et al*³⁵ compared admissions in England and Scotland following the introduction of the BPT (which only applies to England) and found that there was a greater reduction in mortality, readmissions and length of hospital stay during the BPT period in England than in Scotland. It should be noted that the hip fracture BPT has the definitive intervention of surgery that is not present in the COPD BPT, so the two may not necessarily be comparable.

The value of pay-for-performance schemes has been investigated in other healthcare settings;^{6–8} however, it is difficult to draw direct comparisons given differences in healthcare delivery and pay-for-performance models that exist. While financial incentives are often seen as being a key element in changing clinical practice, pay-for-performance does not always lead to better easily measurable outcomes. For example, financial incentives may lead to better overall investment, with effective implementation of components of pay-for-performance schemes themselves difficult to measure.

The primary strength of this analysis comes from the number of patients included. However, this study does have limitations. We have used adjustment to attempt to control for differences between BPT admissions and non-BPT admissions. However, our results suggest that there is unmeasured confounding from admission severity. It may also be that there is confounding from other factors related to the admission such as COPD disease severity, exacerbation frequency and patient frailty. These are all possible confounders that we unfortunately do not have available data on to be able to adjust for and could possibly explain why we have not been able to find an association between the COPD BPT and mortality or readmission. Another possible limitation is that we have used all-cause readmissions as our outcome rather than just AECOPD admissions. It is not clear whether the BPT or discharge bundle aims to reduce just AECOPD readmissions or any readmissions. However, over 50% of the readmissions in our study were for either AECOPD or pneumonia and some of the other studies discussed used all-cause readmission as an outcome too.^{18–31} A limitation of the data set that we used is that it is not clear which specific elements of the discharge bundle have been completed, we are simply provided with a binary 'yes, bundle completed' response and as Morton *et al*¹⁸ noted, certain elements of the discharge bundle are not always well completed.

In conclusion, we found that documentation of conforming to the COPD BPT pay-for-performance scheme criteria or receipt of a discharge care bundle alone does not appear to be associated with a reduction in mortality or readmission. However, receiving a respiratory specialist review at any point during an admission was associated with lower inpatient mortality. Further thought and work is needed to better understand the benefits of pay-for-performance models. The COPD BPT and other financial incentive schemes should be specific in the outcomes they want to improve, so that interventions with the strongest evidence base can be financially incentivised. If the COPD BPT is failing to have the desired improvement to patient outcomes

because of failure to adequately complete all COPD discharge bundle components, it may be sensible to add each bundle item to the COPD BPT separately rather than including them under the single requirement of 'COPD discharge bundle'.

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Contributors PWS ran the analyses and produced the first draft of the manuscript. PWS, AA, JRH, CMR, JKQ made substantial contributions to conception and design of the study, acquisition and interpretation of data; took part in revising the article critically for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

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Data availability statement Data may be obtained from a third party and are not publicly available. Data collected on behalf of Hqip by all NCAPOP projects are routinely reported and these reports are available in the 'Resources' section of the Hqip website (<https://www.hqip.org.uk/resources/>). The reported data are also placed on the data.gov.uk website. Data are also placed upon MyNHS and NHS Choices. For details of how to apply for data that is not in the public domain, please see Hqip's data access webpages (<https://www.hqip.org.uk/national-programmes/accessing-ncaPOP-data/>).

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ARTIGO ORIGINAL

Função pulmonar em crianças com fibrose quística nos EUA e no Reino Unido: uma análise longitudinal comparativa dos dados de registos nacionais

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RESUMO

Contexto Uma análise anterior encontrou uma função pulmonar significativamente mais elevada na população de fibrose quística pediátrica (FC) dos EUA em comparação com o Reino Unido, tendo esta diferença aparentemente diminuído na adolescência e na idade adulta. No entanto, a natureza transversal do estudo dificulta a interpretação destes resultados.

Objetivos Comparar as trajetórias longitudinais da função pulmonar em crianças com FC dos EUA e Reino Unido e explorar as causas das eventuais diferenças.

Métodos Utilizámos a análise de regressão de efeitos mistos para modelar as trajetórias da função pulmonar nas populações estudadas. Utilizando estatísticas descritivas, comparámos o crescimento precoce e a nutrição (altura, peso, índice de massa corporal), infeções (*Pseudomonas aeruginosa*, *Staphylococcus aureus*) e tratamentos (rhD-nase, soro fisiológico hipertónico, antibióticos inalados).

Resultados Incluímos 9463 crianças dos EUA e 3055 crianças do Reino Unido com genótipo homozigoto F508del. A função pulmonar foi mais elevada nos EUA do que no Reino Unido, quando medida pela primeira vez aos seis anos de idade, e permaneceu mais elevada durante toda a infância. Não encontramos diferenças significativas no crescimento precoce e nutrição nem na infeção por *P.aeruginosa*. A prescrição de rhDNase e soro hipertónico foi mais comum nos EUA. Os antibióticos inalados foram prescritos em quantidades semelhantes em ambos os países, mas a tobramicina foi prescrita mais nos EUA e a colistina no Reino Unido. A infeção por *S. aureus* foi mais comum nos EUA do que no Reino Unido.

Conclusões As crianças com FC e genótipo homozigoto F508del nos EUA apresentaram melhor função pulmonar do que as crianças britânicas. Estas diferenças não parecem ser explicadas pelo crescimento precoce ou pela nutrição, mas as diferenças na utilização de tratamentos na fase inicial necessitam de uma investigação mais exaustiva.

BACKGROUND

Cystic fibrosis (CF) is a serious, multiorgan inherited disease characterised by pulmonary infections and progressively declining lung function. Most people with CF die prematurely from their disease through respiratory failure.^{1,2} In the 1960s, median survival in the UK was estimated to be below 10 years of age.³ Over the past decades, outcomes have improved due to multidisciplinary care, nutritional support and new treatments, such that half of the babies born with CF in the UK and the USA today can be expected to live at least in to their late forties.^{2,4-6}

Previous international comparisons of outcomes in people with CF have highlighted the impact of different healthcare practices and approaches to treatment, and have contributed to improvements in care for people with CF. For example, comparisons of nutritional, pulmonary and survival outcomes between the USA and Canadian CF populations provided evidence for high-fat, high-calorie diets for people with CF.^{7,8}

A previous cross-sectional study comparing the 2010 US and UK CF populations suggested better

Key messages

What is the key question?

► Was there a difference in the longitudinal trajectories of lung function in children with cystic fibrosis between the USA and UK during 2003–2014?

What is the bottom line?

► Children with cystic fibrosis and homozygous F508del genotype in the UK had persistently worse lung function than those in the USA.

Why read on?

► This finding does not appear to be explained by differences in casemix or early growth or nutrition, but there are differences in the use of early treatments between the two countries which will need further investigation.

lung function in children in the USA compared with those in the UK. After adjustment for a set of potential demographic and clinical confounders, the authors estimated a difference in percent of predicted forced expiratory volume in 1 s (%FEV₁) of 7.62 percentage points (95%CI 6.24 to 9.00) between children in the USA and UK under the age of 12. This difference seemed to be smaller in adolescence and disappeared by age 30.9. However, due to the cross-sectional nature of the study, the age trends demonstrated could not be interpreted as average trends for individuals over time. The narrowing of the US-UK gap with increasing age was therefore difficult to interpret, conflating potentially different rates in lung function decline between populations with cohort effects and survivor bias later in adulthood. The aim of this study was, therefore, to compare lung function trajectories, that is, lung function at age 6 years and rates of lung function decline, between the US and UK populations. Secondary aims were to explore potential reasons for any differences demonstrated. To ensure comparability of populations, we restricted our analysis to the paediatric populations to reduce the impact of survivor bias, and to people who were homozygous F508del—the most common CF genotype—to reduce differences in case-mix.

METHODS

Study design

We carried out retrospective longitudinal analyses of lung function in comparable cohorts of children with CF aged ≥6 to <18 years and with homozygous F508del genotype captured in the US Cystic Fibrosis Foundation Patient Registry (CFFPR) and UK Cystic Fibrosis Registry.

Data sources

We used the US CFFPR and the UK CF Registry. The current CFFPR includes data from 1986 onwards on over 50000 people with CF and is estimated to capture about 84% of the current US CF population. Since 2003, CF care centres have been encouraged to enter information from all clinical encounters at CF Foundation Care Centre Network facilities.¹⁰ Current CFF guidelines are for people with CF to be seen quarterly for routine care.¹¹

In the UK, it is recommended that care teams submit annual encounter data to the Registry from a clinic visit approximately 12 months after the previous entry and when the patient is clinically stable. Records date back to the 1990s and are estimated to capture approximately 99% of the current CF population.¹² See online supplemental material section 1 for more details.

Setting and participants

We included children aged ≥ 6 to <18 with homozygous F508del genotype with data recorded in the CFFPR or UK CF Registry between January 2003 and December 2014 and with at least one lung function measurement in that time period. Restricting the analysis to children with CF who were homozygous for F508del reduced the differences in casemix between the two countries. The dates were chosen to ensure comparability between populations as it preceded licensing of Orkambi (lumacaftor/ivacaftor) in the USA. For individuals who had a transplant, observations were censored at transplant. We excluded individuals who did not have complete data on sex, year of birth and age at diagnosis.

Outcomes and covariates

Our main outcome of interest was lung function measured by percent of predicted %FEV₁ based on GLI reference equations¹³ and the rate of lung function decline.

Secondary outcomes were time-varying indicators of growth and nutrition (height, weight, body mass index (BMI); raw values and z-scores using the Centers for Disease Control and Prevention (CDC) reference populations in both countries and additionally UK-WHO reference population in the UK), prescribed chronic medications (rhDNase, hypertonic saline), common inhaled antibiotics (Tobramycin, Colistin, Aztreonam) and common infections (*Pseudomonas aeruginosa*, *Staphylococcus aureus*) between birth and age 18 for the study population. More information on secondary outcomes and when they began collection can be found in online supplemental material section 1 table 1.

To adjust for remaining potential differences in case-mix, we included the following baseline covariates in the models used: sex (binary: male/female; reference level: female), year of birth (continuous, centred at 1997) and age at diagnosis (continuous).

Statistical analysis

Using all the collected data on our study population from age 6 up to (excluding) age 18 (encounter data in the USA and annual review data in the UK), we developed models for the longitudinal trajectories of lung function to compare estimated population-level mean lung function and population-level mean lung function decline by age between the US and UK paediatric populations.

We fitted a series of models of different complexity to the US and UK study populations. We fitted models using linear,^{14 15} quadratic and cubic polynomials of age, and models including flexible functions of age^{16 17} using natural cubic splines with one knot at age 12, two knots at ages 8 and 14, 5 knots with one knot every 2 years (8, 10, 12, 14 and 16 years) and 11 knots – one every year. All models included sex, year of birth and age at diagnosis as covariates; year of birth and age at diagnosis entered the models linearly. We did not consider any interactions between functions of age and the covariates (for exploratory plots, see online supplemental material section 2).

To appropriately capture the correlation between repeated measurements within an individual over time, we initially included random intercepts in the models and then added: (1) random slope (only in the model with a linear function of age), (2) random slope and exponential correlation function (only in the model with a linear function of age), (3) exponential correlation function and (4) linear correlation function. Within each country all the model fits were compared using the log-likelihood, Akaike information

criterion (AIC) and Bayesian information criterion (BIC); the best fitting models are those with the highest log-likelihood, lowest AIC and lowest BIC. For more details, see online supplemental material section 3.

To explore reasons for any differences in lung function trajectories we compared indicators of growth and nutrition, treatments, and infections cross-sectionally from birth to age 18 between the two study populations. This included records collected prior to 2003 on individuals in the study population. Observations remained censored at lung transplant. We summarised height, weight and BMI by their median, 25th and 75th percentile at each year of age for all individuals in the study population for whom data were available at that age. For treatments and infections we presented the proportion of individuals with at least one record of receiving the treatments/ having the infections before age 6, before age 12 and before age 18 years; as well as the median, 25th and 75th percentile, minimum and maximum of the age at first recorded treatment/infection.

We stratified these comparisons by year of birth (before and after 1997) as post 1997 data will be more complete with regard to treatments and infections and may give a better representation of health-care practices.

We used R packages nlme18 and splines¹⁹ for data analysis and ggplot2²⁰ and the dns() function from the JMbayes²¹ package for visualisations; online supplemental material used knitr.^{22 23}

Robustness test

To assess the generalisability of our results to more recent paediatric CF populations, we repeated our analysis using the best fitting models applied to the recent cohort born after 1997.

RESULTS

Study populations

There were 9463 and 3055 individuals in the US and UK study population, respectively (see online supplemental material section 4 for the derivation of the study populations). In the USA, individuals had a median of 24 lung function measurements, with a median of 4 (IQR: 3–6) measures per individual per year (table 1). In the UK, each individual had a recorded review measurement approximately once a year, with a median of 4 lung function measurements during the study period. The average lung function for those observed at age 6 was 93 (SD: 17.7) in the USA and 88.2 (SD: 16.9) %FEV₁ in the UK. The populations were generally comparable with regard to their demographic characteristics (table 1, online supplemental material section 5).

Estimated lung function and lung function decline

In both countries, the estimated population-level mean lung function between ages 6 and 18 and the covariate effects were very similar across all the different models (online supplemental material section 6). The best fitting model for lung function in both countries was the model with a linear term for age with random intercept, random slope and exponential correlation function. In the USA, the model including age using a spline with five knots, random intercept and exponential correlation function gave only a marginally worse fit, therefore, we report results for both models.

Population mean lung function was higher in the US study population throughout childhood (figure 1). Based on our model that included a linear function of age, lung function declined at a faster rate in the UK than in the US population (–1.61 per year (95%CI: –1.72 to –1.50) in the UK compared with –1.41 (95% CI: –1.47 to –1.36) in the USA); children in the UK lost on average an additional 0.20percentage points in %FEV₁ per year (95%CI 0.08 to 0.32) compared with the USA. Based on the model that included age using a spline with five knots there was an indication of a faster rate of decline in the UK at almost all ages but the evidence was not clear (figure 1, online supplemental material section 8).

Based on the model with a linear term for age and covariate reference levels (female, born in 1997, diagnosed at birth) the estimated difference between the USA and UK populations at ages 6, 12 and 17 was 3.60 (95% CI 2.40 to 4.80), 4.80 (95% CI 3.38 to 6.22) and 5.80 (95% CI 3.98, 7.62) % FEV₁, respectively. Based on the model including age using a spline model with five knots, the difference between the two countries was 3.89 (95% CI 2.00, 5.77), 4.78 (95%

Table 1 Details of the datasets and study populations in the USA and UK, respectively

	US data	UK data
Sample size	9463	3055
No of FEV ₁ measures per person (median (IQR), (full range))	24 (11–40), (1–199)	4 (2–7), (1–17)
No of individuals with one FEV ₁ measure (%)	251 (2.7)	398 (13.0)
No of FEV ₁ measures per person per year (median (IQR))	4 (3–6)	1 (1–1)
Time in years between first and last FEV ₁ measurement included in the study per person (median (IQR))*	5.5 (2.7–8.4)	4.9 (2.2–7.5)
Informative drop-out during study period (%)		
Lung transplants	142 (1.5)	27 (0.9)
Deaths	263 (2.8)	70 (2.3)
Sex (%)		
Female	4625 (48.9)	1457 (47.7)
Male	4838 (51.1)	1598 (52.3)
Year of birth (median) (IQR)	1996 (1991–2002)	1996 (1991–2002)
Race (%)		
Non-Caucasian	384 (4.1)	71 (2.3)
Caucasian	9083 (95.9)	2984 (97.7)
Age at diagnosis in years (median (IQR))	0.3 (0.0–1.2)	0.2 (0.0–1.0)
Diagnosis by newborn screening (%)	1079 (11.4)	501 (16.3)
%FEV ₁ at age 6 (mean (SD))	92.96 (17.7)	88.17 (16.9)

*Excluding individuals with only one FEV₁ measurement.

FEV₁, forced expiratory volume in 1 s.

CI 3.10 to 6.47) and 5.69 (95% CI 3.97 to 7.41)% FEV₁ at ages 6, 12 and 17, respectively.

The US-UK gap was estimated to increase over calendar time by 0.13% predicted per year of birth (95%CI 0.003 to 0.25) based on the model with a linear term for age, and 0.12% predicted per year (95%CI –0.01 to 0.25) based on the model including age using a spline with five knots (table 2). In the UK, males had on average

2.50 percentage points (95%CI 1.32 to 3.67) higher %FEV₁ than females, whereas in the USA, the difference was 1.42 percentage points (95%CI 0.70 to 2.14) (based on the model with a linear term for age; results were similar for the model that included age using a spline with five knots). The difference between the US and UK populations may therefore be less for males than females (see online supplemental material section 7 for estimated differences between the US and UK for selected sets of covariate values).

Indicators of growth and nutrition, treatments and infections

Children in the US study population were on average lighter and shorter than children in the UK population during childhood and into adolescence (figure 2, online supplemental material section 9).

Rates of infection with *P. aeruginosa* were similar in both countries but methicillin sensitive and methicillin resistant *S. aureus* infections were more common in the US (online supplemental material section 11).

A larger proportion of the study population was treated with rhD-Nase and hypertonic saline in the USA compared with the UK. In the post 1997 birth cohort, 73% were treated with rhDNase before age 6 in the USA and 96% before age 18 compared with 20% and 86%, respectively, in the UK (online supplemental material section 10). Hypertonic saline was prescribed for 76% of the study population before age 18 in the post 1997 birth cohort in the USA vs 50% in the UK (online supplemental material section 10). Inhaled antibiotics were prescribed at slightly higher levels before age 6 in the USA but prescribed at similar levels at later ages (online supplemental material section 10). However, there was a big difference in the inhaled antibiotic of choice between the two countries. Tobramycin was the most prescribed inhaled antibiotic in the USA, whereas Colistin was prescribed most in the UK (online supplemental material section 10).

Robustness test

In both countries lung function decline was less steep in the population born after 1997 compared with the whole study population. The estimated gap in absolute level of lung function was comparable to the estimates derived from the whole population (online supplemental material section 12).

DISCUSSION

We assessed longitudinal lung function trajectories in comparable populations of children in the USA and UK using data from national registries and found that lung function was better in US children over the entire age range from 6 up to age 18 years. For

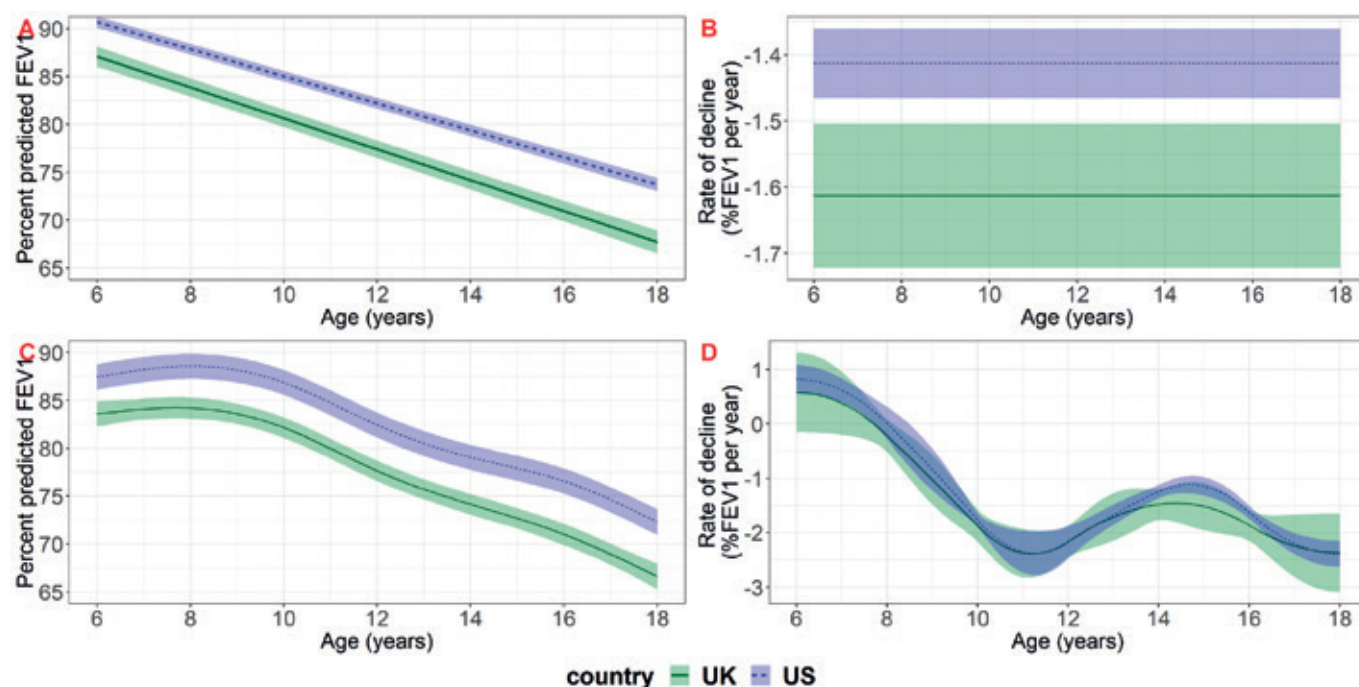


Figure 1 Estimated population-level mean lung function (panels A, C) and lung function decline (panels B, D) in the UK and US study populations for reference covariate values (female, born in 1997, diagnosed at birth). The top row (A, B) shows results based on the model that included a linear term for age with random intercept and slope and exponential correlation function; the bottom row (C, D) shows results based on the model that included age using a spline with five knots with random intercept and exponential correlation function. FEV₁, forced expiratory volume in 1 s.

Table 2 Estimated covariate effects (95% CIs) based on the model that included a linear term for age with random intercept, random slope and exponential correlation function and the model that included age using a spline with five knots, random intercept and exponential correlation function

	US		UK	
	Linear function	Spline	Linear function	Spline
Sex=male	1.42 (0.70, 2.14)	1.80 (1.04, 2.55)	2.5 (1.33, 3.7)	2.71 (1.49, 3.93)
Age at diagnosis	0.59 (0.43, 0.74)	0.57 (0.42, 0.72)	0.62 (0.30, 0.95)	0.6 (0.28, 0.92)
Year of birth	0.37 (0.30, 0.43)	0.42 (0.35, 0.48)	0.24 (0.13, 0.35)	0.3 (0.19, 0.41)

example, based on the best fitting longitudinal model, females in the USA were estimated to have approximately 3.60 (95% CI 2.40 to 4.80) and 5.80 (95% CI 3.88 to 7.62) percentage points higher %FEV₁ than females in the UK at age 6 and 17, respectively. The gap was slightly smaller for males. Children in the USA with CF may have a slower rate of decline in lung function compared with UK children, but the strength of evidence for this was sensitive to modelling choices and was less clear in more recent cohorts born after 1997.

Strengths and limitations

A major strength of this study is the use of high quality, longitudinal data with broad national coverage in each country and the application of statistical methods suitable for longitudinal data analysis which enabled us to compare population level mean lung function trajectories across childhood. We fitted a range of models to reduce the possibility that estimated differences in lung function were due to suboptimal model fit in the populations. Our main results were consistent across models.

A further strength is the reduction of differences in case-mix between the two populations through the restriction to the F508del homozygous population and the adjustment for important covariates. We also reduced the influence of survivor bias by only considering the paediatric populations. However, this does mean that our results may not be generalisable to the whole CF population and further studies are needed to understand whether the differences we found also exist for different genotypes.

The previous study by Goss et al⁹ accounted for differences in data collection methods between registries by merging the US and UK datasets into a single data set and matching a single US clinic visit to a UK annual visit based on month of calendar year.

In this study we did not try to harmonise the datasets but rather used identical inclusion/exclusion criteria and analysis methods. By including all available data points, we can more precisely estimate trends in lung function and rates of decline, but this may lead to bias due to seasonality or time between clinic visits (online supplemental

material section 1). However, we do not expect this to have a major impact on our results as seasonality has been shown to have a negligible effect on lung function.^{15,24}

The difference in the number of data points between the two populations is also unlikely to have significantly impacted our results based on preliminary findings from a parallel investigation of different analysis strategies applied to the US CFFPR. The potential impacts of these strategies on estimating lung function decline have been reported in abstract form from a Cystic Fibrosis Foundation workgroup.²⁵ The findings show that lung function trajectory estimates were similar if using all available encounter-level %FEV₁ data, median quarterly data or median annual data. It has been noted that in the UK CF population, the average best measured %FEV₁ per year is significantly higher (approximately 4 percentage points) than the annual review %FEV₁ that we used in this study.²⁶ Best FEV₁ has only been collected in the UK CF Registry since 2012 and therefore we could not conduct a full comparison of this measure between the two countries. However, a cross-sectional description of annual vs best %FEV₁ in the UK and average-per-year vs best %FEV₁ in the USA, showed similar differences in the two countries and indicated that an analysis using best %FEV₁ would likely return similar results to our findings (see online supplemental material section 13).

Although we adjusted for a number of baseline covariates, a limitation remains the potential difference in casemix, especially due to socioeconomic factors. These have been shown to impact outcomes in CF^{14,27,28} but due to differences in measuring socioeconomic status between countries and differences in data collection between registries, it was not possible to adjust for these. It has previously been suggested that the US CFFPR may not capture the full spectrum of socioeconomic conditions as the UK CF Registry does. A sensitivity analysis of this assumption in relation to the study by Goss et al, however did not alter their results significantly and is therefore not likely to have a major impact on our findings.²⁹ A related open question is whether individuals not captured in the registries differ significantly from those who are. If this is the case, then any results

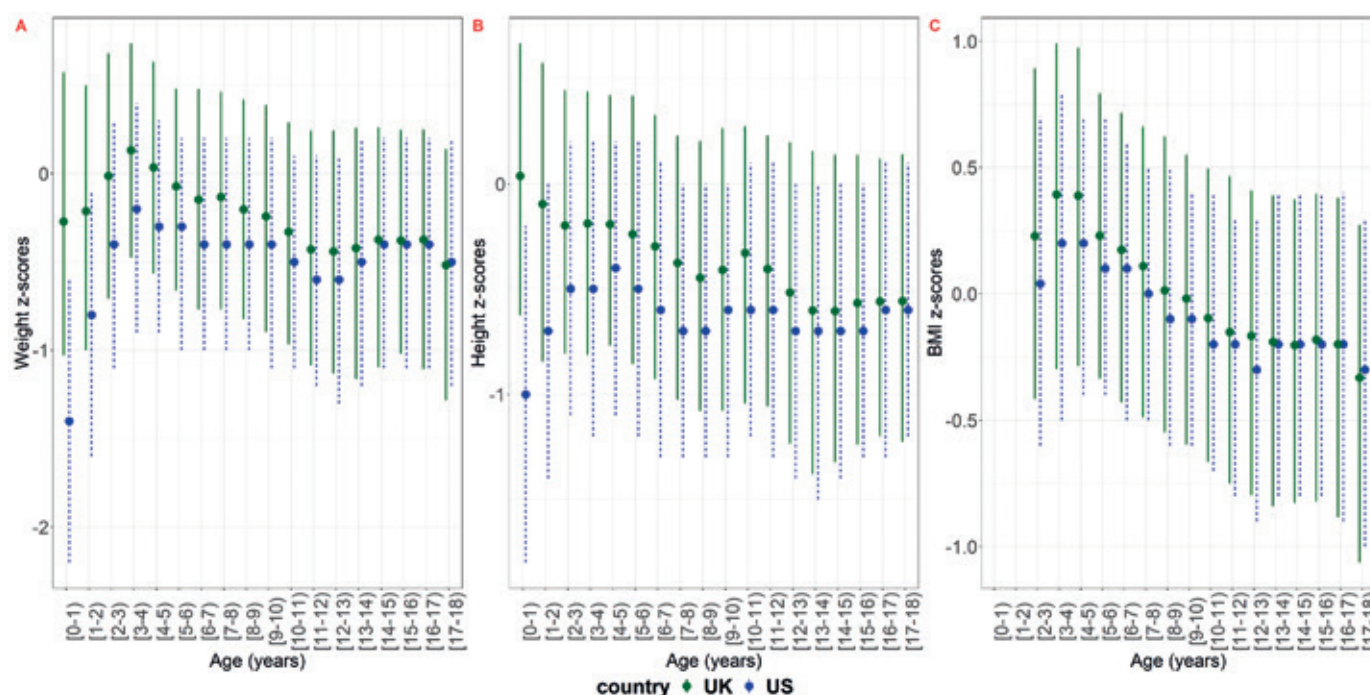


Figure 2 Cross-sectional summary measures of weight, height and BMI z-scores of the study population based on the CDC reference population in the US and the UK. The dots show the median and the lines the IQR. BMI, body mass index.

from analyses of the registry population may not be generalisable to the population as a whole. Therefore, when interpreting the findings from our study, we need to be mindful that about 16% of the US CF population is not captured by the CFFPR and in the UK it is only since 2012 that 99% have been captured.

A further limitation is the generalisability of these results to the CF population in the era of new cystic fibrosis transmembrane conductance regulator (CFTR) modulators. In future studies, it will be important to assess whether the observed differences have widened with the earlier introduction of Orkambi (lumacavtor/ivacavtor) in the USA compared with the UK and whether we can expect the difference to decrease in the next generation when both countries will have access to CFTR modulators, including the triple combination therapy, for almost the whole population. However, the fast-paced development and the variation in introduction and eligibility criteria for CFTR modulator therapies across different countries pose additional difficulties for conducting cross-country comparison analyses of registry data.

Comparison with previous studies

Our overarching finding, that the paediatric homozygous F508del population in the USA had higher lung function than this population in the UK, corroborates the results from the cross-sectional study by Goss et al. However, the longitudinal nature of our study enabled us to compare the population-level mean lung function trajectories throughout childhood. We showed that the gap between the two populations was sustained and may even be increasing during childhood and adolescence. These findings are in contrast to Goss et al who had previously found that cross-sectionally the gap in lung function between the USA and UK appeared to be decreasing in adolescence and disappeared at age 30. Their findings are likely due to cohort effects and could be explained by our result that the gap between the two countries may be widening with calendar time.

Implications for clinical practice

The sustained gap in lung function between the USA and UK which may be increasing with age and calendar time is a major concern for the UK CF community. As suboptimal nutritional status early in life is associated with lower pulmonary function,³⁰ we compared anthropomorphic measures between the two study populations. Children in our UK study population had on average better early nutritional status than children in the US study population. If anything, this would portend, if all other things were equal, that lung function in the UK would be better than in the USA. In other words, the factors contributing to the difference in lung function between the two populations may be responsible for an even greater difference than just the difference reported in our study.

Additional factors such as differential use of medications between the countries may impact lung function.^{31,32} We found big differences in the proportion of children receiving rhDNase and hypertonic saline with much more aggressive treatment at younger ages in the USA compared with the UK. In the pivotal study, once daily rhDNase reduced pulmonary exacerbations by 28% and improved FEV₁ by 5.8% compared with placebo³² but a recent study in the UK found that rhDNase may only improve lung function in individuals with reduced FEV₁ at baseline.³³ In both studies, however, children under 5 years of age were excluded and there remains a paucity of data on the use of rhDNase in preschool children. Although overall levels of prescribed inhaled antibiotics were similar between the countries, US children were almost entirely treated with Tobramycin. Whereas in the UK, colistin was used almost exclusively, especially in children under the age of 6. These results raise the question whether the earlier prescription of mucoactive agents in the USA led to improved lung function at age 6, or whether differences between the US and UK in early antibiotic use, both nebulised and oral,³⁴ may have an impact on lung function. Further work will be needed to investigate this and other potential reasons for the observed differences. This will include investigating whether there are differences in lung function between the healthy populations in the USA and the UK. We will also need to understand the generalisability of these findings to the whole CF population and the implications for long term outcomes including survival or time to lung transplant.

CONCLUSIONS

Non-humidified Using patient registry data to conduct international comparisons of health among people with CF is challenging due to variation in data collection methods but may highlight differences in healthcare and health outcomes between countries. In our comparative longitudinal analysis of children with CF, we found significant differences in lung function between the USA and UK. Children in the USA had higher lung function at age six which was sustained throughout childhood and adolescence. The rate of decline in lung function with age may also be slower in the USA. Further work will need to investigate possible reasons for the gap in lung function between the USA and the UK at age 6 including a more detailed analysis of treatment patterns.

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Contributors NAM, JWD, FWH, FKAG, DTA and JB designed the experiments. SS and FKAG analysed the data, with BRB and JPR providing supervisory support and analysis. EM coordinated inpatients with COVID-19, CW and AJM coordinated the study. KRW provided expert opinion and analysis on respiratory support. JWD is the guarantor.

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Ethics approval This study was performed as part of the wider AERATOR Study to assess the risk of aerosolised transmission of SARS-CoV-2 in healthcare settings. Ethical approval was given by the North West Research Ethics Committee (Ref: 20/NW/0393, HRA approved 18/9/20).

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Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information. Anonymised aerosol data from the AERATOR Study will be submitted to the Bristol data repository (data.bris.ac.uk) on completion of the full study.

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Passado, presente e futuro da oxigenoterapia conservadora nos cuidados críticos

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OXIGENOTERAPIA CONSERVADORA

A oxigenoterapia conservadora (COT) consiste na administração de níveis de oxigénio suplementar abaixo do habitual para tolerar um nível de oxigenação arterial (seja a pressão parcial (PaO₂) ou a saturação da hemoglobina) abaixo do normal. O seu objetivo é reduzir a exposição global de um paciente a um acréscimo de oxigénio para minimizar o risco de toxicidade do oxigénio.¹ Esta abordagem à oxigenoterapia também tem sido designada por hipoxemia permissiva e os termos são frequentemente utilizados de forma indiscriminada. Aqui, referimo-nos a todos os esforços realizados para reduzir a administração de oxigénio suplementar ou a oxigenação arterial como COT. Foram realizados estudos num extenso conjunto de condições médicas, para determinar se a COT melhora os resultados dos pacientes e parece existir algum benefício entre os pacientes gravemente doentes.² Porém, o objetivo deste artigo é de apenas se centrar nos pacientes graves admitidos nas unidades de cuidados intensivos (UCI).

Estes pacientes apresentam frequentemente insuficiência respiratória hipoxêmica aguda e necessitam oxigénio de alta concentração para restabelecer a oxigenação arterial normal. Existe a preocupação de que um dos principais pilares de apoio a estes pacientes, o oxigénio, possa inadvertidamente estar a causar-lhes danos, o que atribuímos indevidamente a um agravamento da sua patologia subjacente. Não existe ainda consenso sobre como ou quando utilizar a COT em pacientes gravemente doentes, sendo imperativo que abordemos estas questões o mais rapidamente possível.

O PASSADO

Antes da pandemia COVID-19, uma série de estudos observacionais procurou compreender a relação entre a oxigenação arterial e a sobrevivência utilizando dados de bases de dados retrospectivas. Alguns resul-

tados apoiaram a noção de que a hiperoxemia estava associada a danos³ enquanto outros não.⁴ Estes estudos iniciais baseavam-se numa quantidade extremamente limitada de dados recolhidos regularmente, geralmente utilizando apenas um único valor de oxigenação por paciente. Os seus resultados apresentavam um risco elevado de confusão por indicação de tratamento e não forneciam qualquer informação sobre a causalidade. Mais recentemente, os investigadores tentaram mitigar os efeitos destas limitações metodológicas utilizando técnicas analíticas mais sofisticadas, com resultados que indicavam um sinal evidente de danos em doentes críticos expostos a hiperoxemia.⁵

Foram também realizados ensaios aleatórios controlados (RCT) para determinar a existência de benefícios clínicos na implementação da COT e novos dados continuam a surgir. As mais recentes sínteses destes dados concluíram que não existe um sinal evidente de benefício ou dano para a COT em doentes críticos.^{6,7} É evidente, a partir das parcelas florestais nestas meta-análises, que os RCT realizados e reportados até à data não produziram resultados consistentes. Isto, em parte, deve-se provavelmente a diferenças na conceção do estudo em termos de: tipo de pacientes incluídos, intervenções avaliadas e a gestão da oxigenação no grupo de comparação, o que torna a interpretação dos resultados da meta-análise extremamente difícil. Também vale a pena referir que, ao criar-se um grupo de comparação no qual se incentiva a hiperoxemia, a eficácia da intervenção COT (se existir) é altamente provável que seja exagerada no caso de o excesso de oxigénio ser prejudicial.

Também existe uma sobreposição de alguns COT e comparadores no seio de alguns estudos. Além disso, os estudos exclusivamente incluíam, excluía ou eram ambivalentes quanto à insuficiência respiratória hipoxêmica grave e incluem uma mistura de pacientes ventilados mecanicamente e a respirar espontaneamente com várias patologias. Embora alguns destes fatores sejam difíceis de resolver numa UCI, devido à heterogeneidade inata dos pacientes gravemente doentes, a grande variação nos parâmetros de intervenção e controlo nestes estudos significa que ainda não existe uma conclusão clara sobre a questão.

O PRESENTE

A pandemia da COVID-19 está longe de ter terminado e, na altura em que este artigo estava a ser redigido, a nova variante Omicron do SARS-CoV-2 estava a espal-

har-se rapidamente pelo planeta. Durante as fases iniciais da pandemia, existiam poucos dados para ajudar os clínicos a tomar decisões informadas sobre a utilização da COT.⁸ A pandemia perturbou os sistemas de saúde (e os programas de investigação clínica) em todo o mundo e trouxe consigo um lembrete preocupante de que ainda temos de estabelecer respostas baseadas em evidências sobre o como ou quando da COT. Consequentemente, a COT não poderia ser recomendada como uma intervenção terapêutica benéfica para pacientes ventilados mecanicamente com pneumonia COVID-19. O número de doentes hipoxêmicos nos hospitais não tinha precedentes e levou os hospitais ao seu ponto de rutura em termos de prestação de apoio respiratório adequado e seguro aos doentes.

Os sistemas de saúde foram forçados a considerar as consequências inimagináveis de a procura local de oxigénio exceder a oferta. Em resposta a esta situação no Reino Unido, as orientações nacionais da *British Thoracic Society* aconselharam que o objetivo habitual de saturação periférica de oxigénio (SpO₂) para um doente adulto gravemente doente de 94%-98% deveria ser modificada para 92%-96%. As orientações nacionais no Reino Unido também sugeriram que se deveria considerar uma maior redução para uma SpO₂ de 90%-94%, caso se considerasse clinicamente adequado e estando disponível uma monitorização contínua do paciente. Da mesma forma, a orientação do *National Health Service England* (NHSE) sobre a gestão de cuidados críticos para adultos com COVID-19, aprovada pela Sociedade de Cuidados Intensivos e pela Faculdade de Medicina de Cuidados Intensivos, recomendou uma meta de SpO₂ de 90%-93% como aceitável em pacientes com oximetria de pulso visível e contínua em ambientes de cuidados devidamente monitorizados com pessoal devidamente qualificado para monitorizar a deterioração clínica.¹⁰

Os resultados da revisão sistemática e meta-análise sobre a Melhoria da Oxigenoterapia em Doenças Agudas foram utilizados para apoiar estas recomendações nacionais; ainda que a meta-análise tenha sido dominada por doentes admitidos por enfarte do miocárdio e AVC em vez de insuficiência respiratória.² Apesar da falta de evidências para apoiar a COT em doentes críticos com COVID-19, era prática comum no Reino Unido que os doentes em UCI fossem geridos de acordo com as orientações nacionais ou com valores de SpO₂ ainda mais baixos (por exemplo, 88%-92%).

Um inquérito realizado no Reino Unido em maio de 2020 indicou que a maioria dos inquiridos se sentia confortável com a COT.¹¹ Nunca saberemos ao certo se foi a terapia mais indicada para esses doentes, uma vez que não foi formalmente avaliada no âmbito de um RCT. Uma pequena análise de subgrupo *pós-hoc* do ensaio *Handling Oxygen Targets in the ICU* (HOT-ICU) avaliou o impacto da COT em apenas

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110 pacientes com COVID-19 e encontrou uma mortalidade a 90 dias reduzida e sem significância na coorte COT (40,7% vs. 41,8%, rácio de risco ajustado 0,87, 95% IC 0,58 a 1,32).¹²

Com base nesta descoberta, os autores estão neste momento a realizar o ensaio *Handling Oxygenation Targets in COVID-19* (HOT-COVID) (<https://clinicaltrials.gov/ct2/show/NCT04425031>), uma adaptação do seu ensaio HOT-ICU¹³ que continuará a avaliar um alvo PaO₂ de 60 vs 90mm Hg em 780 pacientes adultos agudamente doentes com COVID-19 e insuficiência respiratória hipoxémica. Como resultado da pandemia COVID-19 em curso, parece haver um sentimento geral entre os clínicos de que se sentem agora mais confortáveis com a utilização da COT em pacientes com doença grave sob ventilação mecânica. Contudo, existe o risco de isto se transformar lentamente na crença de que a COT é de facto benéfica do ponto de vista terapêutico em comparação com a oxigenação normal. Este potencial colapso do equilíbrio clínico, sem evidências que sustentem a hipótese, poderia ter impacto nos ensaios em curso que procuram avaliar a COT. Para que um RCT seja viável, o equilíbrio clínico é essencial; deve existir incerteza clínica suficiente sobre o facto de a intervenção a avaliar ser superior à terapia padrão ou ao placebo (o comparador).¹⁴

Se houver consenso de que a intervenção em questão é superior ao comparador, a ética do ensaio fica comprometida e a tentativa de persistir no sentido de obter uma resposta à questão da investigação pode tornar-se impossível. Os médicos não recrutarão participantes num ensaio para o qual acreditam que a resposta já é conhecida. O que também devemos recordar é que a COVID-19 é uma entidade específica da doença, com a qual nunca nos deparámos antes, pelo que as terapias que acreditamos serem eficazes durante a pandemia podem não ser aplicáveis às populações UCI não-COVID-19 gravemente doentes. Para tal, devemos ser extremamente cautelosos quanto às 'lições aprendidas' de práticas que tiveram lugar nas circunstâncias extraordinárias que acompanharam esta pandemia e a aplicá-las à nossa prática de cuidados críticos não COVID-19. Durante a pandemia, era imperativo que reagíssemos rapidamente às novas evidências produzidas e por vezes incompletas. Contudo, não devemos deixar que isto degrade uma abordagem robusta à criação de cuidados baseados em evidências quando a nor-

malidade recomençar. Seria uma enorme pena se a tendência para uma hiperoxemia desnecessária nas UCI no final do século XX e início do século XXI, que era consequência de hábitos e crenças clínicas não baseadas em evidências na altura, fosse substituída por um conjunto de hábitos e crenças clínicas semelhantes não baseados em evidências, favorecendo a hipoxemia na terceira década do século XXI.

O FUTURO

Á medida que emergimos da pandemia COVID-19, é fundamental que, como especialidade, continuemos a nossa exploração da COT em pacientes gravemente doentes, com base nas evidências precedentes. Olhando para o futuro, dois grandes RCT multicêntricos estão a avaliar o benefício da COT em pacientes críticos sob ventilação mecânica: Mega-ROX (<http://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379432&isReview=true>) é global e UK-ROX (<https://www.isrctn.com/ISRCTN13384956>) está sediado no Reino Unido. Com o objetivo de incluir números elevados (40000 participantes para Mega-ROX e 16500 para UK-ROX), estes dois ensaios foram concebidos prospetivamente para permitir uma meta-análise individual dos dados dos doentes após a sua conclusão. Utilizando novos desenhos de ensaios para assegurar a realização rápida de ensaios de grande dimensão, os investigadores estão a apelar às comunidades de cuidados intensivos de todo o mundo para responderem às suas perguntas o mais rapidamente possível. É pouco provável que tenhamos uma conclusão clara sobre a história da COT até que ambos os RCT tenham transmitido os seus resultados. Até lá, devemos considerar esta simples intervenção terapêutica como experimental e manter uma mente aberta sobre se é benéfica, prejudicial ou nenhuma das duas.

CONCLUSÕES

Antes da pandemia da COVID-19, não sabíamos se devíamos utilizar a COT em pacientes ventilados mecanicamente e a pandemia não alterou esta situação. Não existiam evidências suficientes para recomendar a COT nessa altura e não há evidências suficientes para recomendar a COT agora. A recomendação para atingir valores de SpO₂ inferiores ao normal durante a pandemia de COVID-19 foi uma necessidade logística e, quando essa necessidade diminuiu, devemos ser lembrados para regressar às nossas práticas anteriores até que surjam novas evidências.

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Aceitabilidade de intervenções de higiene, cobertura facial e distanciamento social para prevenir exacerbações em pessoas que vivem com doenças das vias aéreas

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RESUMO

As intervenções para prevenir a propagação do SARS-CoV-2 foram associadas a reduções substanciais nas agudizações de doenças das vias aéreas, provavelmente por meio da redução da transmissão de outros vírus respiratórios. Pesquisamos 4.442 pessoas com doenças das vias aéreas (asma = 3.627, bronquiectasias = 258, doença pulmonar obstrutiva crônica = 557) para avaliar atitudes e intenções de continuar essas medidas após a pandemia de COVID-19. 47% pretendiam continuar usando uma máscara facial em espaços públicos internos e 61% achavam que todos deveriam ser obrigados a fazê-lo durante a 'temporada da gripe'. Mulheres, pessoas com bronquiectasias e idosos eram geralmente mais cautelosos. Medidas de controle de infecção por vírus respiratórios devem ser consideradas nas diretrizes clínicas e recomendações de saúde pública.

INTRODUCTION

Chronic airway diseases are common.^{1–3} People living with these conditions are susceptible to 'exacerbations' which drive much of the morbidity, mortality and cost.^{1–3} Most exacerbations are caused by respiratory viruses.

During the COVID-19 pandemic, a range of measures to reduce the transmission of SARSCoV-2 were introduced, including encouraging hand hygiene, social (physical) distancing, wearing face coverings and isolation of suspected and/or confirmed cases. People with airway diseases were considered particularly vulnerable⁴ and advised to take additional precautions, including 'shielding' (maximal reduction of social contact). Recommendations varied within and between countries, and over time.

Multiple studies subsequently reported a substantial reduction in hospitalisations due to asthma and chronic obstructive pulmonary disease (COPD) exacerbations, temporally associated with introduction of COVID-19 infection control measures,⁵ likely because people avoiding SARS-CoV-2 were also avoiding viruses that cause exacerbations.⁶

Current guidelines such as the Global Initiative for Asthma¹, Global Initiative for Chronic Obstructive Lung Disease³ and European Respiratory Society guidelines on bronchiectasis² focus on exacerbation prevention but do not recommend respiratory virus infection control measures. This is despite a Cochrane review demonstrating efficacy.⁷ While the COVID-19 pandemic has demonstrated that individuals are accepting of measures to reduce the transmission of infection, understanding ongoing intentions of people with

respiratory disease would be an important first step in developing future guidance in this area.

METHODS

An online survey of people with airway diseases was conducted by the Asthma UK–British Lung Foundation partnership, seeking their views about measures to reduce respiratory virus transmission. Questions were framed to cover a future period after the COVID-19 pandemic, based on the possibility that such measures could reduce the risk of exacerbations. Data were analysed in SPSS (V.25). Proportions were compared with χ^2 . $P \leq 0.05$ was considered statistically significant.

RESULTS

The survey was distributed via social media and mailing lists (164285 recipients) and open on 3–10 March 2021. Overall, 4442 people completed the survey: 3627 (81.7%) with asthma, 258 (5.8%) with bronchiectasis and 557 (12.5%) with COPD. The most common age categories were 50–59 (n=1165) and 60–69 years (n=1200). Overall, 3381 (76%) were female. A total of 4260 (96%) reported their ethnicity as 'white'.

Responses on the longer-term acceptability of respiratory virus infection control measures in this population are presented in table 1. A substantial proportion of respondents expected to continue to take some steps to reduce their future risk of exacerbation, for example, 79.5% would continue increased handwashing and 68.6% would continue social distancing indoors. Overall, 46.9% would continue to wear a face mask in indoor public places. There was little support for wearing face coverings or social distancing outdoors.

Regarding policy for people more generally, responses were generally lower when considering what the population should do 'at all times' compared with 'during the influenza season'. Around half of the respondents wanted healthcare professionals to continue wearing a mask when seeing patients.

There were differences between the three respiratory conditions with the suggestion that people living with bronchiectasis were most cautious (table 1). Women were more likely to continue measures than men (online supplemental table 1).

We examined the effect of age on support for respiratory virus infection control measures in people with asthma (online supplemental table 2). There were statistically significant differences and differences of more than 10% points between age groups for five interventions (figure 1). In general, older people were more cautious, with the exception of not visiting unwell friends and family.



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Table 1 Acceptability of respiratory virus infection control interventions in people living with asthma (n=3627), bronchiectasis (n=258) and COPD (n=557)

	Thinking about the future (after the lockdown has been eased and most people have been vaccinated against COVID-19), would you continue to do yourself, even if it wasn't policy...	Thinking about the future (after the lockdown has been eased and most people have been vaccinated against COVID-19), which of the following do you think should carry on as policies for everyone at all times? Spline	Thinking about the future (after the lockdown has been eased and most people have been vaccinated against COVID-19), which of the following do you think should carry on as policies for everyone during the influenza season?
Wearing a face covering in indoor public places	Overall 46.9%* Asthma 46.0% Bronchiectasis 56.2% COPD 48.5%	Overall 44.9%* Asthma 43.5% Bronchiectasis 54.3% COPD 50.3%	Overall 60.7%*† Asthma 60.0% Bronchiectasis 70.5% COPD 61.0%
Wearing a face covering on public transport	Overall 45.7% Asthma 45.6% Bronchiectasis 51.6% COPD 43.4%	Overall 50.8% Asthma 50.1% Bronchiectasis 55.8% COPD 53.0%	Overall 59.5%† Asthma 59.5% Bronchiectasis 63.6% COPD 57.8%
Wearing a face covering outdoors	Overall 11.6% Asthma 11.5% Bronchiectasis 12.4% COPD 11.8%	Overall 10.9% Asthma 10.6% Bronchiectasis 11.2% COPD 13.1%	Overall 12.9%† Asthma 12.5% Bronchiectasis 14.7% COPD 15.3%
Hand sanitiser being widely available to clean hands	Not applicable	Overall 79.7%* Asthma 80.9% Bronchiectasis 81.09% COPD 71.3%	Overall 81.7%* Asthma 83.1% Bronchiectasis 81.4% COPD 72.3%
Washing hands more often	Overall 79.5%* Asthma 80.7% Bronchiectasis 81.0% COPD 70.6%	Overall 73.7%* Asthma 74.7% Bronchiectasis 76.7% COPD 65.7%	Overall 75.9%*† Asthma 76.8% Bronchiectasis 79.1% COPD 68.4%
Keeping more of a distance from others when in an indoor public space	Overall 68.6% Asthma 67.8% Bronchiectasis 73.6% COPD 70.9%	Overall 52.5%* Asthma 50.8% Bronchiectasis 58.89% COPD 60.3%	Overall 62.9%*† Asthma 61.4% Bronchiectasis 70.5% COPD 68.6%
Keeping more of a distance from others when in an outdoor public space	Overall 38.0% Asthma 37.8% Bronchiectasis 38.0% COPD 39.5%	Not asked	Not asked
Avoiding busy public spaces	Overall 60.0%* Asthma 58.9% Bronchiectasis 71.7% COPD 61.8%	Not asked	Not asked
Avoid seeing friends or family if they are unwell with a cold or influenza	Overall 59.3%* Asthma 59.9% Bronchiectasis 70.2% COPD 50.8%	Not asked	Not asked
Healthcare staff to wear masks when seeing patients	Not applicable	Overall 45.6% Asthma 45.5% Bronchiectasis 50.8% COPD 43.6%	Overall 51.5%† Asthma 51.6% Bronchiectasis 56.2% COPD 48.7%

Data are % answering yes (total n=4442).

*P<0.05 for differences across respiratory diseases.

†P<0.05 for overall difference between policy at all times compared with only during the influenza season.

COPD, chronic obstructive pulmonary disease.

DISCUSSION

Substantial proportions of people living with airway diseases report that they would continue infection control measures adopted during the COVID-19 pandemic to reduce their future risk of exacerbations. There was also support for the adoption of measures in the general population, especially during the influenza season, which should prompt discussion about behaviours in enclosed public spaces. The findings were consistent across different airways diseases, although older people, women and those with bronchiectasis were most willing to adopt a more cautious approach.

The reduction in hospitalisations for exacerbations during the pandemic is of greater magnitude than ever previously achieved with optimisation of care.¹⁻³ Given the evidence base supporting the

effectiveness of measures to reduce exacerbations, consideration should be given to including such measures in future guidelines.

Frequent hand washing would be the simplest measure to encourage as it is already a part of social behaviour. If measures other than hand hygiene are most effective, further work will be required to support people in making behaviour changes. Understanding differences in effectiveness of interventions together with willingness for people to adopt them will be critical in informing policy change. Compliance with recommendations in the general population is related to confidence in the source of advice.⁸ Acceptability of interventions is dependent on many factors including cultural norms and, as here, age and gender. In some jurisdictions, face coverings have become politicised which may further affect implementation, and some people with respiratory disease have been exempt from

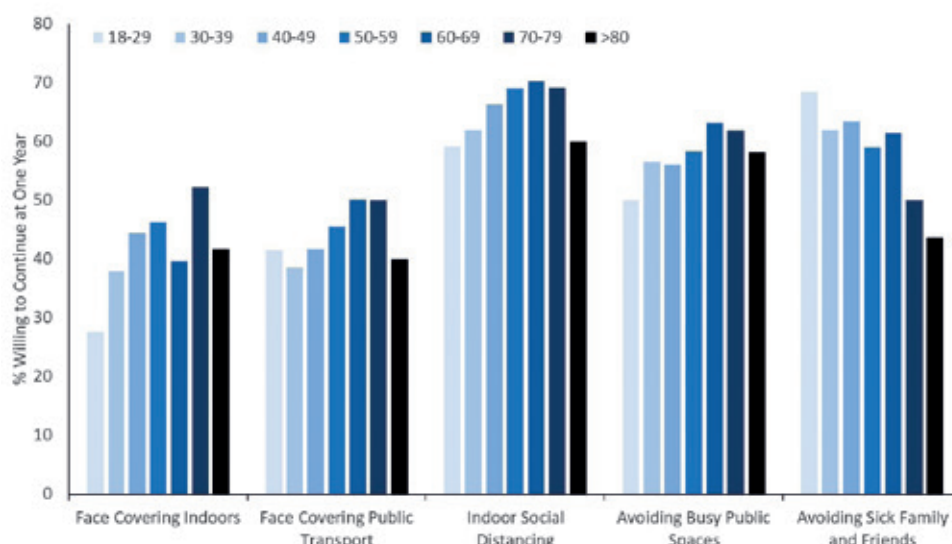


Figure 2 The acceptability of respiratory virus infection control interventions in adults living with asthma, by age (in years). n=3627.

wearing face coverings which could limit future adoption. The potential benefits of measures must be balanced against potential harms including costs and psychological harms such as stigma.^{9,10} It is possible that by reducing regular exposure to common respiratory viruses, there could be increased risk of more severe disease over time.

Our survey was conducted online, so required digital literacy, and non-white ethnic groups and men were under-represented despite the large sample size. Although the questions were framed to address the period 'after COVID-19', attitudes may change over time. Importantly, there was little enthusiasm for outdoor mask wearing suggesting that responses were measured and proportionate. Infection control strategies are affordable and not pathogen specific.⁷ Their dramatic impact during the pandemic indicates that guideline committees in asthma, bronchiectasis and COPD should consider including them in future advice on preventing exacerbations. Our data show that there is a significant level of acceptance by people with these conditions and that they are likely to be well tolerated. As well as enabling people living with airways diseases to make informed choices about modifying their own risk of exacerbation, the general public can also be informed and advised as to how they can continue to protect members of society who may be especially vulnerable to infections.

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